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

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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, arylpyridazinecarboxylic acids, alkylpyridazinecarboxylic acids, aminopyridazinyl aryl ketones, and chloro- or alkylpyridazinecarbonitriles represent the key intermediates.

CONTENTS

1. Introduction
2. Annelation of Five-Membered Rings
   2.1. Cyclopentapyridazines
   2.2. Furo-, Pyrrolo- and Thiencopyridazines
   2.3. Pyrazolo- and Isoxazolopyridazines
   2.4. Tetrazolopyridazines
3. Annelation of Six-Membered Rings
   3.1. Pyranopyridazines
   3.2. Diazaquinolines
      3.2.1. Pyrido[2,3-d]pyridazines
      3.2.2. Pyrido[2,3-c]pyridazines
   3.3. Diazaisoquinolines
   3.4. Diazaquinazolines
      3.4.1. Pyrimido[4,5-d]pyridazines
      3.4.2. Pyrimido[4,5-c]pyridazines
   3.5. Diazaphthalazines
   3.6. Pyridazine-Containing Tricyclic Systems
      3.6.1. Diazaxanthenes
      3.6.2. Diazaanthoxanthenes
      3.6.3. Diazacridines
      3.6.4. Diazaphenothiazines
4. Annelation of Seven-Membered Rings
   4.1. Diazadibenzocyloheptanes
   4.2. Diazabenzodiazepines

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. Thus, for instance, the chemistry of pyrido-fused five-, six-, and seven-membered heterocycles has been explored to a large extent. 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. In addition, more recent developments in this field are discussed in ref. 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) 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. 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 (I), reaction with acyl radicals (generated from the corresponding aldehydes according to Minisci's method) in acidic medium leads to cyclopenta[d]pyridazines of type 2 due to intramolecular aldol reaction of intermediate 4,5-diaclypyridazines. If the carbon atom α to the keto function bears at least one hydrogen, unsaturated congeners of type 3 are isolated.
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 methanolyis 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). Methanolyis 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

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
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-aryloyl-4-pyridazinocarboxylic acids (4a)\(^1\)] 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\(^{13}\).
2.4. Tetrazolopyridazines

Synthesis of the tetrazolo[1,5-b]pyridazine-8-carbonitrile (18) can be achieved by treatment of 3-chloro-4-pyridazinonecarbonitrile (8) with sodium azide. 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, 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

\[ \text{8} \xrightarrow{\text{NaN}_3} \text{18} \xrightarrow{1) \text{PPh}_3, 2) \text{H}^+} \text{19} \]
\[ \text{18} \xrightarrow{\text{PhMgCl}} \text{20} \]

It is noteworthy that compound (18) for the first time provides an access to 3-amino-4-pyridazinonecarbonitrile (19) 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 pyran[3,4-d]pyridazine (26) occurs on acidic hydrolysis of 5-methyl-4-(sym-trioxanyl)-pyridazine (24) (obtained by homolytic trioxanylation of 4-methylpyridazine). 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 benzylidenemalonlic acid derivatives in the presence of a weak base, affording the polyfunctional pyrano[2,3-d]pyridazines (31a,b).18

Scheme 8

Ring-closure to a pyrano[4,3-c]pyridazine (compound 33) was observed upon heating of 3-(2-phenylethynyl)-4-pyridazincarbonitrile (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
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-aryl diazaquinolines (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.

**Scheme 10**

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\(_1^1\) = R\(_2^2\) = 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). Even with amides (38) where the acyl group is a benzylxycarbonyl-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.

Scheme 11

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, catalytic transfer hydrogenation of 40 affords the dehalogenated congener (41) in high yield. 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. 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). 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.
A variety of N-8-substituted derivatives of the pyrido[2,3-\text{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.\(^5\)

A representative of the pyrido[2,3-\text{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).\(^{23}\)
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. The educt (50) can be obtained from commercially available 4-methylpyridazine by a radical two-phase alkoxy-carbonylation procedure previously developed in our laboratory.

An analogous pyridine ring annelation process was applied for the preparation of 5-arylpyrido[3,4-d]pyridazines (55). Here, ketones of type 53 (accessible from 4-methylpyridazine by homolytic arylation) were employed as starting materials. 5,7,8-Triarylpyrido[3,4-d]pyridazines (57a) can be prepared by DBU-mediated cyclocondensation of 4,5-diarylpyridazines with benzylation. Similarly, employment of ethyl glycinate as a NH₂CH₂ 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).
Preparation of phenyl substituted diazaIsoquinolones of type 59 was achieved by ammonolysis/aminolysis of the enamino ester (28). 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).

Scheme 17

3.4. Diazaquinazolines

3.4.1. Pyrimido[4,5-d]pyridazines

Annellation 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 diazaquinazolones 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.
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

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) (R² = aryl), the corresponding 7-alkyl
derivatives are smoothly available in a single step from compounds (68) upon cyclisation with ortho esters, whereas attempted pyrimidine ring annelation employing acid chlorides remained unsuccessful.

N-8-Unsubstituted representatives of compounds (70) (R₁ = H), which are of interest as 2-aza analogs of pyrido[2,3-d]pyrimidine diuretics, can be prepared from 3-amino-4-pyridazinecarboxamide by heating in an excess of an aromatic aldehyde.

Scheme 20

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. Also attempts to functionalize the nitrile group in 19 have been reported. 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). The use of 3-amino-5-phenyl-4-pyridazincarbonitrile for the annelation of a pyrimidine system to the 1,2-diazine moiety had been reported previously.

Scheme 21
3.5. Diazaphthalazines

Symmetrically 1,4-disubstituted pyridazino[4,5-d]pyridazines (76) are conveniently prepared by cyclisation of 4,5-diaclypyridazines (resulting from radical acylation of the protonated parent system) with semicarbazide or hydrazine, respectively. 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. Compounds of type 78b (R = cycloamino) have been found to exhibit diuretic activity with a potassium-saving profile.

Scheme 22

![Scheme 22](image)

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.

Scheme 23

![Scheme 23](image)
3.6. Pyridazine-Containing Tricyclic Systems

3.6.1. Diazaanthrenes

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). 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.

Scheme 24

3.6.2. Diaza-thioxanthenes

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. 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. Diaza-acridines

Base-catalyzed intramolecular nucleophilic substitution of the activated fluorine in the amino ketone (83) affords the diaza-acridone (92) in excellent yield. Alkylation of the NH compound (92) is governed by attack at the pyridazine N-2 atom to give 2-alkyl derivatives (94) exclusively. The preparation of N-5 alkyl
isomers (93) can be accomplished either by employment of alkylamino ketones (91) as cyclisation precursors or by quaternisation of 2-benzylpyridazino[4,5-b]quinolin-10(2H)-one (94, R = C₆H₅CH₂) and subsequent aluminium trichloride-mediated debenzylation.

Scheme 26

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

Surprisingly, acetylation of 95 had been found to lead to the 2-acetyldihydromiazaacridones (96) (most probably via N-acylpyridazinium intermediates) which could be oxidized (albeit in only low yields) to 93. Consequently, the high susceptibility 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-alkyl diazaacridones (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.
This principle, featuring formation of an annelated pyridazine from a monosubstituted 1,2-diazone 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
4. ANNELATION OF SEVEN-MEMBERED RINGS

4.1. Diazadibenzocycloheptanes

All three possible isomeric pyridazine analogs of the 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one system could be made available recently by PPA-promoted cyclisation of the appropriate phenylethyl substituted pyridazincarboxylic acids. 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 (compounds 106, 108) or by a modified Reissert-type cyanation process.

Scheme 31
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

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