RECENT ADVANCES IN THE CHEMISTRY OF CONDENSED PYRIDAZINES: SYNTHESIS OF BI- AND TRICYCLIC SYSTEMS BY ANNELATION OF FIVE-, SIX-, AND SEVEN-MEMBERED RINGS TO A PREFORMED 1,2-DIAZINE NUCLEUS

Norbert Haider[a] and Gottfried Heinisch[b]*

[a] Institute of Pharmaceutical Chemistry, University of Vienna,
Währinger Straße 10, A-1090 Vienna, Austria

[b] Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck,
Innrain 52a, A-6020 Innsbruck, Austria

Abstract - Methods for the preparation of a wide variety of pyridazine-containing bi- and tricyclic ring systems, starting from appropriately substituted pyridazines are reviewed. The compilation comprises pyridazine-fused five-, six-, and seven-membered carbo- and heterocyclic systems. Particular interest is focused on compounds bearing no additional substituents in the 1,2-diazine moiety. In the syntheses discussed, diaroylpyridazines, aroylpyridazinecarboxylic acids, alkyl-pyridazinecarboxylic acids, aminopyridazinyl aryl ketones, and chloro- or alkylpyridazinecarbonitriles represent the key intermediates.

CONTENTS

Dedicated with best wishes to Prof. Edward C. Taylor on the occasion of his 70th birthday.

1. INTRODUCTION

Since numerous benzo-annelated heterocycles represent essential subunits of a wide variety of biologically active compounds, there is continuing interest also in the chemistry of aza-isosteric systems, in which the benzo moiety is replaced by an N-heteroaromatic system.[1] Thus, for instance, the chemistry of pyrido-fused five-, six-, and seven-membered heterocycles has been explored to a large extent.[1] The past decades have witnessed an increasing interest also in the corresponding pyridazino-fused systems. A comprehensive review on the chemistry of condensed pyridazines covering the literature up to 1971 was provided by *Castle*.[2] In addition, more recent developments in this field are discussed in ref.[1] As can be seen from these compilations, so far the construction of heterocycle-fused pyridazines in most cases has been accomplished by annelation of the pyridazine ring to an appropriately disubstituted heterocyclic system. Unless in a few cases, in which o-diformylheterocycles were employed in cyclisation reactions with hydrazine or equivalents thereof, this approach gives rise to the formation of fused systems bearing one or two substituents in the 1,2-diazine moiety.

Our continuing interest in the bio-isosterism of the 1,2-diazine system (for selected contributions to this field cf. refs[3-5]) has prompted us to develop synthetic pathways to various fused 1,2-diazines starting from a preformed pyridazine nucleus. Most of the required, appropriately *vic*-disubstituted building blocks could be made conveniently available in the authors' laboratory.[6,7] This approach not only provides access to a variety of pyridazine-containing bi- and tricyclic ring systems lacking any additional substituents in the diazine moiety, but also is characterized by a high degree of variability of the substitution pattern in the non-pyridazine part of the condensed system.

The present review is an attempt to summarize the results of our investigations which were performed mainly in view of analogy considerations with respect to bio-active bi- and tricyclic molecules.

2. ANNELATION OF FIVE-MEMBERED RINGS

2.1. Cyclopentapyridazines

Starting from commercially available pyridazine (**1**), reaction with acyl radicals (generated from the corresponding aldehydes according to *Minisci's* method[8]) in acidic medium leads to cyclopenta[*d*]pyridazines of type **2** due to intramolecular aldol reaction of intermediate 4,5-diacylpyridazines. If the carbon atom α to the keto function bears at least one hydrogen, unsaturated congeners of type **3** are isolated.[9]

Scheme 1

2a $R^1 = R^2 = CH_3$
    $R^3 = $ 2-propyl
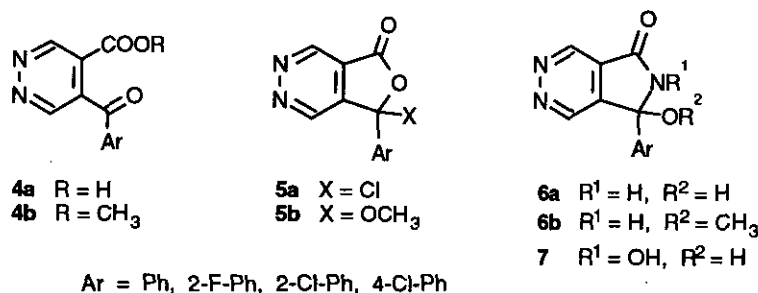2b $R^1 = R^2 = CH_3$
    $R^3 = C_2H_5$
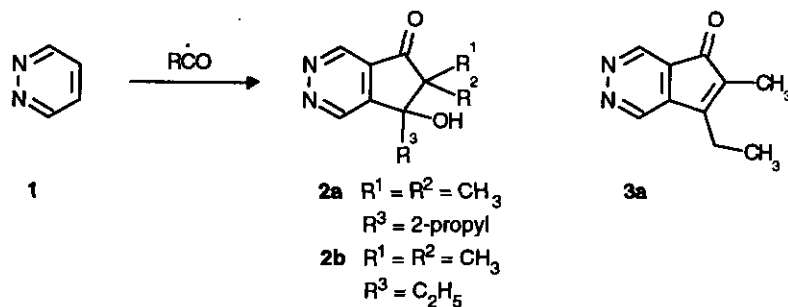
2.2. Furo-, Pyrrolo- and Thienopyridazines

Furo[3,4-d]pyridazines of type **5a** are conveniently accessible from 4-pyridazinecarboxylic acid upon radical aroylation (to give **4a**) and subsequent reaction with thionyl chloride. The furan ring in **5a** is cleaved on methanolysis in the presence of pyridine, yielding the keto ester (**4b**). On the other hand, 7-alkoxyfuro[3,4-d]-pyridazines (**5b**) are formed on acid-catalyzed alcoholysis of **5a** (affording ketals of **4a**) and subsequent thermolysis.[10]

Upon treatment of alkyl esters of **4a** with ethanolic ammonia or hydroxylamine, formation of pyrrolo[3,4-d]-pyridazines (**6a, 7**) can be accomplished. The N-hydroxy compound (**7**) exists exclusively in the bicyclic form displayed in Scheme 2, whereas a ring-chain tautomerism has been established for the amide (**6a**). Methanolysis of **6a** in the presence of dry hydrogen chloride smoothly leads to the 7-methoxy derivative (**6b**). By contrast, reaction of **7** under the same conditions results in pyrrole ring fission to give an oxime of the keto ester (**4b**).[10]

Scheme 2

4a R = H
4b R = CH$_3$

5a X = Cl
5b X = OCH$_3$

6a $R^1 = H$, $R^2 = H$
6b $R^1 = H$, $R^2 = CH_3$
7   $R^1 = OH$, $R^2 = H$

Ar = Ph, 2-F-Ph, 2-Cl-Ph, 4-Cl-Ph

Thieno[2,3-c]pyridazines (**9a,b**) can be prepared in high yield starting from the conveniently available chloro nitrile (**8**)[11] on reaction with appropriate mercaptoacetic acid derivatives.[12] Condensation of the amide (**9b**) with triethyl orthoformate provides a smooth access to the pyrimido[4',5':4,5]thieno[2,3-c]pyridazine (**10**), a previously unknown ring system.[12]

Scheme 3

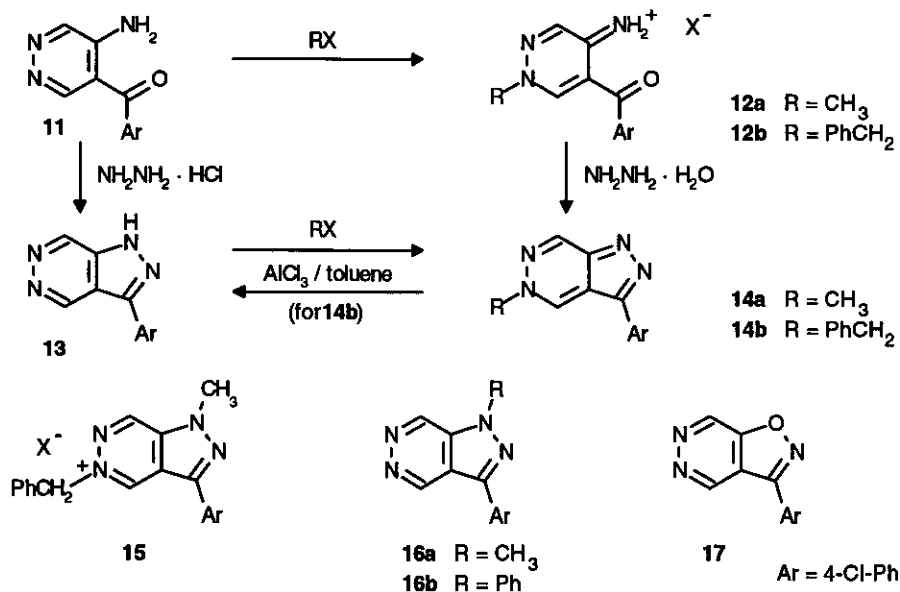| 8 | 9a X = OCH$_3$ | 10 |
| | 9b X = NH$_2$ | |
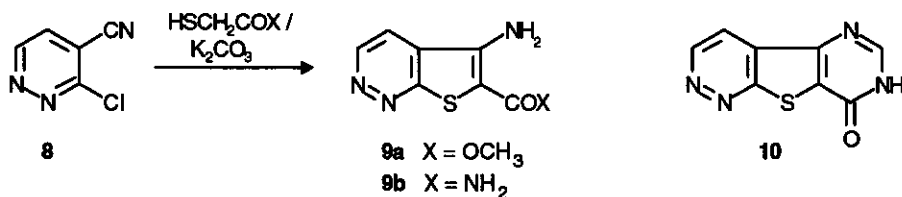
2.3. Pyrazolo- and Isoxazolopyridazines

N-Unsubstituted 3-arylpyrazolo[3,4-*d*]pyridazines (13) are obtained in satisfactory yield by cyclisation of amino ketones of type 11 [conveniently available from 5-aroyl-4-pyridazinecarboxylic acids (4a)[10]] with hydrazine hydrochloride.[13] In a similar manner (reaction with phenylhydrazine hydrochloride), 1,3-diaryl derivatives (16b) are readily accessible from 11 in a single step. However, 1-alkyl-3-aryl congeners (16a) are formed under these conditions in only moderate yield. An efficient route to such compounds consists in quaternisation of the benzyl derivative (14b) [which can be obtained either by benzylation of 13 or by hydrazinolysis of the reactive iminium salt (12b)] and subsequent aluminium chloride-mediated debenzylation of compound (15) thus obtained.[13] The regioselectivity found for alkylation of 13 (attack at position 5) is evident from comparison of the reaction products (14a,b) with those obtained *via* 12. In the case of 16a,b, the position of the substituents R at N-1 follows from NOE experiments.[13]

Isoxazolo[4,5-*d*]pyridazines (17) can be prepared in satisfactory yield by reacting the amino ketone (11) with hydroxylamine hydrochloride. In this case, isolation of a reaction intermediate (an oxime of 11) permits unequivocal discrimination from the theoretically possible isomeric isoxazolo[3,4-*d*]pyridazine structure.[13]

Scheme 4

12a R = CH$_3$
12b R = PhCH$_2$

14a R = CH$_3$
14b R = PhCH$_2$

15   16a R = CH$_3$ 17
            16b R = Ph

Ar = 4-Cl-Ph

2.4. Tetrazolopyridazines

Synthesis of the tetrazolo[1,5-*b*]pyridazine-8-carbonitrile (**18**) can be achieved by treatment of 3-chloro-4-pyridazinecarbonitrile (**8**) with sodium azide.[14] An 8-phenyl substituted representative of this ring system (**23**) is available from the pyridazinone (**22**). It should be emphasized that the latter can be conveniently obtained by reaction of the nitrile (**21**) with phenylmagnesium chloride,[15] whereas the nitrile (**18**) with the same Grignard reagent, interestingly, affords the 7-substituted tetrazolopyridazine (**20**). In this case, not even traces of an expected aryl heteroaryl ketone could be detected.
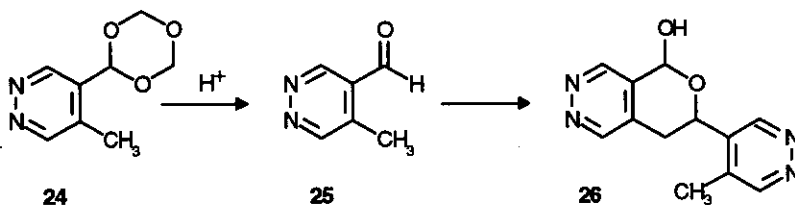
Scheme 5
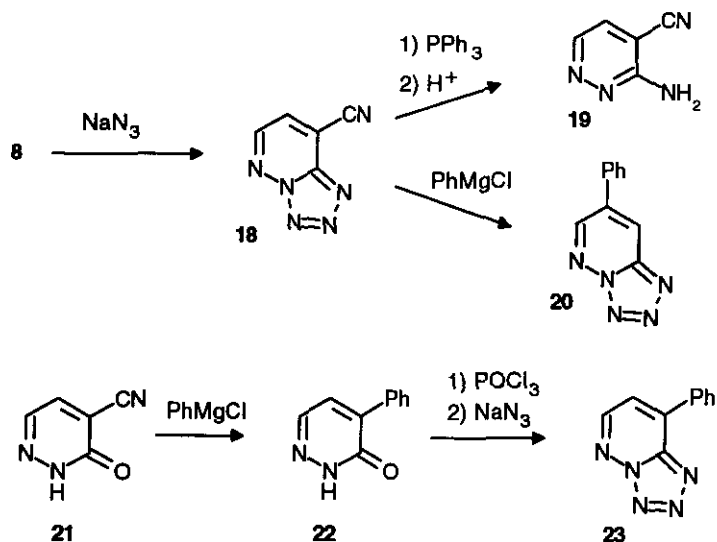
It is noteworthy that compound (**18**) for the first time provides an access to 3-amino-4-pyridazinecarbonitrile (**19**)[14] which, in turn, is a versatile intermediate for further ring annelations, as discussed below.

# 3. ANNELATION OF SIX-MEMBERED RINGS

3.1. Pyranopyridazines

Formation of the pyrano[3,4-*d*]pyridazine (**26**) occurs on acidic hydrolysis of 5-methyl-4-(*sym*-trioxanyl)-pyridazine (**24**) (obtained by homolytic trioxanylation of 4-methylpyridazine).[16] This was interpreted in terms of the high tendency of the intermediate aldehyde (**25**) (which can be trapped only at lower temperatures) for self-condensation.

Scheme 6

Acid-catalyzed ring closure of the enamino ester (**28**), conveniently prepared from the active methylene compound (**27**), affords the pyrano[3,4-*d*]pyridazine (**29**) in reasonable yield.[17]

Scheme 7
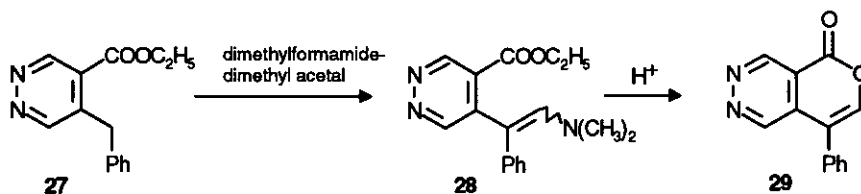
Annelation of a pyrane ring to a preformed 1,2-diazine system of type **30** was found to occur readily on treatment of **30** with benzylidenemalonic acid derivatives in the presence of a weak base, affording the polyfunctional pyrano[2,3-*d*]pyridazines (**31a,b**).[18]

Scheme 8

31a X = CN
31b X = COOC$_2$H$_5$
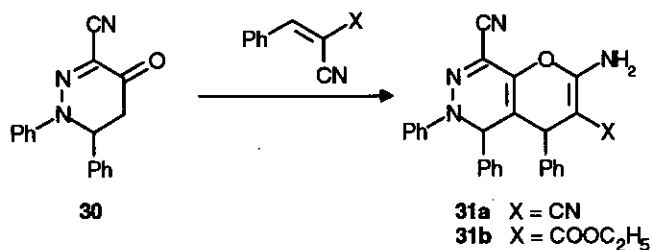
Ring-closure to a pyrano[4,3-*c*]pyridazine (compound **33**) was observed upon heating of 3-(2-phenylethinyl)-4-pyridazinecarbonitrile (**32**) in polyphosphoric acid.[19] Compound (**32**) is available from the chloro nitrile (**8**) in high yield by palladium-mediated cross-coupling with phenylacetylene.[19]
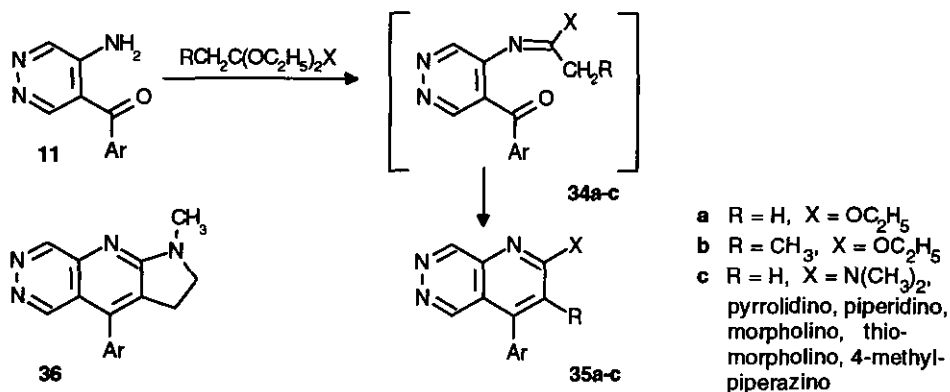
Scheme 9
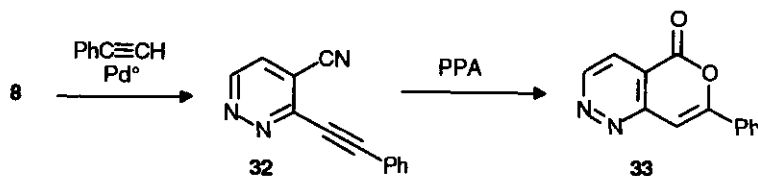
3.2. Diazaquinolines

3.2.1. Pyrido[2,3-d]pyridazines

An efficient access to a variety of pyrido[2,3-d]pyridazines permitting variation of the substitution pattern in the pyridine moiety (positions 1, 2, 3, 4) within a wide range could be elaborated employing amino ketones of type 11 or 37 as precursors.

Thus, condensation of 11 with ortho esters affords 2-alkoxy substituted 4-aryldiazaquinolines (35a,b) via imido ester intermediates.[20] In a similar manner, the C-H acidity in the corresponding amidines of type 34 (available by treatment of 11 with amide acetals) could be exploited for the construction of a series of 2-di-alkylamino congeners (35c).[17,20] Application of the latter procedure also furnished compound (36), a derivative of the previously unknown pyrrolo[3,2:5,6]pyrido[2,3-d]pyridazine system.[17] Whereas transformation of imido esters of type 34 (X = OC$_2$H$_5$) into the bicyclic system requires refluxing in the presence of a base, the corresponding amidines (X = dialkylamino) were found to cyclize spontaneously.

Schmem 10
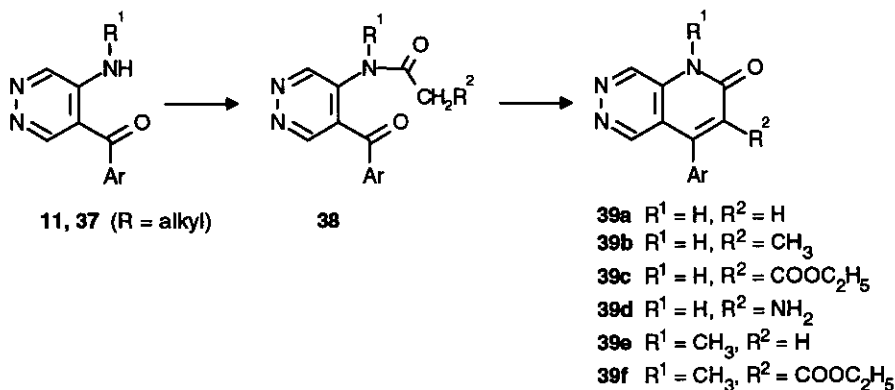

a R = H, X = OC$_2$H$_5$
b R = CH$_3$, X = OC$_2$H$_5$
c R = H, X = N(CH$_3$)$_2$, pyrrolidino, piperidino, morpholino, thio-morpholino, 4-methyl-piperazino

Synthesis of the pyridazine-fused pyridone (39a) can be achieved either by acidic hydrolysis of the ethoxy compound (35a) (similarly, 39b can be prepared from 35b) or by base-catalyzed ring-closure of the acetyl-amino ketone (38) (R^1 = R^2 = H).[20] An analogous approach was chosen to obtain the N-1-substituted diazaquinolone (39e), as alkylation of 39a had to be expected to occur at N-6 rather than at N-1.[20] The facile one-step conversion of 11 as well as of 37 into diazaquinolones bearing an ester function at C-3 (compounds

39c,f) is based on the highly activated methylene group in amides of type **38** ($R^2 = COOC_2H_5$).[20] Even with amides (**38**) where the acyl group is a benzyloxycarbonyl-protected glycyl moiety, cyclisation to give a pyrido[2,3-*d*]pyridazine takes place readily, thus providing access also to 3-amino congeners of type **39d**.[20]
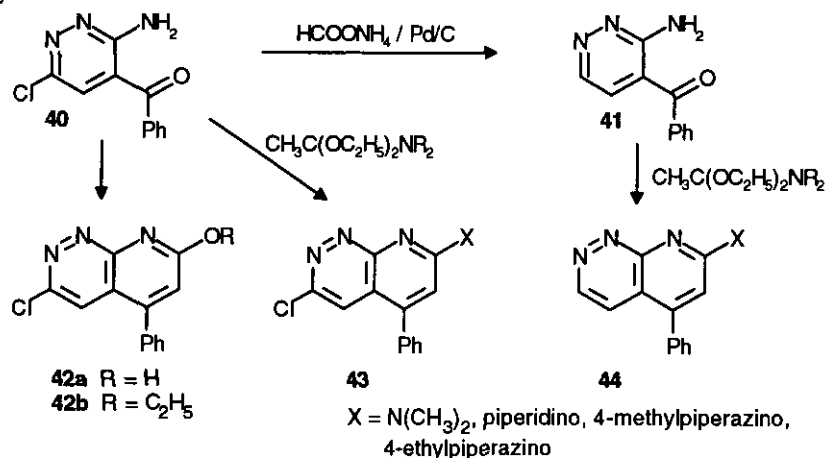
Scheme 11

11, 37 (R = alkyl)   **38**

39a $R^1 = H$, $R^2 = H$
39b $R^1 = H$, $R^2 = CH_3$
39c $R^1 = H$, $R^2 = COOC_2H_5$
39d $R^1 = H$, $R^2 = NH_2$
39e $R^1 = CH_3$, $R^2 = H$
39f $R^1 = CH_3$, $R^2 = COOC_2H_5$
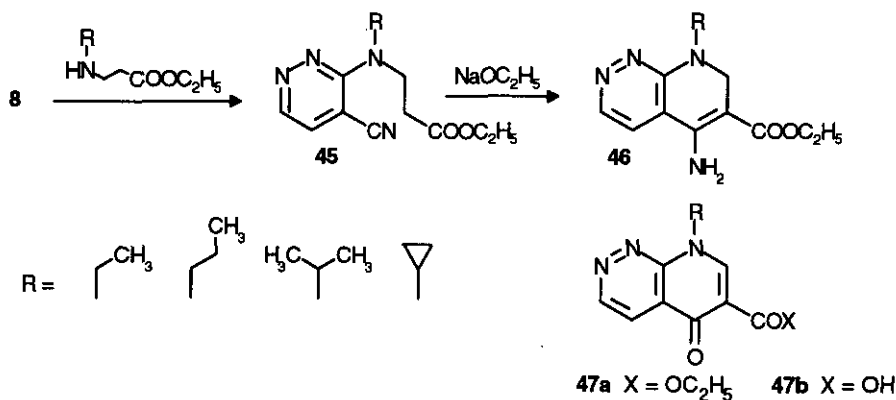
3.2.2. Pyrido[2,3-*c*]pyridazines

Efficient syntheses of 5-phenyl substituted pyrido[2,3-*c*]pyridazines (**42-44**) could be elaborated starting from amino ketones (**40**) or (**41**), respectively. Compound (**40**) can be obtained from 3,6-dichloro-4-pyridazinyl phenyl ketone,[21] catalytic transfer hydrogenation of **40** affords the dehalogenated congener (**41**) in high yield.[22] Similar to the transformation **11 → 35a** (see Scheme 10), reaction of **40** with triethyl orthoacetate, followed by base-catalyzed cyclisation gives the alkoxy substituted diazaquinoline (**42b**). Whereas attempted hydrolysis of the ether function in **42b** had failed, the fused pyridone (**42a**) became available by acetylation of **40** and subsequent potassium carbonate-promoted ring-closure.[22] A simple one-step pyridine annelation procedure employing amide acetals as reagents (compare also preparation of compounds **35c**; Scheme 10) also permits high-yield preparation of 3-chloro-5-phenyl substituted 7-dialkylaminopyrido[2,3-*c*]pyridazines (**43**).[22] For the preparation of the dechlorinated congeners (**44**), an analogous process starting with the novel amino ketone (**41**) had to be chosen, as reductive dechlorination of compounds (**43**) gave only poor yields.[22]

Scheme 12

42a R = H
42b R = C₂H₅

43

44

X = N(CH₃)₂, piperidino, 4-methylpiperazino,
4-ethylpiperazino

A variety of N-8-substituted derivatives of the pyrido[2,3-c]pyridazine ring system bearing an amino function at C-5 and an ester group at C-6 are available from the chloro nitrile (8) *via* the substituted amino nitriles (45), as outlined in Scheme 13. The 5-oxo derivatives (47a) could be prepared by hydrolysis/oxidation of compounds (46) and finally were transformed into the corresponding carboxylic acids (47b) which are structurally related to the gyrase inhibitor nalidixic acid.[5]

Scheme 13

45

46

R =

47a X = OC₂H₅   47b X = OH

A representative of the pyrido[2,3-c]pyridazine ring system with two nitrogen substituents (located at C-5 and C-7) could be obtained from the amidine (48) which is accessible from the amino nitrile (19).[23] Other than in pyridine ring annelation reactions starting from ketones of type 11, 40, or 41 (compare Schemes 10, 12), intramolecular cyclisation, in this case, requires deprotonation of the amidine methyl group by a strong base (LDA).[23]

Scheme 14
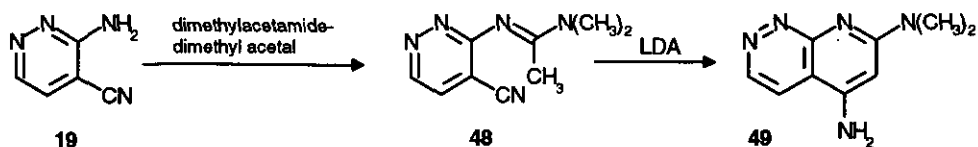
3.3. Diazaisoquinolines

Syntheses for a series of pyrido[3,4-*d*]pyridazines, which can be regarded as diaza analogs of the isoquinoline system, have been elaborated recently.

Diazaisoquinolones of type **52** were synthesized in good yields starting from the methyl substituted pyridazinecarboxylic acid ester (**50**) in two steps by condensation with dimethylformamide dimethyl acetal and subsequent ring closure of the enamine (**51**) with ammonia or butylamine/trifluoroacetic acid.[24] The educt (**50**) can be obtained from commercially available 4-methylpyridazine by a radical two-phase alkoxycarbonylation procedure previously developed in our laboratory.[25]

Scheme 15
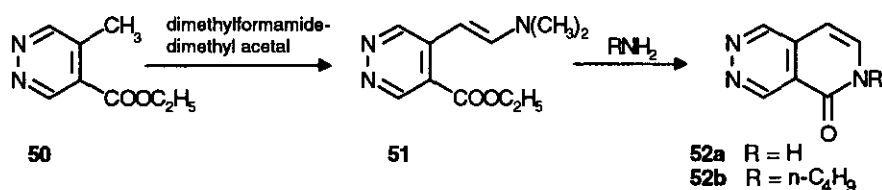
An analogous pyridine ring annelation process was applied for the preparation of 5-arylpyrido[3,4-*d*]pyridazines (**55**).[24] Here, ketones of type **53** (accessible from 4-methylpyridazine by homolytic aroylation[24,26]) were employed as starting materials.

5,7,8-Triarylpyrido[3,4-*d*]pyridazines (**57a**) can be prepared by DBU-mediated cyclocondensation of 4,5-diaroylpyridazines[9] with benzylamine. Similarly, employment of ethyl glycinate as a NH_2CH_2 building block affords satisfactory yields of 5,8-diaryl-7-carboxylic acid esters of type **57b**, which - after hydrolysis and subsequent decarboxylation - finally made available also the 5,8-diaryl-diazaisoquinolines (**58**).[24]

Scheme 16
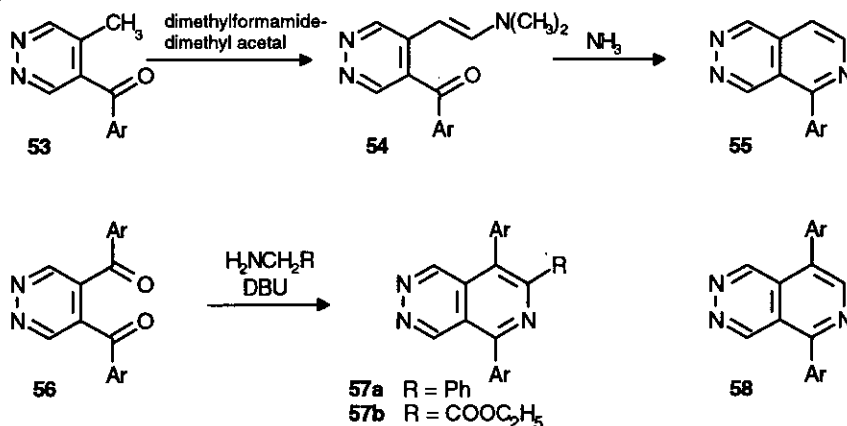
Preparation of phenyl substituted diazaisoquinolones of type **59** was achieved by ammonolysis/aminolysis of the enamino ester (**28**).[17] The N-unsubstituted fused pyridone can be easily converted into the 5-dialkylamino-8-phenylpyrido[3,4-*d*]pyridazines (**61**) *via* the reactive chloro compound (**60**).[17]
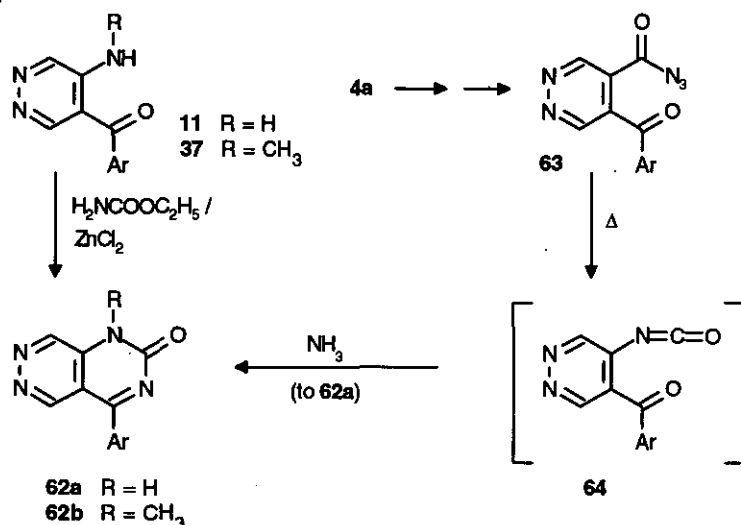
Scheme 17
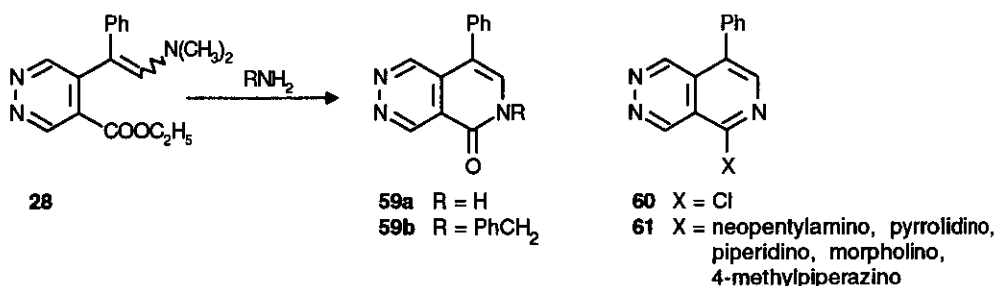
3.4. Diazaquinazolines

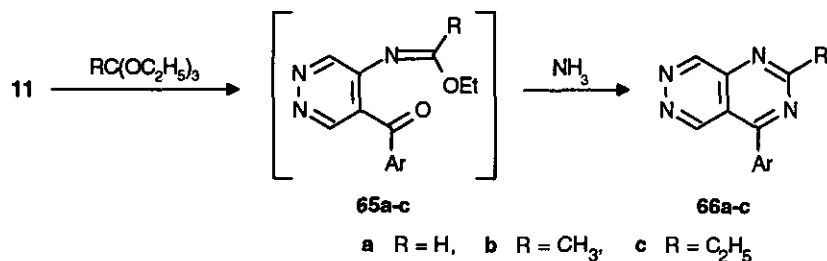### 3.4.1. Pyrimido[4,5-*d*]pyridazines

Annelation of a pyrimidine system to positions 4/5 of the pyridazine ring to give 4-aryl substituted pyrimido-[4,5-*d*]pyridazines can be accomplished starting from amino ketones of type **11** or **37**. Thus, fusion of such primary or secondary amino ketones with ethyl urethane in the presence of zinc chloride affords diaza-quinazolones of type **62**. An alternative route to the N-1-unsubstituted compound (**62a**) utilizes the keto-carboxylic acid azide (**63**) [smoothly available from the keto acid (**4a**) *via* the chloro lactone (**5a**)], which on thermolysis gives an isocyanate (**64**) susceptible to ring closure on treatment with ammonia.[27]

Scheme 18

11 R = H
37 R = CH$_3$

62a R = H
62b R = CH$_3$

63

64

4-Aryl-diazaquinazolines of type **66** are conveniently accessible by the one-pot procedure given in Scheme 19. Refluxing of an amino ketone (**11**) with an appropriate ortho ester, followed by cyclocondensation with ammonia, gives 2-alkyl-4-arylpyrimido[4,5-d]pyridazines (**66b,c**) in satisfactory yields. Employment of triethyl orthoformate gives the 4-aryl substituted parent system.[27]

Scheme 19

65a-c   **66a-c**

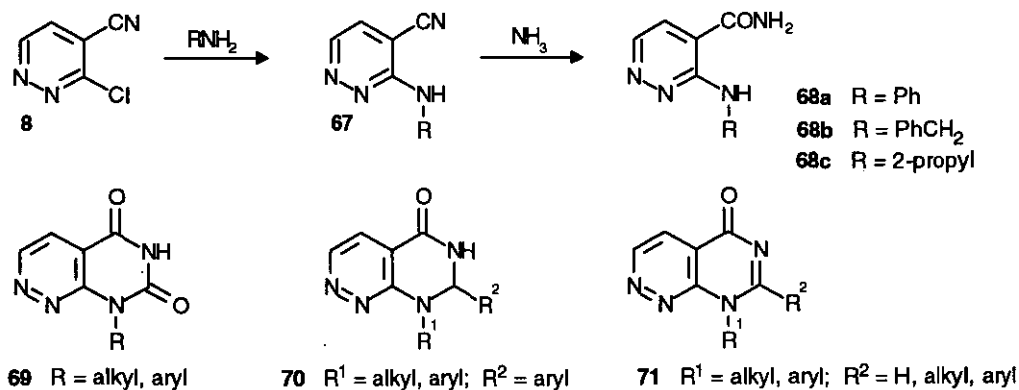a R = H,   b R = CH$_3$,   c R = C$_2$H$_5$

3.4.2. Pyrimido[4,5-c]pyridazines

3-Alkylamino- or 3-arylamino-4-pyridazinecarboxamides (**68**) [available from the chloro nitrile (**8**) *via* amino nitriles (**67**)] represent valuable precursors for pyrimido[4,5-c]pyridazines differently substituted in the 1,3-diazine moiety. N-8-Alkyl or aryl substituted pyrimido[4,5-c]pyridazine-5,7-(6H,8H)-diones (**69**) are obtained on reaction with urea at high temperature; similarly, heating of the amino amides (**68**) with neat aromatic carbaldehydes affords the pyridazine-fused dihydropyrimidones (**70**). Permanganate oxidation of the latter provides a convenient route to the diazaquinazolones (**71**) (R^2 = aryl), the corresponding 7-alkyl

derivatives are smoothly available in a single step from compounds (68) upon cyclisation with ortho esters,[14] whereas attempted pyrimidine ring annelation employing acid chlorides remained unsuccessful.

N-8-Unsubstituted representatives of compounds (70) (R^1 = H), which are of interest as 2-aza analogs of pyrido[2,3-d]pyrimidine diuretics,[28] can be prepared from 3-amino-4-pyridazinecarboxamide by heating in an excess of an aromatic aldehyde.[23]

Scheme 20

	68a	R = Ph
	68b	R = PhCH$_2$
	68c	R = 2-propyl

69 R = alkyl, aryl   70 R^1 = alkyl, aryl; R^2 = aryl   71 R^1 = alkyl, aryl; R^2 = H, alkyl, aryl

An access to the 6-phenyl substituted fused pyrimidinedione derivative (72) is provided by prolonged refluxing of the amino nitrile (19) with phenyl isocyanate in dimethylformamide solution.[23] Also attempts to functionalize the nitrile group in 19 have been reported.[23] The amidrazone obtained on hydrazinolysis readily reacts with acetic anhydride to give, after two consecutive cyclisation steps, the triazolo-annelated pyrimido[4,5-c]pyridazine (74).[23] The use of 3-amino-5-phenyl-4-pyridazinecarbonitrile for the annelation of a pyrimidine system to the 1,2-diazine moiety had been reported previously.[29]
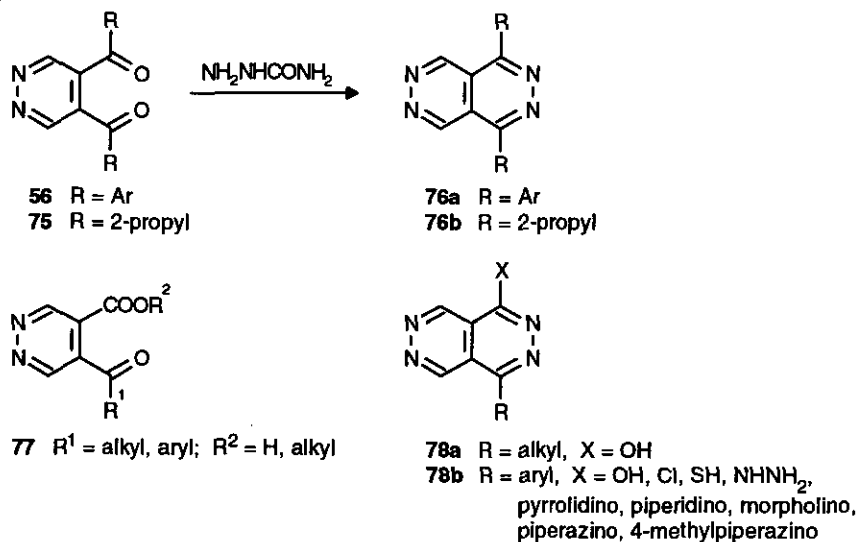
Scheme 21


19   72

73   74
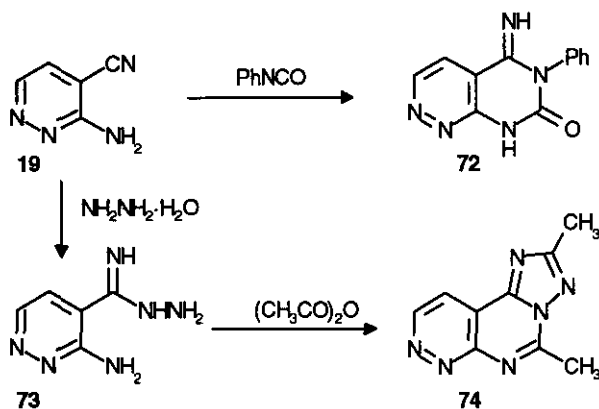
3.5. Diazaphthalazines

Symmetrically 1,4-disubstituted pyridazino[4,5-*d*]pyridazines (**76**) are conveniently prepared by cyclisation of 4,5-diacylpyridazines (resulting from radical acylation of the protonated parent system) with semicarbazide or hydrazine, respectively.[9] For the synthesis of 4-alkyl- or 4-arylpyridazino[4,5-*d*]pyridazines bearing a heteroatom substituent (OH, Cl, SH, cycloamino, hydrazino) at C-1 (compounds **78a,b**), keto acids or esters of type **77** are versatile precursors.[30,31] Compounds of type **78b** (R = cycloamino) have been found to exhibit diuretic activity with a potassium-saving profile.[31]

Scheme 22

56 R = Ar
75 R = 2-propyl

76a R = Ar
76b R = 2-propyl

77 R^1 = alkyl, aryl; R^2 = H, alkyl

78a R = alkyl, X = OH
78b R = aryl, X = OH, Cl, SH, NHNH$_2$,
              pyrrolidino, piperidino, morpholino,
              piperazino, 4-methylpiperazino

Recently, it has been demonstrated that 1,4-diarylpyridazino[4,5-*d*]pyridazines (**76a**) can be used as reactive azadienes in inverse-electron-demand Diels-Alder reactions, giving rise to an effective access to the substituted/condensed phthalazines displayed in Scheme 23.[32]

Scheme 23

79
R = Ph, morpholino

80

81
n = 1, 2

82
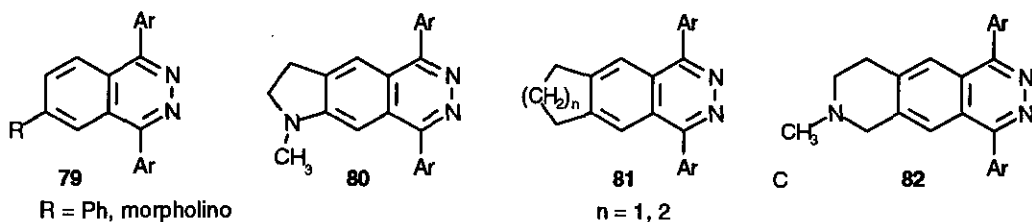
3.6. Pyridazine-Containing Tricyclic Systems

3.6.1. Diazaxanthenes

 Intramolecular nucleophilic aromatic substitution of the activated fluorine in the aroylpyridazinone (84) under alkaline conditions permits preparation of 10H-[1]benzopyrano[2,3-d]pyridazin-10-one (85).[33] The educt (84) is accessible in satisfactory overall yield from the amino ketone (83) by benzylation of the pyridazine N-2 atom, followed by a hydrolysis-debenzylation sequence.

For the synthesis of the isomeric tricyclic system (compound 87), polyphosphoric acid-mediated ring closure of the phenoxy nitrile (86) can be applied.[34]

Scheme 24
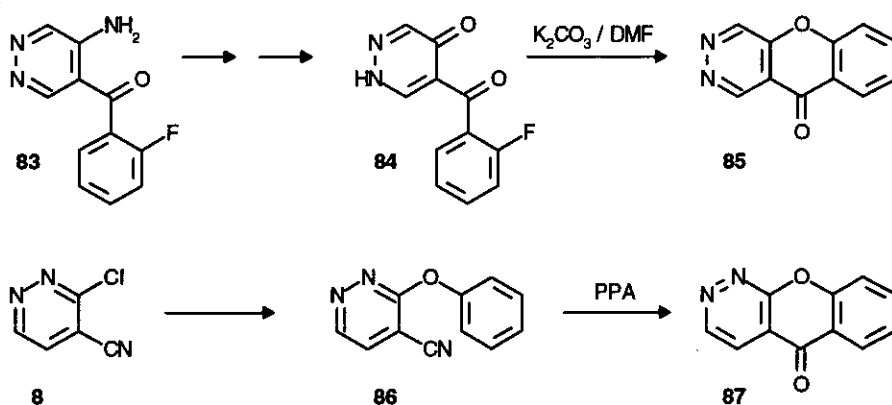
3.6.2. Diazathioxanthenes

Reaction of the o-fluorobenzoyl substituted pyridazinone (84) with phosphorus pentasulfide in refluxing pyridine directly leads to the 10H-[1]benzothiopyrano[2,3-d]pyridazin-10-one (88) without further oxo → thioxo conversion under the conditions applied.[33] The isomeric 5H-[1]benzothiopyrano[2,3-c]pyridazin-5-one is readily available in analogy to the synthesis of compound (87) by acid-catalyzed cyclisation.

Scheme 25
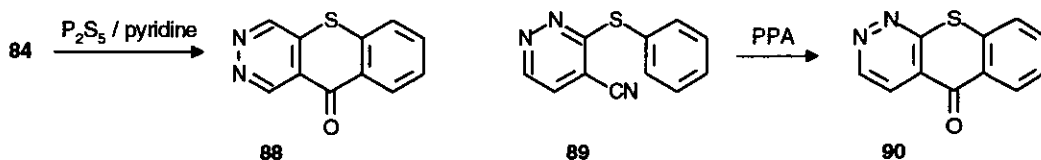
### 3.6.3. Diazaacridines

Base-catalyzed intramolecular nucleophilic substitution of the activated fluorine in the amino ketone (83) affords the diazaacridone (92) in excellent yield.[33] Alkylation of the NH compound (92) is governed by attack at the pyridazine N-2 atom to give 2-alkyl derivatives (94) exclusively.[33] The preparation of N-5 alkyl

isomers (93) can be accomplished either by employment of alkylamino ketones (91) as cyclisation pre-cursors[33,35] or by quaternisation of 2-benzylpyridazino[4,5-*b*]quinolin-10(2*H*)-one (94, R = $C_6H_5CH_2$) and subsequent aluminium trichloride-mediated debenzylation.[33]

Scheme 26

83 R = H
91 R = alkyl

92 R = H
93 R = alkyl

94 R = alkyl
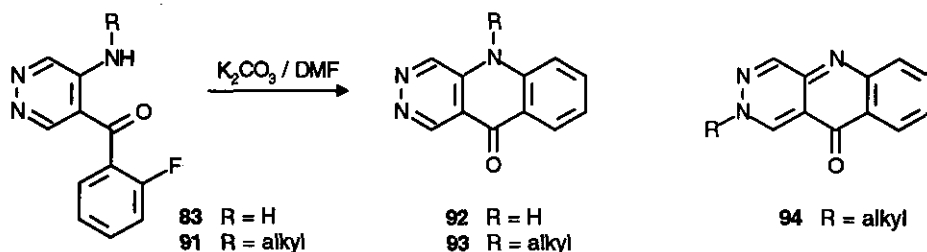
The most efficient pathway to diazaacridones of type 93 (permitting the synthesis even of compounds bearing a functionalized side chain at C-5), utilizes a remarkable reactivity observed with conveniently available 2-alkylaminophenyl 4-pyridazinyl ketones (95) (Scheme 27).
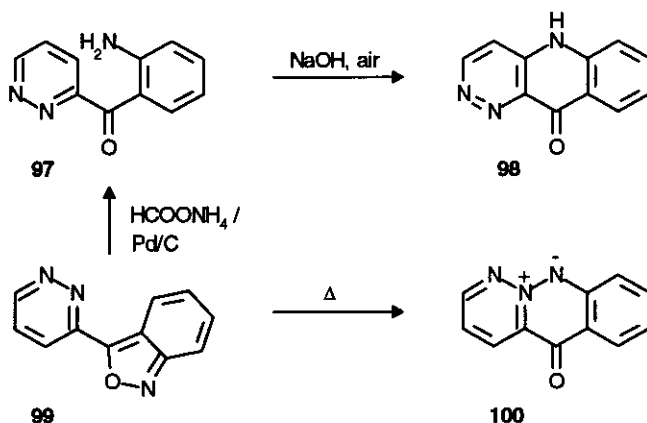
Scheme 27

95 R = alkyl

96
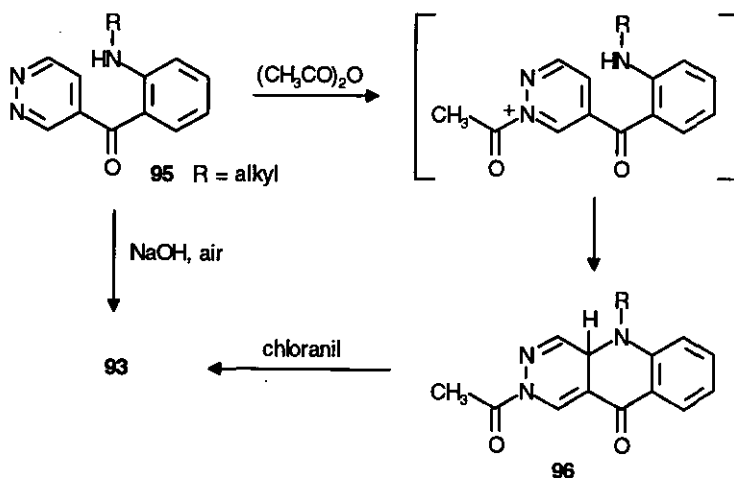
Surprisingly, acetylation of 95 had been found to lead to the 2-acetyldihydrodiazaacridones (96) (most probably *via* N-acylpyridazinium intermediates) which could be oxidized (albeit in only low yields) to 93. Consequently, the high susceptibilty of the pyridazine C-5 atom in 95 towards intramolecular nucleophilic attack was exploited for the elaboration of a regiospecific single-step cyclisation of 95 to N-5-alkyldiaza-acridones (93) simply by refluxing 95 in aqueous alkali: under these conditions, an intramolecular σ-adduct (which is obviously formed by attack of the aniline nitrogen on C-5 of the pyridazine system) is oxidized by air oxygen.[36]

This principle, featuring formation of an annelated pyridazine from a monosubstituted 1,2-diazine precursor, could be applied also for the synthesis of pyridazino[4,3-b]quinolin-10(5H)-one (98) from the amino ketone (97) [available by hydrogenolysis of the pyridazinyl substituted 2,1-benzisoxazole (99)] as displayed in Scheme 28.[37]

Pyrolysis of the anthranil (99) leads to the mesoionic diazaacridone (100), the first representative of the previously unknown pyridazino[2,3-b]cinnoline ring system.[37]

Scheme 28

An additional diazaacridone system, characterized by two adjacent nitrogen atoms (compounds of type 102), is available from the chloro nitrile (8) via anilino substituted nitriles (101).[34]

Scheme 29
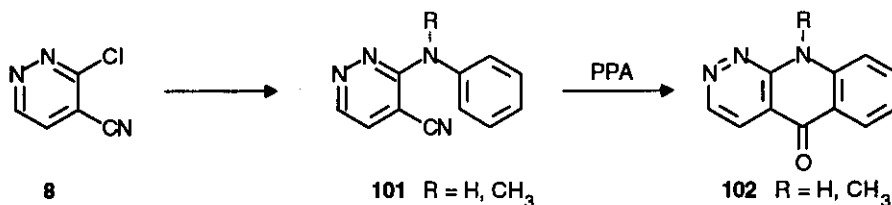
3.6.4. Diazaphenothiazines

A variety of pyridazino[3,4-b][1,4]benzothiazines bearing substituents at C-3 and N-5 have been reported in the literature,[38] the corresponding parent system (105), however, had remained undescribed until very recently. In the course of attempted preparation of tricycles of type 104 from the pyridazine precursor (103), an efficient route to the diazaphenothiazine (105) was found. Here, action of sodium methylsulfinyl methanide surprisingly did not result in addition of the amino group to the nitrile function, but in an intramolecular substitution reaction.[12]

Scheme 30

104 X = O, NH

105
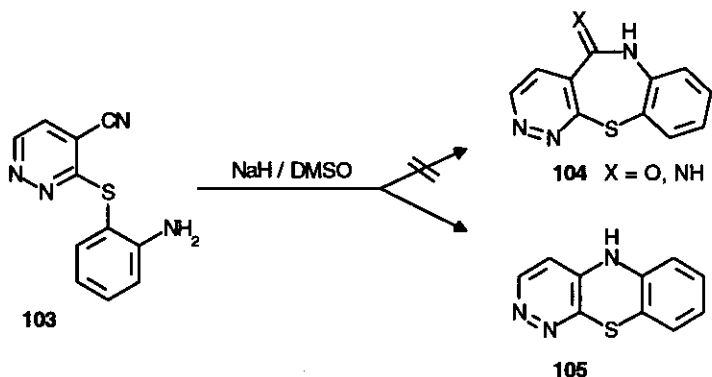
4. ANNELATION OF SEVEN-MEMBERED RINGS

4.1. Diazadibenzocycloheptanes

All three possible isomeric pyridazine analogs of the 10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one
system could be made available recently by PPA-promoted cyclisation of the appropriate phenylethyl
substituted pyridazinecarboxylic acids.[19] The introduction of the required carboxyl functionality into the
phenylethylpyridazines used as educts can be accomplished by radical ethoxycarbonylation, employing a two
phase system technique developed in this laboratory[39] (compounds 106, 108) or by a modified Reissert-type
cyanation process.[19]

Scheme 31

106   PPA   109

107   PPA   110

108   PPA   111
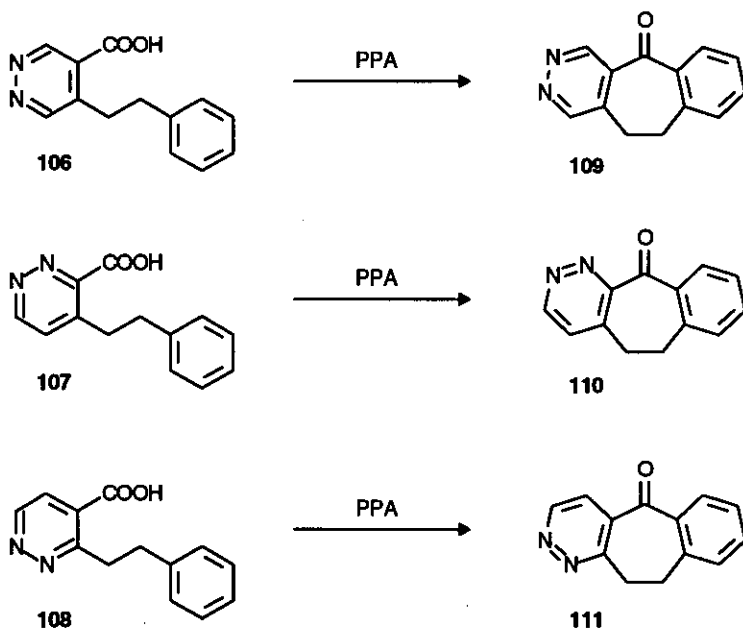
## 4.2. Diazabenzodiazepines

In 1988, the first examples of pyridazine-fused 1,4-diazepine derivatives (compounds **113**) were reported. Initial attempts to achieve diazepine ring annelation by treating amino ketones (**11**) with ethyl glycinate had failed. The construction of such potential pharmaceuticals, however, could be accomplished finally by employing the butyloxycarbonyl-protected glycinamides (**112**).[40]

Scheme 32
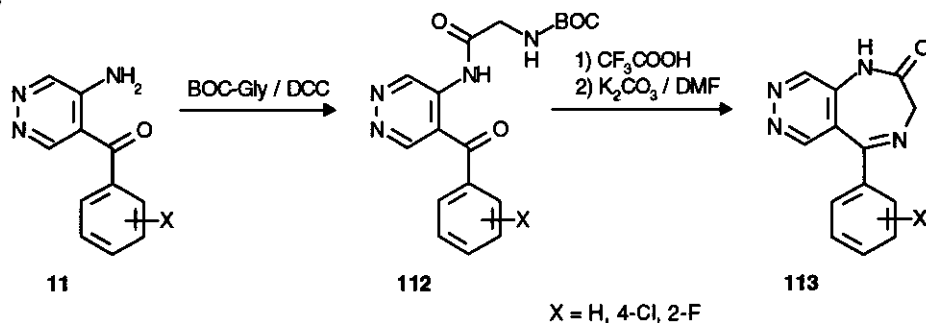
X = H, 4-Cl, 2-F

ACKNOWLEDGEMENT

REFERENCES

1. *'Comprehensive Heterocyclic Chemistry'*, A.R. Katritzky and C.W. Rees (eds.), Pergamon Press, Oxford, 1984.

2. *'Condensed Pyridazines including Cinnolines and Phthalazines'* (The Chemistry of Heterocyclic Compounds, Vol. 27), R.N. Castle (ed.), Wiley, New York, 1973.

3. J. Easmon, G. Heinisch, W. Holzer, and B. Rosenwirth, *Arzneim.-Forsch./Drug Res.*, 1989, **39**, 1196.

4. N. Haider, G. Heinisch, and S. Offenberger, *Pharmazie*, 1989, **44**, 598.

5. P.Y. Boamah, N. Haider, and G. Heinisch, *Arch. Pharm.* (Weinheim), 1990, **323**, 207.

6. G. Heinisch, *Heterocycles*, 1987, **26**, 481.

7. G. Heinisch, *Bull. Soc. Chim. Belg.*, 1992, **101**, 579.

8. F. Minisci, *Synthesis*, 1973, 1.

9. M. Braun, G. Hanel, and G. Heinisch, *Monatsh. Chem.*, 1978, **109**, 63.

10. N. Haider, G. Heinisch, I. Kurzmann-Rauscher, and M. Wolf, *Liebigs Ann. Chem.*, 1985, 167.

11. a) A. Dornow and W. Abele, *Chem. Ber.*, 1964, **97**, 3349; b) M. Yanai, S. Takeda, and T. Mitsuoka, *Chem. Pharm. Bull.*, 1977, **25**, 1708.

12. K. Czech, N. Haider, and G. Heinisch, *Monatsh. Chem.*, 1991, **122**, 413.

13. N. Haider and G. Heinisch, *J. Chem. Soc., Perkin Trans 1*, 1986, 169.

14. N. Haider, G. Heinisch, and D. Laßnigg, *J. Heterocycl. Chem.*, 1988, **25**, 119.

15. N. Haider, G. Heinisch, and J. Moshuber, *Tetrahedron*, 1991, **47**, 8573.

16. G. Heinisch and I. Kirchner, *J. Heterocycl. Chem.*, 1980, **17**, 1501.

17. P.Y. Boamah, N. Haider, G. Heinisch, and J. Moshuber, *J. Heterocycl. Chem.*, 1988, **25**, 879.

18. G. Heinisch, W. Holzer, and G.A.M. Nawwar, *J. Heterocycl. Chem.*, 1986, **23**, 93.

19. W. Dostal, G. Heinisch, and G. Lötsch, *Monatsh. Chem.*, 1988, **119**, 751.

20. N. Haider and G. Heinisch, *Synthesis*, 1986, 862.

21. T. Eichhorn, S. Piesch, and W. Ried, *Helv. Chim. Acta*, 1988, **71**, 988.

22. N. Haider, G. Heinisch, and J. Moshuber, *Pharmazie*, 1992, in the press.

23. N. Haider, G. Heinisch, and R. Wanko, *J. Heterocycl. Chem.*, 1991, **28**, 1441.

24. P.Y. Boamah, N. Haider, and G. Heinisch, *J. Heterocycl. Chem.*, 1989, **26**, 933.

25. G. Heinisch and G. Lötsch, *Tetrahedron*, 1985, **41**, 1199.

26. G. Heinisch and R. Waglechner, *J. Heterocycl. Chem.*, 1984, **21**, 1727.

27. N. Haider and G. Heinisch, *Arch. Pharm.* (Weinheim), 1986, **319**, 850.

28. H.A. Parish, R.D. Gilliom, W.P. Purcell, R.K. Browne, R.F. Spirk, and H.D. White, *J. Med. Chem.*, 1982, **25**, 98.

29. B. Stanovnik, V. Stibilj, and M. Tišler, *Synthesis*, 1986, 807.

30. G. Heinisch and I. Kirchner, *Monatsh. Chem.*, 1979, **110**, 365.

31. N. Haider, G. Heinisch, and I. Kirchner, *Arch. Pharm.* (Weinheim), 1982, **315**, 778.

32. N. Haider, *Tetrahedron*, 1991, **47**, 3959.

33. N. Haider and G. Heinisch, *J. Chem. Soc., Perkin Trans. 1*, 1988, 401.

34. G. Heinisch and D. Laßnigg, *Arch. Pharm.* (Weinheim), 1987, **320**, 1222.

35. N. Haider, G. Heinisch, and I. Volf, *Heterocycles*, 1989, **29**, 1309.

36. M. Grabenwöger, N. Haider, and G. Heinisch, *Liebigs Ann. Chem.*, 1989, 481.

37. N. Haider, G. Heinisch, and J. Moshuber, unpublished results.

38. F. Yoneda and T. Ohtaka, *Yakugaku Zasshi*, 1968, **88**, 1638 (*Chem. Abstr.*, 1969, **70**, 77897a).

39. G. Heinisch and G. Lötsch, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 692.

40. N. Haider and G. Heinisch, *Arch. Pharm.* (Weinheim), 1988, **321**, 309.