# 8.08
# 1,3,4-Oxadiazines and 1,3,4-Thiadiazines

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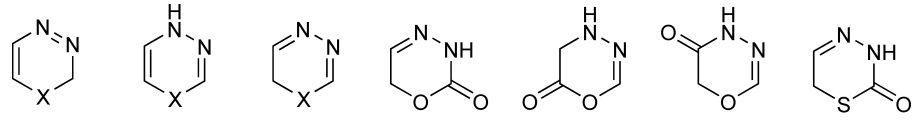
## 8.08.1 Introduction

Of the different oxa- and thiadiazines, the 1-oxa- and 1-thia-3,4-diazines have been most extensively studied. The 1-oxa- and 1-thia-3,4-diazines may exist in different tautomeric forms. The compounds **1–3** shown are designated as 2*H*-1,3,4-oxadiazines **1** (X = O), 4*H*-1,3,4-oxadiazines **2** (X = O), 6*H*-1,3,4-oxadiazines **3** (X = O), 2*H*-1,3,4-thiadiazines **1** (X = S), 4*H*-1,3,4-thiadiazines **2** (X = S), and 6*H*-1,3,4-thiadiazines **3** (X = S). The 4*H*-derivatives represent potentially antiaromatic 8π-systems. 3*H*,6*H*-1,3,4-Oxadiazin-2-ones **4** and 4*H*,5*H*-1,3,4-oxadiazin-6-ones **5** are lactones. 4*H*,6*H*-1,3,4-Oxadiazin-5-ones **6** are δ-lactams. 3*H*,6*H*-1,3,4-Oxadiazin-2-ones **4** and 3*H*,6*H*-1,3,4-thiadiazin-2-ones **7** exhibit excellent cardiotonic activities (Section 8.08.11). 1-Oxa- and 1-thia-3,4-diazines have been the subject of numerous review articles <B-1959MI(IVc)1559, 1969ZC361, 1970QRS177, 1978MI135, 1979COC(4)1051, 1984CHEC(3)1039, 1988AHC(50)81, 1988MI38, 1991KGS435, 1991KGS1443, 1996CHEC-II(6)737, 1998H(49)557, 1998HOU(E9c)427, 1998HOU(E9c)483, 1998HOU(E9c)518>.




## 8.08.2 Experimental Structural Methods

### 8.08.2.1 Spectroscopic Studies

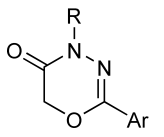
#### 8.08.2.1.1 Ultraviolet and infrared spectra

The carbonyl stretching frequency for 1,3,4-oxadiazin-2-ones is seen at 1660–1710 $cm^{-1}$ <2003CHE1057>. The main infrared (IR) absorption bands for some substituted 4*H*-1,3,4-thiadiazines have been assigned <2003SL2392>. 2,5-Di(trifluoromethyl)-6,6-diaryl-6*H*-1,3,4-thiadiazines absorb at 261–279 nm <1998EJO2861>. 2-Alkylimino-3-alkyl-6*H*-1,3,4-thiadiazines exhibit absorption maxima at 227–243 and 331–339 nm, whereas for 2-dialkylamino-6*H*-1,3,4-thiadiazines $\lambda_{max}$ occurs at 297 and 344 nm <2006UP1>.

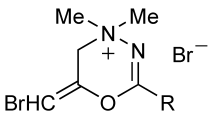
### 8.08.2.1.2 NMR spectra

#### 8.08.2.1.2(i) Proton NMR spectra

5.6-Dihydro-5-oxo-4*H*-1,3,4-oxadiazine-4-propanenitriles **8** (R = $CH_2$–$CH_2$–CN) exhibit C-6 proton resonances at $\delta$ 4.78–4.85 all $\delta$ values in ppm <2002HCA559>. The C-5 methylene protons of 6-bromomethylidene-4,4-dimethyl-5*H*-1,3,4-oxadiazinum bromides **9** (R = Ar, HetAr) appear in the range 4.84–4.95 <2003RJO1561>. 5-Phenyl-2,3,5,6-tetrahydro-1,3,4-oxadiazin-2-ones **10** (R = H, Bn) exhibit C-6 methylene protons at $\delta$ 3.40–3.75 <2000S1170>.




**8**

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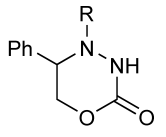
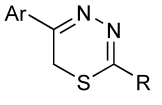
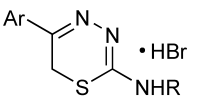



**10**

2-Amino-, 2-alkylamino-, and 2-morpholino-5-aryl-6*H*-1,3,4-thiadiazines <1998RJO417, 2004IJH283, 2006UP1, 2006UP2> **11** (R = $NH_2$, MeNH, EtNH, morpholino) have C-6 methylene proton resonances at 3.45–3.61, whereas 2-amino- and 2-alkylamino-5-aryl-6*H*-1,3,4-thiadiazine hydrobromides **12** exhibit C-6 methylene proton resonances at $\delta$ 4.27-4.36 <2001JME3231>. The C-6 proton signal of 2-amino-5-methoxycarbonyl-6-phenyl-6*H*-1,3,4-thiadiazine **13** is found at $\delta$ 5.46 <1996CHE1089>. The C-5 proton resonance of 2-amino-4-phenyl-4*H*-1,3,4-thiadiazine derivative **14** <2005H(65)1569> appears at $\delta$ 7.29, whereas 2-isopropylimino-3,4-dimethyl-5-aryl-4*H*-2,3-dihydro-1,3,4-thiadiazines **15** have C-6 proton resonances at $\delta$ 6.26–6.30 <2003SL2392>. 5,6-Dihydro-5-oxo-4*H*-1,3,4-thiadiazines **16** (R = aryl) exhibit C-6 proton resonances at $\delta$ 3.47–3.49 <1998SUL163>.




**11**

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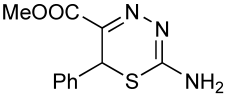


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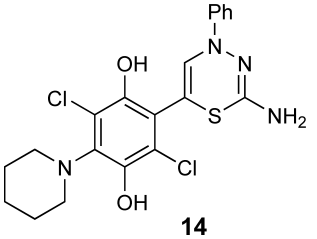


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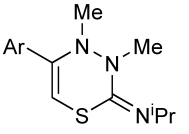
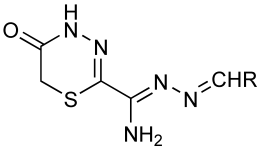


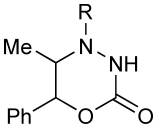

**15**



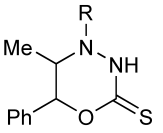

**16**

#### 8.08.2.1.2(ii) Carbon-13 NMR

The carbon resonances for the 2-alkylamino-5-phenyl-6*H*-1,3,4-thiadiazines **11** occur at $\delta$ 30.6–39.1 (C-6) and $\delta$ 149.4–149.6 (C-2) <2006UP2>. 5-Phenyl-2,3,5,6-tetrahydro-1,3,4-oxadiazin-2-ones **10** (R = H, Bn) exhibit carbon resonances at $\delta$ 55.6–59.6 (C-6) and $\delta$ 151.7–155.1 <2000S1170>. The carbon resonances for 2,3,5,6-tetrahydro-1,3,4-oxadiazin-2-ones **17** (R = $Pr^n$, $Bu^t$, Bn) are at $\delta$ 152–158.8 (C-2) <2002JHC823>. Carbon resonances at $\delta$ 180.1–182 (C-2) have been reported for 2,3,5,6-tetrahydro-1,3,4-oxadiazin-2-thiones **18** <2002JHC1113>.



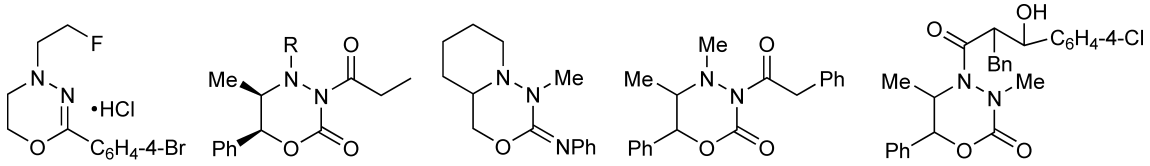

**17**




**18**

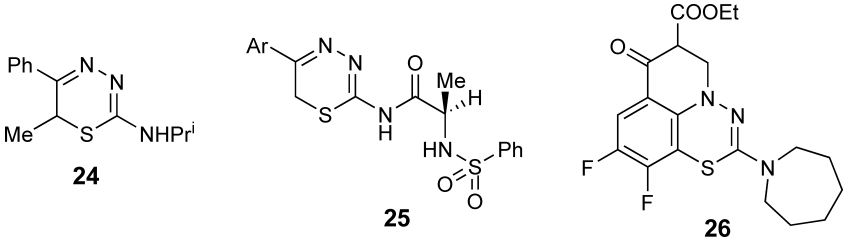
### 8.08.2.2 X-Ray Crystallography

The X-ray crystal structures for 2-(4-bromophenyl)-4-(2-fluoroethyl)-5,6-dihydro-4*H*-1,3,4-oxadiazine hydrochloride **19** <1995CJC853>, 3-*N*-propionyl-4-*N*-bornyl-5-methyl-4-phenyl-3,4,5,6-tetrahydro-1,3,4-oxadiazin-4-one **20** (R = *N*-bornyl) <2005TA1047>, 2-phenylimino-3-methyl-perhydropyrido[1,2][1,3,4]-oxadiazine **21** <1997H(45)927> and 4,5-dimethyl-6-phenyl-3-phenylacetyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one **22** <2001T9789> have been recorded. The X-ray crystal structure of 3,5-dimethyl-6-phenyl-3,4,5,6-tetrahydro-1,3,4-oxadiazin-2-one derivative **23** has been reported <2004JOC727>. The structure of **23** may be described as a twisted boat conformation.




**19** **20** **21** **22** **23**

The X-ray crystal structure has been determined for 2-isopropylamino-5-phenyl-6-methyl-6*H*-1,3,4-thiadiazine **24** <1993ACS302>. The structure of this compound may be described as a skew boat form. The bond lengths C(2)–NHPr$^{i}$ and C(2)–N(3) indicate that the amine tautomer is preferred in the solid state. Analogous results are observed for *N*-[5-aryl-6*H*-1,3,4-thiadiazin-2-yl]2-[(phenylsulfonyl)amino]propanamides **25** <2001AXC593>. The X-ray crystal structure of the 1,3,4-thiadiazino[6,5,4-*i,j*]quinoline derivative **26** has been reported <1998MC131>.



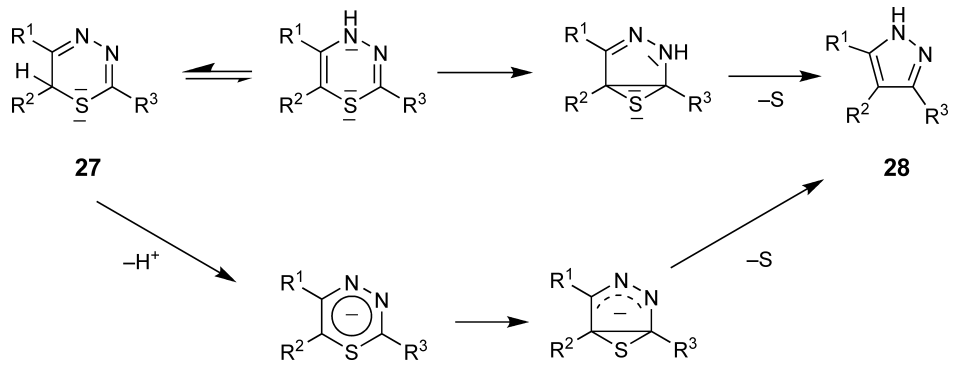

**24** **25** **26**

## 8.08.3 Thermodynamic Aspects

### 8.08.3.1 Antiaromaticity, Tautomerism, and Ring Conformation

The 4*H*-form of 1,3,4-thiadiazines **27** and the 1,3,4-thiadiazinyl anions are antiaromatic ring systems which extrude sulfur to give pyrazoles <1998HOU(E9c)483, 1992MI173>. The thermodynamically favored 6*H*-tautomer is in equilibrium with the energetically higher 4*H*-1,3,4-thiadiazine tautomer. The formation of the 4*H* species is the rate-limiting step of the reaction. A valence isomerization of this 8π-tautomer then follows to form a thia-σ-homopyrazole with an episulfide ring in the molecule. Finally, the opening of the three-membered ring follows with sulfur extrusion to form the pyrazoles **28** <2003SL2392>. 5-Aryl-1,3,4-thiadiazines with an unsubstituted 6-position can undergo ring contraction, with the sulfur atom being retained in the molecule as a sulfanyl group in the product pyrazole-4-thiols. The formation of 1,3,4-thiadiazinyl anions by reaction of butyllithium with 4*H*-1,3,4-thiadiazines has been reported <1998HOU(E9c)483, 1982ZC137, 1975TL33>. The thiadiazinyl anions are antiaromatic ring systems, which undergo sulfur extrusion to form the pyrazoles **28**. Analogous 1,3,4-selenadiazines can be converted to pyrazoles by selenium extrusion (**Scheme 1**).

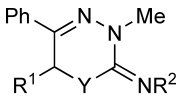
The amino–imino tautomerism of 1,3,4-thiadiazines was investigated by ultraviolet (UV) spectroscopy and X-ray analysis <1993ACS302, 2001AXC593>. The conformational behavior of the (4S,4aS)-2-phenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazine was elucidated by means of nuclear magnetic resonance (NMR) spectroscopy and X-ray analysis <1999H(51)2575>.




**Scheme 1**

## 8.08.3.2 Kinetic Investigations and Determinations of Enthalpies and Entropies

Kinetic parameters for the chalcogen extrusion from 1,3,4-thiadiazines and 1,3,4-selenadiazines **29** to pyrazoles have been determined <1993PHA732, 2006UP1>. It was found that the activation energy and enthalpy of activation are higher for 1,3,4-selenadiazines and the kinetic investigations indicate that the selenium derivatives are more stable than the sulfur-containing compounds (**Table 1**).



**29**

**Table 1** Kinetic parameters for dechalcogenation of **29** to pyrazoles in acetic acid

| $Y$ | $R^1$ | $R^2$ | $E_A$ ($kJ\,mol^{-1}$) $ln\,k_0$ | $\Delta H^{\neq}$ ($kJ\,mol^{-1}$) | $\Delta S^{\neq}$ ($J\,mol^{-1}\,K^{-1}$) | $k_{80\,^\circ C}$ ($s^{-1}$) | $t_{1/2}$ ($min$) |
|---|---|---|---|---|---|---|---|
| S | Ph | $Pr^i$ | 104.5<br>26.8 | 101.1 | −31.7 | $1.52 \times 10^{-4}$ | 76 |
| S | Me | $Pr^i$ | 113.9<br>25.9 | 112.0 | −36.9 | $2.52 \times 10^{-6}$ | 4600[a] |
| S | Ph | Ph | 88.3<br>20.1 | 85.3 | −87.1 | $5.15 \times 10^{-5}$ | 225 |
| Se | Ph | $Pr^i$ | 106.9<br>26.7 | 103.3 | −35.2 | $6.08 \times 10^{-5}$ | 190 |
| Se | Me | $Pr^i$ | 130.7<br>30.4 | 127.2 | −3.7 | $7.42 \times 10^{-7}$ | 15 600[a] |
| Se | Ph | Ph | 93.1<br>20.9 | 90.0 | −81.1 | $2.02 \times 10^{-5}$ | 570 |

[a]Determination by extrapolation.

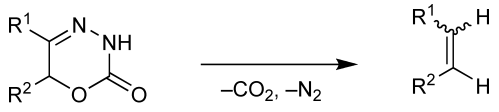
## 8.08.3.3 Chromatographic Behavior of Chiral 1,3,4-Thiadiazines

6-Substituted 1,3,4-thiadiazines exhibit optical activity. Chiral 1,3,4-thiadiazines can be separated by high-performance liquid chromatography (HPLC) with a chiral stationary phase <1994PHA401, 2005JCH(1075)65>, respectively by nonaqueous capillary electrophoresis <2001JBB155>.

## 8.08.4 Reactivity of Fully Conjugated Rings

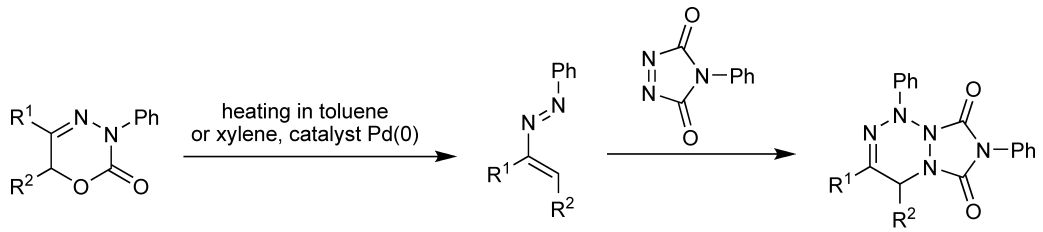
### 8.08.4.1 Thermal and Photochemical Reactions

3*H*-1,3,4-Oxadiazin-2-ones **30** ($R^1 = R^2 = Ar$) decompose to alkenes **31** on thermolysis or photolysis (Equation 1) <1998HOU(E9c)427>. The 5,6-diphenyl derivative yields a mixture of *cis*- and *trans*-stilbene in this reaction.




**30** **31** (1)

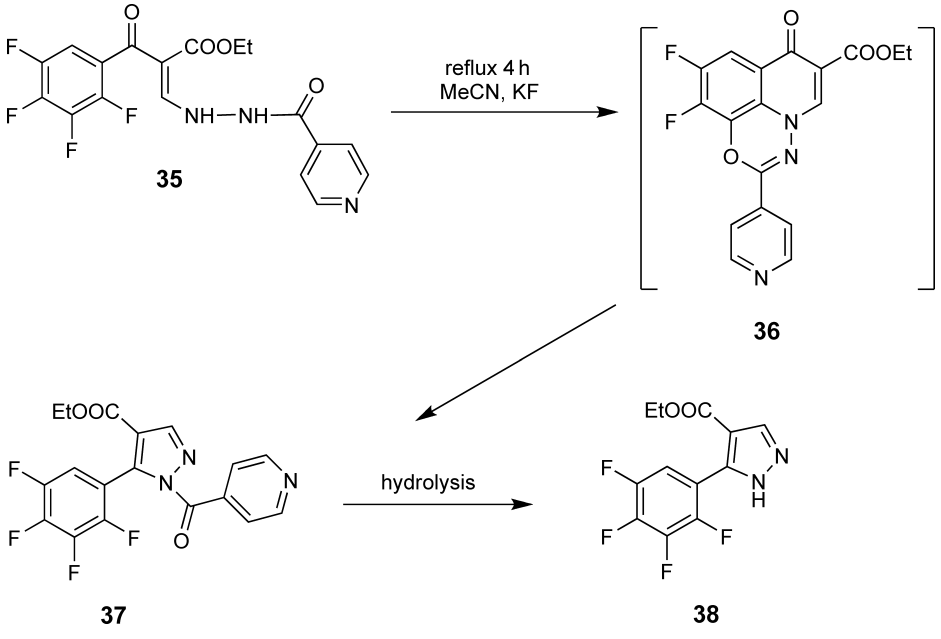
The thermolysis of 1,3,4-oxadiazin-2-ones **32** ($R^1 = R^2 =$ Alk, Ar, OAr, SAr) affords reactive diazadienes **33**, which react with *N*-phenyldiazamaleimide to give Diels–Alder adducts **34** (**Scheme 2**) <2001OL3647>.




**32** **33** **34**

**Scheme 2**

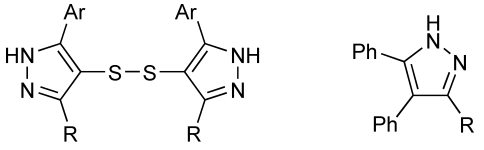
When 3-(4-pyridylcarbonylhydrazino)-2-(tetra-2,3,4,5-tetrafluorobenzoyl)acrylate **35** was refluxed in acetonitrile in the presence of potassium fluoride for 4 h, cyclization to the intermediate 1,3,4-oxadiazino[6,5,4-*i*,*j*]quinoline **36** took place. Ring opening of the 1,3,4-oxadiazine and pyridine ring of **36** and recyclization led to the 4,5-substituted pyrazole **37**, which upon hydrolysis affords compound **38** (**Scheme 3**) <2001CHE1278>.




**35** **36** **37** **38**

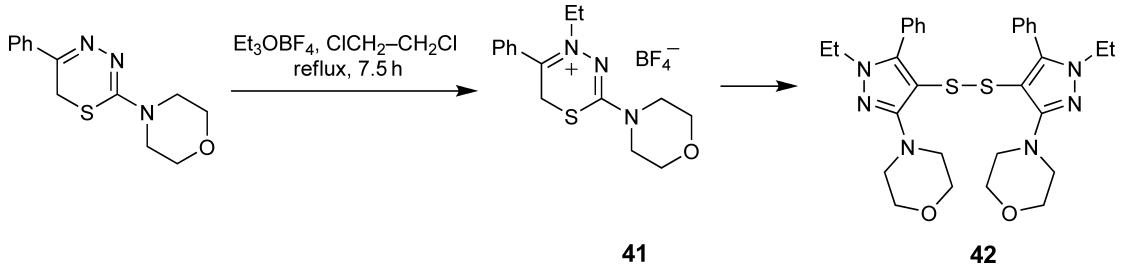
**Scheme 3**

5-Aryl-1,3,4-thiadiazines unsubstituted in the 6-position can undergo ring contraction on longer heating in toluene with formation of pyrazolyl disulfides **39** (R = Ar, Bn, NHMe, NHPr$^{i}$, NHBu$^{n}$, NHBu$^{t}$, $NMe_2$, piperidino, morpholino) <1991DEP288824>. The formation of pyrazolyl disulfides **39** (R = Ar, Bn, NHMe, NHPr$^{i}$, NHBu$^{n}$, NHBu$^{i}$, NHBu$^{s}$, $NMe_2$, piperidino) by heating of 1,3,4-thiadiazines above their melting point has been reported <1992MI173, 1986DEP235640>. The ring contraction of 1,3,4-thiadiazines to pyrazoles **40** also has been carried out using ultrasound in neutral solvents, such as ethanol or toluene, and at lower temperatures <1987ZC296, 1988DEP253030, 1992MI173, 1993KGS565>.



**39** **40**

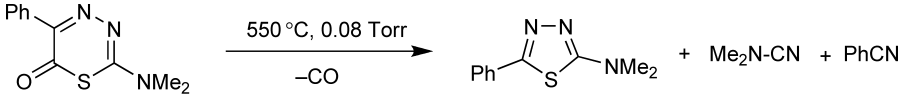
2-Morpholino-5-phenyl-6*H*-1,3,4-thiadiazine reacts on heating with triethyloxonium tetrafluoroborate for 7.5 h to give 35% of the quaternary 1,3,4-thiadiazinium tetrafluoroborate **41** and 55% of the 1,1′-diethyldipyrazolyl disulfide **42** <1998RJO417>. The intermediate tetrafluoroborate **41** undergoes ring contraction with retention of the sulfur atom to form dipyrazolyldisulfide **42** (**Scheme 4**).




**41** **42**

**Scheme 4**

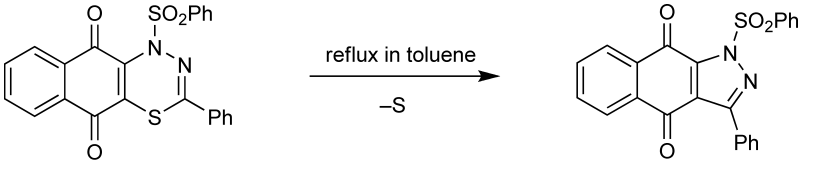
Flash vacuum pyrolysis of 2-dimethylamino-5-phenyl-6*H*-1,3,4-thiadiazin-6-one at 550 °C and 0.08 Torr results in thermal fragmentation and formation of the corresponding *N*,*N*-dimethyl-5-phenyl-1,3,4-thiadiazol-2-amine **43** together with dimethylcyanamide and benzonitrile (Equation 2) <1981CC1003, 1998HOU(E9c)483>.




(2)

**43**

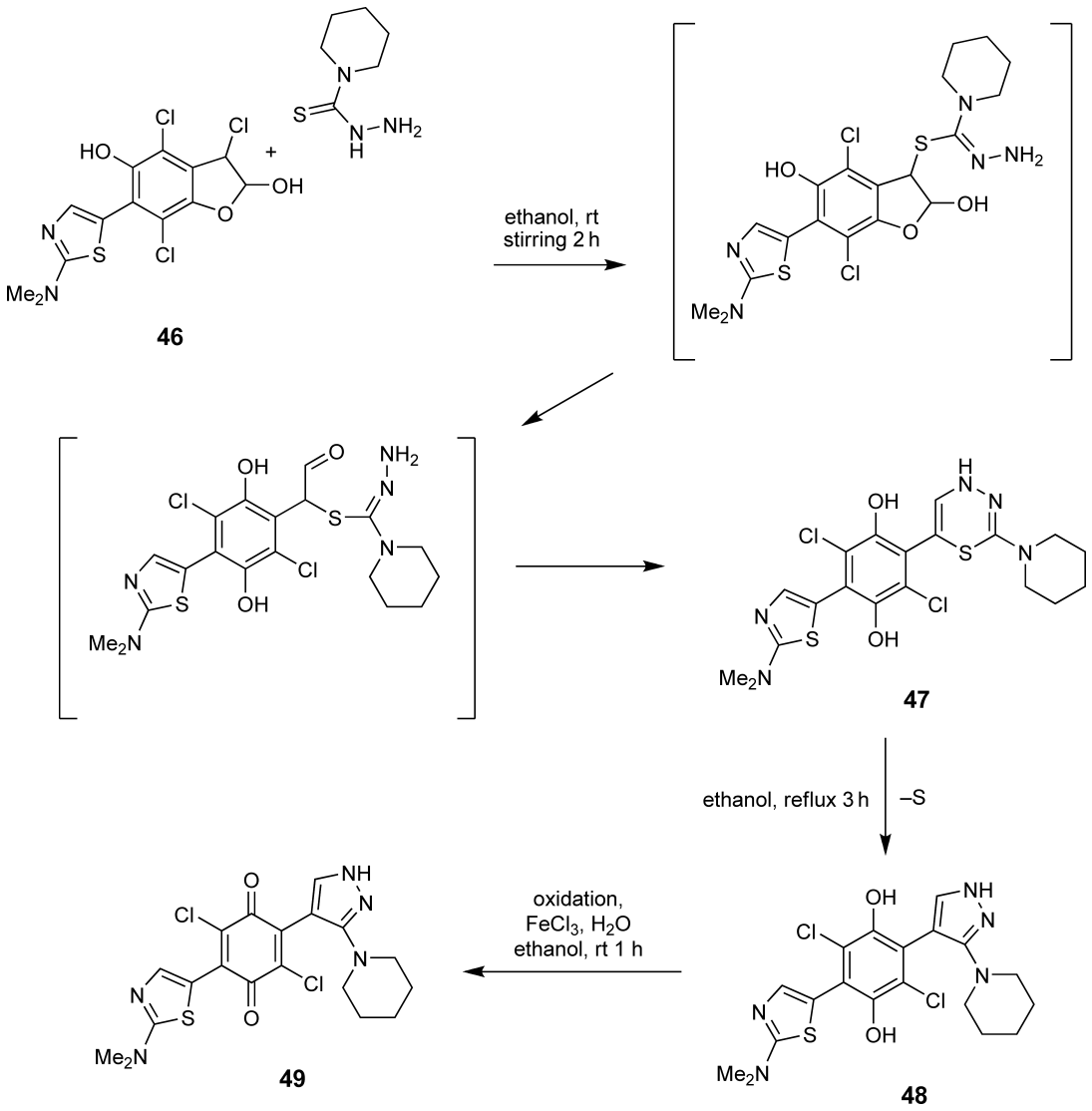
1-(Benzenesulfonyl)-3-phenylnaphtho[2,3-*e*]1,3,4-thiadiazine-5,10-dione **44** can be converted to 1-(benzenesulfonyl)-3-phenyl-1*H*-benzo[*f*]indazole-4,9-dione **45** by heating under reflux (Equation 3) <2003PS627>.




(3)

**44** **45**

The benzofuran derivative **46** and piperidinothiocarbonylhydrazine react in ethanol at room temperature under stirring to form the 1,3,4-thiadiazine intermediate **47**, which undergoes extrusion of sulfur upon heating to form pyrazole derivative **48**. Subsequent oxidation gives compound **49** (**Scheme 5**) <2005H(65)1569>.

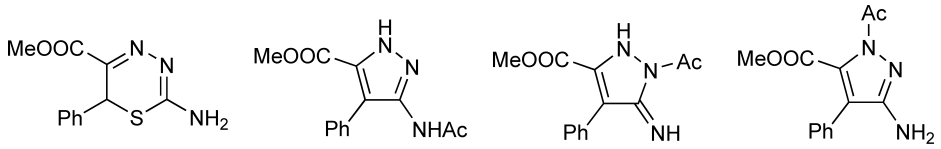



**46** **47** **48** **49**

**Scheme 5**

## 8.08.4.2 Electrophilic Attack at Nitrogen

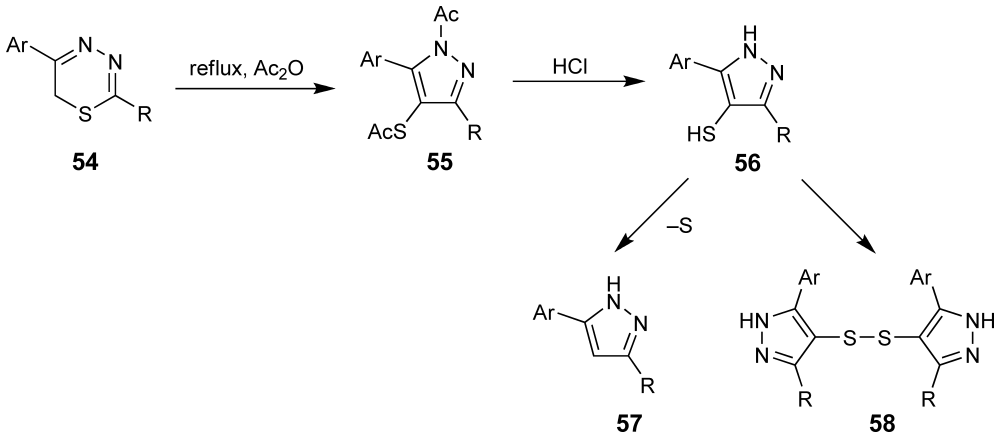
In boiling acetic anhydride, 1,3,4-thiadiazine **50** undergoes ring contraction with sulfur extrusion to yield acetylpyrazoles **51–53** <1996CHE1089>.



**50** **51** **52** **53**

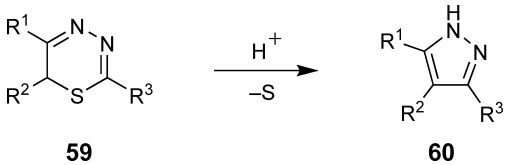
Treatment of 6-unsubstituted 2-dialkylamino-5-aryl-6*H*-1,3,4-thiadiazines **54** (R = $NMe_2$, piperidino, morpholino, pyrrolidino, 1-methylpiperazino) with boiling acetic anhydride results in ring contraction to give pyrazoles and simultaneous acetylation, with the sulfur group remaining in the products **55** in the form of a sulfanyl group <1969ZC361, 1970LA45, 1976ZC80, 1991KGS435, 1998HOU(E9c)483, 2006UP2>. The hydrolysis of **55** with

hydrochloric acid gives 4-mercaptopyrazoles **56**, which can be converted into pyrazoles **57** and pyrazolyl disulfides **58** upon aerial oxidation (**Scheme 6**). Analogously, thiadiazines **54** react in boiling trifluoroacetic anhydride to form 3-substituted 1-trifluoroacetyl-4-trifluoroacetylsulfanyl-5-arylpyrazoles <1991JFC(54)292>.



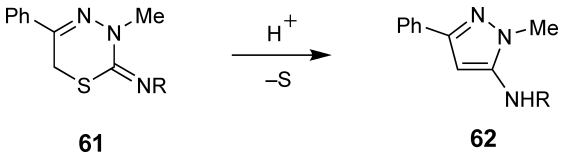

**Scheme 6**

5,6-Substituted 1,3,4-thiadiazines **59** ($R^1$ = H, Me Et, Ar, COOEt, Ac; $R^2$ = H, Alk, Ar; $R^3$ = NHAlk, NHAr, $NMe_2$, piperidino, morpholino, pyrrolidino, Ph, Bn) can be converted to pyrazoles **60** by sulfur elimination in ethanolic hydrogen chloride, or dilute or concentrated hydrochloric acid <1969ZC361, 1970LA45, 1976JPR971, 1978MI135, 1978ZC65, 1993PHA732, 1994PHA401, 1998HOU(E9c)483>. The rearrangement of 1,3,4-thiadiazines to pyrazoles also takes place in boiling acetic acid (Equation 4) <1977ZC173, 1977ZC219, 1978CCC1227, 1978MI135, 1989ZC288, 1992MI173, 1993PHA732, 1994PHA401, 1997PHA831, 1998HOU(E9c)483> or trifluoroacetic acid (TFA) <1991JFC(54)292>. The tendency for pyrazole formation depends very strongly on both the substituents in the 5- and the 6-positions of the 1,3,4-thiadiazines. The best results for a ring contraction are obtained with weak acids if the substituent in the 6-position of the 1,3,4-thiadiazine is phenyl or an electron-withdrawing group, such as ethoxycarbonyl or acetyl. The mechanism of this reaction is shown in Section 8.08.3.1.

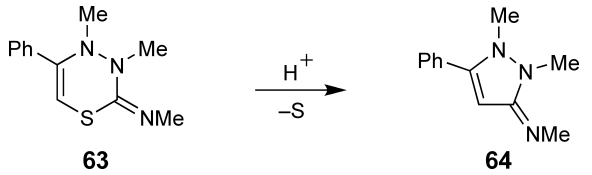



(4)

The desulfuration of 6-unsubstituted-3-methyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **61** (R = Me, $Pr^i$) in boiling glacial acetic acid affords pyrazoles **62** <2003SL2392>. In contrast to the rapid sulfur extrusion of 6-phenyl- or 6-ethoxycarbonyl-6*H*-1,3,4-thiadiazines **59** ($R^2$ = Ph, $CO_2Et$) to pyrazoles, a much longer reaction time (40 h) was required to achieve a complete desulfuration of **61** (Equation 5). The treatment of 4*H*-1,3,4-thiadiazine **63** with concentrated hydrochloric acid or hydrobromic acid (48%) afforded the 5-imino-1,2-dimethylpyrazoles **64** in 40% and 30% yield, respectively (Equation 6). The yield was increased to 53% by the use of glacial acetic acid. The sulfur extrusion proceeded very rapidly and precipitation of considerable amounts of sulfur was observed even after stirring for only 5 min.

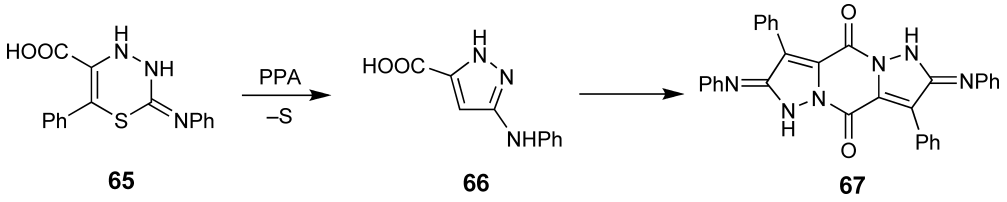



(5)




63 64 (6)

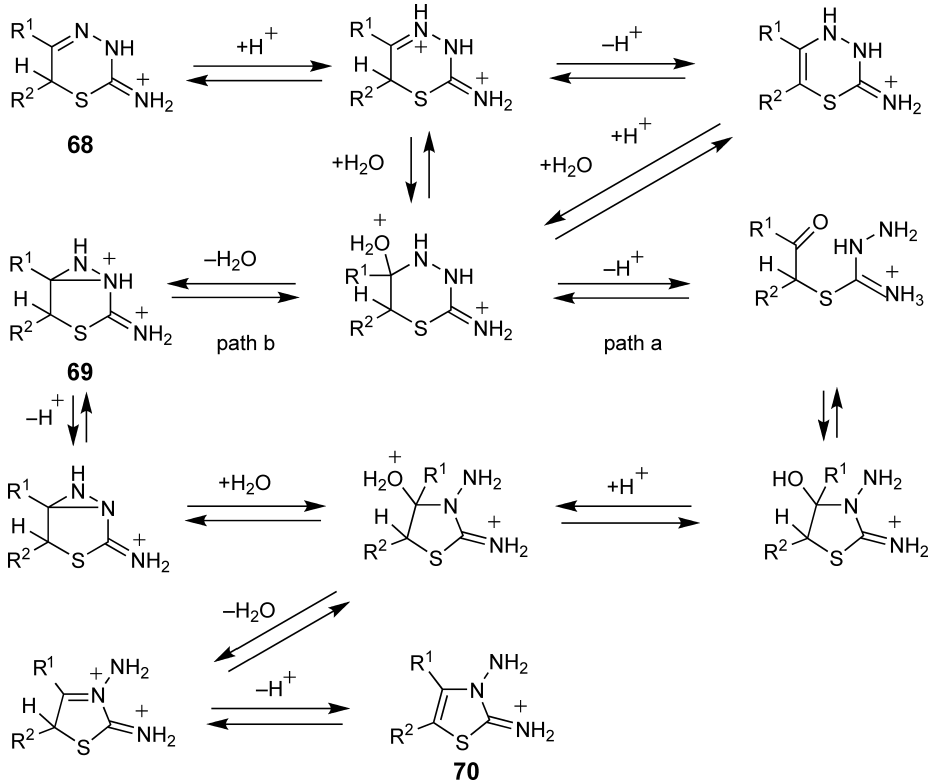
In the presence of polyphosphoric acid (PPA), 5-carboxy-6-phenyl-2-phenylimino-6*H*-1,3,4-thiadiazine **65** undergoes desulfuration to form the intermediate pyrazole **66**, which affords 3,8-diphenyl-2,7-diphenylimino-1*H*,6*H*-dipyrazolo[1,5-*a*,1′,5′-*d*]pyrazine **67** by intermolecular cyclodehydration (**Scheme 7**) <2005RCB441>.




65 66 67

**Scheme 7**

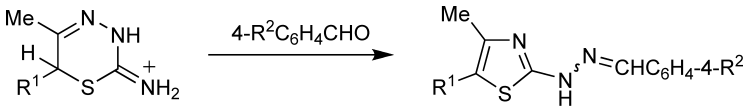
Depending on the substituents, 1,3,4-thiadiazines can undergo rearrangement to 2,3-dihydrothiazole derivatives upon acid hydrolysis. While 1,3,4-thiadiazines with an aromatic substituent in the 5-position are relatively stable, 2-imino- or 2-alkylimino-5-methyl-6*H*-1,3,4-thiadiazines **68**, for example, undergo ring contraction to give 2-amino- or 2-[alkyl(aryl)amino]-4-methyl-2,3-dihydro-1,3-thiazoles **70** <1978MI135, 1998HOU(E9c)483, 2006UP1>. 5-Alkyl-6*H*-1,3,4-thiadiazines behave like cyclic thiosemicarbazones that are extremely sensitive to protonation; hydrolysis of the N(4)–C(5) double bond is followed by renewed ring closure to give the 2-imino- or 2-[alkyl(aryl)amino]-4-alkyl-2,3-dihydro-1,3-thiazoles **70** (**Scheme 8**, path a). An alternative mechanism for the 1,3,4-thiadiazine-thiazoline rearrangement involves the formation of the bicyclic diaziridine intermediate **69** (**Scheme 8**, path b) <1980J(P2)890>.




68 69 70

**Scheme 8**

5-Methyl-6*H*-1,3,4-thiadiazinamines **71** ($R^1$ = H, Me, COOEt, Ph) tend also to undergo ring contraction when heated with benzaldehyde or 4-nitrobenzaldehyde ($R^2$ = H, $NO_2$) in the presence of acid, yielding 2-(benzylidenehydrazino) or 2-[(4-nitrobenzylidene)hydrazino]thiazoles **72** (Equation 7) <1978MI135>, <1998HOU(E9c)483>.

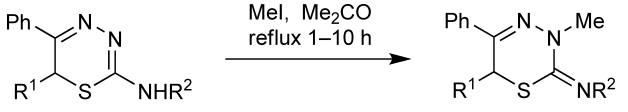



**71** **72**

$R^1$ = H, Me, $CO_2Et$, Ph
$R^2$ = H, $NO_2$

(7)

2-Amino- or 2-alkylamino-5-phenyl-6*H*-1,3,4-thiadiazines **73** react with methyl iodide to give 2-alkylimino-3-methyl-4-phenyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **74** (Equation 8) <2006UP1>. 3-Substituted-2-imino-5-methyl-2,3-dihydro-6*H*-1,3,4-thiadiazines are prepared from 2-amino-5-methyl-6*H*-1,3,4-thiadiazine by alkylation with alkyl or arylalkyl halides in the presence of sodium acetate in dimethylformamide (DMF) <1998PHA820>.

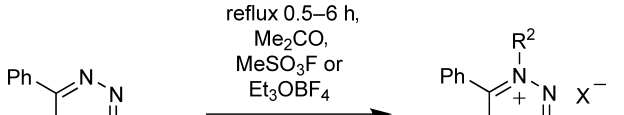



**73** **74**

$R^1$ = H, Me
$R^2$ = H, Me, $Pr^i$

(8)

2-Dialkylamino-5-aryl-6*H*-1,3,4-thiadiazines cannot be alkylated with methyl iodide. 1,3,4-Thiadiazine hydroiodides are obtained by the reaction of 2-dialkylamino-6*H*-1,3,4-thiadiazines with methyl iodide in anhydrous ethanol in the presence of dimethyl sulfoxide (DMSO) <1998RJO417>. The reaction of 2-pyrrolidino- or 2-cyclohexylamino-5-phenyl-6*H*-1,3,4-thiadiazine with methanesulfonyl fluoride or triethyloxonium tetrafluoroborate affords quaternary 2-dialkylamino-5-phenyl-6*H*-1,3,4-thiadiazines **75** in excellent yields (Equation 9) <1998RJO417>.

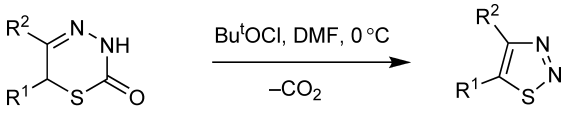



**75**

$R^1$ = morpholino, pyrrolidino
$R^2$ = Me, Et

(9)

6*H*-1,3,4-Thiadiazin-2(3*H*)-ones eliminate carbon dioxide to yield 1,2,3-thiadiazoles **76** <1998HOU(E9c)483>. The reaction proceeds by an attack of $Cl^+$ on the N- or S-atom, followed by ring contraction and carbondioxide elimination (Equation 10).

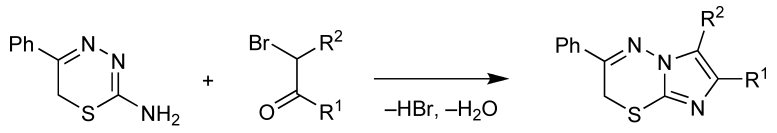



**76**

$R^1$ = H, Me
$R^2$ = Ar

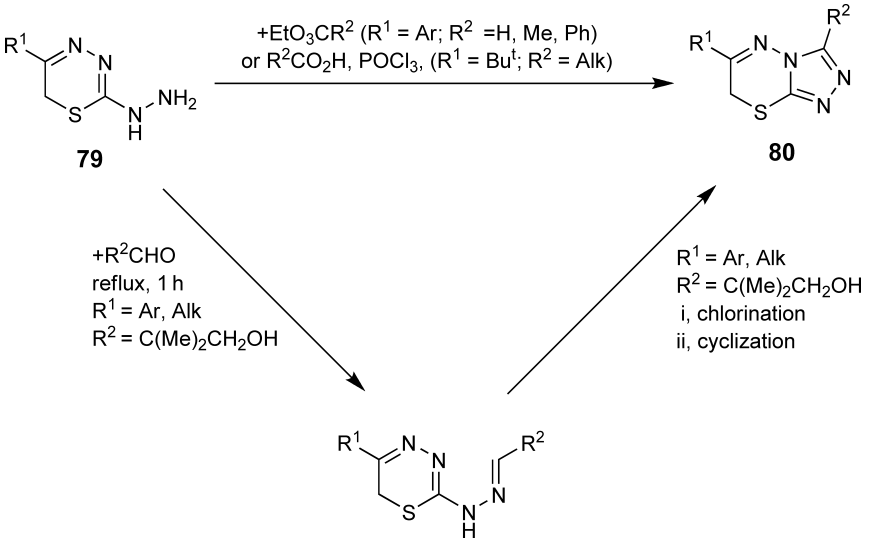
(10)

The reactions of 6*H*-1,3,4-thiadiazin-2-amine **77** with α-halo ketones afford 2*H*-imidazo[2,1-*b*]6*H*-1,3,4-thiadiazines **78** ($R^1$ = Ar; $R^2$ = H, Ph; Equation 11). <1975ZC482>.




(11)

2-Hydrazino-5-aryl-6*H*-1,3,4-thiadiazines **79** react with orthocarbonate esters to give 7*H*-triazolo[3,4-*b*][6*H*-1,3,4]thiadiazines **80** ($R^1 = Ar$; $R^2 = H$, Me, Ph; **Scheme 9**) <1977ZC15>. Compounds **80** are also prepared by reaction of **79** with hydroxypivalaldehyde in acetonitrile under reflux for 1 h, chlorination with 1,3-dichloro-5,5-dimethylhydantoin at 20 °C for 30 min, and cyclization in the presence of triethylamine at 10–45 °C for 80 min ($R^1 = Ar$, Alk; $R^2 = C(Me_2)CH_2OH$) <2002JPP2002302493>. 7*H*-Triazolo[3,4-*b*][6*H*-1,3,4]thiadiazines **80** are also obtained by heating of **79** with carboxylic acids in the presence of $PCl_3$ or $P_4O_{10}$ or acyl chlorides <1999JPP11240885, 2000JPP2000143664>.

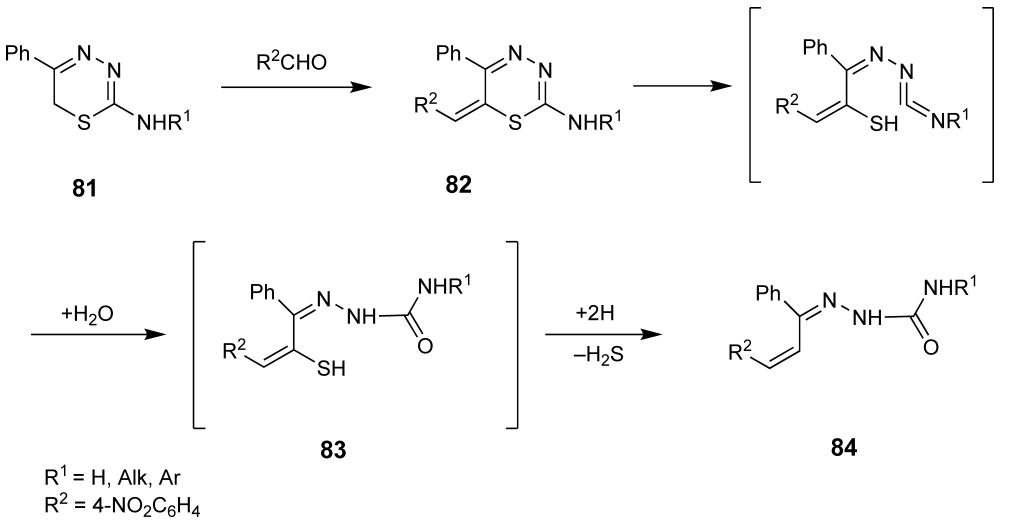



**Scheme 9**

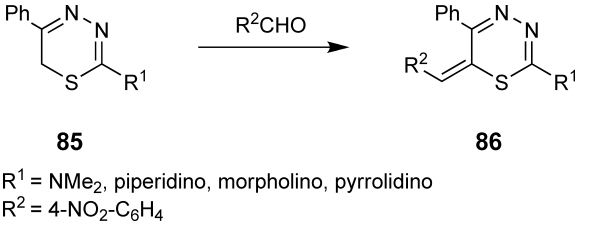
## 8.08.4.3 Electrophilic Attack at Carbon

A ring cleavage of 2-amino- and 2-alkyl(aryl)amino-5-phenyl-6*H*-1,3,4-thiadiazines **81** is observed on treatment with 4-nitrobenzaldehyde; elimination of hydrogen sulfide is accompanied by formation of semicarbazones **84** (**Scheme 10**) <1998HOU(E9c)483, 2006UP1>. 6-(4-Nitrobenzylidene)-6*H*-1,3,4-thiadiazines **82** are formed in the first step of the reaction. The stability of the thiadiazine ring is reduced markedly by the presence of the electron-attracting 6-(4-nitrobenzylidene) group. Ring cleavage of **82** at the S(1)–C(2) bond and subsequent nucleophilic attack of water on the intermediate carbodiimide unit leads to the semicarbazone **83**, which then takes up two hydrogen atoms and liberates hydrogen sulfide to yield the final product **84**. The reduction may be attributed to ethanol present in the solvent.

In the case of 2-dialkylamino-5-phenyl-6*H*-1,3,4-thiadiazines **85**, the reaction stops at the 6-(4-nitrobenzylidene) compounds **86** since ring opening and formation of a carbodiimide moiety are not possible with the 2-dialkylamino compounds (Equation 12) <1998HOU(E9c)483>.



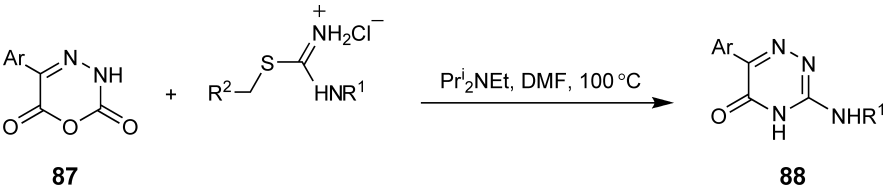

**Scheme 10**




(12)

## 8.08.4.4 Nucleophilic Attack at Carbon

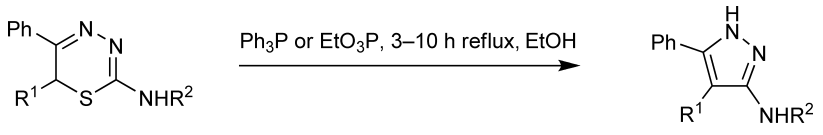
Heating of oxadiazine-2,6-diones **87** with polymer-bound isothiourea in anhydrous DMF in the presence of diisopropylethylamine affords 3-amino-1,2,4-triazin-5(4*H*)-ones **88** (Equation 13) <2001TL4433>.




(13)

## 8.08.4.5 Nucleophilic Attack at Sulfur

The ring contraction of 6-unsubstituted 6*H*-1,3,4-thiadiazines **89** with triphenylphosphine or triethylphosphite affords pyrazoles and, by ring opening, mercaptopyrazoles and dipyrazolyl disulfide <1977S485>. This rearrangement also occurs with 6-substituted 1,3,4-thiadiazines (Equation 14) <2006UP1> By the ring contraction of 1,3,4-thiadiazines **89**, only the formation of pyrazoles **90** takes place.

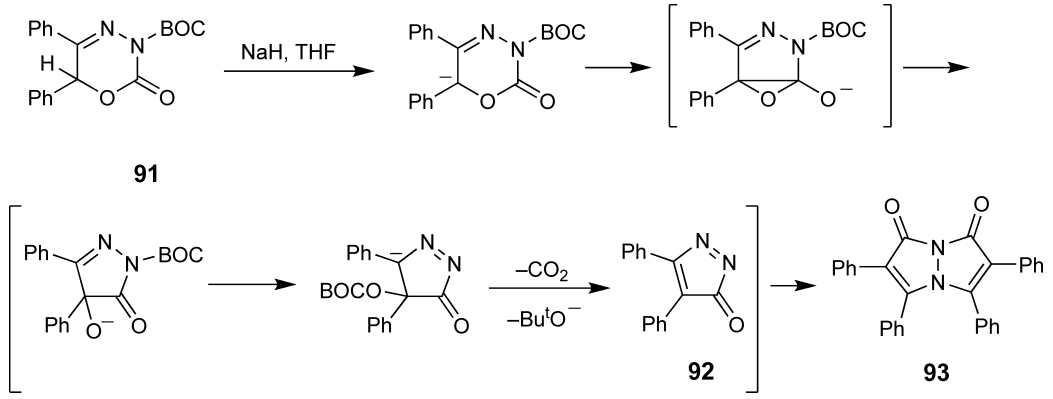



89 90 (14)

$R^1$ = Ph, Me
$R^2$ = Ac, H, Ph, Me, $Pr^n$, $Pr^i$, $Bu^t$, $NMe_2$, piperidino morpholino, pyrrolidino

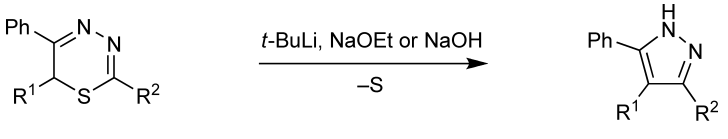
### 8.08.4.6 Nucleophilic Attack at Hydrogen (Proton Abstraction)

The reaction of 1,3,4-oxadiazin-2-one **91** with sodium hydride in tetrahydrofuran (THF) leads to an unprecedented Favorski-like ring contraction to form the 4,5-diphenylpyrazol-3-one **92**, which then dimerizes with loss of one molecule of nitrogen to give 3,4,6,7-tetraphenyl-1,5-diazabicyclo[3.3.0]octa-3,6-dien-2,8-dione **93** (**Scheme 11**) <1996TL5039>.




**Scheme 11**

1,3,4-Thiadiazines **94** can be converted to pyrazoles **95** by sulfur elimination in the presence of *t*-butyllithium or lithium diisopropylamide at −78 °C <1975TL33>. Base-induced ring contraction and desulfuration of 1,3,4-thiadiazines to pyrazoles occurs also with sodium ethoxide, aqueous sodium hydroxide, or potassium *t*-butoxide (Equation 15) <1977S196, 1984DEP211343> Kinetic studies of chalcogen extrusion from 1,3,4-thiadiazines **94** and 1,3,4-selenadiazines to yield pyrazoles **95** in the presence of sodium ethoxide or sodium methoxide demonstrate a higher stability for the 1,3,4-selenadiazines <2006UP1>. The base-induced ring contraction of 1,3,4-thiadiazines to pyrazoles takes place via an antiaromatic 1,3,4-thiadiazinyl anion. The mechanism of this reaction is shown in Section 8.08.3.1 (**Scheme 1**).

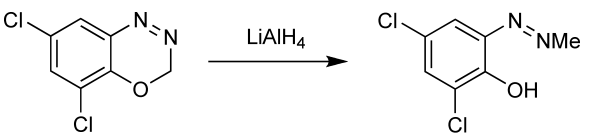



94 95 (15)

$R^1$ = Ph, Me, Et
$R^2$ = $NH_2$, NH–$NH_2$, Ph, Bn, SMe,
NHMe, $NHPr^i$, $NHBu^t$, NHPh, $NMe_2$, piperidino,
morpholino, pyrrolidino, N-Me-piperazino

### 8.08.4.7 Reduction

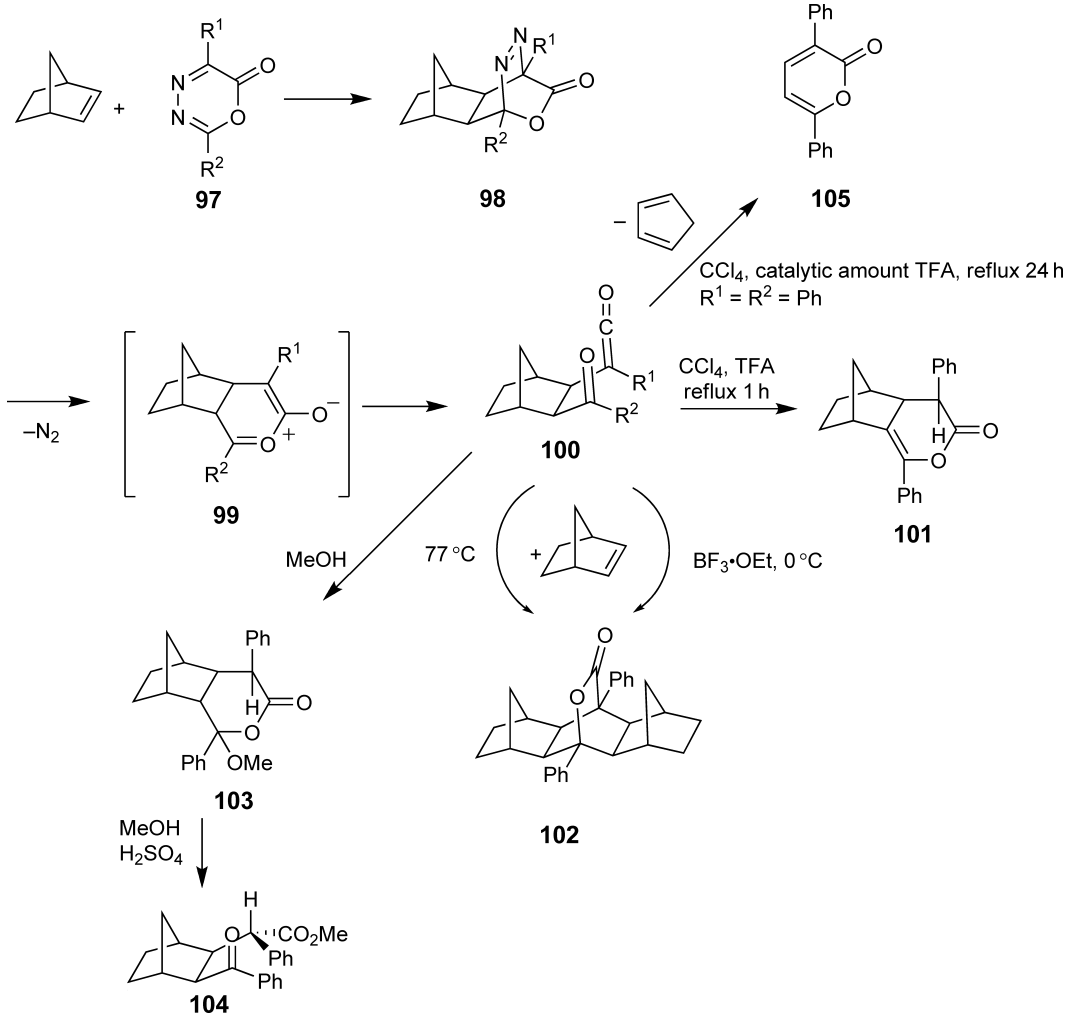
The heterocyclic ring of *2H*-benzooxadiazines can be opened by the action of lithium aluminum hydride, as illustrated by the formation of azene **96** <1998HOU(E9c)427> (Equation 16).




**96** (16)

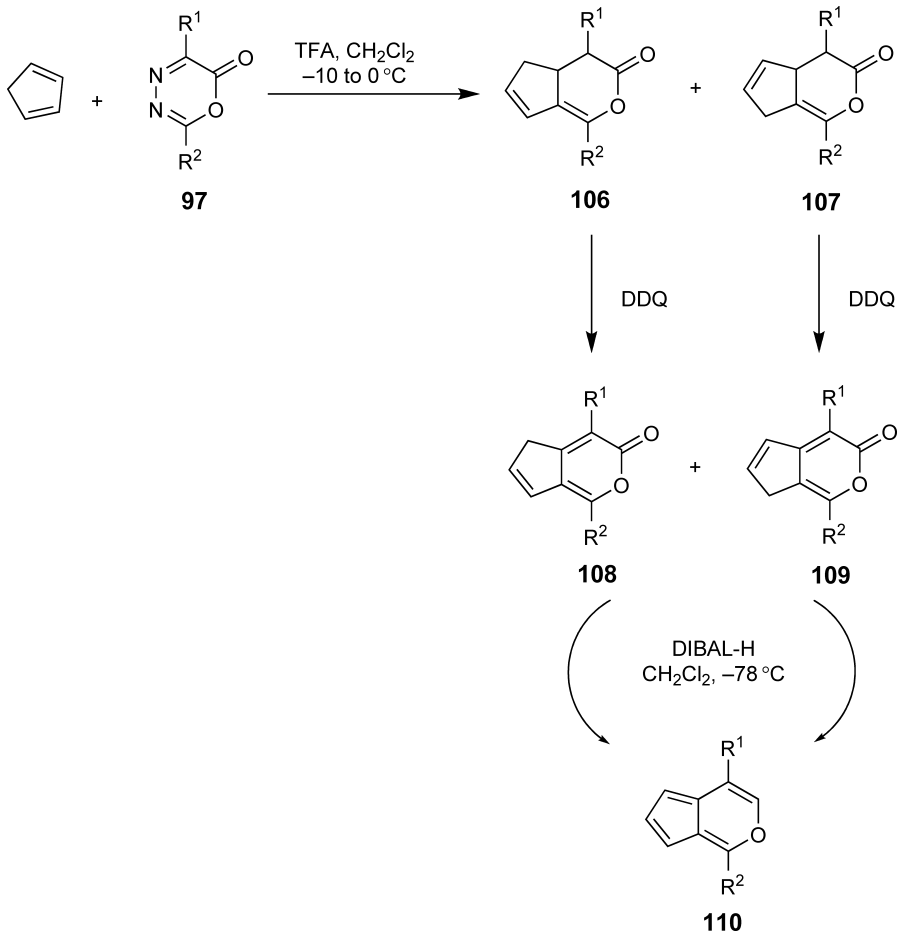
### 8.08.4.8 Cycloadditions

The cycloaddition of 1,3,4-oxadiazin-6-ones **97** with norbornene proceeds via γ-oxoketenes **100** by loss of $N_2$ from the initial adducts **98** and subsequent ring opening of intermediates **99** ($R^1$ = Ar, $Pr^i$; $R^2$ = Ar, Me, $CO_2Me$) <1995JPR659, 1996LA853>. Isomerization of **100** ($R^1 = R^2$ = Ph) in hot carbon tetrachloride yields the enol lactone **101**. Heating of **100** ($R^1 = R^2$ = Ph) in the presence of norbornene leads to the formation of the symmetrical γ-lactone **102**. The treatment of **100** ($R^1 = R^2$ = Ph) with boron trifluoride etherate proved to be a useful preparative alternative for the formation of **102**. The reaction of **100** ($R^1 = R^2 = CO_2Me$) with boron trifluoride etherate affords a γ-pyrone **105**; a product of type **102** is not observed. On treatment with methanol, the pseudo-ester **103** is formed and, in the presence of sulfuric acid, **103** is converted to the methyl ester **104** (**Scheme 12**).




**Scheme 12**

The cycloaddition of 1,3,4-oxadiazin-6-ones **97** ($R^1$ = Ph, $Pr^i$; $R^2$ = Ar, $CO_2Me$) to cyclopentadiene in the presence of TFA leads to the formation of regioisomeric dihydro-$\alpha$-pyrones **106** and **107** <1998CC2387>. The dehydrogenation of **106** and **107** with dichlorodicyanoquinone (DDQ) affords the $\alpha$-pyrones **108** and **109**. The latter are converted to cyclopenta[*c*]pyrans **110** with diisobutylaluminum hydride (DIBAL-H) (**Scheme 13**).

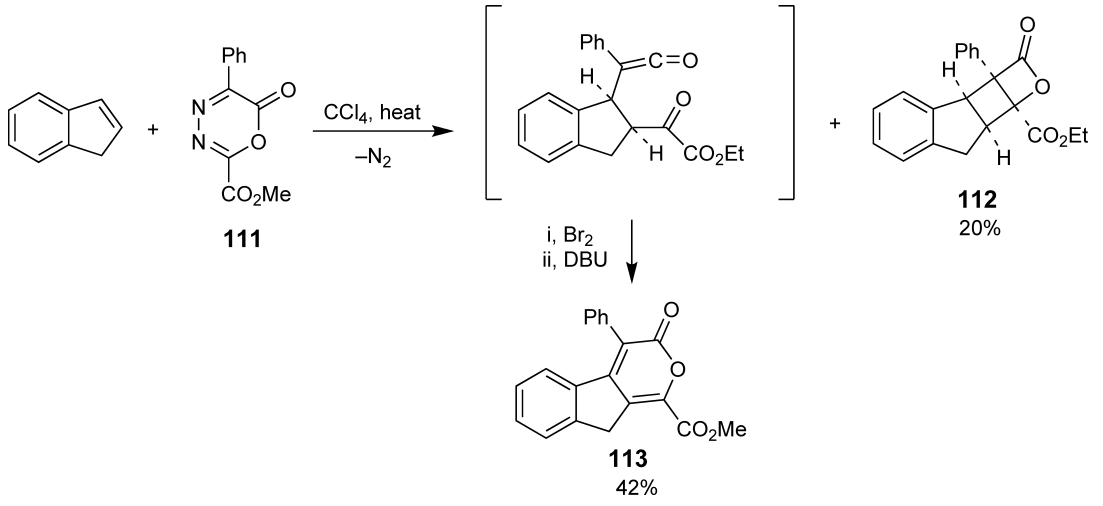



**97** **106** **107** **108** **109** **110**

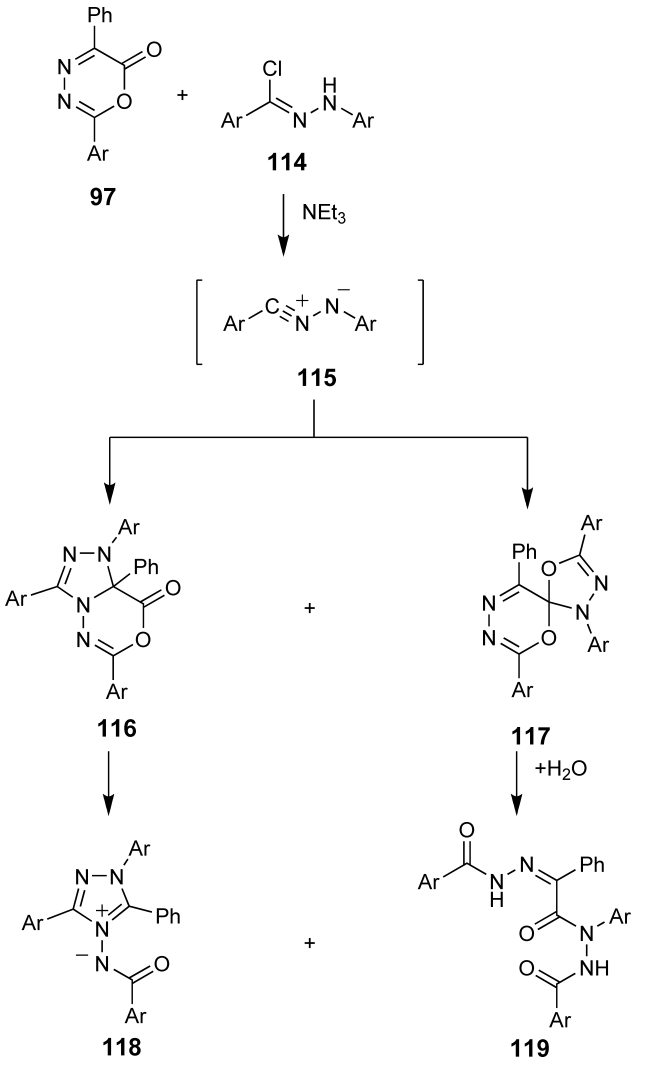
**Scheme 13**

Similarly, the 2-carboxymethyl-5-phenyloxadiazin-6-one **111** reacts with indene to form primarily a $\gamma$-oxoketene. The latter reacts with bromine in the presence of diaza(1,3)bicyclo[5.4.0]undecane (DBU) to give 4-phenylindeno[2,1-*c*]pyran **113**. From this procedure, a $\beta$-lactone **112** was isolated as by-product in 20% yield <1998J(P1)2031> (**Scheme 14**).

Cycloaddition reactions of 1,3,4-oxadiazin-6-ones **97** ($R^1$ = Ph, $R^2$ = Ar), via their 2,3-diaza-1,3-diene functionality, are observed by treatment with dipolarophiles. Thus, 2,5-diaryl-1,3,4-oxadiazines **97** react with diaryl nitrilimines **115**, which are liberated *in situ* from the corresponding hydrazonoyl chlorides **114** and triethylamine, to give 1*H*-1,2,4-triazole *N*-imines **118** and open-chain products **119** <1996JHC591>. It is reasonable to conclude that intermediates **116** are formed initially from cycloaddition across the adjacent carbonyl-carbon nitrogen double bond and that subsequent CO abstraction gives 1*H*-1,2,4-triazole *N*-imine derivatives **118**. The open-chain adducts **119** are formed from intermediates **117**, which result from the reaction of **115** at the carbonyl double bond of the oxadiazinones **97** (**Scheme 15**).




**Scheme 14**

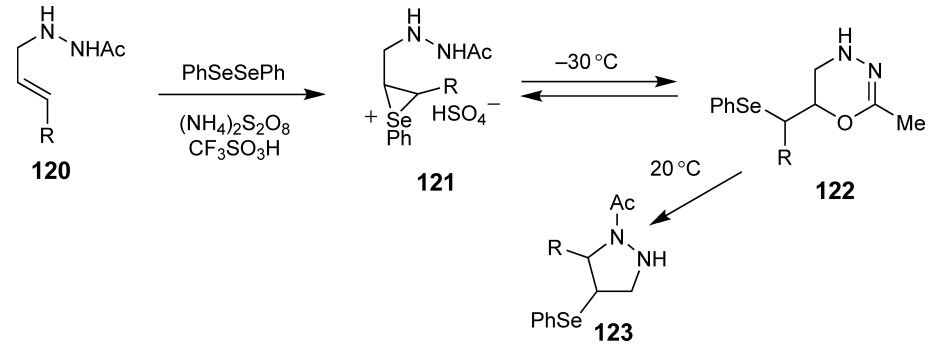



**Scheme 15**

## 8.08.5 Reactivity of Nonconjugated Rings

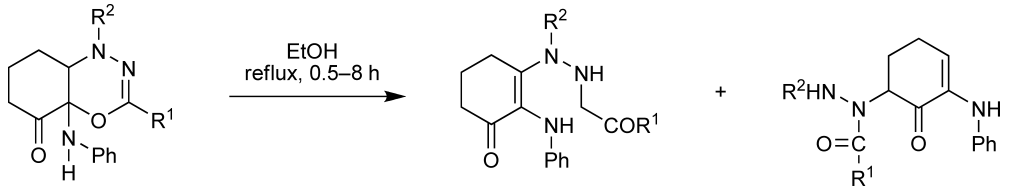
### 8.08.5.1 Thermal Reactions

The treatment of *N*-allylacetylhydrazides **120** with diphenyl diselenide at −30 °C affords 5,6-dihydro-4*H*-1,3,4-oxadiazines **122** via intermediates **121** <1996T11841>. At room temperature, the initially formed 1,3,4-oxadiazines **122** are converted completely to *N*-acetyl pyrazolidines **123** (**Scheme 16**).




**Scheme 16**

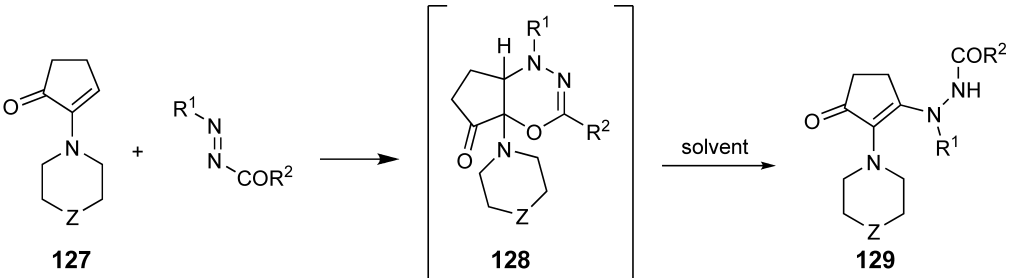
The oxadiazine derivatives **124** undergo ring opening by heating in ethanol to give keto enamines **125** and **126** <1996G297>. The tendency to ring opening is very strongly dependent on the substituents $R^1$ and $R^2$. The ring stability is elevated by the presence of a nitro group in the aromatic ring. The conversion of the nitro compounds **124b** and **124c** to the open-chain adducts **125b**,**c** and **126b**,**c** occurs only by treatment in ethanol under reflux for 5–8 h. In contrast, an ethanolic solution of **124a** undergoes ring opening to **125a** and **126a** at room temperature after standing for 72 h or after only 30 min heating (Equation 17).




(17)

**a**: $R^1 = R^2 = Ph$
**b**: $R^1 = Ph$; $R^2 = 4\text{-}NO_2C_6H_4$
**c**: $R^1 = 4\text{-}NO_2C_6H_4$; $R^2 = Ph$

Treatment of the ketoenamine **127** (Z = O) with a diazene ($R^1 = R^2 = Ph$) affords a mixture of 1,3,4-oxadiazine cycloadducts **128** and the open-chain isomeric compounds **129**. In all other cases of this reaction, **128** cannot be isolated since these heterocyclic compounds are unstable at room temperature. The intermediates undergo rearrangement to form the monoadducts **129** (Equation 18) <1997G387>.

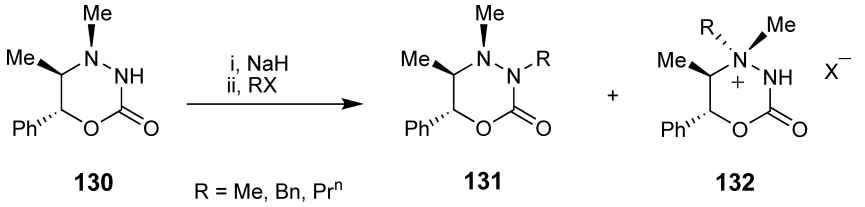



(18)

$R^1$ = Ph, $CO_2Et$, Bz
$R^2$ = Ph, OEt
Z = O, $CH_2$

### 8.08.5.2 Electrophilic Attack at Nitrogen

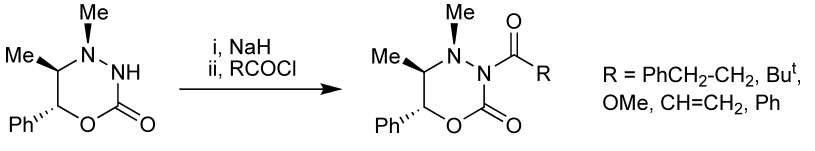
The perhydro-1,3,4-oxadiazin-2-one **130** yields the 3-alkyl-substituted perhydro-1,3,4-oxadiazin-2-ones **131** and the perhydrooxadiazinium salts **132** upon treatment with sodium hydride and subsequent alkylation with iodomethane, 1-iodopropane, or benzyl bromide (**Scheme 17**) <2002JOC8871>.




**130** **131** **132**

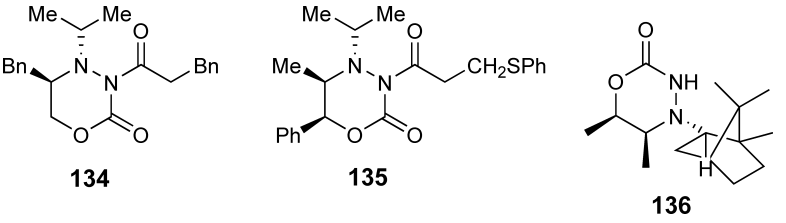
**Scheme 17**

Similarly, **130** reacts with sodium hydride and acyl halides to give 3-acyl-perhydro-1,3,4-oxadiazinon-2-ones **133** (**Scheme 18**) <2002JOC8871, 2001T9789>. Compounds **134–136** have also been prepared by this method <2004JOC714, 2005TA1047, 2006TA2386>.



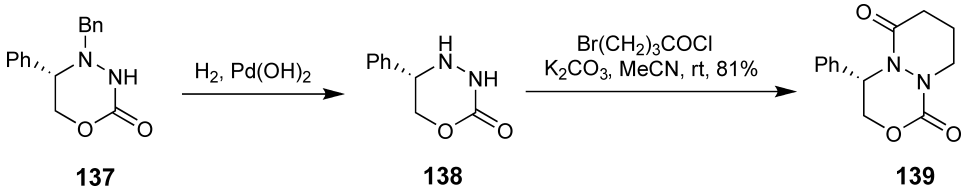

**130** **133**

**Scheme 18**



**134** **135** **136**

Compound **138** is obtained from 4-benzyl-5-phenylperhydro-1,3,4-oxadiazin-2-one **137** by N-debenzylation with hydrogen under pressure in the presence of $Pd(OH)_2$ as catalyst. Subsequent treatment with 4-bromobutanoyl chloride yields a bicyclic hydrazinolactam derivative **139** (**Scheme 19**) <1998TL8081>.

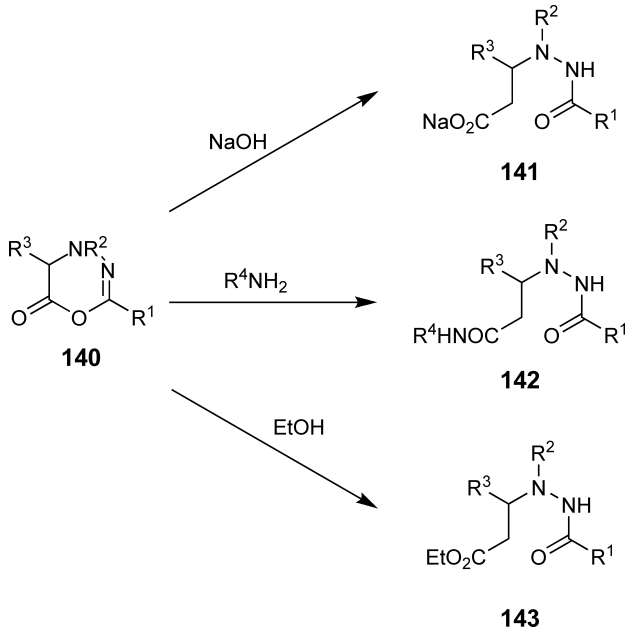



**137** **138** **139**

**Scheme 19**

### 8.08.5.3 Nucleophilic Attack at Carbon

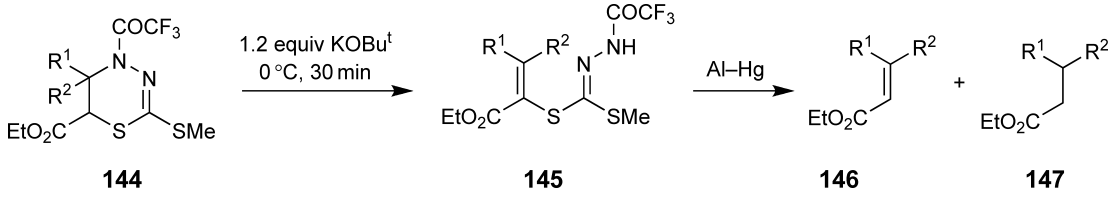
4,5-Dihydro-4*H*-1,3,4-oxadiazines **140** ($R^1 = R^2 = R^3 =$ Ar, Alk, H; $R^4 =$ Ar, Alk) behave like lactones, being hydrolyzed by sodium hydroxide to sodium salts of acyl hydrazinocarboxylic acids **141**. Compounds **140** also react with amines or alcohols to give amide or esters of acylhydrazinocarboxylic acids **142** and **143** (Equation 19) <1998HOU(E9c)427>.




(19)

### 8.08.5.4 Nucleophilic Attack at Hydrogen (Proton Abstraction)

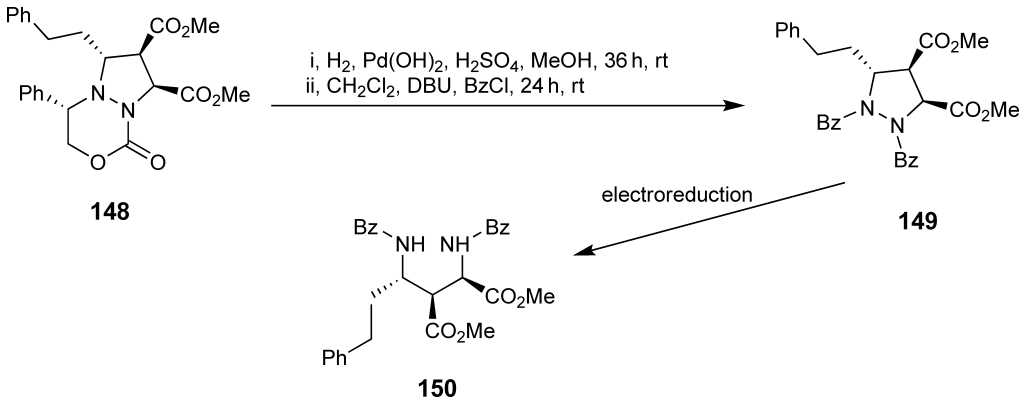
The reaction of 2-methylsulfanyl-5,6-dihydro-1,3,4-thiadiazines with trifluoroacetic anhydride yields the *N*-trifluoroacetyl compounds **144**. Treatment of **144** in THF or benzene with 1.2 molar equiv of $KOBu^t$ at 0 °C gives *S*-alkenyl hydrazinecarbodithiolates possessing an ester group **145** (**Scheme 20**). These compounds are converted to **146** and **147** by reductive desulfuration using Al–Hg. Treatment of **144** with an excess amount of base at room temperature affords 2-methysulfanyl-6-alkylidene-4*H*-1,3,4-thiadiazin-5-ones <1998CL329> (see Section 8.08.9.2).



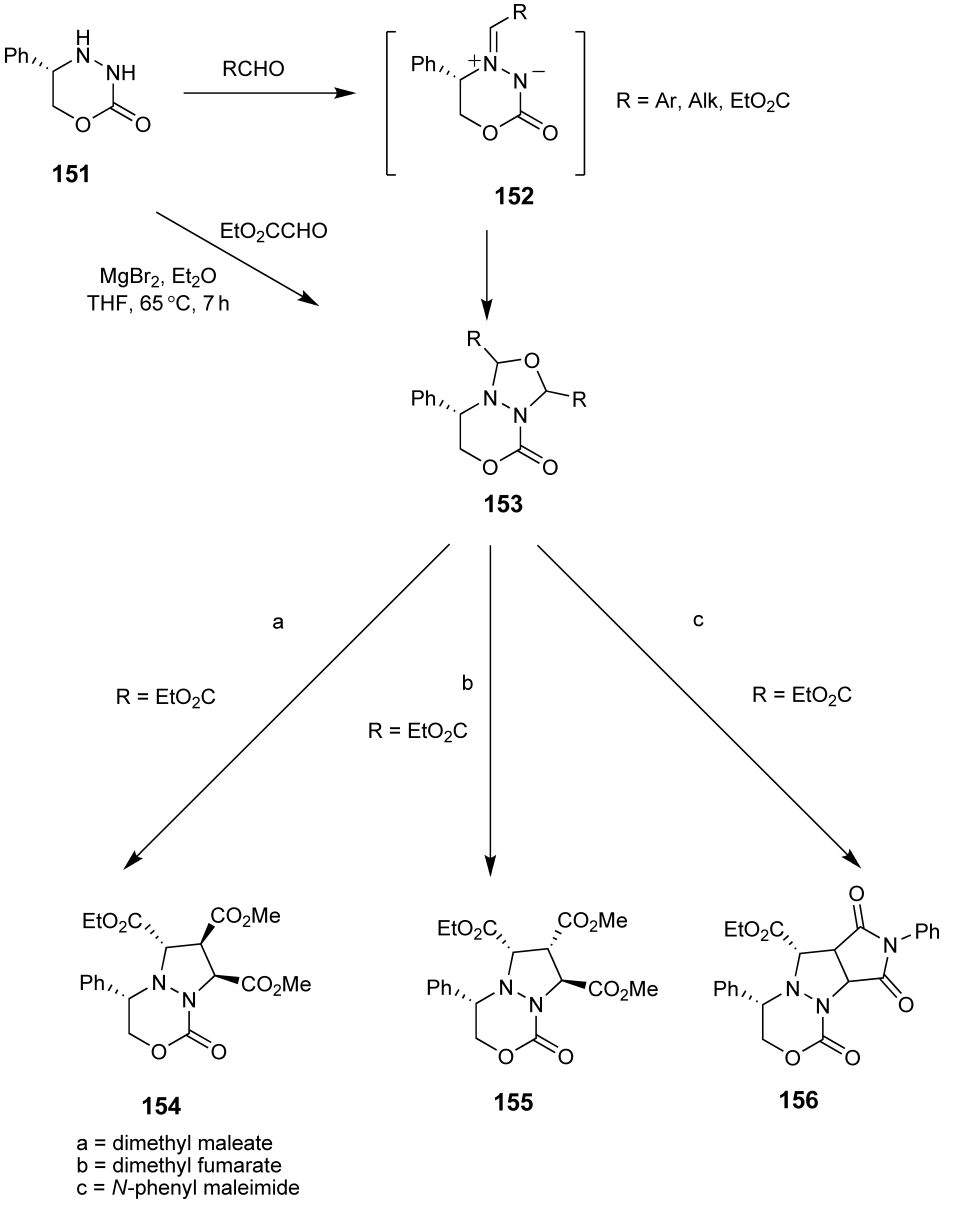

**Scheme 20**

### 8.08.5.5 Reduction

Tetrahydropyrazolo[1,2-*c*][1,3,4]oxadiazine **148** undergoes a ring cleavage by treatment with hydrogen in the presence of $Pd(OH)_2$ and sulfuric acid in methanol to give pyrazolidine **149** (**Scheme 21**) <2002S1885, 2004TL3127>. Unprotected pyrazolidines are unstable and are readily oxidized into the corresponding $\Delta^2$-pyrazolines. Accordingly, this intermediate type was protected by treatment of the crude hydrogenolysis reaction products with benzoyl chloride under basic conditions. Full protection of both nitrogen atoms could be realized by performing the benzoylation with DBU. For example, pyrazoline **149** is obtained from **148** in a yield of 79%. The electroreduction of pyrazolidine **149** affords diamines **150** by cleavage of the N–N bond (**Scheme 21**).




**Scheme 21**

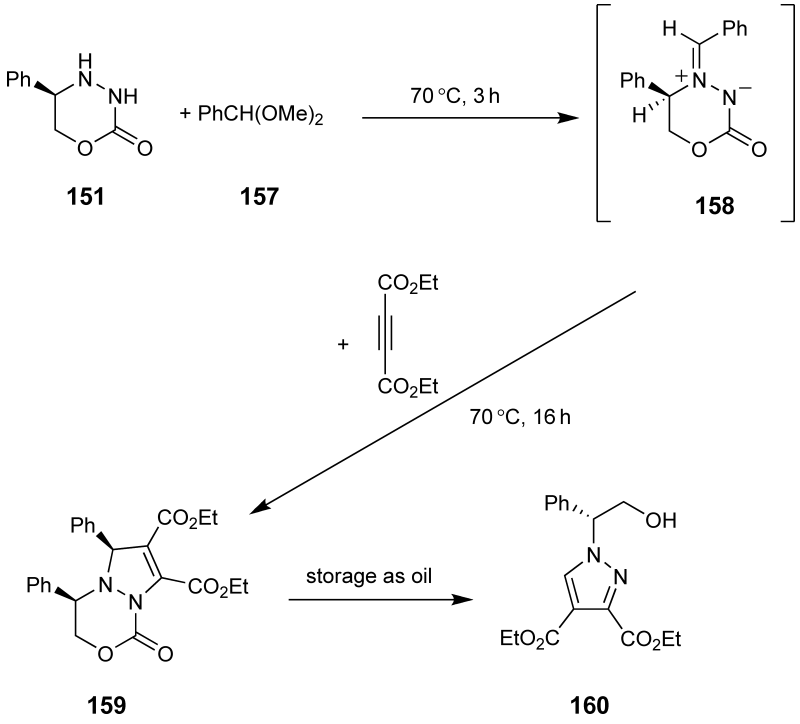



**Scheme 22**

### 8.08.5.6 Cycloadditions

5-Phenylperhydro-1,3,4-oxadiazin-2-ones **151** react with aliphatic or aromatic aldehydes or ethyl 2-oxoacetate to give the intermediates **152**. The azomethine imine ylides **152** yield primary oxazolidines **153** <2000S1170, 2002S1885, 2004TL3127>. These compounds can be synthesized also by treatment of **151** with ethyl oxoacetate or aldehydes in the presence of magnesium bromide etherate. The tandem cycloreversion–cycloaddition of **153** with various electron-poor dipolarophiles then leads to pyrazolidines **154–156** (**Scheme 22**).

The reaction of **151** with benzaldehyde dimethylacetal **157** proceeds in a similar fashion <1999TL3727, 2000S1170>. The resulting azomethine imine intermediate **158** reacts with the dipolarophilic diethyl acetylenedicarboxylate to give **159**. When kept as an oil, the latter is oxidized rapidly in the presence of air to give pyrazole **160** (**Scheme 23**).



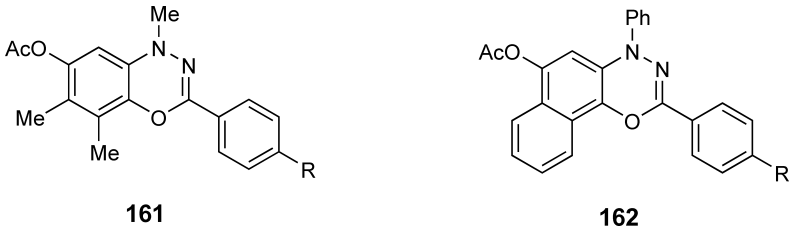

151 157 158 159 160

**Scheme 23**

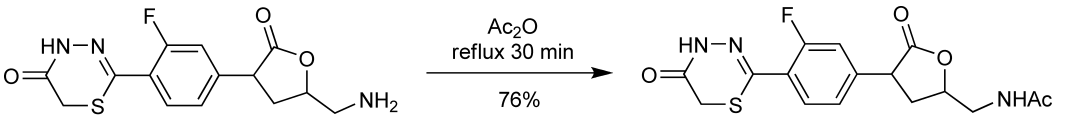
## 8.08.6 Reactivity of Substituents Attached to Ring Carbon Atoms

### 8.08.6.1 Substituted Arenes and Heterocycles

7-Hydroxy-1,5,6-trimethyl-3-aryl-1*H*-benzo[1,3,4]oxadiazines and 9-hydroxy-1-phenyl-3-aryl-1*H*-naphtho[3,4-*e*]-1,3,4-oxadiazines afford 7-hydroxy-1,5,6-trimethyl-3-aryl-1*H*-benzo[1,3,4]oxadiazin-7-yl acetates **161** (R = H, MeO) and 3-aryl-1-phenyl-1*H*-naphtho[1,2-*e*]oxadiazin-9-yl acetates **162** (R = Me, MeO) in excellent yields by heating in acetic anhydride <2000T5137, 2003CPA342>. Acylation of the 5-aminomethyloxazolidine derivative **163** yields the corresponding *N*-acyl compound **164** (Equation 20) <2003WOP2003066631>. This thiadiazinone derivative is useful for treatment of bacterial infections.




161 162

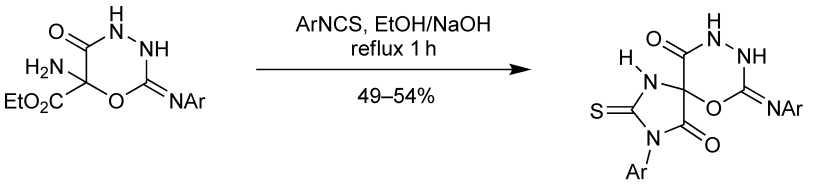



(20)

**163** **164**

## 8.08.6.2 Amino Groups

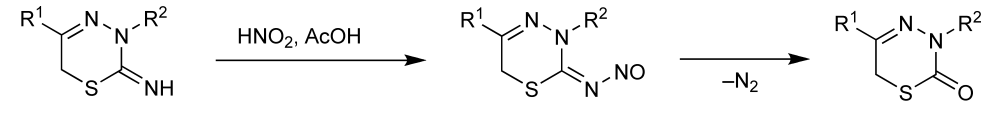
2-Alkyl(aryl)imino-6-amino-6-carboethoxy-5-oxo-3*H*,4*H*-1,3,4-thiadiazines **165** afford the spiro[5.4]decane derivative **166** upon reflux with aryl isothiocyanates in ethanolic sodium hydroxide solution (Equation 21) <1999IJB932>.




(21)

**165** **166**

3-Alkyl-5-aryl-2,3-dihydro-6*H*-1,3,4-thiadiazines **167** react with nitrous acid in glacial acid at 0 °C to give 2-(nitrosoimino)-3-alkyl-5-aryl-2,3-dihydro-6*H*-1,3,4-thadiazines **168** <1998PHA820>. Upon standing, these intermediates **168** undergo decomposition with elimination of molecular nitrogen to yield 2-oxo-3-alkyl-5-aryl-2,3-dihydro-6*H*-1,3,4-thiadiazines **169** (**Scheme 24**).

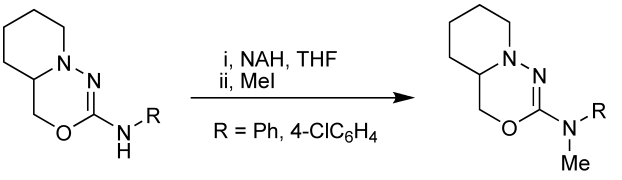



**167**
$R^1$ = Ph, 4-$ClC_6H_4$
$R^2$ = Bn, allyl, *n*-$C_6H_{11}$, *n*-$C_7H_{13}$, *n*-$C_{10}H_{21}$

**168** **169**

**Scheme 24**

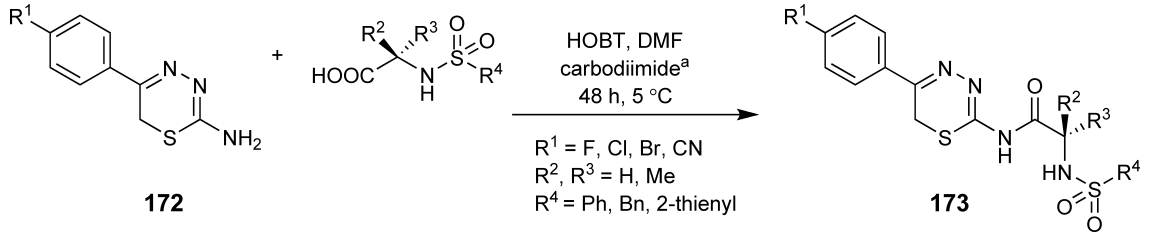
When the perhydropyrido[1,2-*d*][1,3,4]oxadiazines **170** are treated with sodium hydride, followed by methyl iodide, the 2-(*N*-aryl-*N*-methylamino) derivatives **171** are formed (**Scheme 25**) <1997H(45)927>. The NMR spectra and X-ray crystallographic analysis indicated that the 1,3,4-oxadiazines adopt rigid *cis*- or *trans*-fused ring conformations. It was found that for the 1,3,4-oxadiazines **170** involving a potential tautomeric equilibrium, the amino form is most likely to be predominant.




**170** **171**

**Scheme 25**

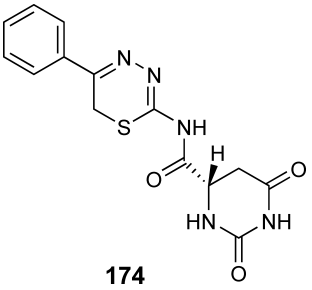
Acylation of 5-substituted 6*H*-1,3,4-thiadiazines **172** with the carboxylic group of carboxysulfonamides was mediated by a mixture of *N*-ethyl-*N*′-(3-dimethylamino propyl)carbodiimide hydrochloride, 1-hydroxybenzotriazole (HOBT), and 4-methylmorpholine in DMF at 5 °C to yield 1,3,4-thiadiazin-2-yl-2-[(phenylsulfonyl)amino]propanamides **173** (Equation 22) <2001JME3231>. Analogous dihydroorotic acid derivatives **174** were also prepared. Such 1,3,4-thiadiazine derivatives are important matrix metalloproteinase inhibitors.




**172** **173**

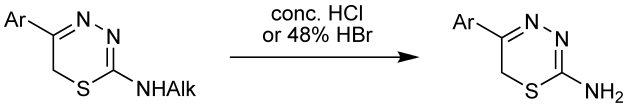
[a]*N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide hydrochloride

(22)



**174**

2-Alkylamino-5-aryl-6*H*-1,3,4-thiadiazines undergo N-dealkylation to give the corresponding 2-amino-5-aryl-6*H*-1,3,4-thiadiazines **175** by heating in concentrated hydrochloric acid or 48% hydrobromic acid <1978ZC65, 2006UP1> (Equation 23).



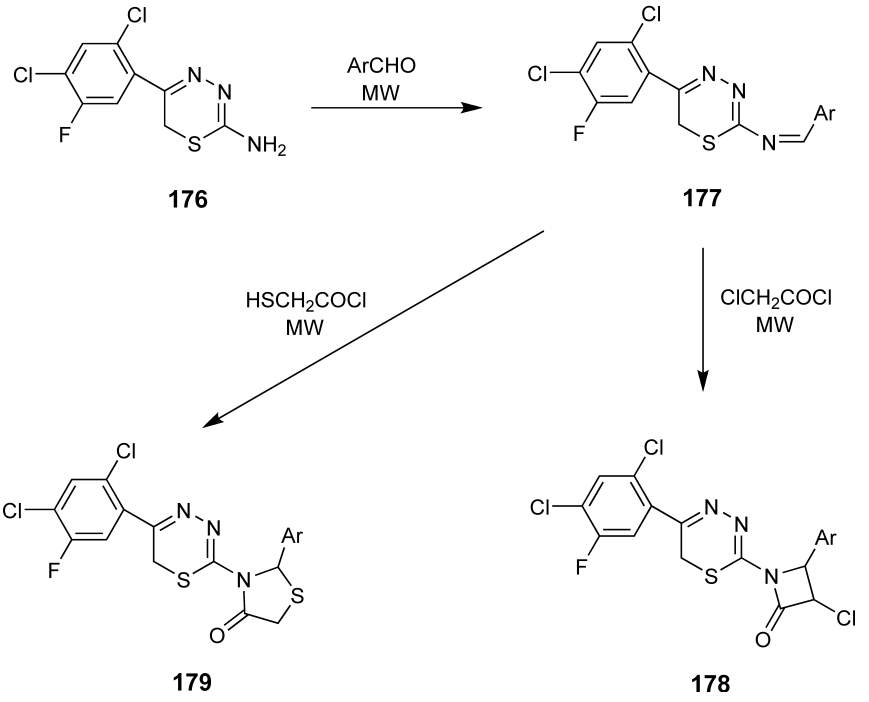

Alk = Bu[t], $Ph_3C$, $C(CH_3)_2$-$CH_2$-$C(CH_3)_3$ **175**

(23)

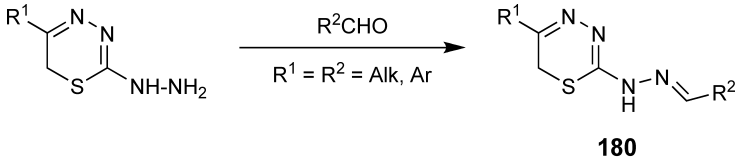
The condensation of 2-amino-5-(2,4-dichloro-5-fluorophenyl)-6*H*-1,3,4-thiadiazine **176** with various aromatic aldehydes under microwave irradiation furnished 2-arylideneamino-6*H*-1,3,4-thadiazines **177**. The cyclocondensation of **177** with chloroacetyl chloride under microwave irradiation afforded 2-oxoazetidine derivatives **178** in excellent yields. The reaction of **177** with 2-sulfanylacetic acid yielded 4-thiazolidinones **179** (**Scheme 26**) <2005IJB2158>.

## 8.08.6.3 Hydrazino Groups

2-Hydrazino-1,3,4-thiadiazines react with aldehydes to give 2-alkyl(aryl)idenehydra-zino-6*H*-1,3,4-thiadiazines **180** <2001JPP2001072682, 2002JPP2002302493> (Equation 24). These compounds are starting materials for the synthesis of 7*H*-triazolo[3,4-*b*][6*H*-1,3,4]thiadiazines <2002JPP2002302493> (Section 8.08.4.2). 2-Hydrazino-6*H*-1,3,4-thiadiazines cyclize with acyl chlorides or carboxylic acids in the presence of $PCl_3$ or $P_4O_{10}$ to yield 7*H*-triazolo[3,4-*b*][6*H*-1,3,4]thiadiazines **80** (Section 8.08.4.2) <1999JPP11240885, 2000JPP2000143664>.

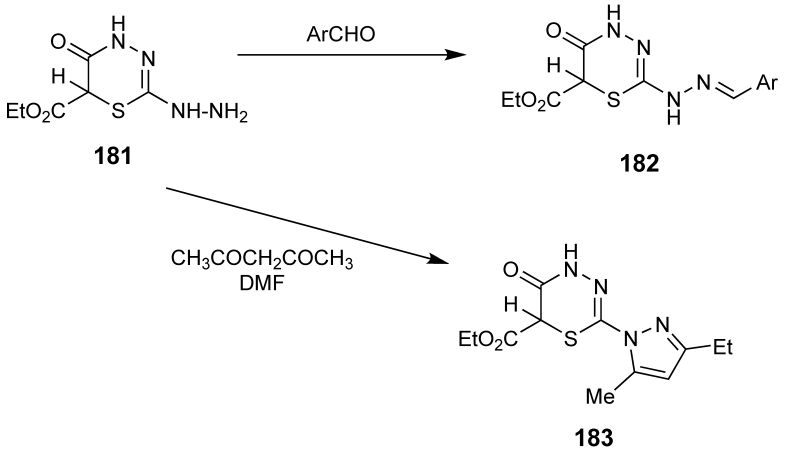



**Scheme 26**




(24)

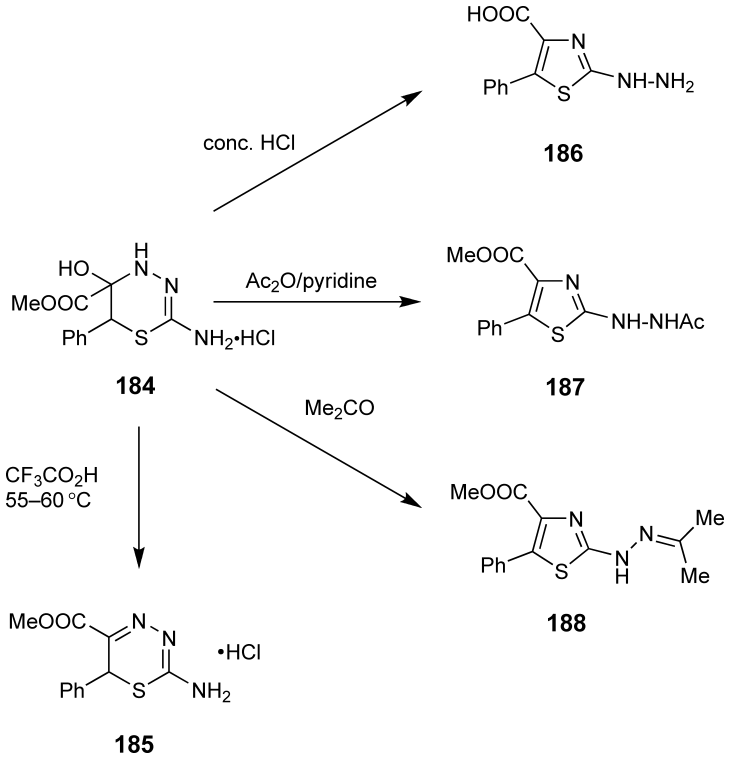
The reaction of 6-carbethoxy-2-hydrazino-4*H*,6*H*-1,3,4-thiadiazine **181** with aromatic aldehydes provides the corresponding Schiff's bases **182**. 2-Pyrazol-1-yl-1,3,4-thiadiazine **183** is produced by reaction of **181** with acetylacetone (Equation 25) <2000IJB603>.




(25)

### 8.08.6.4 Hydroxy Groups

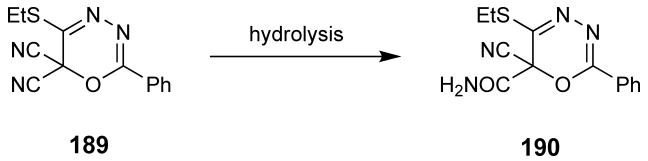
Dehydration of 2-amino-5-carboxymethyl-5-hydroxy-6-phenyl-2,3,4,5-6*H*-1,3,4-thiadiazine hydrochloride **184** to the 1,3,4-thiadiazine hydrochloride **185** takes place with TFA in acetonitrile at 55–60 °C <1996CHE1089>. Dehydration and subsequent ring transformation to 2-hydrazino-4-carboxy-5-phenyl-1,3-thiazole **186** occurs by heating **184** in concentrated hydrochloric acid <1996CHE1089>. Compound **184** also exhibits a tendency to undergo ring contraction to 2-hydrazino-1,3-thiazole derivatives **187** and **188** when heated with acetic anhydride in pyridine or acetone (Equation 26).




(26)

### 8.08.6.5 Cyano Groups

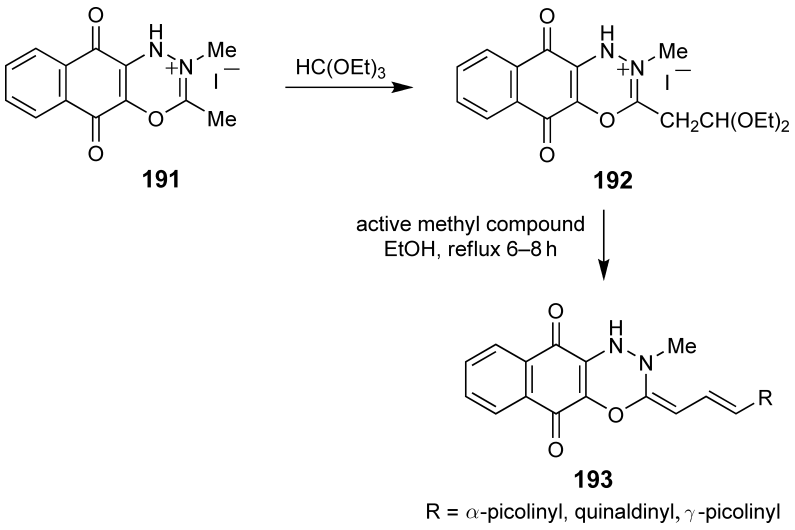
The hydrolysis of 2-ethylsulfanyl-2-phenyl-6*H*-1,3,4-oxadiazine-6,6-dicarbonitrile **189** affords the corresponding amide derivative **190** (Equation 27) <1997JCM144>.




(27)

### 8.08.6.6 Alkyl Groups

Naphthoquinone[2,3-*e*]oxadiazine derivative **191** reacts with triethyl orthoformate in the presence of acetic anhydride to give compound **192**. Further reaction with active methyl compounds ($\alpha$-picoline, $\gamma$-picoline, quinaldine) affords the corresponding cyanine dyes **193** (**Scheme 27**) <1996IJH305>.



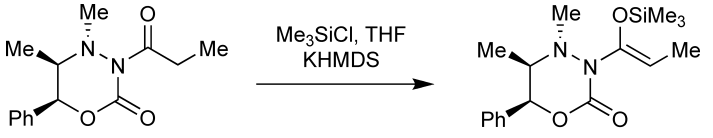

191 192 193

**Scheme 27**

## 8.08.7 Reactivity of Substituents Attached to Ring Heteroatoms

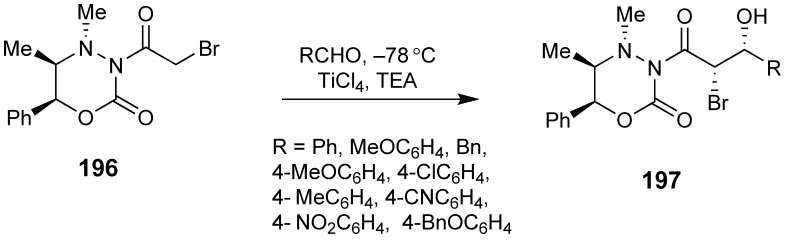
### 8.08.7.1 Carbonyl and Acyl Groups

The treatment of 3-propionyl-3,4,5,6-tetrahydro-1,3,4-oxadiazin-2-one **194** with chlorotrimethylsilane in the presence of the non-nucleophilic base, potassium hexamethyldisilazane (KHMDS), in THF yields enol silane **195** (Equation 28) <2002OL3739>. Compound **195** is used as a starting material for subsequent aldol reactions.

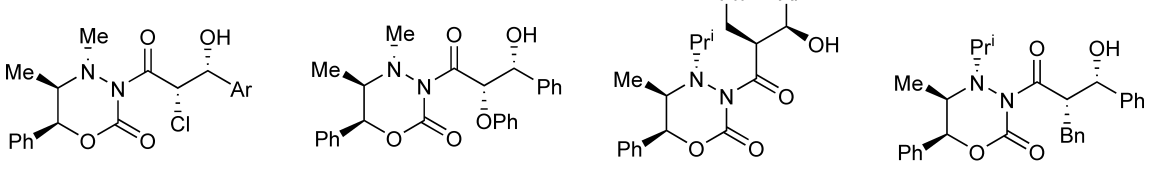



194 195 (28)

The asymmetric aldol reaction of 3-acyl-1,3,4-oxadiazin-2-ones **196** with aldehydes in the presence of titanium tetrachloride and triethylamine (TEA) at −78 °C furnishes ephedrine-based 1,3,4-oxadiazin-2-ones **197** (Equation 29) <2006TA1831>. Further ephedrine-based compounds **198–201** have been prepared by this method <2002JHC1113, 2003TA517, 2003TA3233, 2004JOC714, 2004JOC727, 2004TA3449, 2005T10965>.

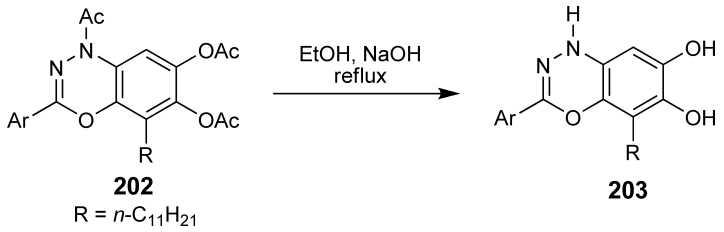



196 197 (29)



198 199 200 201

Deacylation of 3-acetyl-2-aryl-6,7-diacetoxy-8-undecyl-4*H*-1,3,4-benzoxadiazines **202** to give **203** occurs upon heating in ethanolic sodium hydroxide (Equation 30) <1997IJB68>.




**202**
R = *n*-$C_{11}H_{21}$

**203**

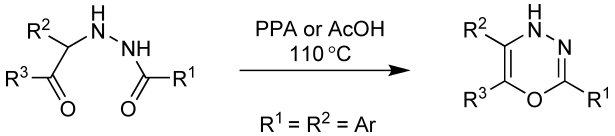
(30)

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

### 8.08.8.1 By Formation of One Bond

#### 8.08.8.1.1 Between carbon and oxygen (fragment)

2,6-Diaryl-4*H*-1,3,4-oxadiazines **205** can be prepared by dehydration of 1-aroyl-2-phenacylhydrazine derivatives **204** with polyphosphoric acid or acetic acid at 110 °C (Equation 31) <1998HOU(E9c)427>.



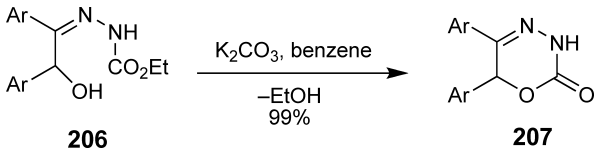

**204**

$R^1 = R^2 = Ar$
$R^2 = H, Ar$
$R^3 = Ph$

**205**

(31)

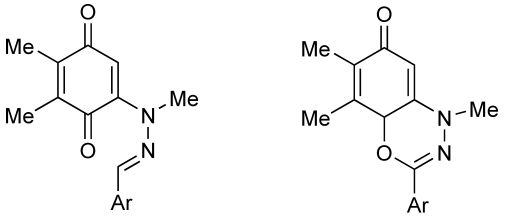
Treatment of ethoxycarbonylhydrazones of α-hydroxyketones **206** with base readily affords 3*H*-1,3,4-oxadiazin-2(6*H*)-ones **207** <1998HOU(E9c)427> (Equation 32). Bicyclic 1,3,4-oxadiazinones **209** are obtained by brief heating of 5-(*N*′-arylylidene-*N*-methylhydrazino)-2,3-dimethyl-1,4-benzoquinones **208** in methanol <2000T5137>.




**206**

**207**

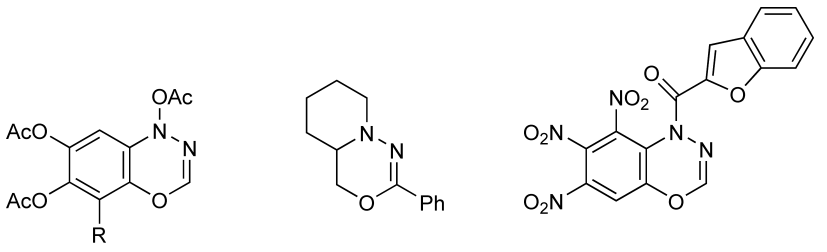
(32)




**208**

**209**

4*H*-1,3,4-Benzoxadiazine **210** is obtained from 2-acyl-hydrazino-1,4-quinones by heating in acetic anhydride <1997IJB68>. 2-Phenylperhydropyrido[1,2-*d*][1,3,4]oxadiazine **211** is obtained from 1-benzoylamino-2-chloromethyl-piperidine <1997H(45)95>. *N*-Picryl-*N*,*N*′-di(2-furoyl)hydrazine cyclizes in the presence of triethylamine to yield the 1,3,4-oxadiazine derivative **212** <1999RJO933>. Cyclization of 2-chloro-3-(*N*-benzoylhydrazino)-1,4-naphthoquinone with benzenesulfonyl chloride in DMF/triethylamine affords the 1-benzenesulfonyl-3-phenylnaphtho[2,3-*e*][1,3,4]-oxadiazine-5,10-dione **213** <2003PS627>. 1-(2-Hydroxycyclohexyl)-4-arylthiosemicarbazides cyclize by treatment with methyl iodide and methanolic potassium hydroxide to the corresponding hexahydro-4*H*-1,3,4-benzoxadiazines **214** <1999ACS103>. Similarly, perhydropyrrolo[1,2,-*d*][1,3,4]oxadiazines **169** and perhydropyrido[1,2-*d*][1,3,4]oxadiazines **171** are obtained from pyrrolidino or piperidinothiourea derivatives <1997H(45)927> (see Section 8.08.6.2).



**210**

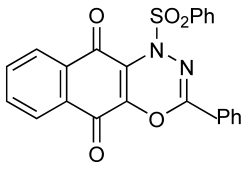
R = Ph, Me



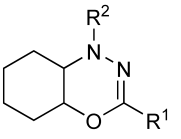
**211**



**212**



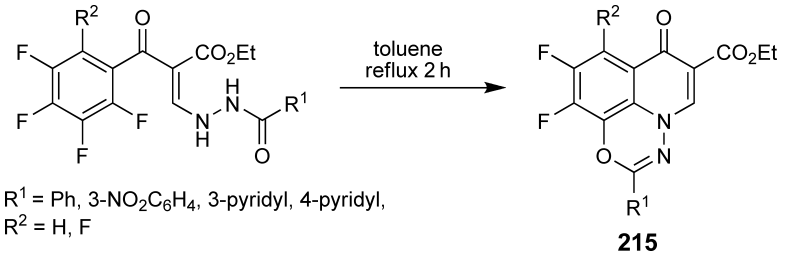
**213**



**214**

$R^1$ = NHAr; $R^2$ = Me, Bn

3-(Acylhydrazino)-2-tetra(penta)fluorobenzoylacrylates are converted readily to 1,3,4-oxadiazino[6,5,4-*i*,*f*]quinolines **215** by heating in toluene (Equation 33) <2001CHE1278, 1998MC131>.



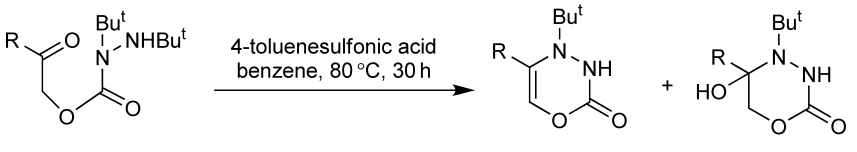
$R^1$ = Ph, 3-$NO_2C_6H_4$, 3-pyridyl, 4-pyridyl,
$R^2$ = H, F

**215**

(33)

### 8.08.8.1.2 Between carbon and nitrogen (fragment)

When acylmethyl carbazates **216** are treated with a catalytic amount of 4-toluenesulfonic acid in benzene at 80 °C, 1,3,4-oxadiazin-2-one derivatives **217** and **218** are obtained (Equation 34) <2000H(52)541>. The reaction of 2-[(2-aminophenyl)sulfonyl]-*N*,*N*-dialkylacetamides **219** with acetic acid and sodium nitrite affords 4,2,1-benzothiadiazin-3-carboxylate 4,4-dioxides **220** via diazonium salt intermediates (Equation 35) <1996JHC347>.



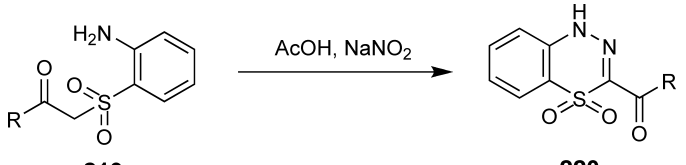
**216**

R = Me, Ph

**217**

**218**

(34)



**219**

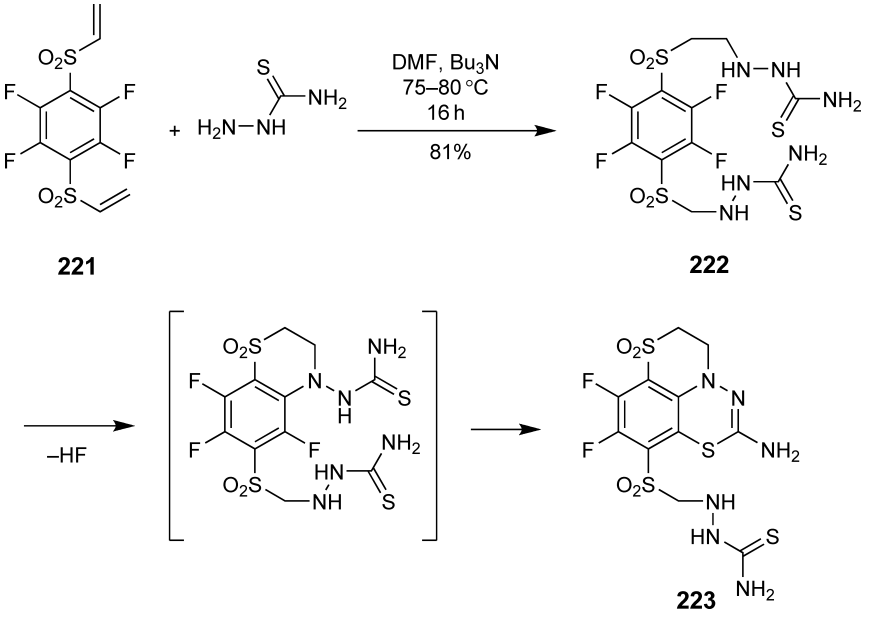
**220**

R = $NEt_2$, piperidino, morpholino

(35)

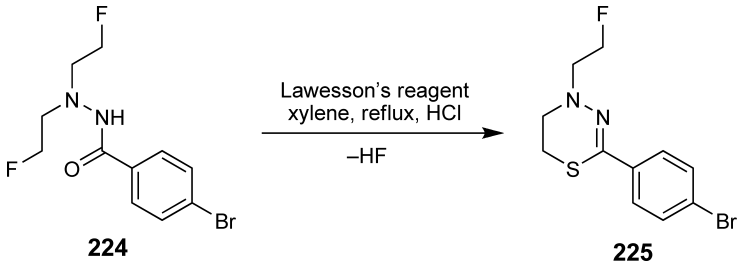
#### 8.08.8.1.3 Between carbon and sulfur (fragment)

Heating vinylsulfonylfluorobenzene **221** with thiosemicarbazide in DMF at 75–80 °C in the presence of tributylamine affords 5,6-dihydro[*h*,*i*]-1,4-thiazino[4,3-*d*]1,3,4thiadiazine-7,7-dioxide **223** (**Scheme 28**) <2004MI269>. The formation of compound **223** takes place by initial addition of the 1-$NH_2$ group of the thiosemicarbazide to both activated double bonds of vinylsulfonylfluorobenzene **221** to give the adduct **222**. Subsequent intramolecular substitution of fluorine atoms occurs in the *o*-position by the NH group, and in the *m*-position by the second nucleophilic center in the thiosemicarbazide, the sulfur atom. Increasing the reaction temperature to 75–80 °C under conditions of medium basicity facilitates the nucleophilic substitution of fluorine atoms in the benzene ring, affording **223**.




**Scheme 28**

2,2-Bis-(2-fluoroethyl)-4-bromobenzhydrazide **224** reacts with Lawesson's reagent in *para*-xylene and, following treatment of the filtrate with gaseous hydrogen chloride, gives 2-aryl-4-fluoroethyl-5,6-dihydro-4*H*-1,3,4-thiadiazine **225** (Equation 36) <1998WO9838181>.

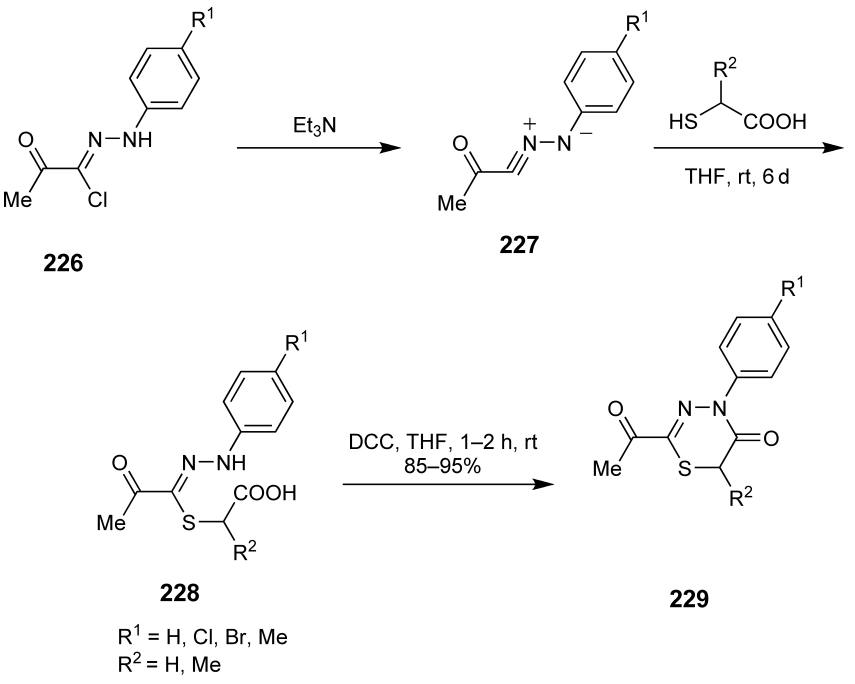



(36)

## 8.08.8.2 By Formation of Two Bonds

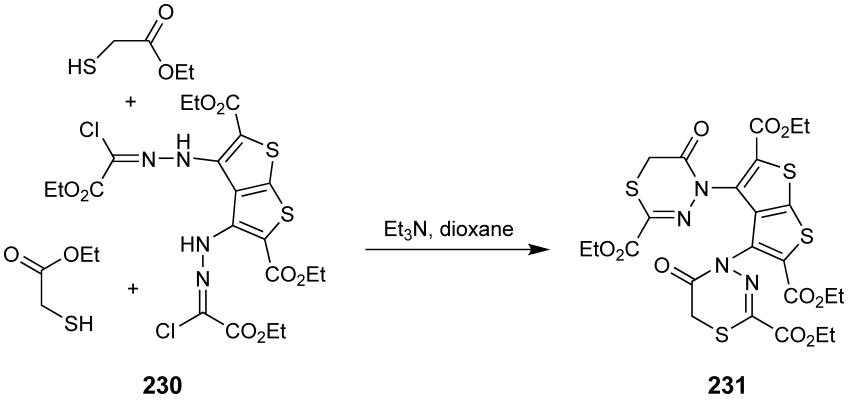
#### 8.08.8.2.1 [3+3] Fragments

The *N*-aryl-substituted hydrazonoyl chlorides **226** react with 2-sulfanylacetic acid or 2-sulfanylpropanoic acid. In the presence of triethylamine, nitrilimines **227** are generated first and these intermediates react with the 2-sulfanylalkanoic acids to form the corresponding adducts **228** with yields of 70–80%. The latter cyclize in THF by reaction with dicyclohexylcarbodiimide (DCC) at room temperature to furnish 1,3,4-thiadiazine-5-ones **229** (**Scheme 29**) <2002M1011>.




**Scheme 29**

Similarly, the hydrazonyl chloride **230** reacts with ethyl sulfanylacetate via a reactive nitrileimine to form the 1,3,4-thadiazine derivative **231** (Equation 37) <2003PS1689>.

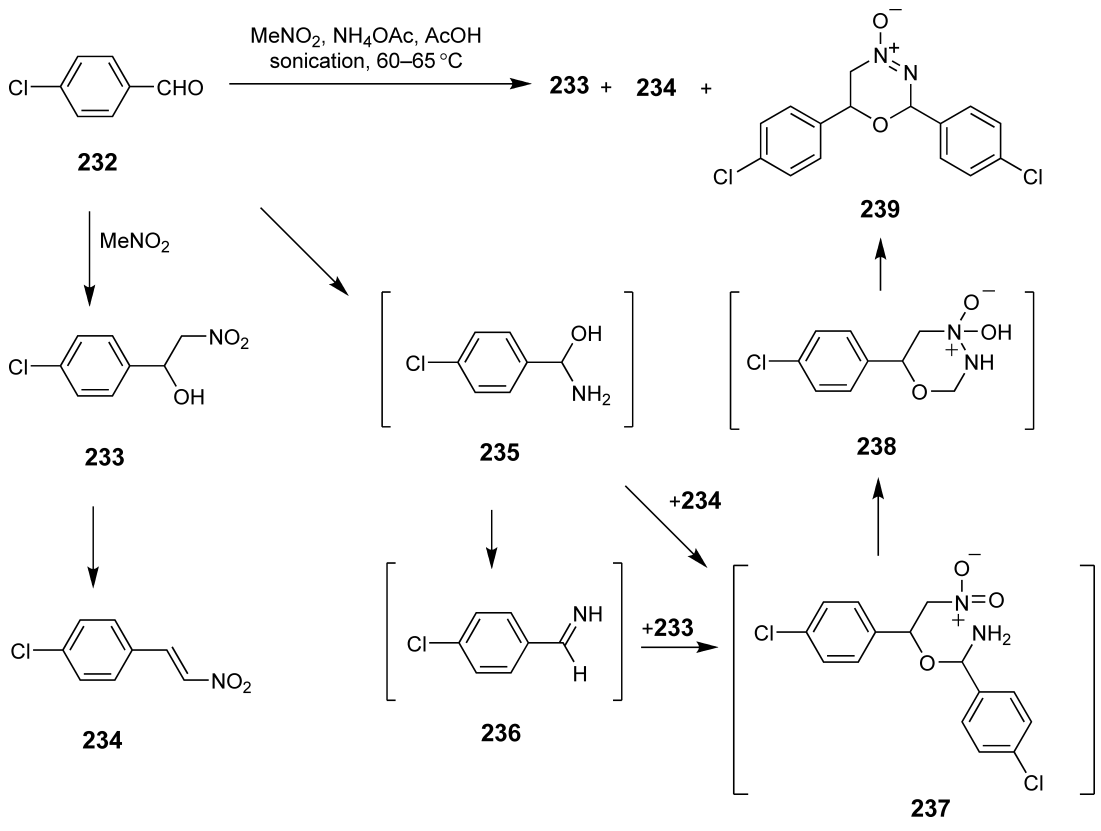



(37)

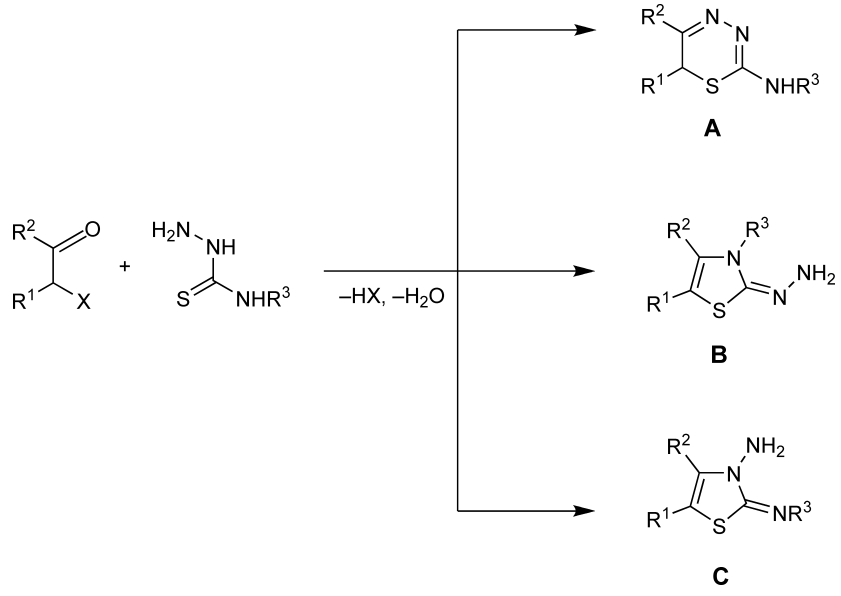
4-Chlorobenzaldehyde **232** reacts with ammonium acetate and acetic acid in nitromethane under ultrasonic irradiation to give the 1,3,4-oxadiazine derivate **239** <2000JOC4750>. From chromatographic investigations the formation of the intermediates **233** and **234** was indicated. A reaction mechanism is proposed in **Scheme 30**.

### 8.08.8.2.2 [4+2] Fragments

1,3,4-Thiadiadiazines are prepared best by condensation of thiohydrazides with $\alpha$-halocarbonyl compounds. As thiohydrazide components, most substituted thiosemicarbazides, aryl and alkyl thiocarbonylhydrazides, or *O*-alkyl dithiocarbazates can be used. The cyclocondensation with thiosemicarbazides and $\alpha$-halocarbonyl compounds can provide three isomeric compounds, 2-amino-1,3,4-thiadiazines **A**, 2-hydrazino-1,3-thiazoles or 2-hydrazono-2,3-dihydro-1,3-thiazoles **B**, and 2-alkyl(aryl)imino-3-amino-2,3-dihydro-1,3-thiazoles **C** (**Scheme 31**). The course of the cyclization of thiosemicarbazides with $\alpha$-halocarbonyl compounds depends on the acidity of the reaction medium and the substituents $R^1$, $R^2$, and $R^3$. The reaction of aromatic $\alpha$-halo ketones with thiosemicarbazides leads under neutral

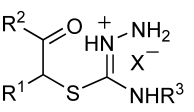



**Scheme 30**



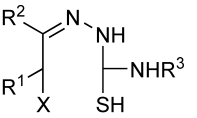

**Scheme 31**

conditions (ethanol) at 0 °C to isolable *S*-ketonyl-isothiosemicarbazide hydrohalogenides **240**. In a weakly acidic environment, α-halo keto-thiosemicarbazones **241** are formed. The compounds **240** and **241** can be converted to 1,3,4-thiadiazines by heating in ethanol <1998HOU(E9c)483>.



**240**

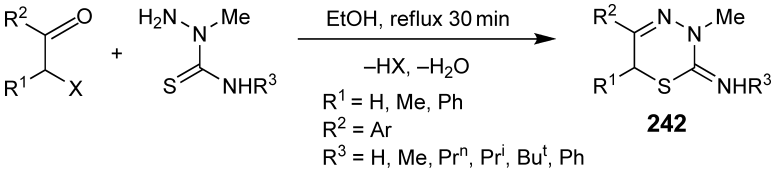
$R^1$ = H, Me, Et
$R^2$ = Ar
$R^3$ = H, Alk, Ar
X = Br, Cl



**241**

$R^1 = R^2$ = Alk, H
$R^3$ = H, Alk, Ar

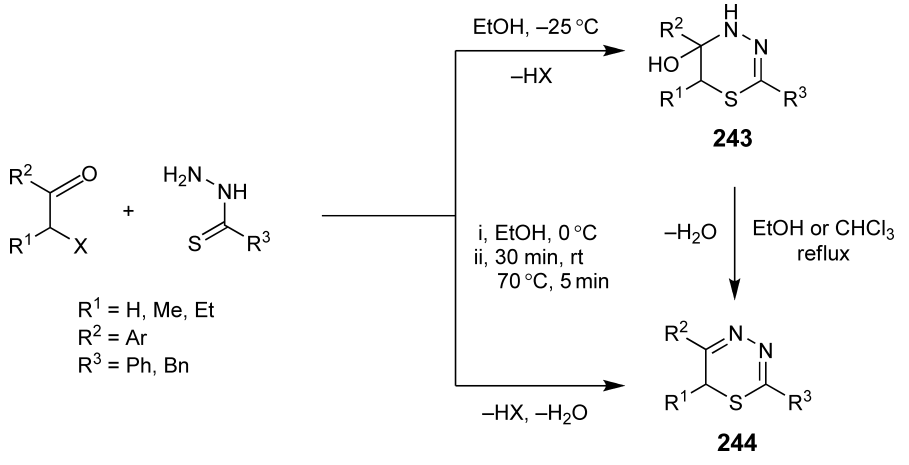
2-Alkyl(aryl)imino-3-methyl-2,3-dihydro-6*H*-1,3,4-thiadiazines **242** are obtained exclusively from α-halo ketones and 2-methyl-4-alkyl(aryl)thiosemicarbazides (Equation 38) <1997PHA831>.



EtOH, reflux 30 min
–HX, $–H_2O$
$R^1$ = H, Me, Ph
$R^2$ = Ar
$R^3$ = H, Me, $Pr^n$, $Pr^i$, $Bu^t$, Ph

**242** (38)

2-Phenyl- and 5-aryl-benzyl-6*H*-1,3,4-thiadiazines are synthesized by cyclocondensation of α-halocarbonyl compounds with thiobenzhydrazide or phenylthioacetic acid hydrazide <1998HOU(E9c)483>. Under appropriate conditions, it is possible to isolate the initially formed 4,5-dihydro-6*H*-1,3,4-thiadiazin-5-ol intermediates **243**. For this purpose, the thiohydrazide is added to an equimolar amount of sodium ethoxide solution, followed by, at −25 °C, an ethanolic solution of the respective α-halocarbonyl compound. The corresponding intermediate **243** separates as a colorless precipitate. The compounds **243** undergo dehydration by heating in ethanol or chloroform. When the thiohydrazides are allowed to react with the α-halocarbonyl compounds in sodium ethoxide solution under initial cooling in ice/salt, followed by warming, the 1,3,4-thiadiazines **244** are formed directly (**Scheme 32**).



EtOH, –25 °C
–HX

**243**

i, EtOH, 0 °C
ii, 30 min, rt
70 °C, 5 min

$–H_2O$
EtOH or $CHCl_3$
reflux

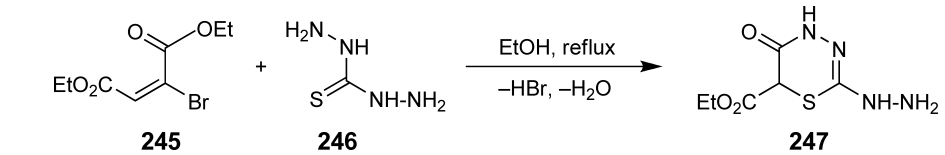
$R^1$ = H, Me, Et
$R^2$ = Ar
$R^3$ = Ph, Bn

–HX, $–H_2O$

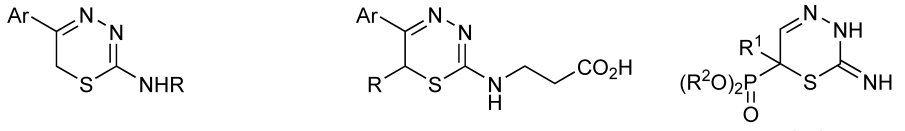
**244**

**Scheme 32**

As an α-halocarbonyl compound, diethyl bromomaleate **245** can also be used. The cyclization of this compound with thiocarbohydrazide **246** affords a 5-oxo-1,3,4-thiadiazine derivative **247** <2000IJC(B)603> (Equation 39). Thiosemicarbazide or thiocarbohydrazide and α-halo ketones cyclize readily by microwave irradiation under basic conditions to give 2-amino- or 2-hydrazino-6*H*-1,3,4-thiadiazines **248** <2002JHC1045>. 3-[5-(Aryl-6*H*-1,3,4-thiadiazin-2-yl)amino]propanoic acid **249** are obtained by cyclization of the corresponding 4-substituted thiosemicarbazides with α-halo ketones <2002TL3309>. The cyclocondensation of phosphoryl-α-chloroacetaldehydes with thiosemicarbazide yields 6-diisopropoxyphosphoryl-2-imino-2,3-dihydro-6*H*-1,3,4-thiadiazines **250** <2003CHE671>. Heterocyclic substituted thiosemicarbazides or methyl dithiocarbazate afford the 1,3,4-thiadiazines **251–253** by reaction with α-halo ketones <1998H557, 2004H2079, 2004T841>.

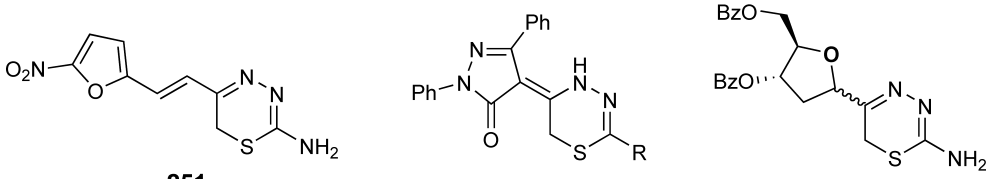



245 246 247 (39)




248 249 250

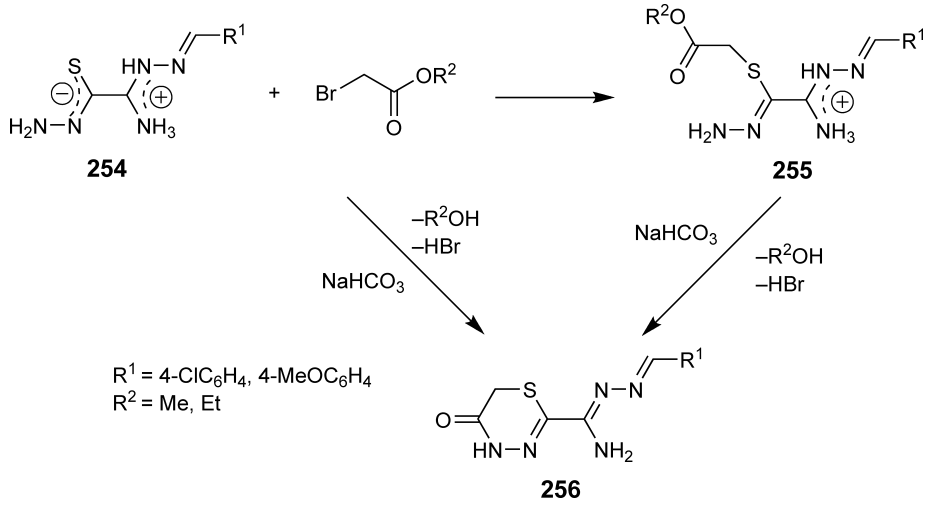
R = H, $NH_2$ R = H, Me $R^1$ = H, Ph, Et $R^2$ = $Pr^i$




251 252 253

R = $NH_2$, NHMe, NHEt, NHPh, SMe

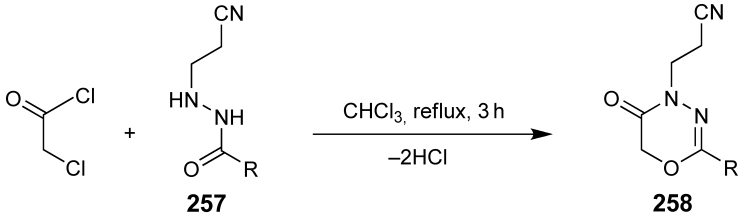
Zwitterionic monobenzylidene thiooxamic acid derivatives **254** react with alkyl bromoacetates in the absence of a base to give the intermediates **255**. The cyclization under basic conditions furnishes 5-oxo-4,6*H*-1,3,4-thiadiazines **256**. These compounds are also obtained by heating of **254** with alkyl bromoacetates in the presence of $NaHCO_3$ (**Scheme 33**) <1998SUL163>.




254 255 256

**Scheme 33**

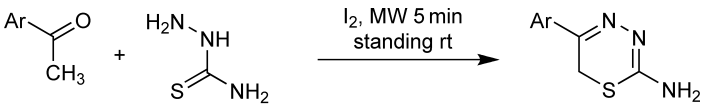
2-Substituted 5,6-dihydro-5-oxo-4*H*-1,3,4-oxadiazines **258** are obtained by cyclocondensation of 2-chloroacetyl chloride with 2-(2-cyanoethyl)hydrazides **257** under basic conditions (Equation 40) <2002HCA559>.




257 258 (40)

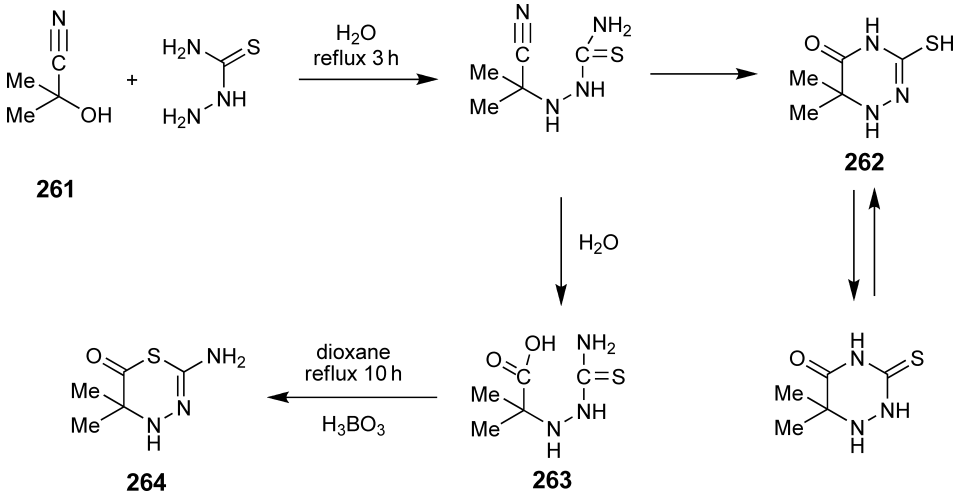
R = Ar, indol-3-yl-$CH_2$

An interesting synthetic method is the one-pot reaction of arylketones **259** with iodine and thiosemicarbazides under microwave irradiation. Initially, the $\alpha$-halo ketones are formed by this reaction, followed by cyclization with the thiosemicarbazide to afford the 1,3,4-thiadiazine derivatives **260** (Equation 41) <2004IJH283, 2005IJB2158>.



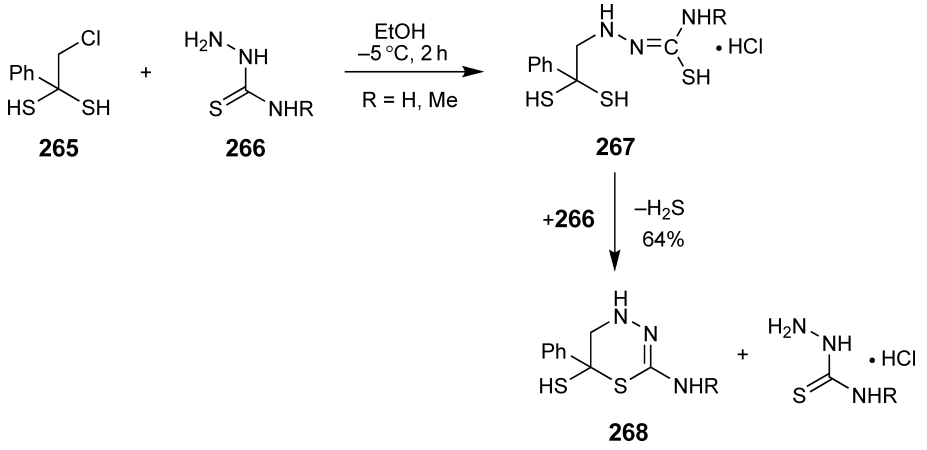

**259** **260** (41)

When acetone cyanohydrin **261** is heated with thiosemicarbazide in water, 3-sulfanyl-6,6-dimethyl-1,2,3-triazin-5-one **262** and 2-methyl-2-thiosemicarbazidopropanoic acid **263** are formed <2002CHE992>. Cyclization of **263** in dioxane in the presence of $H_3BO_3$ yields 2-amino-5,5-dimethyl-1,3,4-thiadiazin-6-one **264** (**Scheme 34**).



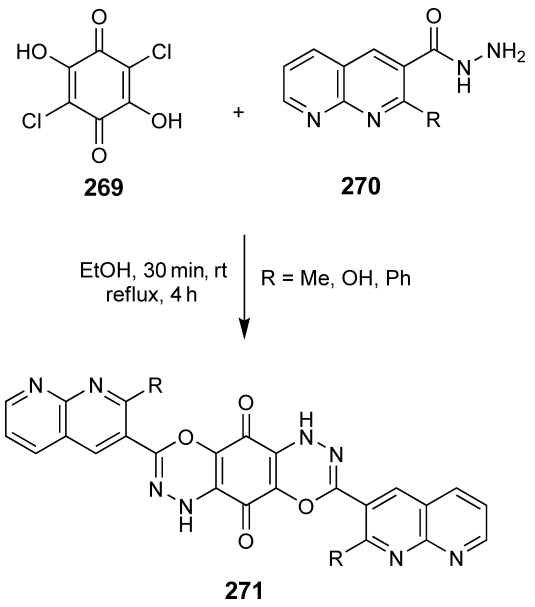

**Scheme 34**

Reaction of 2-chloro-1-phenylethane-1,1-dithiol **265** with thiosemicarbazides **266** in methanol at −5 °C affords 2-amino- or 2-methylamino-6-sulfanyl-6-phenyl-5,6-dihydro-1,3,4-thiadiazines **268** via an isolated intermediate **267** (**Scheme 35**) <2005CHE946>.



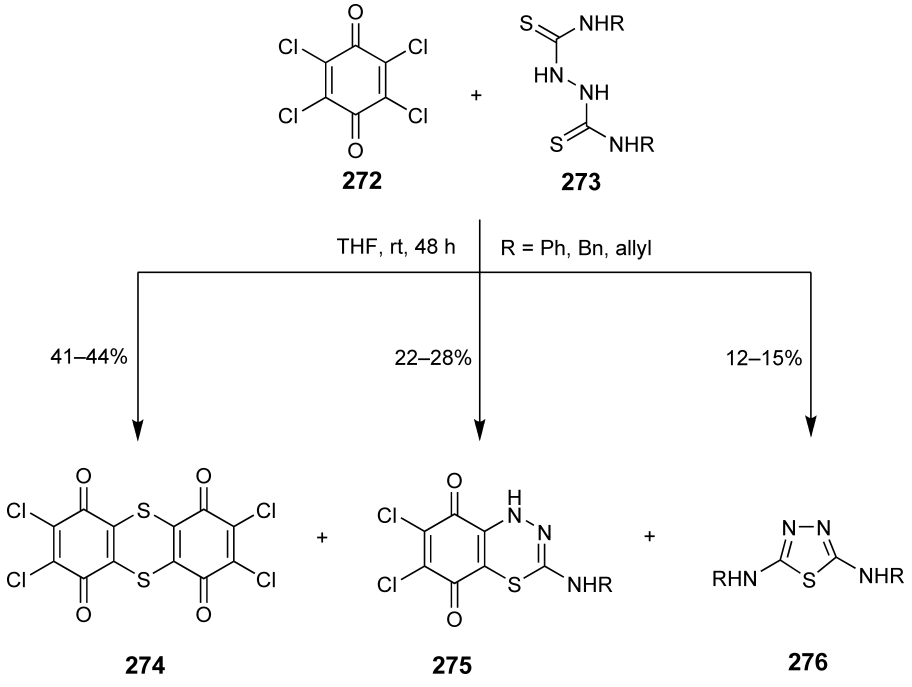

**Scheme 35**

The treatment of 2,5-dichloro-3,6-dihydroxycyclohexa-2,5-diene-1,4-dione **269** with 2-substituted-1,8-naphthyridine-3-carboxylic acid hydrazides **270** in ethanol under reflux resulted in the formation of 3,8-di(2-substituted-1,8-naphthyridin-3-yl)benzo(1,2-*e*:4,5-*e*′)bis[1,3,4]oxadiazine-5,10[1*H*,6*H*]diones **271** <2000IJH311> (Equation 42).



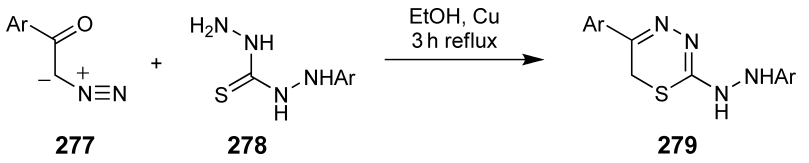

(42)

Similarly, the cyclization of 2,3,5,6-tetrachloro-1,4-quinone **272** with thiourea derivatives **273** in THF at room temperature leads to 2,3,7,8-tetrachlorothianthrene-1,4,6,9-tetrones **274** as the major products (41–44%) and 2,5-disubstituted 3-amino-6,7-dichloro-2,3-dihydro-1*H*-4,1,2-benzothiadiazine-5,8-diones **275** (22–28%), together with 2,5-diamino-1,3,4-thiadiazoles **276** (12–15%) (Equation 43) <2006JHC471>.



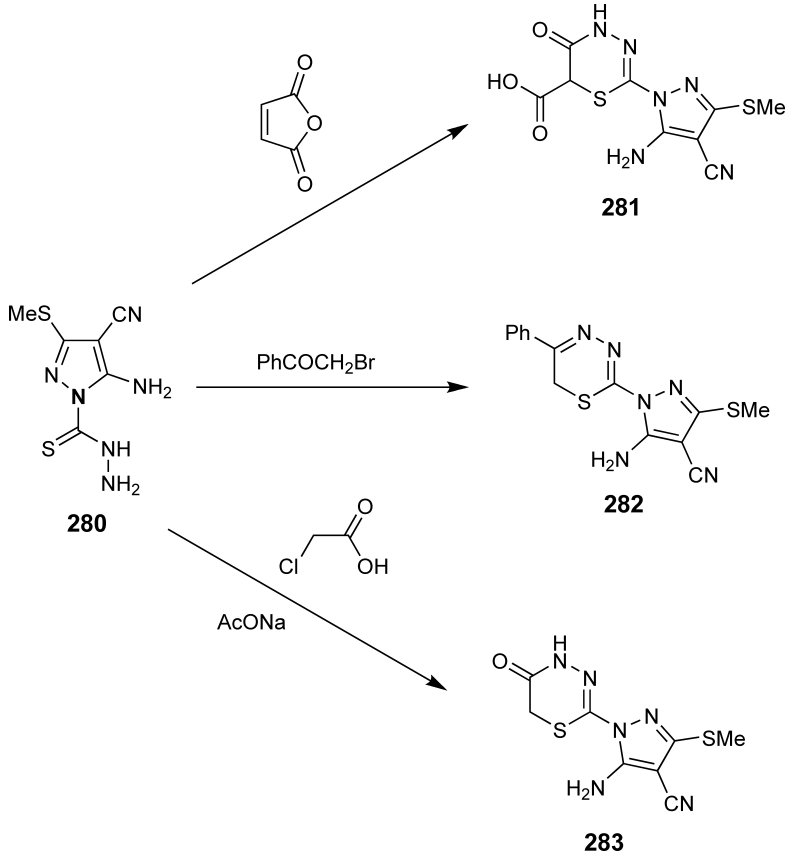

(43)

2-Arylhydrazino-5-aryl-6*H*-1,3,4-thiadiazines **279** are obtained by the cyclocondensation of aryl diazoketones **277** with 1-arylthiocarbohydrazides **278** in boiling ethanol in the presence of copper <1998HOU(E9c)483> (Equation 44).



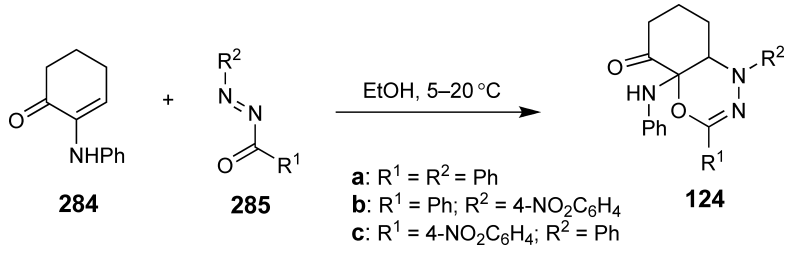

277 278 279 (44)

Treatment of the pyrazolyl-1-thiocarbonylhydrazide derivative **280** with maleic anhydride furnishes **281** <2000JCM544>, whereas the reaction of **280** with phenacyl bromide yields the 1,3,4-thiadiazine **282**. Cyclization of **280** with chloroacetic acid affords the 4,5-dihydro-1,3,4-thiadiazin-5-one **283** (Equation 45). However, when chloroacetyl chloride is used instead of chloroacetic acid, with the aim of obtaining the same product **283**, a thiadiazolylpyrazole derivative was formed <2000JCM544>. The starting material **280** is produced by the reaction of a ketene dithioacetal with thiocarbohydrazide or hydrazinolysis of pyrazolyldithiocarbonate <2000JCM544>.



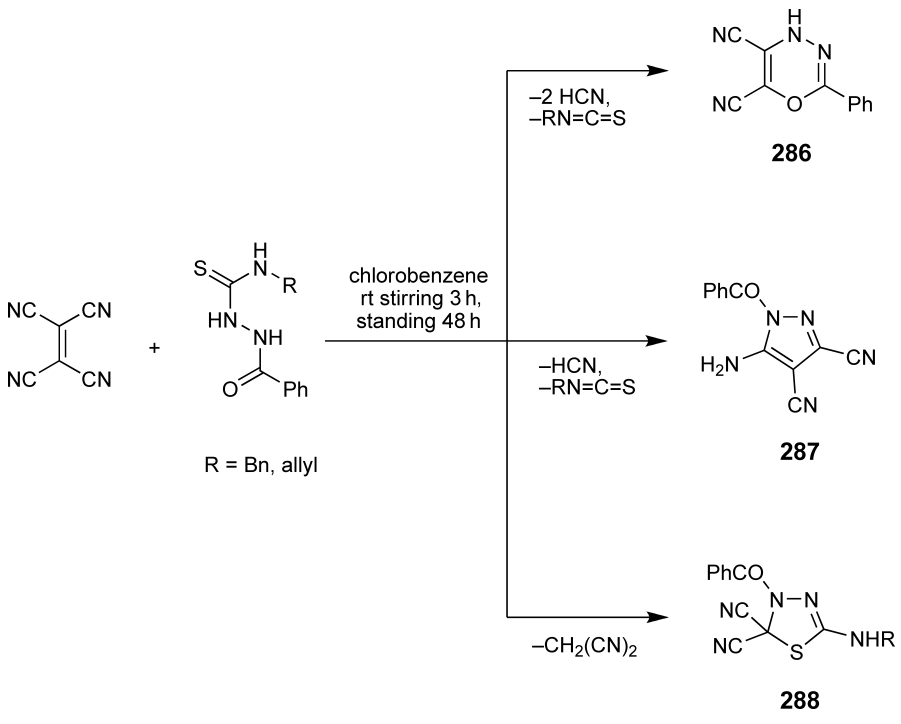

(45)

The cyclization of aromatic α-ketoenamines **284** with electrophilic diazenes **285** at 5–20 °C in ethanol furnishes 1,3,4-oxadiazine derivatives **124** (Equation 46) <1996G297, 1997G387>. Compounds **124b** and **124c** exhibit greater stability than **124a**, which undergoes ring opening after 30 min heating in ethanol to give keto enamines **125a** and **126a** (see Section 8.08.5.1). In contrast, ring opening of **124b**,**c** to form **125b**,**c** and **126b**,**c** takes place by refluxing for 5–6 h in ethanol.




(46)

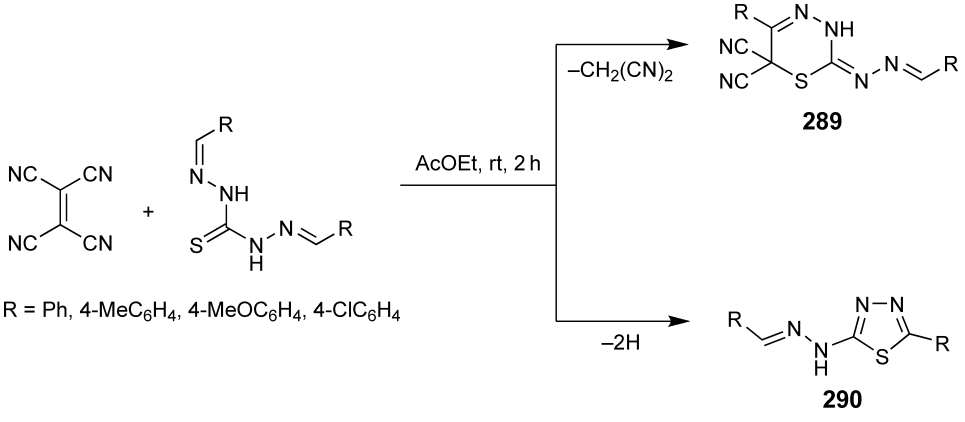
Ethenetetracarbonitrile reacts with 1,4-disubstituted thiosemicarbazides in chlorobenzene to give 2-phenyl-1,3,4-oxadiazine **286**, pyrazole **287**, and 1,3,4-thiadiazoles **288** (Equation 47) <2005HAC12>.




(47)

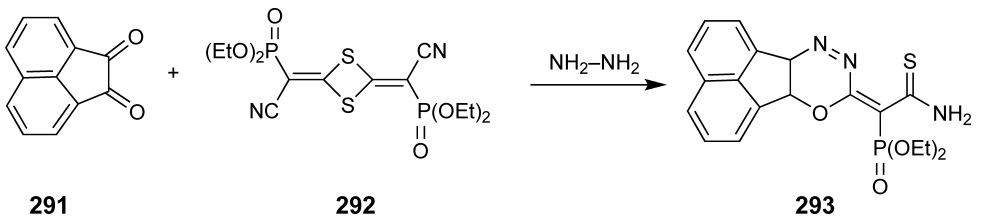
### 8.08.8.2.3 [5+1] Fragments

The cyclization of ethenetetracarbonitrile with diarylidenethiocarbohydrazides affords 1,3,4-thiadiazine derivatives **289**. 1,3,4-Thiadiazoles **290** are obtained as by-products through oxidative cyclization of the diarylidenethiocarbohydrazides (Equation 48) <1997M61>.

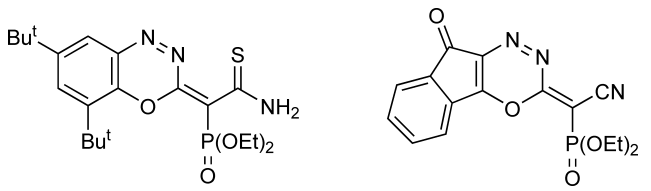



(48)

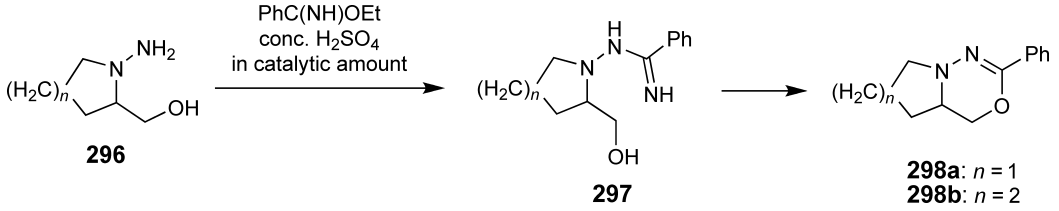
The condensation of acenaphthenequinone **291** with hydrazine in ethanol furnishes a monohydrazone derivative which, by heating with a half equivalent of 1,3-dithiethane **292**, provides the fused 1,3,4-oxadiazine **293** (Equation 49) <2002PS1885>. The treatment of 3,5-di-*tert*-butylbenzoquinonehydrazone or 1,3-indandione-2-hydrazone with 1,3-dithiethane **292** affords the 1,3,4-oxadiazine derivatives **294** and **295**.




(49)

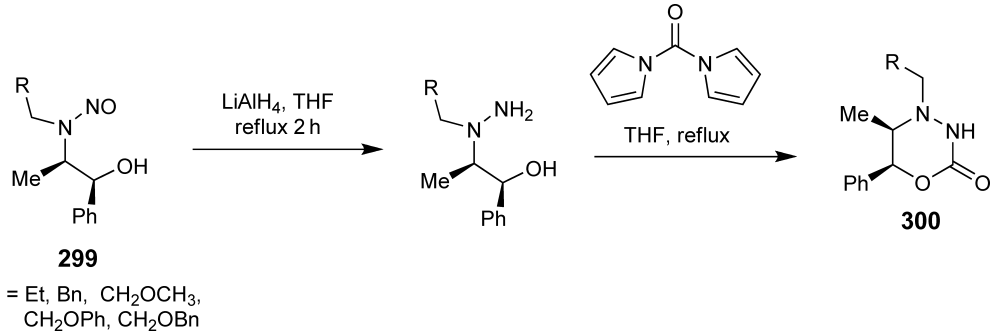



Hydrazino alcohols **296** react with ethyl benzimidate to form pyrrolo[1,2-*d*][1,3,4]oxadiazine **298a** or pyrido[1,2-*d*]-[1,3,4]oxadiazine **298b** via the intermediates **297** (**Scheme 36**) <1997H(45)95>.

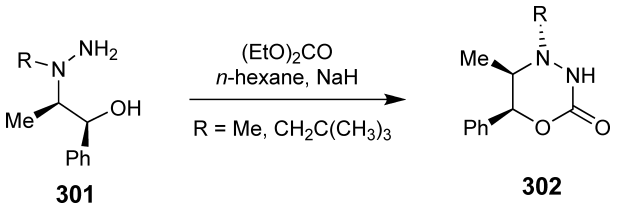



**Scheme 36**

Oxadiazinan-2-ones **300** are obtained from norephedrine in good yield via N-alkylation, nitrosation, reduction, and cyclization <2002JHC823, 1996JME3938>. The nitroso compounds **299** are reduced with lithium aluminum hydride and the intermediate hydrazine alcohols cyclized with carbonyldiimidazole to afford compounds **300** (**Scheme 37**). Similarly, 1,3,4-oxadiazinan-2-one derivatives **302** are obtained by reaction of hydrazino alcohols **301** with diethylcarbonate and sodium hydride (Equation 50) <2004SC835>.




**Scheme 37**

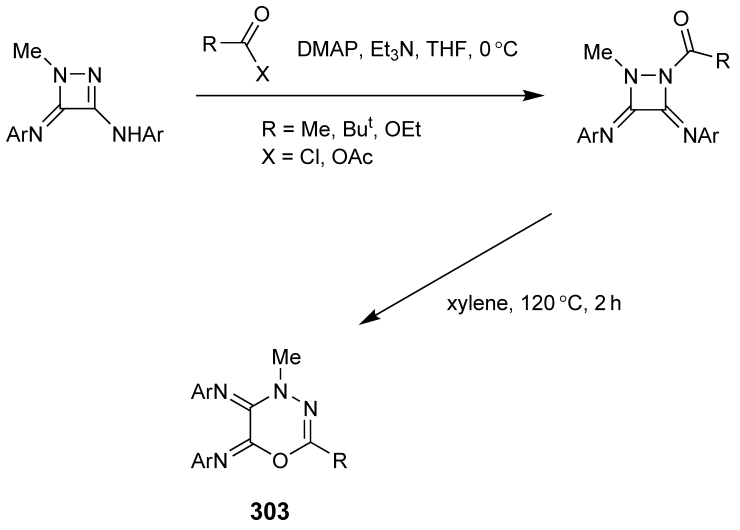



(50)

## 8.08.9 Ring Syntheses by Transformations of Another Ring

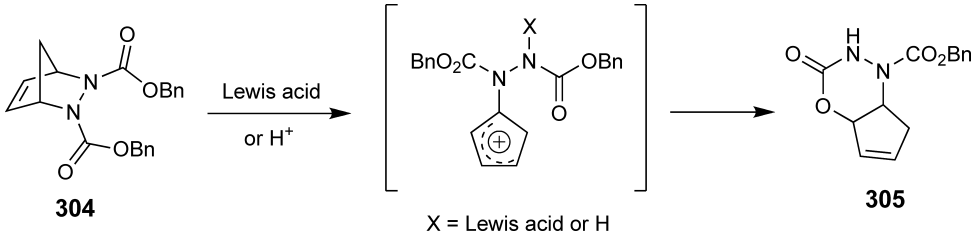
### 8.08.9.1 1,3,4-Oxadiazines

Treatment of $\Delta^2$-1,2-diazetines with acid chlorides or anhydrides in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) affords acylated 1,2-diazetidines which undergo a thermally induced ring transformation to 1,4,3-oxadiazines **303** (**Scheme 38**) <2006S514>.



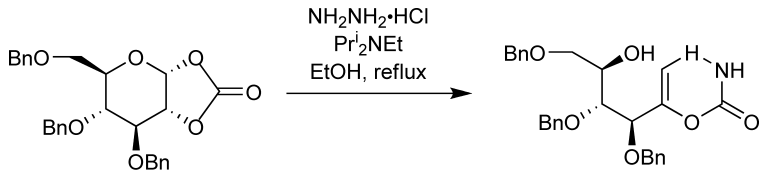

**Scheme 38**

The acid-catalyzed ring opening of 2,3-dibenzyloxycarbonyl-2,3-diazabicyclo[2.2.1]heptene **304** gives the bicyclic 1,3,4-oxadiazine derivative **305** via an intermediate cation (**Scheme 39**) <2003OL4771, 2005JOC3316>.



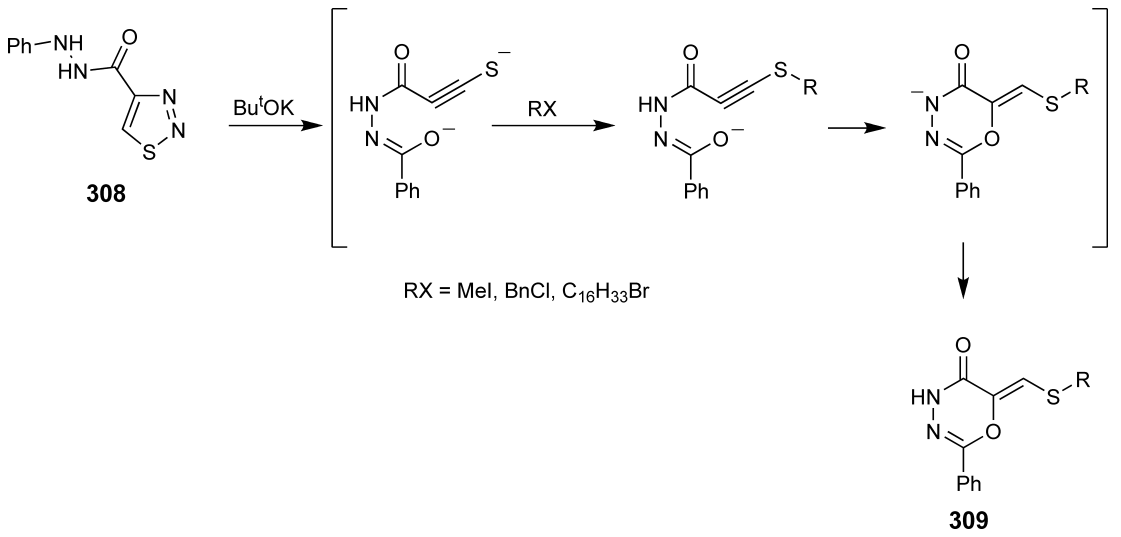

**Scheme 39**

The reaction of the cyclic carbonate **306** with hydrazine hydrochloride and $Pr^i_2NEt$ in ethanol at reflux produced the cyclic hydrazone **307** via partial, regioselective hydrazinolysis of **306** followed by intramolecular condensation of the resultant hydrazide with the unmasked hemiacetal group (Equation 51) <2005SL2607>.




306 307 (51)

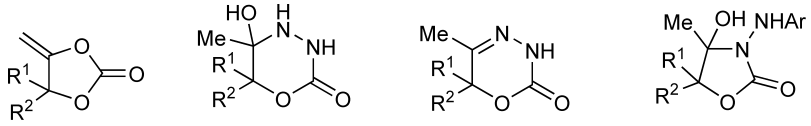
The ring cleavage of hydrazide **308** in the presence of 2 equiv of Bu$^t$OK, followed by alkylation, results in 1,3,4-oxadiazin-5-one derivatives **309** (**Scheme 40**) <2002TL1015>.




308 309

**Scheme 40**

The treatment of 2-methylene-1,3-dioxolan-2-ones **310** ($R^1 = R^2 = Me$; $R^1 + R^2 = (CH_2)_5$; $R^1 = Me$, $R^2 = Me_2C{=}CH{-}CH_2{-}CH_2$) with hydrazine hydrate leads to carbamate intermediates, which undergo cyclization to give 5-hydroxy-5.6-dihydro-4*H*-1,3,4-oxadiazin-2(3*H*)-ones **311**. The thermal dehydration of **311** gives 1,3,4-oxadiazin-2(3*H*)-ones **312** <2003CHE1057>. In contrast to the case with hydrazine hydrate, the reaction of aromatic hydrazines with 1,3-dioxolan-2-ones **310** provides 3-arylamino-4-hydroxyoxazolidin-2(3*H*)-ones **313**.

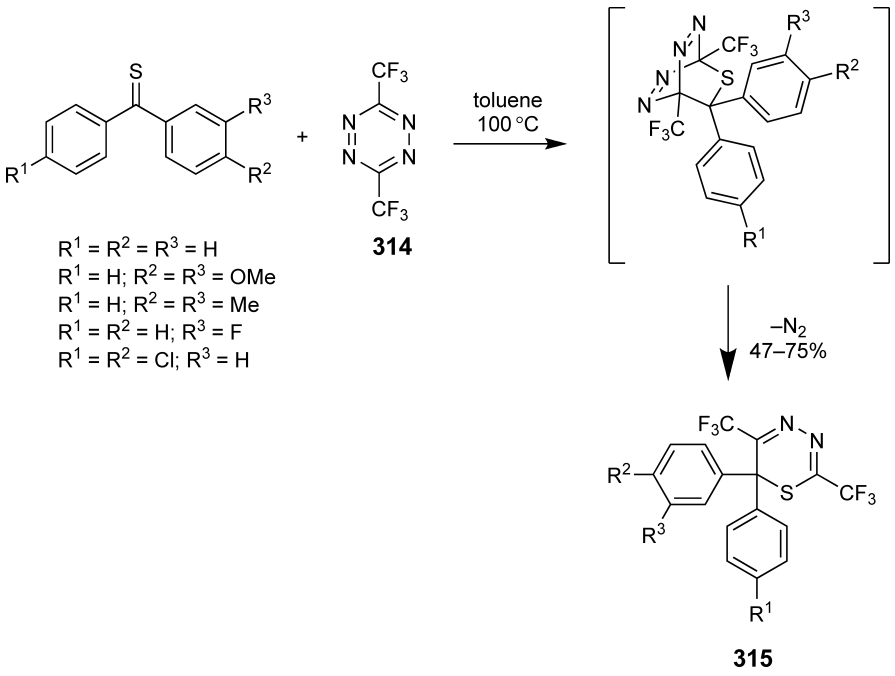


310 311 312 313

## 8.08.9.2 1,3,4-Thiadiazines

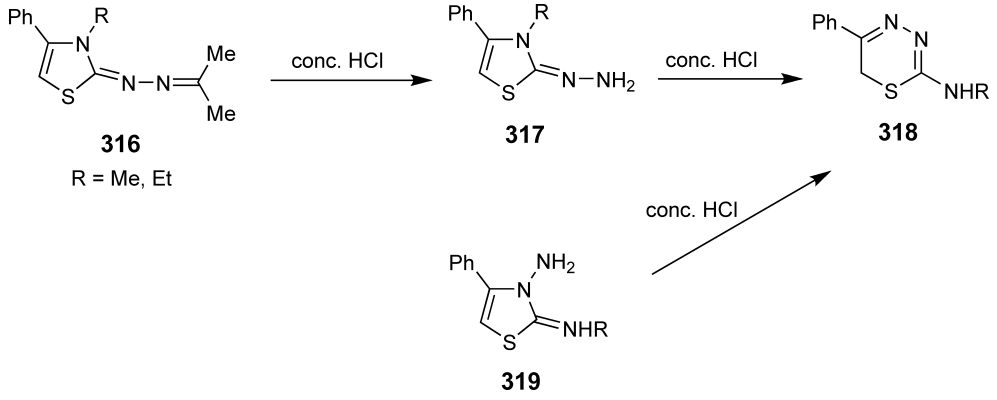
3,6-Bis(trifluoromethyl)-1,2,4,5-tetrazine **314** reacts with substituted thiobenzophenones by [4+2] cycloaddition via a Diels–Alder adduct which is not isolable. Cycloreversion, with elimination of nitrogen, then gives 6*H*-1,3,4-thiadiazines **315** in yields of 47–75% (**Scheme 41**) <1998EJO2861>. Similarly, the treatment of **314** with alkylthioformates yields 2,5,6-substituted-6*H*-1,3,4-thiadiazines <1984AGE890>.

Hydrolysis of 3-alkyl-2-(isopropylidenehydrazono)-4-phenyl-2,3-dihydro-1,3-thiazoles **316** with concentrated hydrochloric acid proceeds via the intermediate 3-alkyl-2-hydrazono-4-phenyl-2,3-dihydro-1,3-thiazoles **317** with ring expansion to the *N*-alkyl-5-phenyl-6*H*-1,3,4-thiadiazine-2-amines **318** (**Scheme 42**) <1998HOU(E9c)483, 2006UP1>.



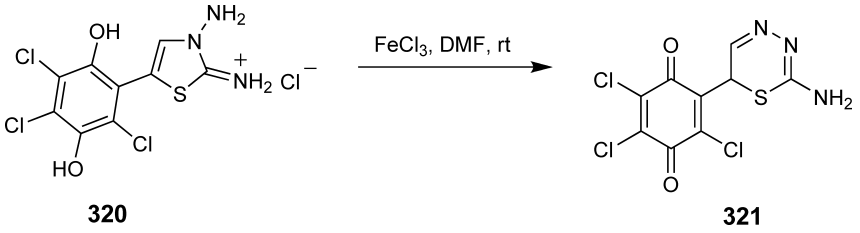

$R^1 = R^2 = R^3 = H$
$R^1 = H; R^2 = R^3 = OMe$
$R^1 = H; R^2 = R^3 = Me$
$R^1 = R^2 = H; R^3 = F$
$R^1 = R^2 = Cl; R^3 = H$

**Scheme 41**



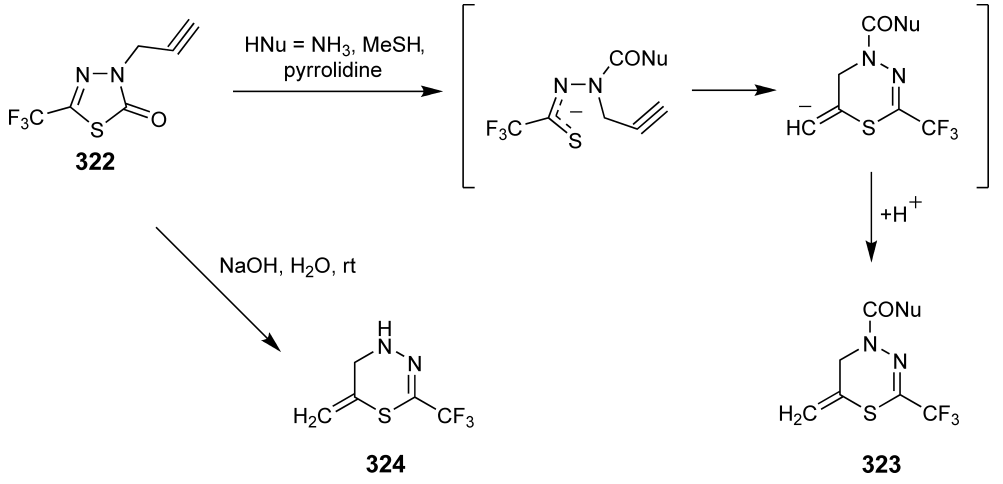

**Scheme 42**

The 2-(alkylimino)-3-amino-4-phenyl-2,3-dihydro-1,3-thiazol-3-amines **319** behave similarly and undergo ring expansion on heating with concentrated hydrochloric acid to give the 1,3,4-thiadiazines **318**. The 1,3-thiazole derivative **320** also undergoes a ring expansion to the 1,3,4-thiadiazine **321** by treatment with $FeCl_3$ in DMF (Equation 52) <1996KGS1424>.



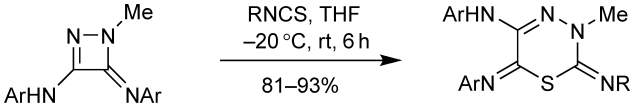

(52)

3-(Prop-2-ynyl)-5-(trifluoromethyl)-1,3,4-thiadiazol-2(3*H*)-one **322** reacts with nucleophiles (ammonia, pyrrolidine, or potassium methylthiolate) to form 6-methylene-2-(trifluoromethyl)-5,6-dihydro-4*H*-1,3,4-thiadiazine-4-carboxamides or *S*-methyl 6-methylene-2-(trifluoromethyl)-5,6-dihydro-4*H*-1,3,4-thiadiazine-4-thiocarboxylates **323**. The reaction of aqueous sodium hydroxide with **322** gives the 4*H*-1,3,4-thiadiazine **324**, which also bears an exocyclic methylene group (**Scheme 43**) <1998HOU(E9c)483>.




**Scheme 43**

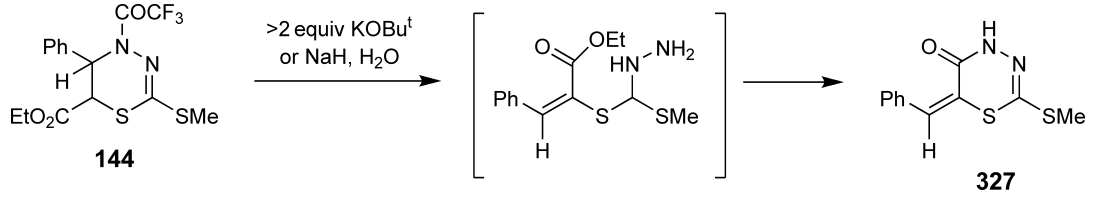
On treatment with isothiocyanates, 1,2-diazetines **325** undergo ring transformation under mild conditions to afford 1,3,4-thiadiazines **326** (Equation 53) <2005H(65)1311>. The mechanism proceeds via an electrocyclic ring-opening–cycloaddition pathway or, at lower temperatures, via a nucleophilic attack of the *N*-methyl nitrogen atom of **325** on the isothiocyanate followed by ring expansion to **326**.




(53)

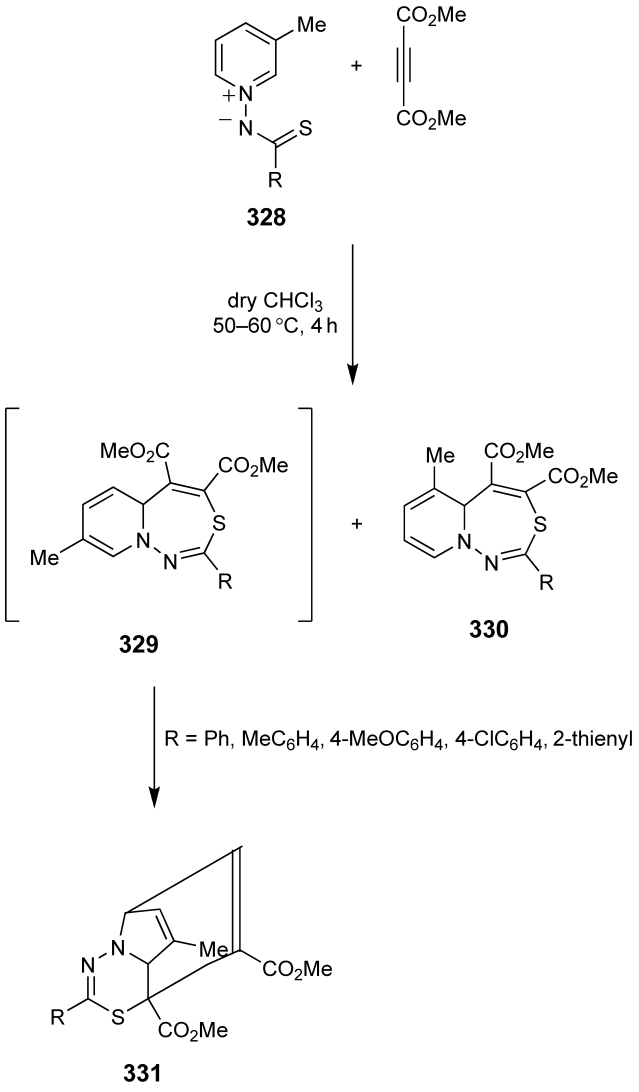
R = Ph, Bn, Me, Et, $CH_2$–CH=$CH_2$, $CH_2COOEt$

Rearrangement of 2-methylsulfanyl-4-trifluoroacetyl-5-phenyl-6-ethoxycarbonyl-4,5-dihydro-6*H*-1,3,4-thiadiazine **144** (see Section 8.08.5.4) by treatment with an excess of potassium *t*-butylate or sodium hydride affords 6-alkylidene-4*H*-1,3,4-thiadiazin-5-one **327** (**Scheme 44**) <1998CL329>.




**Scheme 44**

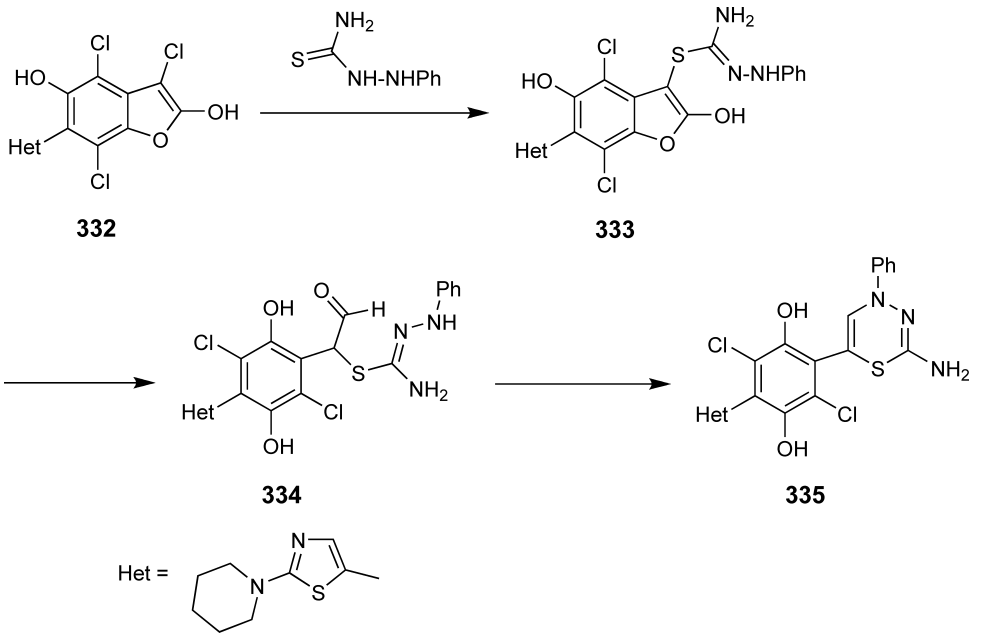
1-Pyridino- or 1-(3-methylpyridino)arenethiocarbonyl amidates **328** cyclized with dimethyl acetylenedicarboxylate (DMAD) by heating in chloroform to give primarily the bicyclic adducts **329** and **330**. Compounds **330** can be isolated, whereas the intermediates **329** undergo a rearrangement to the tricycles **331** (**Scheme 45**) <1997JOC7788>.



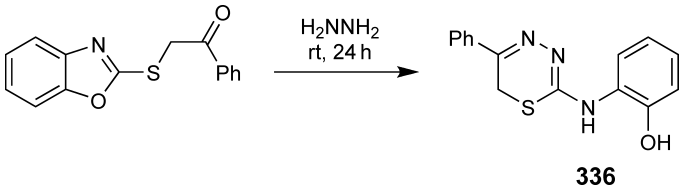

**Scheme 45**

Benzofuran **332** reacts with 1-phenylthiosemicarbazide to give the benzofuran derivative **333**, which undergoes ring cleavage to the intermediate **334** and subsequent cyclization to the 1,3,4-thiadiazine **335** <2005H(65)1569>. The reactions of benzofuran **332** with 4,4-dialkylthiosemicarbazides proceed with extrusion of a sulfur atom from the 1,3,4-thiadiazine intermediate and the formation of pyrazole derivatives (**Scheme 46**) <2005H(65)1569>.

The $\alpha$-(benzoxazol-2-ylsulfanyl) ketone reacts with hydrazine hydrate in acetic acid to yield *N*-(2-hydroxyphenyl)-5-phenyl-6*H*-1,3,4-thiadiazine-2-amine **336** (Equation 54) <1998HOU(E9c)518>.

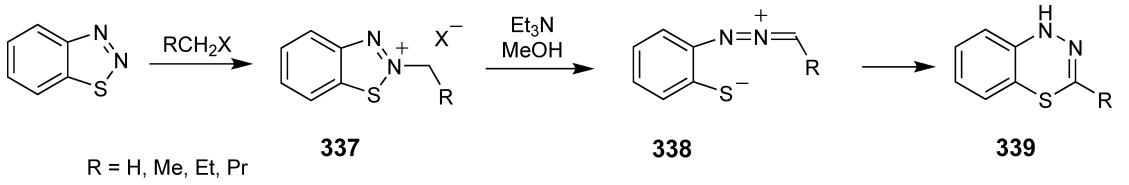



**Scheme 46**




(54)

1*H*-4,1,2-Benzothiadiazines **339** can be prepared by ring expansion of intermediate 3-alkyl-1,2,3-benzothiadiazolium salts **337**, possibly via nitrogen ylides **338** (**Scheme 47**) <1998HOU(E9c)518>.



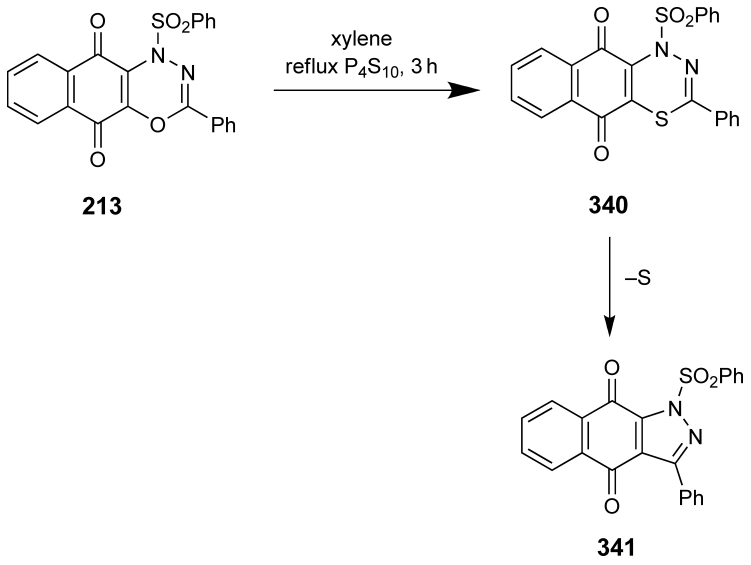

**Scheme 47**

Heating the 1,3,4-oxadiazine **213** (see Section 8.08.8.1.1) with phosphorus pentasulfide in xylene effects ring transformation to give the corresponding 1,3,4-thiadiazine **340** and the pyrazole derivative **341** (**Scheme 48**) <2003PS627>.

## 8.08.10 Synthesis of Particular Classes of Compounds and Critical Comparsion of the Various Routes Available

### 8.08.10.1 1,3,4-Oxadiazines

Diaryl-4*H*-1,3,4-oxadiazines can be prepared by hydration of 1-aryl-2-phenacyl hydrazine derivatives (Section 8.08.8.1.1). 3*H*-1,3,4-Oxadiazin-2-ones are obtained by cyclization of ethoxycarbonylhydrazones of $\alpha$-hydroxy ketones (Section 8.08.8.1.1). 4*H*-1,3,4-Oxadiazin-5-ones are synthesized by ring closure of 1-acetyl-2-chloroacetylhydrazines.




213 340 341

**Scheme 48**

Cyclization of 2-chloro-3-(*N*-benzoylhydrazino)-1,4-naphthoquinones with benzenesulfonyl chloride affords the 4-naphtho[2,3-*e*][1,3,4]oxadiazines (Section 8.08.8.1.1). The diazotization of 2-[(2-aminophenyl)sulfonyl]-*N*,*N*-dialkylacetamides affords 4,1,2-benzothiadiazin-3-carboxylate 4,4-dioxides (Section 8.08.8.2). 1,3,4-Oxadiazines are the products of a remarkable ring transformation of 2,3-dibenzyloxycarbonyl-2,3-diazabicyclo[2.2.1]heptenes (Section 8.08.9.1). In addition, 1,3,4-oxadiazines are obtained by the interesting ring cleavage and recyclization of 1,2,3-thiadiazol-4-yl-carboxyarylhydrazides (Section 8.08.9.1).

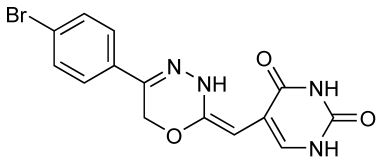
### 8.08.10.2 1,3,4-Thiadiazines

1,3,4-Thiadiazines are prepared best by cyclocondensation of thiohydrazides with $\alpha$-halo ketones (Section 8.08.8.2.2). Pharmacologically interesting 2,3-dihydro-1,3,4-thiadiazin-2-ones are obtained by cyclocondensation of *O*-alkyl thiocarbazates (Section 8.08.8.2.2). By the reactions of $\alpha$-halo carboxylic acids or $\alpha$-halo carbonic esters, 1,3,4-thiadiazin-5-ones are formed (Section 8.08.8.2.2). Hydrazonyl chlorides react with ethyl sulfanylacetate to afford 1,3,4-thiadiazin-5-ones (Section 8.08.8.2.1). A rare example of the synthesis of 1,3,4-thiadiazines is the cyclization of 1-phenyl-2-thiocyanatoethan-1-one and hydrazine <1956CB107>. Transformation of 1,3,4-oxadiazines to 1,3,4-thiadiazines with phosphorus pentasulfide has been reported (Section 8.08.9.2). The ring transformation of tetrazines with thioformate is a remarkable method for the synthesis of 1,3,4-thiadiazines (Section 8.08.9.2). The ring expansion of 3-alkyl-2-hydrazono-4-aryl-2,3-dihydro-1,3-thiazoles by heating in concentrated hydrochloric acid is also a useful reaction (Section 8.08.9.2).

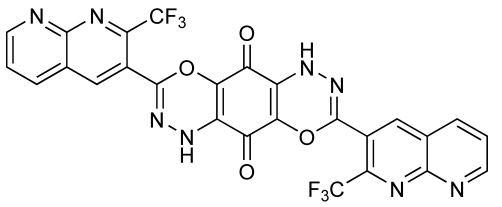
## 8.08.11 Important Compounds and Applications

### 8.08.11.1 1,3,4-Oxadiazines

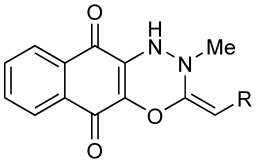
1,3,4-Oxadiazines show a broad spectrum of biological activity. 2-(4-Uracilmethylene)-(4-bromophenyl-6-hydroxy-2,3-dihydro-6*H*-1,3,4-thiadiazine **342** (trade name Oxadin) exhibits antiviral (herpes simplex virus, HSV) and antibacterial activities <1997PHA409, 1998MI57, 1999MI31, 1999MI63, 1999MI67, 2000PHA548, 2000MI53, 2001MI79, 2002PHA337, 2002MI73>. Antibacterial activity is exhibited by 3,8-bis-(2-substituted 1,8-naphthyridin-3-yl)benzo[1,2-*e*:4,5-*e*′]bis[1,3,4]oxadiazine-5,10(1*H*,6*H*)dione **343** <2000IJH311> and 1*H*-naphtho[2,3-*e*][1,3,4]oxadiazine-5,10-dione **344** (R = N-methylpyridiniumiodide, N-methylquionolinium iodide, N-methylisoquinolinium iodide residues) <1995CPA192>.



342

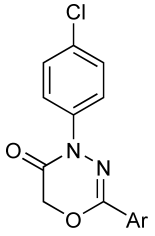


343



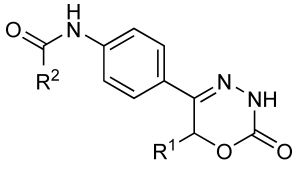
344

2-Aryl-4-(chlorophenyl)-6*H*-1,3,4-oxadiazin-5-ones **345** are $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists <2000WOP2000047567>.



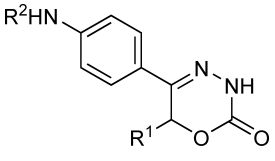
345

*N*-[4-(2-Oxo(3*H*,6*H*-1,3,4-oxadiazin-5-yl))hetaryl]amides **346** ($R^1 = H$, Alk; $R^2 = HetAr$) can be used for treatment of anemia <2001WOP2001000601>.



346

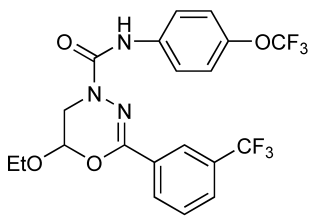
Cardiotonic activity is shown by 3,6-dihydro-5-aminophenyl-2*H*-1,3,4-oxadiazin-2-one derivatives **347** ($R^1 = H$, Alk; $R^2 = HetAr$) <1995JPP07291971>.



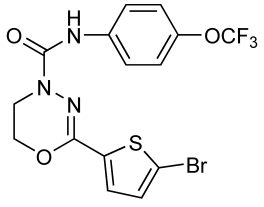
347

1,3,4-Oxadiazine derivatives are widely used in agrochemistry as insecticides, herbicides, fungicides, and pesticides. For example, 2-aryl-4-alkyl-5,6-dihydro-1,3,4-oxadiazines are useful insecticidal and acaricidal compounds

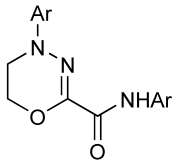
<1999JPP11049755>. [6-Ethoxy-2-(3-trifluoromethylphenyl)-5,6-dihydro-1,3,4-oxadiazin-4-yl]-*N*-[4-(trifluoromethoxyphenyl)]carboxamide **348** <2001USP6197766>, [2-(5-bromo-2-thienyl)-5,6-dihydro-1,3,4-oxadiazin-4-yl]-*N*-[4-(trifluoromethoxyphenyl)]carboxamide **349** <1998USP5804579, 1999WOP9941245>, and 4-aryl-5,6-dihydro-1,3,4-oxadiazin-2-yl-*N*-arylcarboxamides **350** are also insecticides <1998USP5728693>.



**348**

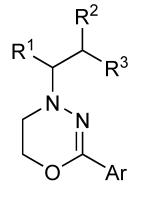


**349**



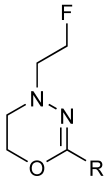
**350**

Some 4-substituted-2-aryl-5,6-dihydro-1,3,4-oxadiazines **351** <1996DEP4444865>, 2-heterocyclic-substituted 4-fluoroethyl-5,6-dihydro-1,3,4-oxadiazines **352** <2000USP6083942>, 2-aryl-5,6-dihydro-1,3,4-oxadiazin-4-yl-carboxamides **353** <1998WOP9833794>, and 7-chloro-3*H*-indano[1,2-*e*]1,3,4-oxadiazine derivatives **354** <1999USP5869657, 1995WOP9529171> exhibit pesticidal activity. Benzo[4,2,1]oxadiazines are used as herbicides **355** <1998USP5739326>.



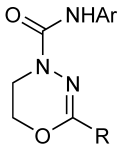
**351**

$R^1$ = $R^2$ = H, Alk
$R^3$ = Ar, HetAr



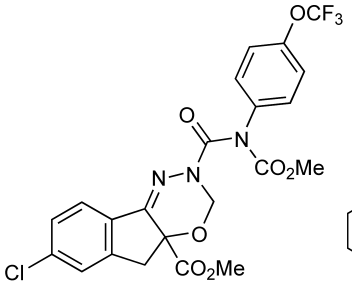
**352**

R = heterocycle

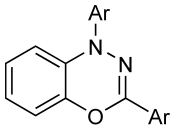


**353**

R = heterocycle



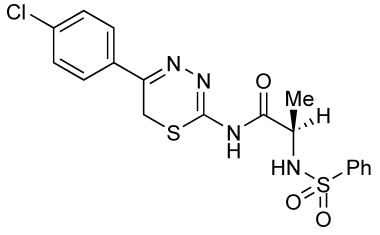
**354**



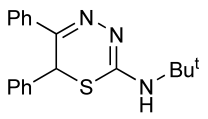
**355**

## 8.08.11.2 1,3,4-Thiadiazines

1,3,4-Thiadiazines are biologically very active compounds. Many 1,3,4-thiadiazine-2-yl-amine derivatives **356** are important matrix metalloproteinase inhibitors <2002EPP1191024, 2001JME3231>. 2-*tert*-Butylamino-5,6-diphenyl-6*H*-1,3,4-thiadiazine **357** <2006UP3> shows antituberculostatic activity against *Mycobacterium tuberculosis* with an inhibition of 96% at a concentration of 12.5 $\mu g\,ml^{-1}$.



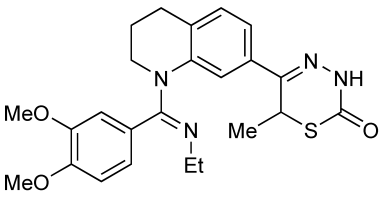
**356**



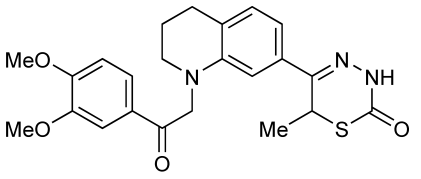
**357**

1,3,4-Thiadiazines display excellent cardiotonic and hypertensive activities. For example, (+)-5-[1-(α-ethylimino-3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroquinoline-6-yl]-2,3-dihydro-6*H*-1,3,4-thiadiazin-2-one **358** <1997MI733, 1999JJP55, 1999MI301> (EMD60263) is a cardiotonic with calcium-sensitizing activity. The (–)-enantiomer of this compound (EMD60264) exhibits phosphodiesterase inhibition. 5-[1-(3,4-Dimethoxybenzoyl)-1,2,3,4-tetrahydroquinoline-6-yl]-2,3-dihydro-6*H*-1,3,4-thiadiazin-2-one **359** shows similar properties <1996EPP721950, 1996EPP723962,

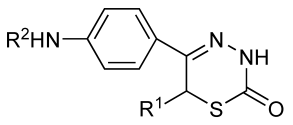
1996MI334, 1997JPR315, 2005BJ905>. 5-(4-Hetarylaminophenyl)-2,3-dihydro-6*H*-1,3,4-thiadiazin-2-one (**360**) ($R^1$ = H, Alkyl, $R^2$ = Hetar) <1995EPP679651> also exhibits cardiotonic activity.



**358**

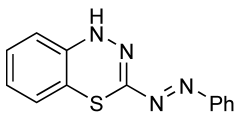


**359**

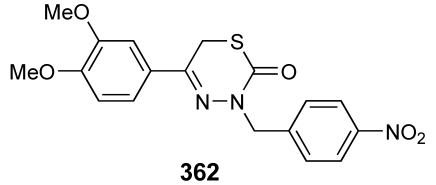


**360**

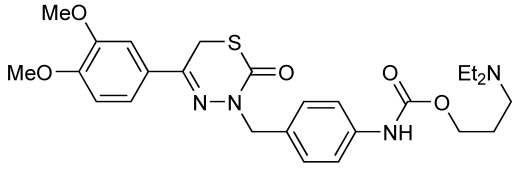
2-Alkylimino- and 2-alkyamino-1,3,4-thiadiazines are used as cardiotonic and spasmolytic agents <1983DEP204092, 1984DEP209196, 1985DEP220311, 1990DEP280760, 1991DEP293351, 1991DEP289272>. 5-Aryl-1,3,4-thiadiazin-2-ones are phosphodiesterase III/IV inhibitors <1999WOP9947505>. 1,3,4-Thiadiazin-2-ones <1998WOP9810765> are nonsteroidal contraception agents for females <1998WOP9810765>. Some 1,3,4-thiadiazin-2-ones can be used for the treatment of erectile dysfunction <2000USP6156753>. 5-(1,2,3,4-Tetrahydroquinolin-6-yl)-6-methyl-1,3,4-thiadiazin-2-ones can be used for preventing and/or treating anemia <2001WOP2001000188>. 3-Phenylazo-1*H*-4,2,1-thiadiazine **361** is an agent for treating deficient bone growth <1997WOP9715308>. 3-Nitrobenzyl-5-aryl-1,3,4-thiadiazin-2-ones **362** <1996EPP723962> and 1,3,4-thiadiazin-2-ones <2003DEP10150517, 2004WOP2004067006> are phosphodiesterase IV inhibitors and can be used for treatment of tumors and acquired immune deficiency syndrome (AIDS) <2003DEP10150517, 2004WOP2004067006>. 3-(*N*,*N*-diethylamino)propyl *N*-[4-(5-(3,4-dimethoxyphenyl)-2-oxo-2,3-dihydro-6*H*-1,3,4-thiadiazin-3-ylmethyl)phenyl]carbamic acid ester **363** is used for treatment of asthma and allergies <1997DEP19604388>.



**361**



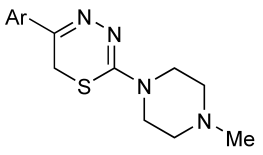
**362**



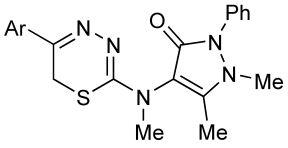
**363**

*N*-Morpholinyl-, *N*-thiomorpholinyl-, or *N*-piperidinyl-1,3,4-thiadiazines exhibit antithrombotic <2005RUP2259371> and bactericidal activities <1996RUP2058307>.

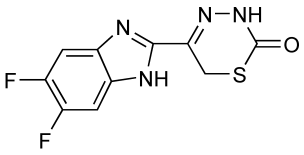
2-Nitrosimino-3,6-dihydro-2*H*-1,3,4-thiadiazines exhibit antiplatelet and antithrombotic properties <1998PHA820>. 2-(*N*-methylpiperazino)-5-aryl-6*H*-1,3,4-thiadiazine dihydrobromides **364** display antiarrhythmic activity <1996RUP2058314>. Thiadiazinone derivatives are useful in the treatment of bacterial infections <2003WOP2003066631>. Substituted 6*H*-1,3,4-thiadiazine-2-amines <1997WOP9724353> and *N*-(1-phenyl-2,3-dimethylpyrazol-5-on-4-yl)-6*H*-1,3,4-thiadiazine-2-amines **365** <1997WOP9724354> are anesthetics and cardiovascular and hypometabolic agents. (+)-[[4-(3,6-Dihydro-6-methyl-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propane dinitrile is an anti-inflammatory drug <2002WOP2002040025>. 5,6-Difluoro-2-(3,6-dihydro-2-oxo-2*H*-1,3,4-thiadiazin-5-yl)benzimidazole hydrochloride **366** is used for treatment of heart failure <1995JPP07101954>.




**364**




**365**




**366**

1,3,4-Thiadiazines may be used in agriculture as herbicides <1971JPP7041593, 1974USP377936, 1975USP3854924, 1975USP3862183, 1981USP4254259, 1984USP4436549>, fungicides <1967MI539, 1967JPP8033, 1969MI689>, pesticides <1973HCA2186>, insecticides <1979USP4144335, 1998WOP9838181>, and plant-growth regulators <1981USP4254259>. 1,2,4-Triazolo[1,3,4-*b*][1,3,4]thiadiazines can be used as photographic magenta couplers <2000JPP2000143664, 2001JPP2001072682, 2002JPP2002302493 >. 1,3,4-Thiadiazin-2-yl amines are used as agents for radiator protection <1980MI31, 1999MI223>.

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## Biographical Sketch

Wolf-Diethard Pfeiffer studied for his graduation degree in chemistry in 1962–67 in Greifswald (Germany). In 1971, he completed his dissertation and in 1986 his habilitation. His fields of research include heterocycles' synthesis (thiadiazines, selenadiazines, thiazoles and selenazoles, quinazolines), ring transformation of heterocycles, and kinetic investigations. He has been involved in teaching, and his students have gone on to become chemists, pharmacists, physicans, biologists, and teachers.