Review

Synthetic Pathways to Pyrido[3,4-c]pyridazines and Their Polycyclic Derivatives

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Abstract: Pyrido[3,4-c]pyridazines are nitrogen-containing scaffolds that have been described as being promising in medicinal chemistry, but they are rather rare chemicals. In this review article, the literature on synthetic pathways towards pyrido[3,4-c]pyridazines is listed exhaustively, first with the bicyclic systems themselves that are obtained starting either from pyridines, pyridazines or other heterocycles. Then, the reports on the related tricyclic derivatives are discussed, again according to the source heterocycle, and finally we mention some examples on polycyclic systems.

Keywords: pyrido[3,4-c]pyridazines; heterocycle; pyridopyridazine; pyridine; bispyridopyridazine

1. Introduction

Nitrogen-containing heterocycles play an important role in nature [1] and are also part of the structure of many small molecule drugs. A 2014 study estimated that 59% of the FDA-approved drugs had a nitrogen-containing ring in their structure [2]. However, among those drugs there are clearly much more of the “common” monoheterocycles such as the six-membered pyridine, piperidine and piperazine, or five-membered thiazole, pyrrolidine and imidazoles. Bicyclic structures are somewhat less popular, and in those cephem, penam, indoles and benzimidazoles constitute the majority. Clearly, medicinal chemists have in the past mainly relied on only a few well-known heterocyclic building blocks. W. R. Pitt et al., in “heteroaromatic molecules of the future”, referred to a virtual list of unexplored chemicals selected on synthetic tractability [3]. These 22 bicyclic molecules all had at least one nitrogen in their structure. Among those molecules, one was a derivative of the pyrido[3,4-c]pyridazine 1, the 6-oxo-derivative 2. The synthesis of differently fused pyridopyridazine isomers 1, 3–8 (Figure 1) has been previously reviewed [4], but specific derivatives of 1 or 2 were only briefly mentioned in these texts. In a 2019 follow-up article on the “heteroaromatic molecules of the future”, the literature of 2009–2019 was reviewed [5] and indeed synthetic chemists had risen to the challenge, with reports appearing on 15 of the 22 aforementioned heteroaromatic molecules, but notably the pyridopyrazidinone 2 was not among these, although there had been two theoretical studies on this scaffold [6,7] concerning enhanced inhibition of cytochrome P450s and hydrogen bonding accepting properties, respectively.

With this short review we hope to increase the interest in the heterocycle 1 and its derivatives by exhaustively summarizing synthetic efforts so far. Earlier reviews on “pyridopyridazines” [5,8,9] focus on the other isomers and have mentioned almost nothing on the title subject. As far as we know, this is the first dedicated effort of bringing together all literature on the synthesis of pyrido[3,4-c]pyridazine 1. At the same time, we will also have a detailed look at the related tricyclic and polycyclic analogs of this bicyclic system. Where appropriate, we will also mention any biological properties of the different compounds synthetized.
2. Discussion

2.1. Bicyclic Pyrido[3,4-c]pyridazine Derivatives

2.1.1. Starting from Pyridine Derivatives

One of the earliest procedures towards pyrido[3,4-c]pyridazines led to the synthesis of 10, named 1,2,7-triazanaphthalenes [10], which was based on the Widman-Stoermer cinnoline synthesis, involving a one-pot diazotisation/cyclization sequence of 4-propenyl-3-aminopyridines 9. Unfortunately, only a low yield of 10 (14–17%) was obtained after chromatography. In a later effort [11], the same strategy was applied to obtain the corresponding pyrido[3,4-c]pyridazine-4-one 12b from 4-acetyl-3-aminopyridine 11. This Borsche reaction probably involves the electron rich enol form of the acetyl substituent, to afford (38% yield) a tautomeric equilibrium mixture of 12a,b. This molecule was referred to as a 7-azacinnolin-4(1H)-one. The tautomerism of compound 12 was studied in detail with 1H, 13C and 15N NMR spectroscopy, concluding that the main isomer is indeed 12b in polar solvents such as deuterated DMSO, methanol and water (Scheme 1). Further examples of pyridopyridazinone analogs of 12 prepared by Borsche cyclization of acyl substituted pyridines have been described in the patent literature [12].

The Japp-Klingemann approach was also used to synthesize 3,8-disubstituted pyridopyridazinone from the reaction with 2-chloro-3-aminopyrididine 13. The corresponding diazonium salt of 9 is combined with Ethyl-2-methyl-acetoacetate to afford the hydrazone.
which was then cyclized in polyphosphoric acid to give a low yield of the 8-chloro-3-methyl-pyridopyridazine-4-one 15, which was described as the 4-hydroxy tautomer [13], although probably based on the later study [10] on the analog 12, the structure should be reassigned as the keto tautomer 15 (Scheme 2).

Scheme 2. Synthesis of pyridopyrazin-8-one by acid-catalyzed cyclization of hydrazone.

A Hetero-Diels-Alder cycloaddition reaction of 2-vinylpyridines and electron poor azo derivatives was studied by Gurnos et al. [14,15] as an entry into different pyridopyrimidine isomers, including the pyrido[3,4-c]pyrimidine. 2-Vinylpyridine 16 and azodicarboxylates 17 (R = Et, t-Bu) to afford the tetrahydropyridopyrimidines 18 (16% yield for R = t-Bu), that are subsequently deprotected (R = t-Bu) with trifluoroacetic acid (TFA) and oxidized with red mercuric oxide, with a 52% yield for the two final steps leading to the parent compound 1. The cycloaddition reaction is incomplete and possibly polymerization of 16 occurs, explaining the low yield in the first step (Scheme 3).

Scheme 3. The parent pyrido[3,4-c]pyridazine by cycloaddition/deprotection/oxidation.

Starting from N-protected 3-pyridone-4-acetate derivative 19 [16,17] after condensation with hydrazine and oxidation with bromine in acetic acid, the tetrahydropyridopyridazinone 20 is obtained. The latter can then be chlorinated with phosphoryl chloride to the chloro derivative 21, which is used as a convenient building block for further derivatization at the piperidine nitrogen (after deprotection) and/or after reaction of the reactive chlorine, e.g., amine substitutions, and Suzuki arylation (Scheme 4). We do not describe these reactions in detail as they are no longer ring forming reactions but rather standard derivatizations. These derivatives constitute the largest and most studied library of pyridopyridazine analogs in the literature. Different biological properties of these compounds were investigated, including inhibitors of the dipeptidyl peptidase-IV enzyme useful in the treatment of type 2 diabetes [18], histamine H3 receptor binders with CNS activity [16], kinase inhibitors [19], gamma-aminobutyric acid A receptor subunit alpha 5 (GABA_A α5) positive allosteric modulators [20] or sphingosine-1-phosphate (S1P) inhibitor activity [21].
The 4-methyl-3-cyano-pyridine-2,6-diones 22 are easily available from the condensation reaction of acetoacetate esters and N-arylcyanoacetamide. Azo coupling with phenyl-diazonium salt then gave the hydrazone 23. The latter underwent a one-pot conversion with dimethyl formamide dimethylacetal (DMFDMA) to an enamine 24, followed by cyclocondensation with evolution of dimethylamine, affording the 6,8-dione derivative 25. The reaction takes place either in xylene at reflux (77% yield) or solventless after microwave irradiation (no yield given, Scheme 5) [22].

The N-unsubstituted pyridinedione derivatives 26 were condensed with arylidene-malononitrile in the presence of piperidine base in ethanol solvent at reflux. After the Michael addition of the deprotonated methyl to the electron poor alkene, malononitrile is eliminated by intramolecular substitution. The intermediate 3,4-dihydro compounds 27 are aromatized in situ to the final products 28 (6 examples, 70–75% yield) by ambient oxygen (Scheme 6) [23,24]. A similar entry to analogs of 28 (6-C(CN)2 instead of 6-oxo) by Knoevenagel condensation of 4-methyl-6-dicyanomethylpyridones with aromatic aldehydes was reported [25].
2.1.2. Starting from Pyridazine Derivatives

Pyridopyridazine-3,8-dione 31 was prepared from 4-methyl pyridazine-6-one 29 [26] by a strategy involving condensation of the methyl group with DMFDMA, followed by treatment of enamine intermediate 30 with aniline. On the other hand, the condensation of the 4-ethyl analog of 29 with DMFDMA and subsequent hydrolysis gave ring closure involving the 5-cyano group or the hydrolyzed carboxamide, giving access to isomeric pyrido[3,4-\(d\)]pyridazinone derivatives (Scheme 7).

Several variants on this condensation/cyclization strategy starting from pyridazinones have been reported [27–29], leading to different pyridopyridazinedione derivatives 32–34 (Figure 2). Compounds 32a,b were obtained in poor yield (around 10%) from the condensation of 2-(arylhydrazono)-3-oxobutyrate with two equivalents of ethyl cyanoacetate. Pyridazinones analogous to 29a,b (Ar = 3,4-dimethylphenyl or 3-chloro-4-methylphenyl) were the main isolated products (70% yield), but also the intermediates towards 32a,b, via an aldol-type of condensation of 29 to a second equivalent of the hydrazine and cyclization were obtained. The structure of 32a,b was confirmed by an extensive NMR study [27]. Condensation of 29 (Ar = 4-methylphenyl) with triethyl orthoformate and 4-methylaniline in the presence of piperidine gave further analogs of 31, while condensation of enamine 30 (piperidine instead of dimethylamino) with hydrazine gave the 7-amino derivative 33 [28]. The hydrazones derived from aromatic aldehydes and the carbohydrazide derivative of 29 (Ar = 4-MeOC$_6$H$_5$) were involved in a Knoevenagel condensation/cyclization, affording hydrazones 34 with different combinations of the two aryl groups Ar’ and Ar” [1997PSS]. Further examples of analogues of 31–34 prepared similarly from derivatives of 29 have been reported in the literature [30–32].
The 4,6-dichloropyridazine-3-carboxylate 35 could be converted via regioselective nucleophilic substitution at the 4-position with t-butyl ethyl malonate and acid-catalyzed decarboxylation of intermediate 36 to the diester 37. Subsequent cyclocondensation of 37 with ammonia in methanol lead to the dihydroxypyridopyridazine 38. This compound was brominated to a trishalogenated pyridopyridazine derivative 39, which then was converted in a number of synthetic steps, involving nucleophilic substitutions at positions 3 and 8 (reactivity towards nitrogen nucleophiles apparently selective in this order) and then Suzuki arylation on the remaining 6-bromide (Scheme 8). The final compounds were tested as HPK1 inhibitors, of interest in the treatment of certain cancers [33].

Scheme 8. Synthesis of 3-chloro-6,8-dibromopyridopyridazine.

2.1.3. Starting from Other Building Blocks

Hetero Diels-Alder cycloaddition of 1,2,4,5-tetrazine-3,6-dicarboxylate 40 with the enamine tautomers of cyclic imines such as 5,5-dimethylpyrrole 41 led to fused pyridazine 42 (28% yield) via non-isolable cycloadducts that extruded dinitrogen, then underwent aromatization with liberation of the amine that then formed a lactam with one of the two esters. Likewise, pyridazine 43 was formed in a 52% yield from 2-phenylpyrrole (Scheme 9) [34].
2.2. Tricyclic Derivatives

2.2.1. Benzo Fused Tricyclic Derivatives Starting from Quinolines

4-Acetyl-3-amino-2-phenylquinoline $44$ ($R = H$) was diazotized with nitrous acid and ring closed in alkaline medium, forming the pyridazino[3,4-c]quinoline named 4-hydroxy-10-phenyl-1,2,9-triazaphenanthrene by the authors (more probable the oxo tautomer $45$ shown). The Borsche reaction product $45$ was obtained in 80% yield on a 10 g scale by precipitation from the reaction mixture. Chlorination of $45$ with phosphorous pentachloride gave the chloro derivative $46$, which could then be converted to a number of derivatives $47$ by nucleophilic substitution $[35,36]$. Some of the above reactions were also carried out on the 4-propionyl derivative $44$ ($R = Me$). Methylation of the compound $45$ occurred regioselectively on one of the pyrazine nitrogens, affording a zwitterionic pyridazinoquinoline $48$. Widman-Stoermer reaction starting from 4-alkenyl-3-aminoquinoline substrates as shown before for the synthesis of bicyclic pyridopyridazines $10$ analogously gave the tricyclic derivatives $49$, in low to good yields $[10]$ (Scheme 10).

![Scheme 9. From tetrazines to pyridopyridazines.](image)

![Scheme 10. Borsche and Widman-Stoermer reactions leading to pyridazinoquinoline derivatives.](image)
Starting from the 3-aminobenzazepine-2,5-dione derivative 50, nitrosation was accompanied by a ring contraction, leading to diazo compound 51, which in acidic medium underwent a Borsche-like cyclization to form tricyclic pyrazinoquinolinedione derivative 52 in almost quantitative yield. However, there seems to be only this one example in the literature of this interesting transformation [37] (Scheme 11).

Scheme 11. Pyridazinoquinolines via diazotation, ring contraction and cyclization.

2.2.2. Benzo Fused Tricyclic Derivatives Starting from Pyridines

Diazotation of 4-aryl-3-aminopyridine derivatives 53 resulted in intramolecular electrophilic substitution of the very electron rich 3,4,5-trimethoxyphenyl substituent to afford the tricyclic pyrido[3,4-c]cinnolines 54 in 64–84% yield, similar to the Widman-Stoermer approach whereas for other less electron rich aryl groups the diazonium salt can be used without such cyclization to prepared azides, that then were thermolysed in xylene to carboline derivatives 55 (Scheme 12) [38].

Scheme 12. Cyclization of diazonium salts to pyridocinnolines.

Photocyclization of 3-phenylazopyridine 56 (R=H) in concentrated sulfuric acid by irradiation at 400–450 nm gave a low yield (19%) of the pyrido[3,4-c]cinnoline 57, together with an even smaller amount of the [3,2-c] fused isomer 58. Both isomers were subjected to vacuum pyrolysis at 800 °C, giving the respective azabiphenylenes 59 (58%) and 60 (34%) after dinitrogen extrusion [39]. In a later study, the hydrochloride salt of the diamino analog of 56 (R = NH₂) was irradiated with a 400 W medium pressure mercury vapor lamp in a dilute methanol solution, affording 35% of the product 57 (R = NH₂), together with small amounts of several products resulting from N-N cleavage [40] (Scheme 13).
Scheme 13. Pyridocinnolines by photocyclization.

Static pyrolysis of 2,6-diaryl-3-cyano-5-phenylazopyridine 61a–c at 400 °C gave low yields of pyridocinnolines 62a–c (3–14%) next to N-N reduction products 63a–c (20–51%) and aniline 64 (21–57%) (Scheme 14) [41].

Scheme 14. Pyridocinnolines by static pyrolysis.

In an early study, formazan 65 was oxidized to a tetrazolium salt 66, which upon irradiation with an ultraviolet high pressure immersion lamp PL 313 at 25° cyclized to the fused tetrazolium salt 67. The reduction in the latter gave the parent pyridocinnoline 57 (R = H) [42] (Scheme 15).

Scheme 15. Synthesis of pyridocinnoline by reduction in tetrazolium salt.
2.2.3. Benzo Fused Tricyclic Derivatives Starting from Cinnolines, Pyridazines or Tetrazines

Moreover, 3-Bromocinnoline-4-one 68 could be substituted with copper cyanide to the nitrile 69, and the latter was chlorinated to 4-chloro-3-cyanocinnoline 70. Nucleophilic aromatic substitution of 70 with acetylacetone, and base-catalysed hydrolysis to the amide and ring closure then gave the pyridocinnolinone 71 in a 38% yield [43] (Scheme 16).

![Scheme 16. Benzofused tricyclic derivatives from cinnolines.](image)

Reductive cyclization of 4-(2-nitrophenyl) -pyridazine-3-carboxylate esters 72 with iron in acetic acid gave the lactams 73. However, when the reduction was carried out with zinc and ammonium chloride, the hydroxamic acid derivative 74 was isolated. (Scheme 17). The inhibition of soybean 5-lipoxygenase was tested for the latter compounds and found to be only weak [44,45].

![Scheme 17. Reductive cyclization leading to pyridazoquinolinones.](image)

Inverse Diels-Alder reaction of N-methylindole 74 with 1,2,4,5-tetrazine-3,6-d-carboxylate 40 in dichloromethane at reflux gave after nitrogen extrusion a ring opening/ring closure sequence, giving another entry into pyridazoquinolones 75. [46] (Scheme 18). The reaction was also carried out on 2,2′-bis-N-methylindolyl, affording protein kinase C inhibitors [47].

![Scheme 18. Inverse Diels-Alder reaction leading to pyridazoquinolinones.](image)
2.2.4. Heterocycle Fused Tricyclic Derivatives

Reduction of 2,2′-dinitro-4,4′-bipyridyl 76 with sodium sulfide initially led to a 3:1 mixture of bispyridopyridazine 77 (59% yield) and its N-oxide 78. The latter could be deoxygenated with iron at 250 °C. [48] The reduction with sodium sulfide could be optimized later to give 89% of only 77. Reduction of 76 with arsenuous oxide gave the N, N′-oxide 79, whereas the Pd/C catalyzed hydrogenation gave the diamine 80 [49]. The bispyridopyridazine 77 was used in these and many subsequent studies for the synthesis of 2,7-diazabiphenylene 81 in a 57% yield [50] by extrusion of nitrogen under different vacuum pyrolysis conditions. The bispyridopyridazine 77 can also be prepared from diamine 80 by diazotation in a 38% yield [51]. The reaction sequence in Scheme 19 was also used to prepared unsymmetrically fused bispyridopyridazine 82 by reductive cyclization of the corresponding ortho, ortho′-dinitro-2,4′-bipyridine [52].

Scheme 19. Synthesis of Bispyridopyridazines.

Widman-Stoermer type cyclization of 3-pyridyl diazonium salts involving the electrophilic substitution of electron rich five membered rings placed at the 4-position, similar to Scheme 12, was carried out successfully, affording different pyridopyridazines fused with thiophens (83, 85% yield and 84, 72% yield), pyrroles (85, 77% yield) and furans (86, 76% yield) [53,54] (Figure 3).

Figure 3. Pyridopyridazines fused with five-membered rings.

An isomeric pyrrolo fused pyridopyridazine 89 was prepared by reducing 5-nitro-4-acetyl-8-azaindole 87 and applying the Borsche cinnoline reaction on the obtained amine 88 after nitrosation and cyclization. Chlorination of 88 with phosphoryl chloride in chloroben-
zene gave the building clock 90, that was used in a study of treatment of diseases that are mediated by JAK activity [55] (Scheme 20).

![Scheme 20. Pyrrolo fused pyridopyridazine.](image1)

A 1,2,4-triazolo fused pyridopyridazine has been reported. The enamine 91, prepared from 29 (Ar = 4-Me-phenyl) by condensation with triethyl orthoformate and piperidine, was condensed with 2-cyanoacetohydrazide by heating at reflux in dimethyl formamide solution, to afford tricyclic 92 in a 71% yield [28] (Scheme 21).

![Scheme 21. 1,2,4-Triazolo fused pyridopyridazine.](image2)

An interesting diastereoselective synthesis of partially reduced triazoledione fused pyridopyridazines 95 was reported by Diels-Alder cycloaddition of 4-vinyl-1,2,5,6-tetrahydropyridine dienes 93 with N-phenyl-1,2,4-triazoledione dienophile 94. The reactions proceeded within a few hours at low temperature with good to excellent chemical yields (7 examples, 67–97%) and very good diastereoselectivities (>20:1) [56] (Scheme 22).

A special case of a pyridine fused pyridopyridazine salt 98, called the 8a-azonia-3,4-diazaphenanthrene cation by the authors, was available in a 36% yield as the only product obtained after hetero-Diels-Alder cycloaddition of 3,6-(2-pyridyl)-1,2,4,5-tetrazine 96 with cis-3,4-dichlorocyclobutene. The expected product 97 was not isolated, but under the reaction circumstances it is probable that ring opening of cyclobutyl/ring closure involving pyridine nitrogen occurs, finally affording 98. The structure of the salt 98 was proven unambiguously by single crystal X-ray crystallographic analysis [57] (Scheme 23).
2.3. Polycyclic Derivatives

Pentacyclic analogs 99 or their N-oxide analogs could be prepared from bis(nitroquinolines) similarly to the chemistry in Scheme 19 [48]. Thermolysis of 99 led to the condensed derivative 100 [49]. In a series of publications, thebaine or other morphinanediene derivatives were combined in a room temperature Diels-Alder reaction with diazodicarboxylate, triazole dione or other cyclic diazo dienophiles, to afford diverse complex polycyclic derivatives 101 that strictly speaking contain a reduced pyridopyridazine but are somewhat out of the scope of this review. A β-face attack of the dienophile occurs in the case of the natural products containing a furan ring, whereas the derivatives with opened furan favor α-attack [58–61]. No biological properties seem to have been reported for these compounds (Figure 4).

![Scheme 22. Triazolo fused (reduced)pyridopyridazines by Diels-Alder reaction.](image1)

![Scheme 23. Pyridine fused pyridopyridazine salt.](image2)

![Figure 4. Different polycyclic pyridopyridazine derivatives.](image3)
3. Conclusions

The pyrido[3,4-c]pyridazines and their fused derivatives remain rare chemicals and the reports that have appeared so far are widely scattered, with often only a few examples given in low or only fair yield without any follow-up studies to widen the scope. Therefore, applications of this scaffold as biologically active compounds have been limited. To make further advances and to realize the recognized potential of this moiety in medical chemistry, more attention should be given in the future to apply new advances in organic synthesis, including transition metal catalyzed reactions, as well as organocatalytic, photocatalytic and electrocatalytic processes. We hope to meet this challenge in following reports of our laboratories; it was also our aim to have stimulated further research by our colleagues in the field of heterocyclic and medicinal chemistry.

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