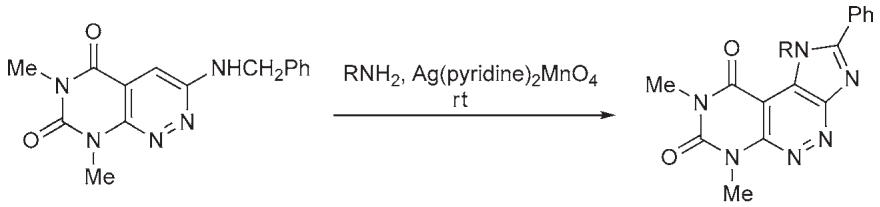
attack on C-4 and oxidation, results in imidazole annulation. Oxidation of the 3-alkylamino group to the corresponding imine and subsequent addition of alkylamine on the imine, followed by intramolecular nucleophilic attack at C-4 and oxidation, can also proceed yielding another substitution pattern. The exact mechanism depends on the relative ease of oxidation of 3-alkylamino in comparison with alkylamine. Equation (10) gives some representative examples starting from 3-benzylamino-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione **54**. Depending on the type of alkylamines used also imidazolines are obtained.



54 R = Pr (63%), Bu (64%), Hex[c] (37%), Bn (18%) (10)

8.01.5.4.3 Hydrazine

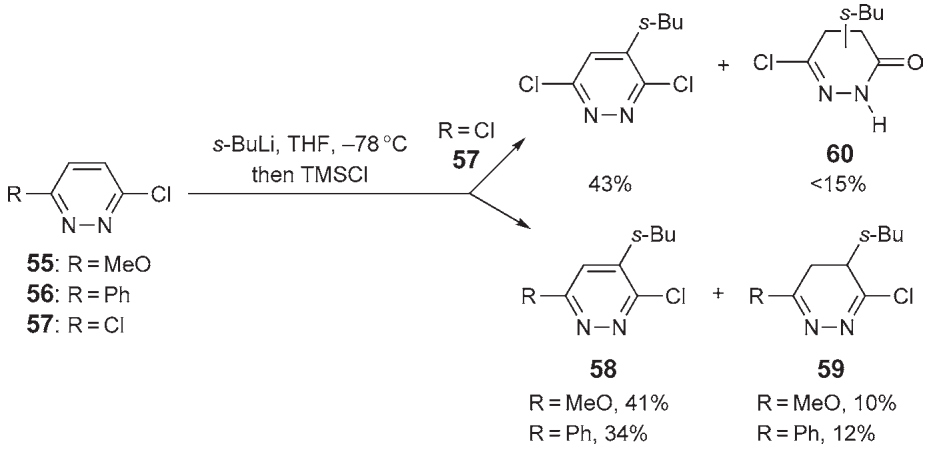
The synthesis of 4-aminopyridazin-3(2*H*)-ones by reaction of the corresponding pyridazin-3(2*H*)-ones with hydrazine was mentioned in CHEC-II(1996) <1996CHEC-II(6)1>. In 1999, Cignarella and co-workers provided examples on cinnolin-3(*2H*)-ones. Heating benzo- and thieno-fused cinnolin-3(*2H*)-ones with hydrazine hydrate gave access to the corresponding 4-aminocinnolin-3(*2H*)-ones <1998JHC1161, 1999JHC485, 1999JHC1253>.

8.01.5.4.4 Carbon nucleophiles

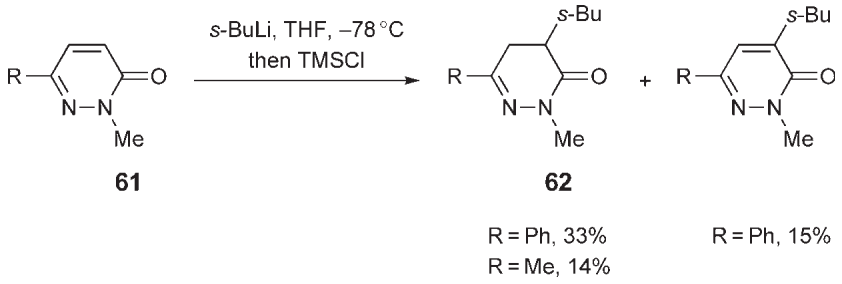
This section has been the subject of many papers and it is covered very well by CHEC(1984) <1984CHEC(2)1> and CHEC-II(1996) <1996CHEC-II(6)1>.

8.01.5.4.4(i) Organometallic compounds

The reaction of 6-substituted 3-chloropyridazines **55–57** with alkyllithium compounds yields mainly the corresponding 4-alkylated pyridazines **58** <1998SL762>. The main product was accompanied by a low amount of the corresponding 4-alkylated-4,5-dihydropyridazines **59** and traces of 5-alkylated regioisomers (**Scheme 12**). For 3,6-dichloropyridazine **57** as substrate regioisomeric 4(5)-alkylated 4,5-dihydropyridazin-3(2*H*)-ones **60** were formed as side compounds (**Scheme 12**). Interestingly, a similar reaction with less reactive organolithium compounds such as phenylithium or vinyllithium did not proceed. A similar alkylation reaction on 6-substituted 2-methylpyridazin-3(2*H*)-ones **61** gave predominantly 4-alkylated 6-substituted 2-methyl-4,5-dihydropyridazin-3(2*H*)-ones **62** (Equation 11) <1998SL762>. In all these alkylation reactions trimethylsilyl chloride (TMSCl) was used to quench the reaction mixture yielding neutral dihydropyridazin[-3(2*H*)-on]es allowing rearomatization.



Scheme 12



61 **62**

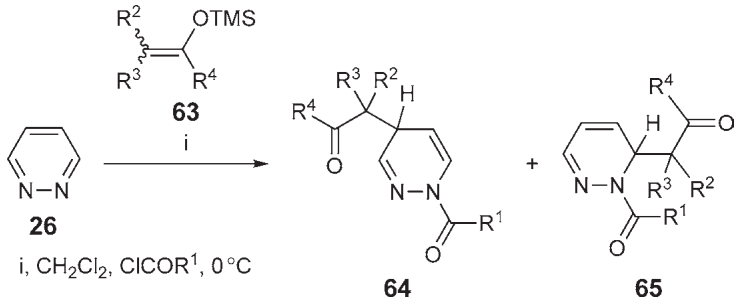
R = Ph, 33% R = Ph, 15%
R = Me, 14%

(11)

Treatment of pyridazine *N*-oxide with the dilithium salt of TosMIC followed by benzyl bromide yields a 1-hydroxydiazene <2004H(62)357>. This reaction is in agreement with the well-known fact that pyridazine *N*-oxide is known to yield ring-opened product as the main component in reactions with nucleophiles. Nucleophilic addition of MeMgI on 2-alkylphthalazinium halides in diethyl ether gave 2-alkyl-1-methyl-1,2-dihydrophthalazines in good yield <1995JHC643>. 2-Alkyl-1-methylphthalazinium halides were also successfully used as substrates in a similar reaction yielding 2-alkyl-1,1-dimethyl-1,2-dihydrophthalazines <1995JHC643>.

8.01.5.4.4(ii) Activated methyl and methylene carbanions

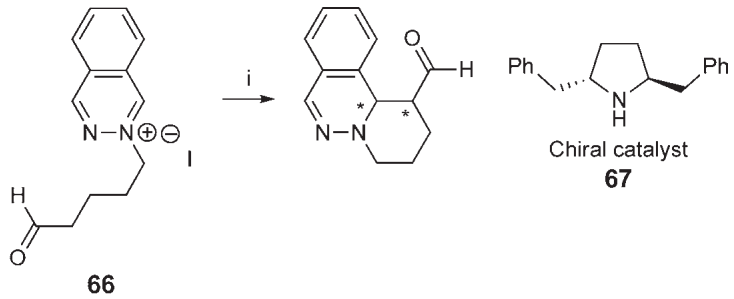
Reaction of pyridazine **26** with ethyl chloroformate (in pyridine) yields an activated intermediate that reacts with electron-rich five-membered rings such as the pyrazole unit in pyrazolo[1,5-*a*]pyridine <1999JME779>. Oxidation of the 4-substituted 1-ethoxycarbonyl-1,4-dihydropyridazine was achieved with air and $KOBu^t$ in Bu^tOH. In a reaction with silyl enol ethers **63** on 1-ethoxycarbonylpyridazinium salt both attack in the α **65** and γ **64** position was observed (Equation (12) and **Table 5**) <1997H(46)83>. The ratio depends on the substitution pattern of the enol nucleophile. The same team also investigated the reaction with allyltrimethylsilane <1998H(49)67>. Interestingly, the addition of an equimolar amount of TBDMSOTf is beneficial. The triflate ion seems to be both a promoter of quaternary salt formation (1-ethoxycarbonylpyridazinium salt) as well as a stabilizer. Also phthalazine was used as substrate but in this case 0.2 equiv of TMSOTf was used. *N*-(5-Oxopentyl)phthalazinium iodide **66** could undergo intramolecular nucleophilic addition in a stereoselective way using chiral pyrrolidines as catalyst <2005AGE6058>. *In situ* enamine (and water) is formed with the chiral pyrrolidine **67** which acts as the nucleophile. The water allows hydrolysis of the iminium iodide after ring closure, releasing the chiral catalyst for the asymmetric annulation reaction (Equation 13). 2-(4,5-Dihydro-1*H*-imidazol-2-yl)-substituted phthalazinium salt can be generated *in situ* from 1-hydroxy-2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazine <2003H(60)571>. Reaction with (hetero)aryl methyl ketones yields 1-[2-(hetero)aryl-2-oxoethyl]-2-(4,5-dihydro-1*H*-imidazol-2-yl)-1,2-dihydrophthalazines.



(12)

Table 5 Reaction of **63** in the α **65** and γ **64** position of 1-ethoxycarbonylpyridazinium salt

R^1	R^2	R^3	R^4	*Yield of* **64** (%)	*Yield of* **65** (%)
OEt	Me	Me	OMe	89	0
OEt	Me	H	OMe	49	48
OEt	TMS	H	OMe	31	40
CH(OAc)Ph	Me	H	OMe	55	22
OEt	H	H	Ph	35	54
OEt	H	H	OPh	6	78

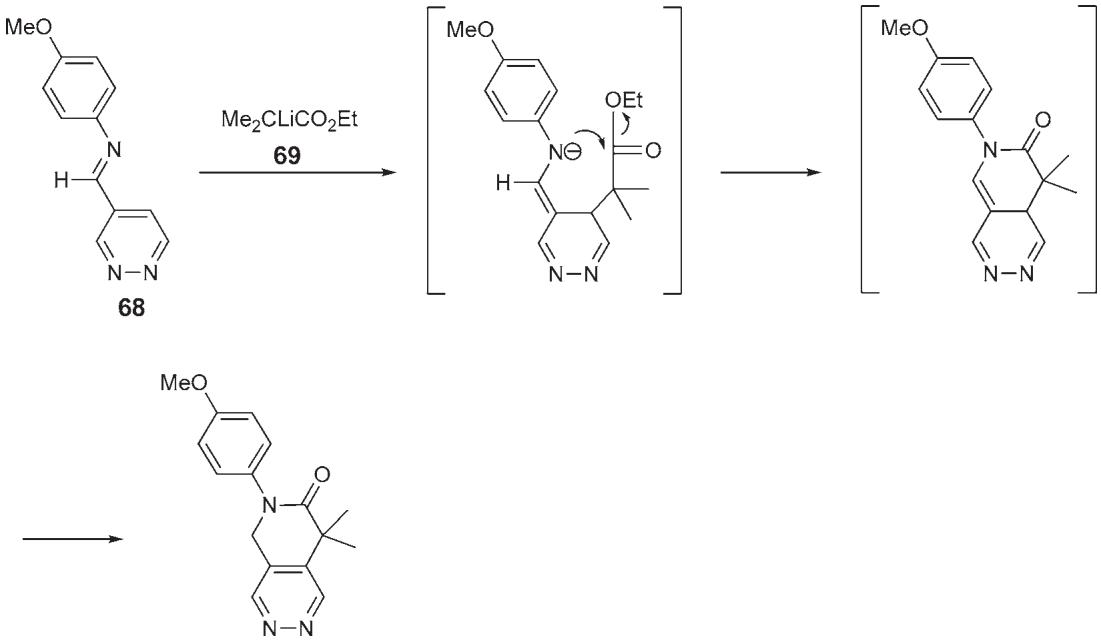


(13)

i, 10 mol% chiral pyrrolidine catalyst, NEt_3, CH_2Cl_2, –40 °C, overnight

Vicarious nucleophilic substitution was studied on pyridazinium 1-dicyanomethylides with $ClCHXSO_2Ar$ (X = Cl or H) and KO*t*-Bu as base in THF–DMF (THF – tetrahydrofuran) <1998J(P1)1637>. Even with substituents in the 3-position regioselective introduction of $CHXSO_2Ar$ in the 4-position was achieved. Since the dicyanomethylene group can be removed via a radical reaction with $(NH_4)_2S_2O_8$, this procedure gives an easy access to 3,4-disubstituted pyridazines.

4-Imino-substituted pyridazine **68** reacted in the 5-position with the lithium enolate of ethyl 2-methylpropanoate **69** via an interesting cascade of nucleophilic addition, ring closure via addition–elimination and tautomerization (**Scheme 13**) <1996JHC1731>.



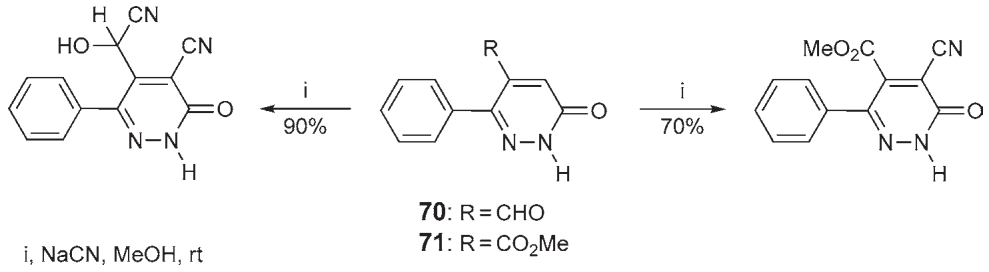
Scheme 13

8.01.5.4.4(iii) Cyanide ions, Including Reissert reactions

More examples of Reissert-type reactions on pyridazine *N*-oxides have been published exemplified by the reaction of 3,4-di(4-methoxyphenyl)pyridazine 1-oxide with KCN and BnCl in H_2O at 0 °C which yields 69% of 3-cyano-5,6-di(4-methoxyphenyl)pyridazine <2001BML2369>. A modified Reissert reaction using phosgene, trimethylsilyl cyanide, and a catalytic amount of BF_3 on phthalazine gave the stable carbonyl chloride 1-cyano-2-chlorocarbonyl-1,2-dihydrophthalazine in 52% yield <1995JHC643>. Also diphosgene and triphosgene could be used to replace phosgene. Even the 1-methylated and 1,1-dimethylated 2-alkyl-1,2-dihydrophthalazines gave Reissert compounds <1995JHC643>.

With triphosgene also 2-trichloromethoxycarbonyl derivatives were formed. More examples on nucleophilic substitution of hydrogen by cyano in pyridazin-3(2*H*)-ones have also appeared. Substrates **70** and **71** were used in

a reaction with cyanide in MeOH (**Scheme 14**) <2001TL2863>. The reaction can proceed at room temperature due to the activation of the 5-substituent. The mechanism involves Michael addition of the cyanide to the α,β unsaturated carbonyl followed by air oxidation of the dihydropyridazin-3(2*H*)-one.



Scheme 14

8.01.5.4.5 Chemical reduction

The reduction of the 1,2-diazine nucleus has been discussed in detail in CHEC-II(1996) <1996CHEC-II(6)1> as this part was not present in CHEC(1984) <1984CHEC(2)1>. Dubreuil investigated electrochemical reduction of pyridazines substituted with electron-withdrawing groups. Initially, 1,2-dihydro derivatives were obtained which, depending on the nature of the ring substituents, can rearrange into 1,4-dihydropyridazine isomers or further be electrochemically reduced into activated pyrroles <2000TL647, 2004TL1031>. Selective 1,2-dihydrophthalazine formation was achieved via reduction with H_2 using a PtO_2 catalyst <2002BML5>. Reduction of 2-alkylphthalazinium halide with $NaBH_4$ in water yields 2-alkyl 1,2-dihydrophthalazine <1995JHC643>. For more examples, see Section 8.01.6.

8.01.5.5 Nucleophilic Attack at Hydrogen Attached to Ring Carbon or Nitrogen

8.01.5.5.1 Metallation at carbon

The metallation, especially the lithiation, of pyridazines, mentioned briefly in CHEC-II(1996) <1996CHEC-II(6)1>, has been developed extensively since 1995 by Quéguiner and co-workers for the derivatization of pyridazines and benzopyridazines. The bases of choice are usually lithium 2,2,6,6-tetramethylpiperidide (LTMP) and lithium diisopropylamide (LDA). Special efforts have been made to achieve regioselective lithiations.

Pyridazines with an *ortho*-directing group at C-4 are lithiated regioselectively at C-5 <1995JHC841>. 3-Bromo-6-phenylpyridazine gives C-4 metallation. LDA has been shown to be a better base than LTMP <2005JHC509>. 3-Chloro-6-methoxypyridazine can be lithiated selectively at C-5 only with the use of very hindered lithium dialkylamides <1996T10417>. 3-Methoxy-6-(phenylthio)pyridazine is lithiated regioselectively *ortho* to the methoxy group. On the contrary, 3-methoxy-6-(phenylsulfinyl)pyridazine is lithiated *ortho* to the phenylsulfinyl group. In the case of 3-methoxy-6-(phenylsulfonyl)pyridazine C-4 and C-5 lithiation is observed, the latter being the major pathway <1997JHC621>. Pyridazine-3-carboxamides are lithiated *ortho* to the carboxamide group. However, the use of iodine as electrophile afforded the *meta*-iodo derivative as the result of a 'halogen-dance'. Also an unexpected regioselectivity at the *meta*-position of the pyridazin-3-thiocarboxamide was observed and a mechanistic explanation for this has been proposed <2002T2743>. In the lithiation of 3-phenyl-6-pyridin-2-ylpyridazine the pyridine group, via its N-atom, has shown to be a good *ortho*-directing group <2005T9637>.

Lithiated 3,6-dimethoxypyridazine, obtained by reaction with Bu^nLi, has been transmetallated to the corresponding organozinc compound with zinc chloride <1998H(49)205>.

Attempts to lithiate the benzene moiety of 1,4-dimethoxyphthalazine and of 1-methoxy-4-phenylphthalazine were unsuccessful. However, treatment of 6-chloro-1,4-dimethoxyphthalazine with Bu^nLi results in the regioselective lithiation at C-7 <1999T5389>.

4-Chloro- and 4-methoxycinnoline were lithiated selectively at C-3 and 3-chloro-, 3-methoxy-, and 3-sulfinylcinnolines at C-4 <1995T13045, 2005T8924>. A further lithiation at C-8 of the 3,4-disubstituted cinnolines is observed <1995T13045>. Using this interesting observation 4-arylcinnolines have been lithiated at C-3, treated with chloro(trimethyl)silane, and once again lithiated at C-8 <2000T5499>.

Reactions of the metallated compounds with electrophiles are discussed in Section 8.01.7.16.