10.10
Bicyclic 5-6 systems with One bridgehead (Ring Junction) Nitrogen Atom: One Extra Heteroatom 1:0

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10.10.1 Introduction

The organization of this chapter can easily be visualized by considering the series of molecules shown in **Figure 1**, all of them being shown in their fully conjugated aromatic form. The next section will deal with pyrazolo[1,5-*a*]pyridines, for which most of new synthetic work was devoted to the aromatic system. Then, the cationic isoxazolo- and isothiazolo[2,3-*a*]pyridines will be covered together; for these compounds, and in contrast with their nitrogen equivalents, the quasi-exclusive amount of work is now devoted to partially reduced systems. The same type of organization will be used for imidazo[1,5-*a*]pyridines and their oxygen and sulfur analogues, the latter being reviewed together. Finally, imidazo[1,2-*a*]pyridines and their oxygen and sulfur analogues will be presented independently

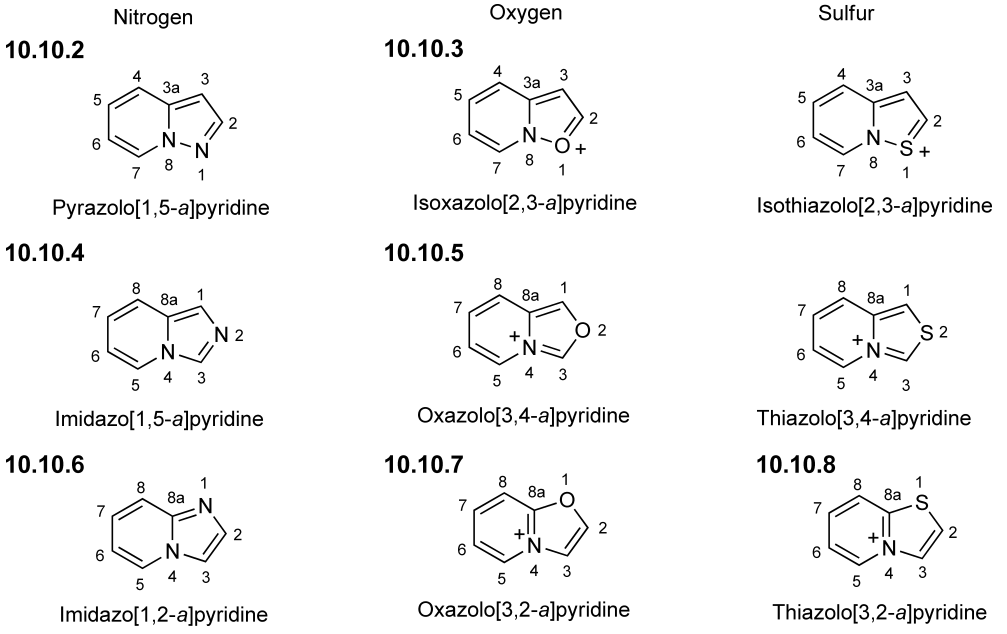


Figure 1

since the important synthetic work devoted to partially or totally reduced oxazolo[3,2-*a*] systems clearly merits an independent section. This chapter concludes with a brief description of ring systems containing a less common heteroatom than nitrogen, oxygen, or sulfur in the five-membered ring.

10.10.2 Pyrazolo[1,5-*a*]pyridine

10.10.2.1 Introduction

Pyrazolo[1,5-*a*]pyridines can be viewed as 8-aza analogues of indoles <2000S1727>. Considering the metabolic unstability of these latter and their high biological relevance, it is not surprising that these indole isosteres have been the subject of considerable work in the field of medicinal chemistry. This class of heterocycles was covered with other fused diazines and triazines in volume 5 (chapter 4.05) in CHEC(1984) <1984CHEC-I(5)305> and in an independent section in CHEC-II(1996) (volume 8, chapter 8.10.2) <1996CHEC-II(8)249>. The organization of this section roughly follows the one used in CHEC-II(1996) but focuses on new synthetic methodologies available for this heterocyclic system.

10.10.2.2 Theoretical Methods

No new calculations were specifically devoted to this heterocylic system since CHEC-II(1996) <1996CHEC-II(8)249>. However, modeling of bioactive compounds containing this heterocycle have been published as exemplified by the the use of the highly potent dopamine D4 receptor ligand FAUC113 as template for comparative molecular field analysis (CoMFA) of dopamine D4 receptor antagonists <2001JME1151>.

10.10.2.3 Experimental Structural Methods

Similarly to the above section, no additional specific nuclear magnetic resonance (NMR) data complete CHEC(1984) and CHEC-II(1996) <1996CHEC-II(8)249>: NMR data for new substituted compounds are routinely reported. Several X-ray structures of bioactive molecules possessing this heterocyclic core have been reported <1999BML1979, 1999JME779>.

10.10.2.4 Thermodynamic Aspects

Similarly to the above section, no additional specific studies complete CHEC(1984) and CHEC-II(1996) <1996CHEC-II(8)249>.

10.10.2.5 Reactivity of Fully Conjugated Rings

As specified in CHEC-II(1996) <1996CHEC-II(8)249>, pyrazolo[1,5-*a*] pyridines are aromatic systems in which the bridgehead nitrogen N-8 contributes to the aromaticity with its lone pair. Therefore, this is a 'pyrrole-like' nitrogen of low pK_a and nucleophilicity. On the other hand, the N-1 is a 'pyridine-like' nitrogen and is indeed the site of protonation. An important amount of synthetic work has been devoted to electrophilic substitution, reactions that occur with high regioselectivity at the C-3 position and additional examples will be presented. **Figure 2** summarizes these main characteristics. Functionalizations through metal-catalyzed coupling reactions have gained importance since the previous issue and will be especially highlighted in the following paragraphs.

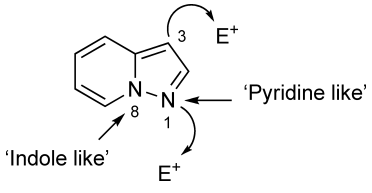
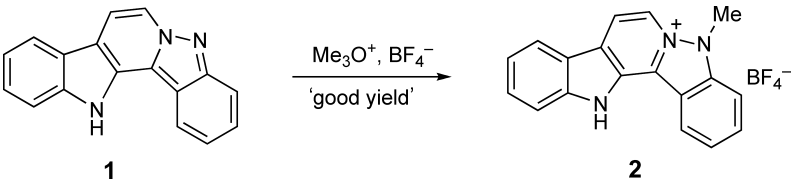


Figure 2

10.10.2.5.1 Electrophilic attack at nitrogen

Alkylation of the 'pyridine-like' nitrogen in **1** with the Meerwein's salt allowed the preparation of a derivative **2** of this ring system suitable for the evaluation of intercalating properties (**Scheme 1**) <2000BML1767, 1996BML2831>.

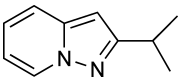
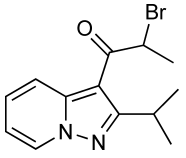
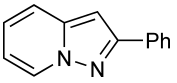
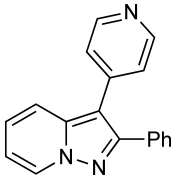
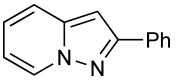
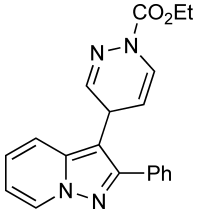
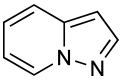
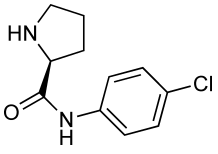
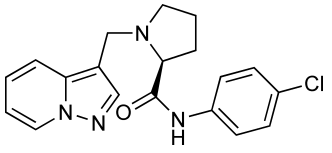


Scheme 1

10.10.2.5.2 Electrophilic attack at carbon

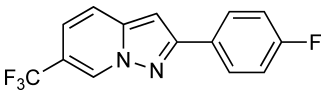
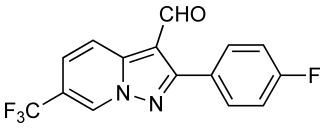
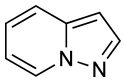
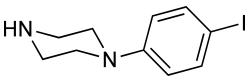
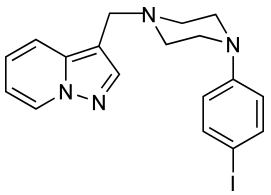
Electrophilic attack at carbon is a well-documented reaction which occurs regioselectively at the C-3 position. It was illustrated by numerous examples, including nitrations, halogenations, acylations, and Mannich reactions in CHEC(1984) and CHEC-II(1996) <1996CHEC-II(8)249>. **Table 1** reports some additional recent examples. It should be noted that all these synthetic transformations were carried out in the field of medicinal chemistry.

Table 1 Electrophilic attack at C-3

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	$BrCOCHBrMe$ $AlCl_3$		77	2003TA529
	$ClCO_2Et$, pyridine Then *t*-BuOK, air		34	1999JME779
	$ClCO_2Et$ Pyridazine		53	1999JME779
	 CH_2O, Et_2NMe AcOH		82	2002TA2303

(*Continued*)

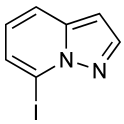
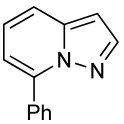
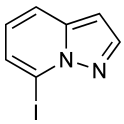
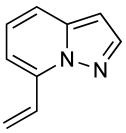
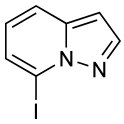
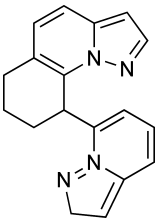
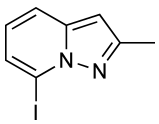
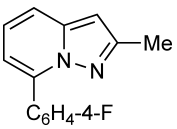
Table 1 (Continued)

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	$POCl_3$ DMF		94	2006BMC944
	 CH_2O, AcOH		42	1999BML97

10.10.2.5.3 Nucleophilic attack at carbon

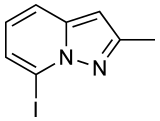
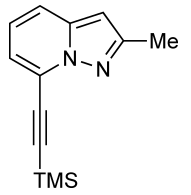
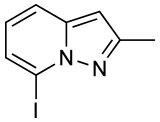
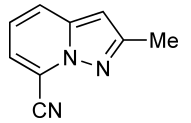
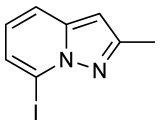
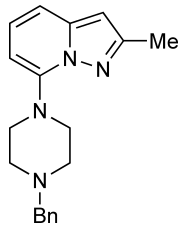
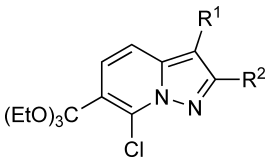
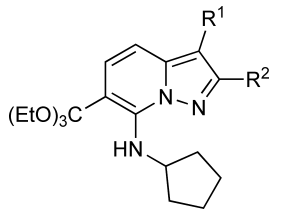
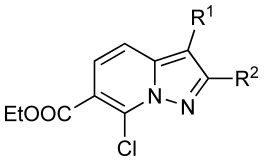
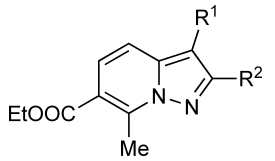
As mentioned in CHEC(1984) and CHEC-II(1996), nucleophilic substitution of hydrogen atoms has not been reported, but substitution of halogens either through direct S_NAr or using metal-catalyzed coupling reactions have been explored. This field was investigated in detail quite recently by Gmeiner and co-workers in the case of easily available 7-iodo derivatives <2000S1727>, and some representative examples are reported in **Table 2**.

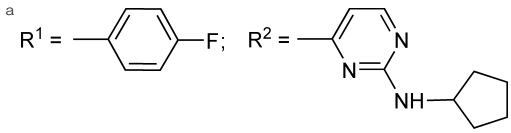
Table 2 Functionalization of 7-halo derivatives

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	$PhSnBu_3$ $Pd(PPh_3)_4$ Toluene, reflux		82	2000S1727
	$CH_2{=}CHSnBu_3$ $Pd(PPh_3)_4$ Toluene, reflux		62	2000S1727
	$CH_2{=}CHSnBu_3$ $PdCl_2(PPh_3)_2$ NMP, 120 °C		83	2000S1727
	4-FC_6H_5-$B(OH)_2$ $Pd(PPh_3)_4$ Toluene, H_2O $NaHCO_3$, reflux		80	2000S1727

(*Continued*)

Table 2 (Continued)

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	TMSC≡CH $Pd(PPh_3)_4$ CuI, $EtNMe_2$, rt		66	2000S1727
	CuCN, $Pd_2(dba)_3$ DPPF, dioxane Reflux		95	2000S1727
	4-Bn-piperazine $Pd_2(dba)_3$, P(*t*-Bu)$_3$ Na-*t*-BuO, toluene 120 °C		50	2000S1727
	Cyclopentylamine 80 °C		96[a]	2006BMC944
	Me_2Zn, $Pd(PPh_3)_4$ THF, 60 °C		45[a]	2006BMC944

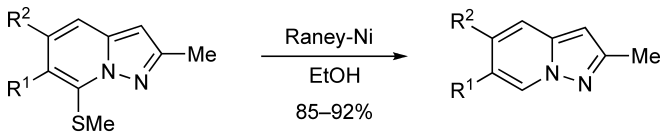
[a] 

10.10.2.5.4 Nucleophilic attack at hydrogen

Deprotonation readily occurs at C-7, and the resulting anion can further react with various electrophiles. Thus, treatment with BuLi at −78 °C followed by reaction with diiodoethane was used to prepare the 7-iodo derivatives depicted in **Table 2**, while the 7-chloro derivatives were prepared by lithiation with lithium diisopropylamide (LDA), followed by reaction with CCl_4. The 7-formyl derivative of the parent pyrazolo[1,5-*a*]pyridine has been prepared in 82% yield by reaction of the BuLi-generated anion with ethyl formate <2001JME2691>.

10.10.2.5.5 Reaction at surfaces

As previously reported in CHEC-II(1996) <1996CHEC-II(8)249>, this ring system is fairly resistant to reduction, and, under more forcing conditions, the six-membered ring is reduced preferably. Desulfurization with Raney-Ni of 7-SMe derivatives was reported <1999T7645> to occur efficiently, as shown in **Scheme 2**.

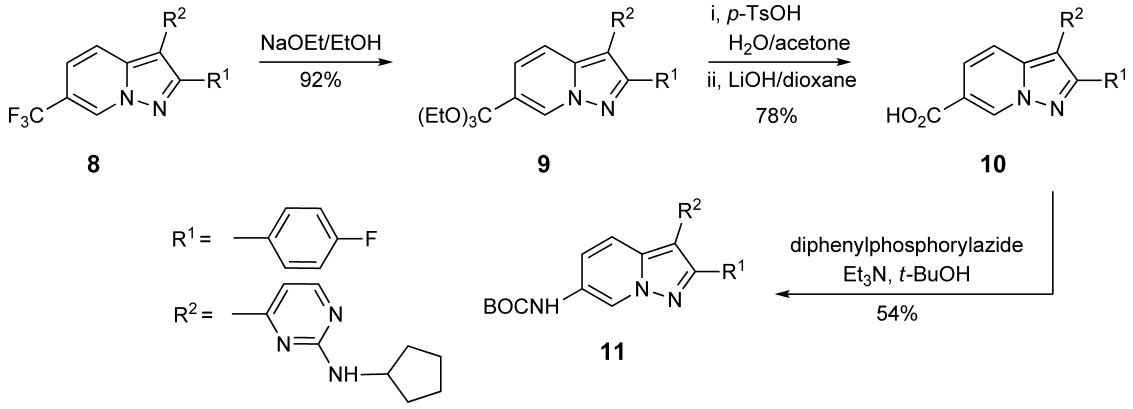


3: R^1 = Me; R^2 = Me
4: R^1 = Me; R^2 = H
5: R^1 = Ph; R^2 = H
6: R^1 = 4-$MeOC_6H_4$; R^2 = H
7: $R^1 = R^2 = -(CH_2)_n-$

Scheme 2

10.10.2.6 Reactivity of Substituents Attached to Ring Carbon Atoms

Apart from classical functional group interconversions that have already been discussed in previous issues, several interesting synthetic transformations of substituents attached to the ring need to be mentioned. First, carboxylic acids at C-2 or C-3 can be conveniently transformed into their acyl chloride derivatives by reaction with oxalyl chloride <2002JME4594>. Further reaction of the acyl chlorides with amines gives the corresponding amides in good yields. Interesting functional group interconversions have been recently reported by Allen *et al.* <2006BMC944>, some of them involving the overall transformation of a trifluoromethyl group at C-8 into an N-protected amine. This synthesis is depicted in **Scheme 3**.



Scheme 3

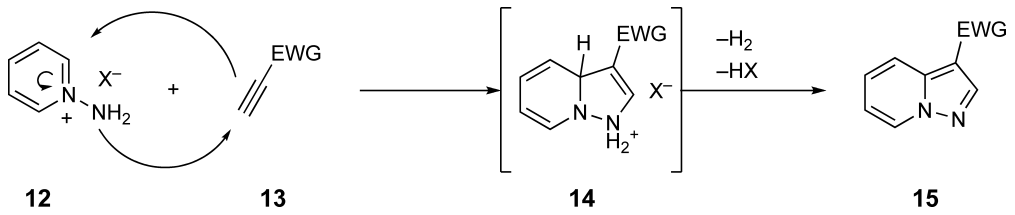
O-Alkylation of 4-hydroxylated <1996H(43)2249> or 5-hydroxylated <1996T8471> derivatives was reported to occur without competitive N-alkylation.

10.10.2.7 Synthesis

10.10.2.7.1 Fully conjugated ring

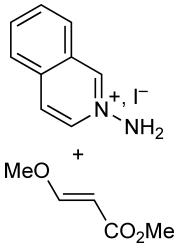
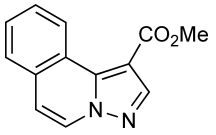
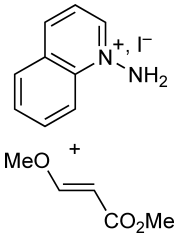
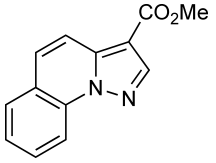
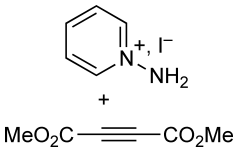
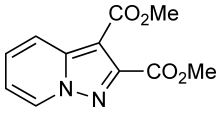
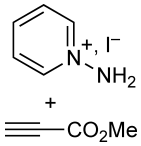
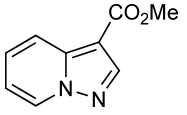
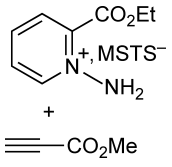
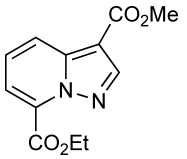
The most widely used approach to synthesize this heterocycle continues to be the condensation of *N*-aminopyridinium derivatives **12** with 1,2-ambident synthons such as **13** bringing two carbons and resulting in the ring closure of the five-membered ring. As outlined in **Scheme 4**, this ring closure requires further dehydrogenation of intermediate **14** for the production of **15**. This process most often occurs spontaneously, but sometimes is facilitated by bubbling air or oxygen into the reaction medium.

Many different ambident synthons have been used in this synthesis, and recent examples collected in **Table 3** complete the array of substrates that can be used for this ring closure mentioned in previous issues.



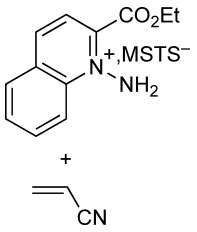
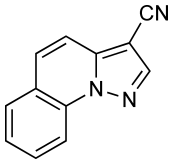
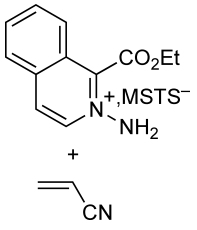
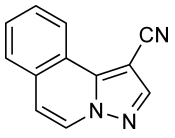
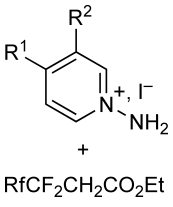
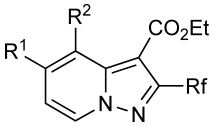
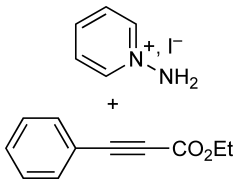
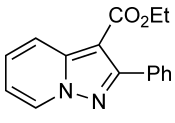
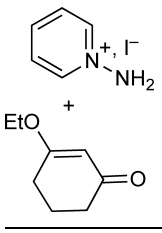
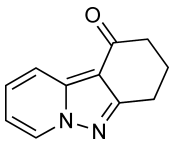
Scheme 4

Table 3 Synthesis through ring closure of *N*-aminopyridinium derivatives

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	Et_3N, EtOH Reflux, 5 h		72–80	1999BML97
	Et_3N, EtOH Reflux, 5 h		72–80	1999BML97
	K_2CO_3, air–O_2 DMF, rt, 2 h		45	2001JME2691
	K_2CO_3, air–O_2 DMF, rt, 1.5 h		72	2001JME2691
	(i-Pr)$_2$EtN DCM, reflux 6 h		36[a]	1999JOC9001

(*Continued*)

Table 3 (Continued)

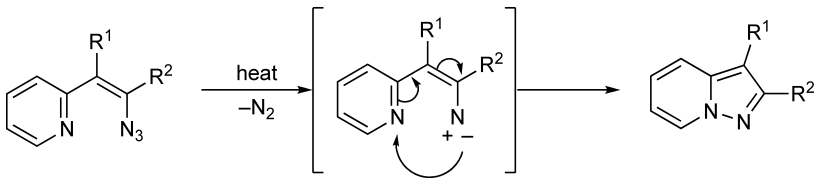
Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	$(i\text{-Pr})_2$EtN MeCN, reflux 20 h		61[a]	1999JOC9001
	$(i\text{-Pr})_2$EtN MeCN, reflux 48 h		23[a]	1999JOC9001
	K_2CO_3/NEt_3 DMF, 50 °C, 5–6 h		54–95	1998JFC57
	KOH, DMF		32	1996BML2059
	K_2CO_3, ethylene glycol 130 °C, 16 h		38	2002BML2377

[a]$MSTS^-$ = mesitylenesulfonate.

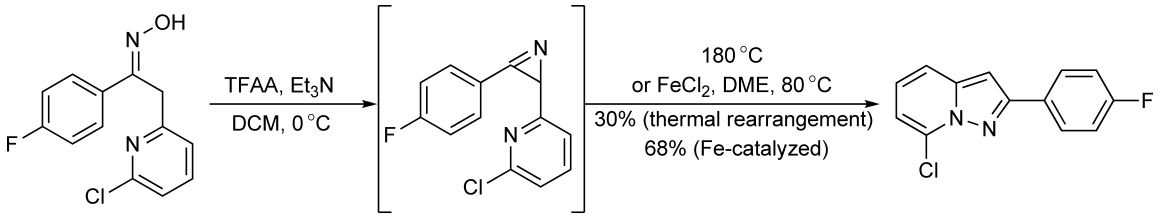
Examples reported in **Table 3** merit additional comments: the high regioselectivity observed with nonsymmetric aminopyridiniums is clearly an advantage of this synthetic route; however, most yields are quite low.

Another synthetic methodology of growing importance is based on the rearrangement of a transient nitrene, most often generated by thermolysis of an azido group as depicted in **Scheme 5**.

In this case, the efficiency of the synthetic route of course clearly depends on the availability of the azido substrate, but the key ring closure is quite efficient in most cases <2000BML1767, 2004JHC531, 1996BML2831>. Interestingly, the transient nitrene can also be generated from the rearrangement of an intermediate azirine **17**, generated from an oxime **16** (**Scheme 6**) <2003T9001>.



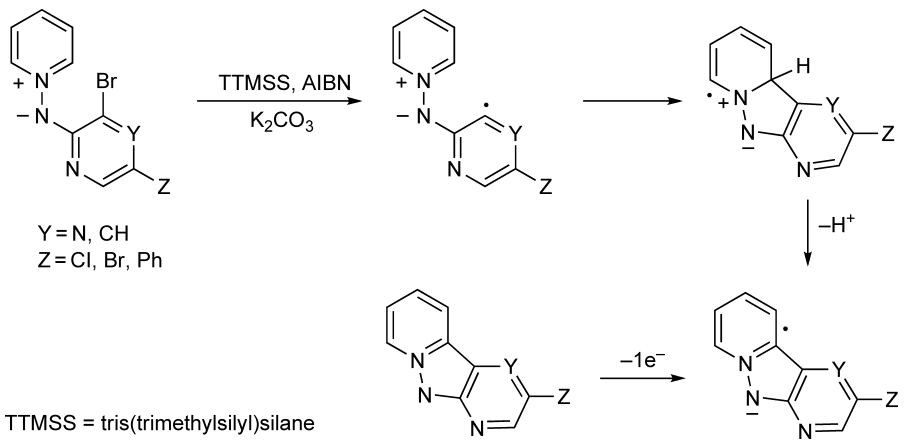
Scheme 5



16 **17** **18**

Scheme 6

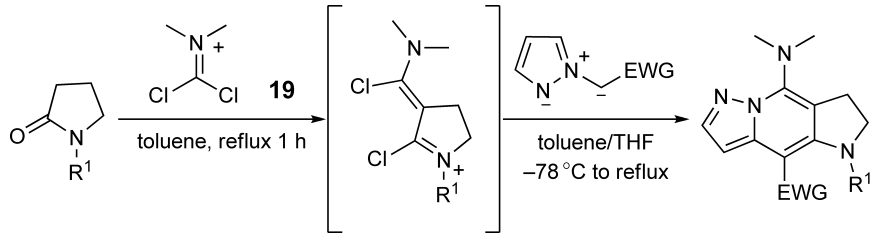
Apart from these important synthetic methodologies, other new approaches have appeared, and they can be classified depending on the size (five- or six-membered ring) of the heterocyclic ring formed in the process. A ring closure involving the formation of the five-membered ring was reported to proceed through a radical cyclization as depicted in **Scheme 7**. However, this methodology suffers from low yields (2–56%) due to competitive reduction of the starting material yielding 2-aminopyridines <2002SL1093>.



Scheme 7

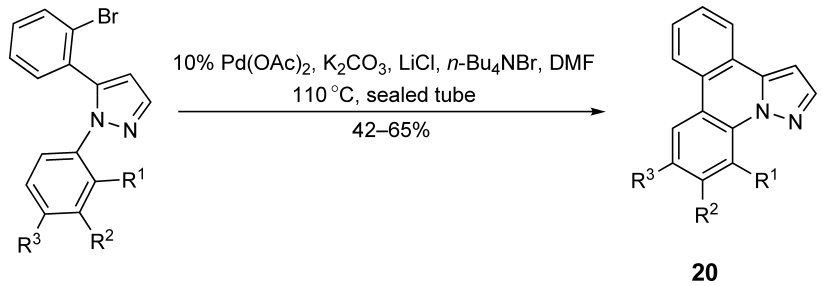
A new and general entry to azolo[1,5-*a*]pyridines possessing a dimethylamino moiety at C-7 was recently devised from Viehe's salt **19** <2006TL1395>. This reaction gives access to a large array of substituted heterocycles in good yields (44–69%) and efficient reaction sequences. As depicted in **Scheme 8**, this new synthetic methodology involves the construction of the six-membered ring as shown by selected examples.

Another contribution involving formation of the six-membered ring was reported by Dominguez <2003OL1095>. In this case, the key step involves a biaryl Mizoroki–Heck-type coupling. Fair yields (42–65%) of pyrazolophenanthridines **20** can be obtained from easily available starting materials prepared from acetophenones and hydrazines (**Scheme 9**).



R^1	*EWG*	*Yield* (%)
Me	CO_2Me	44
C_6H_{11}	CN	47
Ph	CO_2Me	62

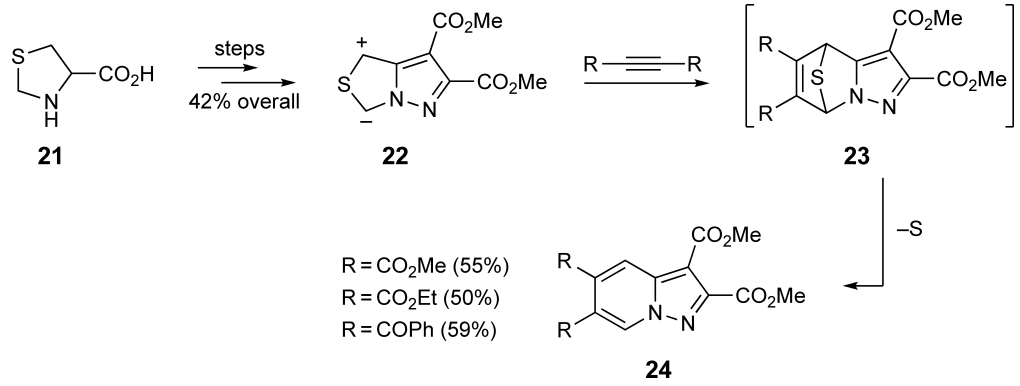
Scheme 8



20

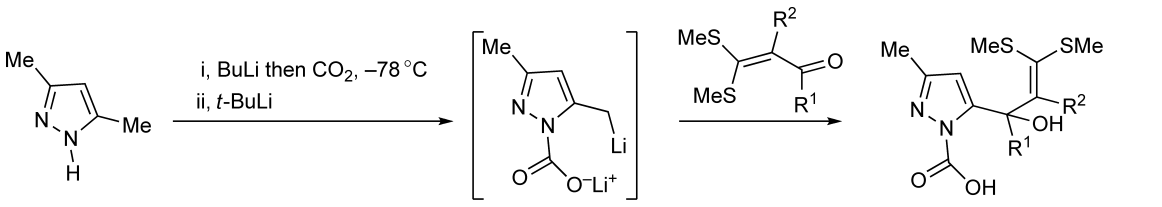
Scheme 9

A cycloaddition process involving dipole **22**, readily prepared from thiazolidine **21**, was reported to produce adducts such as **23** in the presence of sufficiently reactive dipolarophiles <2000T10011>. These adducts furnished substituted pyrazolo[1,5-*a*]pyridines **24** in fair yields upon further heating and extrusion of sulfur. However, diphenylacetylene did not react with dipole **22** (**Scheme 10**).



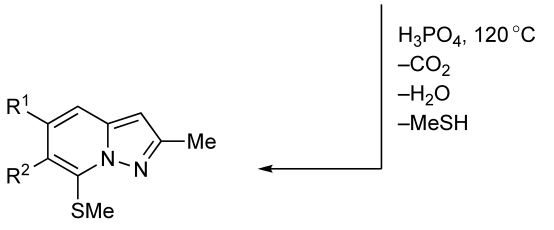
Scheme 10

Finally, another interesting new procedure <1999T7645> involving construction of the six-membered ring should be mentioned in this section. Dianion **26** resulting from the successive treatment of 3,5-dimethylpyrazole with organolithium reagents and carbon dioxide was reacted with an α-oxoketene dithioacetal. Treatment of the resulting adduct **27** with phosphoric acid induced the ring closure to form the six-membered ring present in **28** (**Scheme 11**). The latter could be conveniently desulfurized upon reaction with Raney-Ni.



25 **26** **27**

R^1	R^2	*Yield* (%)
Me	Me	78
Me	H	72
Ph	H	80
4-$MeOC_6H_4$	H	82
-$(CH_2)_3$-		67
-$(CH_2)_4$-		70
-$(CH_2)_5$-		67

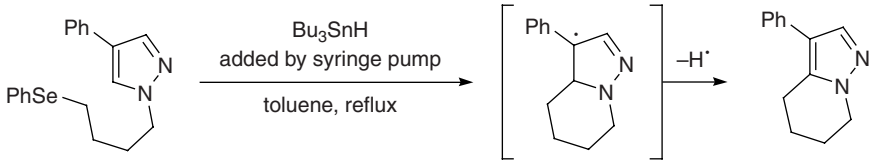


28

Scheme 11

10.10.2.7.2 Partially saturated rings

Tetrahydropyrazolo[1,5-*a*]pyridine derivatives possessing a fully reduced six-membered ring can be prepared by partial reduction of the aromatic ring <1999BML97, 1999BML1979>. Numerous other strategies have appeared for this synthetic purpose. The saturated six-membered ring can be formed by radical cyclization <2002TL4191> starting from selenide **29**: the success of this ring closure depends on the ability of the substituent attached on the pyrazole ring (a phenyl is shown in **Scheme 12**) to stabilize the intermediate radical **30**. In case of an ester instead of a phenyl substituent, the yield drops to 36% (versus 66% with a phenyl) while no cyclized product is produced when a dimethyl acetal group is attached to the starting pyrazole.



29 **30** **31**

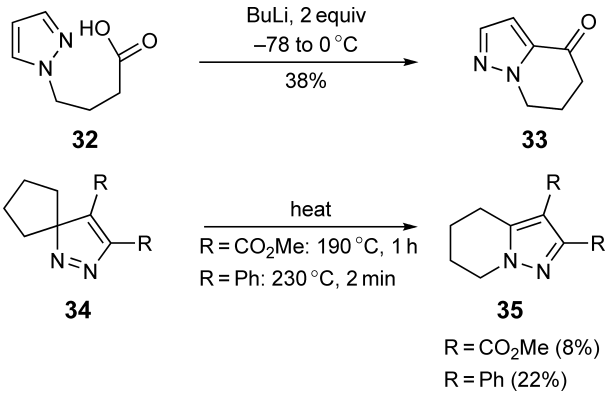
Scheme 12

Anionic ring closure of N-substituted pyrazole **32** can be carried out by its treatment with BuLi <1997S1013>. Although the yield is modest, this is a quite straightforward approach to these heterocycles. Thermal rearrangement of 3,3-spiro-pyrazoles **34** was also found to give (besides other products) the tetrahydro derivatives **35** (**Scheme 13**) <2001H1859>.

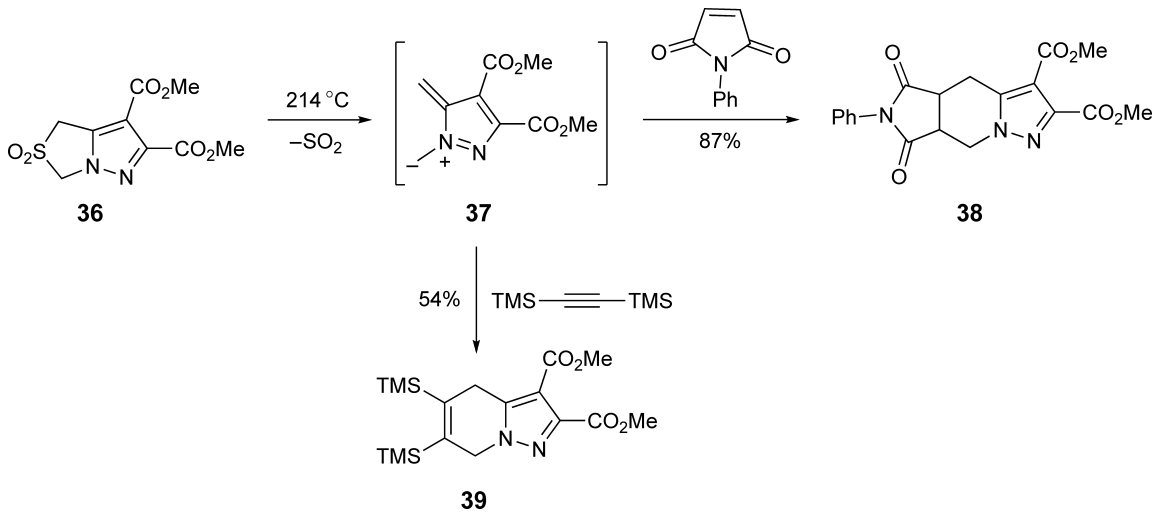
An elegant strategy to pyrazolo[1,5-*a*]pyridines derivatives in which the six-membered ring is partially or totally reduced relies on the cycloaddition of diazafulvenium methide **37**, generated through SO_2 extrusion from pyrazolo sulfone **38** in refluxing 1,2,4-trichlorobenzene, with various dipolarophiles <2006TL791> (**Scheme 14**).

The preparation of partially reduced derivatives in which the five-membered ring is reduced is less well documented. In a series of papers, Huisgen reported the 1,3-dipolar reactivity of isoquinolinium imide **41** in which loss of aromaticity occurs during cycloaddition <1998EJO379, 1998EJO387, 1998T9848>. Cycloaddition of this compound with dimethyl fumarate or maleate gives **42** and **43** as mixture of diastereoisomers (**Scheme 15**).

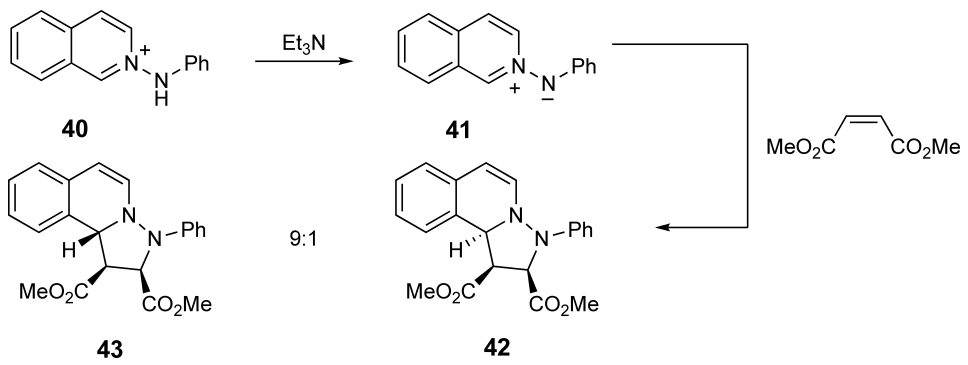
Finally, fully reduced heterocycles have been prepared either from a sequential azomethine imine cycloaddition–palladium-mediated cyclization process <2003T4451>, or from the reaction of *N*-(1-benzotriazolylalkyl)-*N*,*N*-disubstituted hydrazine with methylvinyl ether <1997JOC8210>.



Scheme 13



Scheme 14

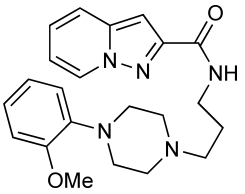
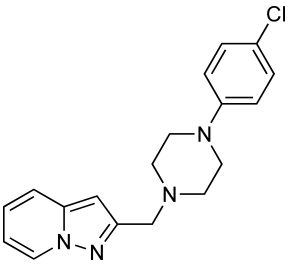
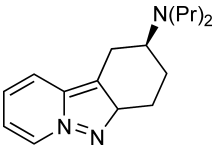
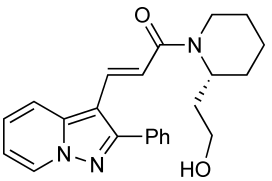
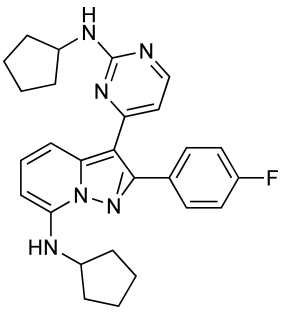


Scheme 15

10.10.2.8 Important Compounds and Applications

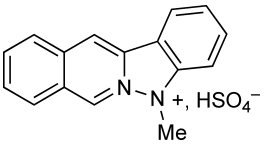
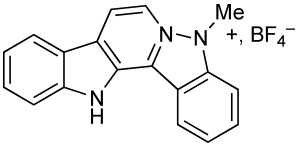
As mentioned in the introduction of this section, an important amount of synthetic work was devoted to this heterocyclic system and was mostly conducted by medicinal chemists. Aiming at developing selective ligands for the dopamine D4 receptor subtypes, the group of Gmeiner has published a series of papers reporting the use of this heterocyclic system as a scaffold for such molecules. Considering that dopamine receptors D4 are associated with neuropathologies such as schizophrenia, attention-deficit disorder, mood disorders, and Parkinson's disease, the potential of new selective ligands as drug candidates is quite high. Important compounds, together with their various biological activities issued from the Gmeiner's group and others, are collected in **Table 4**.

Table 4 Biologically active compounds including the pyrazolo[1,5-*a*]pyridine core

Compound	*Biological activity*	*Reference*
	Dopamine D3 antagonist (FAUC 329)	2002JME4594
	Dopamine D4 antagonist (FAUC 213)	2001JME2691
	Dopamine D3 agonist (FAUC 725)	2002BML2377
	Diuretic Adenosine A1 antagonist (FK453)	1996BML2059
	Antiherpetic (GW3733)	2006BMC944

(*Continued*)

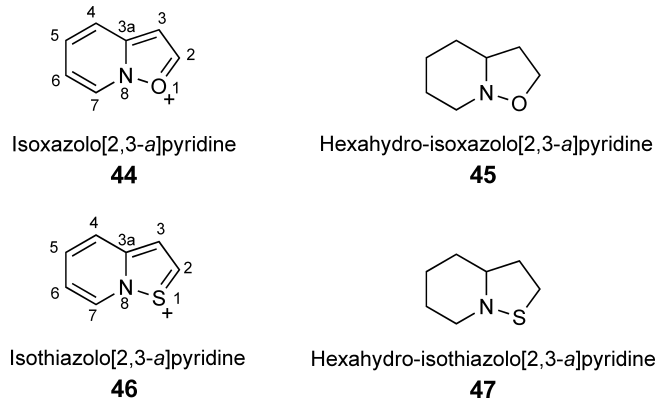
Table 4 (Continued)

Compound	*Biological activity*	*Reference*
	Inhibitor of reverse transcriptase (Ellipticin analogue)	1996BML2831
	Intercalating agent	2000BML1767

10.10.3 Isoxazolo[2,3-*a*]pyridine and Isothiazolo[2,3-*a*]pyridine

10.10.3.1 Introduction

Isoxazolo[2,3-*a*]pyridines **44**, isothiazolo[2,3-*a*]pyridines **46**, and their fully saturated derivatives **45** and **47** (**Scheme 16**) were discussed in CHEC(1984) <1984CHEC(6)617, 1984CHEC(6)635> and CHEC-II(1996) <1996CHEC-II(8)256>. Very little information was available on the isothiazolo[2,3-*a*]pyridine ring system while most of the informations given on the oxygenated parent, isoxazolo[2,3-*a*]pyridines, concerned the fully saturated system. Careful examination of the literature clearly show that the situation did not change much: almost no references have been reported on isothiazolo[2,3-*a*]pyridines and most of the work done in the last decade concerns the synthesis and reactivity of hexahydro-isoxazolo[2,3-*a*] pyridines **45**. Therefore, this chapter will briefly describe the new reactions of fully conjugated systems and will focus on the partially/completely saturated derivatives.



Scheme 16

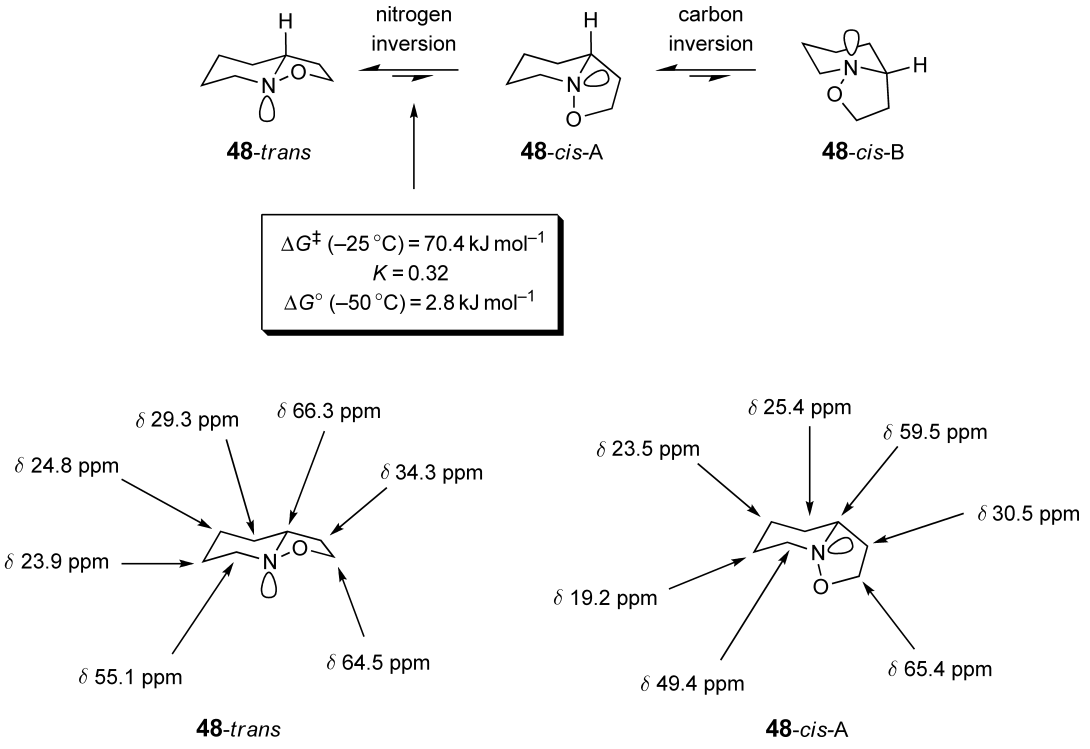
10.10.3.2 Theoretical Methods

No new calculations were specifically devoted to this ring system.

10.10.3.3 Experimental Structural Methods

NMR data for new compounds are routinely reported. The hexahydro-isoxazolo[2,3-*a*]pyridine ring system **48** can exist as a mixture of three conformers **48**-*trans*, **48**-*cis*-A, and **48**-*cis*-B (**Scheme 17**). While the two conformers possessing a *cis* ring junction **48**-*cis*-A and **48**-*cis*-B are interconverted by chair inversion, conversion of the *cis*-conformer **48**-*cis*-A to **48**-*trans* requires inversion of the nitrogen. The presence of the adjacent oxygen slows down

the lone-pair inversion in the nitrogen to such an extent that the presence of two interconverting isomers could be identified by ^{13}C NMR spectroscopy which offers a convenient way to measure the nitrogen inversion barrier as well as the relative stability of the *cis*- and *trans*-isomers <1997T11869>: typical data can be found in **Scheme 17** and show the higher stability of the *trans*-isomer. Concerning the *cis*-pair, the equilibrium is in favor of conformer A, which is in accordance with the fact that an oxygen substituent is better tolerated than an alkyl substituent in axial position.



Scheme 17

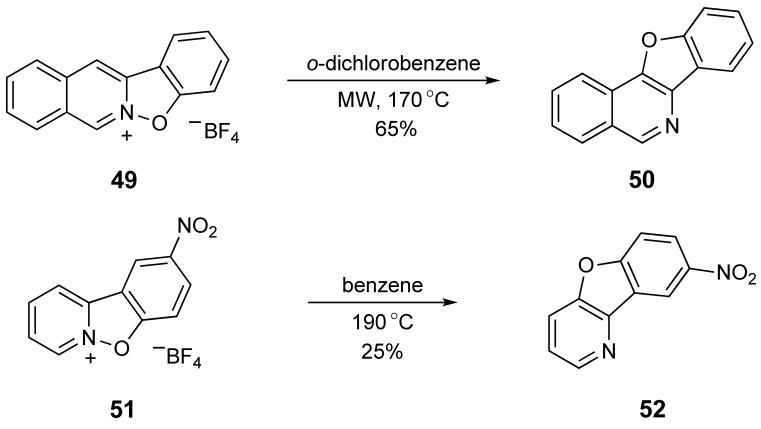
NMR data depicted in **Scheme 17** deserve some additional comments since they can be especially useful to indicate which conformer is the major one. In the minor *cis*-isomer, all carbon atoms, except C-2, are more shielded than the corresponding carbon in the *trans*-isomer. This can be easily explained by considering that the axial oxygen in **48**-*cis*-A or the axial CH_2 in **48**-*cis*-B respectively causes shielding of C-4, C-6 and C-5, C-7 due to their γ-*gauche*-interactions.

10.10.3.4 Thermodynamic Aspects

The NMR studies described in the precedent section allowed to determine the thermodynamic parameters of the equilibrium depicted in **Scheme 17**.

10.10.3.5 Reactivity of Fully Conjugated Rings

Apart from isolated reports summarized in **Scheme 18**, the chemistry of the fully conjugated ring systems has not been especially developed since CHEC-II(1996). In 2002, Timári and co-workers reported the generation of aryloxenium ions from thermolysis of isoxazolo[2,3-*a*]pyridinium tetrafluoroborates **49** and **51** and their subsequent cyclization, respectively, to benzofuro[3,2-*b*]pyridine **50** and **52** <2002TL6035>. In addition, it was shown that isoxazolo[2,3-*a*]pyridinium acetate could be attacked by alcohols in the presence of Na_2CO_3 to afford 6-alkoxy-substituted 2-phenacylpyridines in moderate yields <1996H(43)1179>.



49 **50** **51** **52**

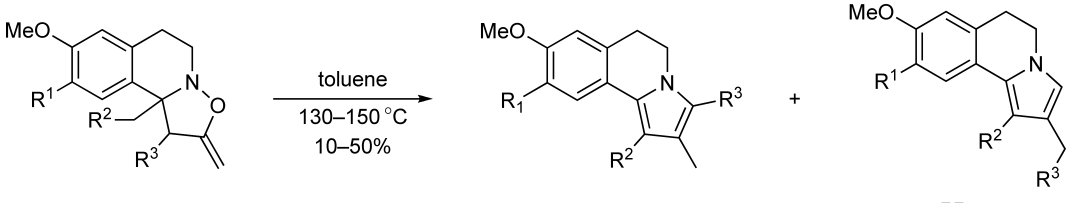
Scheme 18

10.10.3.6 Reactivity of Nonconjugated Rings

In contrast to the conjugated system, the reactivity of hexahydro-isoxazolo[2,3-*a*] pyridines has been the subject of considerably more attention, which can most certainly be attributed to its greater synthetic potential, as demonstrated by the synthesis of many complex natural products. However, most of the reactions reported since 1996 have been known for many years and the last decade was in fact characterized by their use in syntheses or optimization. After a brief survey of the thermal reactions, procedures involving the reductive cleavage of the N–O bond will be detailed.

10.10.3.6.1 Unimolecular thermal reactions

In 1997, Zhao and Eguchi demonstrated that 2-methylene-1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinolines **53**, obtained by 1,3-dipolar cycloaddition of isoquinoline *N*-oxides with electron-deficient allenes, undergo thermal rearrangement when heated at 130–150 °C in toluene to afford two isomers, **54** and **55**, of 5,6-dihydro-pyrrolo[2,1-*a*]-isoquinoline derivatives (**Scheme 19**). The formation of these fused-ring pyrroles can be rationalized on the basis of occurrence of two competitive consecutive rearrangements, one of which, as the minor route, involves an initial 1,3-hydrogen shift to give 4-isoxazolines followed by known rearrangement via acylaziridine intermediates, while the other, the major one, involves transient formation of pyrrolidin-3-ones followed by a novel rearrangement via bond scission and cyclocondensation <1997J(P1)2973>.



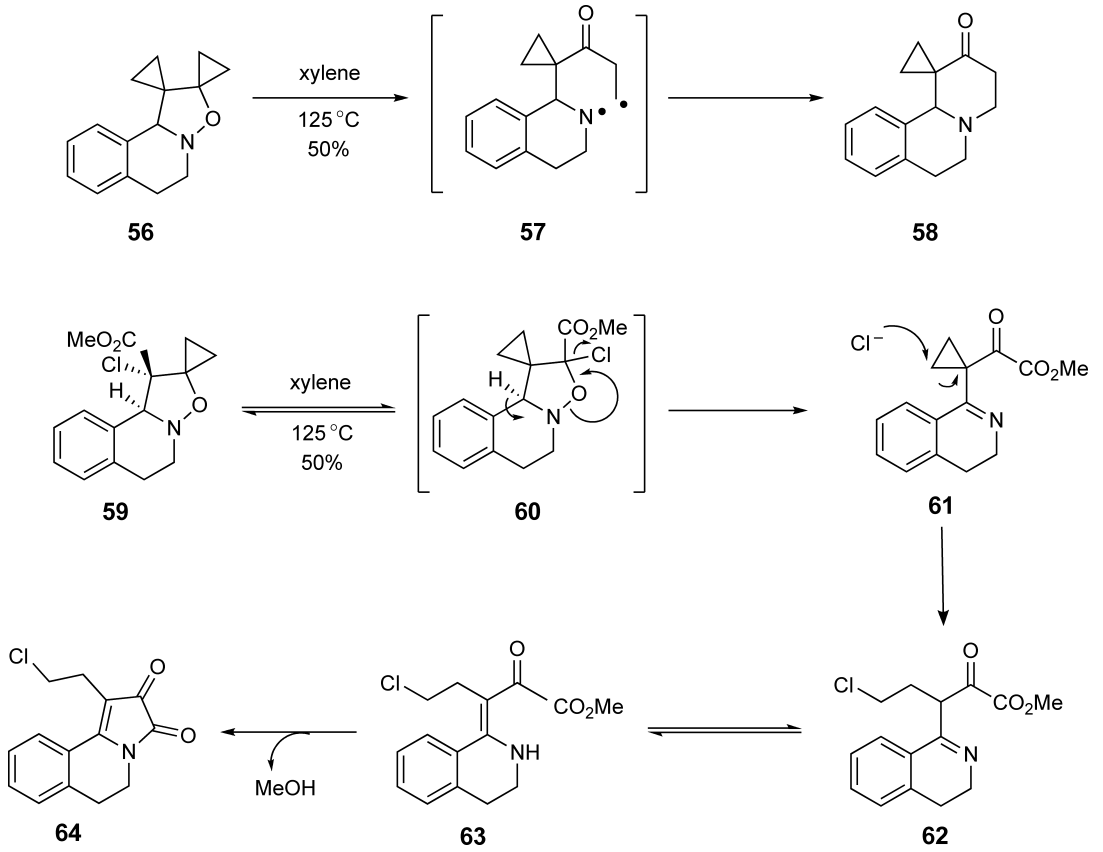
53 **54** **55**

R^1 = OMe, H
R^2 = H, Me, Ph
R^3 = CN, CO_2Et

Scheme 19

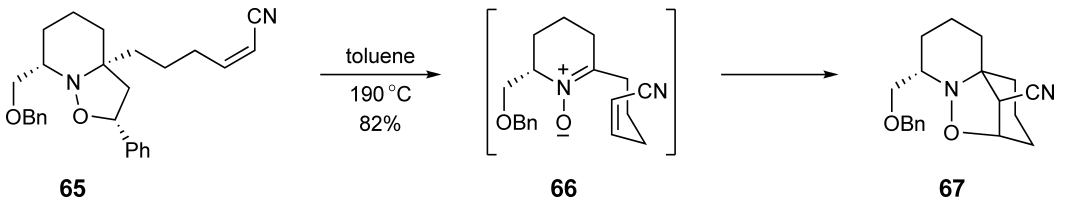
An interesting thermally induced rearrangement concerns strained bis-spirocyclopropanated hexahydro-isoxazolo[2,3-*a*]pyridines such as **56** which easily rearrange upon heating with selective opening of one of the two spiro-fused cyclopropane rings. This process produces 4-pyridones such as **58** in good yield <1999JOC1665> (**Scheme 20**). In contrast, replacing the second cyclopropyl group by a chloroester **59** dramatically reverses the

reactivity since **64** is now produced. The formation of compound **64** can be rationalized only assuming that the primary cycloadducts **59** undergo a cycloreversion–recycloaddition sequence finally leading to the thermodynamically more stable cycloadducts **60**. Once the cycloaddition–cycloreversion equilibrium is established, a mixture of cycloadducts based on their relative thermodynamic stability is formed. The 4-spirocyclopropaneisoxazolidine **60**, which must form in this process, can undergo a sequential ring opening followed by nucleophilic attack of chloride on the bisacceptor-substituted cyclopropane ring in **61** to form the α-ketoester **62** (**Scheme 20**). The enamine tautomer **63** then cyclizes with loss of methanol to produce **64** <1999JOC755>.



Scheme 20

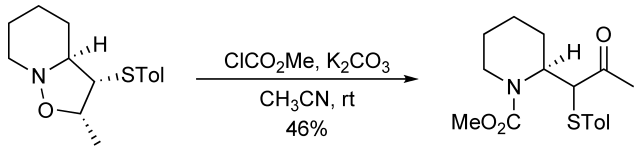
Finally, the reversibility of the nitrone/alkene [3+2] cycloaddition, mainly used to access the hexahydro-isoxazolo[2,3-*a*]pyridine ring system (see Section 10.10.3.7), can be used to functionalize these heterocycles. Accordingly, Holmes and co-workers found that a cycloreversion–cycloaddition reaction could be performed from **65** by simple heating in toluene at 190 °C. Under these conditions, the product of the reaction was found to be the *exo*-adduct **67** (**Scheme 21**) <2002J(P1)1494>.



Scheme 21

10.10.3.6.2 Electrophilic attack at nitrogen

In addition to the hydrogenolytic cleavage exploited in most cases for the cleavage of the N–O bond (see Section 10.10.3.5.3), hexahydro-isoxazolo[2,3-*a*]pyridines are excellent substrates for heterolytic ring-opening reactions. In particular, activation of **68** through quaternization of the nitrogen atom by reaction with methyl chloroformate, followed by a Hofmann-like elimination process, leads to β-amino ketone **69** in correct yield (**Scheme 22**) <1997TA109>.



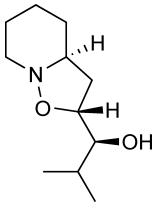
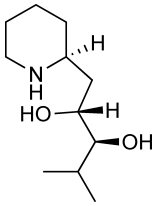
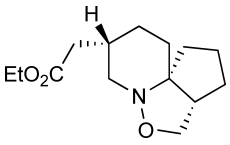
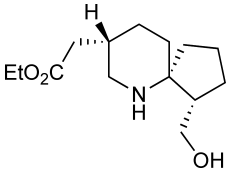
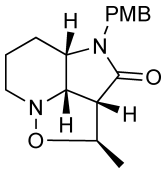
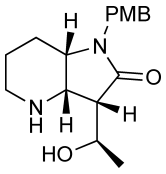
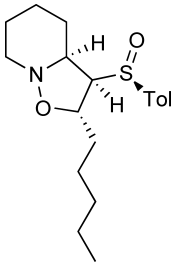
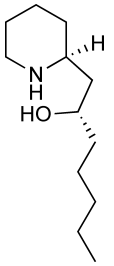
68 **69**

Scheme 22

10.10.3.6.3 N–O Bond reduction

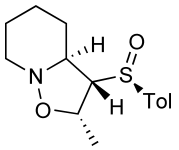
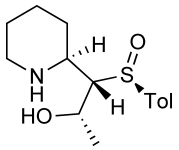
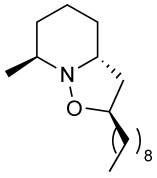
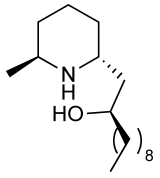
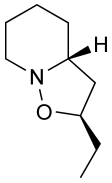
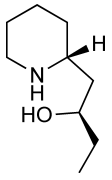
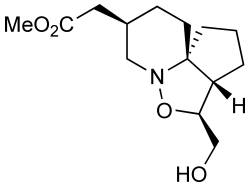
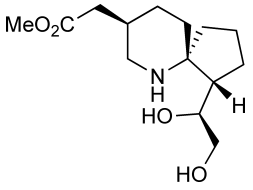
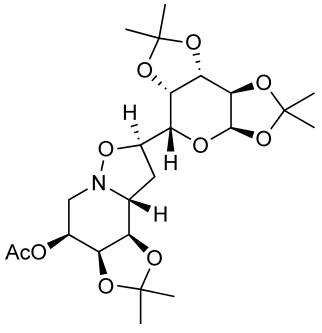
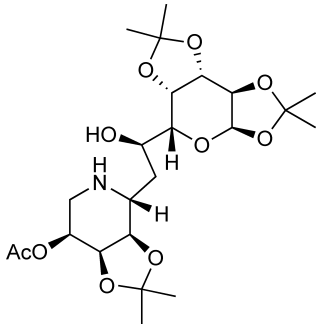
Most of the reactions of interest involve the opening of the isoxazole ring. This reductive opening has been known for years and was reported in CHEC(1984) and CHEC-II(1996). Over the years, many different reagents have been used and/or developed for this ring-opening process: examples of the most useful ones are collected in **Table 5** and give an overview of the protocols available for N–O bond reduction.

Table 5 N–O bond reduction

Substrate	*Reducing agent, Conditions*	*Product*	*Yield (%)*	*Reference*
	H_2, $PdCl_2$ MeOH, 6.5 atm, rt		91	1996JOC1023
	H_2, Pd/C EtOH, 5 atm, rt		100	2000TL929
	H_2, $Pd(OH)_2$ MeOH, rt		91	2002SL1344
	H_2, Raney-Ni MeOH, rt		84	1997TA109

(*Continued*)

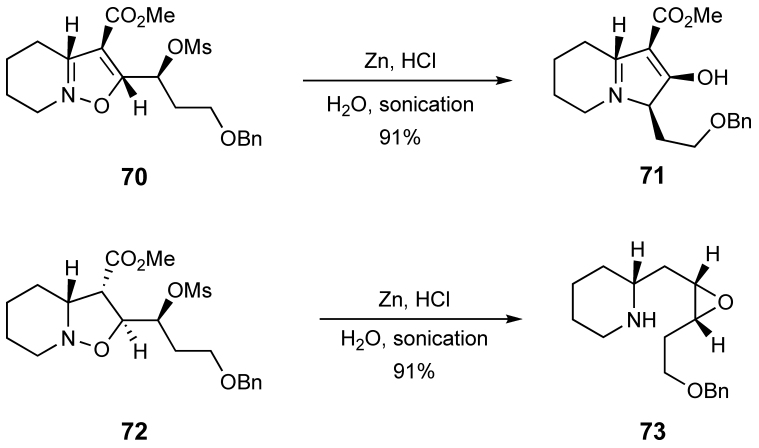
Table 5 (Continued)

Substrate	*Reducing agent, Conditions*	*Product*	*Yield (%)*	*Reference*
	Ni/Al, KOH MeOH, rt		92	1997TA109
	Zn, AcOH 70 °C		86	1997T11203
	$LiAlH_4$ THF, reflux		86	1996LA2083
	SmI_2 THF, rt		64	2001OL413
	$Mo(CO)_6$ H_2O/CH_3CN, reflux		67	2000CC2127

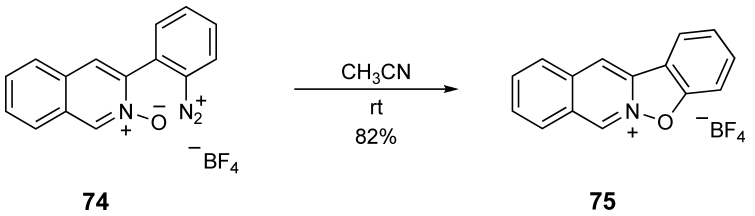
Interestingly, both the amino and the hydroxy groups can participate in another reaction with a suitable reacting group present in the molecule as shown with the two examples in **Scheme 23** <1998T11581>. Finally, it should be mentioned that this N–O bond reduction is also efficient starting from quaternary ammonium derivatives of hexahydro-isoxazolo[2,3-*a*]pyridines <1999JOC1932>.

10.10.3.7 Ring Syntheses from Acyclic Compounds

As was the case for their reactivity, fully conjugated ring systems have received only little attention since CHEC-II(1996). In 2002, Timári and co-workers reported the synthesis of isoxazolo[2,3-*a*]pyridinium tetrafluoroborate **75** from pyridinium *N*-oxide **74** (**Scheme 24**) <2002TL6035>. Formation of the new ring system can be interpreted by a nucleophilic attack of the *N*-oxide at the electrophilic carbon atom bearing the diazonium group, followed by nitrogen elimination, a reaction that was earlier observed by Abramovitch and Inbasekaran <1978CC149>.



Scheme 23



Scheme 24

10.10.3.8 Ring Syntheses of Saturated Rings from Acyclic Compounds

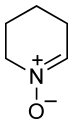
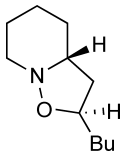
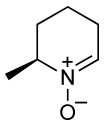
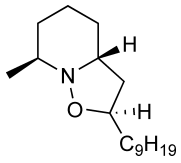
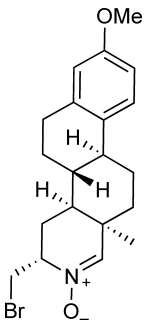
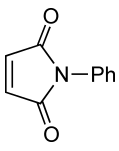
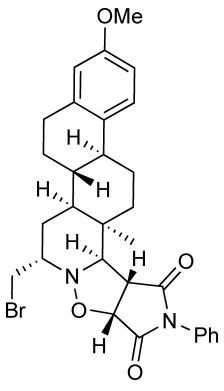
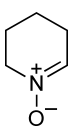
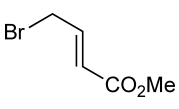
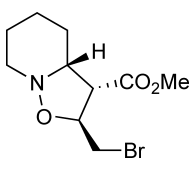
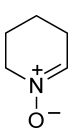
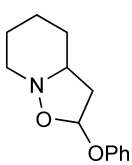
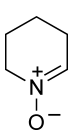
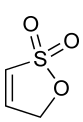
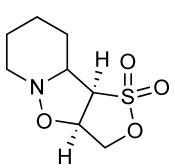
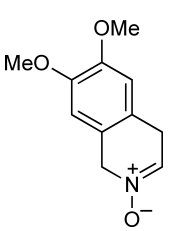
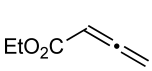
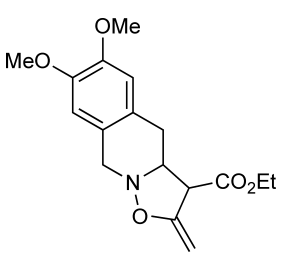
The importance of hexahydro-isoxazolo[2,3-*a*]pyridines as intermediates for the asymmetric synthesis of complex molecules and alkaloids has led to a continued interest in their preparation. A close look at the literature clearly reveals that the method of choice for their preparation remains the 1,3-dipolar cycloaddition between a tetrahydropiperidine *N*-oxide and an alkene <B-2003MI1>. A condition for such a reaction to take place is a good overlap between the interacting highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) orbitals, which depends on the relative orbital energies of both the dipolarophile and the dipole. Electron-withdrawing groups on the dipolarophile normally favor an interaction of the LUMO of the dipolarophile with the HOMO of the dipole that leads to the formation of the new bonds, whereas electron-donating groups on the dipolarophile normally favor the inverse of this interaction. Concerning the regioselectivity of the reaction, simple, alkyl-monosubstituted alkenes usually produce hexahydro-isoxazolo[2,3-*a*]pyridines possessing the substituent at C-2 while electron-deficient olefins usually lead to hexahydro-isoxazolo[2,3-*a*]pyridine adducts with the electron-withdrawing group attached to position 3, in agreement with the frontier molecular orbital (FMO) theory. Finally, concerning the stereoselectivity of the reaction, the *exo*-mode is usually favored. It is worth noting that this 1,3-dipolar cycloaddition is commonly referred as a [3+2] cycloaddition, which is not the correct symbolism. According to IUPAC recommendations, this cycloaddition is either a [4+2] (number of electrons involved in the process) or a [3+2] cycloaddition (number of atoms participating in the reaction).

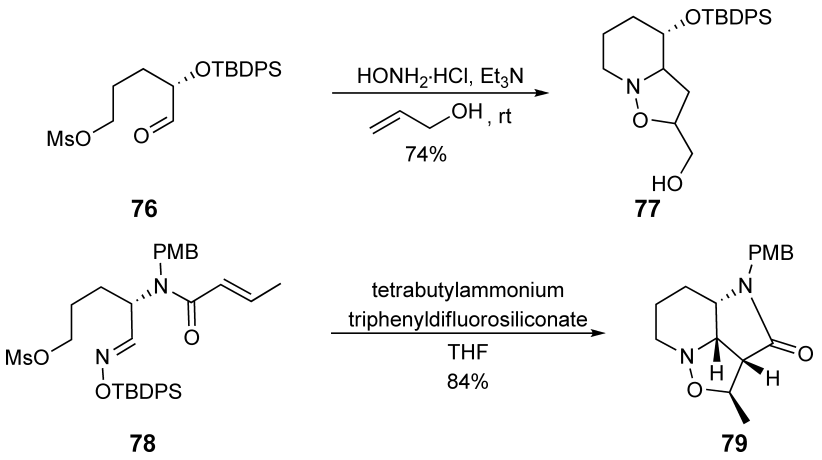
Representative examples illustrating these concepts and 'general rules' as well as giving an overview of all different dipolarophiles engaged in the formation of hexahydro-isoxazolo[2,3-*a*]pyridines are collected in **Table 6**.

Interestingly, the nitrone can be formed *in situ* by direct condensation of an aldehyde possessing a suitable leaving group and hydroxylamine hydrochloride, as in the synthesis of **77** from **76** <2001OL953> (**Scheme 25**) or by deprotection of a silyl-protected oxime as exemplified by the synthesis of cycloadduct **79** <2002SL1344>. Epoxides <1997T13165> or double bonds together with activating agents (*N*-bromosuccinimide (NBS), iodine) <2001T1119> can also be used in place of the internal leaving groups.

High levels of convergence and efficiency can be reached starting from fully acyclic substrates possessing an oxime (or a ketone precursor) and two alkenes: tandem intramolecular Michael addition/cycloaddition reactions yield fused

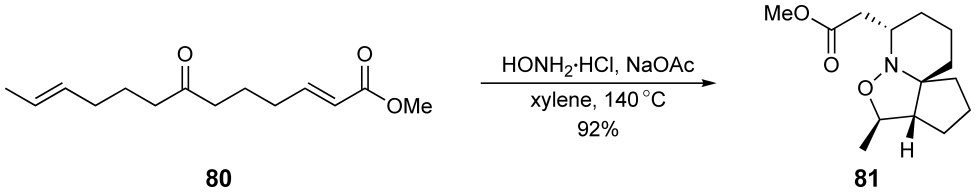
Table 6 [3+2] cycloaddition to hexahydro-isoxazolo[2,3-*a*]pyridines

Dipole	*Dipolarophile*	*Conditions*	*Product*	*Yield (%)*	*Reference*
		$CHCl_3$/MeOH 60 °C, 2.5 d		93	1996CJC2434
		Neat 145 °C 45 min		81	1997T11203
		Benzene 50 °C, 2 h		81	2005SL637
		$CHCl_3$ 60 °C, 13 h		51	1998T6947
		$C_2H_2Cl_4$ 50 °C, 16 h		58	2003S1221
		Toluene 40 °C, 12 h		86	2003S1329
		CH_2Cl_2 rt		80	1997T9575



Scheme 25

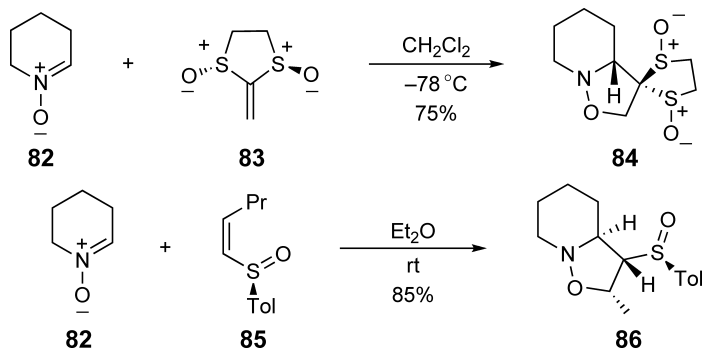
hexahydro-isoxazolo[2,3-*a*]pyridines in good yields and excellent selectivities as exemplified by the cycloaddition to **81**, en route to halichlorine and pinnaic acid (**Scheme 26**) <1999TL7921>. When the use of high temperatures is prohibited, an alternative protocol relying on the use of a catalytic palladium(II)-mediated cyclization–intermolecular cycloaddition cascade can be used in place of the thermal reaction <1997T15051>.



Scheme 26

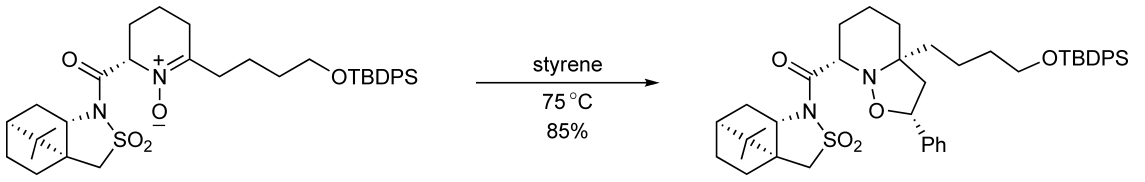
The development of this 1,3-dipolar cycloaddition reaction has entered a new stage in recent years as control of the stereochemistry in the addition step is now the major challenge. The selectivity challenge is to control the regio-, diastereo-, and enantioselectivity of the 1,3-dipolar reaction <1998CRV863>. The stereochemistry can be controlled by either choosing the appropriate substrates or controlling the reaction by a metal complex acting as a catalyst, stategies that have all been applied to the synthesis of hexahydro-isoxazolo[2,3-*a*]pyridines.

Various chiral dipolarophiles have been used in the asymmetric synthesis of hexahydro-isoxazolo[2,3-*a*]pyridines. Examples include *trans*-2-methylene-1,3-dithiolane 1,3-dioxide **83** <1998JOC3481>, chiral vinyl sulfoxide **85** <1997TA109>, or chiral dioxolanes <2001TA1747> (**Scheme 27**).



Scheme 27

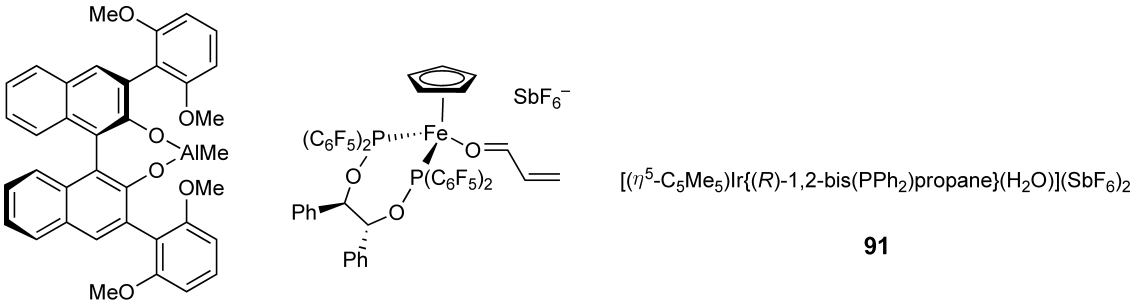
On the nitrone side, high levels of selectivities have been reached using camphorsultam-derived nitrone **87** since hexahydro-isoxazolo[2,3-*a*]pyridine **88** en route to (−)-histrionicotoxin was obtained as a single regio- and diastereoisomer <1999JA4900> (**Scheme 28**). A polyhydroxylated hexahydro-isoxazolo[2,3-*a*]pyridine could also be obtained starting from a nitrone derived from a C_2-symmetric piperidine <2002TL9357>.



87 **88**

Scheme 28

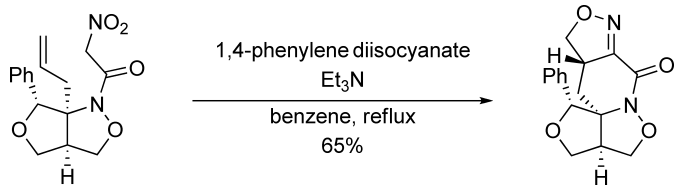
Finally, the catalytic enantioselective 1,3-dipolar cycloaddition reaction has recently been developed to be a highly selective reaction of nitrones with electron-deficient alkenes activated by chiral Lewis acids. High levels of regio-, diastereo-, and enantioselectivities can now be reached using catalysts **89** <2000JOC9080>, **90** <2002JA4968>, or **91** <2005JA13386> (**Scheme 29**).



89 **90** **91**

Scheme 29

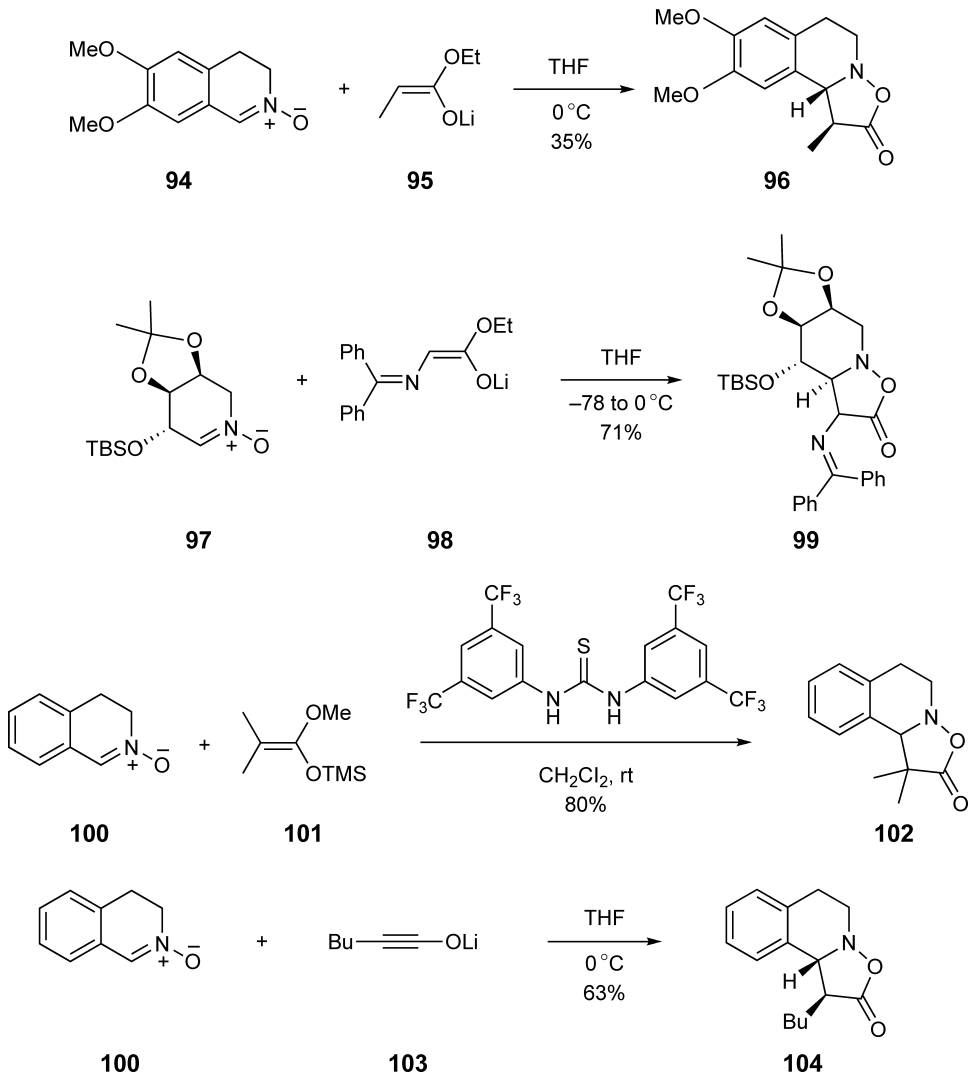
If nitrones have been widely used as 1,3-dipoles in the synthesis of hexahydro-isoxazolo[2,3-*a*]pyridines, the use of nitroacetates such as **92** in the cycloaddition sequence allows for an efficient access to hexahydro-isoxazolo[2,3-*a*]pyridin-7-ones such as **93** after spontaneous dehydration (**Scheme 30**) <2000JOC499>.



92 **93**

Scheme 30

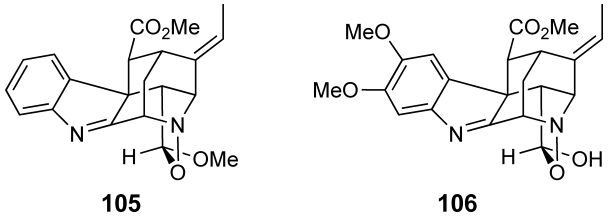
An efficient preparation of hexahydro-isoxazolo[2,3-*a*]pyridin-2-ones relies on the anionic addition of nucleophiles at the electrophilic carbon of the nitrone followed by cyclization of the resulting *N*-oxide. As shown by results collected in **Scheme 31**, various nucleophiles can be engaged in the reaction and include enolates **95** <2002OL3119> or **98** <2000BML1811>, silyl acetals **101** <2003TL2817>, or ynolates **103** <2002OL3119> (**Scheme 31**).



Scheme 31

10.10.3.9 Important Compounds and Applications

Few isoxazolo[2,3-*a*]pyridines have found important applications in the field of chemistry and/or medicinal chemistry. Natural products of the nareline family such as nareline methyl ester **105** <1997P1303> or 10,11-dimethoxynareline **106** <2004JNP547> have been isolated (**Scheme 32**).



Scheme 32

10.10.4 Imidazo[1,5-*a*]pyridine

10.10.4.1 Introduction

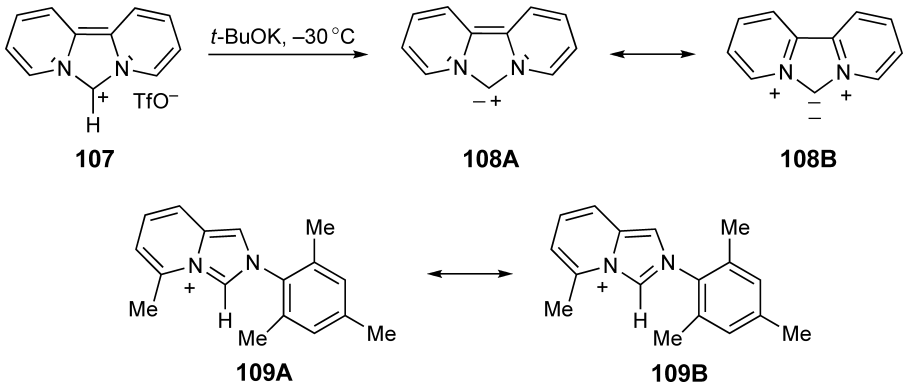
Imidazo[1,5-*a*]pyridines can be viewed as imidazoles fused to a benzene ring. This class of heterocycles was briefly covered in CHEC(1984) <1984CHEC(6)607> along with other imidazoles fused to six-membered rings and it was covered together with imidazo[1,2-*a*]pyridines in CHEC-II(1996) <1996CHEC-II(8)249>. Chemistry published on this heterocycle is less abundant in comparison to their isomers covered in Sections 10.10.2 and 10.10.6. Quite recently, a growing interest for this heterocyle has appeared due to the development of N-heterocyclic carbene (NHC) ligands: special focus will be put on this specific topic in this chapter.

10.10.4.2 Theoretical Methods

No new calculations were specifically devoted to this heterocylic system since CHEC-II(1996). Redox properties of chalcogeno-ureas possessing this heterocyclic skeleton and resulting from the reaction of Arduengo carbenes such as **108** with sulfur or selenium was investigated through semi-empirical calculations <2000EJI1935>.

10.10.4.3 Experimental Structural Methods

As for the previous section, no additional specific NMR data has been published since CHEC(1984) and CHEC-II(1996): NMR data for new substituted compounds are routinely reported. Several X-ray structures including new substituted compounds <2002AG3104>, imidazopyridinium derivatives <2002EJO375, 1999H(50)887>, fused derivatives <1995JA3278>, and carbene ligands <2005T6207, 1998AGE344, 2005JA3290> have been reported. Carbenes, such as **108** generated by deprotonation of cationic salt **107**, were thoroughly investigated by Weiss <1998AGE344>. On the basis of *ab initio* calculations (3-21G*), they were shown to be better represented by canonical form **108A** (**Scheme 33**). Similarly, on the basis of X-ray studies, the most important canonical forms **109A** and **109B** of imidazolium salts **109** were determined <2005T6207>.



Scheme 33

10.10.4.4 Thermodynamic Aspects

No specific studies on this topic were published in the last decade.

10.10.4.5 Reactivity of Fully Conjugated Rings

Imidazo[1,5-*a*]pyridines are aromatic systems in which the bridgehead nitrogen N-4 contributes to the aromaticity with its lone pair. Therefore, this nitrogen atom is not nucleophilic and electrophilic attacks occur at the N-2 position. S_EAr occurs at C-1, but also sometimes at C-3, depending on the conditions used (**Figure 3**).

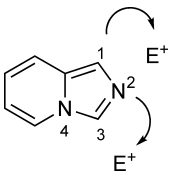
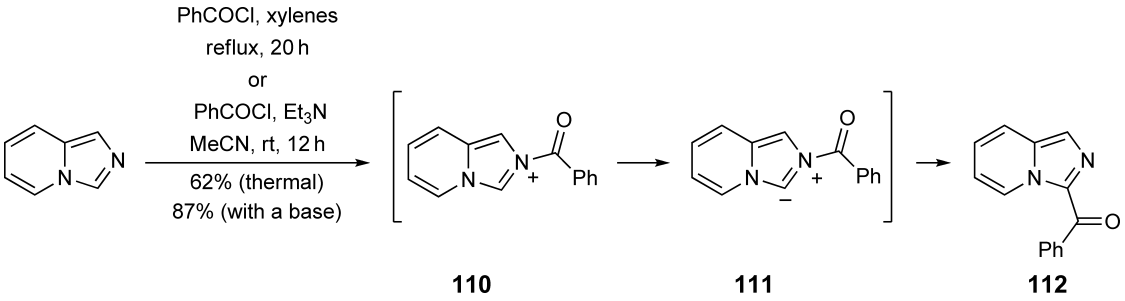


Figure 3

10.10.4.5.1 Electrophilic attack at nitrogen

Alkylation at N-2 readily occurs with alkyl iodides or benzyl bromide <2003BML3475, 2005JA3290>. In case of acyl chlorides, such as benzoyl chloride, N-acylation gives an intermediate imidazo[1,5-*a*]pyridinium ion **110** which reacts further in the presence of triethylamine, or under thermal conditions, to give an intermediate ylide **111**. A subsequent 1,2-rearrangement exclusively gives the C-3-substituted product (**Scheme 34**). Sterically hindered aryl chlorides only gave recovered starting material under these conditions <1998H(48)1015>.



Scheme 34

10.10.4.5.2 Electrophilic attack at carbon

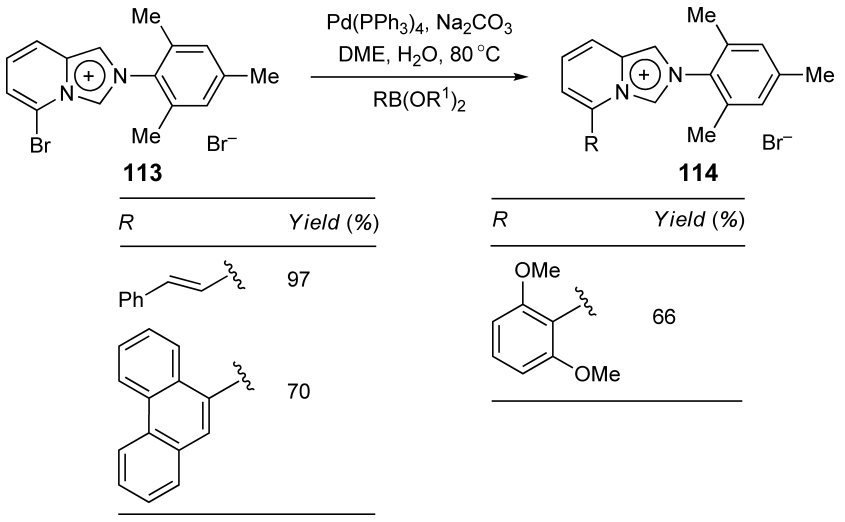
Electrophilic attack at carbon occurs regioselectively at the C-1 position, although the reaction shown in **Scheme 34** might interfere to give small amounts of C-3-substituted product. This was illustrated by some examples in CHEC(1984). Additional recent examples include acylations under Friedel–Crafts conditions <1998H(48)1015, 2001CPB799>.

10.10.4.5.3 Nucleophilic attack at carbon

No examples of such reactions have been disclosed. Displacement of halogens on the parent heterocycle through metal-catalyzed processes have surprisingly not been reported to our knowledge on the neutral heterocycle. Recently, Suzuki–Miyaura cross-coupling reactions of imidazolium bromide **113** with various boronic acids or esters were reported <2005T6207> to proceed in good yield, without deprotonation at the C-3 position (**Scheme 35**).

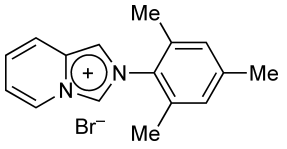
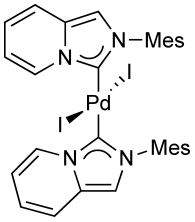
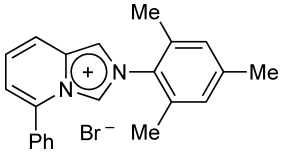
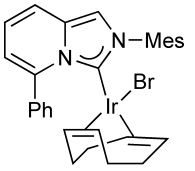
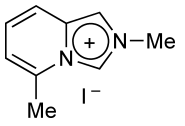
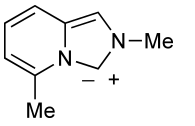
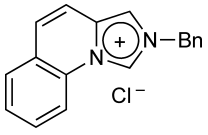
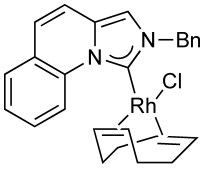
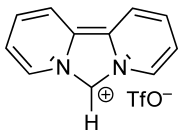
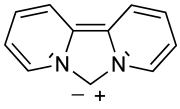
10.10.4.5.4 Nucleophilic attack at hydrogen

Deprotonation of imidazo[1,5-*a*]pyridines occurs at C-3. This was illustrated by some examples in CHEC(1984). A more recent report describes lithiation at C-3 position with *n*-Buli, followed by reaction of the resulting anion with TsCN, thus affording the corresponding 3-cyano derivative <1997H(46)443>. When imidazolinium ions are treated with a base, deprotonation then occurs at C-3 to give carbenes. These compounds were found to be excellent C-ligands for transition metals. **Table 7** summarizes some carbenes possessing this heterocyclic skeleton that have been prepared through this manner, and, in some cases, directly used for the preparation of various complexes.



Scheme 35

Table 7 Generation of NHC from imidazo[1,5-*a*]pyridinium ions

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	$Pd(OAc)_2$ NaI, *t*-BuOK, THF		52	2005T6207
	$[Ir(COD)Cl]_2$ *t*-BuOK, THF		77	2005T6207
	NaH, *t*-BuOK (cat.)		n.r.[a]	2005JA3290
	NaH, *t*-BuOK (cat.) Then $[Rh(COD)Cl]_2$		91	2005JA3290
	*t*-BuOK, THF −30 °C		n.r.[a]	1998AGE344

[a]n.r. = not reported.

10.10.4.5.5 Reactions at surfaces

The six-membered ring was reported to be selectively reduced over the five-membered ring in CHEC(1984) and CHEC-II(1996). More recent examples confirm this reactivity <1998H(48)1015, 1996CPB991>.

10.10.4.6 Reactivity of Substituents Attached to the Ring

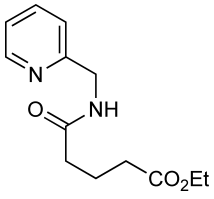
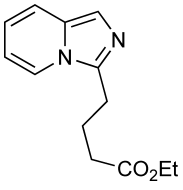
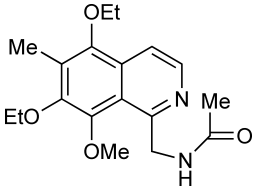
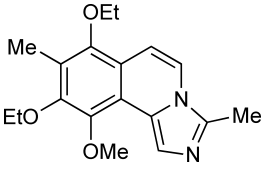
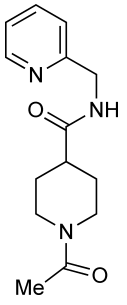
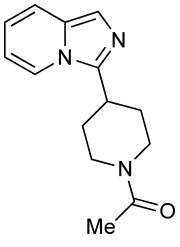
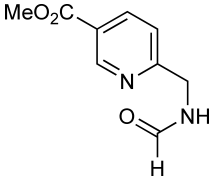
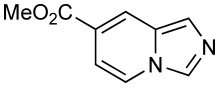
Among the rare reports of chemical transformation of substituents attached to the ring, the total reduction of an aromatic ketone linked at C-1 (lithium aluminum hydride (LAH), then Et_3SiH/trifluoroacetic acid (TFA), overall yield 20%) is of interest <1998H(48)1015>. One example related to Wittig olefination of the 1-formyl derivative of the parent heterocyle was reported to occur in low yield <2001CPB799>.

10.10.4.7 Synthesis

10.10.4.7.1 Fully conjugated ring

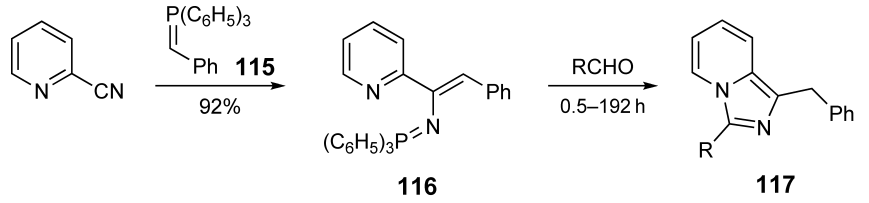
Most of the synthetic methods available for the synthesis of this heterocylic core rely on the construction of the five-membered ring. The most 'classical' method involves the cyclocondensation of 2-aminomethylpyridine amide derivatives under various dehydrating conditions. This was examplified by numerous examples in CHEC(1984) and CHEC-II(1996). Additional and more recent examples, together with their yields and conditions, are gathered in **Table 8**.

Table 8 Synthesis of imidazo[1,5-a]pyridines through cyclocondensation of 2-aminomethylpyridine amide derivatives

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	$POCl_3$		94	2001CPB799
	$POCl_3$ Toluene, 110 °C		77	2004H(63)2355
	PPA 120 °C, 18 h		n.r.[a]	2005BML2129
	$POCl_3$ DCM, reflux, 3 h		93	2002BML465

[a]n.r. = not reported.

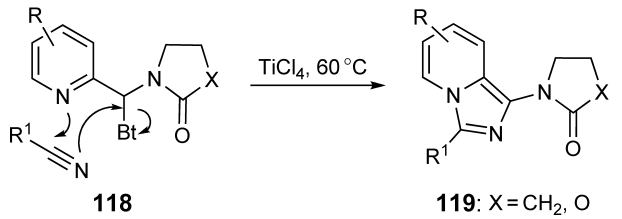
New strategies have appeared for the formation of the five-membered ring. The first one relies on a tandem aza-Wittig/electrocyclic ring closure of N-vinylic phosphazenes <1995T3683>. Thus, azaphosphazane **116**, resulting from the reaction of 2-cyanopyridine and ylide **115**, was reacted with different aldehydes to afford the C-3 substituted derivatives **117**. Although the reported yields were satisfactory, protracted reaction times were most often needed (**Scheme 36**).



R	*Yield* (%)
Ph	79
3-Pyr	82
i-Bu	76
CO_2Et	73

Scheme 36

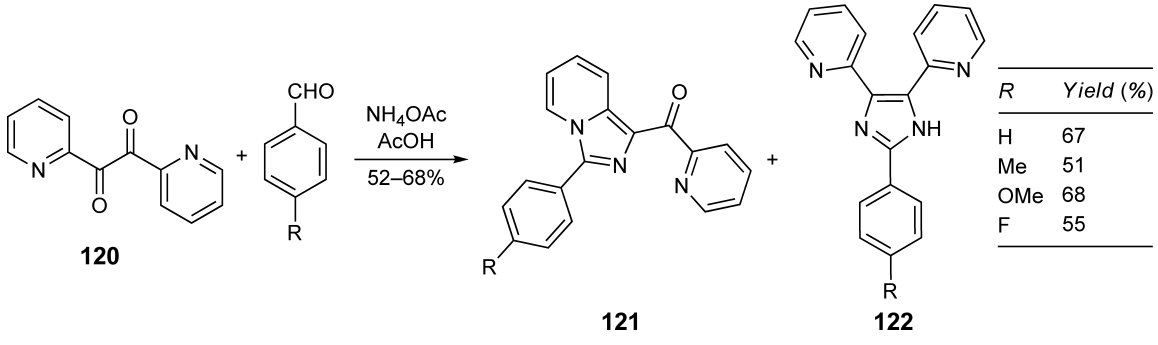
Katritzky *et al.* reported a straightforward access to 1-amido-3-alkylamino[1,5-*a*]pyridines **119** involving the ring closure of the five-membered ring by reaction of nitriles and benzotriazole derivatives **118** induced by $TiCl_4$ <2001JOC2862, 1999TA255>. Compounds **118** are in turn obtained in high yields by a condensation reaction between the 2-formyl pyridine, the required amide, and benzotriazole. Yields are good to excellent, and the reaction tolerates various substituents at C-3 (**Scheme 37**).



R	*X*	R^1	*Yield* (%)
H	O	C_5H_{11}	91
H	O	Allyl	81
H	CH_2	4-CH_3-C_6H_4	92
5-CH_3	CH_2	C_2H_5	82

Scheme 37

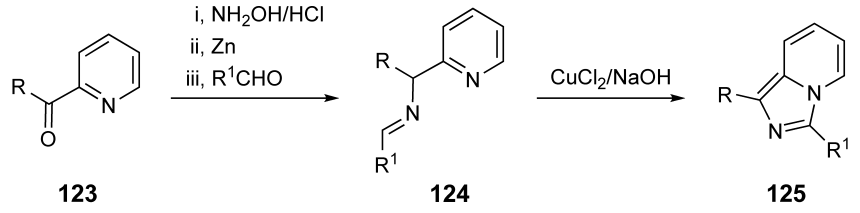
More recently, a new and straightforward one-pot approach was reported by Bu *et al.* <2003JOC5415>. This reaction involves the cyclocondensation of 1,2-dipyridin-2-yl-ethane-1,2-dione **120** and arylaldehydes, in the presence of ammonium acetate. Imidazo[1,5-*a*]pyridines **121** were obtained in reasonable yields, but competitive formation of imidazoles **122** was observed. The amount of ammonium acetate used in this reaction was also shown to strongly influence the yield of the cyclization (**Scheme 38**).



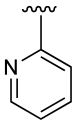
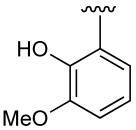
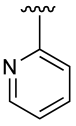
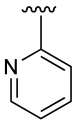
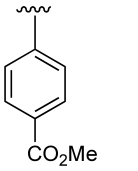
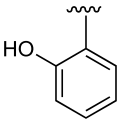
R	*Yield* (%)
H	67
Me	51
OMe	68
F	55

Scheme 38

This methodology was recently extended to the use of 2,2′-dipyridyl ketones and aromatic (or heteroaromatic) aldehydes <2005JOC2353>. In these cases, imidazoles were indeed not produced and the isolated yields of 1-(2-pyridyl)-3-aryl-imidazo[1,5-*a*]pyridines were very good (70–90%). Related cyclizations (**Scheme 39**) leading to **125** can also be promoted by copper(II) chloride, starting from Schiff bases **124**, themselves synthesized from 2-pyridyl ketones **123**: the proposed mechanism involves an oxidative cyclization of **124**, resulting in a reduction of copper(II) to copper(I), which is then reoxidized to copper(II) by oxygen. However, the yields are quite low <2002AG3104>.

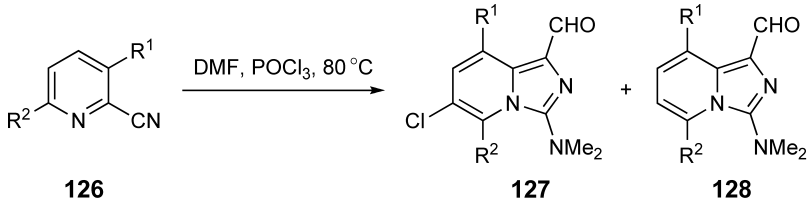


123 **124** **125**

R	R^1	*Yield* (%)	*R*	R^1	*Yield* (%)
		45		*t*-Bu	40
		35	Me		50

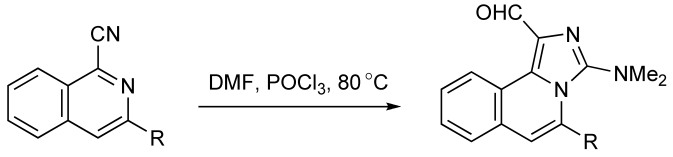
Scheme 39

A Vilsmeier reaction of pyridine-2-carbonitriles **126** was found to produce mixtures of 1-formyl-2-dimethylamino[1,5-*a*]pyridines with a chlorine atom **127** or a hydrogen **128** at the C-7 position <1998J(P1)3851>. When extended to isoquinoline-1-carbonitriles such as **129**, this reaction gave in modest yield compounds **130** (**Scheme 40**). Later on, it was demonstrated that this reaction leads to imidazo[1,5-*a*]pyridinium chlorides when *N*,*N*-dimethylbenzamides were used instead of dimethylformamide (DMF) <1999H(50)887>.



126 **127** **128**

		Yield (%)	
R^1	R^2	**127**	**128**
H	H	39	10
Me	H	51	25
H	Me	28	10

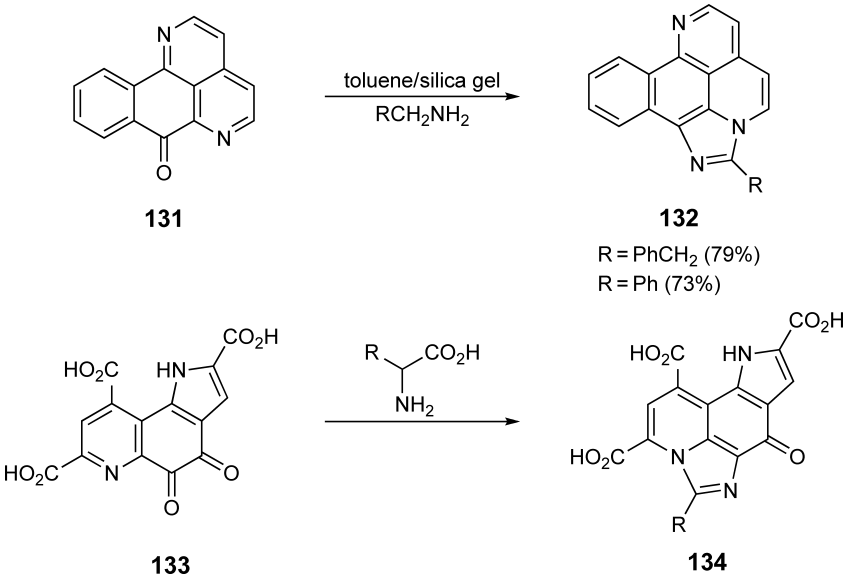


129 **130**

R = H (38%)
R = Me (42%)

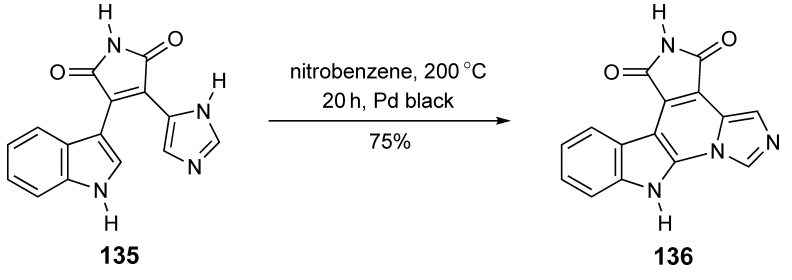
Scheme 40

Reaction of pyridines in neat isocyanides, in the presence of triflic acid, gives good yields of imidazo[1,5-*a*] pyridinium derivatives <2002EJO375>. Other examples of ring closure of the five-membered ring that appear to be restricted to specific substrates are depicted in **Scheme 41**: reaction of sampangine **131**, a natural antifungal alkaloid, with amines in the presence of silica gel gave fused heterocycles **132** possessing an imidazo[1,5-*a*]pyridine core in good yield <2001H(54)721>. Similarly, pyrroloquinolinequinone (PPQ) **133**, identified as a cofactor of methanol dehydrogenase, was found to react with amino acids to give imidazopyrroloquinolines (IPQs) **134** <1996CPB1493, 1995JA3278, 1996J(P2)1331>.



Scheme 41

A single example of strategy involving the synthesis of the parent heterocyclic core via six-membered ring formation could be found (**Scheme 42**). This synthesis was developed in the field of natural product synthesis, aiming at prepare isogranulatimide **136** from didemnidide A **135**, both isolated from the Brazilian ascidian *Didemnum granulatum*. Compound **136** belongs to an important class of natural bioactive substances: it was shown to be a G2 checkpoint inhibitor <1998JOC9850, 1998T1745, 2000JOC530>.

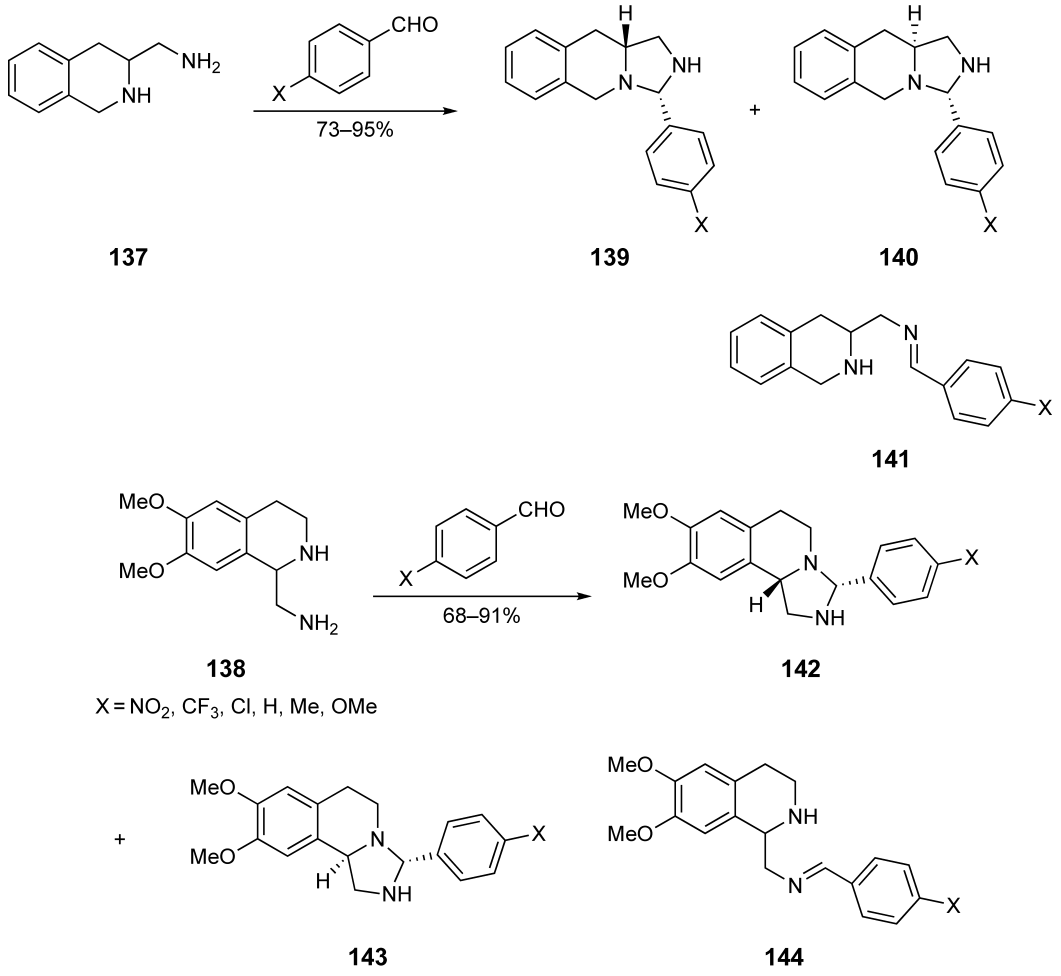


Scheme 42

10.10.4.7.2 Partially saturated rings

Synthesis of the heterocyclic core possessing a fully saturated six-membered ring can be achieved using a catalytic hydrogenation (see Section 10.10.4.4.5). The six-membered ring can also be formed starting from the appropriate

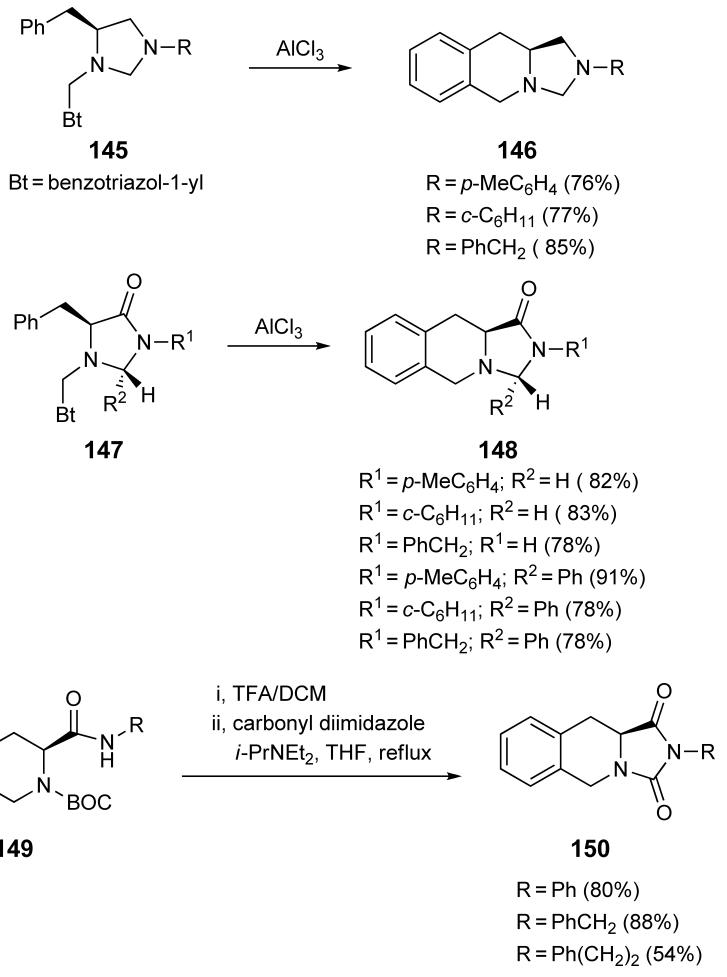
1,2-disubstituted imidazole using conventional chemistry <1996CPB991>. Fully saturated compounds can be prepared through condensation of 3-aminomethyl-1,2,3,4-tetrahydroisoquinoline **137** or 1-aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **138** with aldehydes <2003JOC5705>. This condensation affords mixtures of stereoisomers at the newly created stereocenter that were shown to be in equilibrium with the intermediate imines **141** or **144**. In case of diamine **137**, the stereoisomer **140** was the major component (almost 90%) of the mixture, while in case of **138**, compound **142** predominated to a maximum amount of 70% (**Scheme 43**).



Scheme 43

Enantiomerically pure hexahydroimidazo[1,5-*b*]isoquinolines **146** can be generated by treating benzotriazolyl intermediates **145** with aluminum chloride. Similarly, their 1-oxo derivatives **148** were produced in good yields from **147** (**Scheme 44**) <2002JOC8224>. Compounds **145** and **147** are easily prepared from L-phenylalanine. An optimized synthesis of tetrahydroisoquinoline hydantoins **150** has recently appeared <2004TL7081> with the aim of combining bulky pharmacophore moieties with hydantoins, the latter appearing frequently in combinatorial libraries prepared in medicinal chemistry <1996TL937>. Thus, the best overall yield was obtained using the strategy depicted in **Scheme 44**.

Several fully saturated derivatives that can be viewed as aza analogues of polyhydroxylated indolizidine alkaloids have also been prepared for their biological evaluation <2000JOC136, 2000T1005>.



Scheme 44

10.10.4.8 Important Compounds and Applications

Quite few natural products including the imidazo[1,5-*a*]pyridine skeleton have been reported. Apart from isogranulatimide **136**, already mentioned in Section 10.10.4.7.1, compounds of general structure **151** have been isolated from the marine sponge *Xestospongia* sp. <2003T6539>, cribrosatatin 6 **152** has been isolated from the marine sponge *Chribrochalina* sp. and shows interesting biological activity as growth inhibitor of cancer cells and a number of pathogenic bacteria as well as fungi <2003JNP544>. It has been synthesized by the group of Nakahara (**Figure 4**) <2004H2355>.

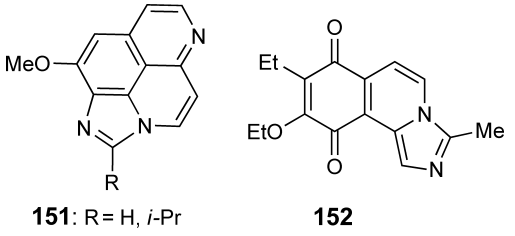
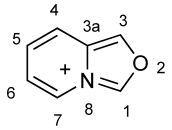


Figure 4

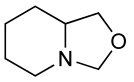
10.10.5 Oxazolo[3,4-*a*]pyridine and Thiazolo[3,4-*a*]pyridine

10.10.5.1 Introduction

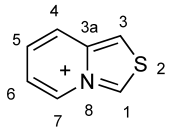
Oxazolo[3,4-*a*]pyridines **153**, thiazolo[3,4-*a*]pyridines **155**, and their fully saturated derivatives **154** and **156** were discussed in CHEC(1984) <1984CHEC(6)613> and CHEC-II(1996) <1996CHEC-II(8)274>: very little information was available on the thiazolo[3,4-*a*]pyridine ring system while most of the information concerned the fully saturated oxygenated parent, oxazolo[3,4-*a*]pyridines. Careful examination of the literature clearly indicated that the situation has not changed much: almost no references were reported on thiazolo[3,4-*a*]pyridines and most of the work done in the last decade concerns the synthesis and reactivity of hexahydro-oxazolo[2,3-*a*]pyridines **154**. Therefore, this chapter will briefly describe the new reactions of fully conjugated systems and will focus on the partially/completely saturated derivatives (**Scheme 45**).



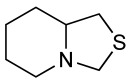
Oxazolo[3,4-*a*]pyridine **153**



Hexahydro-oxazolo[3,4-*a*]pyridine **154**



Thiazolo[3,4-*a*]pyridine **155**



Hexahydro-thiazolo[3,4-*a*]pyridine **156**

Scheme 45

10.10.5.2 Theoretical Methods

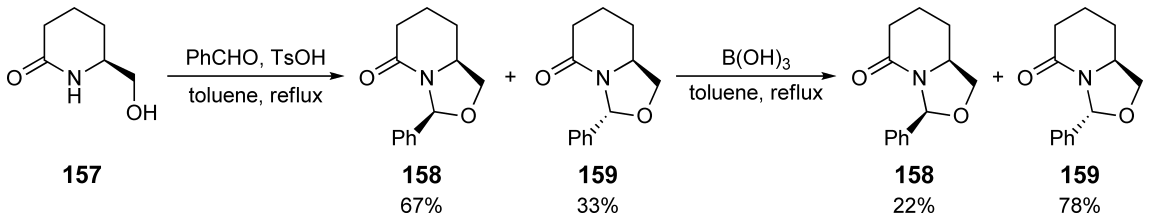
No new calculations were specifically devoted to this ring system.

10.10.5.3 Experimental Structural Methods

NMR data for new compounds are routinely reported. The conformational preference of the hexahydro-oxazolo[3,4-*a*]pyridine ring system **154** for the *trans*-conformer was discussed in detail in CHEC(1984) and CHEC-II(1996) and will therefore not be detailed here. Note should be made that the major conformer observed in solution is not necessarily the major one in the solid state <2002TA47>. As for other ring systems, careful analysis of coupling constants can permit the structure determination of the major isomer in solution <2002TA47, 2000EJO645, 1996T10609>.

10.10.5.4 Thermodynamic Aspects

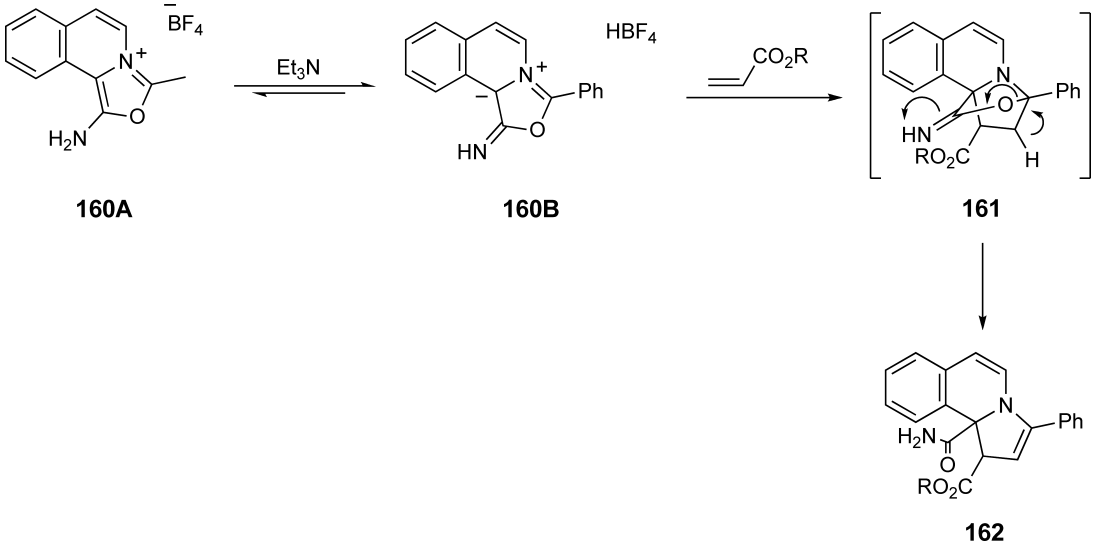
An important feature of saturated oxazolo[3,4-*a*]pyridines is their easy epimerization at the aminal C-1 stereocenter. A quite explicit example has been reported by Moloney and co-workers and is depicted in **Scheme 46**. The reaction between lactam **157** and benzaldehyde produces a mixture of hexahydro-oxazolo[3,4-*a*]pyridines, the kinetic product **158** being the major one. Equilibration of the mixture with boric acid allows the ratio of diasteroisomers to be reversed since *trans*-oxazolidine **159** is now the major product <1998TL1025>; the equilibration of epimeric oxazolidines via ring-chain tautomerism has been investigated in detail and explains the epimerization observed for some hexahydro-oxazolo[3,4-*a*]pyridines <1993JOC1967>.



Scheme 46

10.10.5.5 Reactivity of Fully Conjugated Rings

Apart from isolated reports summarized in **Scheme 47**, the chemistry of the fully conjugated ring systems has not been especially developed since CHEC-II(1996). In 1999, Monnier *et al.* reported the 1,3-dipolar cycloaddition of Reissert compound **160** with acrylates. Addition of triethylamine traps hydrofluoroboric acid and increases the proportion of münchnone imine **160B**; the reaction therefore predominantly yields 1,3-adduct **161** which evolves to **162** (**Scheme 47**) <1996BSB777, 1999EJO297>.



Scheme 47

10.10.5.6 Reactivity of Nonconjugated Rings

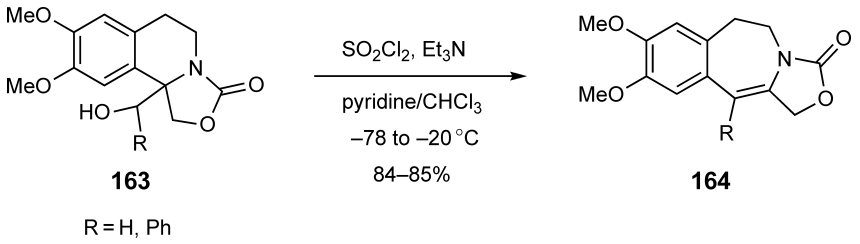
In contrast with the conjugated system, the reactivity of hexahydro-oxazolo[3,4-*a*]pyridines has been the subject of considerably more attention, which can most certainly be attributed to their greater synthetic potential, as demonstrated with the synthesis of many complex natural products. However, most of the reactions reported since 1996 have been known for many years, and the last decade was in fact characterized by their use in syntheses or optimization. After a brief survey of the thermal reactions, procedures involving the opening of the five-membered ring will be surveyed and the last part of this section will be devoted to the functionalization of the C-6 and C-7 positions.

10.10.5.6.1 Unimolecular reactions

The ring rearrangement of 8a-(1-hydroxy-alkyl)-hexahydro-oxazolo[3,4-*a*]pyridin-3-ones **163** upon treatment with sulfuryl chloride was reported in 2004: activation of the alcohol and ring extension produces 5,6-dihydro-1*H*-oxazolo[3,4-*a*]azepin-3-ones **164** in excellent yields (**Scheme 48**) <2004H(63)17>.

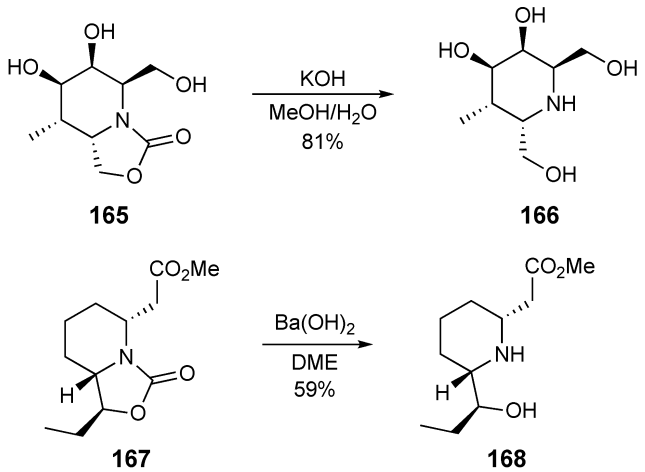
10.10.5.6.2 Nucleophilic attack at carbon

Most of the reactions involving nucleophilic attack at a carbon atom of the ring result in cleavage of the five-membered ring system (which is in most cases either an oxazolidine or an oxazolidinone). Basic hydrolysis of



Scheme 48

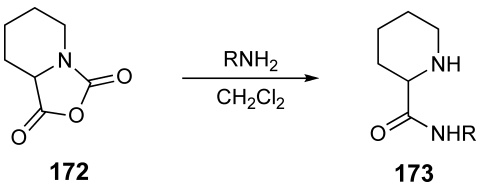
hexahydro-oxazolo[3,4-*a*]pyridin-3-ones is probably the most common of these reactions since it has been used in a lot of syntheses of natural products. Some examples are collected in **Scheme 49** and show that polysubstituted 2-hydroxymethyl-piperidines are usually produced in high yields <2001BMC1269, 2004AGE2001>. Care should, however, be taken during the hydrolysis of base-sensitive substrates since epimerization might occur and the choice of the base can therefore be crucial, as exemplified for the hydrolysis of **169** (**Scheme 49**) <1998JOC3918>.



R	*Conditions*	**170**	:	**171**
Me	6 M NaOH, MeOH reflux	1		1
Me	*t*-BuOK, THF reflux	1		6
H	*t*-BuOK, THF reflux	0		100

Scheme 49

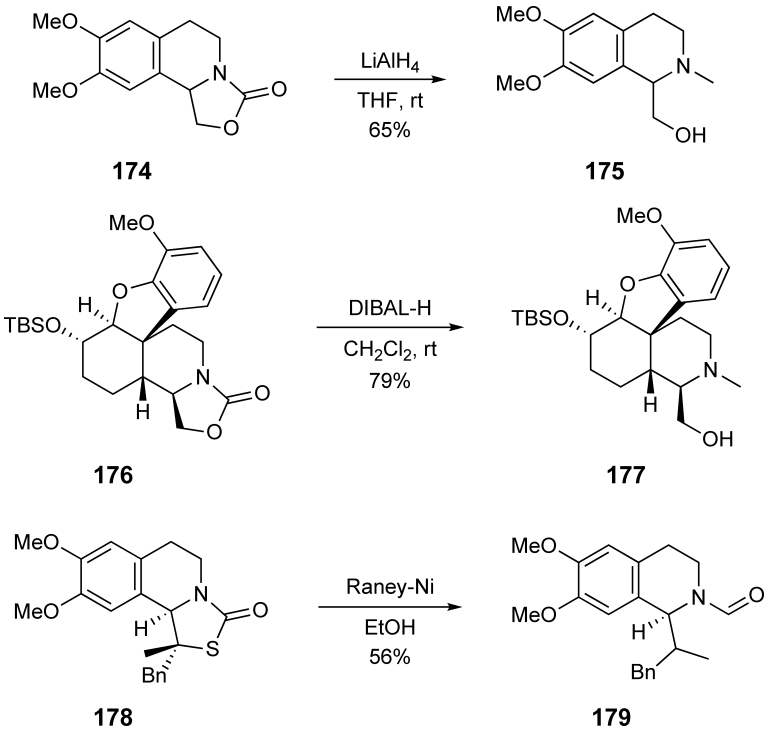
Instead of water (or hydroxide ion), amines can be used to cleave the five-membered ring of tetrahydro-oxazolo[3,4-*a*]pyridine-1,3-dione **172**: pipecolic acid amides **173** are usually obtained in good yields (36–93%, **Scheme 50**) <1998EJM23>.



172 **173**

Scheme 50

Finally, the nucleophile involved in this ring-opening process can also be a hydride or other reducing agent. In this case, polysubstituted *N*-methyl-2-hydroxymethyl-piperidines are obtained starting from hexahydro-oxazolo[3,4-*a*]pyridin-3-ones such as **174** <1996H(43)545> or **176** <1998S665>. Importantly, reduction of hexahydro-thiazolo[3,4-*a*]pyridin-3-one **178** with Raney-Ni in ethanol results in concomitant desulfurization, producing *N*-formyl piperidine **179** in good yield (**Scheme 51**) <2001EJO1267>.



174 **175**

176 **177**

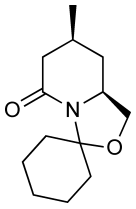
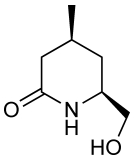
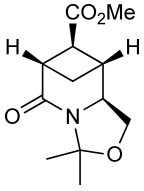
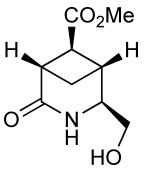
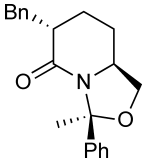
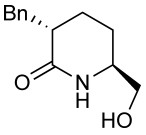
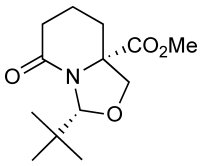
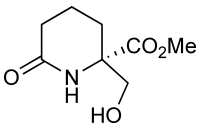
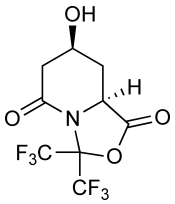
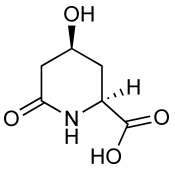
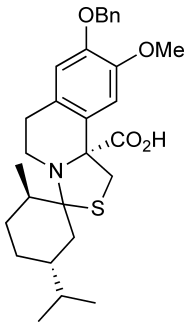
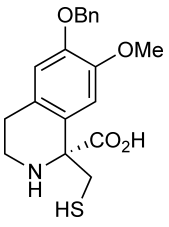
178 **179**

Scheme 51

Another quite common reaction involving nucleophilic attack at a carbon atom of the ring is the hydrolysis of hexahydro-oxazolo[3,4-*a*]pyridines and tetrahydro-oxazolo[3,4-*a*]pyridin-1-ones. This reaction has been known for years and is best performed under acidic conditions, respectively, producing 2-hydroxymethyl-piperidines or pipecolic acid derivatives in good yields; representative examples are collected in **Table 9**. Ammoniolysis of tetrahydro-oxazolo[3,4-*a*]pyridin-1-ones with amino acid derivatives has also been reported and produces substituted pipecolic acid amides in good yields <2003H(61)259>.

Ring opening of the oxazolidine ring is an efficient method to functionalize the hexahydro-oxazolo[3,4-*a*]pyridine skeleton. Many nucleophiles can be used in this reaction and the most common one is hydride, producing an amino alcohol such as **181**; different hydride sources can be used and a combination of sodium borohydride and chloro-trimethylsilane has been recently reported as an especially efficient reagent for this transformation <2000SL104>. Carbon nucleophiles have also been successfully used but require activation of the oxazolidine with a Lewis acid to form the intermediate iminium ion. High yields of addition products are however usually reached using this functionalization method as shown by the reaction of **182** with trimethylsilyl cyanide (TMSCN) and $BF_3{\cdot}OEt_2$ (**Scheme 52**) <2005JOC4397>.

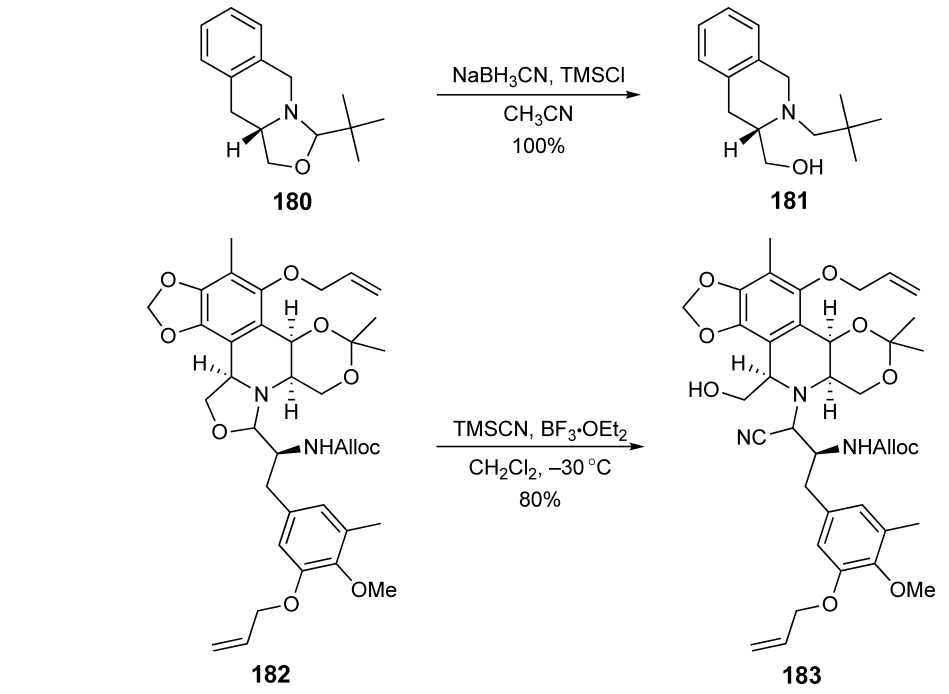
Table 9 Hydrolysis of hexahydro-oxazolo[3,4-*a*]pyridines and tetrahydro-oxazolo[3,4-*a*]pyridin-1-ones

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	AcOH, H_2O		98	2001TA3173
	Dowex 50Wx4 MeOH, rt		87	1998H(49)73
	TFA, H_2O/CH_2Cl_2 rt		73	2004OBC1031
	$HSCH_2CH_2SH$, HCl CF_3CH_2OH, rt		75	1996J(P1)227
	H_2O, *i*-PrOH CF_3CH_2OH, rt		77	1996T14757
	HCl, H_2O/MeOH Reflux		98	1996TL7163

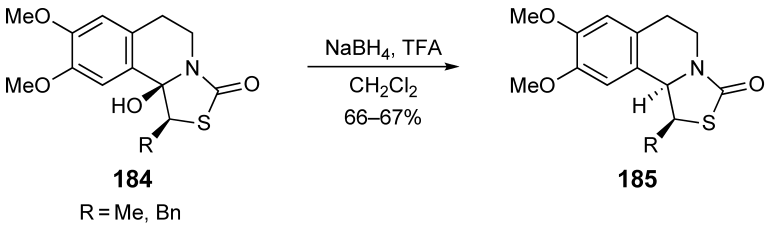
Treatment of α-hydroxy- or α-alkoxy-substituted hexahydro-oxazolo[3,4-*a*]pyridin-3-ones with an acid allows for the generation of bicyclic *N*-acyliminium ions which can then smoothly react with nucleophiles, usually with high diastereoselectivities (**Scheme 53**) <2001EJO1267, 1998SL206>.

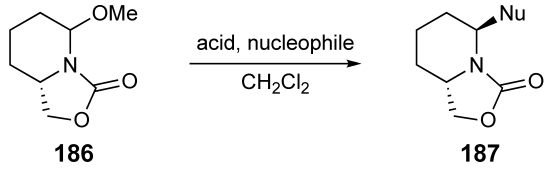
10.10.5.6.3 Nucleophilic attack at hydrogen (deprotonation) – Alkylation

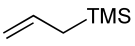
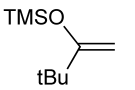
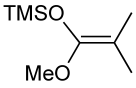
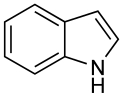
A deprotonation–alkylation sequence from tetrahydro-oxazolo[3,4-*a*]pyridin-5-ones or hexahydro-oxazolo[3,4-*a*]pyridin-3-ones is an especially efficient method for diastereoselective functionalization, respectively, via the lactam enolate or



Scheme 52

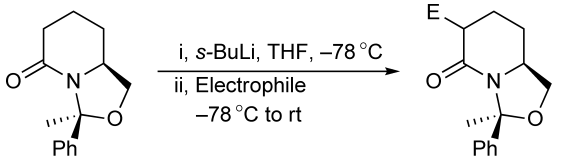




Acid	*Nucleophile*	*Yield* (%)
$TiCl_4$		86
$TiCl_4$	TMSCN	72
$TiCl_4$		70
TMSOTf		95
TsOH		78
TsOH		78

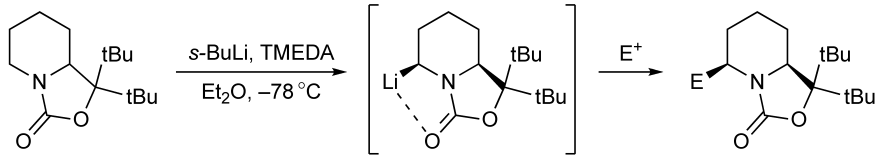
Scheme 53

α-lithio-amine, and is a strategy that has proved to be very successful, permitting ring manipulations in a highly diastereocontrolled sense. In 2001, Moloney and co-workers demonstrated that alkylation of lactam **188** with a wide range of electrophiles proceeds with predominantly *exo*-diastereoselectivity, but the efficiency of this process depends on the substitution at the hemiaminal ether system and the stereoselectivity remains low with some electrophiles. Products obtained can be readily deprotected to give substituted hydroxymethyl lactams in good yield (**Scheme 54**) <2004OBC1031>. An especially interesting and useful procedure was reported by Gross and Beak, who investigated lithiation substitutions of **190**: treatment with *s*-BuLi and tetramethylethylenediamine (TMEDA) followed by dimethyl sulfate provided diastereomerically pure **192** in 85% yield. The reaction of **190** with benzophenone was also highly stereoselective, while the substitution of the intermediate organolithium derivative **191** with chlorodimethylphenylsilane was not completely selective. The origin of the diastereoselectivity was attributed to the intermediacy of the configurationally stable organolithium derivative **191** due to the chelation with the carbamate (**Scheme 54**) <2001JA315>.



188 **189**

Electrophile	*exo*:*endo*	*Yield* (%)
MeI	1:1	80
BnBr	10:1	69
p-Nitrobenzyl bromide	3:2	28
Tosyl chloride	5:3	51
PhSeCl	7:4	52
BnOCOCl	1:1	72

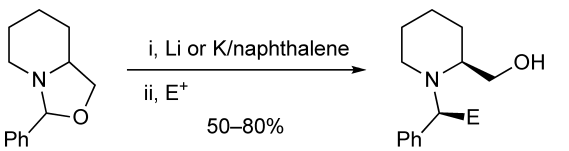


190 **191** **192**

Electrophile	*de* (%)	*Yield* (%)
Me_2SO_4	>95	85
Ph_2CO	>95	62
$PhMe_2SiCl$	66	60

Scheme 54

Finally, Azzena reported on the reductive functionalization of hexahydro-oxazolo[3,4-*a*]pyridine **193**: its reaction with potassium or lithium and naphthalene followed by trapping of the intermediate organolithium derivative allowed for the isolation of piperidine **194** with useful levels of selectivities (**Scheme 55**) <2002J(P1)360>.



193 **194**

E = Bu, C_6H_{13}, Bn, H

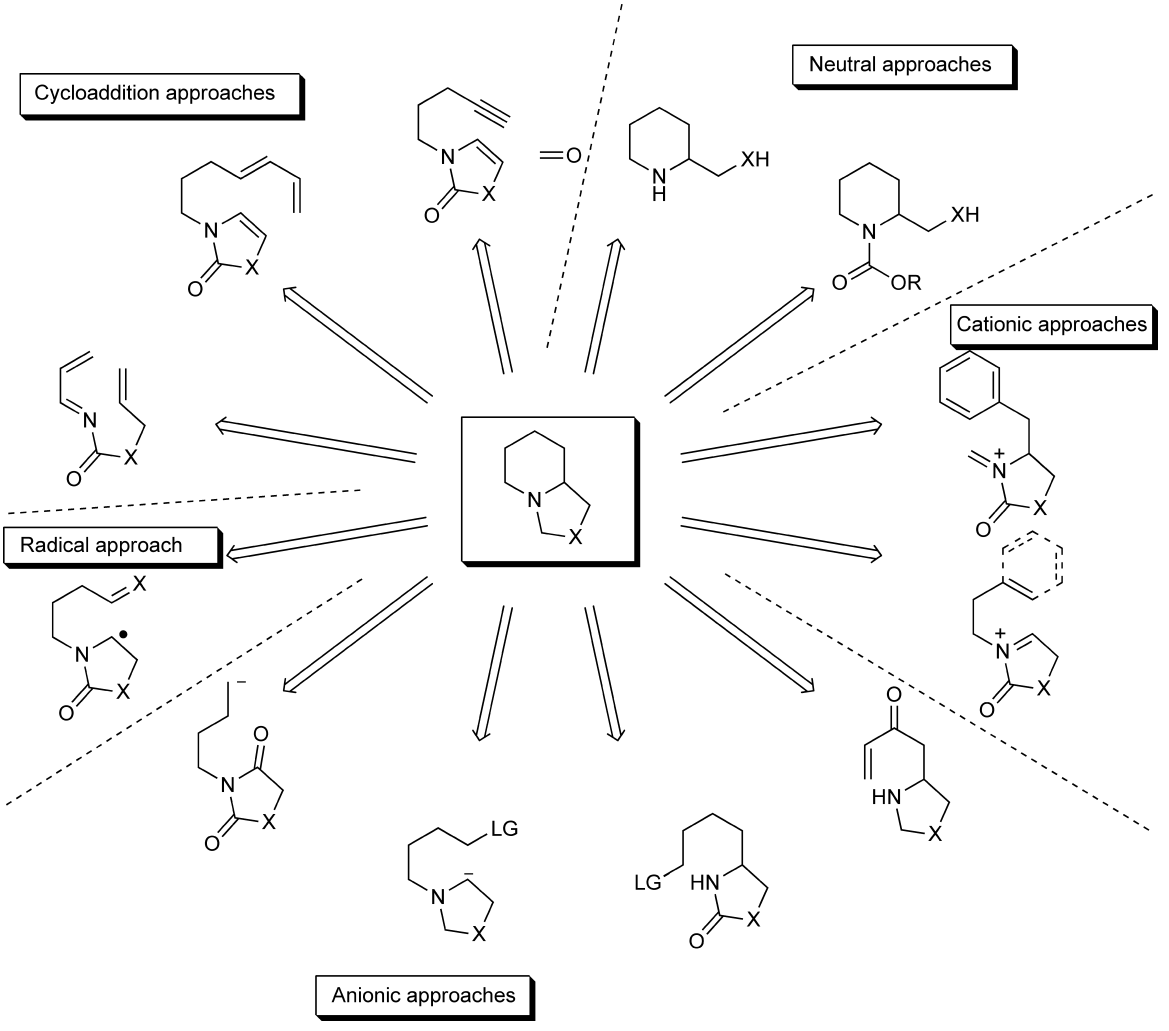
Scheme 55

10.10.5.7 Ring Syntheses from Acyclic Compounds

No new or original methods for the preparation of oxazolo[3,4-*a*]pyridines or thiazolo[3,4-*a*]pyridines have been reported since CHEC-II(1996). Emphasis will therefore be put on the synthesis of their fully saturated derivatives.

10.10.5.8 Ring Syntheses of Saturated Rings from Acyclic Compounds

If little was done since CHEC-II(1996) for the synthesis of unsaturated compounds, an amazing amount of work has been devoted to the synthesis of their saturated counterparts, as it can be judged by the increasing number of publications dealing with this matter. A lot of different options are available to access the saturated oxazolo[3,4-*a*]pyridine or thiazolo[3,4-*a*]pyridine ring systems, and **Scheme 56** gives an overview of the possibilities or disconnections that can be envisioned. The most logical way of organizing those syntheses is to classify them depending on the nature (anionic, cationic, radical, etc.) of the key step involved in the process; reactions discussed in this section will be classified accordingly.

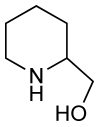
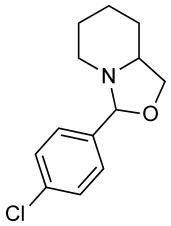
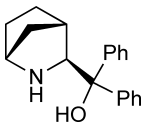
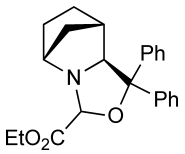
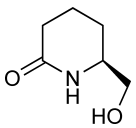
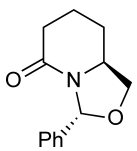
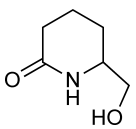
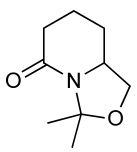
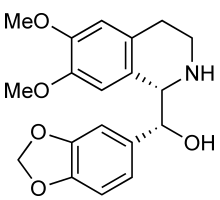
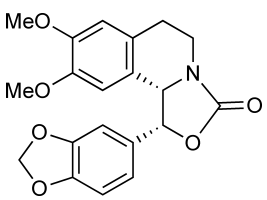
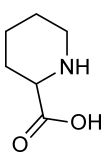
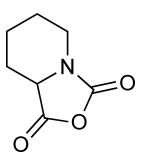
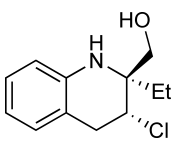
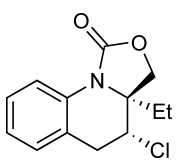
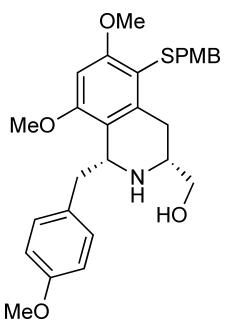
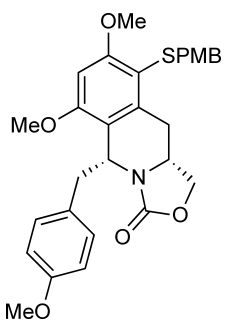


Scheme 56

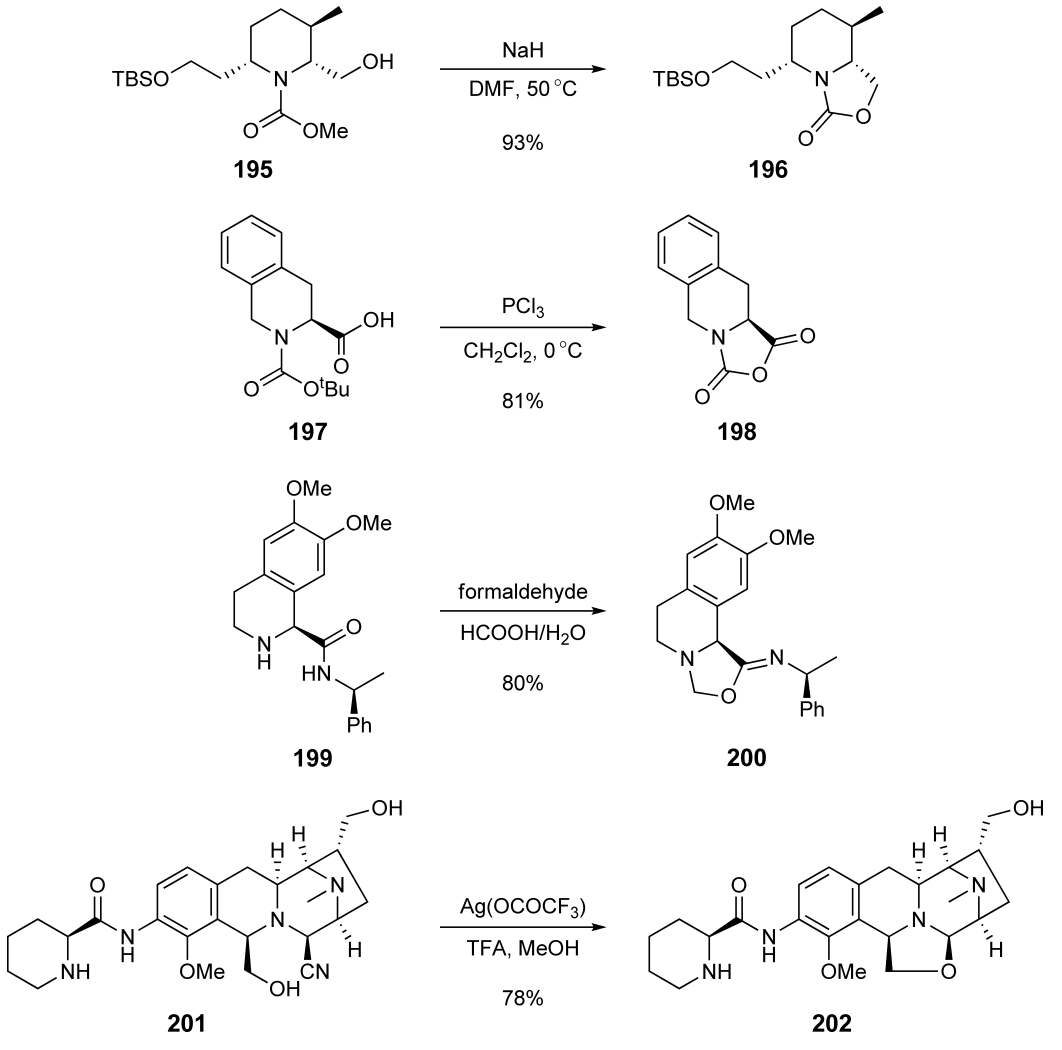
10.10.5.8.1 Neutral approaches: Formation of the five-membered ring

A quite simple way to form the oxazolo[3,4-*a*]pyridine or thiazolo[3,4-*a*]pyridine ring system is to build the five-membered ring, respectively, starting from a 2-hydroxymethyl-piperidine or 2-thiomethyl-piperidine. The reaction of the latter compounds with aldehydes, acetals, phosgene, carbonates, or synthetic equivalents have been known for years and will therefore not be detailed here. Representative and typical examples are summarized in **Table 10**.

Table 10 Formation of saturated oxazolo[3,4-*a*]pyridines or thiazolo[3,4-*a*]pyridines from 2-hydroxymethyl-piperidines or 2-thiomethyl-piperidines

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	4-Cl-C_6H_4-CHO		82	2005TL5451
	Ethyl glyoxylate Benzene, reflux		100	2002H(56)457
	$PhCH(OMe)_2$ TsOH, $B(OH)_3$ Toluene, reflux		82	1998TL1025
	2-Methoxy-propene TsOH, toluene Reflux		54	2004OBC1031
	Phosgene, Et_3N THF, rt		73	1996JOC8103
	Triphosgene THF, 40 °C		84	1996JME2781
	$(Im)_2CO$ Toluene, 35 °C		76	1996TL10609
	$(EtO)_2CO$ NaOEt, EtOH		98	1999T4999

The five-membered ring can also be formed by intramolecular nucleophilic attack of an alkoxide on a carbamate such as for the formation of **196** from **195** <1997T9553>, by dehydration of *N*-carbamate-pipecolic acid derivatives <2002EJO3936>, by treatment of amino-amides under Eschweiler–Clarke conditions <1999TA3371>, or by treatment of hydroxyl aminonitriles with silver trifluoroacetate <2002JA2951> (**Scheme 57**).



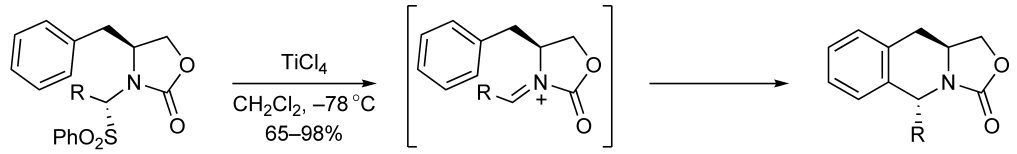
Scheme 57

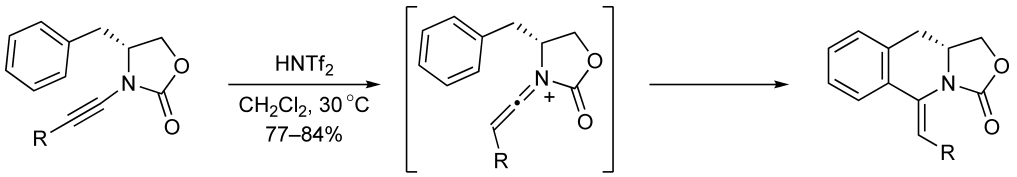
10.10.5.8.2 Cationic approaches: Formation of the six-membered ring

The Pictet–Spengler reaction provides useful routes to the saturated oxazolo[3,4-*a*]pyridine ring system. In a series of publications, Petrini and co-workers have shown that chiral *N*-acyliminium ions **204** obtained by treatment of optically active *N*-[1-(phenylsulfonyl)alkyl]oxazolidin-2-ones **203** with titanium tetrachloride react with electron-rich aromatic compounds to afford the corresponding adducts **205** in good yields and variable diastereoselectivities. The utilization of 4-benzyloxazolidin-2-one as a chiral auxiliary leads to intramolecular cyclization with exclusive formation of one diastereomer (**Scheme 58**) <2003TA1171, 2004TL2133>. The use of benzotriazole instead of the phenylsulfone has also been reported for the generation of the intermediate iminium ion <1999TA255> and treatment of *N*-alkynyl-oxazolidinones **206** with catalytic amount of $HNTf_2$ allows for the generation of intermediate keteniminium ions **207** which stereoselectively cyclize to **208** (**Scheme 58**) <2005OL1047>.

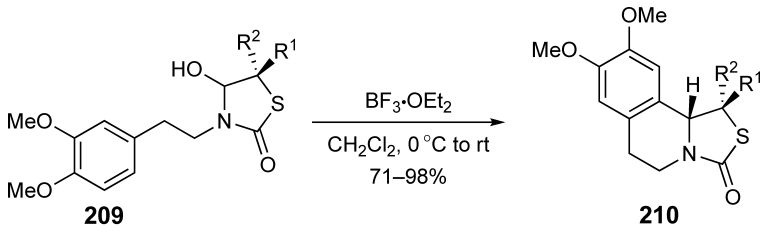
A related approach consists in the generation of endocyclic iminium ions from *N*-acylaminals **209**. As in the previous case, their treatment with boron trifluoride induces a diastereoselective cyclization, and thiazolo[3,4-*a*]pyridines **210** are isolated in good yields (**Scheme 59**) <2001EJO1267>. Alkenes can also participate and react well with the intermediate

iminium ions; in this case, a chloride atom from $TiCl_4$ is incorporated in the resulting cyclic product <1997TL8833>, or an additional hydroxyl group when $BF_3{\cdot}OEt_2$ is used to form the iminium ion <1999CCC203>.





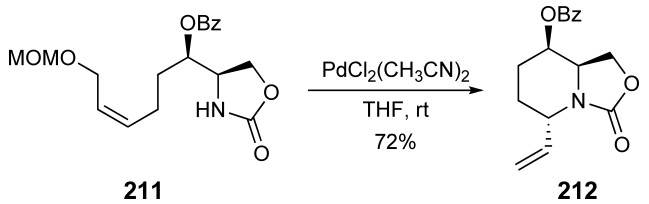
Scheme 58



Scheme 59

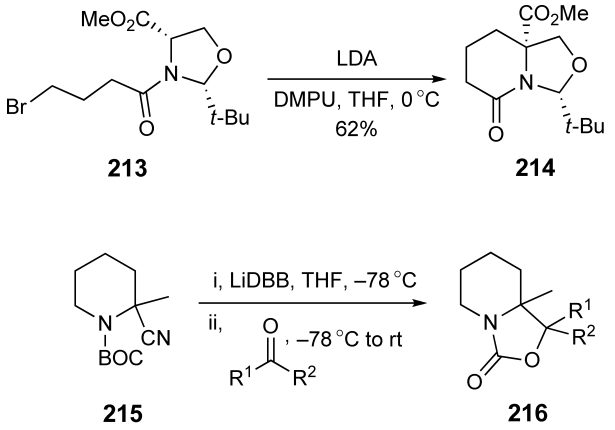
10.10.5.8.3 Anionic approaches

Different synthetic routes based on an anionic or related cyclization to form the six-membered ring have been developed. Therefore, cyclization of 4-(4-chloro-butyl)-oxazolidin-2-ones <1996TL5723> and 4-(3-carboxy-propyl)-oxazolidin-2-ones <2004S3065> have been reported. π-Allylpalladium complexes can also act as nucleophiles: treatment of protected allylic alcohol **211** with $PdCl_2(CH_3CN)_2$ generates a π-allyl intermediate which is trapped by the oxazolidine to form the six-membered ring **212** in good yield (**Scheme 60**) <1997JOC776>. The use of unprotected allylic alcohol has also been reported <2001H(54)871>.



Scheme 60

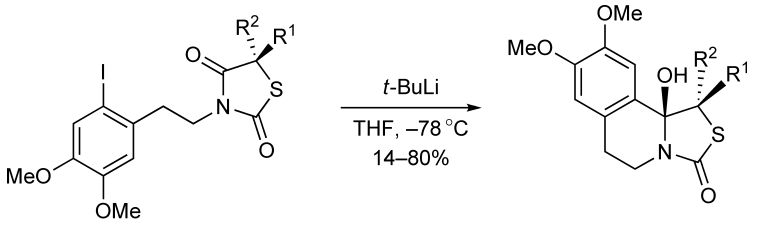
Generation of an enolate from **213** and intramolecular diastereoselective cyclization was reported in 1996 and allowed the synthesis of **214** in good yield <1996J(P1)227>. Interestingly, reductive lithiation of aminonitrile **215** and further reaction with a wide range of aldehydes generates intermediate alkoxides, which finally react with the carbamate to afford bicyclic compounds **216** upon warming up of the reaction mixture (**Scheme 61**) <2004OL2745>.



R^1	R^2	*d.r.*	*Yield* (%)
Et	H	4.5:1	75
i-Pr	H	3.7:1	74
t-Bu	H		59
Ph	H	1.5:1	82
Me	Me		68
Ph	Me	3.3:1	61
Vinyl	Me	1.5:1	65
-$(CH_2)_3$-CH=CH-		2.2:1	84

Scheme 61

Parham cyclization performed on thiazolidinediones **217** (**Scheme 62**) proceeds regioselectively at the more electrophilic amide carbonyl and gives the unstable 10β-hydroxy thiazoloisoquinolinones **218** in good yields. In all cases, attack of the organolithium intermediate occurs from the less-hindered face of the amide carbonyl group, affording the *cis*-compound with good stereoselectivity <2001EJO1267>.



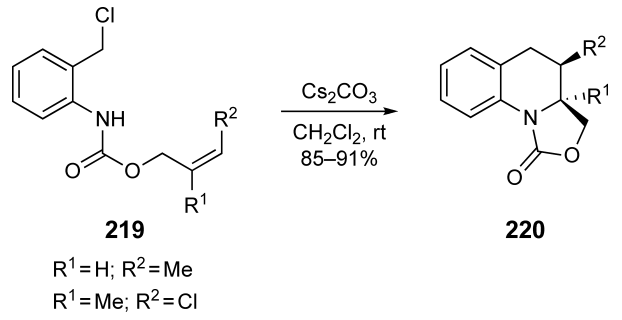
$R^1 = R^2 = Bn$
$R^1 = Me$; $R^2 = H$
$R^1 = Bn$; $R^2 = H$
$R^1 = Bn$; $R^2 = Me$

Scheme 62

Finally, intramolecular Michael addition from a 3-(2-oxo-but-3-enyl)-oxazolidin-5-one was reported to be catalyzed by boron trifluoride and afforded the cyclized product in fair yields. However, substitution at the enone group resulted in a less efficient cyclization <1996TL14757>.

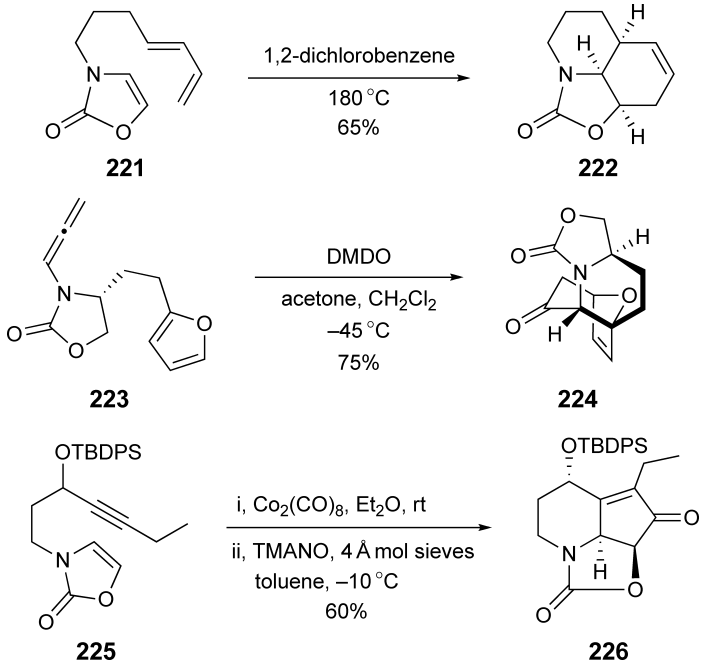
10.10.5.8.4 Cycloaddition approaches

In 1999, Steinhagen and Corey reported on the generation of *o*-azaxylylene by base-induced elimination of hydrogen chloride from *o*-chloromethylanilines **219**. This process was found to be highly effective and the intermediate *o*-azaxylylenes readily undergo intramolecular aza-Diels–Alder reactions under mild conditions to provide hydroquinolines **220** stereospecifically by a suprafacial cycloaddition (**Scheme 63**) <1999AGE1928>.



Scheme 63

Two other cycloaddition routes to the saturated oxazolo[3,4-*a*]pyridine ring systems have been reported: while intramolecular Diels–Alder cycloaddition from ***221*** generated tricyclic oxazolidinone ***222*** in good yield <2002CC438>, stereoselective intramolecular [4+3] cycloaddition of a nitrogen-stabilized chiral oxyallyl cation generated via epoxidation of *N*-tethered allenamide ***223*** afforded ***224*** in 75% yield and as a single diastereoisomer (**Scheme 64**) <2003JA12694>. Finally, an intramolecular Pauson–Khand approach to the tricyclic core of streptazolin and related natural products was reported and afforded **226** in good yield and selectivity (**Scheme 64**) <2004JOC1803>.



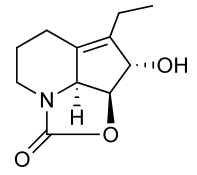
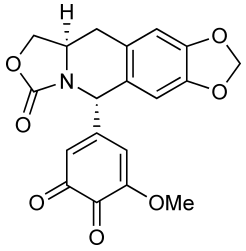
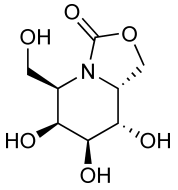
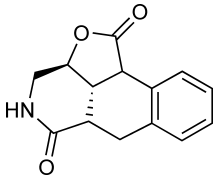
Scheme 64

To complete this paragraph dealing with the synthesis of saturated oxazolo[3,4-*a*]pyridines and thiazolo[3,4-*a*] pyridines, it is worth mentionning that other routes relying on carbenoid insertion <2005TL143> or radical-induced cyclization <1996J(P1)793, 1998S665> have also been developed since CHEC-II(1996).

10.10.5.9 Important Compounds and Applications

Many natural and/or biologically active products possessing an oxazolo[3,4-*a*]pyridine or thiazolo[3,4-*a*]pyridine core have been reported. Selected examples are collected in **Table 11** and show the high potential of molecules possessing these ring systems.

Table 11 Important compounds and applications

Compound	*Application*	*Reference*
 Dihydrostreptazolin	Antimicrobial	1981HCA1752
	DNA topoisomerase II inhibitor	1997BML2565
	Galactosidase inhibitor	2001BMC1269
	Antibacterial	1998BML1231

10.10.6 Imidazo[1,2-*a*]pyridine

10.10.6.1 Introduction

Imidazo[1,2-*a*]pyridines were covered in CHEC(1984) <1984CHEC(6)607> along with others imidazoles fused to six-membered rings and they were reviewed together with imidazo[1,5-*a*]pyridines in CHEC-II(1996) <1996CHEC-II(8)262>. The chemical literature on this heterocycle is very abundant, due to its easy synthesis (most of the preparations use readily available 2-aminopyridines) and to the very broad spectrum of bioactivities displayed by many derivatives. A simple Beilstein search on the fully conjugated heterocycle (free sites everywhere) disclosed ca. 3000 hits for the past decade. Therefore, this chapter cannot be exhaustive in view of space limitations, but will mainly focus on the original synthetic methods that have appeared in the last decade.

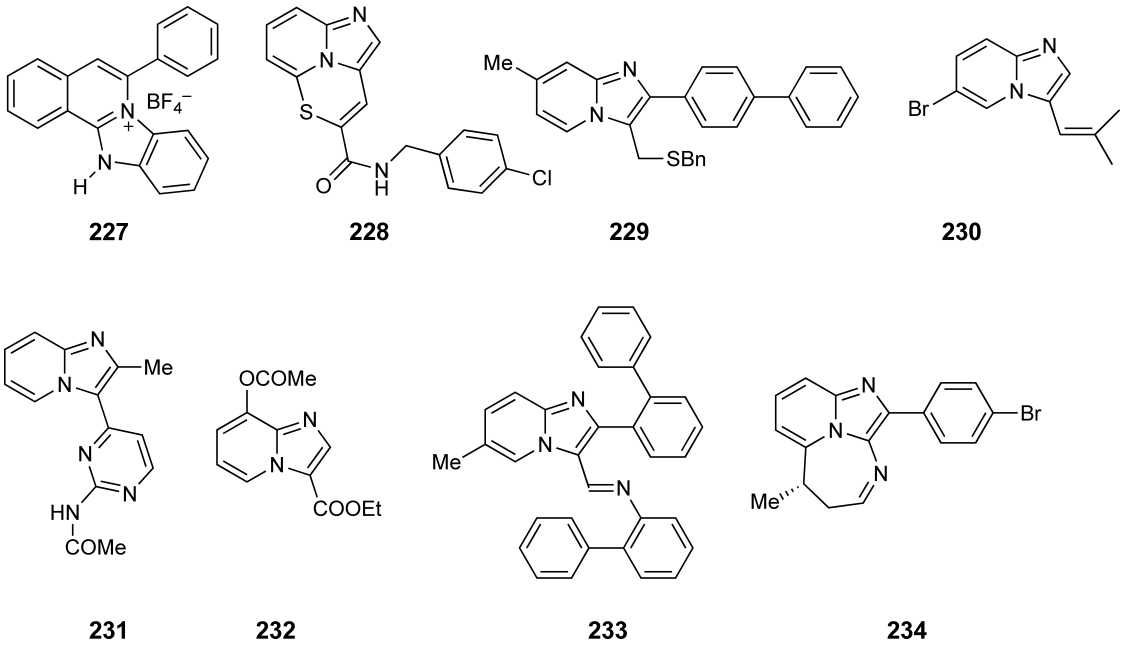
10.10.6.2 Theoretical Methods

To our knowledge, no new calculations were specifically devoted to this heterocyclic system since CHEC-II(1996). AM1 calculations of the electron density in the HOMO of 3-carboethoxy-5-methyl derivative allowed for the rationalization of the regioselectivity of its chlorination <2000T7915>.

10.10.6.3 Experimental Structural Methods

As for the previous section, no additional specific NMR data complete CHEC(1984) and CHEC-II(1996): NMR data for new substituted compounds are routinely reported. Fluorescent properties of a series of derivatives have been

investigated <1999BCJ1327>. X-Ray structures of new substituted compounds appear regularly. Some examples are given in **Figure 5**, such as the tetrafluoroborate salt **227** <2000EJO1433>, the 5-thia derivative **228** <2000TL3447>, or the substituted derivative **229** <2002BML941>. In compound **230**, the alkenyl side chain does not lie in the plane of the heterocycle <2005AXE4037>. Other examples include **231** (crystallized into the active site of cyclin-dependent kinase 2 (CDK2)) <2003BML3021>, the 8-acetoxy derivative **232** <2002T8145>, the 3-imino derivative **233** <2006TL2989>, and the tricyclic compound **234** <2002T295>.

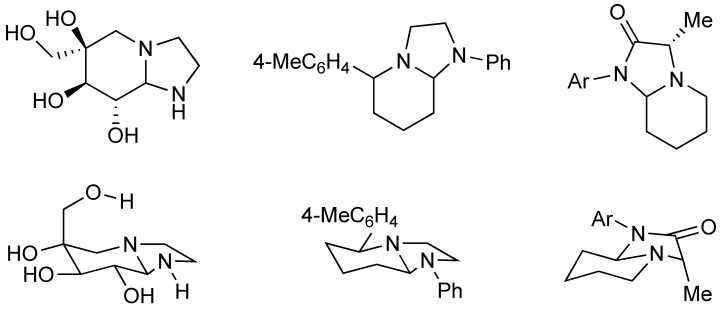


227 **228** **229** **230**

231 **232** **233** **234**

Figure 5

Conformational analysis of some octahydroimidazo[1,2-*a*]pyridine derivatives have been investigated by NMR studies <2004T4039, 2000JOC3683, 2002JOC4951, 2000JOC7208>. For example, compounds **235–237** are depicted in **Scheme 65** in their preferred conformations. The anomeric carbon in such compounds is prone to epimerization, favoring a *trans* ring junction.



235 **236** **237**

Scheme 65

10.10.6.4 Thermodynamic Aspects

No specific studies on this subject were published in the last decade.

10.10.6.5 Reactivity of Fully Conjugated Rings

Imidazo[1,2-*a*]pyridines are aromatic systems in which the bridgehead nitrogen N-4 contributes to the aromaticity with its lone pair. Therefore, this nitrogen atom is not nucleophilic and electrophilic attack occurs at N-1 position. S_EAr occurs at C-3 (**Figure 6**).

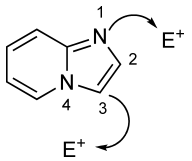
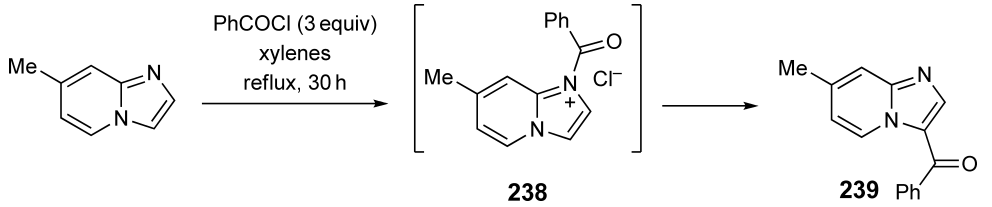


Figure 6

10.10.6.5.1 Electrophilic attack at nitrogen

Alkylation at N-1 readily occurs with alkyl halides or sulfonate esters <2002CHE675, 1997BML2753, 1992JME1650>. In case of reaction with an acyl chloride such as benzoyl chloride, N-acylation gives an intermediate imidazo[1,2-*a*]pyridinium ion **238** which, upon heating, gives the 3-acylated **239** compound in a single operation (**Scheme 66**) <1998TL9685>.

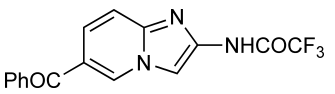
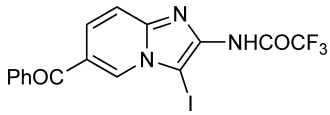
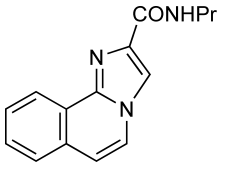
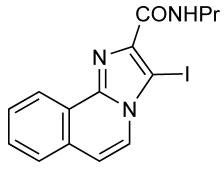
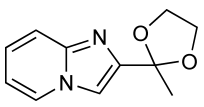
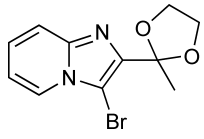


Scheme 66

10.10.6.5.2 Electrophilic attack at carbon

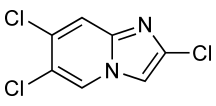
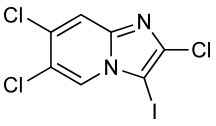
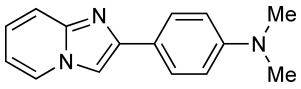
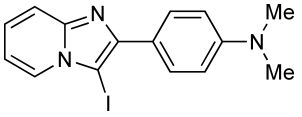
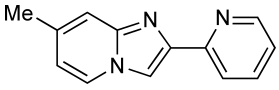
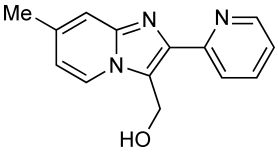
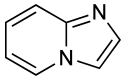
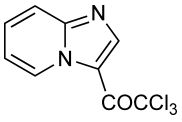
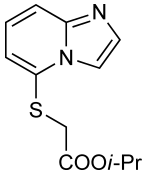
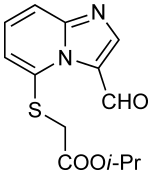
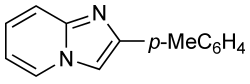
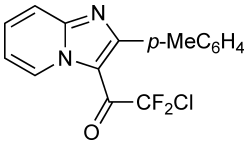
Electrophilic attack at carbon occurs regioselectively at the C-3 position. This was illustrated by numerous examples in CHEC(1984) and CHEC-II(1996). Additional more recent examples are summarized in **Table 12**.

Table 12 Aromatic electrophilic substitution at C-3 in imidazo[1,2-*a*]pyridines

Substrate	*Conditions*	*Product*	*Yield* (%)	*Reference*
	IPy_2BF_4/CH_2Cl_2 23 °C, 3 h		95	1999T541
	I_2, Pyr		91	2005JOC4897
	NBS, MeCN Reflux 3 h		91	2003T5869

(*Continued*)

Table 12 (Continued)

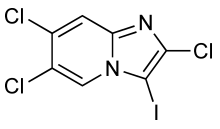
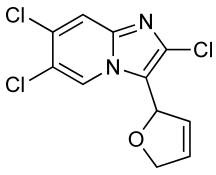
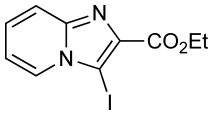
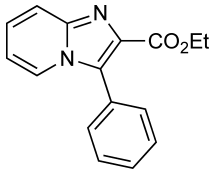
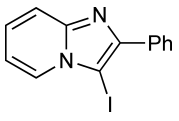
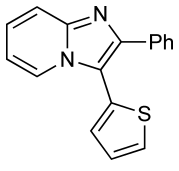
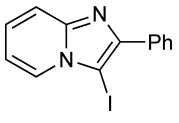
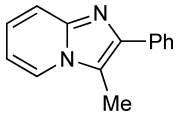
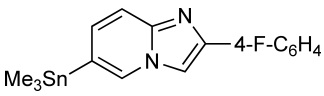
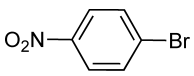
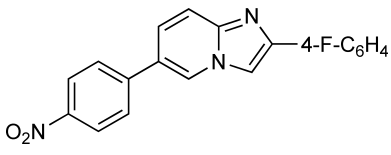
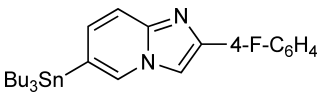
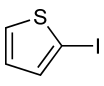
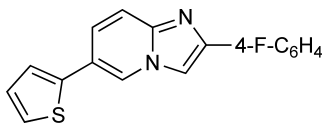
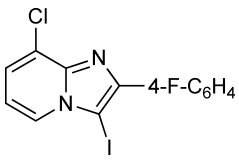
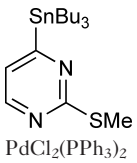
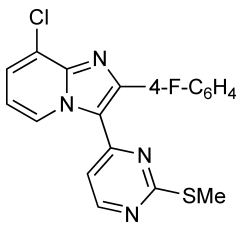
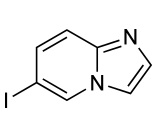
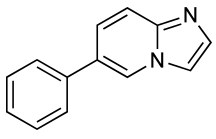
Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	NIS, MeCN rt, 1 h		82	2003JME1449
	I_2, $CHCl_3$		52	2003JME237
	CH_2O AcOH/AcONa Reflux, 3 h		90	2002BML941
	CCl_3COCl DMAP, THF Reflux, 12 h		93	2000TL3447
	$(CH_2)_6N_4$, AcOH 100 °C, 7 h		81	2002T489
	$(ClCF_2CO)_2O$ Dichloroethane Reflux, 24 h		n.r.[a]	2001TL3077

[a]n.r. = not reported.

10.10.6.5.3 Nucleophilic attack at carbon

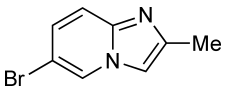
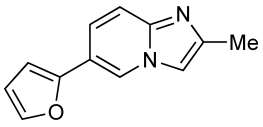
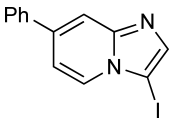
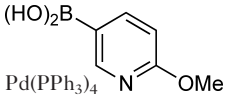
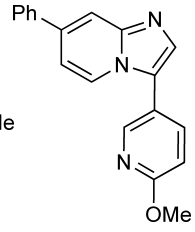
To our knowledge, direct substitution of hydrogen has not been reported. Displacements of halides at C-3 or C-5 are well-documented reactions that have been overviewed in CHEC(1984) and CHEC-II(1996). More recent examples include a copper-catalyzed coupling of an α,α-difluoro Reformatsky reagent with a 3-iodo derivative <2005JOC4897>, substitution of a 3-iodo derivative by a sulfide under Ullmann's conditions <1999T541>, substitution of a 5-chloro or bromo derivative by ethyl thioglycolate <2002T489, 2002H(57)21>, substitution of a 6-iodo derivative by cyanide anion under Pd(0)-catalyzed procedure <1998JME4317>, substitution of 5-chloro derivatives by anilines <1999PHA341>, and Buchwald aminations of 6-halo derivatives <2003JOC5614, 2003JOC4367>. Some of these examples demonstrate that the presence of an electron-withdrawing group attached on the heterocycle is not necessary for the success of the aromatic substitution. As regard to carbon–carbon bond formation, palladium-catalyzed cross-coupling reactions with various halides have been studied. Thus, examples of Negishi, Suzuki, Heck, and Stille reactions are collected in **Table 13**.

Table 13 Palladium-catalyzed C–C bond formation from halo derivatives of imidazo[1,2-*a*]pyridines

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	 $Pd(OAc)_2$ Ph_3As, $AgCO_3$ DMF, 45 °C		98	2003JME1449
	$C_6H_5B(OH)_2$ $Pd(PPh_3)_4$ Na_2CO_3, toluene 75 °C		73	2000JOC6572
	2-ThienylB$(OH)_2$ $Pd(PPh_3)_4$ $Ba(OH)_2$, DME 75 °C		70	2000JOC6572
	$MeB(OH)_2$ $Pd(PPh_3)_4$ NaOH, DME 75 °C		85	2000JOC6572
	 $Pd(PPh_3)_4$ Toluene, reflux		77	2003HCA3661
	 $Pd(PPh_3)_4$ Toluene, reflux		82	2003HCA3661
	 $PdCl_2(PPh_3)_2$ Toluene, 100 °C		45–50	2003OL1369
	$PhB(OH)_2$ $[PdCl_2(DPPF)]$ $Ba(OH)_2$ DME, reflux		58	2001HCA3610

(*Continued*)

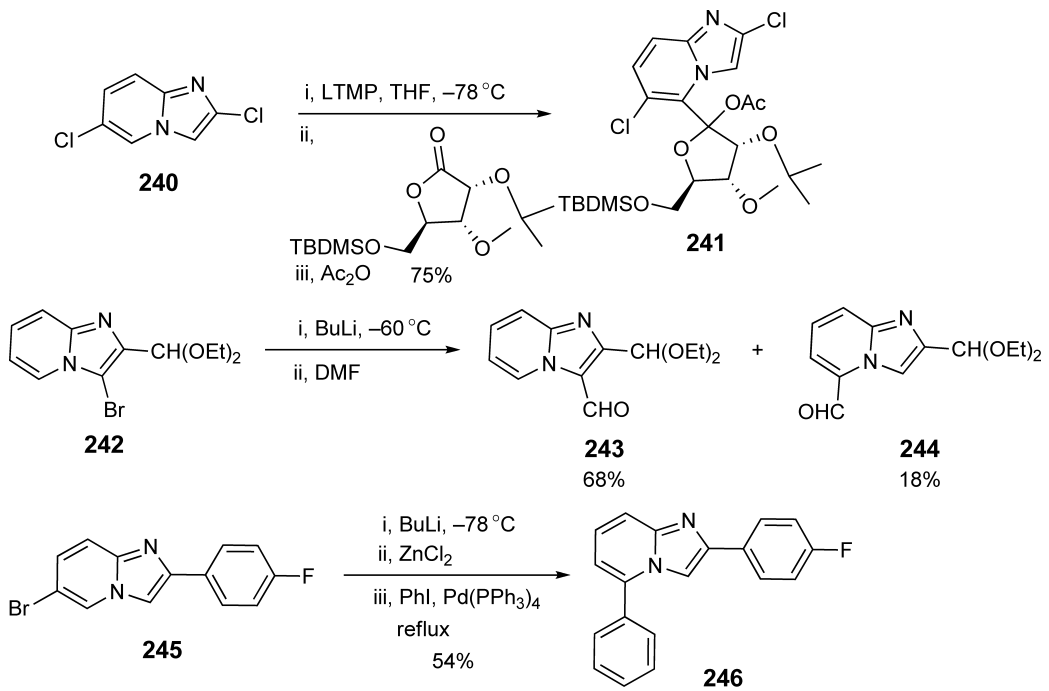
Table 13 (Continued)

Substrate	*Conditions*	*Product*	*Yield (%)*	*Reference*
	Furan-2-yl-B(OH)$_2$ Pd(PPh$_3$)$_4$ NaOH DME, reflux		88	2001HCA3610
	 Pd(PPh$_3$)$_4$ Na$_2$CO$_3$ Dioxane, reflux		n.r.[a]	2004BML909

[a]n.r. = not reported.

10.10.6.5.4 Nucleophilic attack at hydrogen

Deprotonation occurs at C-3 as illustrated by some examples in CHEC(1984) and CHEC-II(1996). It has been shown that the nature of the substituents on the ring can greatly influence the regioselectivity of this deprotonation. For example, compound **240** is selectively deprotonated at C-5 (and not at C-3) with LDA, PhLi, or lithium 2,2,6,6-tetramethylpiperidide (LTMP) <1997JOC3553>, which was most unexpected considering previous reports in this field. In a similar way, when 3-bromo derivative **242** is lithiated by lithium/halogen exchange, formylation with DMF gives both 3- and 5-formyl derivatives **243** and **244** <2003T5869>. This suggests a competitive lithiation at C-5 followed by a 'halogen dance' (bromine–lithium isomerization) at C-3 and C-5. Finally, when heterocycle **245** is lithiated at C-6 through bromine/lithium exchange, a subsequent Negishi coupling gives the 5-phenyl derivative **246** <2003HCA3661>: this also suggests an isomerization of the kinetically formed aryllithium (**Scheme 67**).



Scheme 67

10.10.6.5.5 Reactions at surfaces

The six-membered ring was reported to be selectively reduced in CHEC-II(1996). More recent examples using Pd/C or Raney-Ni confirm this reactivity <2003JOC3498, 2004JME3658>. Desulfurization of methylthio substituents attached to the six-membered ring has been reported, but, depending on the nature of the other substituents on this ring, it can lead to also to a concomitant reduction of the six-membered ring <2003JOC3498>. A pyridine ring attached to this heterocycle was selectively reduced with PtO_2 <2002FA825>.

10.10.6.6 Reactivity of Substituents Attached to the Ring

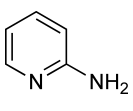
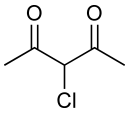
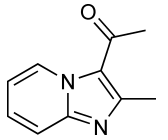
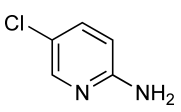
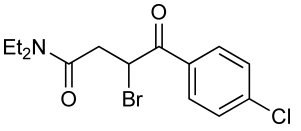
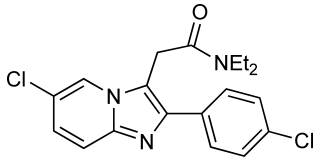
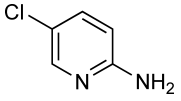
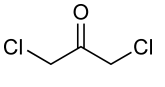
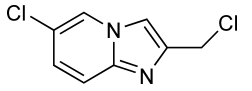
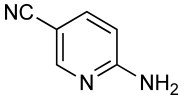
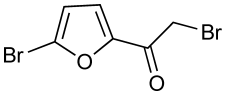
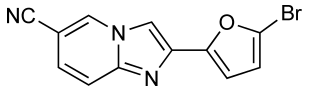
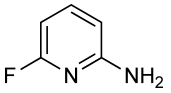
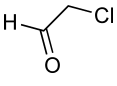
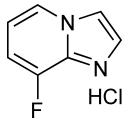
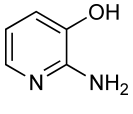
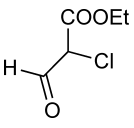
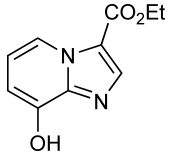
Reactivity of the substituents attached to the ring is quite classical and such transformations are routinely reported. However, some recent and more 'exotic' transformations are reported in this section. Examples include [3+2] cycloaddition of a nitrile oxide, generated at the C-3 position <1998TL8191>, condensation of a methyl ketone at C-3 with *N*,*N*-dimethylamine-formamide dimethyl acetal <2004BML2245>, reduction of an ester at C-3 <1997JME3109>, nucleophilic substitutions at a chloromethyl substituent linked at C-2 <2003ARK273>, the generation of a difluoroacetyl anion linked at C-3 <2001TL3077>, and the oxidation of sulfides linked at C-3 <1999T541>.

10.10.6.7 Synthesis

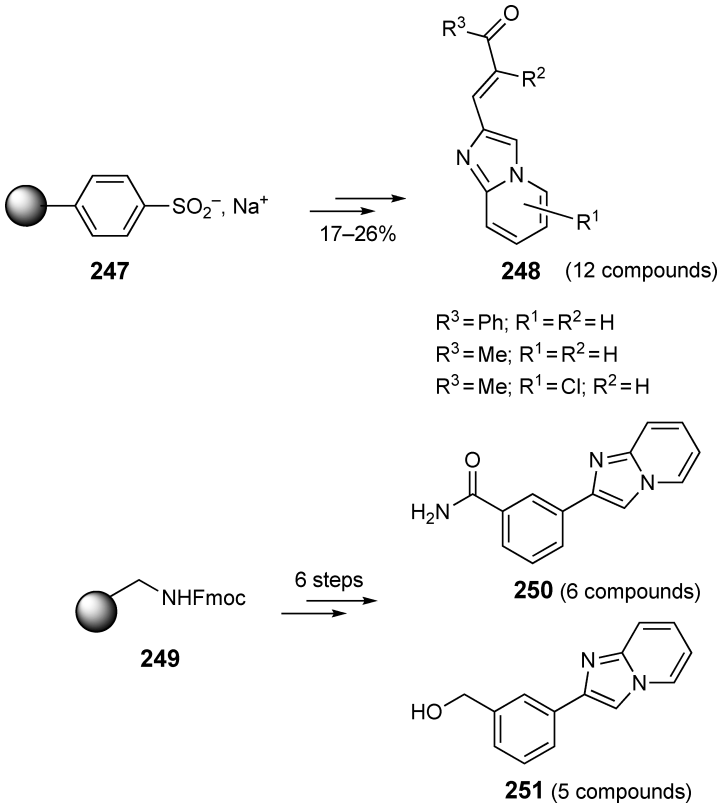
10.10.6.7.1 Fully conjugated ring

A lot of methods are available for the synthesis of this heterocycle, and most of them rely on the formation of the five-membered ring. In this section, only the methodologies of reasonable scope will be reported. The most 'classical' method involves the cyclocondensation of 2-aminopyridine with an α-halo carbonyl compound. Due to the broad availability of the required substrates and the efficiency of this cyclocondensation, it continues to be the method of choice to prepare this heterocycle. New examples highlighting the generality of this reaction are collected in **Table 14**.

Table 14 Synthesis of imidazo[1,2-*a*]pyridines through cyclocondensation of 2-aminopyridine and α-halo carbonyls

2-Aminopyridine	*α-Halo carbonyl*	*Conditions*	*Product*	*Yield (%)*	*Reference*
		EtOH/ THF Reflux, 12 h		44	2004BML2245
		*n*-BuOH Reflux		67	1997JME3109
		EtOH Reflux, 6 h		62	2003ARK273
		EtOH Reflux, 24 h		74	2004JME3658
		Water 60 °C, 2 h		54	2002T489
		EtOH Reflux, 24 h		51	2002T8145

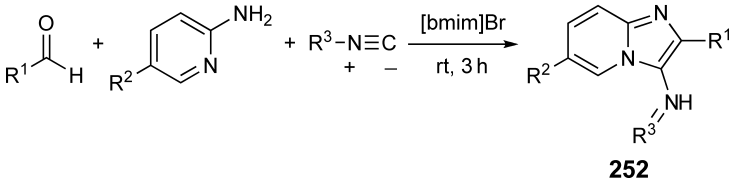
Due to the importance of this heterocycle in medicinal chemistry, solid-phase synthesis of derivatives based on this condensation reaction have been investigated. The first report in this area uses a sodium benzenesulfinate resin **247** and gives access in five steps and good overall yields to a library of imidazo[1,2-*a*]pyridines **248** functionalized at C-2 with an enone moiety <2002OL3935>. Later on, the preparation of libraries of compounds related to **250** or **251** from Rink amide resin **249** have been published (**Scheme 68**) <2003TL6265>.



Scheme 68

An operationally simple procedure involving a variation of this reaction and relying on the use of a polymer-supported [hydroxy(sulfonyloxy)iodo]benzene with aromatic ketones or alcohols has also been published <2004S2673>.

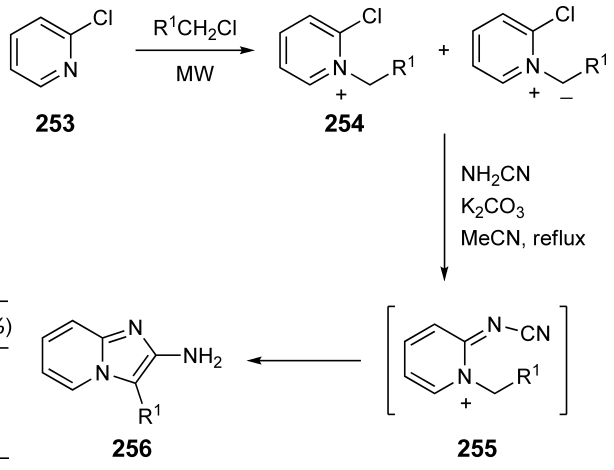
A multiple-component reaction especially suitable for combinatorial synthesis gives a straightforward access to 2-amino derivatives: when a solution of 2-aminopyridine is reacted with an aldehyde (aromatic or aliphatic) and an isonitrile under Lewis acid catalysis ($Sc(OTf)_3$), the corresponding 2-amino imidazo[1,2-*a*]pyridines **252** are produced in good yields (70–95%) <1998TL3635>. Due to the efficiency of this Ugi three-component coupling, improvements in reaction time have been reported by using microwaves <2003TL4369> or ionic liquids (**Scheme 69**) <2006TL3031>.



R^1	R^2	R^3	*Yield* (%)
Ph	Br	Cyclohexyl	98
Ph	Me	*t*-Bu	99
4-Me-C_6H_4	Me	2,6-$(Me)_2C_6H_3$	70

Scheme 69

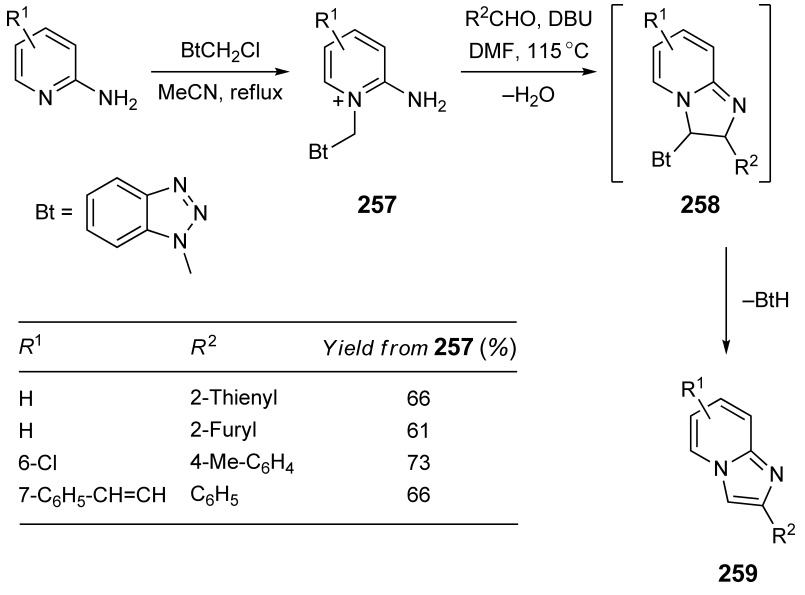
An efficient synthesis of 2-amino derivatives **256** is depicted in **Scheme 70**: 2-halopyridines are first N-alkylated with various halides under microwave activation and next reacted with cyanamide under basic conditions <1999T2317>. A rapid parallel synthesis of derivatives bearing a benzoyl substituent at C-3 based on this reaction has been described <2002SL1544>.



R^1	*Yield* (%)
CO_2Et	51
COPh	50
SMe	66

Scheme 70

Katritzky *et al.* <2000JOC9201> reported an efficient synthesis of derivatives **259** based on the reaction of 2-amino-1-[α-benzotriazol-1-ylmethyl]pyridinium chlorides **257** with aldehydes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. This method is, however, limited to the use of aromatic aldehydes (**Scheme 71**).

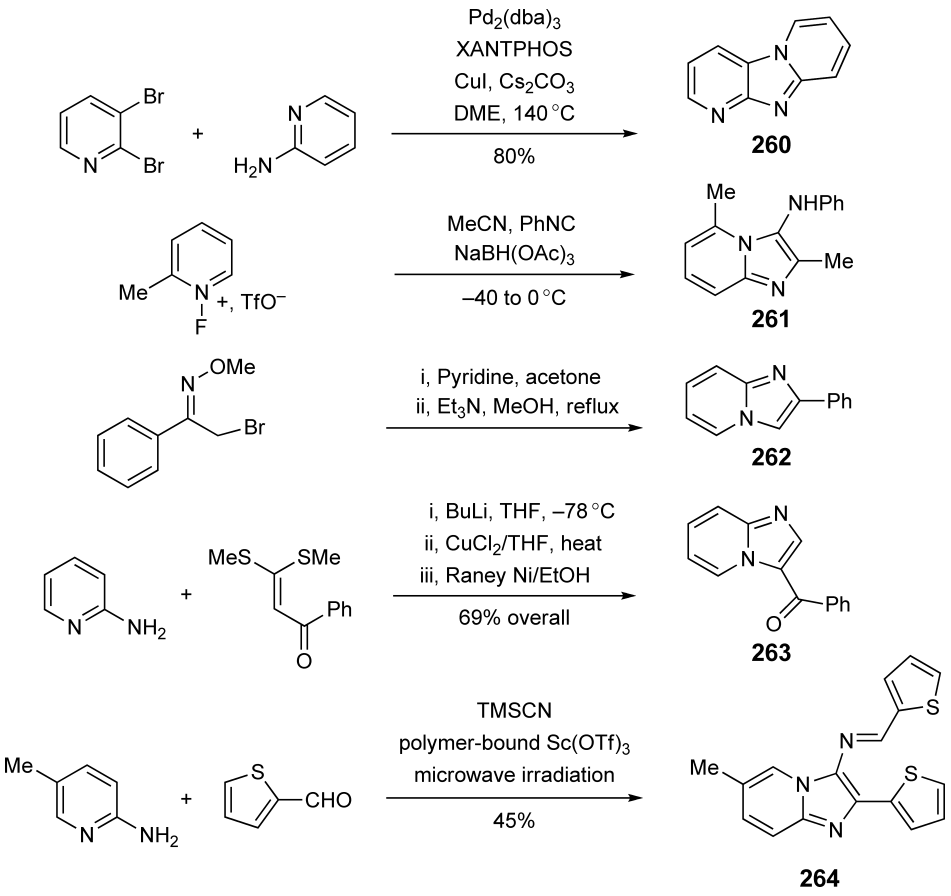


R^1	R^2	*Yield from* **257** (%)
H	2-Thienyl	66
H	2-Furyl	61
6-Cl	4-Me-C_6H_4	73
7-C_6H_5-CH=CH	C_6H_5	66

Scheme 71

Others interesting syntheses based on the formation of the five-membered ring include (1) the orthogonal tandem Pd- and Cu-catalyzed amination of 2,3-dibromopyridine with aminoazines to give **260** <2006JOC260>, (2) the reaction of *N*-fluoropyridinium salts with nitriles and isocyanides under reducing conditions to give **261** <2005TL4487>, (3) the cyclocondensation between pyridine and bromophenacyl bromide *O*-methyloxime, to give **262** <1996S927>, (4) the

reaction of 2-aminopyridines with an-oxoketene *S*,*S*-acetal followed by $CuCl_2$ oxidative ring closure and desulfurization to give **263** <2000JOC1583>, (5) the microwave-assisted three-component reaction involving 2-aminopyridines, an aldehyde, and TMSCN to give **264** <2006TL2989>. All these syntheses are illustrated by one example in **Scheme 72**.



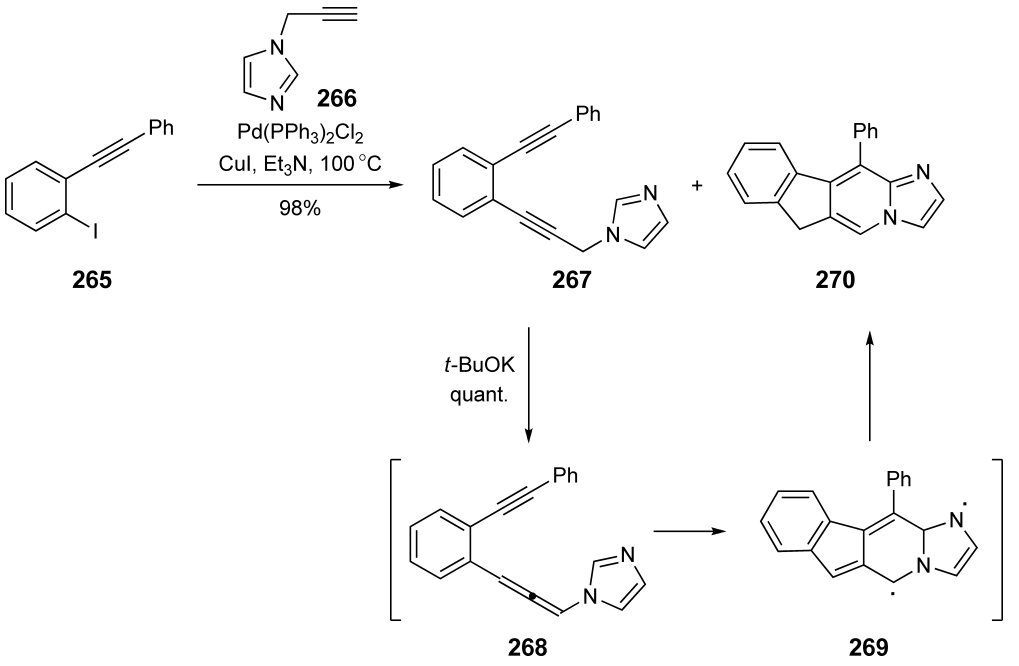
Scheme 72

Syntheses of imidazo[1,2-*a*]pyridines involving ring closure of the six-membered ring are less documented. An elegant route applied to the preparation of various heterocycles involves the reaction of iodide **265** with *N*-propargyl imidazole **266** under Sonogashira coupling conditions. The intermediate enediyne **267** gives enyne-allene **268** and then undergoes a Schmittel cyclization to give intermediate diradical **269** that finally gives **270**, as depicted in **Scheme 73** <2005JOC6647>.

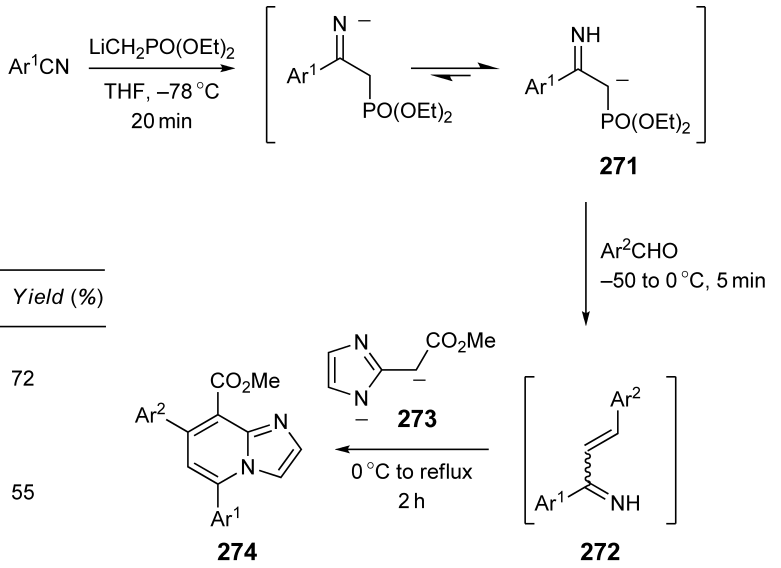
A series of aryl-substituted derivatives **274** have been recently prepared by an original ring-closure reaction <2006TL2941>. In these syntheses, aromatic nitriles react with lithiophosphonate to give **271**. Further reaction with aromatic aldehydes gives conjugated imines **272** and reaction of the latter with dianion **273** finally produces **274** in fair yields. This one-pot procedure is especially convenient to prepare derivatives possessing a substituted six-membered ring (**Scheme 74**).

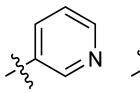
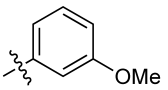
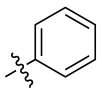
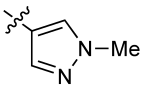
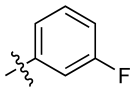
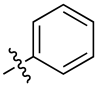
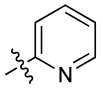
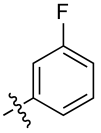
Following a quite similar chemical transformation, the dianion of imidazole derivative **275** reacts with a variety of α-oxoketene dithioacetals **276** to give the adduct resulting from a conjugate addition. This compound spontaneously cyclodehydrates to give **277**. The SMe group may then be reduced using Raney-Ni <2003JOC3498>. Alternatively, the dianion of imidazole **278** adds in a 1,2-fashion to give **279**. Cyclodehydration of this intermediate needs further heating in the presence of phosphoric acid to give **280** (**Scheme 75**).

An elegant synthesis involving simultaneous closure of both five- and six-membered rings ought to be mentioned <2000EJO1433>. Oxidative cyclizations of functionalized aldehydes **281** with *ortho*-phenylene diamine in nitrobenzene directly give fused derivatives **282** in fair yields. In case of furyl derivatives (R^1), this reaction surprisingly gave an isomer of the expected heterocycle (**Scheme 76**).

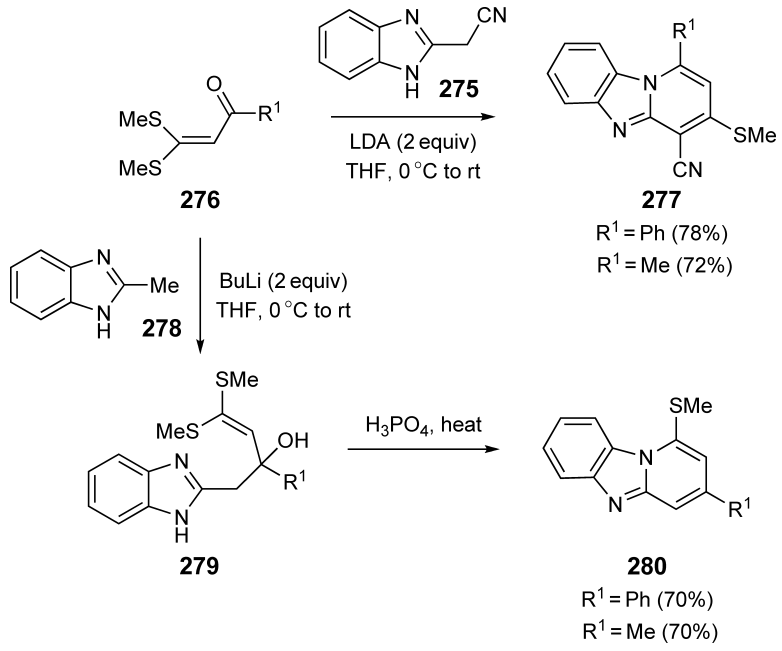


Scheme 73

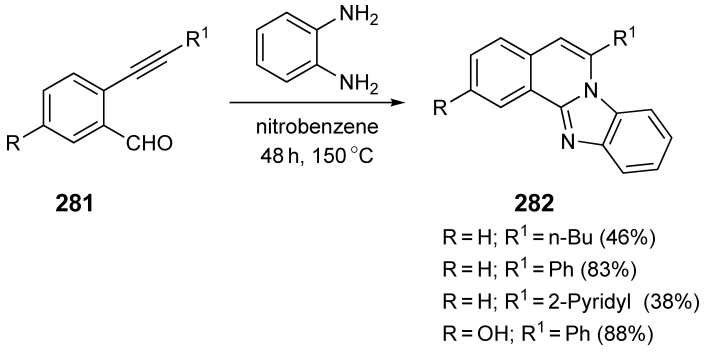


Ar^1	Ar^2	*Yield* (%)
		72
		55
		60
		65

Scheme 74



Scheme 75

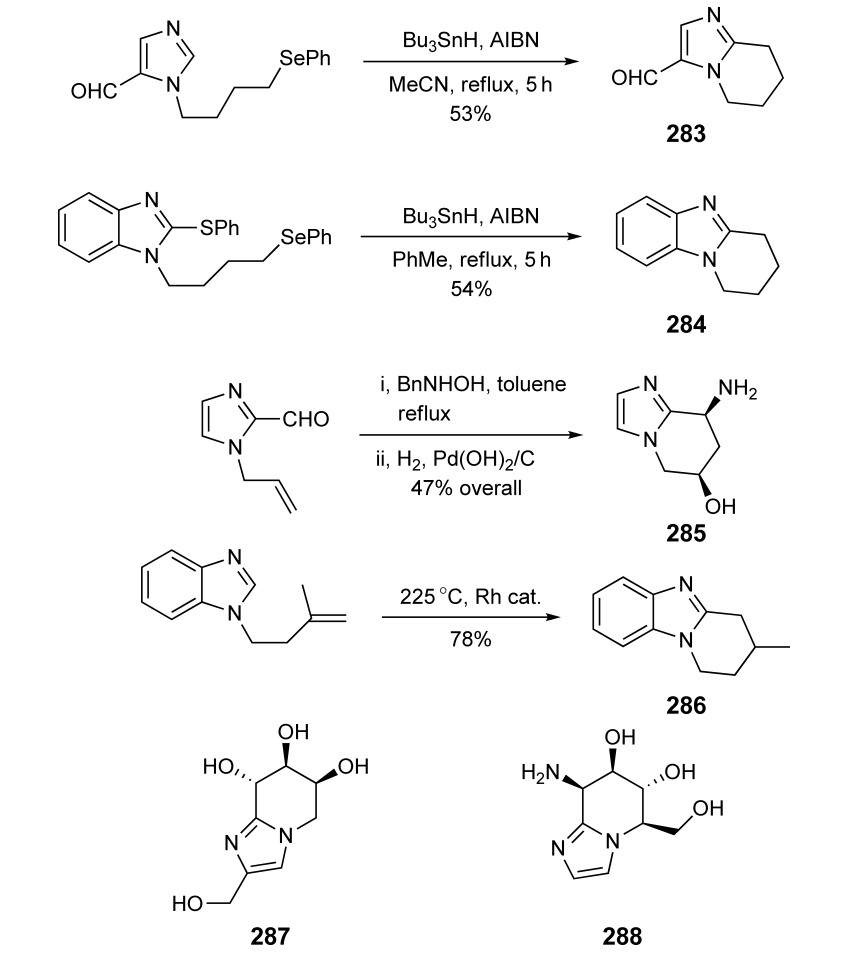


Scheme 76

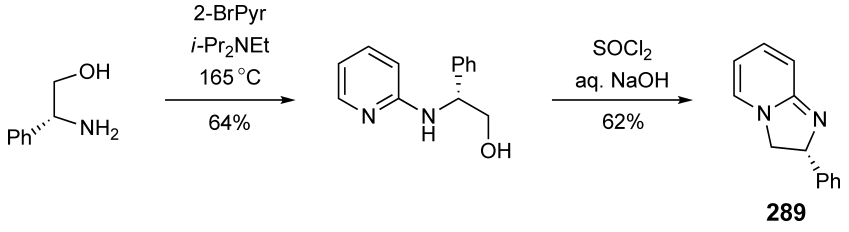
10.10.6.7.2 Partially saturated rings

Synthesis of this heterocyclic core with a fully saturated six-membered ring can be achieved by catalytic hydrogenation (see Section 10.10.6.4.5). The six-membered ring can also be formed starting from the appropriate imidazole using radical ring closure to give **283** <1999T8111> or **284** <1997TL3793>, through intramolecular nitrone cycloaddition <2002T4445> to give **285**, through rhodium-catalyzed CH activation to give **286** <2003OL2131> (**Scheme 77**). The simultaneous closure of both five- and six-membered rings leading to a saturated six-membered ring can be achieved through a [4+2] intramolecular cycloaddition of ketenimine-imine <1999TL6127>. A number of polyhydroxylated derivatives such as **287** or **288** have been synthesized through conventional carbohydrate chemistry <2004BML4039, 2005TA449, 2003TL3667>; these compounds were prepared because of their properties as selective and potent glycosidase inhibitors.

Partially saturated compounds can be prepared through annelation of heterocyclic 2-ketene aminals with various bis-1,3-electrophiles <1998T6191, 1998TL9237>. Natural products (catharsitoxins A–C) have been prepared through imidazole ring closure <2001TL7079>. Partially saturated compounds such as **289**, prepared as outlined in **Scheme 78**, were found to be very efficient catalysts for enantioselective acylation of secondary alcohols <2004JA12226>.

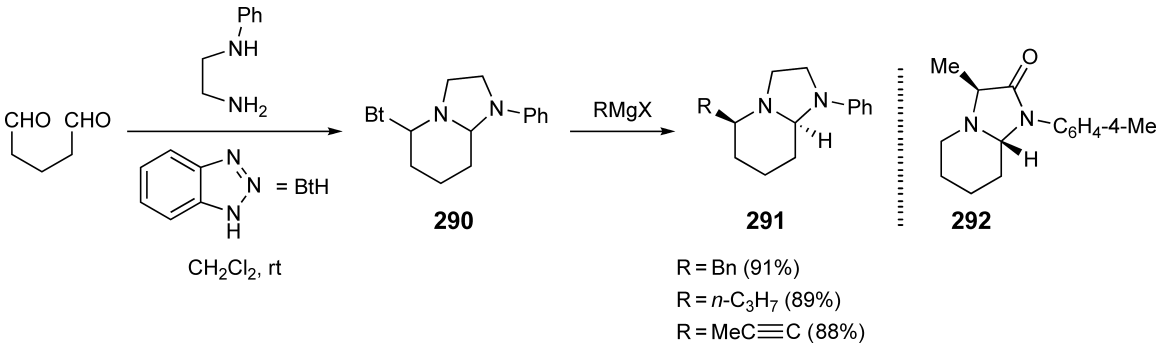


Scheme 77



Scheme 78

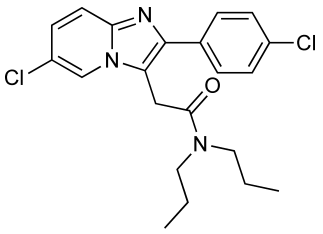
The synthesis and reactivity of imidazopyridinium halides, in which the five-membered ring is totally saturated, have also been investigated <2002JOC2382, 2003JOC10123>. A synthesis of such derivatives has been described by Katritzky *et al.* <2000JOC3683> and relies on the condensation of glutaraldehyde and *N*-phenylethylene diamine in the presence of benzotriazole: bicyclic compound **290** is obtained in nearly quantitative yield. Treatment of the latter with Grignard reagents then furnishes derivatives **291** in very good yields. Careful examination of the NMR data of these compounds revealed that they were produced as single *cis*-stereoisomers as depicted in **Scheme 79**. Compound **292** (major isomer shown) could be prepared following a similar strategy <2002JOC4951>.



Scheme 79

10.10.6.8 Important Compounds and Applications

Imidazo[1,2-*a*]pyridines show an impressively large range of biological activities as illustrated with numerous examples in CHEC(1984) and CHEC-II(1996). This heterocycle continues to be a very popular scaffold for the development of new bioactive molecules, which is probably due to its easy preparation together with the success of some drugs possessing this skeleton. The best example continues to be Sanofi-Synthélabo zolpidem **293** (Stilnox®, Ambien®, Myslee®), a blockbuster for the treatment of sleeping disorders (**Figure 7**). It is most certainly impossible to be exhaustive when dealing with the biological activities of such derivatives considering the enormous literature on this subject. The following references will give an idea of activities reported for some derivatives: antiviral <2003OL1369>, anticancer <2004BML909, 2004BML2249, 2003BML3021>, anxiolytic <2004BML6559>, anti-malarial <2002FA825>, hypnotic <1997JME3109>, antiprotozoal <2004JME3658>, anti-inflammatory <1998JME4053>, activity against gastrointestinal diseases <2004WOP2004101566>. This heterocycle continues to be one of the favorite scaffolds in medicinal chemistry.



293

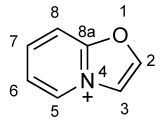
Zolpidem

Figure 7

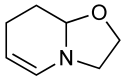
10.10.7 Oxazolo[3,2-*a*]pyridine

10.10.7.1 Introduction

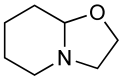
Oxazolo[3,2-*a*]pyridines **294**, first reported by Bradsher and Zinn <1967JHC66> and Pauls and Kröhnke <1976CB3653>, and especially their partially **295** or completely **296** saturated derivatives (**Scheme 80**) clearly emerged as important building blocks since CHEC-II(1996). Specific entries were devoted to this particular heterocycles in CHEC(1984) <1984CHEC(6)645> and CHEC-II(1996) <1996CHEC-II(8)274>. While the literature dealing with the fully conjugated rings is really not abundant (publications reporting on their synthesis or reactivity can be counted on one's fingers), there has been a growing number of publications on the syntheses and uses of saturated derivatives. Therefore, this chapter will briefly describe the new reactions of fully conjugated systems and will then focus on the partially/completely saturated derivatives.



Oxazolo[3,2-*a*]pyridine
294



2,3,8,8a-Tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine
295

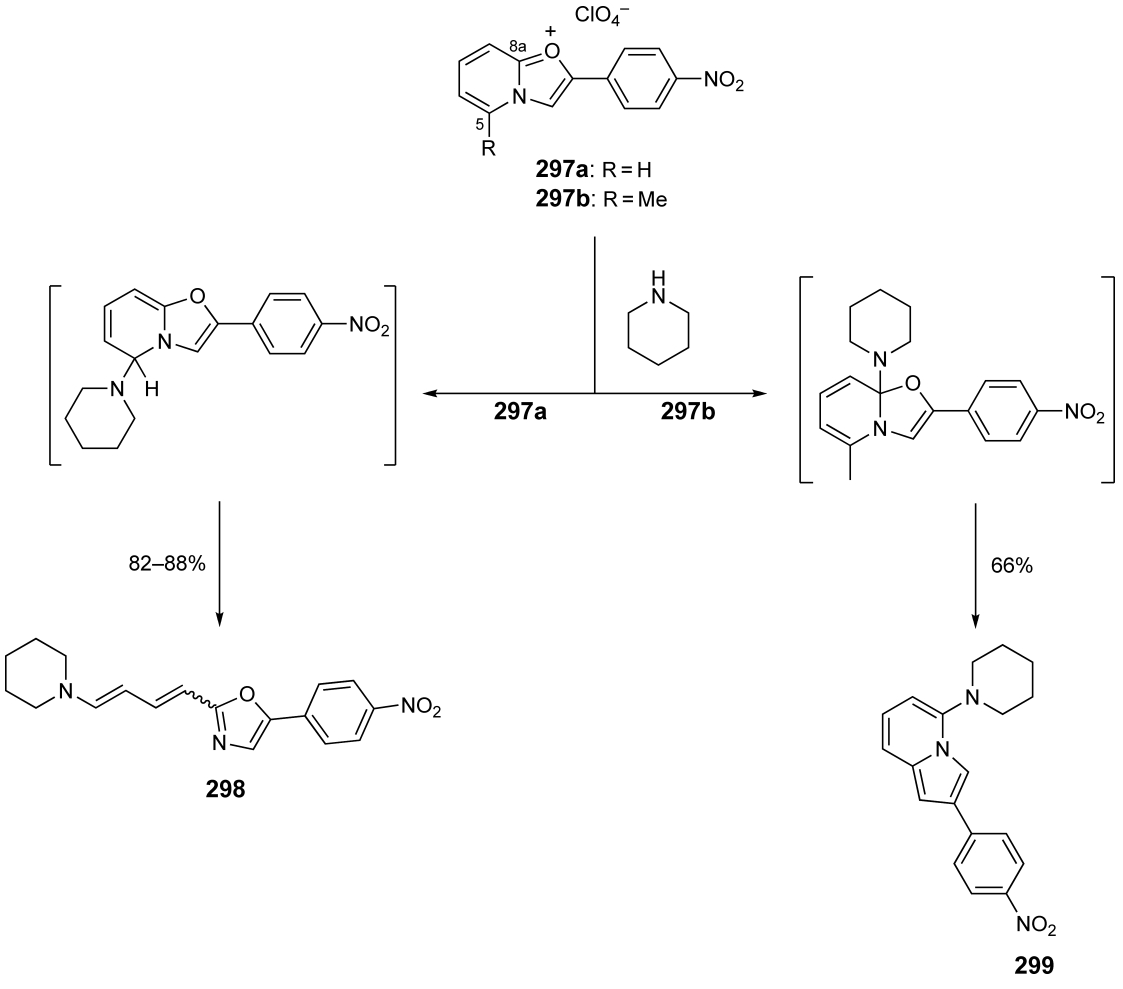


Hexahydro-oxazolo[3,2-*a*] pyridine
296

Scheme 80

10.10.7.2 Theoretical Methods

To our knowledge, no new calculations were specifically devoted to this ring system. Semi-empirical SINDO1 calculations were however used to explain the unusual ambident behavior of oxazolo[3,2-*a*]pyridinium salts **297a** and **297b** toward piperidine (**Scheme 81**). Results obtained with these calculations demonstrate that the C-8a-adduct systematically possesses the lowest energy but in the case of an adduct between **297a** (R = H) and an amine, the difference of energy between addition at C-8a or C-5 is negligible and the energy released during the ring cleavage yielding to **298** becomes the driving force, therefore explaining the difference in reactivity between salts **297a** and **297b** <1998EJO193>.

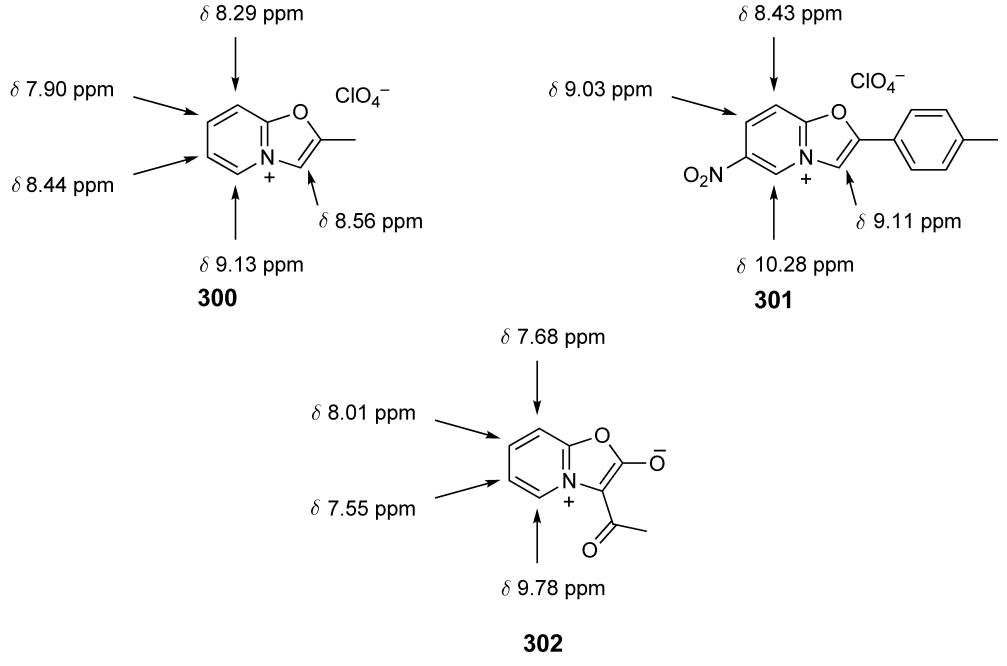


Scheme 81

10.10.7.3 Experimental Structural Methods

10.10.7.3.1 Fully conjugated systems

NMR data for new compounds are routinely reported: examples of ^{1}H NMR chemical shifts for a representative set oxazolo[3,2-*a*]pyridinium salts **300** <2005MOL1109>, **301** <2003MOL460>, as well as mesoionic compound **302** <2005MOL1109> are given in **Scheme 82**.



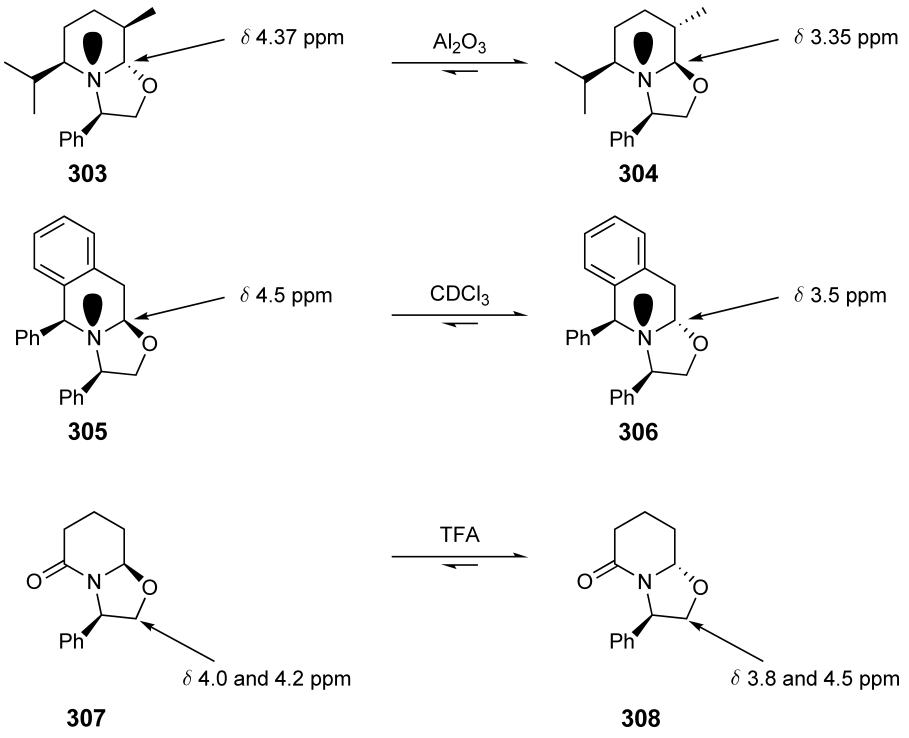
Scheme 82

10.10.7.3.2 Saturated systems

An important feature of polysubstituted perhydrooxazolo[3,2-*a*]pyridines is their high tendency for epimerization under acidic conditions at the C-8a anomeric stereocenter via an open iminium intermediate. This epimerization has been studied by NMR spectroscopy, which is a useful tool for assigning the stereochemistry of the perhydrooxazolo[3,2-*a*]pyridine ring system (**Scheme 83**). An interesting and meaningful example was reported by Marazano and Das who observed a huge difference in chemical shifts (ca. 1 ppm) for diastereoisomers **303**/**304** and **305**/**306**, a difference that was attributed to a deshielding effect due to the *syn*-relationship between the nitrogen doublet and the C-8a proton in **303** and **305** compared to the *anti*-arrangement in compounds **304** and **306** <1998JOC1767, 1998T9357>. Moreover, the predominance of **304** or **306** over **303** or **305** can be explained by destabilizing steric interactions between the phenyl groups of the oxazolidine ring and the substituent (isopropyl or phenyl) at C-5. Interestingly, this phenomenon seems to be quite general since Amat *et al.* reported a similar equilibration of 3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridin-5-one **307** to its more stable isomer **308** under stronger acidic conditions <2003TA293>. Here again, typical chemical shifts allow for assignment of stereochemistry (**Scheme 83**).

10.10.7.3.3 Saturated systems: X-Ray

Structures of a wide number of hexahydro-oxazolo[3,2-*a*]pyridines have been determined using X-ray analysis. In most cases, the objective was structural confirmation and results usually were unexceptional. It should just be mentioned here that the crystal structure of *trans*-(3*R*,2a*S*)-(−)-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridine-5-thione revealed a significant participation of the tautomeric thio-enolic form as reflected by the short N–C(═S) bond length of 1.328 Å <2003AXEo519>.



Scheme 83

10.10.7.4 Thermodynamic Aspects

As seen from the NMR data in the previous section, an important feature of polysubstituted perhydrooxazolo[3,2-*a*]pyridines is their high tendency for epimerization under acidic conditions at the C-8a anomeric.

10.10.7.5 Reactivity of Fully Conjugated Rings

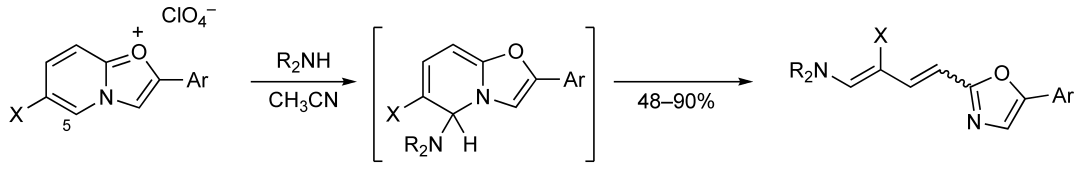
Not much work has been devoted to the reactivity of the oxazolo[3,2-*a*]pyridine ring system in the 1996–2006 time period. Babaev *et al.* however extensively studied the ambident reactivity and novel transformations of oxazolo[3,2-*a*]pyridinium salts which were shown to strongly depend both on the nature of the nucleophile and the salt (**Scheme 84**). When the oxazolo[3,2-*a*]pyridinium salt engaged in the reaction with an amine does not have any substituent at the C-5 position, adducts **310** are formed which evolved to dienes **311** in good yields <1998EJO193, 2003MOL460>. In contrast, substitution at C-5 by an alkyl group blocks the formation of the adduct at this position: the amine now adds to C-8a and indolizines **314** are now exclusively formed <1998EJO193, 2005IZV253>. Note that a similar behavior was observed when sodium methoxide was used in place of the amine.

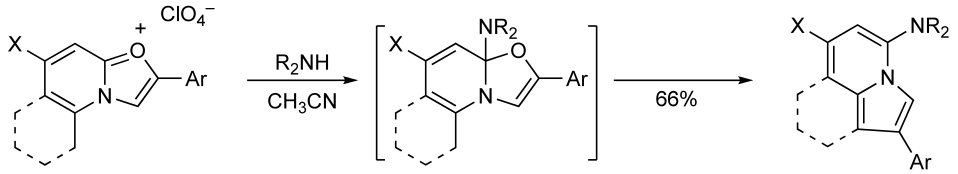
While the reaction with amines gave dienes or indolizines depending on the substitution pattern of the starting oxazolo[3,2-*a*]pyridinium salts, their reaction with water exclusively gives *N*-phenacylpyridones resulting from hydrolysis of the starting material as exemplified by the reaction of **315** with water (**Scheme 85**) <1997AXC1909, 1998EJO193>.

Finally, mesoionic oxazolo[3,2-*a*]pyridines such as **318**, obtained by reaction of **317** with acyl chlorides, are readily hydrolyzed to pyridones **319** by treatment with diluted hydrochloric acid (**Scheme 86**) <2005MOL1109>.

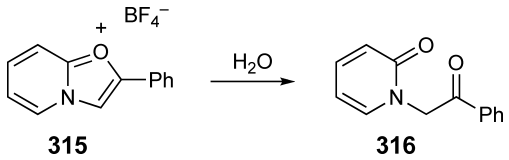
10.10.7.6 Reactivity of Nonconjugated Rings

Considerably boosted by the work of Meyers and Brengel <1997CC1, 1998JOC1619, 2000JOC7240, 2000T9843>, Husson and co-workers <1983JA7754, 1986JOC4475, 1999CSR383>, and Amat *et al.* <2002AGE335, 2003TA1679, 2005OL2817, 2005OL3653>, the reactivity of fully saturated oxazolo[3,2-*a*]pyridines have been extensively studied

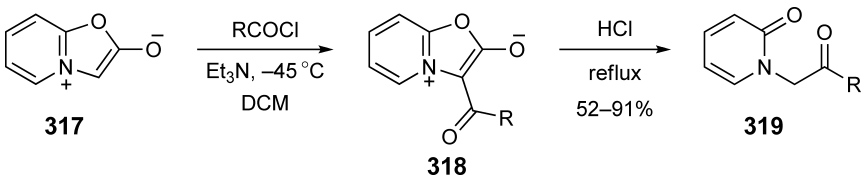




Scheme 84



Scheme 85

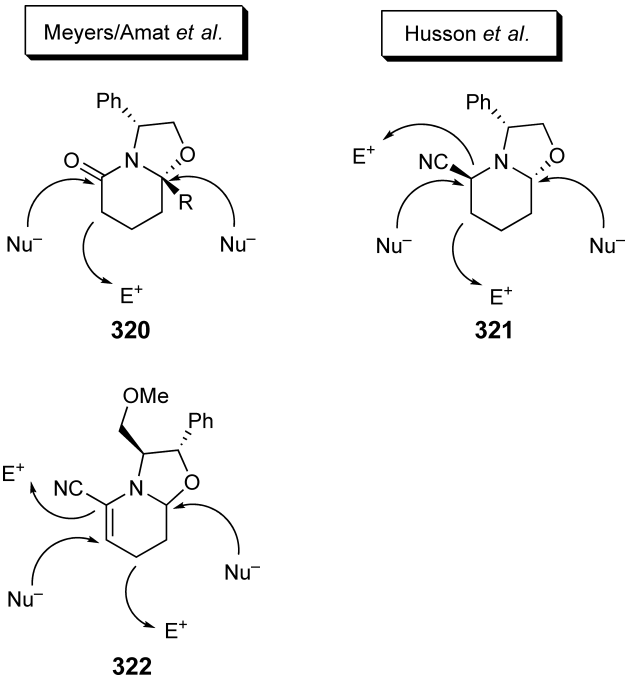


Scheme 86

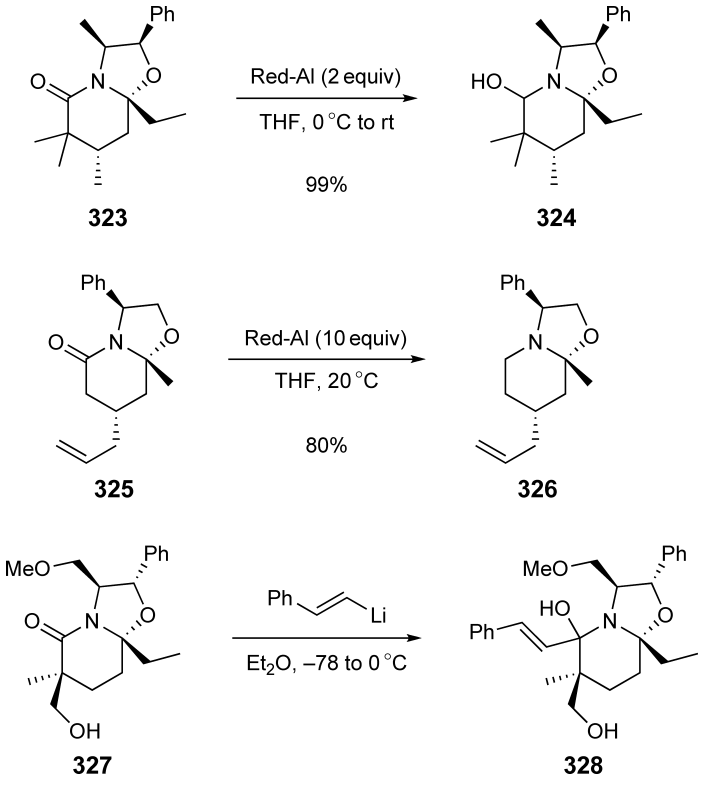
and used in many syntheses of natural products. Depending on the substitution pattern of the chiral perhydrooxazolo[3,2-*a*]pyridine used as molecular scaffold, various chemical transformations have been used to introduce functionalities at different positions of the bicyclic starting materials. **Scheme 87** summarizes the three templates mainly used as well as the strategies employed for their functionalizations. All the possible transformations will not be exhaustively reviewed in this section (excellent reviews have appeared on this topic <1999CSR383, 2000T9843>): instead, an overview of the possibilities and strategies will be discussed, trying to survey all different modes of reactivity of the perhydrooxazolo[3,2-a]pyridine ring system. The corresponding reactions will be classified according to the position of the ring transformed in the process.

10.10.7.6.1 Nucleophilic attack at C-5

The presence of an amide on perhydrooxazolo[3,2-*a*]pyridine skeleton allows for a substituent modification at the C-5 position. Among the possibilities are partial or full reduction of the amide as well as addition of organolithium reagents, respectively, starting from **323** <1998JOC1732>, **325**<1999TL8965>, or **327** (**Scheme 88**).

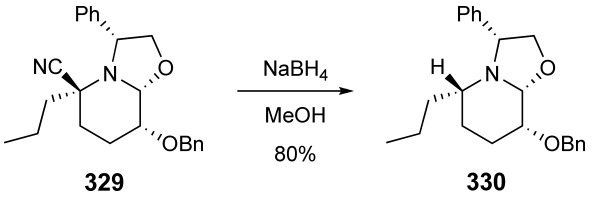


Scheme 87



Scheme 88

If the perhydrooxazolo[3,2-*a*]pyridine now possesses a nitrile at C-5, the aminonitrile can be reduced with sodium borohydride as exemplified in **Scheme 89** <1998T8783>. Another option is to generate an intermediate iminium ion and to further reduce it with zinc borohydride <1998T8783>.

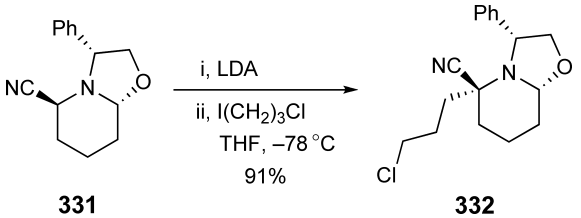


329 **330**

Scheme 89

10.10.7.6.2 Electrophilic attack at C-5

Here again, the presence of a nitrile group at C-5 allow for a great versatility: generation of an anion followed by its trapping with electrophiles allows for the introduction of an additional substituent in this position as exemplified by the diastereoselective alkylation of **331** (**Scheme 90**) <2005JOC4474>.

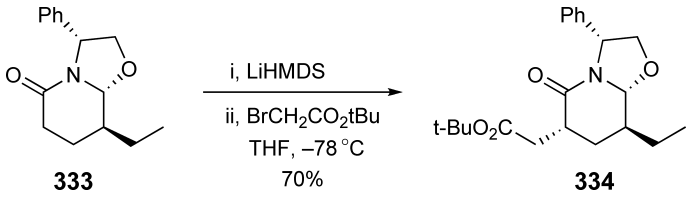


331 **332**

Scheme 90

10.10.7.6.3 Electrophilic attack at C-6

The presence of the amide group in hexahydro-oxazolo[3,2-*a*]pyridin-5-one **333** allows for a diastereoselective introduction of a substituent after generation of an enolate and its quenching with *tert*-butyl bromoacetate (**Scheme 91**) <2003OL3139>. Functionalization at C-6 via transient iminium/enamines starting from simple hexahydro-oxazolo[3,2-*a*]pyridines has also been recently reported <2000AGE1493>.

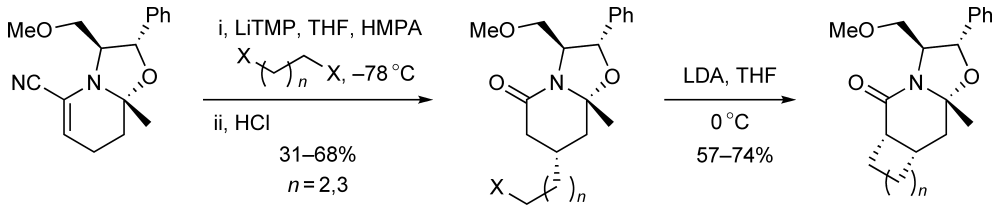


333 **334**

Scheme 91

10.10.7.6.4 Electrophilic attack at C-7

Only few general methods allow for the introduction of a substituent at the C-7 position. However, treatment of cyano-enamide **335** with LiTMP followed by reaction with electrophiles has been successfully used to introduce an alkyl chain at C-7. It is worth noting that the amide obtained by acidic hydrolysis of the cyano-enamide group can be further alkylated to form tricyclic hexahydro-oxazolo[3,2-*a*]pyridin-5-ones **337** (**Scheme 92**) <1998JOC1619>.

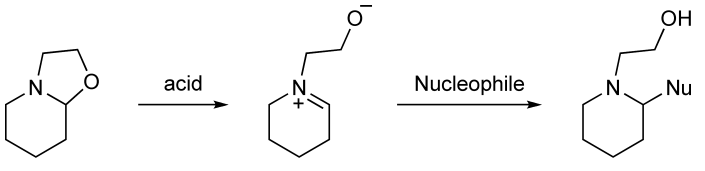


335 **336** **337**

Scheme 92

10.10.7.6.5 Nucleophilic attack at C-8a

Perhydrooxazolo[3,2-*a*]pyridines **338** are excellent precursors of iminium ions **339** obtained after treatment of the oxazolidine with either a Brönsted or Lewis acid. Trapping of these intermediate iminium ions with nucleophiles then allows for substitution at the C-8a position together with ring opening, yielding functionalized piperidines **340** (**Scheme 93**).

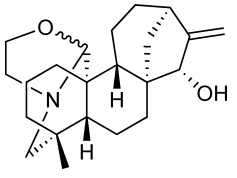
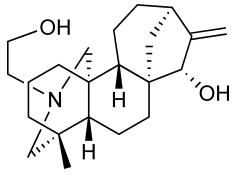
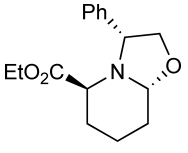
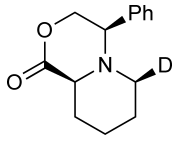
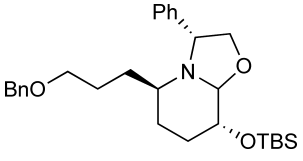
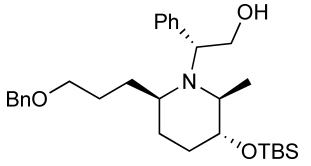


338 **339** **340**

Scheme 93

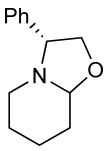
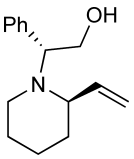
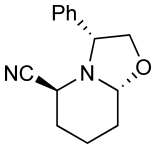
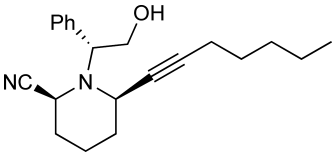
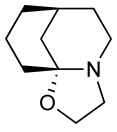
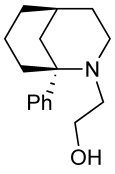
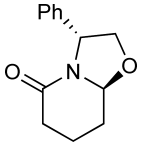
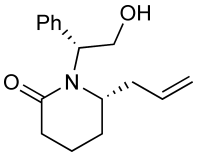
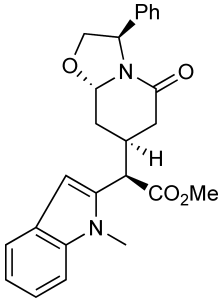
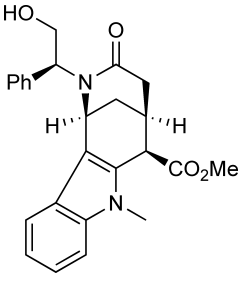
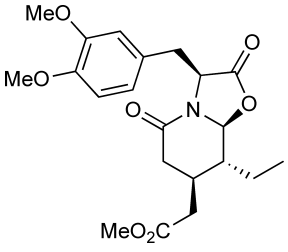
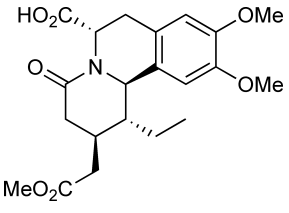
This reaction has been extensively used for the synthesis of polyfunctionalized piperidines with a wide range of nucleophiles: selected and representative examples are collected in **Table 15**. From these results, hydrides, Grignard reagents, aluminum derivatives, allylsilane, as well as aromatics can be used as nucleophiles to give the corresponding C-8a functionalized compounds in good yields and, in most cases, excellent selectivities.

Table 15 Nucleophilic attack at C-8a

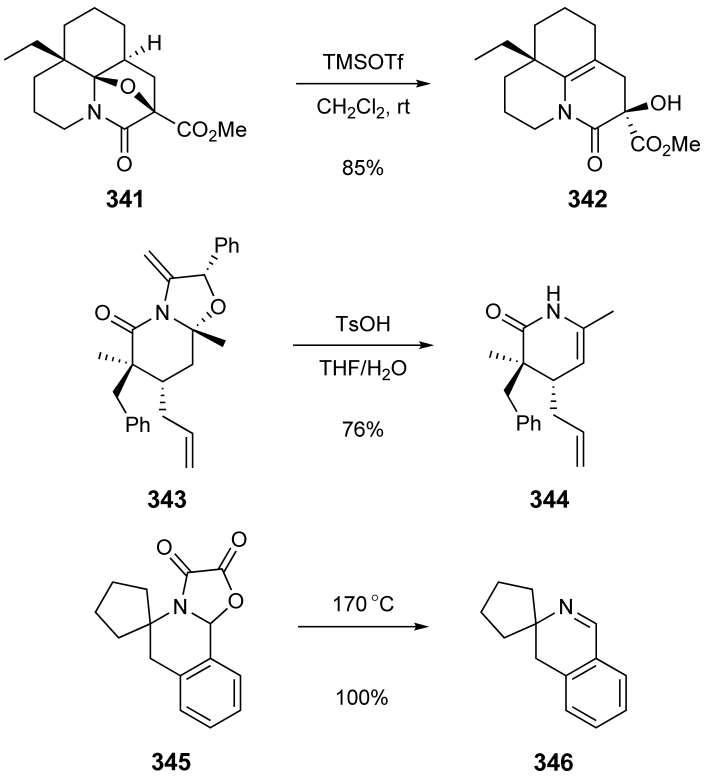
Substrate	*Nucleophile, conditions*	*Product*	*Yield (%)*	*Reference*
	$NaBH_4$ MeOH, rt		62	1997JNP684
	$NaBD_3CN$ $BF_3{\cdot}OEt_2$, THF		75–80	1997JA6446
	MeMgBr THF, rt		89	2003EJO2062

(*Continued*)

Table 15 (Continued)

Substrate	*Nucleophile, conditions*	*Product*	*Yield (%)*	*Reference*
	VinylMgBr THF, rt		95	2004OL1139
	$C_5H_{11}C{\equiv}CH$ $AlMe_3$, Et_3N Toluene, rt		82	2004OL2333
	Ph_3Al Et_2O, rt		89	2001TL3013
	Allylsilane $TiCl_4$, DCM, rt		91	2003JOC1919
	$TiCl_4$, DCM, rt		50	2004CC1602
	$BF_3{\cdot}OEt_2$, DCM Reflux		82	2005OL2817

Interestingly, enamides or imines are produced in the absence of external or internal nucleophiles as shown by the formation of **342**, **344**, and **346**, respectively, obtained from **341** <1998JOC44>, **343** <1998JOC1619>, and **345** <1996SC3471> in good to excellent yields (**Scheme 94**).



Scheme 94

10.10.7.7 Ring Syntheses from Acyclic Compounds

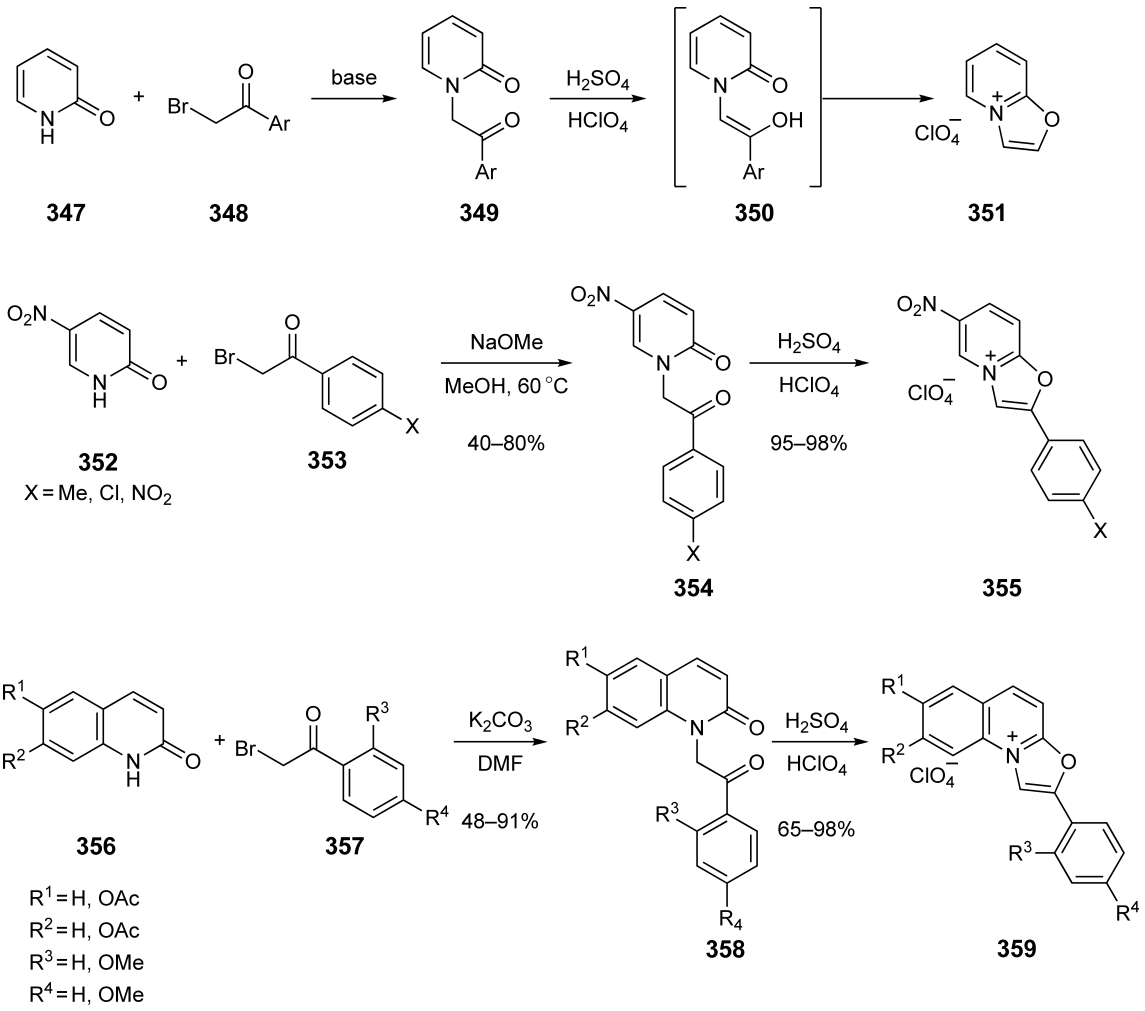
The most efficient routes to the cationic oxazolo[3,2-*a*]pyridine ring system **351** rely on the method of Bradsher and Zinn <1967JHC66> involving the cyclocondensation of *N*-phenacyl-2-pyridones **349** obtained by alkylation of readily available 2-pyridones **347** (**Scheme 95**). This method has been used by Babaev *et al.* to prepare a series of 6-nitro-oxazolo[3,2-*a*]pyridines **355** from 5-nitro-2-pyridone **352** in excellent yields <2003MOL460>. Similarly, tricyclic oxazolo[3,2-*a*]pyridines **359** have been prepared from the corresponding quinolin-2(1*H*)-ones **356** <2003H(60)131>.

10.10.7.8 Ring Syntheses of Saturated or Partially Saturated Rings from Acyclic Compounds

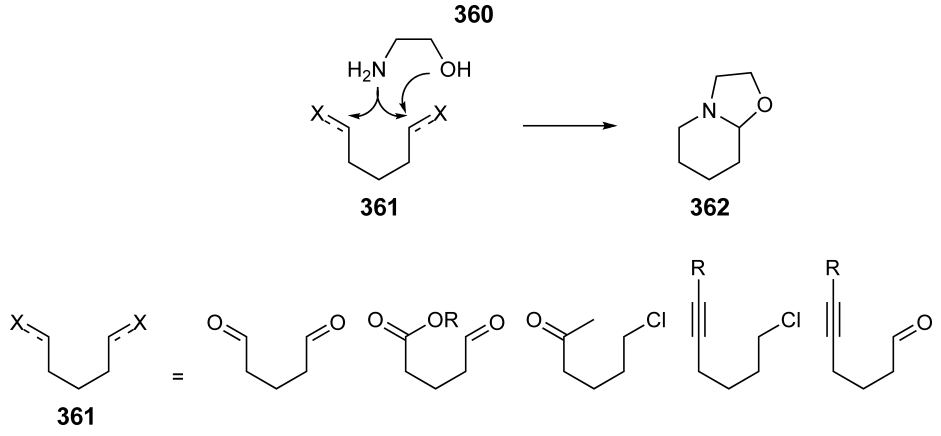
Many synthetic routes have been developed to access the saturated oxazolo[3,2-*a*]pyridine ring system. Among those, the most efficient ones rely on a similar strategy starting from an amino alcohol **360** and a bis-electrophile **361**, the latter being either a bis-aldehyde, a keto-ester, a chloro-ketone, or a chloroalkyne (**Scheme 96**). Among these electrophiles, the first two have demonstrated their utility and generality over the years and have been used for the preparation of many saturated oxazolo[3,2-*a*]pyridines **362**.

Examples of each of the methods are reported in **Table 16** and show the different products obtained from the variation of the bis-electrophile and, when needed or suitable, additional nucleophile.

Another option to build the saturated oxazolo[3,2-*a*]pyridine skeleton relies on commencing from substrates **363** or **366** in which the six-membered ring is already formed. By reacting lactam **363** with sodium hydride and a Grignard reagent <1996TL849> or reducing amino acid-derived piperidine-2,6-dione **366** <1996SC1605>, perhydrooxazolo[3,2-*a*]pyridines **365** and **368** are obtained, respectively (**Scheme 97**).

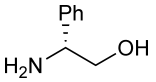
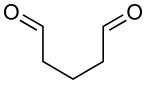
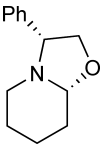
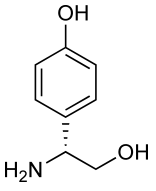
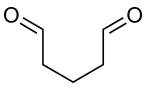
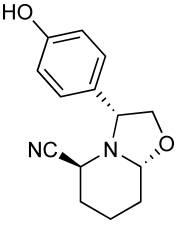
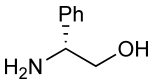
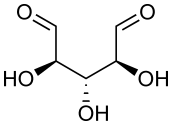
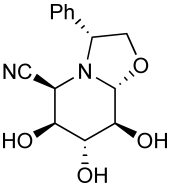
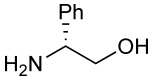
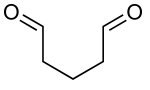
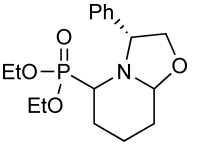
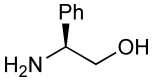
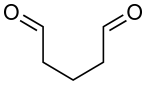
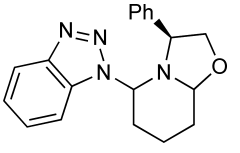
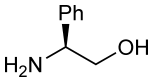
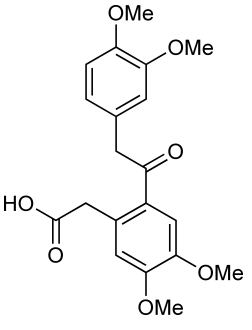
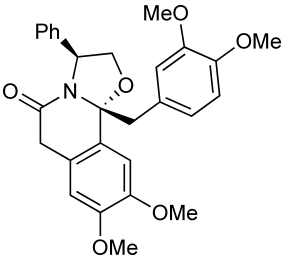
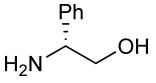
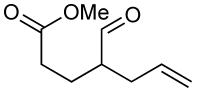
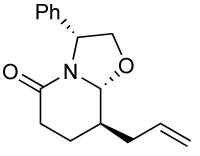


Scheme 95



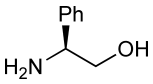
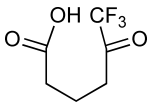
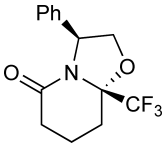
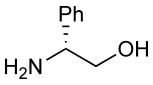
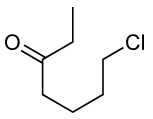
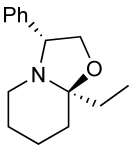
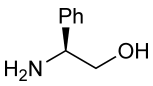
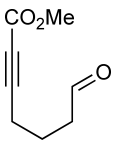
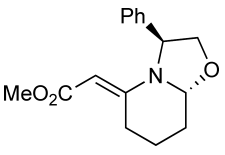
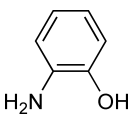
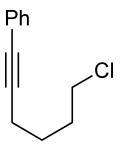
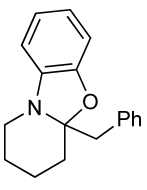
Scheme 96

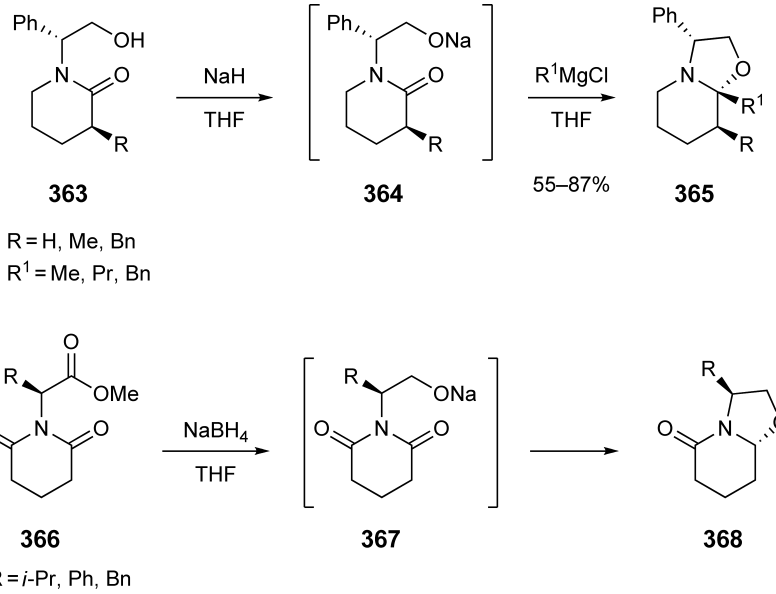
Table 16 Reaction of amino alcohols with bis-electrophiles

Amino alcohol	*Bis-electrophile*	*Additional nucleophile, conditions*	*Product*	*Yield (%)*	*Reference*
		$NaBH_4$ MeOH		50	2000AGE1493
		KCN pH 3, H_2O		69	2001H(55)2273
		i, KCN, citric buffer, H_2O ii, $ZnBr_2$, MeOH		45	2000JOC7208
		$P(OEt)_3$ $MeOH/H_2O$		58	1997T3627
		Benzotriazole CH_2Cl_2/H_2O		95	1998JOC6699
		Toluene Reflux		90	1996JOC4607
		Na_2SO_4, Et_2O		71	2005OL3653

(*Continued*)

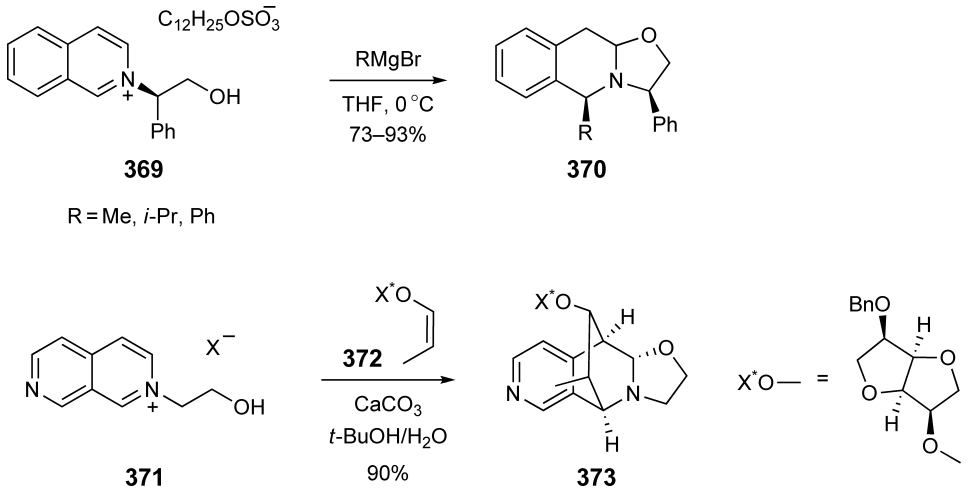
Table 16 (Continued)

Amino alcohol	*Bis-electrophile*	*Additional nucleophile, conditions*	*Product*	*Yield (%)*	*Reference*
		TsOH, Toluene Reflux		70	1999JA593
		Et_3N, Toluene Reflux		72	2000EJO1719
		4 Å mol sieves THF		88	2004JOC2888
		$Pd(NO_3)_2$ Dioxane, 120 °C		50	2002JA12670



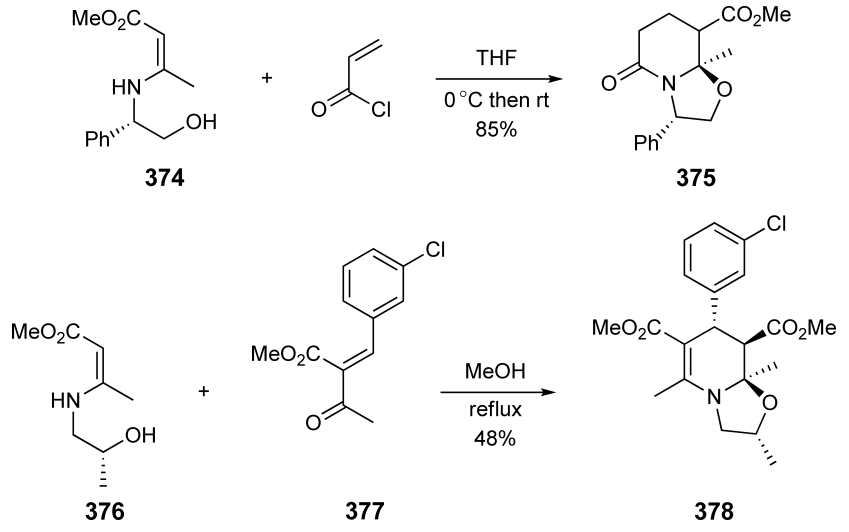
Scheme 97

Isoquinolinium **369** and [2,7]naphthyridin-2-ium **371** salts have also been used for the preparation of 2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine derivatives (**Scheme 98**): addition of Grignard reagents to **369** is followed by a spontaneous cyclization to **370** <1998JOC1767> while an asymmetric version of the Bradsher cycloaddition between **371** and chiral enol ether **372** gives **373** in good yield and selectivities <1996TL7019>.



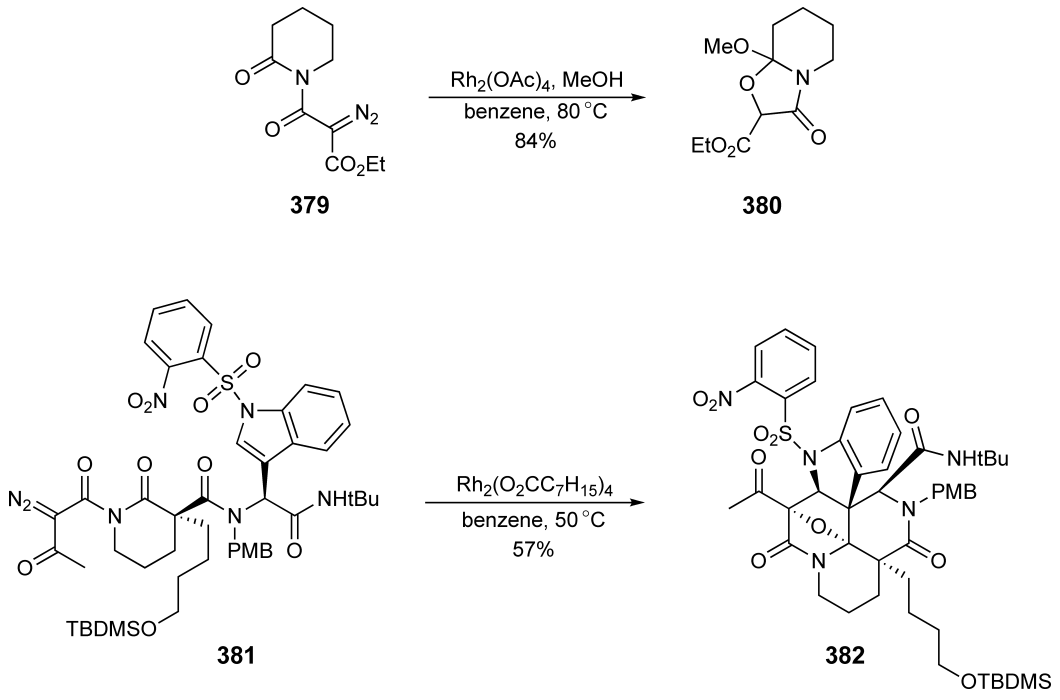
Scheme 98

As shown by the two examples represented in **Scheme 99**, chiral enaminoesters are good candidates for the synthesis of saturated or partially saturated oxazolo[3,2-*a*]pyridine derivatives (**Scheme 99**): acylation of **374** with acryloyl chloride or conjugate addition of **376** to **377** afford in both cases substrates that readily undergo cyclization, respectively to **375** <2002TL2521> and **378** <1996JOC1890>.



Scheme 99

The intramolecular reaction between carbenoids and amides is clearly emerging as a powerful tool for the synthesis of saturated oxazolo[3,2-*a*]pyridine derivatives as shown by the cyclization of simple to extremely functionalized substrates **379** <2003CC440> and **381** <2005OL47> (**Scheme 100**): trapping the intermediate isomünchnone 1,3-dipoles by external (MeOH) or internal (indole) nucleophiles results in new heterocyclic fused systems with especially high efficiency.



Scheme 100

Finally, saturated oxazolo[3,2-*a*]pyridine derivatives can also be accessed via a Pummerer cyclization–deprotonation–cycloaddition cascade from imidosulfoxides <1999JOC2038> or by a [3+2] cycloaddition of nonstabilized azomethine ylides <2004JOC1919>.

10.10.7.9 Important Compounds and Applications

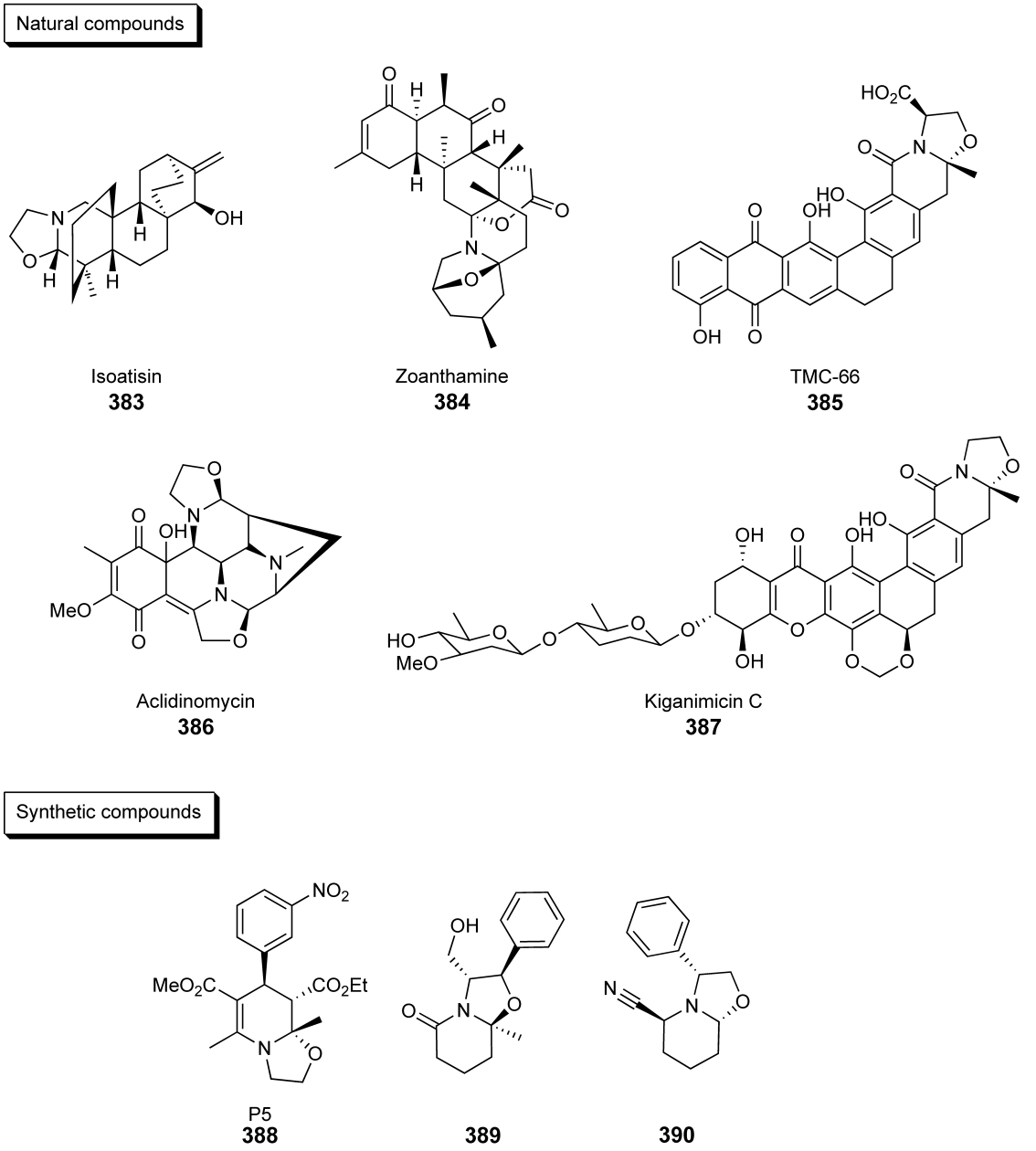
The saturated oxazolo[3,2-*a*]pyridine ring system is found in many natural and/or biologically active products, which has rendered this ring system quite an attractive target. Examples of natural products possessing a saturated oxazolo[3,2-*a*]pyridine moiety include isoatisin **383** <1997H(45)1955>, a muscle relaxant <2002KPS60>, compounds of the zoanthamine **384** family of alkaloids (coagulants/anticoagulants) <2003BMC2301>, the antibiotic TMC-66 **385** <1999JAN607>, the antibacterial/antifungal aclidinomycin A **386**, which possesses two fused saturated oxazolo[3,2-*a*]pyridines <2001JAN304>, as well as the antibiotic kiganimicin C **387** <2005JAN56>. On the synthetic side, E. Martín *et al.* have prepared a series of 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine dicarboxylates which were evaluated for their antihypertensive activity <2000BML319>. Among the compounds tested, P5 **388** was shown to display a long-acting hypertensive activity (**Scheme 101**) <2001MI85>. Finally, it ought to be mentioned here that Meyers' (2*R*,3*R*,8*aS*)-3-(hydroxymethyl)-8*a*-methyl-2-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-5-one **389** and Husson's (3*R*,5*S*,8*aR*)-(−)-hexahydro-3-phenyl-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile **390** molecular scaffolds are now commercially available and can therefore easily be used as templates for the synthesis of functionalized, enantiopure perhydrooxazolo[3,2-*a*]pyridines.

10.10.8 Thiazolo[3,2-*a*]pyridine

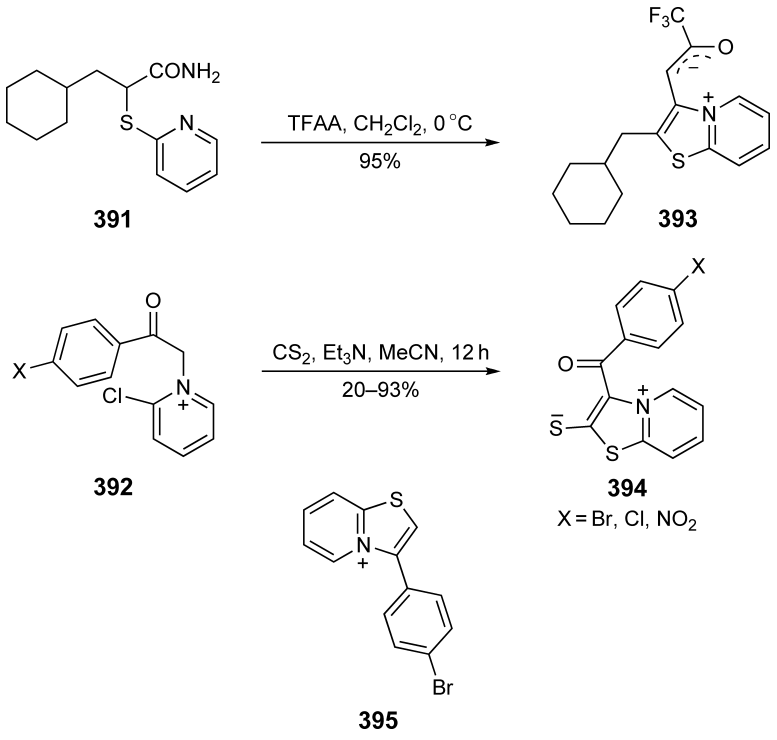
10.10.8.1 Introduction

This class of heterocycle was covered in detail in CHEC(1984) <1984CHEC(6)668> along with others systems and it was reviewed together with thiazolo[3,4-*a*]pyridines in CHEC-II(1996) <1996CHEC-II(8)280>. The literature within the past 10 years for the fully conjugated system is not abundant: only 25 hits were found in the Beilstein

database for the past decade. Therefore, focus will be made on partially or fully saturated systems. Concerning the fully conjugated rings, mesoionic systems **393** <1997TL2435> and **394** <2004IZV176> have been synthesized respectively from **391** and **392** (**Scheme 102**). The structure of **394** (X = NO_2) was determined by X-ray crystallography. NMR spectroscopic studies of a couple of fused thiazoloazinium ring systems such as **395** have been conducted in detail. Basic molecular parameters like anionic charges and bond orders have been determined by *ab initio* and density functional theory (DFT) calculations in order to rationalize the site of reaction of these salts with secondary amines <2003JST295>. Several hitherto unknown thiazolo[3,2-*a*]quinolinium salts have been prepared and thoroughly characterized by NMR spectroscopy <1999JHC937>. The electrochemical behavior of some derivatives has also been investigated <1999JHC943>.



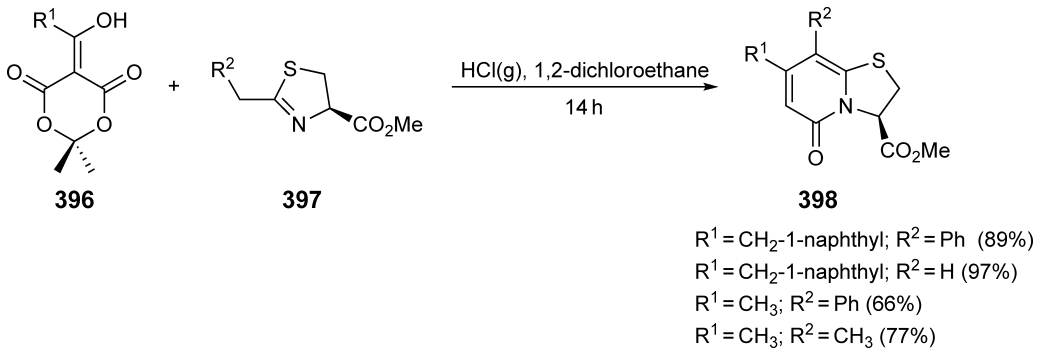
Scheme 101



Scheme 102

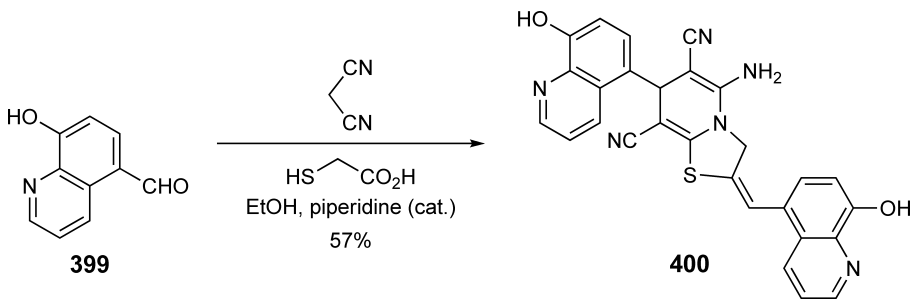
10.10.8.2 Ring Syntheses of Fully or Partially Saturated Rings from Acyclic Compounds

An enantioselective synthesis of 2-pyrimidones **398**, resulting from the condensation of a Δ^2-thiazoline **396** and Meldrum's acid derivative **397**, was reported to occur without (or minimal) racemization, provided that the reaction is run in 1,2-dichloroethane <2001JOC6756>. Its mechanism has been investigated in detail <2004JA13002>. This reaction was improved later on by using microwaves <2003MOD165>, and these compounds were shown to undergo Mannich reaction under microwave irradiation without severe erosion of the optical purity <2004JOC7830> (**Scheme 103**).



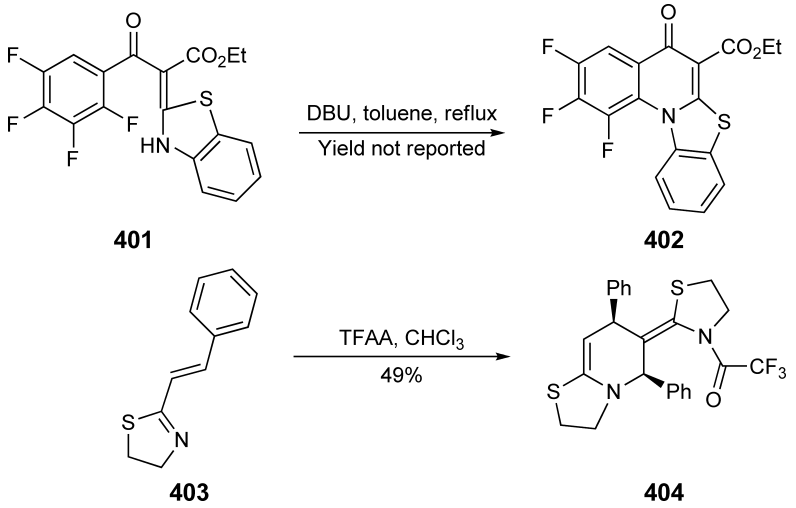
Scheme 103

The reaction of malononitrile, thiogycolic acid, and aldehyde **399** was found to produce compound **400** in fair yield when treated with a catalytic amount of piperidine (**Scheme 104**) <2000FA109>.



Scheme 104

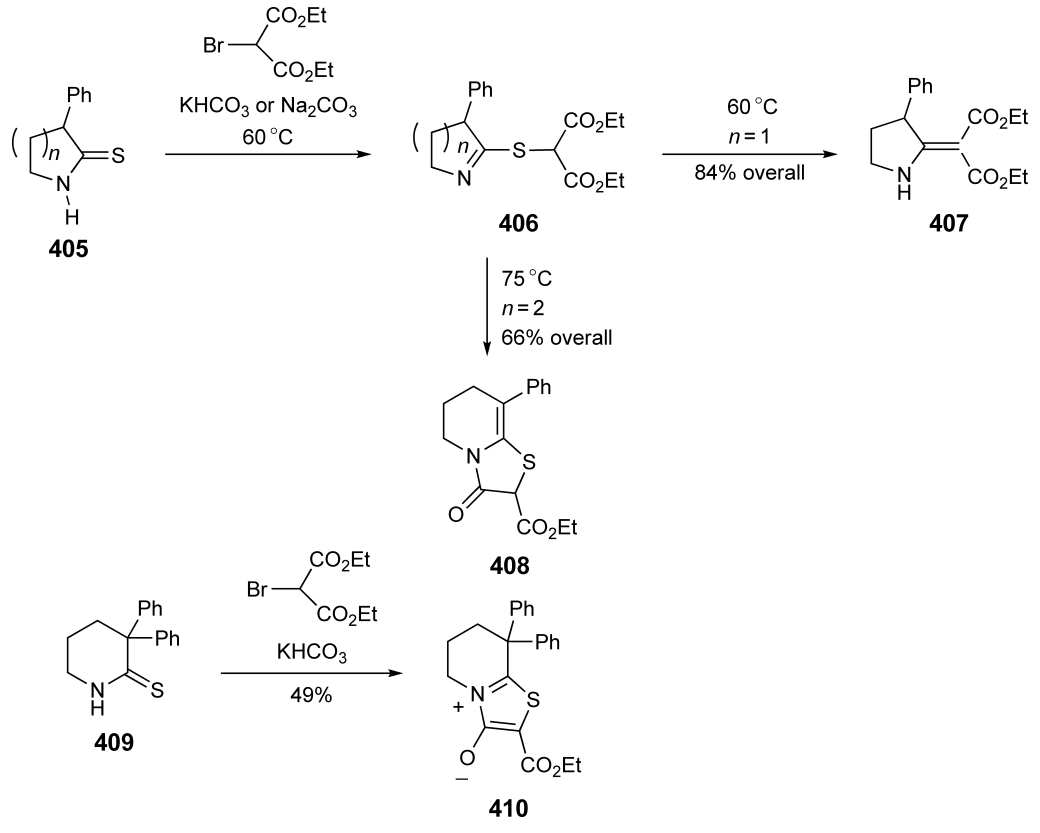
Compound **402** has been prepared in the course of a structure-activity study of new antibacterials <1999BML1339>. The key step for its synthesis relies on an intramolecular S_NAr reaction from **401**, to close the six-membered ring. The yield of this reaction is, however, not mentioned. Dimerization of 2-alkenylthiazolines such as **403** in the presence of trifluoroacetic anhydride provides a straightforward access to **404** <2001TL4937> (**Scheme 105**).



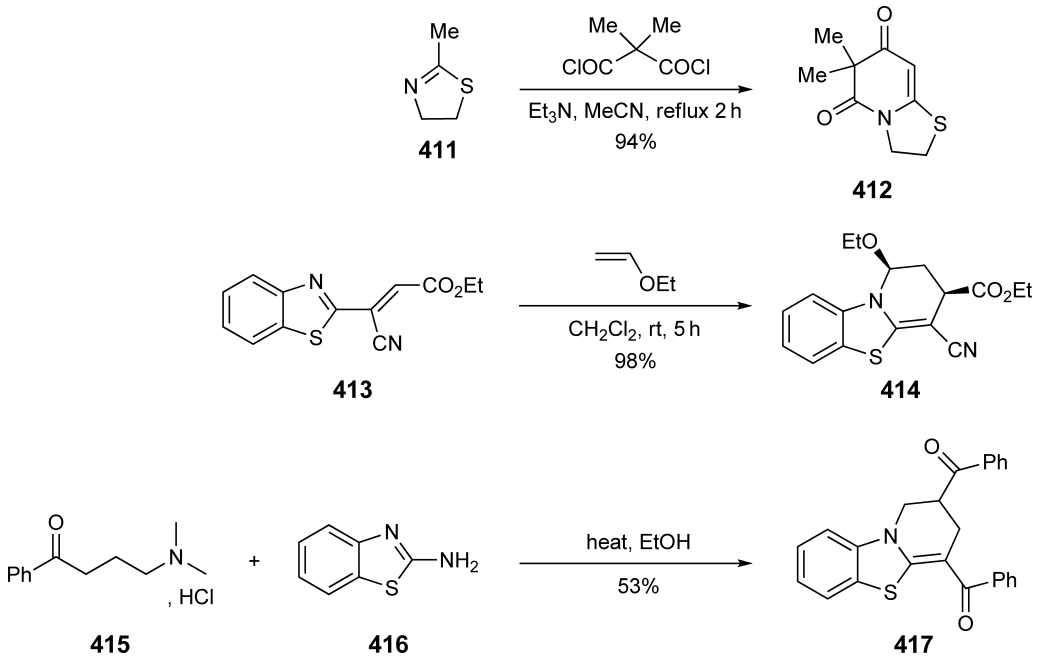
Scheme 105

The extrusion of sulfur from organic sulfides is a useful reaction best exemplified by the Eschenmoser sulfide contraction and has found many applications in synthesis of nitrogen heterocycles. In this reaction, thioamides are treated with enolisable α-halocarbonyl compounds, to form α-thioiminium salts. Recently, it was demonstrated that the size of the thiolactam is a very important parameter for the success of this reaction. As a matter of fact, six-membered ring thiolactams produce bicyclic ketene acetals **408**, whereas the expected β-amino ester **407** is produced from **406** ($n = 1$) <2001J(P1)2055>. Starting from **409**, the thioisomünchone **410** was isolated (**Scheme 106**). More recently, it was found that the nature of the base used in this reaction is also an important parameter and that important amounts of bicyclic thiazolidinone can be produced by using DBU <2004TL1437>.

Some partially saturated derivatives of this heterocycle can be prepared following a strategy involving the closure of the six-membered ring. Following this strategy, a straightforward preparation of *N*-acyl-β-keto cyclic ketene-*N*,*S*-acetals **412** from 2-alkylthiazolines **411** was recently disclosed <2005TL2045>. Similar derivatives **414** can be prepared from the highly reactive 1-aza-1,3-butadiene **413** through a Diels–Alder reaction <1996T733>, or from the reaction of Mannich base **415** with 2-aminobenzothiazole **416** <2002J(P1)555>. Only a single example is shown for clarity in **Scheme 107**; all but these syntheses are of reasonable scope.

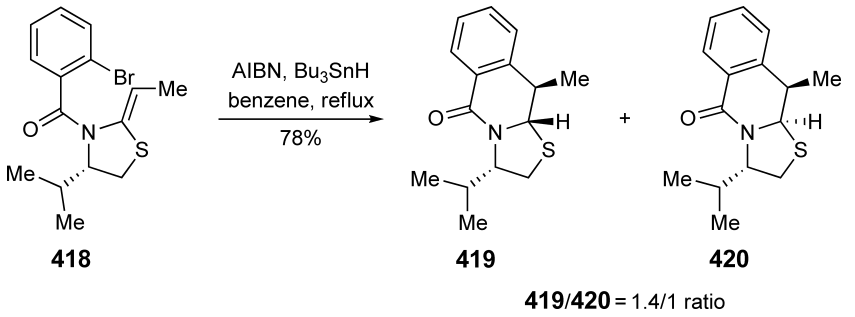


Scheme 106



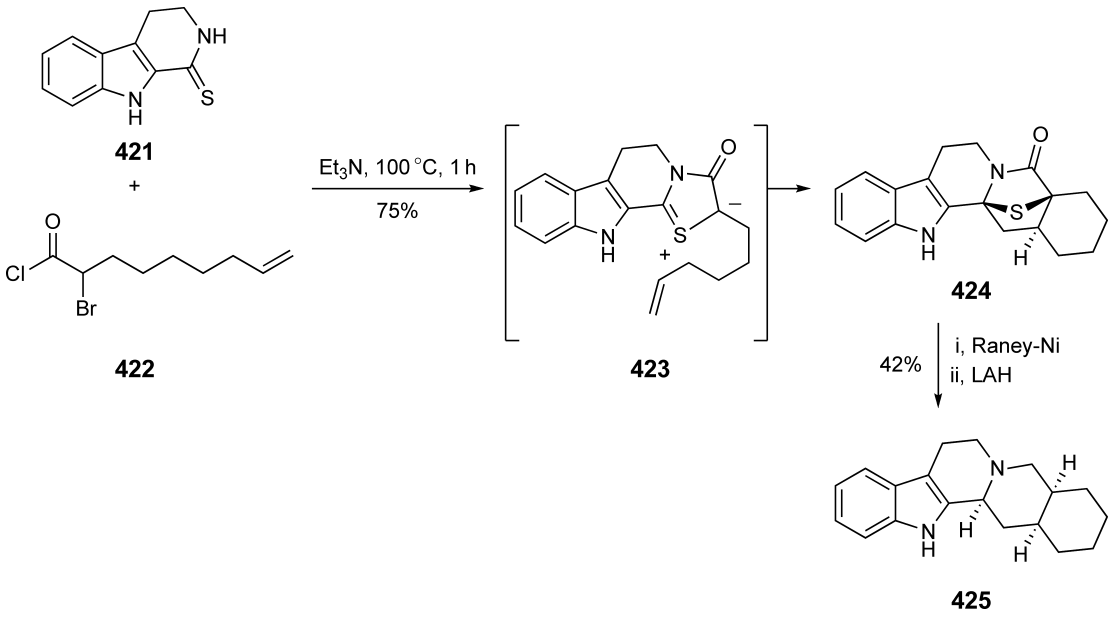
Scheme 107

Partially saturated derivatives can also be prepared through aryl radical cyclization of *N*-2-halobenzoyl cyclic ketene-*N*,*S*-acetals <2005TL3801>. In this event, treatment of ketene-acetal **418** with Bu_3SnH afforded good yield of cyclized products **419** and **420**, as a mixture of two diastereoisomers, but with a total regioselectivity (**Scheme 108**).



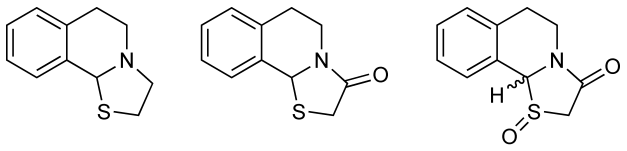
Scheme 108

An elegant one-pot bicycloannulation method for the synthesis of tetrahydroisoquinoline systems has been disclosed by Pawda *et al.* <1998TL4757, 2000JOC2684>. This method generates a transient thioisomünchnone **423** that undergoes an intramolecular dipolar cycloaddition. The thus obtained cycloadduct **424** is next reduced with Raney-Ni, followed by LAH to furnish (±)-alloyohimbane **425** in 31% overall yield from **421** (**Scheme 109**).



Scheme 109

A series of thiazolo[2,3-*a*]isoquinolines **426**, 3-one derivatives **427**, and *S*-oxide derivatives **428** have been studied in detail as regard to their spectroscopic properties <2001T3499, 2002TA2329, 2003T1173>. These compounds have been prepared using previously reported chemistry. One of the 3-one derivatives **427** was prepared in enantiomerically pure form and therefore gave access to optically enriched **428**. Isolated diastereoisomers of this *S*-oxide were however found to be unstable and to epimerize to give a thermodynamic mixture of *syn*- and *anti*-diastereoisomers. This epimerization was accompanied by a racemization (**Scheme 110**).

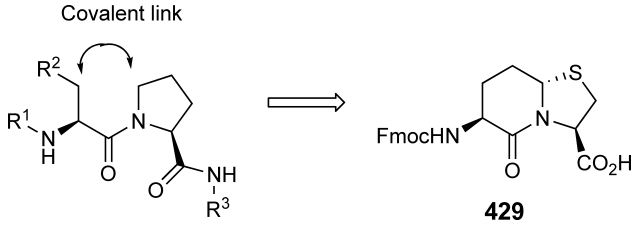


426 **427** **428**

Scheme 110

10.10.8.3 Important Compounds and Applications

The addition of a covalent link between C5 of proline ring and the adjacent amino acid locks the amide bond into the *trans* configuration. This strategy has been thoroughly used for the modification of bioactive peptides, and the bicyclic thiolactam **429** has proved to be a very good tool for this purpose (**Scheme 111**). This compound is stable towards epimerization under physiological conditions, and is furthermore commercially available from Neosystem company (SNPE North America LLC): Fmoc-BTD, catalog number FB02601. Therefore, an important amount of work has been devoted for the preparation of modified peptides derived from this scaffold <1997BML331, 1998JME3664, 2002BML733, 2004BML6129>.

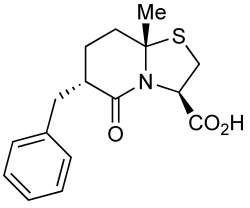
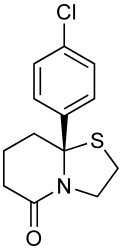


429

Scheme 111

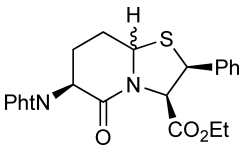
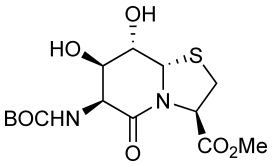
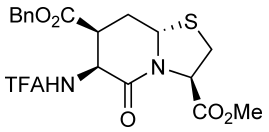
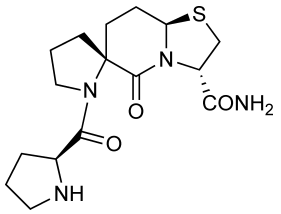
A number of compounds derived from the basic peptidomimetic **429** have been prepared for different purposes in medicinal chemistry. In most cases, the source of the sulfur atom is cysteine. Some examples of structures and targeted applications are reported in **Table 17**.

Table 17 Structure of some peptidomimetics based on fully saturated thiazolo[3,2-*a*]pyridine skeleton

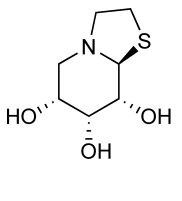
Structure	*Application*	*References*
	Substrate for the design of thrombin inhibitors	1999BML913, 1997TL8807
	Hypoglycemic agent	1998JME4556

(*Continued*)

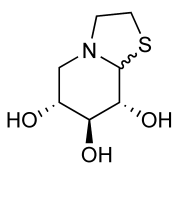
Table 17 (Continued)

Structure	*Application*	*References*
	Leu-enkephalin analogues	2003CC1598
	Carbohydrate-derived peptidomimetic	2003EJO878
	Asp-Gly dipeptide mimetic	2004TL3245
	Peptidomimetic of L-propyl-L-leucyl-glycinamide	1999JME628

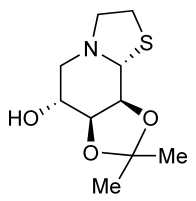
Polyhydroxylated indolizidines have attracted considerable interest due to their potent activity as glycosidase inhibitors. Some analogues of these molecules bearing a sulfur instead of a carbon atom at the anomeric position such as **430–432** have been prepared (**Scheme 112**). Compound **431** was shown to give a 3/7 mixture of epimers at the anomeric position in D_2O.



430
<1996TL49>



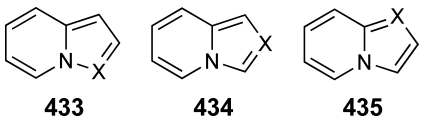
431
<1999T6759>



432
<1997TA3223>

10.10.9 Systems Containing a Less Common Heteroatom

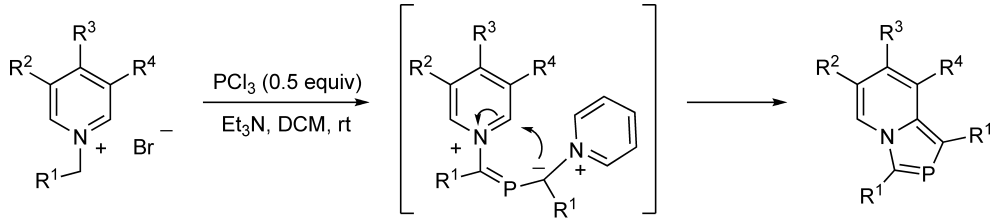
Fully conjugated systems of general formula **433**, **434**, or **435** depicted in **Figure 8**, in which X = P, As, or Se^+ have not been reported to our knowledge in literature in the past decade (1996–2006), though some examples have been reported in CHEC-II(1996) <1996CHEC-II(8)285>.



433 **434** **435**

Figure 8

In fact, a single series of phosphorus-based heterocyclic compounds, 1,3-azaphospholo[5,1-*a*]isoquinolines (**435**: X = P), was reported together with their preparation through 1,5-electrocyclization of bis-(*N*-pyridinium ylidyl)phosphenium chlorides **437**, as shown in **Scheme 113** <1999TL1565>.



436 **437** **438**

$R^1 = CO_2Me$; $R^2 = R^3 = R^4 = H$ (57%)
$R^1 = CO_2Me$; $R^2 = Me$; $R^3 = R^4 = H$ (74%)
$R^1 = CO_2Me$; $R^2 = R^4 = H$; $R^3 = Me$ (18%)
$R^1 = CO_2Me$; $R^2 = R^4 = Me$; $R^3 = H$ (51%)

Scheme 113

Later on, it was demonstrated that these heterocycles can undergo Diels–Alder reactions in the presence of an electrophile (S_8 or MeI) and dienophiles <2002T1573, 2003HAC560>. These phosphorus-containing heterocycles were found to produce, upon reaction with tricarbonyl(cycloheptatriene)molybdenum(0) or tricarbonyl(mesitylene) tungsten(0), σ-complexes of the type $L_2M(CO)_4$ or $L_3M(CO)_3$ instead of π-complexes <1998EJI1079>. Some derivatives of this heterocycle were also found to display remarkable antibacterial activity <2005BML937>.

Further Developments

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