ADVANCES IN THE SYNTHESIS OF SUBSTITUTED PYRIDAZINES VIA INTRODUCTION OF CARBON FUNCTIONAL GROUPS INTO THE PARENT HETEROCYCLE*

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Abstract — Methods for the convenient synthesis of various simple pyridazine derivatives based on Minisci-type reactions are reviewed. Due to the pronounced regioselectivity of radicalic attack at C-4 and/or C-5 of the protonated 1,2-diazine system homolytic substitution reactions with nucleophilic carbon-centered radicals permit an experimentally easy access to pyridazinecarbaldehydes and C-alkyl or C-alkoxycarbonyl derivatives thereof (via trioxanylpyridazines), alkyl and aryl pyridazinylketones (via acyl- or aroylpyridazinecarboxylic acids), pyridazinedicarboxylic acid esters, C-alkylpyridazine monocarboxylic acid esters and α-N-amidoalkylpyridazines. The reactivity and the synthetic utility of these classes of compounds are discussed briefly.
In addition, syntheses of 3-pyridazinecarbonitrile and 4- or 6-alkyl derivatives thereof are described. These compounds are readily obtained via N-arylsulfonyl Reissert compounds.

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*Dedicated with the best wishes to Professor Miha Tišler, Department of Organic Chemistry, University of Ljubljana, on the occasion of his 60th anniversary.

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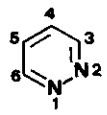
1. INTRODUCTION

The chemistry of the pyridazine system 1 continues to attract considerable attention.[1] Also the biological activities of these compounds met with an increasing interest since in 1971 for the first time pyridazine derivatives were found in nature.[2] It is worth mentioning that quite recently another naturally occurring 1,2-diazine derivative (nigellicine 2[3]) has been described.[4]



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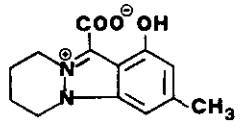

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From the point-of-view of medicinal chemistry the pyridazine system additionally seems to be of interest with regard to its exceptionally high dipole moment (3.95D). One can expect that replacement of a carbocyclic or heterocyclic aromatic moiety by the pyridazine nucleus in a bioactive molecule would alter the physicochemical characteristics of the latter significantly and hence also its pharmacodynamic as well as pharmacokinetic qualities. As an illustrative example may serve the drastical decrease of toxicity which can be achieved by replacing a pyridine nucleus in antiulcer-acting 2,2-diarylthioacetamides by the 1,2-diazine system.[5]

Based on these considerations, our interest in the last decade was focussed on experimentally simple reactions permitting the introduction of various functional groups into the parent ring system in order to gain access to important synthetic building blocks, which so far were not described or were only available by cumbersome multistep procedures. The present paper summarizes the results obtained in the author's laboratory from investigations of Minisci-type and Reissert-type reactions with commercially available or easily accessible pyridazines. In addition, some reactivities and the synthetic utility of the novel classes of compounds obtained are discussed briefly.

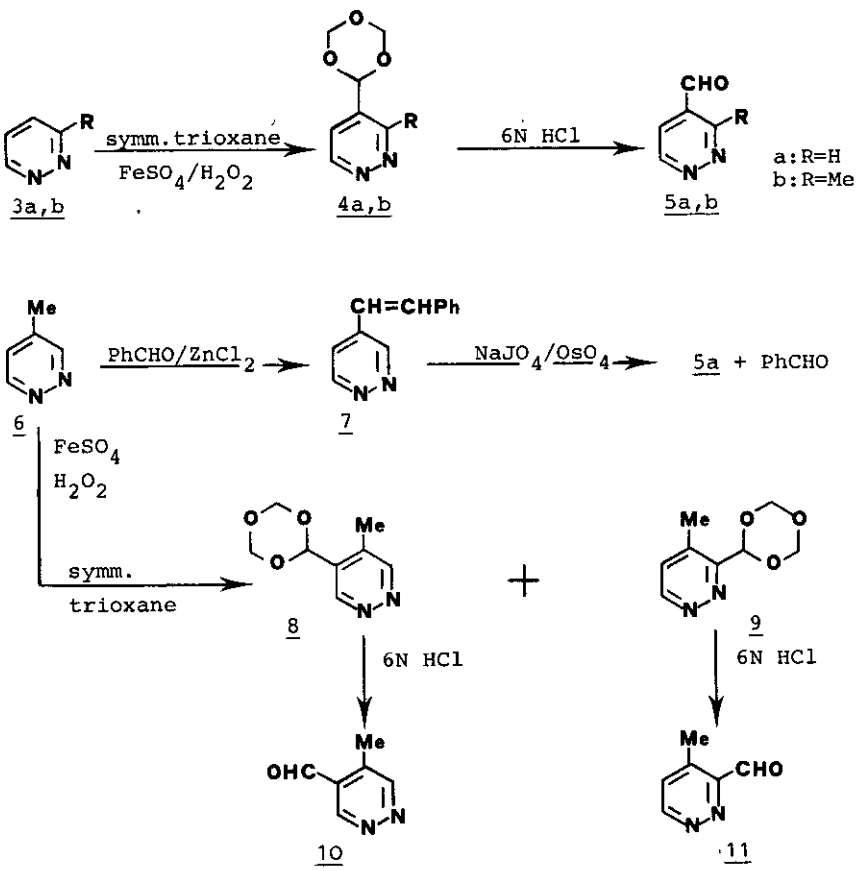
2. REGIOSELECTIVITY OF RADICALIC ATTACK AT THE 1,2-DIAZINE SYSTEM

The concept of reacting protonated π-deficient heteroaromatics with nucleophilic carbon radicals developed by Minisci and co-workers[6] represents a most effective tool for the regioselective introduction of a wide variety of carbon side chains into the α- and/or γ-positions of six-membered N-heteroaromatic systems. Prior to our work there were only few reports dealing with reactions of the 1,2-diazine system with carbon-centered radicals.[7-13] From these investigations and the results outlined below, it becomes evident that there exists a marked difference between pyridazine and other π-deficient N-heteroaromatics with respect to the site-selectivity of the radicalic attack. Not only the (non-nucleophilic) phenyl radical[7,8] but even carbon radicals with pronounced nucleophilic character (e.g. ·COR, ·COOR) attack the 1,2-diazine system preferentially at the ß-positions (C-4, C-5). The ring carbon atoms of lowest electron density (C-3, C-6) are attacked only to a minor degree or not at all.[14] Based on these observations various C-4 substituted or C-4, C-5 disubstituted pyridazines now can be prepared conveniently as shown in Sections 3-6.

3. HOMOLYTIC α-ALKOXYALKYLATION

3.1 Preparation of 4-formylpyridazines

Reactions of pyridazine (3a) and 3-methylpyridazine (3b) with symm. trioxanyl radicals, generated from 1,3,5-trioxane/ ferrous sulfate/ hydrogen peroxide following a reported procedure,[16] are characterized a) by exclusive attack of the radicals at positions ß to a nitrogen atom, b) by the formation of only small amounts of ß,ß'-disubstituted products, obviously due to steric reasons [17] (Scheme 1). Pyridazinecarbaldehydes 5a, 5b are obtained smoothly upon acidic hydrolysis of the trioxanylpyridazines 4a and 4b, respectively.[17] In a similar manner the formylmethylpyridazines 10, 11 can be prepared via the methyltrioxanylpyridazines 8, 9, which are the predominant products in the reaction of the symm. trioxanyl radical with 4-methylpyridazine 6.[17] Caused by low conversion rates in these homolytic substitution reactions, which hitherto could not be raised above 30%,[18] the overall yields of carbaldehydes 5a, 5b, 10, 11 are only low to moderate. However, it has to be pointed out that these syntheses start with commercially available or easily accessible materials and that the unreacted heteroaromatics can be recovered conveniently from the reaction mixtures. In addition, the reaction sequence 3a → 4a → 5a displayed in Scheme 1 is advantageous to the procedure initially proposed for the preparation of pyridazine-4-carbaldehyde[19] (6 → 7 → 5a) since employment of toxic osmium tetroxide is avoided. Furthermore, for the preparation of formylpyridazines bearing additional alkyl groups traditional synthetic methods at all events might not be applicable.



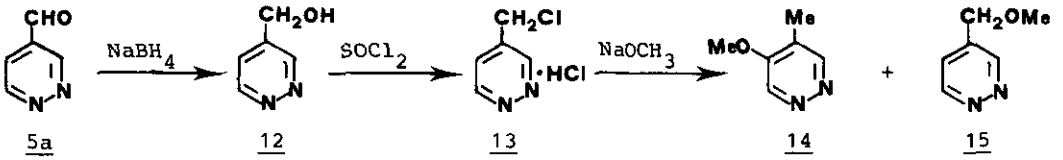
Scheme 1

On the other hand, for the synthesis of alkoxycarbonyl-trioxanylpyridazines (e.g. ethyl 5-trioxanyl-4-pyridazinecarboxylate) homolytic ethoxycarbonylation of a trioxanylpyridazine seems to be superior to trioxanylation of a pyridazinecarboxylic acid ester since in alkoxycarbonylations the conversion rates can be enhanced significantly by applying appropriate reaction conditions (see Section 6.2).

3.2 Reactivity and synthetic utility of 4-formylpyridazines

4-Pyridazinecarbaldehyde 5a undergoes the Cannizzaro reaction on treatment with aqueous potassium hydroxide,[19] and reduction employing sodium borohydride affords 4-hydroxymethylpyridazine 12 quantitatively. The latter can be transformed into chloromethylpyridazine 13 in high yield by reaction with thionyl chloride in absence of a solvent.[20] This procedure so far represents the only method permitting the preparation of simple 4-(α-halogenoalkyl) pyridazines. Interestingly, compound 13 is attacked by methoxide ion at C-5 rather than at the carbon atom of the side chain,[15] thus affording 4-methoxy-5-methylpyridazine 14 in 45% yield.

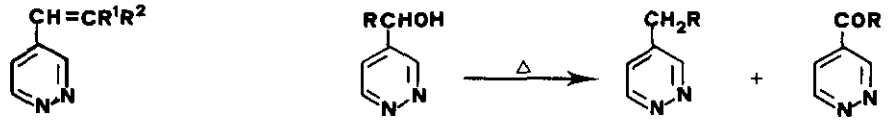
Accordingly, side-chain halogenated pyridazine derivatives like 13 might be expected to be valuable starting materials for various 4-alkylpyridazines bearing an additional O-, S- or N-substituent at C-5. (compare Section 5.3)



5a 12 13 14 15

Scheme 2

The aldehyde groups in the 4-formylpyridazines 5a, 5b, 10 exhibit a high tendency to undergo addition reactions. Stable geminal diols have been obtained from these compounds.[17,19,21] Addition of C-H acids was found to take place under mild conditions,[17,19] starting from aldehyde 5a, compounds 16a-c were prepared.[19,21] However, it should be pointed out that 4-pyridazinylmethanols 17 generally dismutate at elevated temperatures affording mixtures of a 4-alkylpyridazine (18) and a 4-pyridazinylketone (19).[22] Therefore, frequently the products of thermally induced disproportionation are obtained on attempted dehydratation of the intermediate alcohols in aldol-type reactions of 4-formylpyridazines instead of the usual condensation products.[22,23]

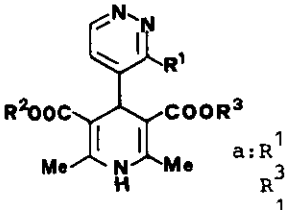


16a-d 17 18 19

	R^1	R^2
a:	H	COOH
b:	CN	COOMe
c:	CN	CN
d:	H	CHO

Scheme 3

However, this problem can be overcome by employing Wittig-type reactions, as shown in the high-yield synthesis of 3-(4-pyridazinyl)propenal (16d).[24] Whereas attempts to obtain simple condensation products of 4-formylpyridazines and ß-ketocarboxylic acid esters so far failed,[21] Hantzsch-type 4-(4-pyridazinyl)dihydropyridines of type 20a,b can be prepared without difficulties.[25]

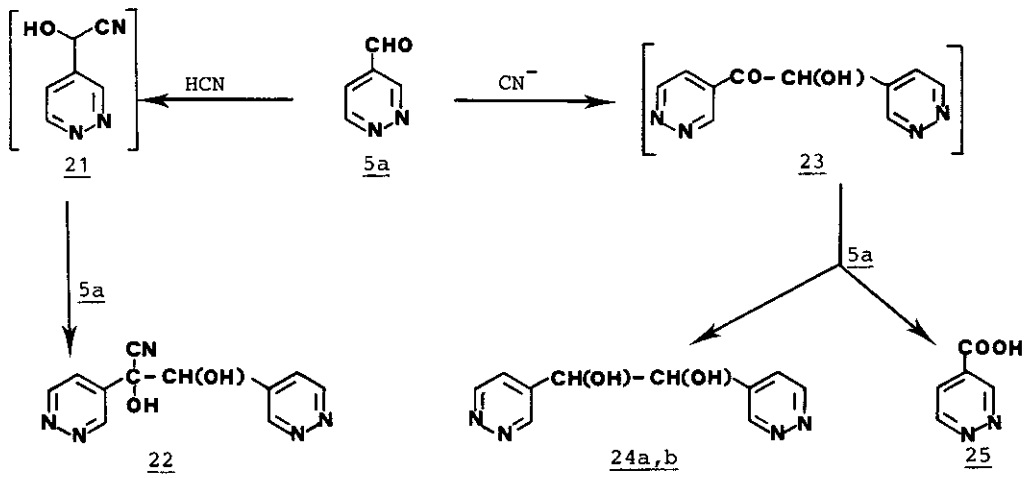


20a,b

a: R^1=H R^2=alkyl R^3=alkyl

b: R^1=Me R^2=alkyl R^3=alkyl

The cyanohydrin 21 could not be obtained yet, since under various reaction conditions, 21 adds to unchanged 4-pyridazinecarbaldehyde affording compound 22 in nearly quantitative yield.[19] The aldehyde 5a shows an unusual behaviour also under conditions of the benzoin-reaction. A mixture of stereoisomeric diols 24a,b and 4-pyridazinecarboxylic acid 25 is obtained. It was shown that these products result from a redox reaction of initially formed 4-pyridazoin 23 with unchanged 5a.[26]



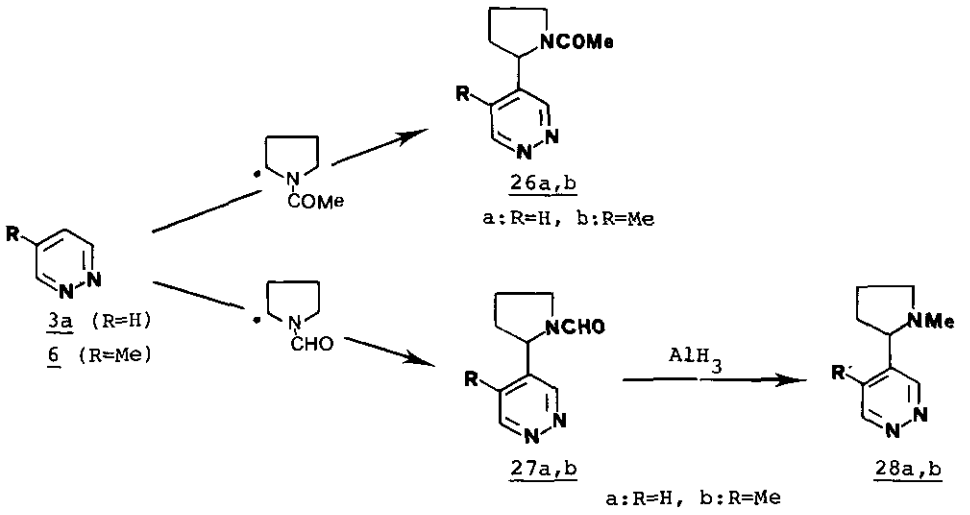
(a:meso form, b:racemic form)

Scheme 4

Condensation reactions of 4-formylpyridazines with NH-compounds obviously can be carried out without any difficulties.[19]

4. HOMOLYTIC α-N-AMIDOALKYLATION

The only report so far available on reactions of the protonated 1,2-diazine system with α-N-amidoalkyl radicals[27] indicates strict regioselectivity of the radicalic attack, which is restricted to only one ß-position, obviously due to the steric requirements of the N-acyl-2-pyrrolidinyl group employed. 4-Methylpyridazine 6 exclusively affords compounds 27b and 26b when subjected to reactions with 1-formylpyrrolidine/$(NH_4)_2S_2O_8$/ferrous sulfate or N-acetylproline/$(NH_4)_2S_2O_8$/ silver nitrate in the presence of sulfuric acid. Pyridazine 3a gives compounds 27a and 26a, respectively, as sole products. When the reaction with 1-formyl-2-pyrrolidinyl radicals is carried out employing 3-methylpyridazine (3b), a C-4 substituted compound as well as a C-5 substituted product is obtained.[28]



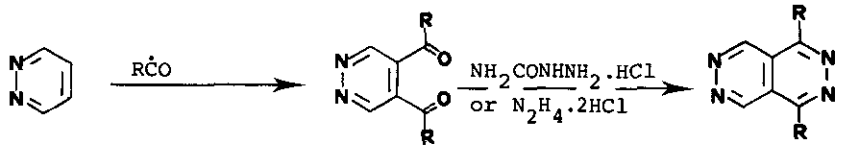
Scheme 5

Since the formyl groups in compounds 27a,b can be reduced smoothly by aluminium hydride,[28] the reaction sequence displayed in Scheme 5 provides an easy access to "aza-nicotine" 28a and related compounds like 28b. The general utility of this convergent approach to nicotinoids was discussed recently.[28]

5. HOMOLYTIC ACYLATION

5.1 Preparation of 4,5-diaroyl- and 4,5-dialkanoylpyridazines

Also aroyl radicals attack the protonated pyridazine system exclusively at the positions ß to the nitrogen atoms. 4,5-Diaroylpyridazines 29a-c can be prepared by reacting pyridazine in acidic solution with aromatic carbaldehydes in the presence of ferrous sulfate/tert. butylhydroperoxide in satisfactory yields.[29,30]

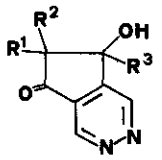


3a 29a-e 30a-d

a:R=Ph, b:R=4-MeOPh, c:R=3,4-diMeOPh
d:R=i-prop., e:R=prop.

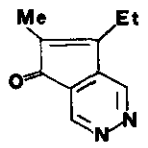
Scheme 6

Similarly, reactions of pyridazine with aliphatic acyl radicals are characterized by the occurrence of 4,5-disubstituted products. However, the initially formed diacylpyridazines 29d,e undergo intramolecular aldol-type reactions with remarkable ease due to activation of the CH-moiety adjacent to the pyridazinylcarbonyl group. Accordingly, cyclopenta[d]pyridazines 31a,b and 32 are obtained unless precautions are taken up during isolation of compounds 29d,e from the reaction mixtures.[30] Compounds 29a-d can be utilized to prepare 1,4-disubstituted pyridazino[4,5-d]pyridazines 30a-d[30] and various pyrido[3,4-d]pyridazine derivatives.[31]



31a,b

a: R^1=H, R^2=Me, R^3=Et
b: R^1=Me, R^2=Me, R^3=i-prop.



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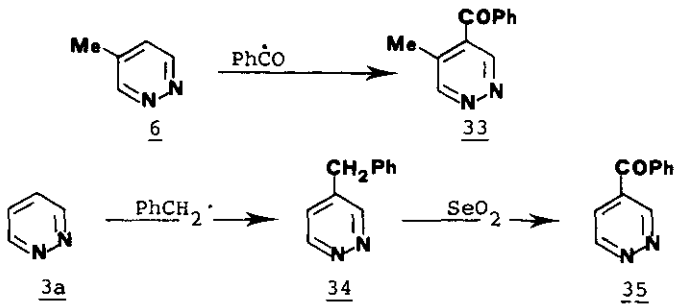
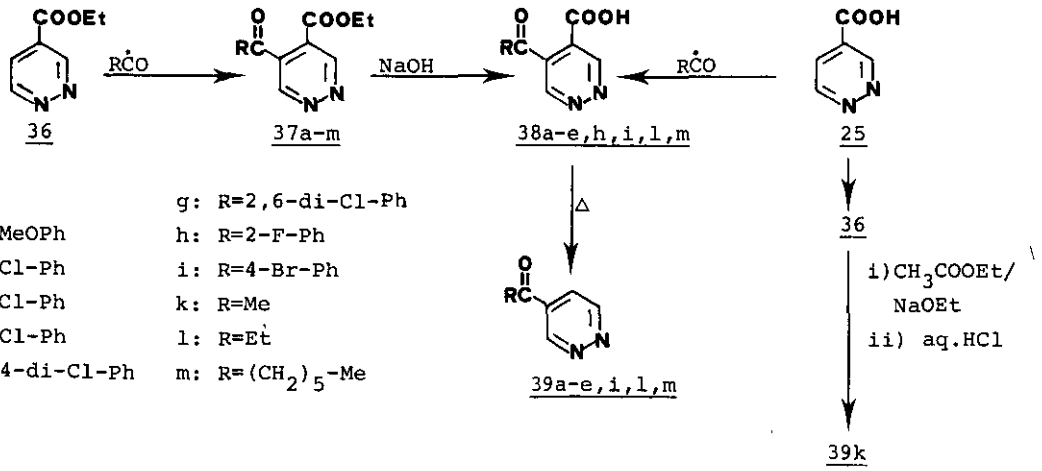
5.2 Preparation of aryl and alkyl 4-pyridazinyl ketones

Although benzophenones and their aza-analogs (aryl pyridyl ketones) represent important building blocks in the synthesis of many biologically active compounds, no efforts have been made to prepare aryl 4-pyridazinyl ketones prior to our work. Minisci-type aroylation reactions[6] starting with the parent heterocycle, cannot be employed in the synthesis of these compounds, since introduction of one aroyl group strongly activates the pyridazine system towards attack of a second aroyl radical as shown in Section 5.1. Attempts to suppress disubstitution by avoiding an excess of the aroyl radical so far met with limited success, since under these conditions the conversion rates are decreasing drastically.[32] Thus, only if one ß-position is occupied by a substituent (e.g. an alkyl group) radicalic aroylation is a suitable method for preparing monoaroylpyridazines like 33.[33]
In contrast to the reactions of protonated pyridazine derivatives with methyl radicals (generated from acetic acid or by redox reaction of ferrous sulfate/tert-butylhydroperoxide) which are characterized by a comparably low degree of regioselectivity,[34] homolytic benzylation of pyridazine yields 4-benzylpyridazine 34 exclusively.[29] Thus, reaction of 3a with benzyl radicals (generated by Ag^+-ion-catalyzed oxidative decarboxylation of phenylacetic acid[6]) and subsequent oxidation of 34 by selenium dioxide initially was proposed to prepare 4-benzoylpyridazine 35.[29] However, this procedure is limited in scope with regard to the availability of appropriately substituted phenylacetic acids and affords the desired products in only moderate yields.



Scheme 7

A convenient general method for the preparation of 4-aroylpyridazines[32] is shown in Scheme 8. It is based on the well known tendency of pyridazinecarboxylic acids to decarboxylate at elevated temperature, particularly when bearing additional electron-withdrawing substituents.[35] Since the ethoxycarbonyl group in ethyl 4-pyridazinecarboxylate 36 not only protects one of the ß-positions of the pyridazine nucleus against radicalic attack but also enhances the reactivity of the second ß-carbon atom towards nucleophilic radicals, ethyl 5-acyl-4-pyridazinecarboxylates 37 can be prepared in high yields by reacting 36 with acyl or aroyl radicals. Alkaline hydrolysis of the esters 37 affords quantitatively the ketocarboxylic acids 38.



Scheme 8

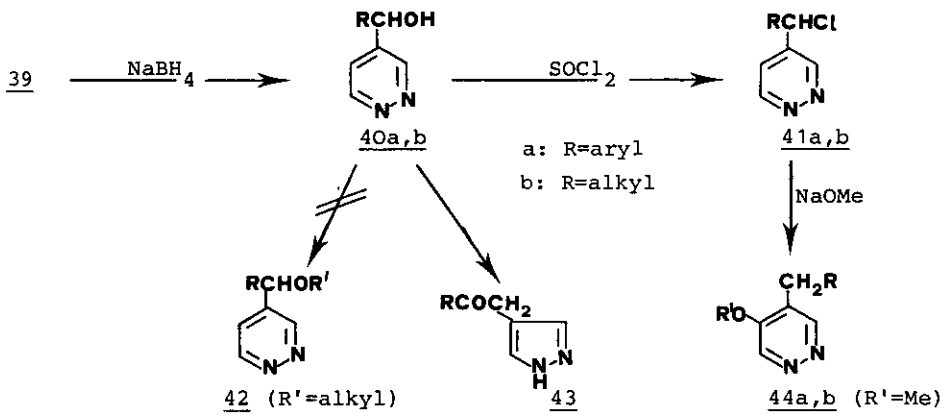
Homolytic acylation of 4-pyridazinecarboxylic acid 25 provides an even more efficient access to compounds 38, since the latter generally precipitate from the reaction mixtures due to the enhanced lipophilicity caused by introduction of an aroyl group into 25.[36] The final reaction step, i.e. thermally induced decarboxylation, then affords pure aryl 4-pyridazinyl ketones 39a-e,i in satisfactory yields.[32]

The procedure described can also be employed in the synthesis of alkyl 4-pyridazinyl ketones like 39 l,m.[32] Only for preparing methyl 4-pyridazinyl ketone the traditional approach 25 → 36 → 39k,[37] displayed in Scheme 8, at present seems to be the more appropriate method.

5.3 Reactivity and synthetic utility of aryl and alkyl 4-pyridazinyl ketones

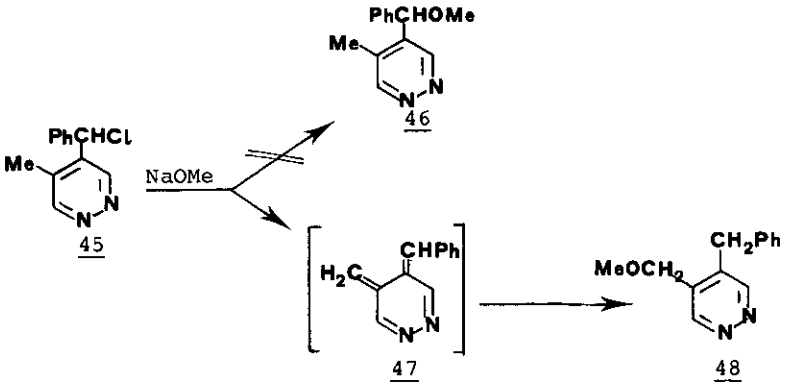
Aryl and alkyl 4-pyridazinyl ketones 39 are reduced smoothly by sodium borohydride affording alcohols of type 40a,b.[20,29,33] The "diaza-benzhydrols" 40a can be transformed readily into the diarylmethyl chlorides 41a by treatment with thionyl chloride.[15] However, attempts to prepare alkyl ethers 42 starting from alcohols 40a under various commonly used conditions so far remained unsuccessful. A novel type of pyridazine ⟶ pyrazole ring contraction, resulting in formation of 1-aryl-2-(4-pyrazolyl)ethanones 43 (R=Ph or R=4-MeOPh), was found to take place, when compounds 40 (R=Ph or R=4-MeOPh) were treated with 4-toluenesulfonic acid at elevated temperature.[33]

Since diarylmethyl chlorides 41a,b are attacked by alkoxide ions predominantly at the ring carbon atoms of position 5, thus yielding 4,5-disubstituted pyridazines 44,[15] also these compounds do not represent suitable precursors for diaza-benzhydryl ethers 42.



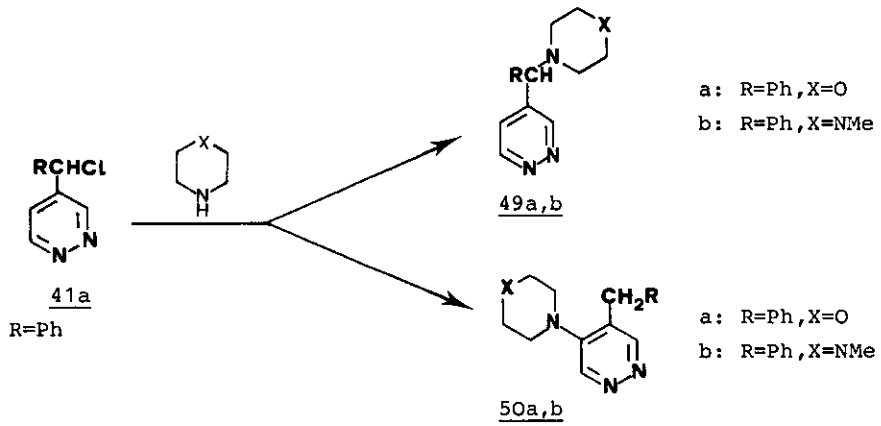
Scheme 9

It seems of interest to note that even with compound 45 action of methoxide ion does not result in the formation of the ether 46, despite the fact that position 5 in this case is occupied by a substituent. The structure of the product obtained in 70% yield was established as 48.[15] A plausible explanation for the occurrence of 48 as the sole product might be 1,4-addition of methanol to a reaction intermediate 47 initially formed by abstraction of a proton from the methyl group in 45, followed by loss of chloride.



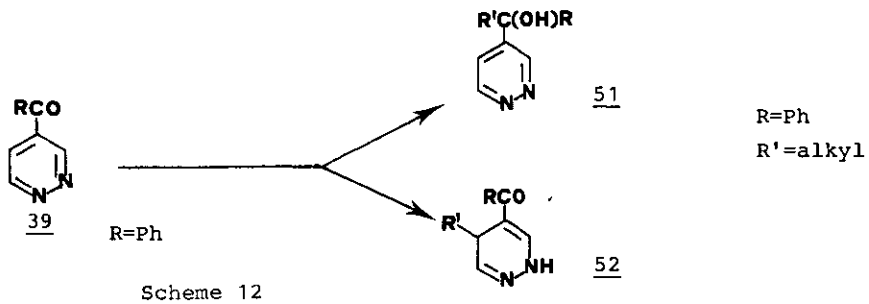
Scheme 10

In contrast to the findings with alkoxide ions, reactions of compounds 41a with secondary amines are characterized by preferential attack of the nucleophile at the side chain; C-5 substituted compounds 50 are formed only to a minor degree.[15]



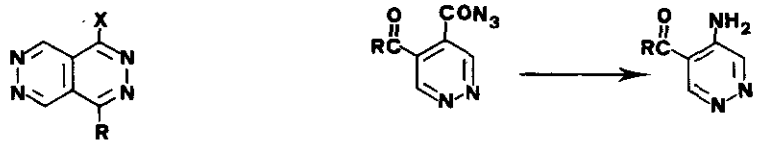
Scheme 11

Tertiary alcohols of type 51 are readily obtained from ketones 39 upon action of Grignard or alkyllithium compounds.[33] From the preparative point-of-view the latter reagents seem to be more appropriate, since substantial amounts of by-products (resulting from attack of the carbanion at C-5 of the 1,2-diazine system) are formed in reactions with alkylmagnesium halides.



Scheme 12

5-Acyl-4-pyridazinecarboxylic acids 38 and functional derivatives thereof (e.g. acid chlorides, acid azides, esters, amides, oximes) have been studied in some detail.[32,38] The esters 37 have been shown to be versatile starting materials in the synthesis of various 4-alkyl- and 4-arylpyridazino[4,5-d]pyridazine derivatives 53.[32,39] Curtius degradation of the acid azides 54 provides a convenient access to diaza-o-aminobenzophenones of type 55.[38]



53 R=alkyl, aryl X=OH, SH, Cl, NR^1R^2

54 R=aryl

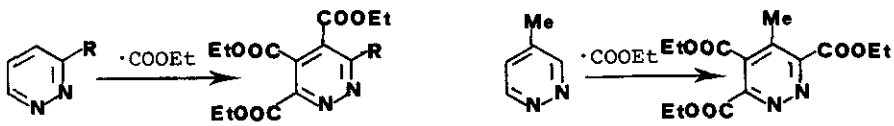
55 R=aryl

Scheme 13

6. HOMOLYTIC ALKOXYCARBONYLATION

6.1 Preparation of pyridazinetricarboxylic acid esters

The regioselectivity of attack of the ethoxycarbonyl radical at the pyridazine nucleus has been found[40] to be comparably low under reaction conditions usually employed in Minisci-type alkoxycarbonylations (redox decomposition of oxyhydroperoxide of ethyl pyruvate[41]). Accordingly, the ethoxycarbonyl group is also introduced into positions α to the nitrogen atoms (at least if both ß-positions are occupied by substituents) when a pyridazine:peroxide ratio of 1:3 is employed in order to provide reasonable conversion rates. Based on this observation a convenient procedure was proposed affording triethyl tricarboxylates derived from pyridazine and C-3 or C-4 alkyl derivatives thereof. Compounds 56a,b and 57 are readily obtained by simply applying a base:peroxide ratio of 1:10.[40]



3a,b 56a,b 6 57

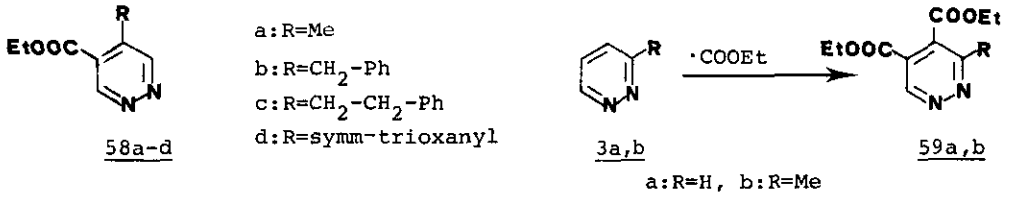
a: R=H
b: R=Me

Scheme 14

6.2 Preparation of C-5 substituted 4-pyridazinecarboxylic acid esters and 4,5-pyridazinedicarboxylic acid esters

A marked enhancement of regioselectivity can be achieved by performing homolytic ethoxycarbonylation reactions with 1,2-diazine derivatives in a two-phase system.[40] Since formation of polysubstitution products can be suppressed drastically when reactions with 4-alkylpyridazines (base:peroxide ratio 1:3) are run in the presence of methylene chloride, the corresponding ethyl 5-alkyl-4-pyridazinecarboxylates 58a,b,c result in satisfactory yields.[40,42] The same procedure can be used to prepare ethyl 5-trioxanyl-4-pyridazinecarboxylate 58d starting from 4-trioxanylpyridazine.[42]

Also with the parent heterocycle and C-3 alkyl substituted derivatives thereof advantage can be taken of the fact that introduction of ethoxycarbonyl groups at both ß-positions not only diminishes basicity but also enhances lipophilicity of the molecules to a degree sufficient for their rapid transfer into the organic layer. Again attack of the radicals at the α-carbon atoms largely can be avoided by application of the two-phase method mentioned above.[40] Thus, experimentally simple and efficient procedures for single-step syntheses of diethyl 4,5-pyridazinedicarboxylate 59a[43] and 3-alkyl derivatives thereof like 59b are now available.[44]



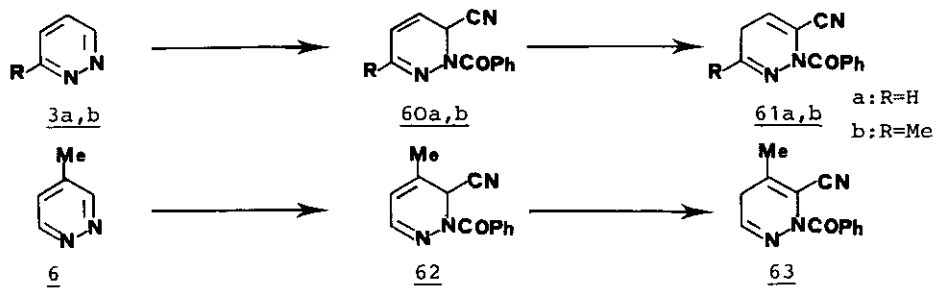
58a-d 3a,b 59a,b

a:R=H, b:R=Me

Scheme 15

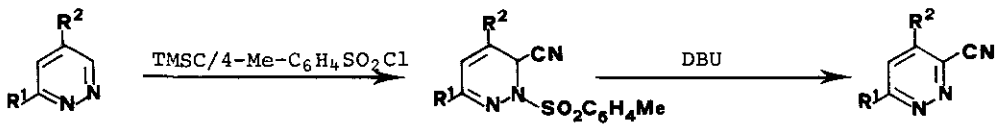
7. PREPARATION OF 3-CYANOPYRIDAZINES *via* REISSERT-TYPE REACTIONS

Despite the high synthetic value of Reissert-type reactions[46] with respect to the introduction of carbon side chains α to the ring nitrogen atom of heteroaromatic systems, Reissert compounds derived from pyridazine and its derivatives remained largely unexplored up to now. The first example of a pyridazine Reissert compound (60b) was provided by Popp and co-workers in 1981.[47] Quite recently, also the 2-benzoyl-2,3-dihydropyridazinecarbonitriles 60a, 62 have been prepared.[48,49] However, these compounds show a high tendency to isomerize affording 2,5-dihydropyridazine derivatives 61a,b, 63 which are capable of being further attacked by excess benzoyl chloride.[48,49] Thus, the yields are only low to moderate.



Scheme 16

In contrast, the N-arylsulfonyl Reissert analogs 65a-d, which can be obtained in satisfactory yields by reacting pyridazine and 3-alkyl or 4-alkyl derivatives thereof with trimethylsilyl cyanide/4-toluenesulfonyl chloride,[49] do not show this behaviour. Thus treatment of compounds 65a,b with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry tetrahydrofuran at room temperature gives rise to efficient novel syntheses of 3-pyridazinecarbonitrile 66a and its 6-methyl derivative 66b.[49] Since 4-alkylpyridazines are attacked by 4-toluenesulfonyl chloride almost exclusively at N-2, this procedure additionally represents a valuable tool for the regioselective introduction of a cyano group into position 3 of 4-alkylated pyridazines as shown in the preparation of compounds 66c,d.[49,21]



Scheme 17

In conclusion, the investigations on simple pyridazines discussed in this review clearly demonstrate the versatility of Minisci-type reactions with respect to the preparation of various 1,2-diazine derivatives via introduction of carbon functional groups into the ß-carbon atoms. On the other hand, sulfonyl Reissert compounds proved to be valuable intermediates in syntheses aimed at the introduction of a cyano group into C-3 of pyridazine and alkyl derivatives thereof. Further investigations of Reissert-type reactions with regard to C-C-bond formation between a carbon functional group and an α-carbon atom of the pyridazine nucleus remain a challenge for the future.

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