12.06
1,4-Diazepines

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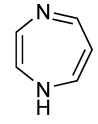
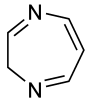
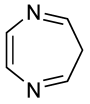
12.06.1 Introduction

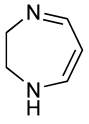
The clinical importance and commercial success associated with the 1,4-benzodiazepine class of central nervous system (CNS)-active agents and the utility of 1,4-diazepines as peptidomimetic scaffolds have led to their recognition by the medicinal chemistry community as privileged structures. This ring system has demonstrated considerable utility in drug design, with derivatives demonstrating a wide range of biological activities. As a consequence, there is an abiding interest in developing a deeper understanding of conformational preferences associated with 1,4-diazepines that permits more effective control of conformer populations with a view to broadening the potential applications. In concert with this, the development of new synthetic approaches to the 1,4-diazepine ring system and their further elaboration have provided access to a broad range of functionalized derivatives that have contributed to advances in understanding the underlying principles of structure and reactivity. In this chapter, the outlines followed by CHEC(1984) <1984CHEC(7)593> and CHEC-II(1996) <1996CHEC-II(9)151> are followed with additional sections as appropriate to reflect developments in the area. This summary augments the literature summarized in CHEC(1984) and CHEC-II(1996), adding examples of new topological ring constructions and updating previously discussed disconnections where new methodology or reagents have been developed that enhance the value of the process. The examples cited are drawn from the literature published between 1995 and the end of 2006 and focus on monocyclic 1,4-diazepines and their benzo-fused homologues. 1,4-Diazepines that incorporate additional fused heterocyclic rings remain an area of considerable interest but are not specifically discussed, although examples are included where such derivatives offer illustrative insights into important and useful aspects of the chemistry.

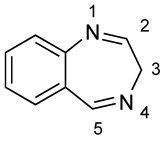
The ring numbering and nomenclature for 1,4-diazepines used in this chapter are illustrated by structures **1**–**7**.

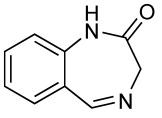

1*H*-1,4-Diazepine
1

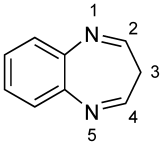

2*H*-1,4-Diazepine
2


6*H*-1,4-Diazepine
3


1*H*-2,3-Dihydro-1,4-diazepine
4


3*H*-1,4-Benzodiazepine
5


1*H*-1,4-Benzodiazepin-2(3*H*)-one
6


3*H*-1,5-Benzodiazepine
7

Reviews of 1,4-diazepines that are of interest include: general reviews <1984CHEC(7)593, 1996CHEC-II(9)151, 2004SOS929, 1997PHC(9)318, 1999PHC(11)319, 2000PHC(12)339, 2001PHC(13)340, 2003PHC(15)385, 2004PHC(16)431, 2005PHC(17)389, 2007PHC(18)402>; combinatorial approaches to benzodiazepine derivatives <1996ACR132, 2006RMC53>; 1,5-benzodiazepines and 1,5-benzodiazepinium salts <1998AHC2>.

12.06.2 Theoretical Methods

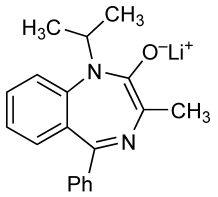
Because 1,4-diazepines have been used extensively in the design of compounds which bind to receptors or enzymes and as templates for modeling protein secondary structure, a large body of computational structural analysis has been published. However, since this material is of a specialized nature and generally limited in scope and application, it will not be discussed. In contrast, numerous studies have appeared which either introduce refinements to existing force fields, reevaluate previous computational analyses using updated, state-of-the-art methodology, or provide additional insights into diazepine conformation and reactivity. Theoretical methods focusing on understanding conformational preferences and transition state geometries in the context of experimental data in addition to the development and understanding of structure–activity relationships are discussed.

A refined set of force field parameters useful for evaluating the preferred conformations of 1,4-benzodiazepines using AMBER or other molecular mechanics programs, particularly those which also include protein and DNA parameters, has been developed <1997JCI951>. The Cambridge Crystallographic Database served as the source of equilibrium parameters while semi-empirical methods (AM1 and PM3) were used for estimating bond stretching and torsion potential force constants. Modeling of representative 1,4-benzodiazepinones accurately predicted their X-ray crystallographic structure to within 0.01 Å for bond lengths, 0.8° for bond angles, and 5° for torsional angles.

There appear to be limited studies that focus on calculating the *M*- to *P*-inversion barrier for 1,4-benzodiazepines using *ab initio* methods rather than molecular mechanics and semi-empirical approaches. To make up for this deficiency and to establish the most appropriate method for treating this ring system, the ring inversion barrier of diazepam, *N*-(1-desmethyl)diazepam, and *N*-(1-desmethyl)-3-methyldiazepam has been examined using Hartree–Fock (HF), unrestricted Hartree–Fock (UHF), and density functional theory (DFT) methods <1999CH651>. DFT appeared to be best able to predict the conformational barriers when compared to experimentally determined values. For diazepam and *N*-(1-desmethyl)diazepam, the calculated transition state energies were 17.6 and 10.9 kcal mol^{-1}, respectively, in close agreement with the experimentally measured values of 17.6 and 12.3 kcal mol^{-1}. The relative energies of the *M*- and *P*-conformations of *C*-(3-methyl)diazepam were also calculated and it was found that the 3-*(S)*-diastereomer preferred the *M*-conformer by 4.3 kcal mol^{-1}. Related to this study, a more extensive analysis of variously substituted 1,4-benzodiazepines has been performed using DFT methods in which the inversion barriers of a series of *N*-(1-substituted)-1,4-benzodiazepinones (N-1 = Me, Bn, *i*-Pr, and $CHPh_2$) were measured <2005JOC1530>. The calculated $\Delta G^{\ddagger}$ values (in dimethyl sulfoxide (DMSO)) of 16.9 (Me), 17.8 (Bn), 21.6 (*i*-Pr) and 20.8 ($CHPh_2$) kcal mol^{-1} were in good agreement with the experimentally (^{1}H nuclear magnetic resonance (NMR)) determined inversion barriers of 18.0, 19.5, 21.3, and 21.5 kcal mol^{-1}, respectively. Moreover, analysis of the geometry of the ring-inversion process identified two transition state pathways of equal energy, reflecting the maintenance of the *M*- or *P*-configuration at the transition state by the benzodiazepine ring which does not flatten during this process.

Theoretical treatment of the conformational properties of the related 1,4-benzodiazepin-2,5-dione ring system has received less attention but HF and DFT methods have been applied to examine the relative conformational energies and activation energy for the *M*-to-*P*-isomer interconversion <2004JST37>. The DFT method provided superior prediction of the bond distances and angles that were comparable to those observed by X-ray crystallography.

Ab initio methods also appear to be useful for predicting the *M- to P*-conformational transition barrier for reactive species, such as enolate **8**. It is known that the presence of an *(S)*-C3-substituent will favor the *M*-conformer in which the C-3 substituent adopts a pseudoequatorial arrangement. Consequently, deprotonation of C-3 at low temperature of certain benzodiazepines can result in single, conformationally chiral, nonracemic enolates locked in the *M*-configuration. The inversion barrier for enolate **8** at 195 K is calculated by DFT methods to be 17.5 kcal mol^{-1}, which compares with 12.4 kcal mol^{-1} for the derivative where the N-1 group is methyl instead of isopropyl <2003JA11482>. These results were used to explain the enantioselective C-3-alkylation method discussed in Section 12.06.4.3. A similar analysis of a C-3,N-4-pyrrolo-fused derivative calculated an interconversion energy of 12.2 kcal mol^{-1} <2005OL5305>.



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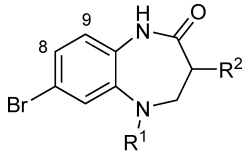
The base-mediated alkylation of (*S*)-3-methyl-4,5-dihydro-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one with aminoethyl chlorides occurred at the more acidic amide moiety under conventional heating in dimethylformamide (DMF) for several hours using excess K_2CO_3 as the base <2006TL3357>. However, brief (90 s) microwave heating resulted in the alkylation being redirected to occur with complete regiospecificity at N-4. Rationalization was sought by conducting *ab initio* calculations (MP2/6-31G* and HF/6-31G*) which indicated that deprotonation is the rate-limiting step for alkylation at N-4 while formation of the N(1)–C bond is rate limiting for the reaction at N1. The microwave conditions lead to greater anion production that is slightly biased toward the higher-energy N-4 anion, which reacts more rapidly than the N-1 anion, leading to functionalization specifically at N-4. This is facilitated by the larger change in dipole moment associated with deprotonation at N-4, a pathway known to be favored under microwave irradiation.

The regioselectivity associated with the nitration of the 7-bromo-1,5-benzodiazepinone **9**, which occurred at C-8 and C-9, was examined by considering the relative atomic charge densities, total p_Z electron population, and the electron population density of the highest occupied molecular orbital (HOMO) at each site. The π-localization energy of the two C-8 and C-9 nitration transition state σ-complexes was better able to predict the observed ratio of products, which favors nitration at C-9 by 3:1 <2003M1629, 2004HAC263>.



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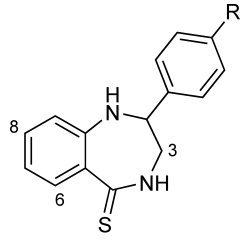
12.06.3 Experimental Structural Methods

The most powerful spectroscopic method for determining structural connectivity and conformational analysis of fused and nonfused 1,4-diazepine rings is NMR, and this technique has been used extensively. Mass spectral data have also been exploited to provide insight into structure based on an analysis of fragmentation patterns. Circular dichroism (CD) is particularly useful for assigning the absolute configuration of 1,4-benzodiazepine *M*- and *P*-atropoisomers since the *P*-isomer typically exhibits a strong negative Cotton effect at 254 nM in the CD spectrum <1997CH495>.

12.06.3.1 NMR Studies

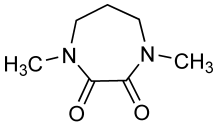
One of the more interesting aspects in the area has been the application of ^{1}H NMR spectroscopy to evaluate conformational properties of benzodiazepine and diazepine peptidomimetics; these studies are discussed in greater detail in the sections that cover specific heterocycles. Numerous papers have been published which tabulate the NMR of potentially interesting new diazepine derivatives, extending data presented in CHEC(1984) and CHEC-II(1996) <1996JHC1159, 1996JHC271, 1996MRC324, 2002JHC1321>.

The protons at C-6 and N-4 of thioamide derivatives **10** exhibit a downfield shift in the ^{1}H NMR spectrum relative to those of the corresponding C-5 amide, indicative of deshielding <2000MRC207>. The protons at C-3 and N-4 of **10** also resonate downfield, while, in contrast, the proton at C-8 is slightly shielded. The observed downfield shifts are attributed to the higher polarizability of the C═S bond leading to an increased magnetic anisotropy of this moiety. The ^{13}C NMR spectra of C-7-substituted compounds reveal a downfield shift of the thiocarbonyl carbon by 30 ppm compared to the corresponding amide while C-2 and C-3 are deshielded by 1.8–2.4 and 3–4 ppm, respectively.



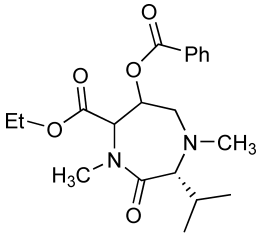
10

The effect of ring size and nitrogen substitution on the ^{17}O NMR shifts of a series of cyclic α-diamides, including the 1,4-diazepin-2,3-dione **11**, has been examined <1998JPO387>. In MeCN, the ^{17}O NMR shift for **11** resonated at 325.3 ppm, which is similar to the corresponding six-membered ring analogue, 323.0 ppm, but deshielded compared to the five-membered ring derivative, 285.5 ppm. Semi-empirical calculations suggested that the dihedral angle for the dicarbonyl unit is 78°.



11

Conformational flexibility has hindered attempts to use NMR spectroscopy to determine the relative and absolute stereochemistry associated with the substituted 1,4-diazepin-2-one ring of liposidomycin. However, stereochemical assignments were made possible by comparing NMR data for the synthetically prepared family of diastereomers of **12**. The results indicated that the relative stereochemistry of liposidomycin is consistent with either the *(R)*-C-3, *(R)*-C-6, *(R)*-C-7 or *(S)*-C-3, *(S)*-C-6, *(S)*-C-7 diastereomer <2001JOC5822>.



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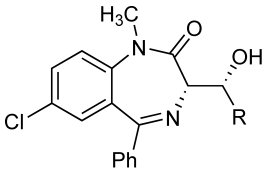
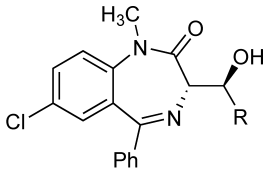
The reaction of diazepam with aldehydes at C-3 yields a mixture of *syn*- and *anti*-aldol derivatives, **13** and **14**, respectively, the relative stereochemistry of which were determined by examining the coupling constant between the C-3 -protons and the exocyclic carbinol proton. In accordance to the standard aldol reaction, the *syn*-diastereomers **13** exhibited coupling constants of ca. 5 Hz, while those for the *anti*-diastereomers **14** were ca. 9 Hz <2000HCA603>. The stereochemical assignments made using ^{1}H NMR were corroborated through single crystal X-ray analysis of representative compounds.



13 (*syn*)



14 (*anti*)

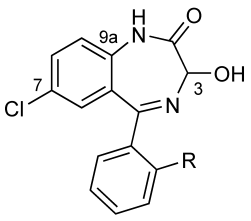
The site of deprotonation of lorazepam and oxazepam (NH vs. OH) was determined by monitoring the change in ^{13}C NMR shifts upon addition of *t*-BuOK to a solution of the compounds in DMSO <2003MI693>. Changes in ^{13}C shifts, summarized in **Table 1**, occurred mainly in the fused phenyl group rather than in the seven-membered diazepam ring, consistent with deprotonation of the amide NH. Nitrazepam and clonazepam, analogues lacking the C-3 hydroxyl, exhibited the same trend in ^{13}C NMR shifts.

12.06.3.2 Mass Spectrometry

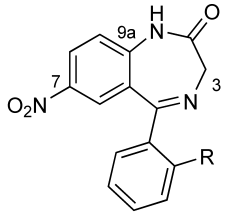
Characteristic trends in the fragmentation patterns of 1,4-benzodiazepines can be observed using ion-trap mass spectrometry (MS). For the 1,4-benzodiazepin-2-one **15**, ion fragmentation was largely dictated by the attached substituents, R^1, R^2, R^3, and R^4 <2000RCM2061>. Using collision-induced ionization (CID) spectrometry, the C-3-unsubstituted analogues were shown to eliminate CO while the hydroxylated compounds predominantly

decomposed by loss of H_2O <2001MI359>. The pyrrolo-benzodiazepine isomers **16** and **17** are difficult to distinguish since they both yield similar fragmentation patterns under low-resolution MS; however, high resolution and tandem MS showed characteristic differences in their corresponding isobaric fragment ions <1996JAM653>.

Table 1 Changes in ^{13}C shifts for substituted 1,4-benzodiazepin-2-ones upon treatment with *t*-BuOK in DMSO

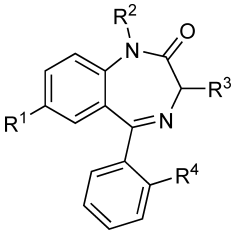


R = H (oxazepam)
R = Cl (lorazepam)



R = H (nitrazepam)
R = Cl (clonazepam)

	$\Delta\ ^{13}C$ *NMR anion – parent* (*ppm*)		
Compound	*C-7*	*C-9a*	*C-3*
Oxazepam	−5.7	+8.7	+0.2
Lorazepam	−5.5	+8.5	+0.2
Nitrazepam	−4.8	+10.0	+2.0
Clonazepam	−3.5	+7.1	+1.9



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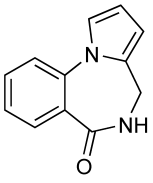

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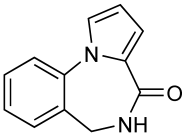

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12.06.4 Thermodynamic Aspects

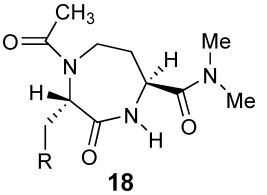
12.06.4.1 General Aspects

Fully unsaturated and conjugated 1,4-diazepines are encountered less often than partially or fully saturated 1,4-diazepines, probably because they contain $4n - \pi$ electrons and thus are not as stable as the $4n + 2 - \pi$ electron systems. Consequently, partially and fully saturated ring systems dominate the literature, and the physical properties that have been of principal interest are associated with the conformational flexibility and tautomeric lability of these heterocycles. Physical/chemical properties associated with specific molecules are discussed in the individual sections. Understanding the fundamental underlying principles of the conformation of 1,4-diazepines and 1,4-benzodiazepines is of considerable importance to the medicinal chemistry community where these ring systems enjoy the high profile accorded to a privileged scaffold. 1,4-Diazepines function as topological mimetics of certain structural elements found in peptides and modulation of the topographical disposition of substituents attached to these heterocycles is frequently critical for drug action. While conformational aspects of 1,4-benzodiazepines are well developed, study of the 1,4-diazepine ring system has proven to be far more challenging due to the inherently greater conformational mobility.

12.06.4.2 Conformation Studies – monocyclic

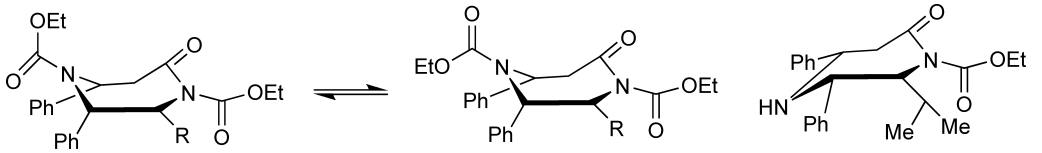
The fully saturated 1,4-diazepine heterocycle is composed of sp^3-hybridized atoms that allow torsional bond flexibility, resulting in a high degree of conformational mobility. Consequently, control of 1,4-diazepine conformation has most frequently been accomplished by annealing additional rings and/or incorporating amide bonds into the heterocyclic ring that are designed to restrict torsional freedom. Conformational bias is also influenced by nonbonded interactions between ring substituents, effects that are beginning to be explored more deeply as part of an effort to broaden the application of 1,4-diazepines in peptide mimicry. However, because the range of conformations available to monocyclic rings is large, spectroscopic analysis is complex and initial studies have been restricted to a somewhat limited set of unique ring systems and patterns of substitution. Nevertheless, these studies are providing new insights into the underlying principles and revealing additional aspects that facilitate some predictivity, although much remains to be understood.

Extensive analysis of ^1H and ^{13}C NMR data combined with computer simulation studies indicate that the trisubstituted 1,4-diazepine-3-one peptidomimetic **18** adopts a boat conformation in which the C-2 substituent, $PhCH_2$ or CH_3, adopts a pseudoaxial arrangement to avoid steric interactions with the N–Ac moiety. The limitations in conformational space available to the ring substituents resulted in an opposed alignment of the N–Ac methyl group and the C-2 substituent, which project into complementary planes of the ring in a fashion that is determined by the absolute configuration at C-2 <1997JA2430>.



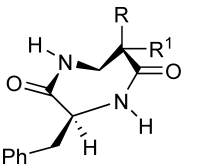
18

The 1,4-diazepine-5-one derivative **19** with R = H or Me adopts a flattened boat conformation that orients the two phenyl groups in a quasi-axial arrangement. This allows the N-1 CO_2Et to undergo rotameric interconversion that is rapid on the NMR timescale, where the barriers were determined to be 11.93 (R = H) and 13.86 (R = Me) kcal mol^{-1}, respectively. In contrast, the rotational barrier for the corresponding *N*-nitroso and *N*-formyl derivatives is considerably higher, >20 kcal mol^{-1}, indicating lower N–C double-bond character for the carbamate **19** <1997JOC7984>. Removal of the N-1 CO_2Et moiety, studied with the 3-isopropyl derivative **20**, relieves steric interactions, allowing the ring to adopt a preferred chair conformation in which the two phenyl groups are equatorial and the C(3)–N(4) bond is partially twisted to relieve allylic 1,3-strain between the *i*-Pr and imidic N–CO_2Et moiety.

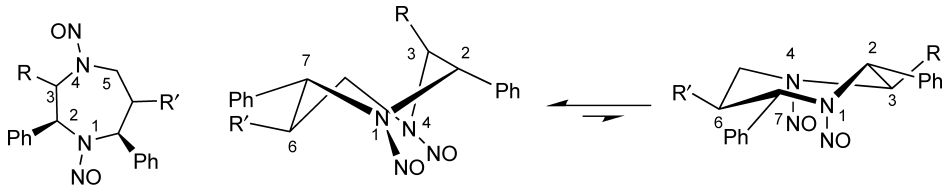


19 **20**

The 3-benzyl-6-phenyl-1,4-diazepine-2,5-diones **21** and **22** exhibited complex NMR spectra indicative of limited conformational mobility in which the ring geometry is dictated by the two *cis*-amide elements, which define individual planes <2003MI187>. Based on an analysis of the nuclear Overhauser effect (NOE) between protons on the ring, the preferred boat conformation in solution projects the 3-benzyl moiety pseudoequatorially with the 6-phenyl substituent disposed axially or equatorially, dependent upon the relative stereochemistry. This conformation is also observed in the solid state for the *cis*-substituted isomer **21** in which the phenyl group is axial. In contrast, the bis-phenyl derivative **23** is conformationally mobile based on the ^1H NMR spectrum where resonances were not resolved.



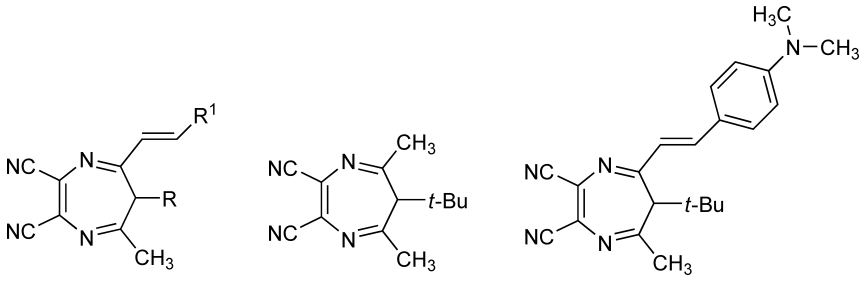
20: R = H; R^1 = Ph
21: R = Ph; R^1 = H
22: R = R^2 = Ph



23

The absence of Bohlmann bands in the infrared (IR) spectrum indicates that the nitrogen lone pairs of the di-*N*-nitroso-1,4-diazepines **23** are delocalized <1995JOC7461>. While the absence of an amide moiety in the ring confers torsional freedom, the *cis*-2,7-di-Ph groups reduce ring flexibility and the ^{1}H NMR data are consistent with major and minor families of four twist chair conformers that project the C-7 Ph and C-6 R′-substituents equatorially. These interconvert by a pseudorotation that allows the C-2 phenyl and C-3 R substituents to adopt a pseudoaxial orientation in the preferred conformer family.

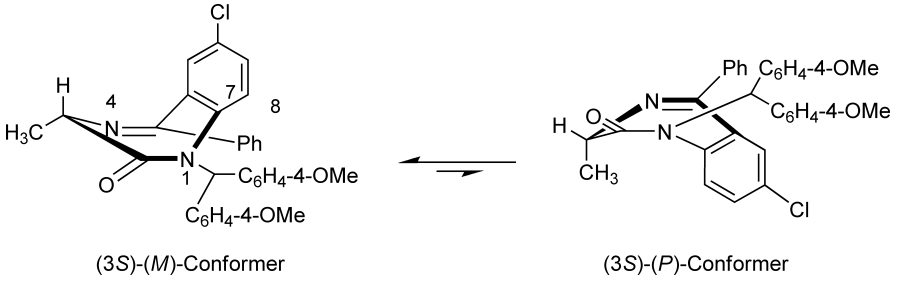
Conformational aspects of more highly unsaturated 1,4-diazepines have been examined in the context of trisubstituted 1,4-diazepine-2,3-dicarbonitrile **24** <2005BCJ316, 2005BCJ1167, 2004CL170>. Monoethylene derivatives of **24** in which R is an alkyl group exist as a mixture of diastereomers as a consequence of the C-6 chiral center and ring atropoisomerism. These compounds typically prefer a conformation in which the C-6 substituent is in the equatorially disposed position. However, the C-6 *t*-butyl derivative of the 5,7-dimethyl-1,4-diazepine **25** was observed to be a mixture of axial and equatorial isomers in a ratio of 2:3, attributed to unfavorable steric interactions with the C-5 and C-7 methyl groups <2005BCJ1167>. These became more dominant with unsaturated exocyclic substituents, exemplified by the styryl derivative **26** where the *t*-butyl moiety was exclusively in the axial position.



24 **25** **26**

12.06.4.3 Conformation Studies – 1,4-Benzodiazepines

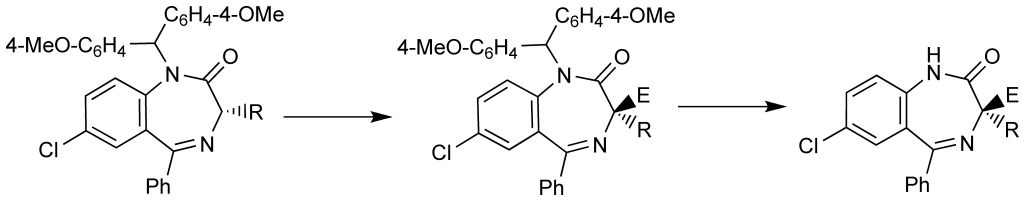
The 2,3-dihydro-1*H*-1,4-benzodiazepin-2-ones exist as an equilibrium mixture of two conformers, designated by the helical descriptors (*M*) and (*P*), that reflect chirality associated with the *R*-N(1)-C(7)-C(8) dihedral angle (**Scheme 1**). The interconversion barrier between the *M*- and *P*- atropoisomers is dependent upon the size of the N-1 substituent with $\Delta G^{\ddagger} = 12.3$, 18.0, 21.1, and >24 kcal mol^{-1} for H, Me, *i*-propyl, and *t*-butyl, respectively, a function of increasing



Scheme 1

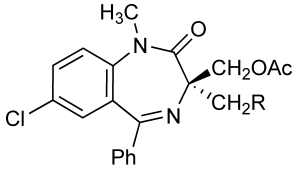
nonbonded *peri*-interactions with the substituent at C-9 <2005JOC1530, 1999CH651, 2005S1>. Atropoisomers with interconversion barriers of $>20\,kcal\,mol^{-1}$ can be separated chromatographically and have been shown to be differentiated by both biological receptors and human serum albumin <1997CH495, 2000JA460>.

Substituents at C-3 typically prefer an equatorial disposition with the absolute configuration influencing conformational bias such that a 3-(*S*)-derivative adopts the *M*-conformation. The 3-(*S*)-methyl derivative of an *N*-(1-substituted)-7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one can be deprotonated and alkylated at C-3 with preservation of chirality, the electrophile approaching C-3 *syn* to the aryl ring in a contrasteric fashion <2005S1>. The success of this process, referred to as memory of chirality, depends upon the conformational stability of the nonracemic enolate, which is critically dependent on the size of the N-1 substituent and the temperature at which the reaction is conducted <2003JA11482, 2005TA2998, 2005S1, 2006JA15215>. A di(*p*-anisyl)methyl (DAM) substituent at N-1 combines excellent conformational control of the enolate with high chemical reactivity toward a range of electrophiles (**Scheme 2**) <2006JA15215>. For the C-3 methyl derivative, KHDMS and hexamethylphosphoramide (HMPA) in tetrahydrofuran (THF) at −78 °C were used to generate the enolate, providing products in good yield (65–96%) and with high enantioselectivity, ee ranging from 96% to >99.5%. For the C-3 ethyl, benzyl, and CH_2CH_2SMe homologues, yields were considerably poorer under these conditions; however, the use of 1,2-dimethoxyethane (DME) rather than THF as solvent and conducting the reaction at −42 °C gave acceptable chemical yields (33–80%) with ee ranging from 72% to >99% <2006JA15215>. The N-alkylated quaternary derivatives, which have been the subject of only limited study, are mixtures of conformers that interconvert slowly on the NMR timescale while the *M*- and *P*-forms of the NH derivatives, obtained by removal of the DAM moiety under acidic conditions, exist in rapid equilibrium. The 3-CN derivatives appear to be an exception, with this substituent preferring an axial orientation, apparently for steric reasons.



Scheme 2

The preferred conformation of chiral C-3-disubstituted, 1,4-benzodiazepine-2-ones depends not only on the identity of the substituents but is also influenced by solvent polarity <1999T1407>. The optically pure alcohol (−)-**27** exists in $CDCl_3$ and DMSO-d_6 as a single isomer that is the same in both solvents and was determined to be the *P*-conformer based on the strong negative Cotton effect at 260 nM in the CD curve, obtained in MeCN. The smaller CH_2OH moiety adopts an axial orientation, since the CH_2 protons resonate at low field, shielded by the ring current associated with the proximal annulated benzene ring, while the CH_2 protons of the CH_2OAc element resonate consistent with an equatorial disposition, derived by comparison with ^1H NMR spectra of the corresponding achiral diol and diacetate. These data allow the absolute configuration of **27** to be designated as the 3-(*R*)-isomer. In contrast, the tosylate **28** and chloride **29** exist as equilibrium mixtures of atropoisomers in both polar and nonpolar solvents. The *P*-isomer of **28**, in which CH_2OTs is axial, is prevalent in both solvents, although somewhat more so in $CDCl_3$, while for **29**, the *P*-isomer is favored over the *M*-isomer by 70:30 in $CDCl_3$ but reversed to 30:70 in DMSO-d_6.

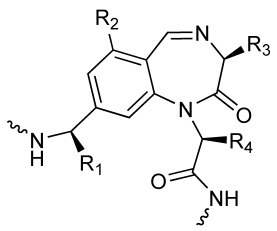


27: R = OH
28: R = O-*p*-Ts
29: R = Cl

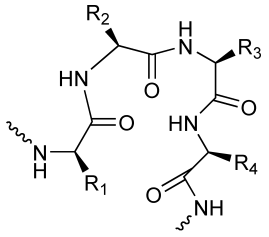
The calculated interconversion barriers between the *M*- and *P*-forms of 3,4-dihydro-1*H*-benzo[1,4]diazepine-2,5-diones depend on the size of the N-1 substituent but not the C-3 and N-4 substituents <2004JST37>. The

atropoisomers of a N-1 *t*-butyl 1,4-benzodiazepine-2,5-dione derivative, in which the inversion barrier was calculated to be >23 kcal mol^{-1}, were separated by chromatography but equilibrated over 24 h <1997JMC717>. Atropoisomers of the N-1 Me analogue, predicted to have a $\Delta G^{\#} = 17$ kcal mol^{-1}, could be separated only when a chlorine atom was introduced at C-9, where the calculated inversion barrier was increased to 23 kcal mol^{-1}, confirming the importance of *peri*-interactions in controlling equilibration. However, this compound also racemized over 24 h. The combination of a N-1 *t*-butyl moiety with a C-9 Cl gave stable atropoisomers, with one demonstrating higher binding affinity for the platelet glycoprotein IIb/IIIa receptor <1997JME717>.

The 1,4-benzodiazepines have been classified as type III mimetics of peptide motifs based on their ability to project functional groups important for molecular recognition in a topologically similar fashion to that of structurally defined protein domains (e.g., β- or γ-turns and α-helices). As depicted in the 1,4-benzodiazepin-2-one **30**, the substituents at C-8, C-6, C-3, and N-1 topologically mimic the Cα substituents of a four-residue β-turn, represented by **31**. Additionally, C-5 substituents are projected toward the region in space occupied by the C-6 substituent, providing a second vector to access this α-side chain element of the β-turn <1993T3593, 2006MI321>. In order to more fully understand the topographical similarities between the heterocycle scaffold and β-turn structure, the two atropoisomeric conformers of the 1,4-benzodiazapin-2-one derivatives **30** and the C-3 enantiomers were modeled in SYBYL 7.1 and fully minimized using the MM3 module. Comparing all of the conformers available to the N-1 and C-8 substituents with experimental and modeled β-turn structures revealed that the side-chain orientations of the four residues of type I, II, III, IV, and VI reverse turns could be readily accessed by the 1,4-benzodizapin-2-one scaffold with only small root-mean-square deviations. However, a single diastereomer can mimic one or more but not all of the experimental β-turn structures. This observation, which does not take account of the relative energy differences between the conformers, provided a rationale for selecting specific patterns of substitution that approximate unique orientations and might be further optimized by the introduction of additional conformation-influencing elements <2006MI321>.



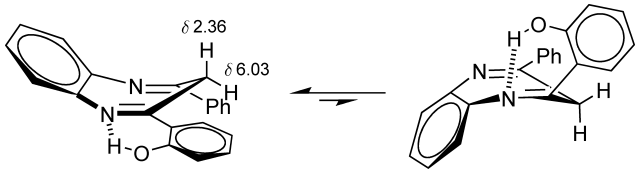
30



31

12.06.4.4 Conformational Studies – 1,5-Benzodiazepines

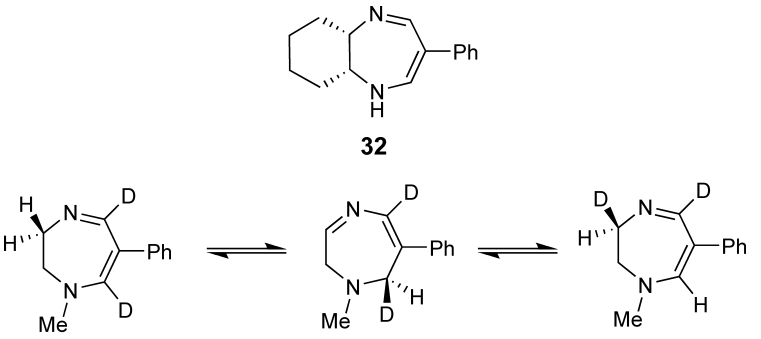
The 2,4-diphenyl-1,5-benzodiazepines interconvert between two boat conformations with the conformer in which the two phenyl groups are pseudoequatorial predominating <1997M633>. The calculated interconversion barrier is ~13 kcal mol^{-1}, rapid on the NMR timescale at 323 K, but slower at 233 K, where the C-3 protons split into doublets, $J_{gem} \sim 11.5$ Hz. The equatorial proton is deshielded by the C-4 aryl ring π-electron current and the axial proton shielded by the annulated benzene ring <1997M633>. The interconversion barrier between the two phenols depicted in **Scheme 3** was calculated from NMR data to be 12.97 kcal mol^{-1}, similar to the 12.61 kcal mol^{-1} calculated for the unsubstituted parent, suggesting that the intramolecular hydrogen bond is preserved during the ring inversion.



Scheme 3

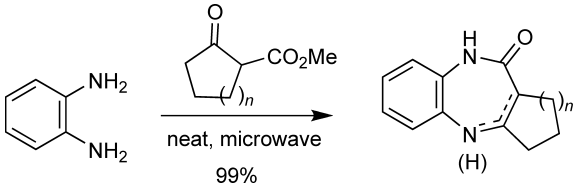
12.06.4.5 Tautomers

Tautomeric rearrangement of unsaturated 1,4-diazepines and benzo-fused homologues occurs under thermal conditions or where extended conjugation lowers the overall energy of the system. Amide and thioamide derivatives of benzodiazepinones have been shown to exist in the oxo form with no evidence for the OH or SH tautomers, even in substrates where there exists the potential for conjugation <2000AHC1>. Similarly, 1,5-benzodiazepine-2,4-dione exists as the dioxo form. However, imines, both within and exocyclic to the ring, will tautomerize to allow conjugation or satisfy opportunities to engage in intra- or intermolecular hydrogen bonding. Flash vacuum pyrolysis (FVP) of the *cis*-fused 2,3-dihydro-1,4-diazepine **32** at temperatures above 450 °C produced the *trans*-fused isomer, as detected by ^{13}C NMR, attributed to imine tautomerization <1995CC2337>. FVP of the deuterium-labeled 2,3-dihydro-1,4-diazepine **33** at 450–500 °C resulted in sequential, suprafacial 1,5-sigmatropic shifts that resulted in rearrangement of hydrogen and deuterium atoms (**Scheme 4**). At higher temperatures, ring contraction to a quinoxaline occurred, presumably via radical intermediates.

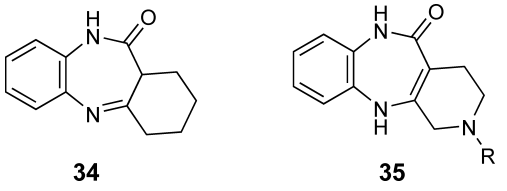


Scheme 4

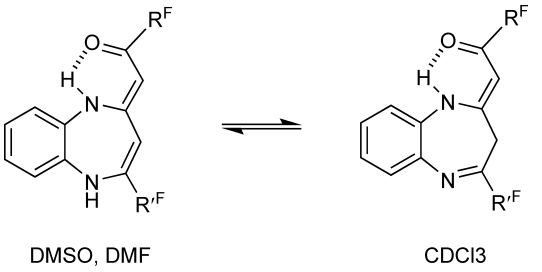
The preferred tautomer of the products derived from the condensation reaction of phenylenediamine with cyclic β-keto esters (**Scheme 5**) is highly dependent on the structure of the β-ketoester <2005JHC1001>. ^{1}H and ^{13}C NMR analysis of the 1,5-benzodiazepin-2-one **34**, formed from methyl 2-oxocyclohexanecarboxylate under microwave conditions, indicated the presence of the C(4)–N(5) imine <2005JHC1001>. In contrast, the products arising from condensation with methyl 2-oxocyclopentanecarboxylate and methyl 1-alkyl-4-oxopiperidine-3-carboxylates were found to be in the enamine form **35**.



Scheme 5

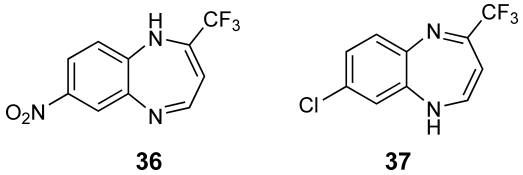


Polyfluoroacyl-containing 1,5-benzodiazepines, prepared from phenylenediamine and fluorinated 1,3,5-triketones, were isolated as mixtures of imine and enamine tautomers based on detailed ^{1}H, ^{13}C, and ^{19}F NMR analysis <2004M23>. The position of equilibrium was independent of the fluoroalkyl moiety but sensitive to solvent, with the imine tautomer favored to the extent of 85–96% in nonpolar $CDCl_3$ after 3 weeks of equilibration (**Scheme 6**). In DMSO and DMF, equilibration was rapid, strongly favoring the enamine tautomer that is stabilized by a hydrogen bond between the enamine NH and solvent <2004M23>. An intramolecular hydrogen bond stabilizes the (*Z*)-form of the enone moiety, a circumstance similar to that seen with a structurally homologous ester <2001TL3227>.



Scheme 6

It is known that completely unsaturated 1,5-benzodiazepines favor the bis-imine tautomer due to the $4n-\pi$ nature of the completely conjugated seven-member ring. However, tautomer preference in this ring system can also be influenced by substituents on the aromatic ring with powerful electron-withdrawing NO_2 and PhCO groups at C-7 stabilizing the 1*H* species **36**, while, chlorine and methyl substituents afforded the 5*H* tautomer **37**. The two isomers are readily differentiated by analyzing coupling patterns in the ^{1}H NMR spectrum and the effects of D_2O on resonance multiplicity <1996TL2845>.

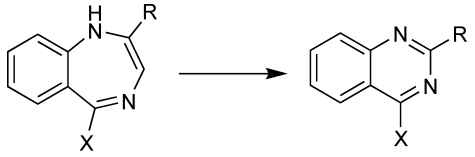


36 **37**

12.06.5 Reactivity of Fully Conjugated Rings (Unsaturated Rings)

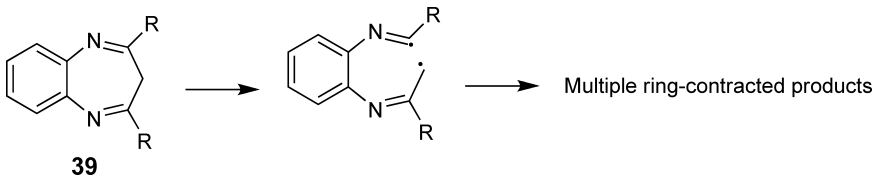
With the exception of ring-contraction reactions that are discussed below, new insights into the reactivity of fully unsaturated diazepine ring systems that add to the current level of understanding have been limited.

Ring-contraction studies that have previously been focused on saturated diazepine ring systems have been extended to fully unsaturated templates. The thermal ring contraction of **38** (X = OMe or NMe_2), conducted at ≤180 °C, appears to be the first example of this type of reaction for unsaturated diazepines, as depicted in **Scheme 7** <1999H(51)2409>. At the much higher temperatures associated with FVP, >800 °C, decomposition of 2,4-dimethyl- or 2,4-diphenyl-1,5-benzodiazepines **39** occurred to produce multiple ring-contracted products that can be traced mechanistically to homolysis of the C(2)–C(3) bond (**Scheme 8**) <1998T9667>; however, subsequent pathways differ for the two compounds, as might be expected.



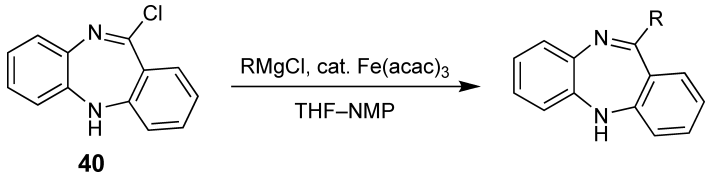
38

Scheme 7



Scheme 8

The application of transition metal catalysis provided new opportunities to introduce diverse functionality to the diazepine ring system. Iron-catalyzed cross-coupling of Grignard reagents with the imidoyl chloride **40** provided a convenient and efficient method for substituting the heterocyclic ring (**Scheme 9**) <2006OL1771>.



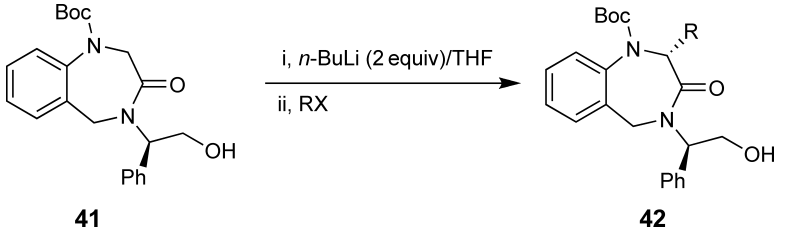
Scheme 9

12.06.6 Reactivity of Nonconjugated Rings (Saturated Rings)

This section is expanded compared to CHEC(1984) and CHEC-II(1996) and is organized according to the ring atom under discussion, starting with the carbon atom at C-2 and proceeding in ascending order before discussing reactivity at the ring nitrogen atoms.

12.06.6.1 Reaction at C-2

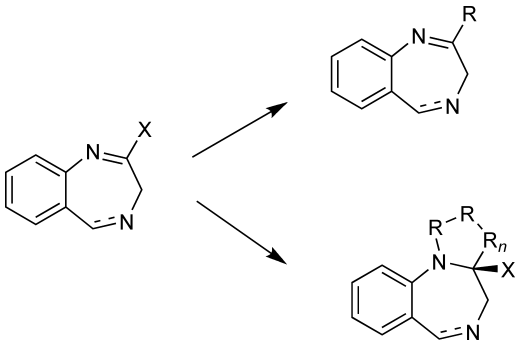
Highly diastereoselective alkylation at C-2 of benzo-1,4-diazepin-3-ones **41** was accomplished in 40–85% chemical yield using an (*R*)-phenylglycinol moiety at N-4, as the chirality-inducing element (**Scheme 10**) <2005EJO1590>. The optimum conditions involve deprotonation of **41** with 2 equiv of *n*-BuLi at −40 °C and alkylation at −78 °C to give products **42** with 86–96% de. A single crystal X-ray diffraction analysis of the methylated derivative determined that the major product formed was the 2-(*R*)-isomer, as depicted in the product **42**.



Scheme 10

The C-2 position is readily manipulated when in the oxidized amide form where conversion to an imino chloride, an imino phosphate, or a thioamide allows introduction of a range of nucleophiles at C-2 or promotes cycloaddition reactions across the N(1)–C(2) bond with concomitant loss of the C-2 leaving group (**Scheme 11**). N(1)–C(2) imines are electrophilic, with reactivity influenced by the size of the substituent at C-2. A hydrogen atom at C-2 provides the basis for the biological activity associated with the pyrrolo[2,1-*c*][1,4]benzodiazepine class of antitumor antibiotic where the N(1)–C(2) imine reacts with N-2 of guanine in the minor groove of DNA <1994CRV433>. A 2-methyl-substituted imine was reduced diastereoselectively to the amine with $NaBH_4$ or diisobutylaluminum (DIBAL), affording a 3:1 ratio favoring the

(*R*)-isomer in a reaction where chirality was transferred from a (*R*)-α-phenylmethyl substituent at N-4 <2004TA687>. The imine double bond of a 1,4-diazepin-5-one can be introduced by oxidation of the saturated amine using tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO), as the co-oxidant <1997T3223>.

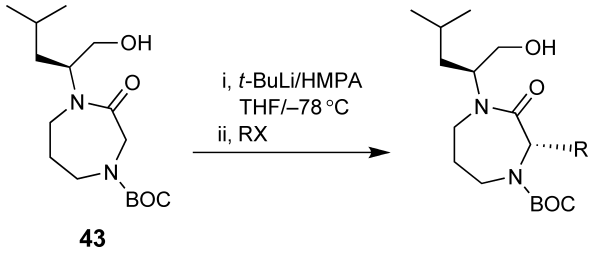


Scheme 11

Relatively simple imino chlorides are quite reactive and, although sensitive to hydrolytic decomposition, structurally novel and synthetically useful examples have been isolated and characterized by single X-ray crystallographic analysis <2001TL5183, 2003TL2425>. A cross-coupling reaction broadens the range of nucleophiles that can be introduced at a C-2 iminoyl chloride to include Grignard reagents in a reaction catalyzed by $Fe(acac)_3$ (acac = acetylacetonate) <2006OL1771>. An *N*-methyl-*N*-nitroso moiety offers a useful and chemically stable alternative leaving group to chlorine, reacting with tosylmethyl isocyanide (TOSMIC) to introduce a 2,3-fused imidazole ring <2004S2697>.

12.06.6.2 Reaction at C-3

Treatment of the 3-oxo-1,4-diazepane **43** with 2 equiv of *t*-BuLi in THF at −78 °C in the presence of HMPA generated a dianion, which was alkylated at the enolate with MeI, benzyl bromide, and allyl bromide to give single diastereomeric products in modest yield (47–53%) (**Scheme 12**) <1997TL5809>. The absolute configuration of the benzylated compound was established as (*S*) by X-ray crystallographic analysis.

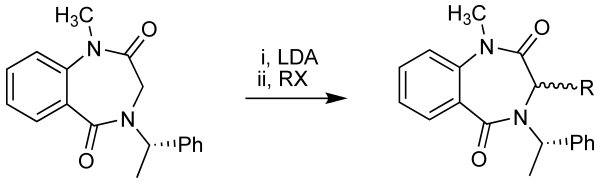


43

Scheme 12

The introduction of electrophiles at C-3 of 1,4-benzodiazepinone derivatives can be accomplished with high diastereoselectivity by taking advantage either of the inherent atropoisomeric chirality of the ring or an appended chiral inducing element, processes that have been established for almost all of the amide isomers. 1,2-Dihydro-1,4-benzodiazepine-2-ones were readily deprotonated at C-3 to generate enolates and these species were reacted with a range of electrophiles, providing access to compounds suitable for further elaboration or to amino acid derivatives after hydrolysis. High levels of asymmetry can be introduced on both C-3-unsubstituted and C-3 monoalkylated compounds, which incorporate bulky N-1 substituents, as discussed in Section 12.06.4.2 <2005TA2998, 2003JA11482, 2006JA15215, 2005S1>. The phosphonium ylide $(Me_2N)_3PC(Me)_2$, easily prepared by alkylation of $(Me_2N)_3P$ with 2-iodopropane followed by deprotonation with *n*-BuLi and extraction into pentane, is an effective base for the C-3 alkylation of *N*-(1-alkylated)-1,4-benzodiazepine-2-ones, providing products, as single diastereomers, under mild conditions <1999JOC3741>.

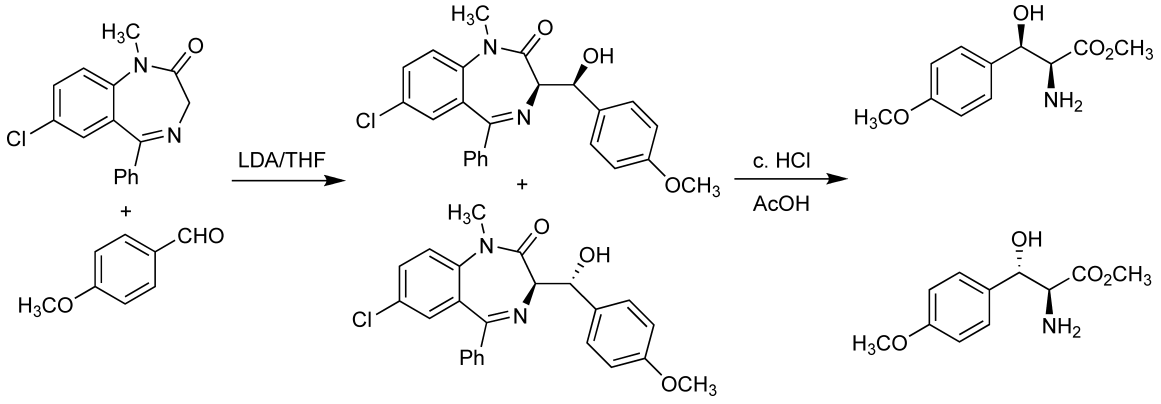
Alkylation of the benzo-1,4-diazepine-2,5-dione **44** occurred in good chemical yield but with moderate and unpredictable diastereoselection (**Scheme 13**) <1999JOC2914>. Although both the yield and de were improved in the presence of excess HMPA, the inclusion of LiCl, as an additive, led to a significant erosion of de. These results could not be rationalized after theoretical analysis of transition state geometries.



44

Scheme 13

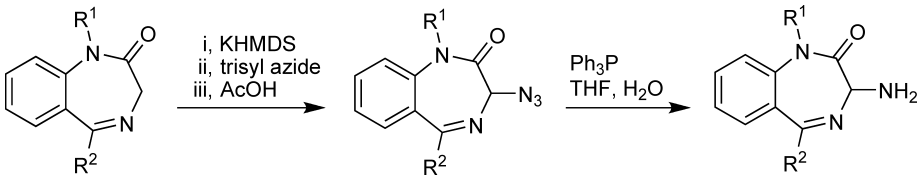
Aldol reactions at C-3 of benzo-1,4-diazepin-2-ones have been examined with both aliphatic and aromatic aldehyde partners and generally proceed in good yield <2000HCA603>. Diastereoselectivity is high for aliphatic aldehydes, affording a racemic mixture of *threo*/*erythro*-adducts with ratios ranging from 11:89 to 6:94, but considerably poorer for aromatic aldehydes, where ratios ranged from 30:70 to 55:45. The structures of the products were established by ^{1}H NMR analysis and confirmed by X-ray crystallography. With α-methylcinnamaldehydes, the slower-moving product on reverse-phase high-performance liquid chromatography (HPLC) was determined to be the racemic *erythro*-diastereomer, formed under kinetic control, while the more mobile *threo*-isomer predominated under equilibrating conditions <2003HCA2247>. The HPLC mobility of the *erythro*-isomer was attributed to a strong intramolecular hydrogen bond between the hydroxyl and amide carbonyl that reduces overall polarity. This chemistry was utilized to synthesize β-hydroxyphenylalanine derivatives as precursors to isomers of the naturally occurring cytokine modulator cytoxazone (**Scheme 14**) <2003S375>.



Scheme 14

A simple and efficient procedure for the direct oxidation of C-3 of 1,4-benzodiazepin-2-ones, applicable to the preparation of the anxiolytic agents oxazepam and lorazepam, has been developed that represents an improvement over the well-established Polonovsky rearrangement of the N-4 oxide <2006OPD1192>. Iodine in AcOH at 65 °C catalyzed acetoxylation in a reaction that involved iodination at C-3 followed by a rapid nucleophilic displacement by KOAc. The liberated HI was recycled to iodine by inclusion of a stoichiometric oxidant, with $K_2S_2O_8$ being the optimal compromise of cost, availability, and efficiency.

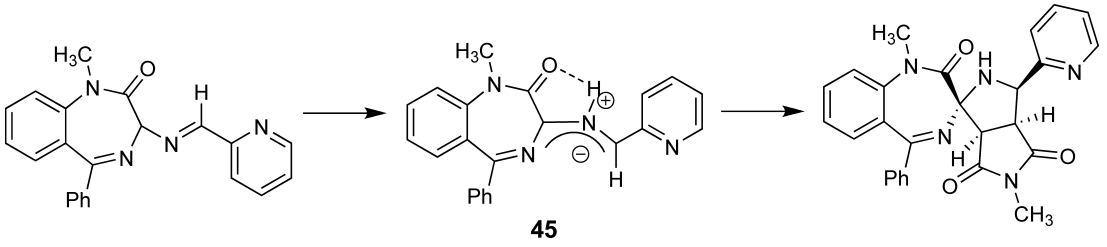
The direct azidation of 1,4-benzodiazepin-2-ones with trisyl azide provided access to 3-amino derivatives after reduction of the intermediate azide in a process that is compatible with a range of N-1 and C-5 substituents (**Scheme 15**) <1996TL6685>. This protocol offers a convenient alternative to the reduction of a C-3 oxime, obtained by reaction of the 1,4-benzo diazepin-2-one with isoamyl nitrite, which requires more vigorous conditions



Scheme 15

that can lead to over-reduction of the imine. This azidation process was also effective with 5-chloro-1-alkyl-1*H*-benzo-1,4-diazepin-2-ones, providing 3-amino derivatives after azide reduction and capture of the amine *in situ* by BOC anhydride (BOC = *t*-butoxycarbonyl) <2003JOC2844>.

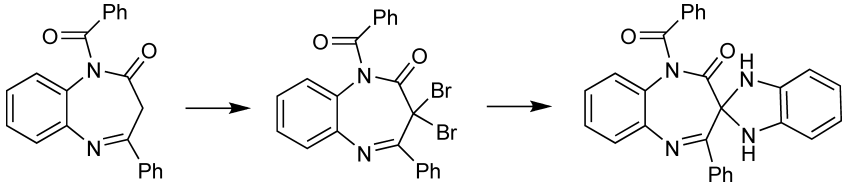
Heating imines derived from 3-amino-1,4-benzodiazepin-2-ones with *N*-methylmaleimide in boiling toluene provided adducts derived from the stereospecific cycloaddition of the resonance-stabilized azo-methine ylide **45**, formed by a 1,2-prototropic rearrangement, in 82–89% yield (**Scheme 16**) <1996T13455>. The relative stereochemistry was established by analysis of ^{1}H NMR NOE data and comparison with the single crystal X-ray structure of an analogous compound.



45

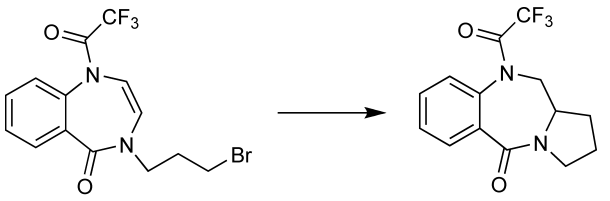
Scheme 16

Reactions occurring at the C-3 position of 3*H*-1,5-benzodiazepines feature prominently in the chemistry of this heterocycle, with bromination providing a particularly useful synthetic intermediate. The C-3 bromine was introduced using standard brominating reagents, such as Br_2 or *N*-bromosuccinimide (NBS), and acts either as an electrophilic or, after metal–halogen exchange, a nucleophilic species. Displacement of the C-3 bromide was facile with a malonate ester while reaction of the derived Grignard reagent with CO_2 introduced a carboxylic acid moiety at C-3 <2001JHC641>. The C-3 bromide of 4-phenyl-1*H*-benzo[1,4]diazepin-2(3*H*)-one reacts with oxygen-, nitrogen-, and sulfur-based nucleophiles <2001SC2523>. Benzoylation of the amide moiety facilitated dibromination at C-3 to give an electrophilic precursor to spiro derivatives, illustrated by the reaction with phenylenediamine, depicted in **Scheme 17**, which proceeded in 65% yield.



Scheme 17

The C(2)–C(3) olefin of a 1,4-benzodiazepin-5-one regiospecifically captured an alkyl radical intramolecularly in a 5-*exo*-*trig*-process that is the critical step in an approach to the construction of the fused tricyclic system found in the pyrrolo[2,1-*c*][1,4]benzodiazepine class of antitumor antibiotic. Treatment of the alkyl bromide **46** with Bu_3SnH afforded the tricyclic product **47** in 90% yield, a reaction that proceeded with equal efficiency with the alkoxy aryl ring substituents found in the naturally occurring (±)DC-81 (**Scheme 18**) <1999OL1835>.

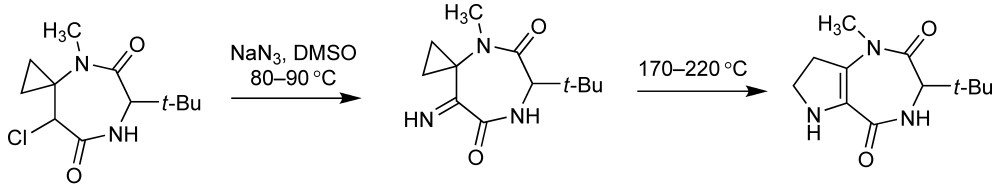


46 **47**

Scheme 18

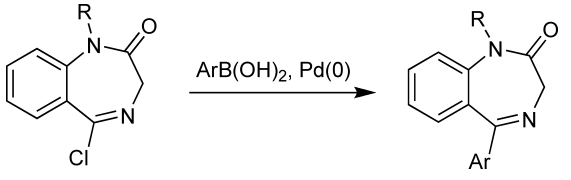
12.06.6.3 Reaction at C-5

Treatment of 5-chloro-1,4-diazepin-2,5-dione **48** with NaN_3 in DMSO effected a facile conversion directly to the imine **49**, which underwent a Cloke rearrangement upon heating *in vacuo* to give the dihydropyrrolo-fused 1,4-diazepin-2,5-one **50** in good overall yield <2000OL4249>. Alternatively, acidic hydrolysis of the imine provided an α-ketoamide, which rearranged thermally to the dihydrofuran corresponding to **50**. These compounds, which are air sensitive, were readily oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide pyrrole- and furan-fused heterocyclic analogues of benzo-1,4-diazepines.



48 **49** **50**

The imidoyl chloride moiety of 5-chloro-1-alkyl-1,4-benzodiazepin-2-ones participates in Pd-catalyzed, Suzuki cross-coupling reactions, reacting with a range of functionalized aromatic boronic acids to provide an efficient and versatile approach to 5-aryl and 5-heteroaryl compounds (**Scheme 19**) <2003JOC2844>. This chemistry readily extends to 3-amino-subsituted compounds that are orally bioavailable inhibitors of the aspartyl protease γ-secretase <2003BML4143>.



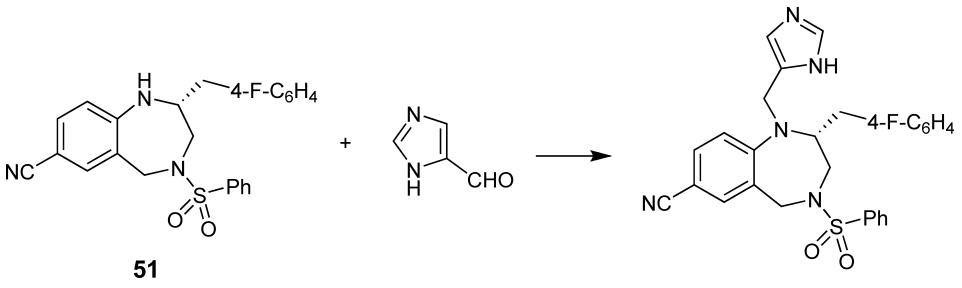
Scheme 19

12.06.6.4 Reaction at N-1

The alkylation at N-1 of the 1,4-benzodiazepine **51** with imidazole-5-carboxaldehyde is readily accomplished in excellent yield via a reductive amination process that involves simply stirring with triethylsilane in a 1:1 mixture of CH_2Cl_2 and CF_3CO_2H at 25 °C for 4 h (**Scheme 20**) <2001TL1245>. This reaction is notable because of the low reactivity associated with electron-deficient aniline derivatives.

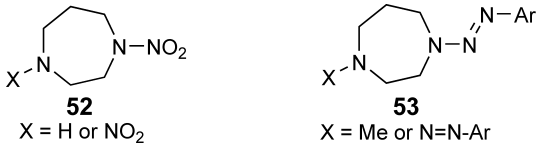
The regiospecificity of alkylation of (*S*)-3-methyl-4,5-dihydro-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one with aminoethyl chlorides is governed by the reaction conditions <2006TL3357>. Under conventional heating in DMF with K_2CO_3 for several hours exclusive N-1 alkylation was observed, while under brief microwave heating alkylation occurred exclusively at N-4. A cyclopropyl ring has been introduced directly to N-1 of a fused 1,5-benzodiazepin-2-one derivative using a cyclopropylbismuth reagent under the influence of a copper additive <2007JA44>.

A convenient method for the monoacylation of homopiperazine and other diamines has been described <1999JOC7661>. Under conventional conditions, the bis-acylated product is favored but treatment of homopiperazine with 2 equiv of *n*-butyllithium to form a dianion followed by reaction with 1 equiv of benzoyl chloride provided a 27:1 ratio of mono- to bisacylated derivatives from which the monoacylated compound was isolated in 91% yield.



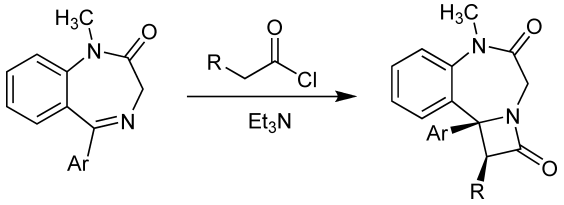
Scheme 20

N-Nitration of homopiperazine using 1 equiv of the new nitrating reagent, 4-chloro-5-methoxy-2-nitropyridazin-3-one, provided the mononitrated product **52** in 86% yield while the use of 2 equiv resulted in nitration of both N atoms <2003JOC9113>. Diazene-substituted 1,4-diazepines are rare, with only one previous reported preparative procedure. Mono- and bis-diazene-substituted homopiperazines **53** were prepared by coupling aryldiazonium salts with homopiperazine or mono-*N*-methyl-homopiperazine <2004CJC1725>.



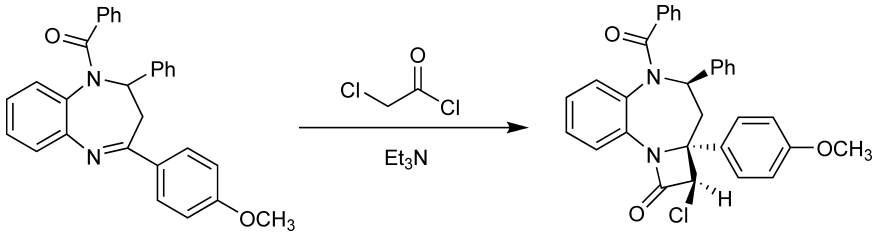
12.06.6.5 Reaction at N-4

The imine moiety of 1*H*-1,4-benzodiazepine-2-(3*H*)ones reacts regio- and stereospecifically with a range of functionalized ketenes to afford substituted, fused *β*-lactam [2+2] cycloaddition adducts (**Scheme 21**) <2004EJO535>. The use of [4-(*S*)-2-oxo-4-phenyloxazolidin-3-yl]acetyl chloride, as a homochiral ketene precursor, afforded a single product, the structure of which was established by X-ray crystallography, while the (4*S*,5*R*)-diphenyl analogue provided a 1.8:1 mixture of chromatographically separable diastereomers.



Scheme 21

Chloroketene adds to the imine moiety of substituted 2,3-dihydro-1*H*-benzo-1,4-diazepines with excellent regio- and diastereoselectivity to afford the (2*S*,2a*R*,4*R*)-fused *β*-lactam adduct and its enantiomer (**Scheme 22**)



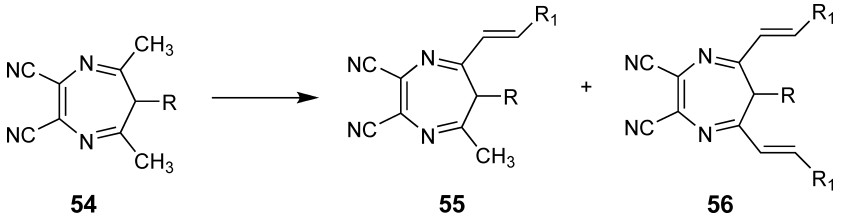
Scheme 22

<2001JHC1031>. This result was rationalized based on stereocontrol originating with the ketene approaching the imine N lone pair from the least hindered side of a boat conformer, opposite the 2-phenyl moiety. In this geometry, the chlorine atom is *exo* to the diazepine ring and a counterclockwise, conrotatory ring closure forms the β-lactam ring.

12.06.7 Reactivity of Substituents Attached to Ring Carbon Atoms

12.06.7.1 Monocyclic 1,4-Diazepines

The exocyclic methyl groups of 6-substituted-5,7-dimethyl-6*H*-1,4-diazepine-2,3-dicarbonitrile derivatives **54** condense with aromatic and heteroaromatic aldehydes in a reaction catalyzed by piperidine (**Scheme 23**) <2005BCJ316, 2005BCJ1167>. Monoethylene derivatives **55** predominated when **54** was condensed with molar equivalents of electron-deficient aldehydes but mixtures were obtained with electron-deficient aldehydes, as the coupling partners; however, bis-ethylene derivatives **56** were the major product when excess aldehyde is used. The products fluoresce in the near-IR in the solid state, the intensity of which is dependent on the nature of intermolecular interactions that are a function of crystal packing. Large substituents at C-6 favor increased intensity by reducing molecular stacking and the potential for fluorescence quenching.

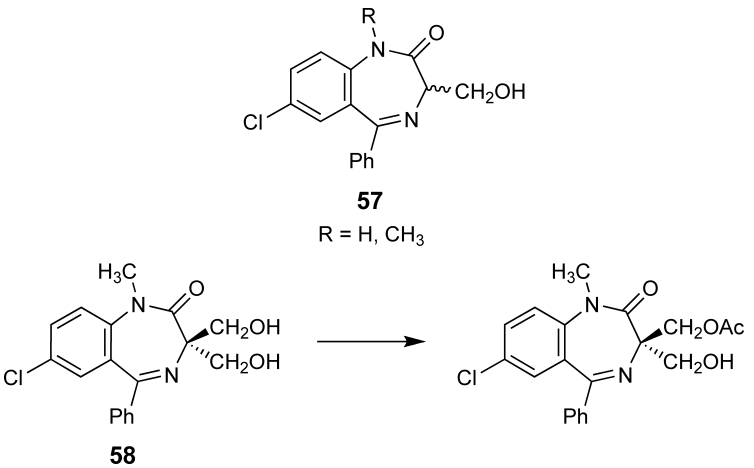


54 **55** **56**

Scheme 23

12.06.7.2 Benzodiazepines

Derivatives of C-3 mono- and dihydroxymethyl-substituted 1,4-benzodiazepin-2-one can be resolved in a kinetic fashion by a lipase-mediated selective transfer of the acetyl moiety of vinyl acetate to the alcohol of one enantiomer <1998HCA85, 1998HCA1567, 2003TA2725>. Immobilized *Mucor miehei* lipase (Lipozyme IM) selectively acetylated the (*R*)-enantiomer of alcohol **57**, known to preferentially exist in the *P*-conformation in which the CH_2OH is equatorial <1998HCA85>. The recovered alcohol is the (*S*)-enantiomer, which prefers the *M*-conformation thereby placing the CH_2OH axial, suggesting steric control in enzyme recognition. For the C-3-disubstituted 1,4-benzodiazepine-2-one **58**, the *pro-(R)*-hydroxymethyl moiety of the diol is acetylated, thought to occur via reaction with the equatorial CH_2OH in the *P*-conformation (**Scheme 24**) <1998HCA1567>.



57

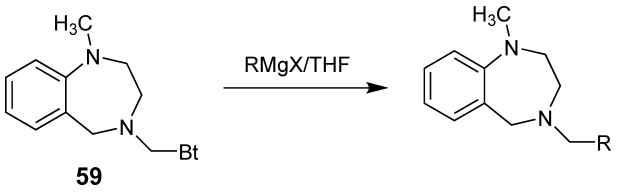
R = H, CH_3

58

Scheme 24

12.06.8 Reactivity of Substituents Attached to Ring Heteroatoms

The *N*-4-(benzotriazolylmethyl)-tetrahydro-1,4-benzodiazepine **59** reacted smoothly with Grignard reagents in THF to provide convenient access to substituted homologues in good yield (**Scheme 25**) <2002J(P1)592>. The benzotriazole moiety can be removed reductively with $NaBH_4$ to provide the simple *N*-methyl compound, while reaction with triethyl phosphite and $ZnBr_2$ in dry THF gave the diethylphosphonate derivative.

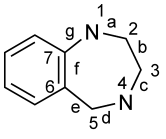


59

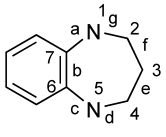
Scheme 25

12.06.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

The system used for defining ring-construction topology from acyclic precursors is the same as that used in CHEC(1984) and CHEC-II(1996), in which the bond(s) being formed are designated by lowercase italicized letters and the precursor fragments are defined by the individual sequences of carbon and nitrogen atoms. Ring syntheses are considered in alphabetical order of the disconnection, with reactions forming two bonds following the single-bond discussion, also in alphabetical order based on the second bond being formed. Thus type *a* is considered first followed by type *ab*, then type *ac*, before type *b* ring closures are discussed. Summaries of monocyclic diazepine and benzodiazepine ring-closure methods are combined under the bond-disconnection designation, whereas 1,5-benzodiazepines are considered in a separate section, following the precedent set by CHEC-II(1996).



1,4-Benzodiazepine



1,5-Benzodiazepine

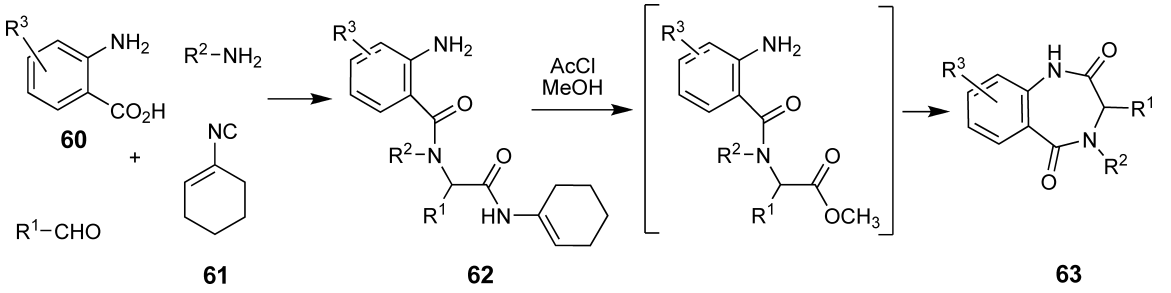
12.06.9.1 Monocyclic 1,4-Diazepines and 1,4-Benzodiazepines

The interest in understanding conformational aspects of monocyclic 1,4-diazepines in the context of peptidomimetics has stimulated the development of new preparative methodologies and procedures designed to improve limitations associated with previously established routes to these compounds. Synthetic approaches to both 1,4- and 1,5-benzodiazepines are generally well described, but the development and application of new methodology, particularly using transition metal catalysis, has resulted in innovative bond-construction strategies that broaden the range and nature of functionality both within the ring and incorporated into substituents. Moreover, the well-established utility of 1,4-diazepines as drug scaffolds in medicinal chemistry has provided a significant impetus to develop combinatorial syntheses that allow access to large numbers of structurally diverse compounds suitable for high-throughput screening campaigns.

12.06.9.1.1 Type *a* (N–C–C–C–C–N–C–C)

The type *a* ring-closure topology is one of the most frequently used methods to synthesize 1,4-benzodiazepine-2,5-diones because of the reliability of amide formation from precursors readily available by acylating α-amino acid derivatives with an activated anthranilic acid or a synthetic surrogate. A particularly useful protocol that relies upon a type *a* ring-closure to synthesize 1,4-benzodiazepine-2,5-diones prepared precursors from anthranilic acids using the Ugi reaction, a four-component process that allowed considerable structural diversity to be introduced in a combinatorial fashion (**Scheme 26**) <1996JA2574, 1996JOC8935>. The most effective reaction protocol takes advantage of the unique chemical properties of 1-isocyanocyclohexene that allow it to function as a 'universal isocyanide'. As illustrated in

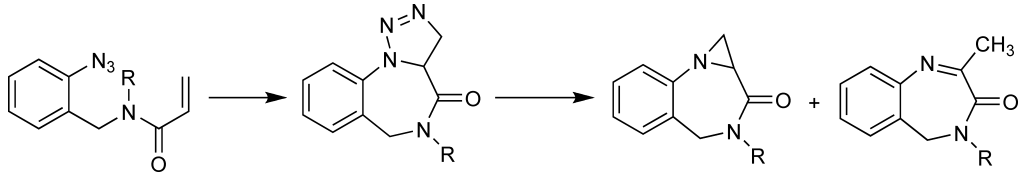
Scheme 26, the combination of an aldehyde, a primary amine, an anthranilic acid **60**, and the isocyanide **61** afforded the acylated amino acid **62** in a process conveniently performed in a single operation. The key step in this process is the conversion of the cyclohexenylamide in **62** to an ester, which occurred under acidic conditions. This step of the sequence was proposed to proceed by way of an intramolecular nucleophilic expulsion of the acylated iminium by the anthranilamide moiety to afford a dipolar münchnone intermediate. This provides a satisfactory explanation for why the ester was formed rather than the primary amide, which would arise from a simple hydrolysis. Cyclization of the intermediate ester to the 1,4-benzodiazepin-2,5-dione **63** was completed by heating. The yield of this reaction can be increased by introducing an *N*-BOC or *N*-Fmoc protecting group onto the anthranilic acid while the use of ethyl glyoxalate led to 3-carboxyamide derivatives (Fmoc = 9-fluorenylmethyloxycarbonyl) <1998JOC8021, 1999TL5295>. The convenience of this procedure is further enhanced by using resin-bound isocyanides <2002OL1167, 2002TL4083>.



Scheme 26

A related process, in which 2-aminoacetophenone is coupled with a 2-nitrobenzoic acid, a ketone, and an isocyanide, afforded 2-aryl-4,5-dihydro-1,4-benzodiazepin-5-ones in good to excellent overall yields after Fe-mediated reduction of the nitro group and ring closure <2005TL711>.

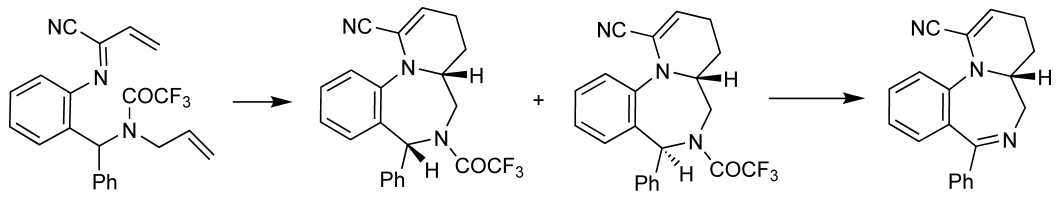
A number of procedures based on a [3+2] intramolecular cycloaddition protocol have been developed, including the intramolecular cycloaddition of an aryl azide to an alkene which provides triazolino-fused diazepine derivatives that extrude N_2 upon heating <2001J(P1)1816, 2001TA1201, 2004TA687>. This process afforded mixtures of two 1,4-benzodiazepine-3-one derivatives in which N-1 is either incorporated into a fused aziridine ring or is part of an imine moiety, as depicted in **Scheme 27**. The outcome of this process depended upon the substitution pattern of the alkene since the cinnamide analogue afforded only the substituted aziridine product upon heating of the azide in toluene. In this case, the product was isolated as a mixture of diastereomers when the R-substituent contains a chiral center. Anthranilamides derived from allyl amine, in which the amide moiety is configured in an alternative topology, form 3-alkyl-1,4-benzodiazepin-5-ones exclusively in good yield, particularly under microwave heating <2001TL2397>.



Scheme 27

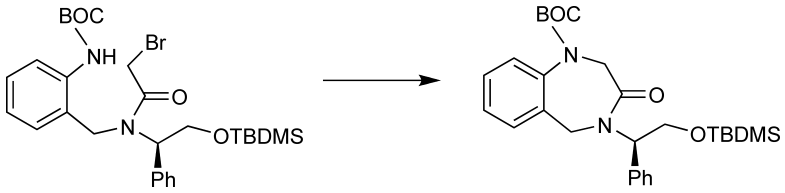
Structurally related nitrile imines, generated *in situ*, add to the pendant alkene to afford fused 1,4-benzodiazepin-3-one and 1,4-benzodiazepin-5-one derivatives depending upon the oxidation state at C-3 and C-5 of the starting material <1999TA2203, 1999TA4447>. The incorporation of chiral elements into the ester moiety or the amide N-substituent is associated with modest diastereoselection <1999TA3873, 2001SC2649>.

A [4+2] cycloaddition strategy involving a hetero-Diels–Alder reaction afforded N-1-, C-2-fused tricyclic 1,4-benzodiazepines <1998TL4283>. Heating the azadiene **64** in toluene at 180 °C afforded a 3:2 mixture of the chromatographically separable *cis*- and *trans*-1,4-benzodiazepines **65** and **66** in 74% yield (**Scheme 28**). The structure of the adducts was determined by ^{1}H NMR, with an NOE observed between the C-4a and C-7 protons for the *cis*-isomer **65**. Removal of the N-protecting group from the *trans*-isomer using K_2CO_3 in MeOH, followed by oxidation with $Pb(OAc)_4$ and iodine, provided the fused 2,3-dihydrobenzo-1,4-diazepine **67** in 76% yield.



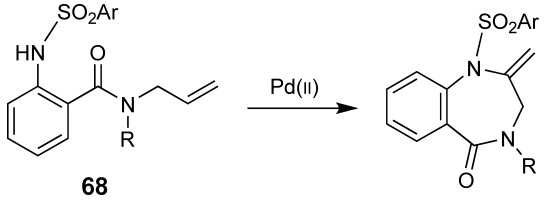
Scheme 28

The intramolecular alkylation of a BOC-protected aniline by an α-bromo amide using NaH in DMF, depicted in **Scheme 29**, provided an example of a type *a* ring closure to 1,4-benzodiazepin-3-ones, a straightforward and effective procedure that, surprisingly, has not been more broadly exploited <2005EJO1590>.



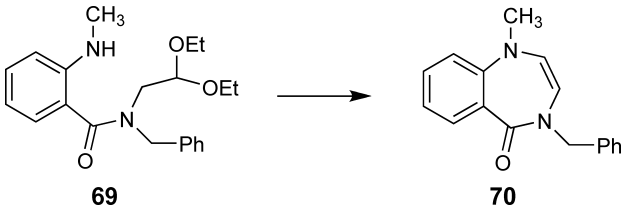
Scheme 29

The Pd-catalyzed cyclization of the allyl anthranilamide **68** to a benzo-1,4-diazepin-5-one was optimized to provide good selectivity for the formation of the seven-membered ring rather than the quinazolin-4-one derivative (**Scheme 30**) <2004JOC5627>. Optimal conditions were determined to be 10 mol% $Pd(OAc)_2$ in xylene at 100 °C with pyridine, as the base, the inclusion of which was essential to the success of this procedure. Notably, the BOC protecting group was unable to substitute for the sulfone moiety, presumably reflecting the requirement for a specific pK_a range. A Pd(0) catalyst promoted a topologically similar intramolecular cyclization of an unsaturated, bicyclic hydroxamide in a reaction that was dependent on the aniline moiety being protected with the heavily electron deficient 2,4-dinitrobenzensulfonamide moiety as a means of reducing the pK_a of the nucleophile precursor <2002OL139>.



Scheme 30

The first example of 1,4-benzodiazepine-5-one that incorporates an unsubstituted 2,3-carbon-bond was obtained by hydrolyzing the acetal **69** in THF in the presence of Amberlyst-15 resin <2000S265>. Subsequent heating of the product in toluene with azeotropic removal of water gave the 1*H*-benzo[*e*][1,4]diazepin-5(4*H*)-one **70** (**Scheme 31**).



Scheme 31

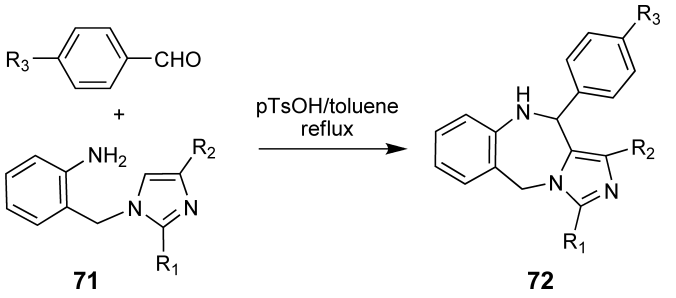
Analysis of ^{1}H NMR spectra revealed that the two enamide protons resonate as doublets at 5.28–5.36 and 5.55–5.62 ppm with a 5.6 Hz coupling constant.

The Michael-type addition of an aniline to an unsaturated ester, generated *in situ*, provided an example of a type *a* ring-closure in which the electrophilic center is sp^2-hybridized <2004BML4147>. This reaction represents a synthetically useful procedure to access tetrahydro-1,4-benzodiazepines.

Several type *a* ring closures have been developed that use solution- and solid-phase methodology to facilitate the application of high-throughput synthesis technology <2000TL1509, 1996TL8081, 2001TL5141>. These procedures provide the type of diverse array of products preferred for screening campaigns and include a library of substituted 1,4-benzodiazepin-2,3-diones.

12.06.9.1.2 Type *ab* (N–C–C–C–N–C + C)

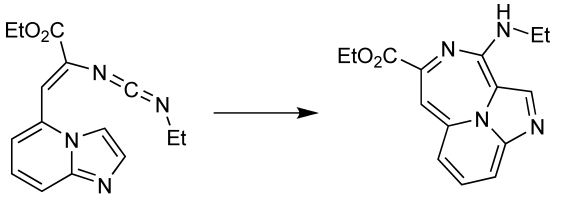
Examples of the type *ab* ring closure that have been described involve the *in situ* capture of an imine derived from an aniline by a nucleophilic olefin moiety and are limited to substrates in which the olefin is part of an azole-derived heterocycle, leading to products in which the diazepine moiety is embedded in a fused ring system <1996CHEC-II(9)151>. Heating the aniline **71** with an aromatic aldehyde in toluene at reflux in the presence of a catalytic amount of TsOH effected a Pictet–Spengler ring closure between the imidazole ring and intermediate imine (**Scheme 32**) <2005JOC4889>. The fused benzo-1,4-diazepine derivatives **72** were isolated in yields ranging from 75% to 88%. This reaction was insensitive to the electronic nature of the 4-substituent on the aldehyde and the steric environment at the 5-position of the imidazole, since the 4-phenyl and 4-methyl derivatives cyclized with equal efficiency.



71 **72**

Scheme 32

The carbodiimide **73**, obtained by reaction of an iminophosphorane with ethyl isocyanate, underwent a thermally induced cyclization in 1,2-dichlorobenzene at reflux to give the azulene **74** in 42% isolated yield (**Scheme 33**) <2001JOC6576>. This process was regiospecific since products arising from reaction with the six-membered ring were not observed.



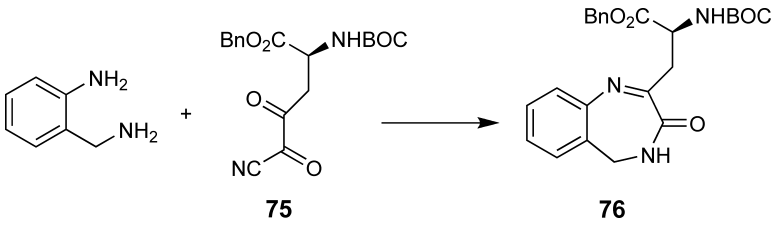
73 **74**

Scheme 33

12.06.9.1.3 Type *ac* (N–C–C–C–N + C–C)

The type *ac* ring-construction process relies upon the reaction of a 1,3-diamine with a two-carbon electrophile, readily available fragments that offer simplicity in reaction design. The reaction of 2-aminobenzylamine with the reactive diketonitrile **75**, derived from aspartic acid, in CH_2Cl_2 proceeded smoothly to furnish the 1,4-benzodiazepin-3-one **76**

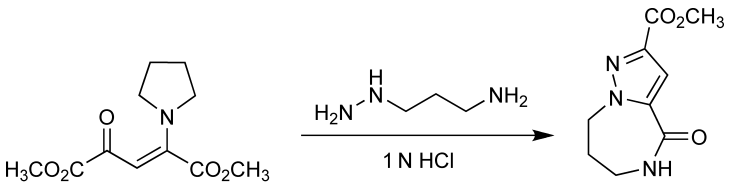
in 64% yield (**Scheme 34**) <2003TL361>. The structure of **76** was not definitively established but assigned based on the expectation that the more nucleophilic primary amine would react more rapidly at the acyl cyanide carbonyl.



75 **76**

Scheme 34

The pyrrolidinyl enamino keto-diester **77** reacted with 3-hydrazinylpropan-1-amine in the presence of 1 N HCl to afford the pyrazolodiazepine **78**, a key intermediate in the preparation of a glycoprotein IIb/IIIa antagonist, in 40% yield (**Scheme 35**) <2003TL5867>. The requirement for the presence of 1 N HCl to promote this process suggested that the diketo diester is the actual intermediate in the process, evaluated by examining the outcome with a mixed methyl/ethyl ester. The product was isolated as a 1:1 mixture of ester isomers, consistent with the intervention of a hydrolytic step that led to symmetrization of the electrophile.

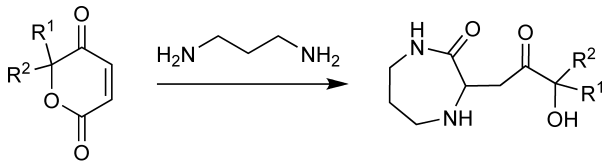


77 **78**

Scheme 35

The reductive amination of a substituted 1,3-diaminopropane with glyoxal provided the saturated 1,4-diazepine derivatives, which have been used as intermediates in the synthesis of a number of biologically active compounds <1998T10671, 2002OPD28>. This process is related to the previously established method for the synthesis of 1,4-diazepin-2-ones that relies upon the combination of glyoxal, or its bis-bisulfite, with a 1,3-diaminopropane derivative under nonreducing conditions <2001JOC5822>.

The ketone moiety of unsaturated 5-ketolactones **79** both directs and facilitates the reactivity of diaminopropane toward a Michael reaction at C-3 and amide formation with the lactone carbonyl, yielding 3-substituted diazepinones **80**, as shown in **Scheme 36** <1996JHC703>.

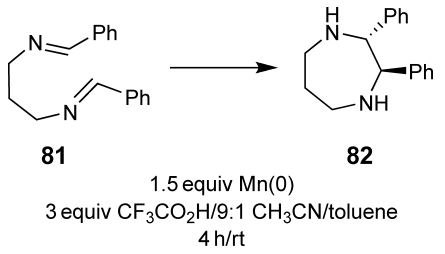


79 **80**

Scheme 36

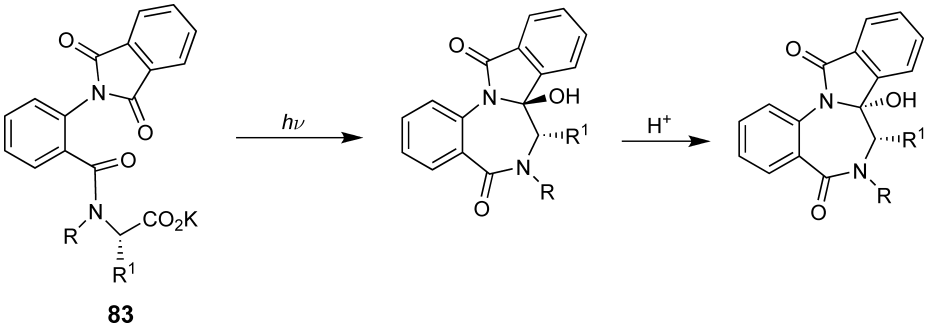
12.06.9.1.4 Type *b* (C–N–C–C–C–N–C)

A chemical approach to the reductive cyclization of the symmetrical diimine **81** provided the *trans*-substituted 1,4-diazepine **82** in 73% yield, thus providing an alternative to the electrochemical processes that have more commonly been described to effect this transformation (**Scheme 37**) <2003OL1591>.



Scheme 37

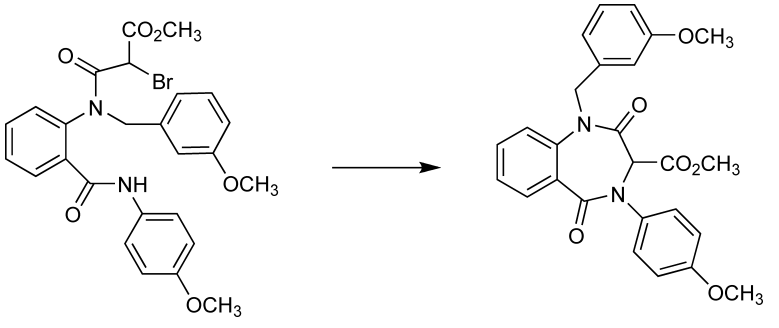
The preparation of 1,4-benzodiazepines using a type *b* ring-closure reaction is rare, restricted to photochemically induced radical cyclizations with uniquely designed substrates <2001AGE577, 2001S1159>. Irradiation of the potassium salts **83** of *N*-phthaloylanthranilamide at 300 nM in aqueous acetone afforded 1,4-benzodiazepin-5-ones in 54–83% yield after a photoinduced decarboxylation that generated a radical, which was trapped by the carbonyl moiety (**Scheme 38**). On a small scale, the product was produced, as a single diastereomer, in which the OH and R^1 moieties are *trans*, the result of a kinetically controlled process. However, larger-scale reactions produced a mixture of *cis*- and *trans*-products, reflecting thermodynamic equilibration that could also be established by exposure of the kinetic product to a catalytic amount of CF_3CO_2H <2001AGE577>. Substrates in which the anthranilic acid element is replaced by *β*-alanine follow a similar reaction manifold to give 1,4-diazepin-5-one derivatives, albeit in lower yield <2001OL537>.



Scheme 38

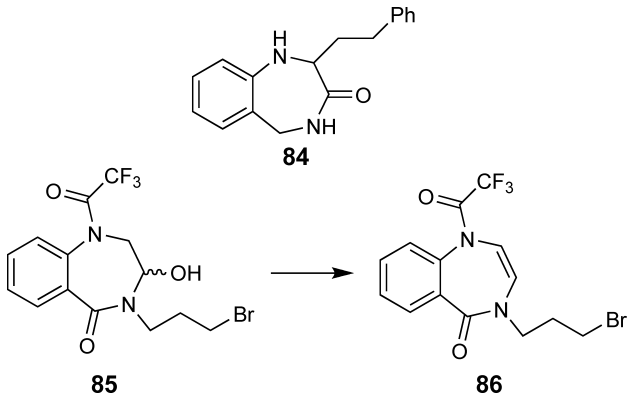
12.06.9.1.5 Type *c* (N–C–C–C–N–C–C)

The intramolecular alkylation of an aryl amide by an activated bromide, readily available by bromination of a malonamide methylene with pyridinium tribromide in the substrate depicted in **Scheme 39**, provided an example of a type *c* ring closure to furnish 3-carboxymethyl-1,4-benzodiazepin-2,5-diones <2006OBC510, 2002H(56)1501, 1999JOC2914>.



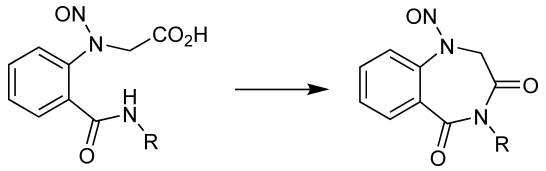
Scheme 39

Type *c* ring closures involving carbonyl-containing electrophiles have been exemplified <1999OL1835, 2004BML1031, 2003OPRD655>. The unmasking of a primary benzylamine from the corresponding nitrile in the presence of an ester resulted in spontaneous cyclization, providing the 1,4-benzodiazepin-3-one **84** in 65% yield <2004BML1031>. 3-Hydroxy-1,4-benzodiazepin-5-ones were produced when an aldehyde was generated in the presence of a secondary amide and the resulting acylated hemiaminals **85** were readily dehydrated to the enamide **86** in good overall yield by heating in toluene in the presence of acid (**Scheme 40**) <1999OL1835>.



Scheme 40

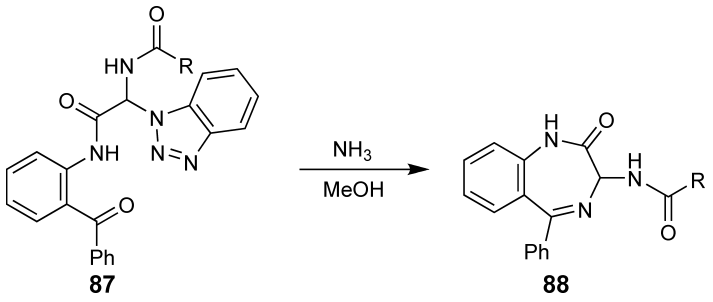
Substituted 1,4-benzodiazepine-3,5-diones can be prepared by capturing an amide with a carboxylic acid that has been activated as the mixed anhydride, as shown in **Scheme 41** <2004JOC6371>. An *N*-nitroso protecting element was essential for the success of this procedure, facilitating the reaction by enhancing the anhydride's electrophilicity. Both alkyl and aryl amides participated and the nitroso moiety was readily removed from the product by heating in CF_3CO_2H in the presence of urea, as a scavenger.



Scheme 41

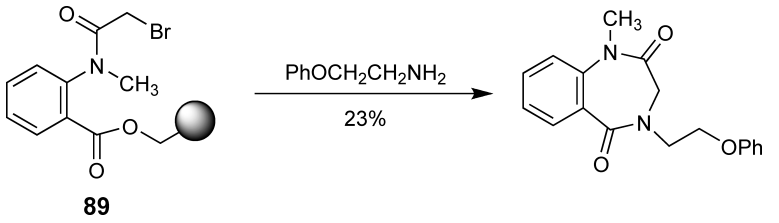
12.06.9.1.6 Type *cd* (C–C–C–N–C–C + N)

The synthetically versatile benzotriazole moiety offers an effective and convenient leaving group that extends the range of substrates that participate in a type *cd* ring-closure. Racemic 3-amino-2,3-dihydrobenzo-1,4-diazepine-2-ones **88** were obtained in 59–77% yield when α-amidobenzotriazoles **87** were exposed to a saturated solution of NH_3 in MeOH (**Scheme 42**) <1995JOC730, 2001M747, 2003JOC2844>.



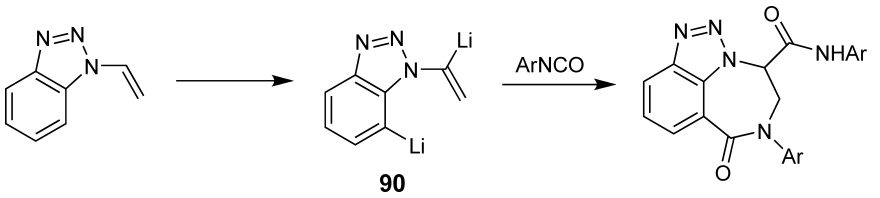
Scheme 42

Heating the Wang resin-bound anthranilic ester **89** at 150 °C with a primary amine in a microwave apparatus effected a tandem N-alkylation–intramolecular cyclization that proceeded with concomitant cleavage of the 1,4-disubstituted-1,4-benzodiazepine-2,5-dione product from the resin (**Scheme 43**) <2005AGE5830>. A topologically similar process provided access to sclerotigenin, a benzodiazepine alkaloid isolated from extracts of sclerotia of *Penicillium sclerotigenum* that is a potential anti-insectant <2002JHC351>.



Scheme 43

Reaction of the dilithio anion of 1-vinylbenzotriazole **90** with 2 equiv of an aryl isocyanate led to a fused 1,4-diazepine ring formation via an intramolecular Michael addition of the intermediate aryl amide to the vinyl moiety, a type *c* ring closure that proceeded in good overall yield (**Scheme 44**) <2003JOC5713>.



Scheme 44

12.06.9.1.7 Type *d* (C–C–C–N–C–C–N)

The type *d* ring closure to access monocyclic 1,4-diazepines is typically accomplished by uniting a nucleophilic nitrogen atom with an electrophilic carbon atom; examples, where the latter is in either an sp^2 or an sp^3 hybridization state, have been described.

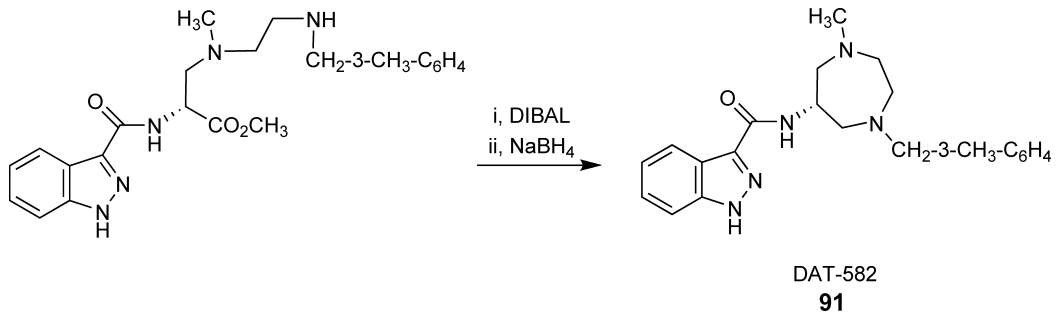
The cyclization of ω-amino acids offers the most logical and straightforward approach to 1,4 diazepines but this process can be problematic and complicated. Low yields have been attributed to dimerization as an alternate reaction pathway, particularly prominent if a secondary amide moiety that favors a transoid geometry intervenes between the reacting termini <2000EJO251>. The use of resin-bound substrates has provided a useful method to isolate reactive intermediates, such that amide bond formation of β-alanine-based dipeptides occurs efficiently, mediated by the base-catalyzed intramolecular reaction of the amine with an ester or activated acid <2001TL5389, 1998BML2273>. ω-Amino acid ester substrates derived from a cyclic β-amino acid cyclized more efficiently in a reaction promoted by the hindered base *N*,*N*-diisopropylethylamine in CH_2Cl_2, a process that occurred without racemization of the ω-amino acid chiral center <2006CL86>.

More highly saturated 1,4-diazepine derivatives can be accessed by reductive amination procedures in which the imine is formed by the interaction of an amine with a pendant aldehyde or ketone moiety. This ring-closure topology has been exploited in a total synthesis of caprazol, the core found in both the caprazamycin family of antituberculosis antibiotics and the liposidomycins, lipid-containing nucleoside antibiotics that inhibit peptidoglycan synthesis <2005AGE1854, 2003H(59)107>. A similar strategy allowed the synthesis of the 1,4-diazepine element found in DAT-582 **91**, a potent and selective $5HT_3$ receptor antagonist (**Scheme 45**) <1997J(P1)3219, 1997TA2367>.

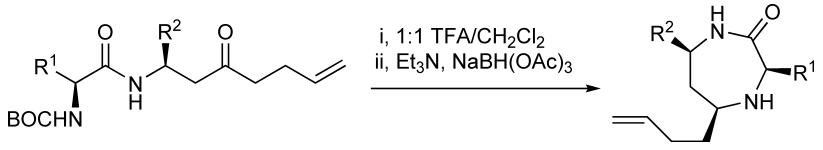
The incorporation of an amide bond in the substrate provided 1,4-diazepin-2-ones as single diastereomers with the stereochemistry at C-5 determined by single crystal X-ray structure analysis, as depicted in **Scheme 46** <2006OL3425>.

The AgOTf-catalyzed, PhSeBr-induced ring closure of the prolinamide-derived cinnamoylamide **92** proceeded via *anti*-addition to the olefin, which afforded the *trans*-substituted pyrrolo[1,2-*a*][1,4]diazepine-1,5(2*H*)-dione **93** in 73%

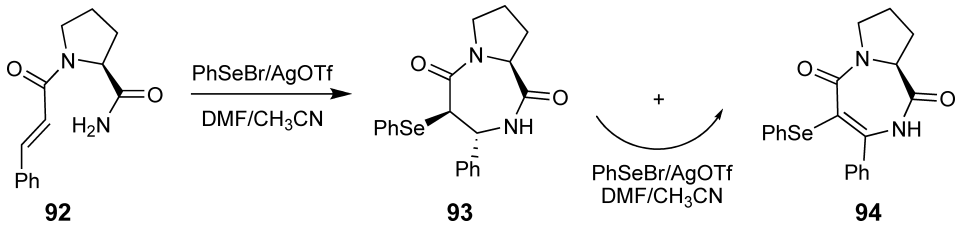
yield (**Scheme 47**) <1998J(P1)969>. In the presence of excess PhSeBr, the unsaturated selenide **94** is produced in 72% yield and the structure of both products was confirmed by X-ray crystallography. The course of this reaction is dependent upon the identity of the unsaturated amide moiety, in a fashion that appears to reflect the inherent electronic properties of the olefin. The 3,3-dimethylacrylamide analogue provided the corresponding diazepine in 22% yield but the crotonamide derivative engaged an alternative reaction manifold leading to a fused diketopiperazine derivative, a result attributed to the poorer carbenium ion stabilization associated with the single methyl substituent. This procedure has been successfully applied to the synthesis of inhibitors of the binding of the oncogenic protein HDM2 to p53 <2005BML1857>.



Scheme 45

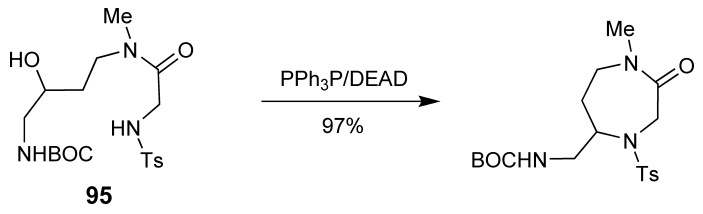


Scheme 46



Scheme 47

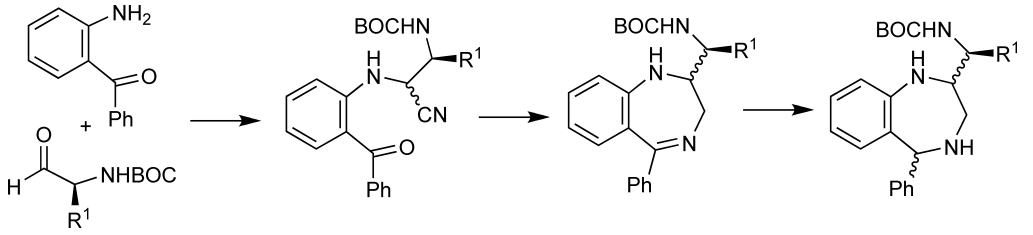
An intramolecular Mitsunobu alkylation applied to 1,7-aminoalcohol derivatives effected ring closure to 1,4-diazepines in a reaction that is only successful if the amine nucleophile is activated by an electron-withdrawing element, that can adjust the pK_a to the range that has been defined as optimal for this reaction <1998TL2099>. The hydroxy sulfonamide **95**, readily derived from glycine, cyclized in high yield to the 1,4-diazepin-2-one, useful as a peptidomimetic scaffold, in a reaction facilitated topologically by the presence of the methylated amide (**Scheme 48**).



Scheme 48

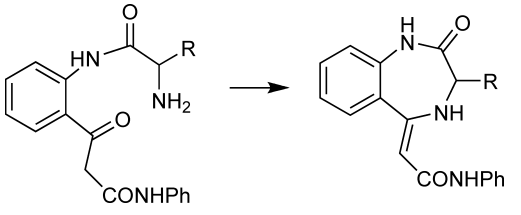
Both an intramolecular alkylation and a Mitsunobu reaction were used to synthesize the [1,4]diazepino[1,2,3-*g*,*h*]purine heterocyclic fragment of the cytotoxic marine sponge metabolite asmarine A <2001TL5941, 2003T6493>. In this reaction, the nucleophile was a heteroaryl alkoxyamine that conferred the appropriate pK_a on the NH. *O*-Alkyl hydroxamic acids are also useful substrates for Mitsunobu reactions. BOC-Ser-Phe-NHOBn and analogous dipeptides cyclized to give 1,4-diazepine-2,5-ones in modest to good yields under microwave heating, which promoted cyclization by populating the *cisoid*-conformation at the central amide bond <2003JOC7893>. This reaction has been extended to more complex systems using a solid-phase-based approach in which the hydroxamic acid oxygen atom is bound to a resin. Reduction of the N–O bond in the cyclized product with concomitant removal from the resin was accomplished by treatment with SmI_2 in THF <2003JOC7893>.

The preparation of 1,4-benzodiazepines using a type *d* ring-closure strategy is well developed and widely applied because of the ready availability of *ortho*-substitued anilines. However, new substrates for this process that provide access to uniquely substituted ring systems continue to be explored and some of the more interesting examples are summarized. The combination of 2′-aminobenzophenone, an N-protected α-aminoaldehyde and trimethylsilyl cyanide (TMSCN) in the presence of $ZnCl_2$, as a catalyst, provided the Strecker products as an epimeric mixture at the newly formed chiral center (**Scheme 49**) <2003JOC4582>. Reduction of the nitrile moiety to the primary amine using Raney nickel in the presence of hydrazine was accompanied by imine formation to give diastereomeric 5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepines. Small amounts of the 2,3,4,5-tetrahydro derivatives were also formed, a transformation that could be completed in a discrete step using $NaBH_3CN$ in AcOH. The identity of the chromatographically separable diastereomeric 2,3-dihydro-1*H*-1,4-benzodiazepines was determined by ^{1}H NMR spectroscopy and the preservation of the chiral center in the N-protected α-aminoaldehyde established by additional experiments. Application of this procedure to an anthranilic ester provided access to structurally less complex 1,2,3,4-tetrahydrobenzodiazepin-5-one derivatives, scaffolds suitable for the synthesis of peptidomimetics <2003T4491>.



Scheme 49

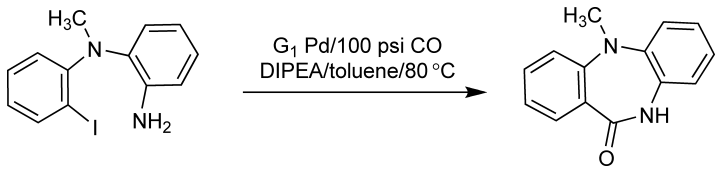
Condensation of an amino acid-derived anilide and a β-ketoamide afforded 1,4-benzodiazepin-2-ones in which the initially formed imine tautomerizes to an exocyclic enamide (**Scheme 50**) <2001TL3227>. Only the (*Z*)-isomer of the enamide was isolated, assigned based on NOE data, and presumably reflecting stabilization by an intramolecular H-bond between the ring NH and exocyclic amide carbonyl.



Scheme 50

12.06.9.1.8 Type *de* (C–C–N–C–C–N + C)

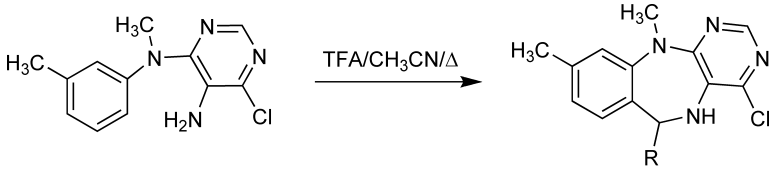
The first examples of a type *de* ring closure to 1,4-benzodiazepines that rely upon different sources of the single carbon atom have been described <2005JA14776, 2006T2563>. The carbonylation of N^1-(2-iodophenyl)-N^1-methylbenzene-1,2-diamine, catalyzed by Pd complexed to a silica-based dendrimer ligand, provided 5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one in 96% yield after capture of the intermediate acyl palladium species by the aniline nitrogen (**Scheme 51**) <2005JA14776>. While the generality of this process has been demonstrated by the



Scheme 51

preparation of a broad range of related heterocycles, it has not been exploited in the context of 1,4-diazepine synthesis beyond this single example.

A CF_3CO_2H-catalyzed Pictet–Spengler reaction between the N,N-disubstituted aniline **96** and aromatic and aliphatic aldehydes afforded fused 1,4-benzodiazepines **97** in 44–95% yields after stirring at reflux in CH_3CN for 16–48 h (**Scheme 52**) <2006T2563>. Electron-deficient aromatic aldehydes provided the best yields, attributed to facile imine formation, while ketones were uniformly unreactive. A single electron-withdrawing fluorine substituent on the aniline markedly slowed the reaction, reducing the yield to 19% after 6 days, while topologically unsymmetrically substituted anilines afforded single products, with the regiochemistry defined by ^{1}H NMR and as depicted in the cyclic product **97**. The absence of the *N*-methyl substituent resulted in imidazolidine formation with benzaldehyde but 1,4-benzodiazepines were isolated in good yield when formaldehyde was used <2005JOC9629>.

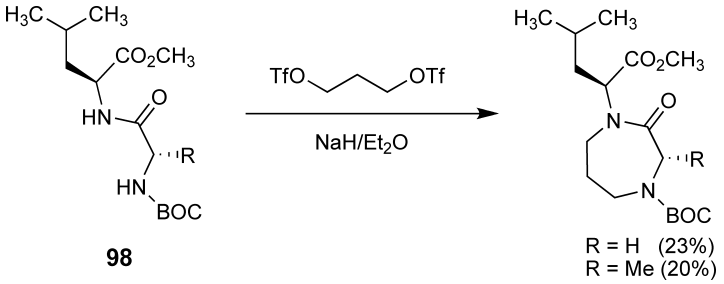


96 **97**

Scheme 52

12.06.9.1.9 Type *dg* (N–C–C–N + C–C–C)

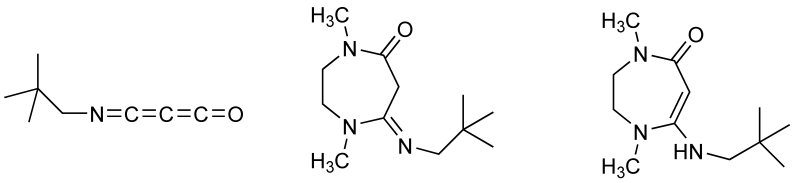
The reaction of ethylenediamine derivatives with a three-carbon substrate incorporating electrophilic elements at the termini constitutes the most straightforward approach to the construction of 1,4-diazepine rings involving a type *dg* ring closure. In what is perhaps the most elementary of synthetic strategies, the double alkylation of the glycinamide **98** with propane-1,3-diyl-bis(trifluoromethanesulfonate) using NaH, as the base, in Et_2O gave the 1,4-diazepine in a modest 23% yield (**Scheme 53**) <1997TL5809>. The alanine homologue provided the analogous product in a similar 20% yield with complete preservation of chirality.



98

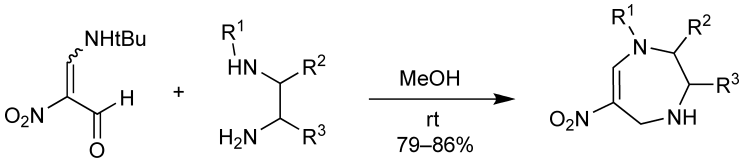
Scheme 53

Iminopropadienones are highly reactive species that have been used as three-carbon fragments in the synthesis of 1,4-diazepines <2002JOC2619>. Aryl- and neopentyl-substituted iminopropadienone derivatives are stable at 25 °C and the latter, **99**, reacted with *N*,*N*′-dimethyl-1,2-diaminoethane to afford a 55% yield of the 1,4-diazepin-5-one **100**, a compound that partially tautomerized to the enamide **101** upon Kugelrohr distillation.



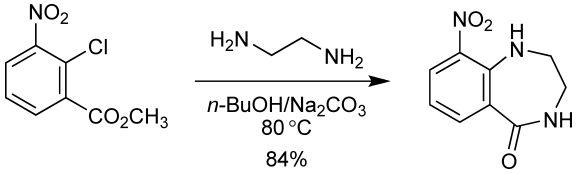
99 **100** **101**

The 3-(*tert*-butylamino)-2-nitroacrylaldehyde is a synthetic equivalent to nitromalonaldehyde that reacts with substituted ethylenediamines in MeOH at 25 °C to provide the first examples of 6-nitro-2,3,4,5-tetrahydro-1*H*-1,4-diazepines in excellent yield (**Scheme 54**) <2004JOC8382, 2002H(56)425>. The slow addition of a solution of the diamine to the nitroenamine was required in order to minimize oligomer formation.



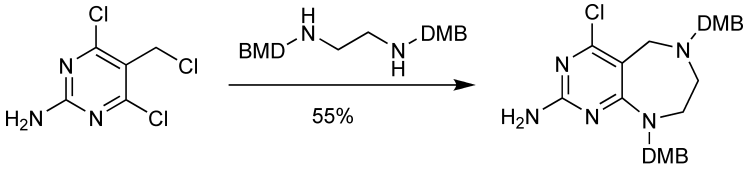
Scheme 54

Heating ethylenediamine with methyl 2-chloro-3-nitrobenzoate and Na_2CO_3 in butanol at 80 °C effected a dual S_N2Ar/acylation reaction to afford 9-nitro-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepin-5(2*H*)-one, an intermediate in the synthesis of inhibitors of poly(ADP-ribose) polymerase-1, in 84% yield (**Scheme 55**) <2003BMC3695>.



Scheme 55

The dual alkylation/S_N2Ar cyclization of N^1,N^2-bis(2,4-dimethoxybenzyl)ethane-1,2-diamine (bis-DMB-ethylenediamine) with the chloromethyl pyrimidine **102** provided the fused ring diazepine **103**, a transformation that could not be accomplished by simply using unprotected ethylenediamine (**Scheme 56**). The product is an intermediate toward the synthesis of potential folate-related antitumor agents that act as glycinamide ribonucleotide formyltransferase inhibitors <2004HCO405>.



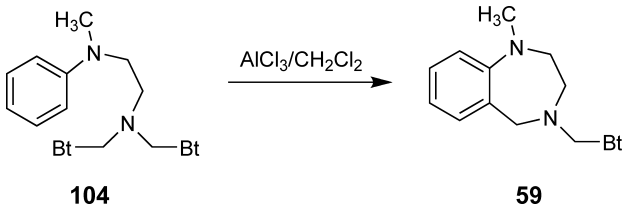
102 **103**

Scheme 56

12.06.9.1.10 Type *e* (C–C–N–C–C–N–C)

The most common form of the type *e* ring-closure reaction to afford 1,4-benzodiazepines is a 7-*endo-trig*-process in which a substituted iminium derivative, typically generated *in situ*, is captured by the aryl ring. Cyclization of the *N*,*N*′-(bis-1,2,3-benzotriazol-1-ylmethyl)amine **104** by a Friedel–Crafts-type ring closure afforded the tetrahydro-1,4-

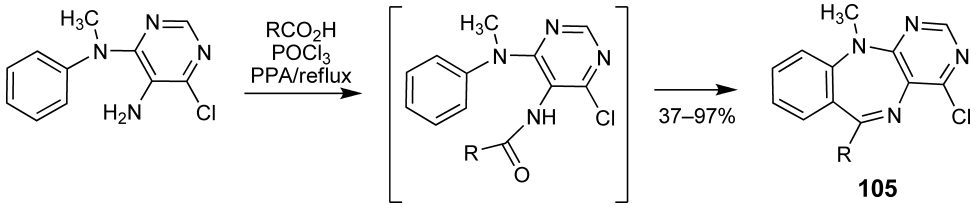
benzodiazepine **59** in 86% yield (**Scheme 57**) <2002J(P1)592>. The starting material was easily obtained by treating the primary amine with 2 molar equiv of benzotriazole and formaldehyde, which afforded the pure N-1 benzotriazole isomer at both heterocycles. Interestingly, the cyclization product was isolated as a 4.4:1 mixture of N-1 and N-2 isomers; however, since benzotriazole isomers are known to have similar stability and reactivity, this observation is inconsequential for subsequent transformations that involve exchange of the heterocycle by a range of nucleophiles, a well-established and versatile synthetic methodology.



104 **59**

Scheme 57

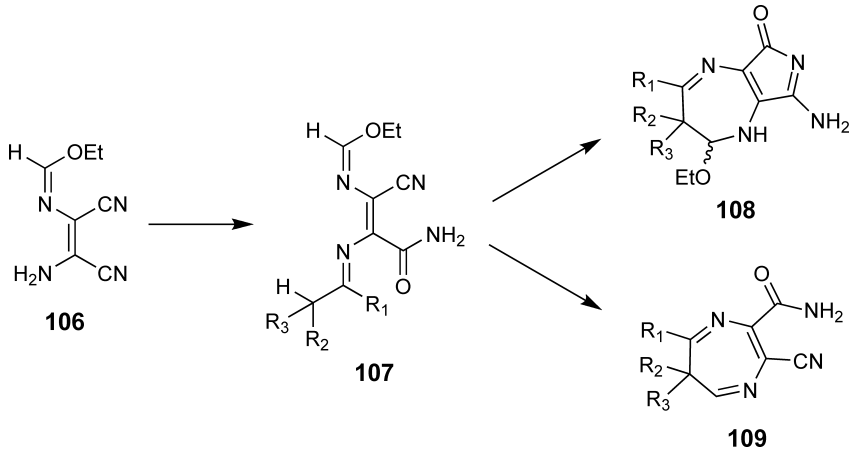
Heating *N*-[2-(arylamino)phenyl]amides under strongly acidic conditions or with powerful chlorinating agents like phosphoryl chloride effects a Bischler–Napieralski-type cyclization to afford 1,4-benzodiazepine derivatives <2004SOS929>. This process has been demonstrated in the context of an aminopyrimidine substrate and it was subsequently shown that acylation of the primary amine with a benzoic acid and the cyclization reaction could be combined into a single, practical preparative procedure <2005OL1541>. The components are simply heated with polyphosphoric acid or with $POCl_3$ to provide the tricyclic products **105** in 37–97% yield (**Scheme 58**).



105

Scheme 58

Reaction of the imidate **106** with an aldehyde or a ketone in EtOH at 0 °C in the presence of Et_3N afforded the Schiff's base **107** in which one of the nitrile groups has been partially hydrolyzed (**Scheme 59**) <2000JHC1041>.

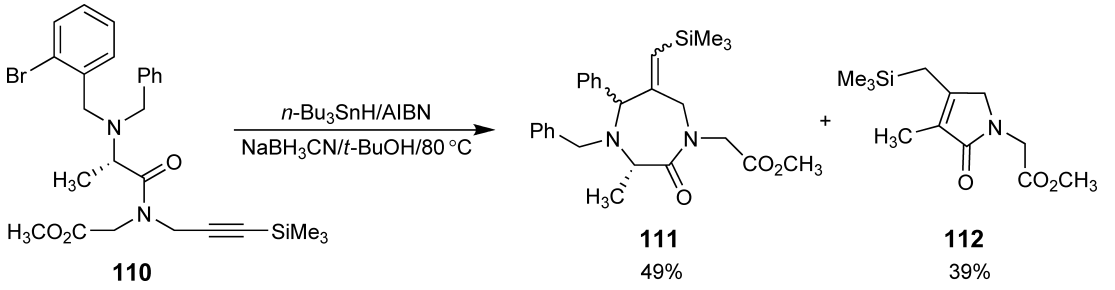


106 **107** **108** **109**

Scheme 59

Prolonged exposure to Et_3N led to a type *e* ring closure, presumably via a 7-*endo*-*trig*-process, accompanied by a slower cyclization of the amide and nitrile moieties to give the fused pyrrole ring **108**. Imine **107** also cyclized in a similar fashion under the influence of mild acid, $PhCO_2H$ in EtOH, but these conditions led to the elimination of EtOH, affording the fully unsaturated ring system **109** in which the amide and nitrile elements are preserved intact. These processes proceeded much more rapidly when activated carbonyl components were used, exemplified with ethyl pyruvate and diacetal.

A particularly interesting approach to a type *e* ring construction arose when the substituted alanine amide **110** was treated with *n*-Bu_3SnH <2003JOC1552>. This reaction generated an aryl radical that has access to two alternative 1,5-shift modes of rearrangement, the first resulting in the radical moving to the Cα of the amino acid, while the alternative 1,5-shift transferred the radical to the methylene of the adjacent benzyl group. The latter radical is poised to add to the alkyne in a 7-*exo*-fashion, which occurs to provide the diazepine **111** in 49% yield (**Scheme 60**). The former radical can also add to the alkyne, a 5-*exo*-ring-closure that leads to a pyrrolidinone intermediate which is subject to a second 1,5-shift with subsequent loss of dibenzylamine and allylic rearrangement of the resulting radical to give the lactam **112** in 39% yield. The yield of the diazepine is considerably lower when the benzyl element is replaced by a methyl substituent, consistent with the proposed rearrangement mechanism. The 2-bromobenzyl element is designated as a protecting/radical-transfer (PRT) moiety.



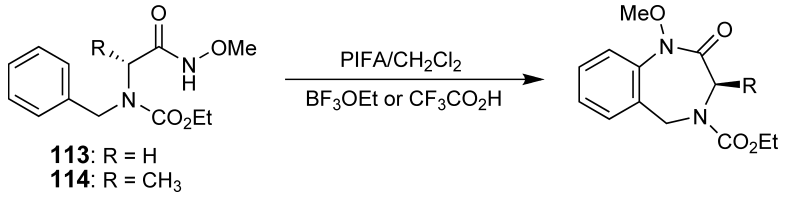
110 **111** 49% **112** 39%

Scheme 60

12.06.9.1.11 Type *g* (N–C–C–N–C–C–C)

The type *g* ring closure as defined in this section was treated as a type *b* ring closure in both CHEC(1984) and CHEC-II(1996) but is considered here as a discrete topological disconnection. Synthetic methodology that allows facile access to 1,4-benzodiazepines by way of a type *g* ring closure has been expanded considerably and two complementary processes have been described. The first depends upon the nitrogen atom being incorporated into functionality that facilitates its activation to an electrophilic species that engages in a Friedel–Crafts–type reaction with the aromatic ring. In the alternative process, the nitrogen atom functions in the more traditional role of that of a nucleophile.

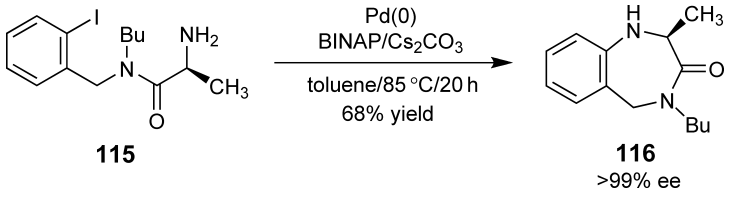
The oxidation of *N*-alkoxyamides with phenyliodine(III)bis(trifluoroacetate) (PIFA) afforded an acyl nitrenium ion that under acid catalysis was trapped by a pendant phenyl ring, a process that has been used to prepare synthetic precursors to the antitumor antibiotic (±)-DC-81 <2003T7103, 2005JOC2256>. This process was initially examined with the *N*-benzylglycine-derived substrate **113** for which $BF_3{\cdot}OEt$ in CH_2Cl_2 at −20 °C was determined to be the superior catalyst and conditions (**Scheme 61**). With the alanine analogue **114**, CF_3CO_2H in CH_2Cl_2 at 0 °C more effectively promoted the cyclization, which occurred without compromising the integrity of the single chiral center. The methoxy moiety was conveniently removed from the N-1 amide in good yield by treatment with $Mo(CO)_6$ in aqueous MeCN <2005JOC2256>.



113: R = H
114: R = CH_3

Scheme 61

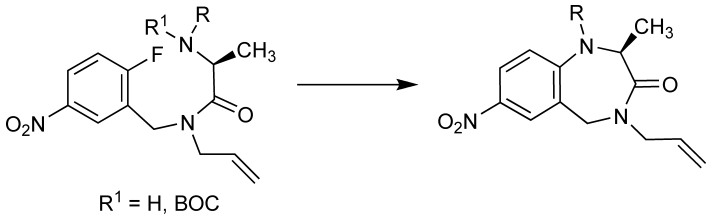
The scope of type *g* ring-closure processes in which the nitrogen atom functions as a nucleophile has been expanded considerably and synthetically useful procedures that afford 1,4-benzodiazepine derivatives have been developed. The more common process relies upon displacement of a leaving group in an S_NAr process while a second approach takes advantage of the activation of a 1,4-diydroxybenzene by oxidation to a quinone intermediate that acts as a powerful electrophile toward the amine. The advent of copper- and palladium-catalyzed processes for the arylation of nucleophilic nitrogen species has allowed access to an intramolecular variant to the preparation of 1,4-benzodiazepine derivatives <2001SL803, 2004JA14475, 2001OL2583, 2004JA14475>. Heating a solution of (*S*)-2-amino-*N*-butyl-*N*-(2-iodobenzyl)propanamide **115** in toluene at 85 °C in the presence of 10 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, the bidentate phosphine ligand 2,2-bis(diphenyl-phosphanyl)-1,1-binaphthyl (BINAP) and Cs_2CO_3 or *t*-BuOK, as base, promoted ring closure to the 1,4-benzodiazepine-2-one **116** (**Scheme 62**) <2001SL803>. This reaction was quite efficient, proceeding in 68% yield, and the conditions are sufficiently mild that the chirality of the amino acid moiety was completely preserved. A CuI/K_2CO_3-mediated process conducted in DMF at 100 °C performed similarly <2001OL2583>. Amides based on a complementary topology are also effective nucleophiles in this process under copper catalysis with optimized conditions involving heating the aryl halide in DMSO at 110 °C in the presence of CuI (10%), thiophene-2-carboxylic acid as ligand (20%), and K_2CO_3, providing access to 1,4-benzodiazepine-2,5-diones in excellent yields <2004JA14475>.



115 **116** >99% ee

Scheme 62

Aryl fluorides are suitable substrates for type *g* ring closures in the absence of transition metal catalysis when activated by the presence of a powerful electron-withdrawing substituent <2001TL4963, 2003TL1947, 2002OPD488, 2005TL3633>. With both primary and secondary amine nucleophiles, this process occurs upon exposure to a base or by simply heating the substrate in DMSO at 200 °C, conditions which effect thermolytic removal of a BOC group protecting the nucleophilic amine, allowing the combination of two steps into a single process <2001TL4963, 2003TL1947, 2002OPD488, 2005TL3633>. These reactions typically proceed without significant racemization of chiral centers. In the example depicted in **Scheme 63**, further elaboration of the product was accomplished by manipulation of the nitro group after reduction and removal of the N-4 allyl protecting moiety, which allowed access to more elaborately substituted homologues <2005TL3633>.



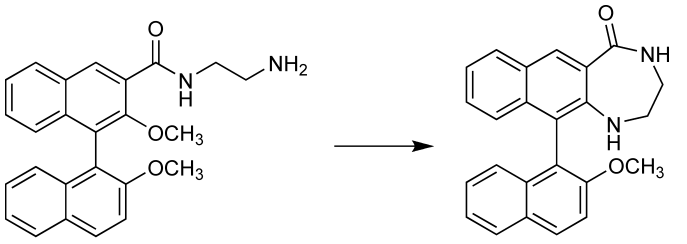
R^1 = H, BOC

Scheme 63

The optically pure bis-naphthalene *ortho*-methoxy amide **117** cyclized to the 1,4-diazepin-5-one **118** in 86% yield and with >95% ee upon refluxing in ethylenediamine for 5 h to provide the first axially chiral 1,4-diazepine derivative (**Scheme 64**) <2000SL1616>. This example of a type *g* ring closure in which the leaving group is MeOH, proceeded in lower yield with an *ortho*-hydroxy substituent, with product distribution largely redirected toward an imidazolidine derivative in which the ethylenediamine reacted solely with the ester. In the structurally simpler salicylic acid ester series, activation of the phenol as the trifluoromethanesulfonate facilitated the S_NAr reaction <1995TL7595>.

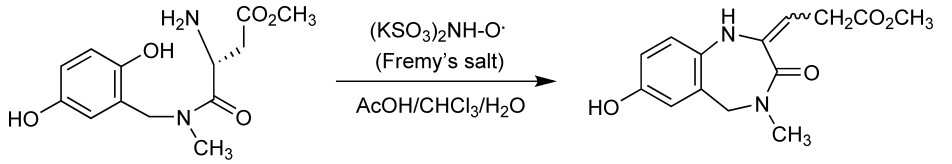
The intramolecular electrophilic capture of an amine by a quinone, accessed by oxidation of a hydroquinone, furnished an intermediate iminoquinone in which tautomerization allowed rearomatization <1999SL865>. The

benzodiazepine-3-one **120**, an intermediate in the synthesis of a glycoprotein IIb/IIIa antagonist, was isolated in 56% yield after oxidation of the substituted hydroquinone **119** using Fremy's salt under acidic conditions (**Scheme 65**); however, the requirement for olefin tautomerization inevitably sacrificed the chiral integrity of the starting material.



117 **118**

Scheme 64

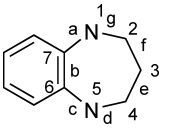


119 **120**

Scheme 65

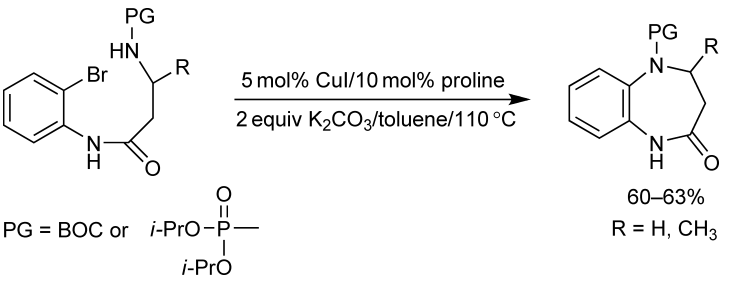
12.06.9.2 1,5-Benzodiazepines

Discussion of preparative methods for 1,5-benzodiazepines is expanded compared to the corresponding sections in CHEC(1984) and CHEC-II(1996), reflecting the development of new synthetic methodology to access these heterocycles. Ring-closure processes are discussed in alphabetical order based on the bond disconnections noted below.



12.06.9.2.1 Type *a* (C–C–N–C–C–C–N)

A Cu-catalyzed, Ullman-type intramolecular arylation of a protected amine afforded 1,5-benzodiazepine-2-ones in good yield via a type *a* ring closure (**Scheme 66**) <2005OL4781>. An *N*-BOC or *N*-diisopropylphosphono (DIPP) protecting group was essential for the success of this reaction since unprotected amines failed to cyclize under the same conditions.

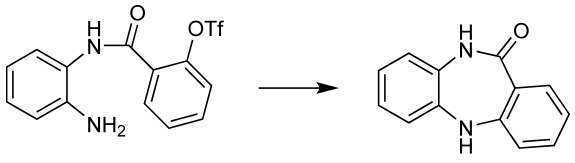


Scheme 66

Aniline nucleophiles readily participate in this type of ring-closure process under palladium catalysis ($Pd(OAc)_2$, BINAP, and Cs_2CO_3 in hot toluene) without resort to protecting groups when an aryl iodide is used <2005T61>.

12.06.9.2.2 Type *d* (C–C–C–C–N–C–C–N)

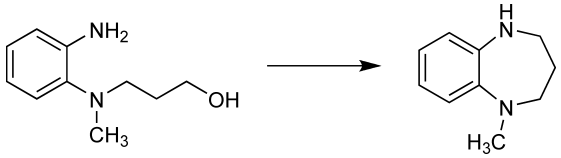
A type *d* S_NAr ring closure of the triflate **121** proceeded smoothly under mild conditions comprising simply heating at reflux in MeCN for 24 h to give **122** in 77% yield (**Scheme 67**) <1995TL7595>. A fluorine leaving group activated by a *para*-NO_2 substituent functioned similarly in a reaction that was promoted by a resin-bound tertiary amine as base <2001TL4963>. Under acidic conditions, primary amine substrates typically cyclize to benzimidazole derivatives.



121 **122**

Scheme 67

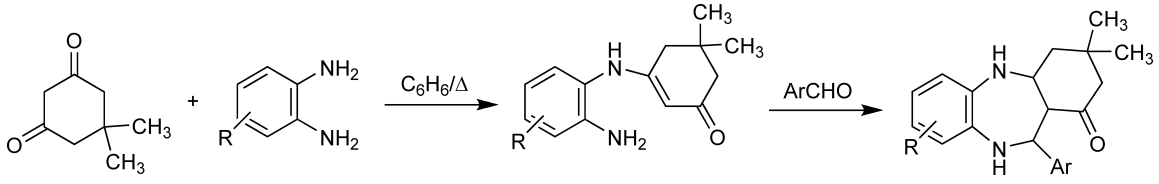
A sequence comprising an Oppenauer-type oxidation, intramolecular imine formation, and reduction, a process mediated by the iridium catalyst $[Cp^*IrCl_2]_2$ and K_2CO_3 in toluene at 120 °C for several days, afforded the structurally simple 1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[1,4]diazepine in 68% yield from *N*-(2-aminophenyl)-(*N*-methylamino)propan-1-ol (**Scheme 68**) <2006TL6899>.



Scheme 68

12.06.9.2.3 Type *de* (N–C–C–N–C–C + C)

The acid-catalyzed reaction of enaminones and enamino-esters with aromatic and aliphatic aldehydes produced 1,5-benzodiazepines via a type *de* ring-closure topology, as depicted in **Scheme 69** <2002JHC55, 2002JHC277, 2002JHC811>. A substituted phenylenediamine, when condensed with dimedone at reflux in anhydrous benzene, provided an enamine in good yield that engaged in a second condensation with an aromatic or heteroaromatic aldehyde to afford the fused tricyclic 1,5-benzodiazepine <2002JHC55, 2004JHC277, 2004KGS949>. Both *ortho*- and *para*-substituted aldehydes participated and the products were extensively characterized spectroscopically, with the single benzylic proton resonating as a doublet at 5.83–6.22 ppm in the ^1H NMR spectrum <2002JHC55>.



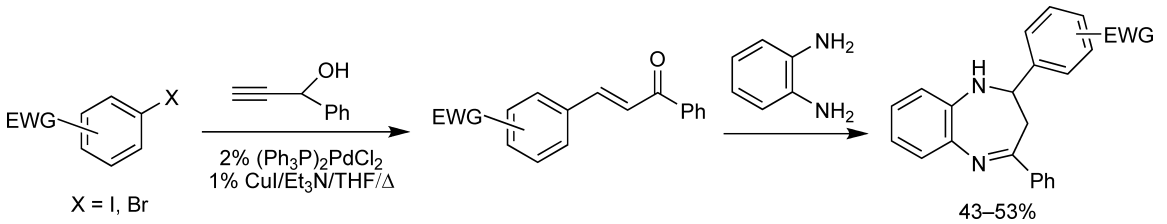
Scheme 69

12.06.9.2.4 Type *dg* (N–C–C–N + C–C–C)

The type *dg* ring disconnection remains the most common and straightforward strategy for accessing the 1,5-benzodiazepine ring system, combining readily available phenylenediamine derivatives with three-carbon components that contain reactive elements at each terminus. Typical electrophiles include acylating agents, carbonyl derivatives that afford imines, optionally as part of a reductive amination protocol, Michael acceptors and alkylating agents, and

combinations thereof. Several new variants that extend the versatility and enhance operational convenience have been described along with new three-carbon fragments and methods of activation.

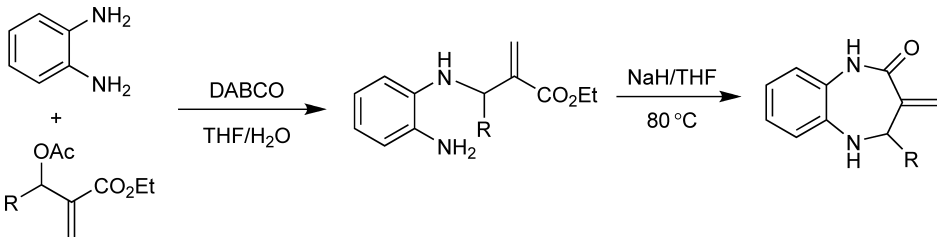
An interesting variant on the reaction of phenylenediamine with an enone relies upon generation of a chalcone *in situ* via the Pd/Cu-catalyzed Sonogashira coupling of an aryl iodide or bromide with a propargylic alcohol, a process that is accompanied by rearrangement to the chalcone (**Scheme 70**) <2004T9463>. The subsequent addition of phenylenediamine provided 1,5-benzodiazepine derivatives in 39–79% overall yield, constituting a convenient, one-pot synthesis that offers advantage based on the structural diversity available in the aryl halide and propargylic alcohol.



Scheme 70

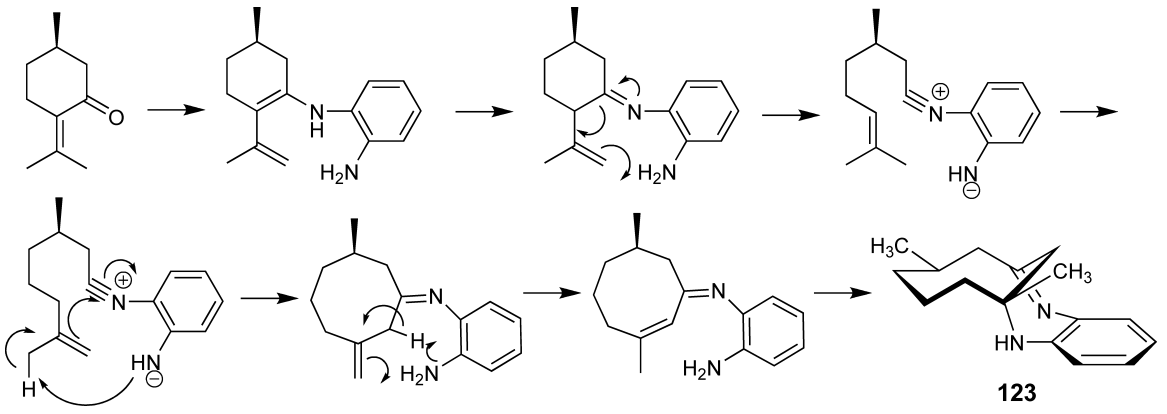
Phenylenediamine reacted with the highly reactive three-carbon electrophile (*N*-mesitylimino)propadienone in THF to afford 4-(mesitylimino)-2,3,4,5-tetrahydrobenzo[*b*][1,4]-diazepin-2-one, as a white solid in 55% yield <2002JOC2619>.

Acetylated derivatives of Baylis–Hillman adducts derived from ethyl acrylate and aromatic and heteroaromatic aldehydes are synthetically accessible three-carbon fragments that readily react with phenylenediamine under the influence of base to provide 1,4-benzodiazepin-2-ones in good overall yield, as depicted in **Scheme 71** <2006S4205>.



Scheme 71

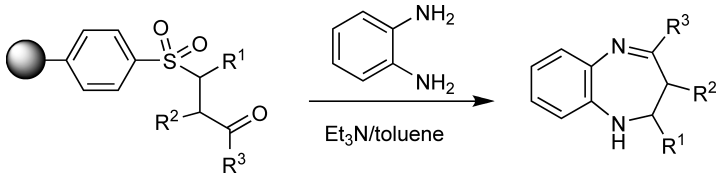
The reaction of phenylenediamine with pulegone in toluene at reflux provided a particularly interesting example of a type *dg* ring construction, producing the bicyclic 1,5-benzodiazepine **123** in 68% yield by the proposed mechanistic pathway outlined in **Scheme 72** <1995T2293>. The structure of **123** was determined after extensive



Scheme 72

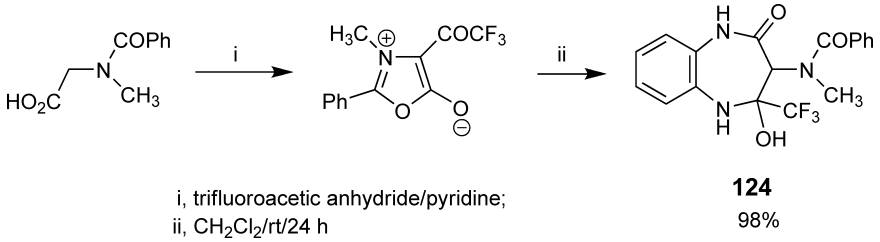
analysis of ^{1}H and ^{13}C NMR spectra with bond connectivities established from correlation spectroscopy (COSY) experiments and long-range coupling data. The stereo- and regioselectivity of this process is quite remarkable, with a 5-Cl- or 5-methyl-substituted phenylenediamine producing a single product in which the substituent resides *para* to the amine moiety. The pattern of substitution was established by NOE difference experiments involving irradiation of the NH while the disposition of the methyl group adjacent to the NH was determined to be equatorial based on NOE enhancement of both of the protons on the adjacent carbon atoms.

Resin-bound γ-keto sulfones, prepared in a straightforward, three-step process comprising alkylation of a resin-bound sulfinate salt, alkylation of a sulfone-supported anion with an epoxide, and Jones oxidation of the γ-hydroxy sulfone, provided a source of structurally diverse three-carbon fragments <2004JCO928>. Reaction with a phenylenediamine to give the 1,5-benzodiazepine presumably occurs via initial imine formation followed by expulsion of the resin-bound sulfone, which acts as a traceless linker (**Scheme 73**). Yields for this process are a modest 10–38%.



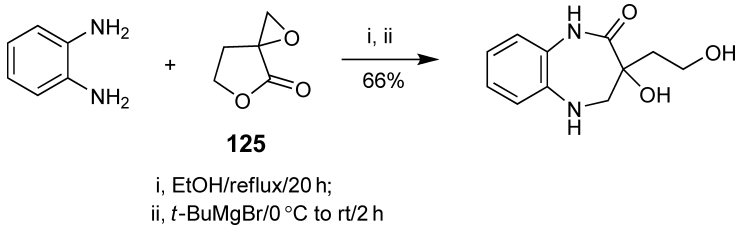
Scheme 73

Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-oloates (münchnones), readily available from glycine, condensed with phenylenediamine at 25 °C in CH_2Cl_2 to afford 3-amino-1,5-benzodiazepine derivatives in excellent yield (**Scheme 74**) <2001H(55)1919>. An *N*-alkyl substituent in the münchnone is essential for success, since the single *N*-phenyl derivative examined gave a complex mixture. The structure of the 1,5-benzodiazepin-2-one **124** was confirmed by X-ray crystallographic analysis, revealing a boat conformation in which the CF_3 and amine moieties are in a *trans*-relationship and occupy equatorial positions.



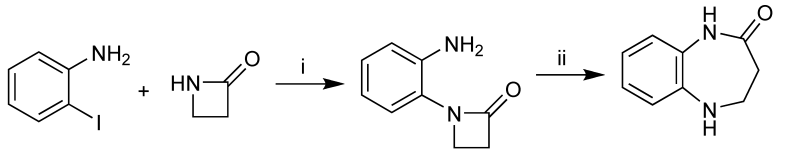
Scheme 74

Reaction of the spiroepoxy lactone **125** with phenylenediamine in EtOH at reflux provided the 1,5-benzodiazepin-2-one after amide formation, mediated by *t*-BuMgBr (**Scheme 75**) <2003S1209>. The scope of this approach may be limited since the single spiroepoxy lactone substituted on the epoxide ring that was studied was an ineffective partner.



Scheme 75

An interesting tandem, Cu-catalyzed arylation of 2-azetidinone with 2-iodoaniline followed by transamidation promoted by 50 mol% $Ti(OiPr)_4$ in toluene at 110 °C provided the parent 1,5-benzodiazepin-2-one in 92% yield (**Scheme 76**) <2004JA3529>.

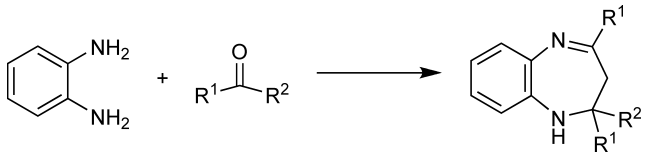


i, 5 mol% CuI/10 mol% *N,N*-dimethylethylenediamine/2 equiv K_2CO_3/toluene/110 °C;
ii, Ti(O*i*-Pr)$_4$/toluene/110 °C

Scheme 76

12.06.9.2.5 Type *e* (C–N–C–C–N–C–C)

The condensation of a phenylenediamine with two molecules of a ketone provided ready access to 2,3-dihydro-1,5-benzodiazepines (**Scheme 77**). Continued interest in this approach has led to further optimization of catalysts and reaction conditions with a view to enhancing convenience and broadening application to a wider range of substrates. The key step in this process is the tautomerization of one of the imines of the intermediate diamine to an enamine which cyclizes via a 7-*endo-trig*-process. A sampling of the effective catalysts that have been developed, many of which are used under heterogeneous, solvent-free conditions, include $MgO/POCl_3$ <2001TL1127>, $Yb(OTf)_3$ <2001TL3193>, $YbCl_3$ <2006SC457>, $InBr_3$ <2005S480>, Al_2O_3/P_2O_5 <2001H(55)1443>, $Sc(Otf)_3$ <2005TL1811>, molecular iodine <2005SL1337>, PVP-supported $FeCl_3$ under microwave conditions <2005MI67>, $Ag_3PW_{12}O_{40}$ (a heteropoly acid that is recyclable) <2004S901>, AcOH/microwave <2002TL1755>, and superacid sulfated zirconia <2003TL4447>. An ionic liquid reaction medium promoted this reaction in the absence of an added catalyst in less than an hour at 25 °C and in 87–96% yield <2003TL1835>. In the examples described, unsymmetrical alkyl methyl ketones afforded single products resulting from reaction of the less-substituted enamine <2005TL1811, 2005SL1337> while the monosubstituted phenylenediamines afforded products in which the substituent resides *para*- to the imine moiety of the product <2005MI67, 05S480>.

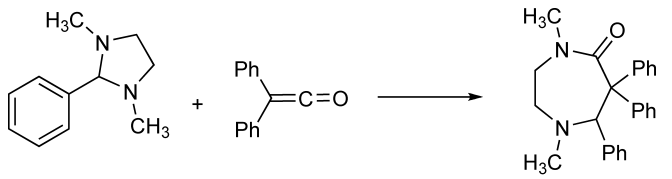


Scheme 77

12.06.10 Ring Syntheses by Transformation of Another Ring

12.06.10.1 Monocyclic

The reaction of diphenylketene with the imidazolidine **126**, catalyzed by $ZnCl_2$ in Et_2O, provided a single example of a reaction that delivers the 1,4-diazepin-5-one **127** in 64% yield (**Scheme 78**) <1998S653>. This reaction is

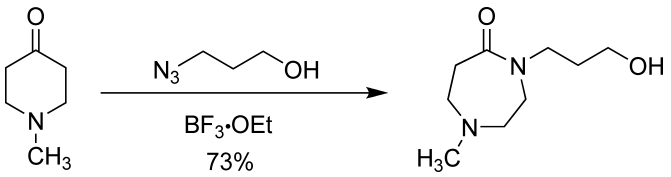


126 **127**

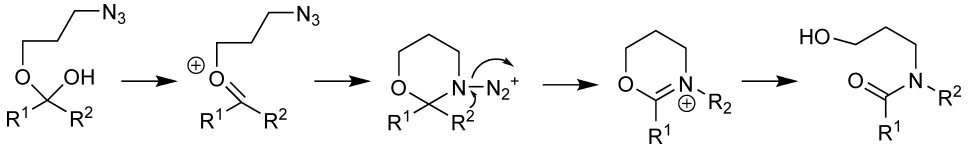
Scheme 78

thought to be initiated by an initial nucleophilic attack of an aminal nitrogen atom on the ketene, followed by ring opening of the imidazolidinium and intramolecular capture of the resultant iminium by the enolate, the final step formally being a type *f* ring closure.

The Schmidt reaction of cyclic ketones with hydrazoic acid affords convenient access to ring-expanded N-unsubstituted lactams but extension of this process to alkyl azides to provide *N*-alkyl lactams is capricious in nature. A protocol that takes advantage of a temporary tethering strategy markedly improved this reaction by rendering it functionally intramolecular, and has been applied to piperidinone substrates to provide access to *N*-alkyl-1,4-diazepan-5-ones (**Scheme 79**) <1997T16241, 2005OL1059>. Basic and nonbasic piperidinones reacted with 3-azidopropanol under Lewis acid catalysis to form ring-expanded lactams in a process postulated to proceed through the intermediacy of a hemiacetal, the precursor to a reactive oxonium intermediate which readily reacts with the tethered azide, as summarized in **Scheme 80**. The products were isolated in good yield and the inclusion of substituents in the hydroxyl azide moiety provided 1,4-diazepan-5-ones that are useful scaffolds for the synthesis of peptidomimetics.

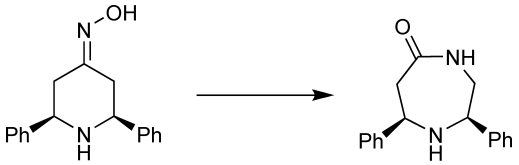


Scheme 79



Scheme 80

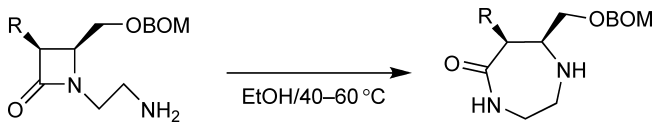
Improved preparative procedures to promote the Beckmann rearrangement of a piperidinone oxime to afford ring-expanded diazepine derivatives have been described, including the use of silica-supported MoO_3, sulfonation, or the dehydrating agent 2-chloro-1,3-dimethylimidazolinium chloride <1999JOC5832, 2004TL4759, 2005MI48>. An illustrative example is the rearrangement of the oxime of 2,6-diphenylpiperidin-4-one **128** which afforded the diazepin-5-one **129** in 89% yield after exposure to silica-supported MoO_3 in EtOH at reflux for 18 h, (**Scheme 81**) <2004TL4759>.



128 **129**

Scheme 81

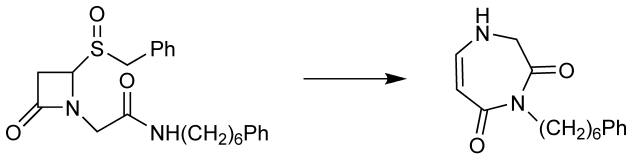
The thermally induced intramolecular transamidation of aminoethyl-substituted *β*-lactams, readily obtained by the Staudinger reaction of ketenes with imines, offers a useful approach to libraries of monocyclic and fused bicyclic 1,4-diazepine-5-ones (**Scheme 82**) <2004OL3361, 1998TL9539, 2003EJO1319, 2005T1531>. The transamidation



Scheme 82

reaction is promoted by electron-deficient ring substituents at C-3 of the β-lactam, which contribute to activation of the carbonyl moiety. For example, a C-3 phenoxy derivative in cyclized 10-fold faster than the C-3 unsubstituted β-lactam.

An electron-withdrawing sulfoxide substituent at C4 of a β-lactam was an even more effective activating element, since the β-lactam **130** underwent a ring-expansion reaction by simply stirring at 25 °C in a pH 9 buffer (**Scheme 83**) <2001SC2713>. In this reaction, the β-lactam is sufficiently activated to react with an amide as the nucleophilic species, affording the N-substituted 3,4-dihydro-1*H*-1,4-diazepine-2,7-dione **131** in 80% yield, as a white solid. The structure was confirmed by both NMR methods and single crystal X-ray analysis.

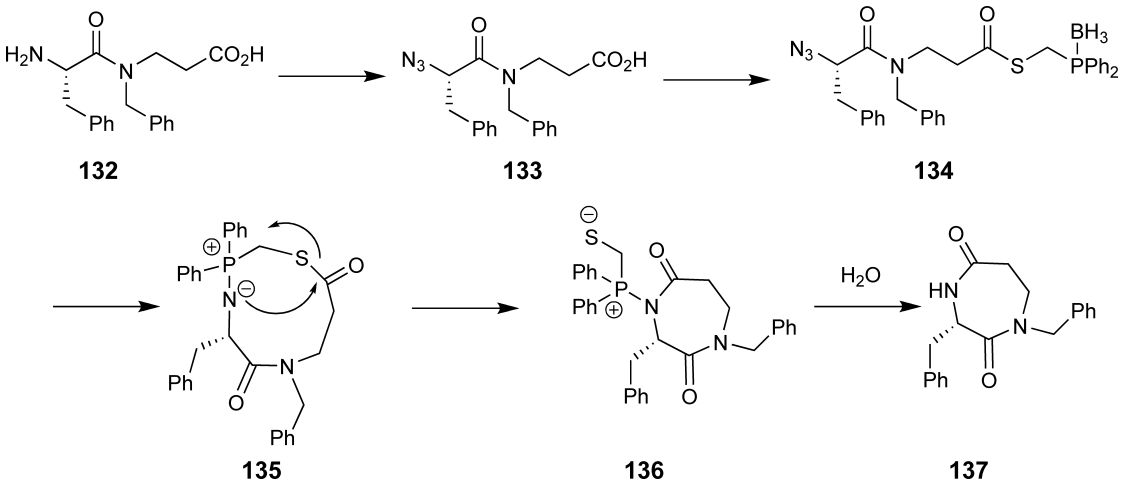


130 **131**

Scheme 83

Ring expansion of 2,6-diaryl-4-azidopyridine derivatives occurred upon irradiation for 3 h in a 1:1 mixture of MeOH/dioxane containing NaOMe to afford the 3,5-diaryl-1*H*-1,4-diazepin-7(6*H*)-one in 60–70% yield after hydrolysis of the imino ether intermediate <2000HCA384>. This rearrangement was postulated to be initiated by an intramolecular reaction of the singlet nitrene, generated by extrusion of nitrogen, to give a strained azirine which reacts with methoxide to give an antiaromatic 1,4-diazepine. Tautomerization afforded the more stable imino ether isomer which hydrolyzed to the amide upon exposure to water during isolation. Unsymmetrically substituted 4-azido pyridine derivatives subjected to this process gave mixtures of the two possible diazepin-4-one isomers. Similar ring expansions have been observed under thermal conditions in the gas phase <2001JA7923>.

An innovative application of the Staudinger ligation reaction was developed to cyclize dipeptide-based ω-amino acid derivatives to medium ring lactams, including 1,4-diazepine derivatives (**Scheme 84**) <2003AGE4373>. In this procedure, the amine of **132** was converted to an azide **133** by diazotransfer from triflyl azide and the acid coupled with the borane adduct of diphenylphosphanylmethanethiol, essential to protect against premature reaction of the phosphane with the azide. The phosphane is released from **134** by treating with 1,4-diazabicyclo[2.2.2]octane (DABCO), promoting a Staudinger reaction with the azide. Elimination of nitrogen furnished an ylide intermediate **135** which reacted intramolecularly with the thioester to provide the 1,4-diazepin-2,5-dione **137** in 80% yield after hydrolytic decomposition of the amidophosphonium salt **136**. The versatility of this process to produce 1,4-diazepines with different substitution patterns was demonstrated with three closely related substrates, which gave cyclic products in yields ranging from 29% to 60%.

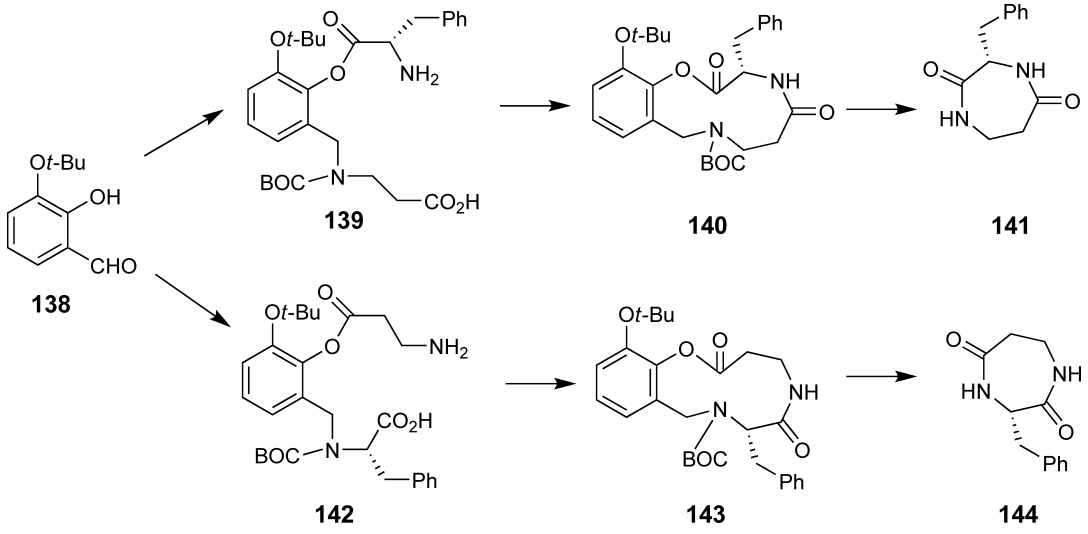


132 **133** **134**

135 **136** **137**

Scheme 84

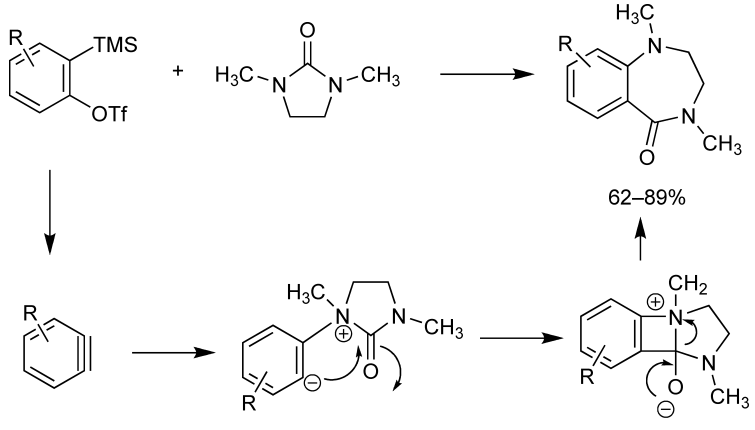
These products were also prepared with similar efficiency by a related strategy that involved a ring contraction mediated by an intramolecular acylation reaction using the benzaldehyde **138** as a templating auxiliary, as summarized in **Scheme 85** <2003OBC1830>. The presence of the aryl O*t*-Bu substituent in **138** is essential to temper reactivity of the ester moiety during construction of the macrolactam precursors **139** and **142** but is readily removed concomitantly with the BOC moiety upon exposure to CF_3CO_2H in CH_2Cl_2. Transannular lactam formation occurred in 79% overall yield when the macrocyclic esters **140** and **143** were treated with $NaHCO_3$ in EtOAc. The vestige of the template moiety was removed from the newly formed amide element by a straightforward, two-step process comprising methylation of the phenols and reduction with Na in liquid NH_3 to give the 1,4-diazepines **141** and **144**.



Scheme 85

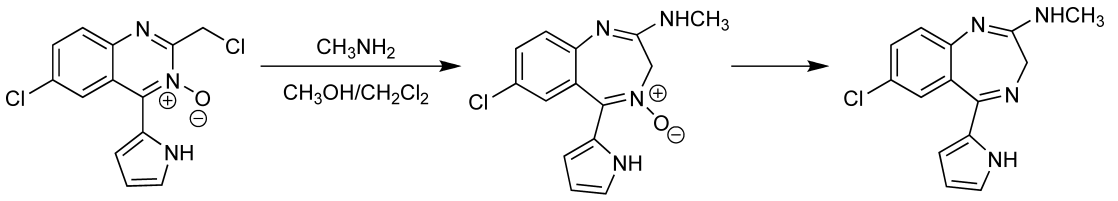
12.06.10.2 1,4-Benzodiazepines

Cyclic ureas add to *in situ*-generated benzynes to give 1,4-benzodiazepine-5-ones in good yield by the mechanism depicted in **Scheme 86** <2002AGE3247>. 3-Substituted benzynes react in a regiospecific fashion, directing the urea nitrogen to add to the sterically less encumbered atom of the transient cyclic alkyne.



Scheme 86

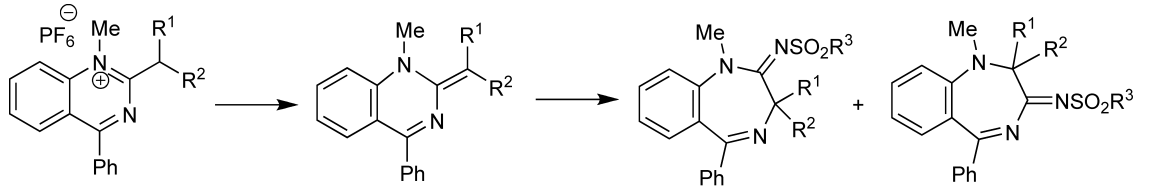
Addition of methylamine to the 2-position of the quinazoline *N*-oxide **145** resulted in a ring expansion to give the 1,4-benzodiazepine *N*-oxide **146**, which was reduced with Raney nickel to provide an improved synthesis of the human immunodeficiency virus (HIV) Tat antagonist **147**, (**Scheme 87**) <1995BMC391>.



145 146 147

Scheme 87

Deprotonation of the quinazolinium salt **148** with NaH or KH gave the dienamine **149** which cycloadds to methylsulfonyl azide or trifluoromethysulfonyl azide included in the reaction to afford a mixture of two sulfonylimino-substituted benzodiazepine derivatives **150** and **151** after a ring expansion mediated by the expulsion of N_2 (**Scheme 88**) <2000EJO1577>.

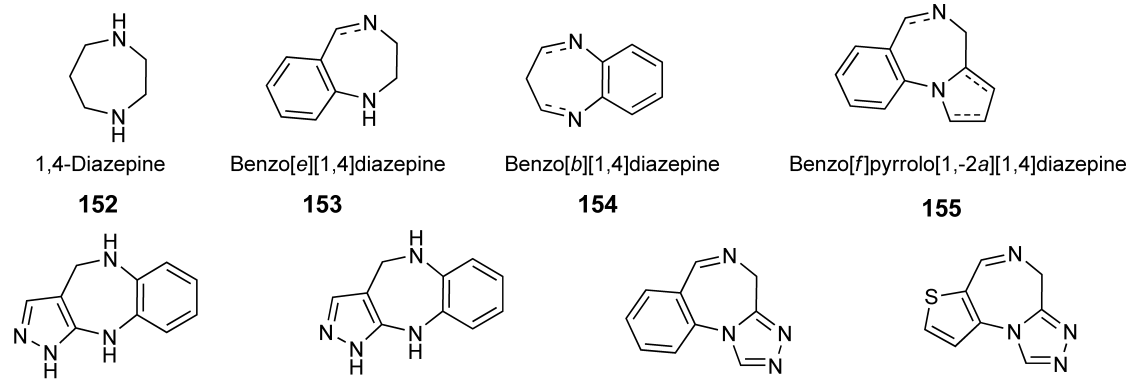


148 149 150 151

Scheme 88

12.06.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Preparative routes to assemble substituted 1,4-benzodiazepines are well established, a direct result of the synthetic utility, the many applications in drug design, and commercial success of compounds based on this ring system. As a consequence, synthetic strategies that reflect almost all of the possible topological disconnections have been described in the literature and the continued interest in accessing uniquely functionalized molecules provides a strong impetus to develop new methodology. Access to 1,5-benzodiazepines and 1,4-diazepines fused to a wide array of heterocyclic rings is similarly mature. The importance of 1,4-diazepines is reflected in a substructure search conducted in SciFinder®, which yielded over 80 000 compounds representing more than 2000 different ring systems! The most highly represented rings systems include homopiperazine **152**, 1,4-benzodiazepine **153**, 1,5-benzodiazepine **154**, and the more complex fused ring heterocycles **155–159** that are depicted in generic form.



1,4-Diazepine **152**

Benzo[*e*][1,4]diazepine **153**

Benzo[*b*][1,4]diazepine **154**

Benzo[*f*]pyrrolo[1,-2*a*][1,4]diazepine **155**

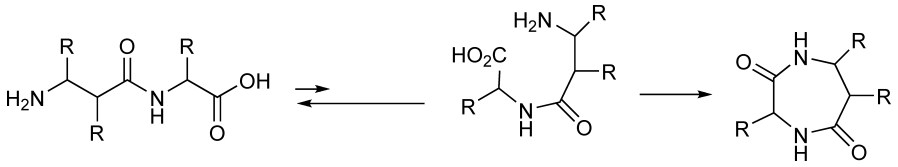
Tetrahydrobenzo[*b*]pyrazolo[3,4-*e*][1,4]diazepine **156**

Tetrahydrobenzo[*b*]pyrazolo[3,4-*e*][1,4]diazepine **157**

Benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine **158**

Thieno[2,3-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine **159**

Derivatives of homopiperazine **152** are the most prominent examples of 1,4-diazepines, largely represented by derivatives that are unsubstituted at the ring carbon atoms and reflecting relatively nonspecific applications. However, the burgeoning interest in using this heterocycle, as a peptidomimetic scaffold, is catalyzing the synthesis and evaluation of more highly substituted homologues. To date, the majority of the synthetic approaches that have been developed to access this heterocyclic rely upon standard reactions, including amide bond formation and alkylation procedures involving the ring nitrogen atoms, while the chirality at the ring carbon atoms is most typically derived from acyclic starting materials. The synthesis of nonfused 1,4-diazepine peptidomimetic scaffolds via lactamization is often hampered by the conformational preferences of the dipeptide substrate that slow ring formation, a consequence of the amide bond being reluctant to assume the generally disfavored *s-cis*-conformation (**Scheme 89**).



Scheme 89

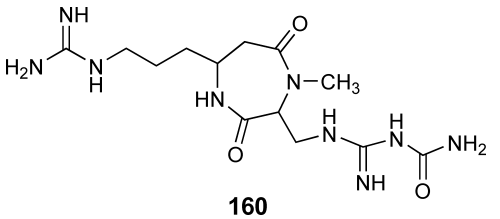
This problem is ameliorated in substrates that afford 1,4-benzodiazepines, a relatively straightforward process that has contributed to these ring systems enjoying a prominent role in medicinal chemistry and producing a wide range of biological activities. The ready availability of aniline and *ortho*-substituted aniline derivatives provides the basis for much of the synthetic methodology that has been developed toward 1,4-benzodiazepine derivatives. The advent of combinatorial strategies and the optimization of the application of procedures such as the Ugi reaction have expanded the utility of these procedures, providing access to molecules incorporating considerably greater structural diversity.

The development of synthetic approaches to 1,4-benzodiazepines that improve on precedented bond disconnections or allow completely new ring-closure topology has grown in concert with the significant expansion in the application of transition metal catalysis to mediate C–N and C–C bond formation. These processes typically proceed under conditions that tolerate a wide range of functionality and have facilitated entry into novel functionalized derivatives by expanding the pool of synthons. Moreover, the advent of improved methods for ring functionalization, including the enantioselective introduction of substituents at C-3 of 1,4-benzodiazepin-2-ones through enolate alkylation or aldol chemistry, has allowed access to a wider range of substitution patterns from preformed diazepine ring systems.

The phenylenediamine moiety embedded in 1,5-benzodiazepines provides a logical synthetic basis for ring formation in which the additional three carbon atoms are installed using 1,3-dicarbonyl or α,β-unsaturated carbonyl synthons. While these synthons are readily made using standard aldol or Claisen condensation chemistry, they can be performed in the presence of phenylenediamine derivatives that allow concomitant diazepine ring formation in a three-component reaction process. The synthesis and elaboration of 1,5-benzodiazepine derivatives have also benefited from the application of transition metal catalysis, processes that most commonly rely upon the formation of the N-C(aryl) bond via nucleophilic substitution. In contrast to developments with the 1,4-benzodiazepine ring system, research into the asymmetric synthesis of 1,5-benzodiazepine derivatives has been limited, possibly a consequence of the tautomeric lability of partially unsaturated ring systems that may lead to racemization of singly substituted chiral carbon atoms.

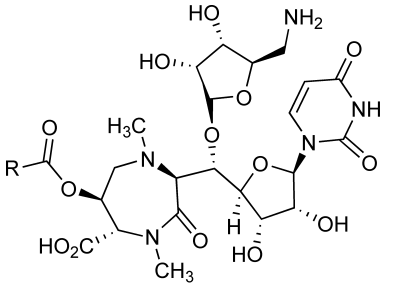
12.06.12 Important Compounds and Applications

Compounds derived from the 1,4-benzodiazepine heterocycle are a prominent class of CNS drugs that demonstrate a range of clinically important properties and many are well-established commercial successes. As a consequence, fused ring 1,4-diazepines have dominated studies with this class of heterocycles in the several decades since the original discovery. However, the 1,4-diazepine ring system demonstrates considerable versatility as a platform for drug design and a wide range of biological activities have been described for structurally diverse members of the class. Monocyclic 1,4-diazepines are emerging as a medicinally useful chemotype that occurs naturally. For example, TAN-1057A-D **160** is a member of a series of 1,4-diazepin-2,5-dione-containing dipeptides isolated from *Flexibacter* bacteria that demonstrate antibiotic activity toward methicillin-resistant *Staphylococcus aureus* <1997JA11777>. This diazepine core has also been used as a scaffold in the design of inhibitors of lymphocyte function-associated antigen-1 (LFA-1), a leukocyte adhesion receptor involved in inflammation and immune responses <2005BML1217>.



160

The caprazamycins **161** are a family of liponucleoside antibiotics isolated from a *Streptomyces* strain that contain a 1,4-dazepin-2-one ring system <2005JAN327, 2005AGE1854>. The *N*,*N*-dialkylated-1,4-diazepane, DAT-582 **91**, is a potent and selective serotonin 5-HT_3 antagonist with antiemetic activity <1995CPB1912>, while AS-8112 **162** combines potent 5-HT_3 and dopamine D_2 antagonism in a single molecule that broadens the antiemetic spectrum <2003JME702, 2001BJP253>.



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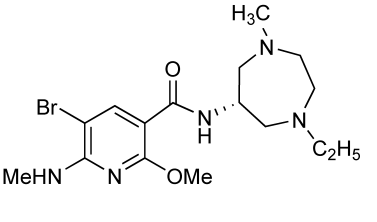
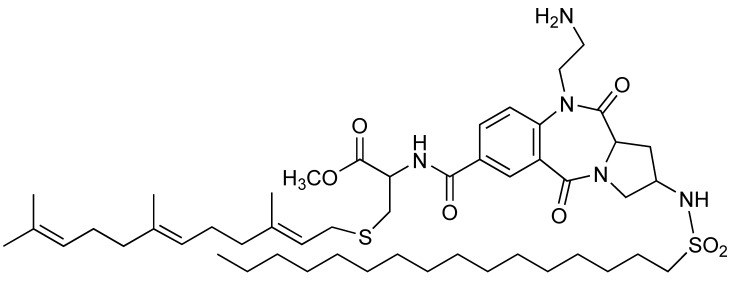


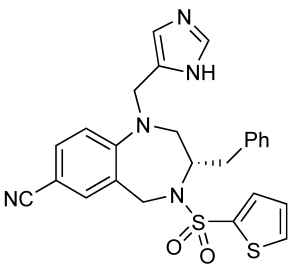
AS-8112

162

The 1,4-benzodiazepin-2,5-dione **163** is a potent inhibitor of acyl protein thioesterase-1 (APT-1), an enzyme that palmitoylates a range of proteins involved in biological signaling <2005AGE4975>. The design of this compound anticipated peptidomimetic activity based on prior studies that established the value of the parent heterocycle in this role. The tetrahydro-1,4-benzodiazepine **164**, designated as BMS-214662, potently inhibits farnesyltransferase and demonstrates antitumor activity *in vitro* and *in vivo* <2000JME3587>. The benzothieno-1,4-diazepin-5-one **165** is an exquisitely potent inhibitor of herpes simplex virus (HSV) replication in cell culture ($EC_{50} = 400$ pM), that appears to interfere with a cellular process involved in the expression of viral immediate early genes <2002BML2981>.



163



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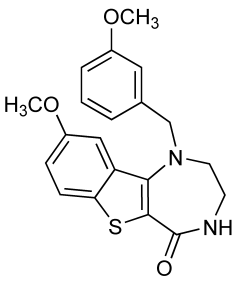
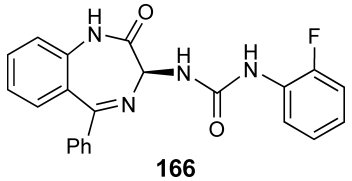


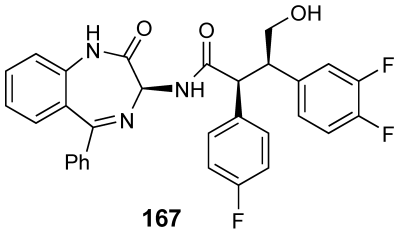
165

Substituted derivatives of 3-amino-5-phenyl-1,4-benzodiazepin-2-one continue to be a rich source of compounds that display a diverse range of biological properties. The 2-fluorophenylurea **166** is an inhibitor of respiratory syncytial virus (RSV) that appears to act by inhibiting the nucleocapsid (N) protein <2006JME2311>. This compound is the first orally active inhibitor of RSV to be advanced into clinical studies.



166

The 2,3-diphenyl-4-hydroxybutyramide **167** is an extremely potent inhibitor of the mammalian aspartyl protease γ-secretase, ($IC_{50} = 60$ pM), that was profiled as an inhibitor of amyloid precursor protein processing with potential utility in the prevention and treatment of Alzheimer's disease <2003JME2275>. The *N*-1-alkylated-3-amido-1,4-benzodiazepin-2-one **168** is a selective blocker of the cardiac slowly activating delayed rectifier potassium current (I_{Ks}), of sufficient interest as a potential class III antiarrhythmic agent that a process suitable for providing clinical grade material was developed <1997JME3865, 1999T909>. Extending the amino substituent to the structurally more complex moiety found in the urea **169** provides a benzodiazepine derivative that is representative of a well-explored series of calcitonin gene-related peptide (CGRP) antagonists <2006BML2595, 2006BML5052>.



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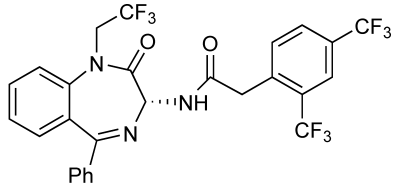

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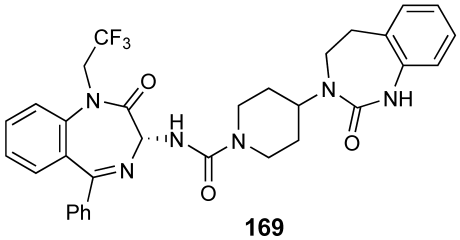
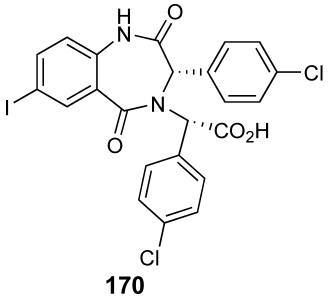
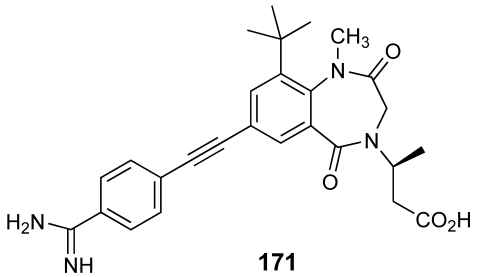


169

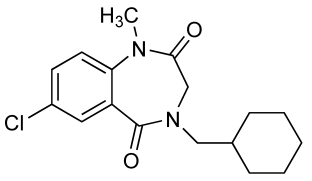
The carboxylic acid **170** is a potent inhibitor of the oncogenic HDM2 protein binding to the tumor suppressor p53 ($IC_{50} = 220$ nM) <2005BML1857, 2005JME909>, while the C-9 *tert*-butyl moiety of the 1,4-benzodiazepin-2,5-dione **171** stabilizes an active atropoisomer recognized by the blood platelet glycoprotein IIb/IIIa receptor <1997JME717>. The 1,4-benzodiazepine-2,5-dione **172** is one of a series of compounds that demonstrate potent antiparasitic activity *in vitro* toward a clinically derived strain of *Leishmania donovani* <2007BML624>. The antibiotic diazepinomicin **173** is a rare example of a 1,5-benzodiazepine-based natural product that was isolated from a marine actinomycete <2004JNP1431>. A 1,5-benzodiazepin-2-one core was used to design potent inhibitors of the cysteine protease caspase-1, also known as interleukin-1β converting enzyme <2002BML1225>.



170



171



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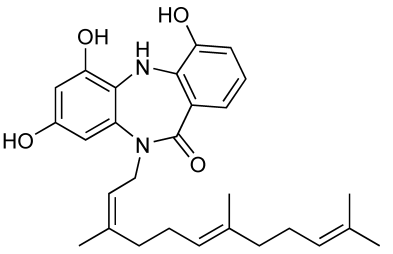

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Further Developments

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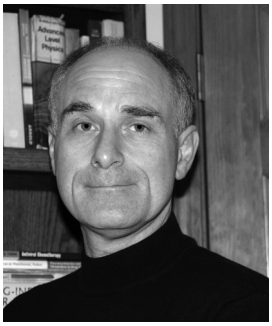
Biographical Sketch



Nicholas A. Meanwell is currently executive director of chemistry at the Bristol-Myers Squibb Pharmaceutical Research Institute in Wallingford, Connecticut. He received his Ph.D. degree in 1979 from the University of Sheffield for studies conducted under the supervision of Dr. D. Neville Jones that focused on the application of alkenyl sulfoxides as synthetic precursors of prostaglandin analogues. A postdoctoral fellowship (1979–82) with Professor Carl R. Johnson at Wayne State University was devoted to the development of new synthetic methodology based on sulfur chemistry and its application to total synthesis. In 1982, he joined Bristol-Myers Squibb where he designed and synthesized inhibitors of blood platelet aggregation as part of the cardiovascular therapeutic focus before contributing to the identification and development of neuroprotective agents. The large-conductance, Ca^{2+}-dependent potassium channel opener Maxipost™, currently in Phase III clinical trials, emerged from those studies. Since 1994, he has been responsible for a team of chemists designing and synthesizing antiviral agents directed toward new developing therapeutic options for the treatment of HIV, HCV, RSV, and influenza.

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