Pyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones: Marvelous Substrates for Study of Nucleophilic Substitution of Hydrogen

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The data on nucleophilic substitution reactions of hydrogen in 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione, its 3-chloride, N_2-oxide and some other derivatives are reviewed. All these compounds possess a remarkable ability to undergo not only simple functionalizations but also tandem and cascade transformations leading to annelation of various heterocyclic rings.

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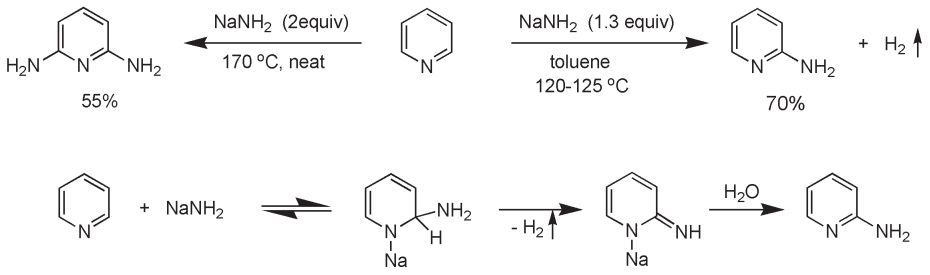
It is well documented that hydride ion is an extremely bad leaving group. Therefore it is not surprising that only few easily proceeding hydrogen nucleophilic substitution reactions in aromatic series are known. One of them is the Chichibabin reaction - sodamide amination of azaheterocycles [1] (reviews: [2,3]). In accordance with a classical protocol, the process is commonly conducted under heterogeneous conditions by heating of heterocyclic substrate with powdered sodium amide in an inert solvent. Thus, pyridine is aminated in toluene giving 2-aminopyridine in good yield. At performing the reaction without solvent and at a higher temperature, 2,6-diaminopyridine can be obtained (Scheme 1). A remarkable peculiarity of the Chichibabin reaction consists in evolution of hydrogen gas that permits conveniently to follow the progress of the amination. Presumably, on the stage of elimination, the hydride ion is combined with an acidic proton, likely from an amino group, to form hydrogen molecule. Without detalization the reaction mechanism is shown in Scheme 1.

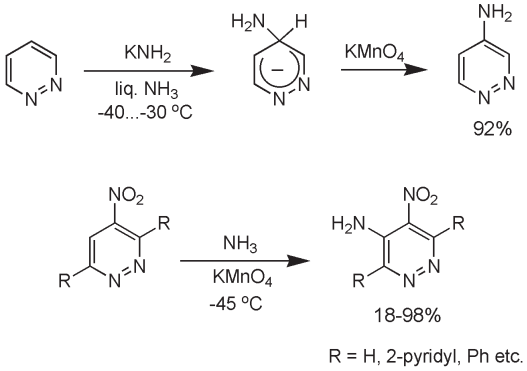
Scheme 1



Unlike pyridine, diazines and triazines at heating with sodamide undergo deep destruction and all attempts of their amination for many decades were unsuccessful [2]. It was professor van der Plas who made a breakthrough in this field. He has demonstrated that potassium permanganate can be used as a very nice acceptor of the hydride ion and with this oxidant the Chichibabin reaction smoothly proceeds even at low temperature, for instance in liquid ammonia [4] (reviews: [5-7]). Thus, pyridazine under these conditions is converted into 4-aminoderivative in excellent yield [4]. At increasing of substrate electron-deficiency, liquid ammonia itself or alkyl amines can be employed as aminating reagents instead of metal amides. For example, 4-nitropyridazines are converted by this way into 4-nitro-5-aminopyridazines (Scheme 2) [8].

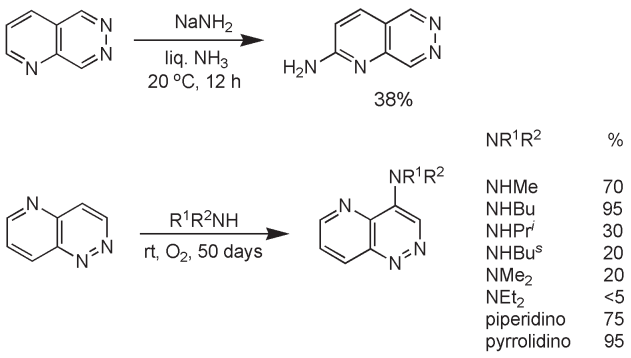
Since all carbon atoms in pyridazine molecule are positively charged, a question arises whether it is possible to achieve its double or even multiple amination. The major problem here is that when the first amino group has entered the molecule it strongly passivates subsequent nucleophilic attack. Apparently, this is a reason why until recent time there has been known no pyridazine substrate capable to multiple amination. It concerns both mononuclear and condensed pyridazines. Thus, cinnoline does not

Scheme 2



undergo even the first Chichibabin amination [9], 5-azaphtalazine is aminated at pyridine ring [10] and 5-azacinnoline at prolonged stirring with alkylamines yields the monoamination products at position 4 (Scheme 3) [11].

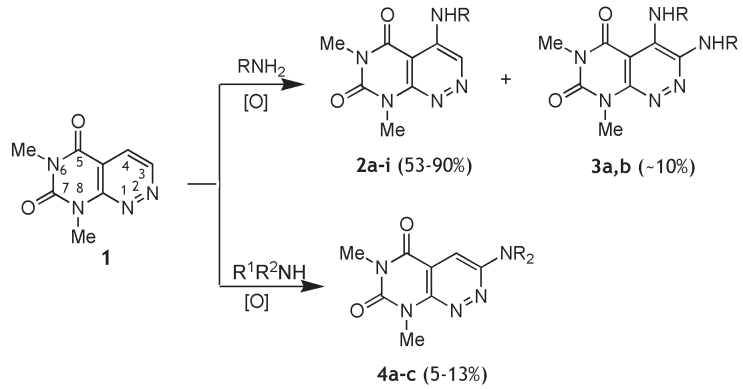
Scheme 3



Recently, we have disclosed the first pyridazine system, namely 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**1**), with a pronounced ability to undergo not only mono- but also double oxidative amination [12]. In addition, this system displays a number of other unusual reactions of nucleophilic substitution of hydrogen. Thus, the compound **1** has been found to react with liquid ammonia or primary alkylamines in the presence of $AgPy_2MnO_4$ [13] at -78÷20 –_ to produce 4-amino derivatives **2a-i** in 53-90% yield (Scheme 4). At using of methyl- and ethylamines the corresponding 3,4-diamino derivatives **3a,b** were also isolated in 10% yield. A higher easiness of amination at position 4 is well correlated with both the π-charge distribution in the molecule (δ_4 = +0.100, δ_3 = +0.047) and the relative values of localization energies (L_4^- = -2.07β , L_3^- = -2.33β).

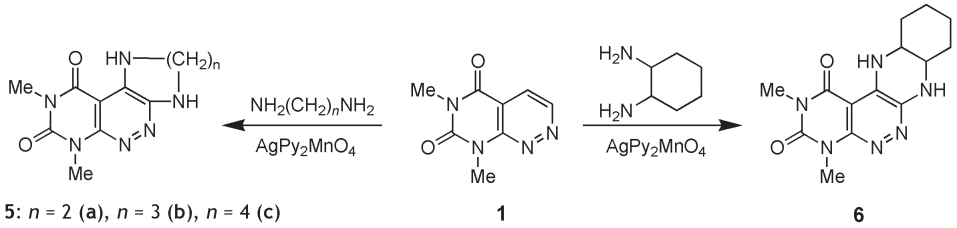
Taking into attention that both aromatic hydrogen atoms in molecule **1** are principally active in nucleophilic displacement we next decided to try bifunctional amines as aminating agents hoping to get the corresponding cyclic amination products. Indeed, the pyridazinouracil **1** reacted at room temperature with an excess of 1,2-diaminoehane, 1,3-diaminopropane, 1,4-diaminobutane and 1,2-diaminocyclohexane in the presence of $AgPy_2MnO_4$ to furnish compounds **5_-c** and **6** (Scheme 4) [14]. Yields were mostly good but steadily decreased as a length of methylene chain in the terminal diamines increased. To the best of our knowledge, this is the first example of tandem S_N^H-S_N^H substitution reaction for neutral azines. All preceeding findings in this field included cycloaddition of bifunctional nucleophiles to azinium cations, isolation of an addition product and its subsequent separate oxidation (see *e.g.* [15]).

Scheme 4



[O] = $KMnO_4$ or $AgPy_2MnO_4$

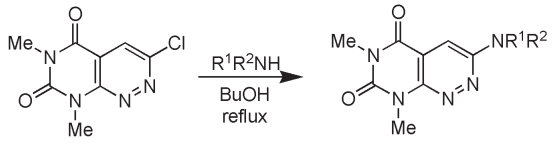
2: R = H (**a**), Me (**b**), Et (**c**), Pr (**d**), Pr^i (**e**), Bu^i (**f**), Bu^t (**g**), *c*-C_6H_{11} (**h**), $PhCH_2$ (**i**)
3: R = H (**a**), Me (**b**)
4: NR^1R^2 = NMe_2 (**a**), piperidino (**b**), morpholino (**c**)



5: *n* = 2 (**a**), *n* = 3 (**b**), *n* = 4 (**c**) **1** **6**

Contrary to primary alkylamines, secondary alkylamines reacted with the compound **1** completely different. One group of secondary amines, including dimethylamine, piperidine and morpholine, were rather unreactive and gave only 3-aminopyridazines **4a-c** in a yield not exceeding 13%, most of the starting material being recovered unchanged [12]. A lack of correlation with the theoretical calculations here can be attributed to steric reasons. However, the compounds **4,** as well as many other 3-alkylamino derivatives are easily prepared through a simple aminodehalogenation of 3-chloride **7** (Scheme 5, see also Schemes 9 and 11).

Scheme 5

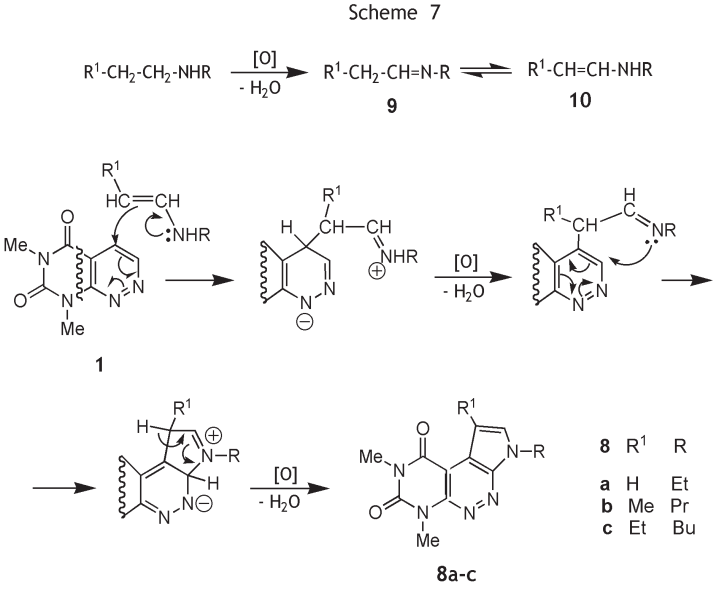


7 **4b-m** (50-77%)

4: NR^1R^2 = piperidino (**b**), morpholino (**c**), NHMe (**d**), NHEt (**e**), NHPr (**f**), $NHBu^s$ (**g**), NH-*c*-C_6H_{11} (**h**), $PhCH_2$ (**i**), NHCH(Me)Ph (**j**), (furyl-2)methylamino (**k**), $NHPr^i$ (**l**), NHBu (**m**)

Much more interesting reactivity was manifested by another group of secondary amines, which have at least one flexible alkyl group with two or more carbon atoms. Thus, compound **1** reacted with diethylamine unexpectedly produced the condensed pyrrole **8_** as a single product in 42% yield (Scheme 6) [16]. The structure of **8a** has been confirmed by X-ray study. When dipropyl- and dibutylamines were taken instead of diethylamine, the pyrroles **8b** and **8c** were obtained, respectively.

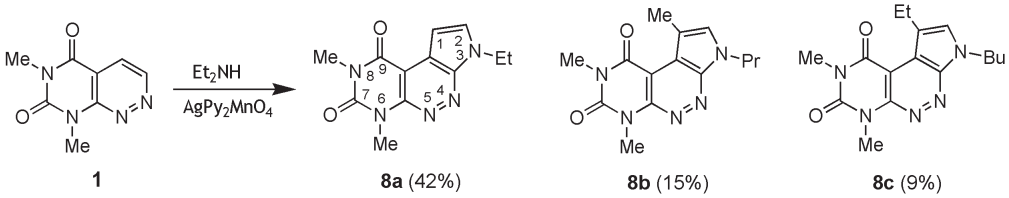
Scheme 7



in oxidation of dialkylamine into imine **9** equilibrating with enamine tautomer **10** (Scheme 7). The latter as a bifunctional C,N-nucleophile firstly attacks position 4 of the pyridazine ring and then intramolecularly position 3 affording after two oxidation steps the annelated pyrrole.

This Scheme has been confirmed in the experiments with authentic imines obtained from the reaction of acetic or propionic aldehydes with secondary amines (Scheme 8). The interaction of these imines with pyridazinouracil **1** lead to formation of pyrroles **8a,b,d-f** (8-39%). Similarly, acetone and cyclohexanone ketimines **11** gave the pyrroles **8g,h** in 72-80% yield. The relatively small yields of pyrroles at using of aldimines is connected with strong tarring in these cases. It should be stressed that this transformation represents not only one more example of tandem S_N^H- S_N^H reaction in

Scheme 6

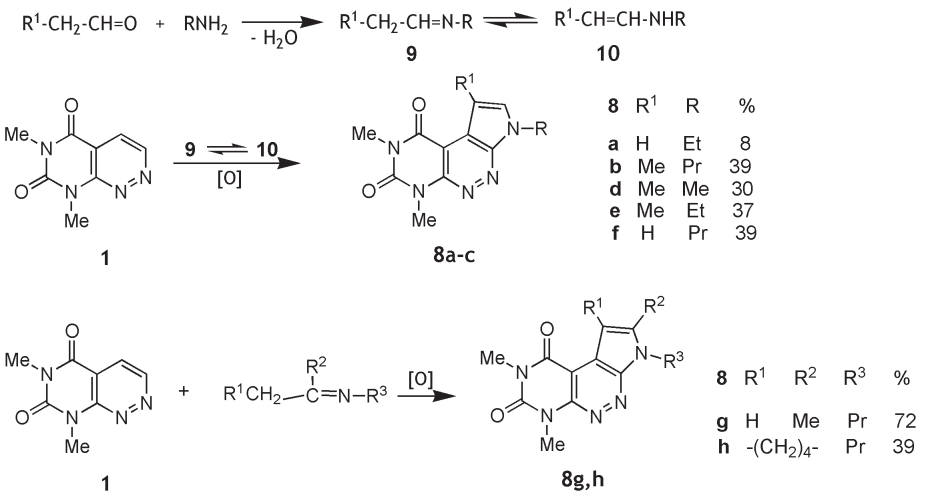


1 **8a** (42%) **8b** (15%) **8c** (9%)

There are several ways to rationalize how the pyrroles **8** are formed. In our opinion the most plausible one consists

neutral azines but also a novel method for pyrrole ring annelation.

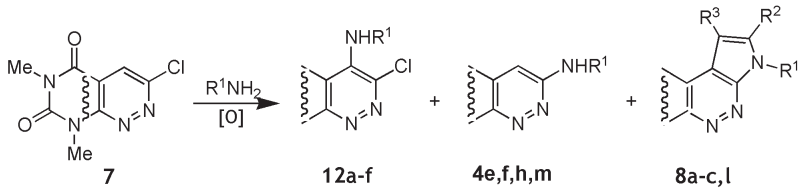
Scheme 8



Along with the unsubstituted pyridazinouracil **1**, its 3-chloride **7** was also subjected to oxidative amination [17]. And again, a strong dependence of the reaction course on alkylamine structure took place. With ammonia and primary alkylamines, the compound **7** undergoes mainly aminodehydrogenation at position 4 to form 3-chloro-4-amino derivatives **12a-f** (Scheme 9). In several instances the 3-amino derivatives **4** and pyrroles **8** were obtained as minor products. With cyclic secondary amines, the chloride **7** gives exclusively the products of aminodehalogenation, whereas with acyclic secondary amines - pyrroles **8** in good yields. Isolation of the stable enamine **13** at using of diethylamine indicates that annelation of pyrrole ring here, as in case of the compound **1** (*cf.* Scheme 7), starts from attack of the enamine **10** on position 4 of pyridazine substrate.

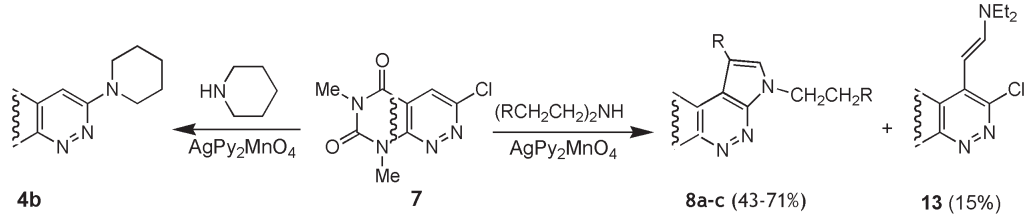
The higher electrophilicity of the C-4 atom in the pyridazines **1** and **7** strictly predetermines a directionality of their reaction with enamines towards exclusive formation of pyrroles **8**. Meanwhile, the isomeric condensed system **14** with another arrangement of pyridazine and pyrrole rings seemed to be even more interesting because of its structural and electronic similarity to biologically important coenzyme

Scheme 9



12: R^1 = H (**a**), Me (**b**), Et (**c**), Pr (**d**), Pr^i (**e**), Bu (**f**), *cyclo*-C_6H_{11} (**g**)
4: R^1 = Et (**e**), Pr (**f**), *cyclo*-C_6H_{11} (**h**), Bu (**m**)
8: R^1 = Et, R^2 = R^3 = H (**a**), R^1 = Pr, R^2 = H, R^3 = Me (**b**), R^1 = Bu, R^2 = H, R^3 = Et (**c**), R^1 = *cyclo*-C_6H_{11}, R^2,R^3 = -$(CH_2)_4$- (**l**)

Reagents and conditions: KNH_2 - NH_3 -$KMnO_4$, -78 °C or R^1NH_2 - $AgPy_2MnO_4$

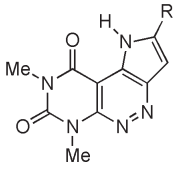


8: R = H (**a**), Me (**b**), Et (**c**)

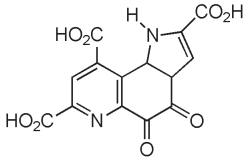
PQQ. We have successfully prepared compounds of type **17** also with the aid of S_NH-methodology (Scheme 10). To achieve this the chloride **7** was firstly converted via the Sonogashira cross-coupling reaction into acetylenes **15**. The latters being subjected to oxidative amination with alkylamines gave straight away the pyrrolopyridazines **14** in high yields [18]. Apparently, the reaction proceeds via 4-amino derivatives **16** which spontaneously cyclize.

Some interesting results were obtained at amination of pyridazine-N_2-oxide **17**[19,20]. In the absence of an oxidant the reaction proceeds only at prolonged reflux with high boiling amines, such as piperidine and morpholine, and gives deoxidized amines **4b** and **4c** in reasonable yields. Under oxidative conditions, the N-oxide **17** reacts with a wide range of alkylamines forming a mixture of both the deoxidized **4** and the oxidized **18** 3-aminoderivatives the latter being usually predominant (Scheme 11).

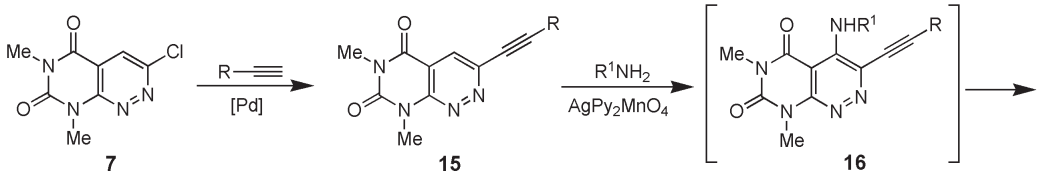
Scheme 10



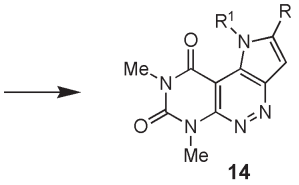
14



Coenzyme PQQ



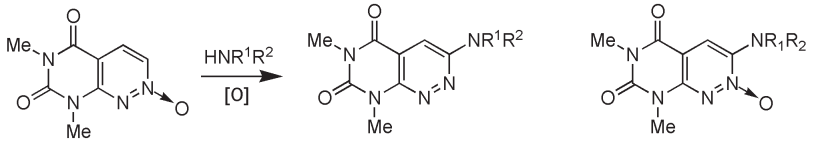
7 **15** **16**



14

R^1 = Et, Pr, Pr^i, Bu, *c*-C_6H_{11}
R = H, CH_2OTHP, *n*-C_6H_{13}, Ph, TMS

Scheme 11



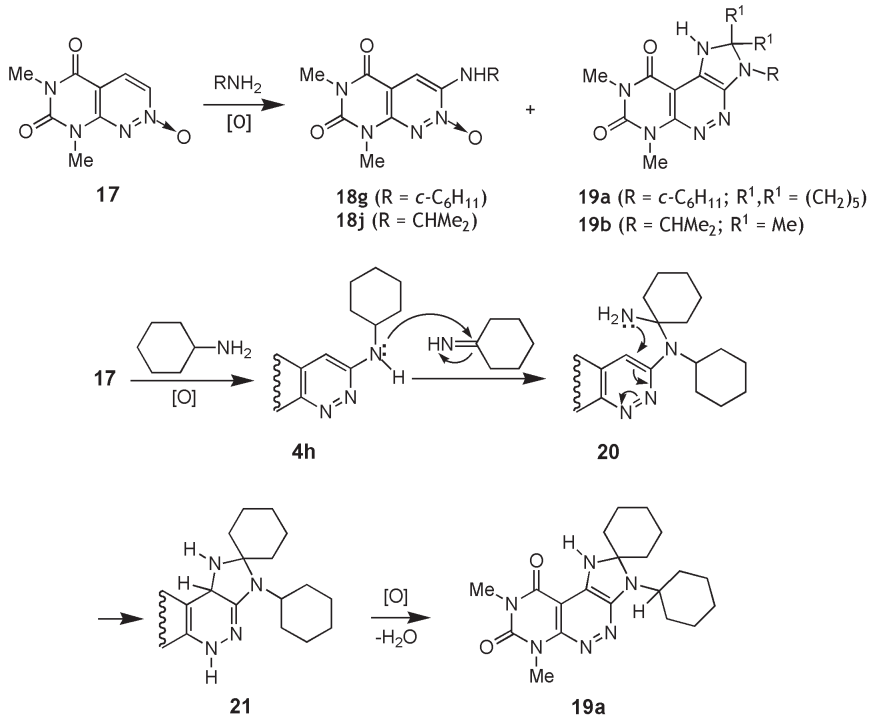
17 **4** **18**

50-68 %

NR^1R^2	Ratio **4**:**18**, %
NMe_2	0:100
piperidino	37:63
morpholino	40:60
NHMe	61:39
NHEt	33:67
NHPr	13:87
NH-*c*-C_6H_{11}	0:100
$NHCH_2Ph$	37:63
NH_2	0:100
NHPr^i	0:100

The interaction of N-oxide **17** with cyclohexyl- and isopropylamines is somewhat specific. [19,20]. For both these amines the imidazolines **19a,b** were unexpectedly obtained in ~5% yield along with the corresponding 3-alkylaminopyridazine-N_2-oxides **18**,.The structure of the **19a** has been established by X-ray study. For imidazoline formation the reaction pathway involving the 3-alkylamino derivatives **4** as key intermediates has been postulated (Scheme 12). It was confirmed by independent synthesis of imidazoline **19a** in 65% yield by interaction of the authentic compound **4h** with cyclohexylamine in the presence of an oxidant. Obviously, the 3-cyclohexylamino derivative **4h** is added across the

Scheme 12



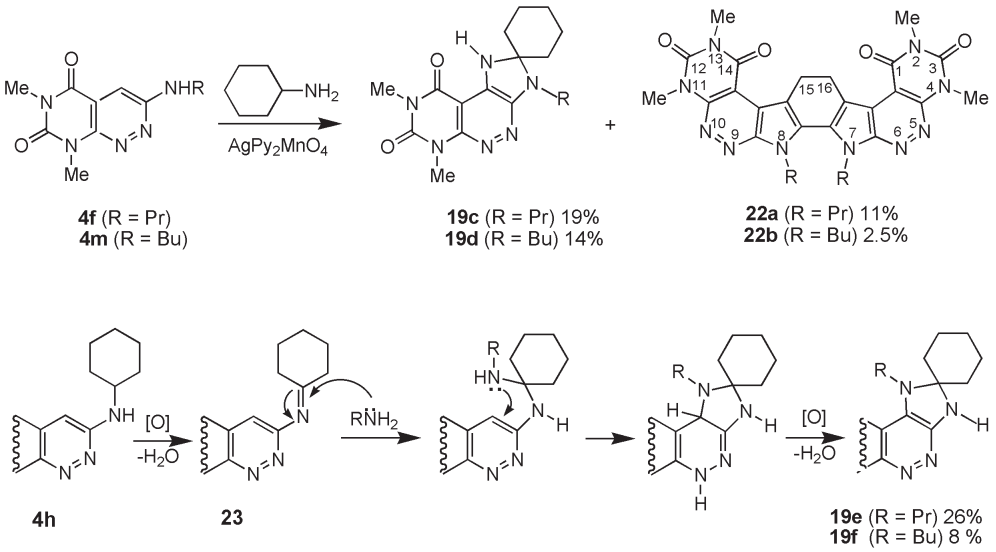
C=N bond of the cyclohexanone imine which is generated *in situ* from cyclohexylamine. Thus forming *gem*-diamine **20** then undergoes intramolecular oxidative amination to afford imidazoline **19a** via intermediate **21**.

The formation of imidazolines **19a,b** at using cyclohexyl- and isopropylamines can be explained by enhanced easiness of oxidation of these amines into the corresponding ketone imines. Nevertheless, we thought that other possibilities for such heterocyclizations might be also realizable. To prove this, we have tested various combinations of 3-alkylaminopyridazinouracils and primary alkylamines to yield new imidazolines of type **19**.

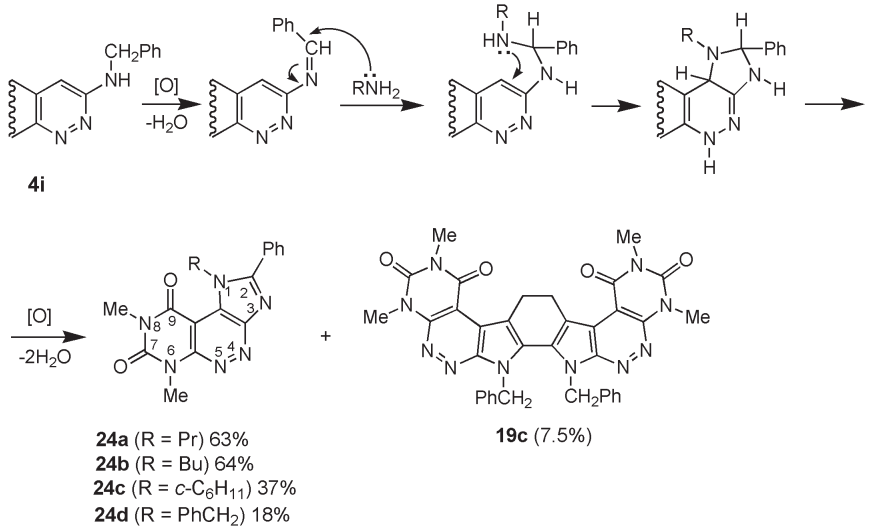
Indeed, the treatment of 3-propylamino- and 3-butylamino derivatives **4f** and **4m** with cyclohexylamine in the presence of an oxidant afforded imidazolines **19c,d** though the reaction was complicated by formation of a small amount of multinuclear compounds **22a,b** (Scheme 13). When, in reversed manner, 3-cyclohexylamino derivative **4h** reacted with propyl- or butyl-amine, the isomeric imidazolines **19e,f** were obtained, apparently, via imine **23**.

3-Benzylaminopyridazine **4i** has been shown to react with alkylamines in a similar way, producing imidazoles **24a-d** in moderate to good yields (Scheme 14). And again, upon using of cyclohexylamine, the polycycle **22c** was isolated as a by-product.

Scheme 13



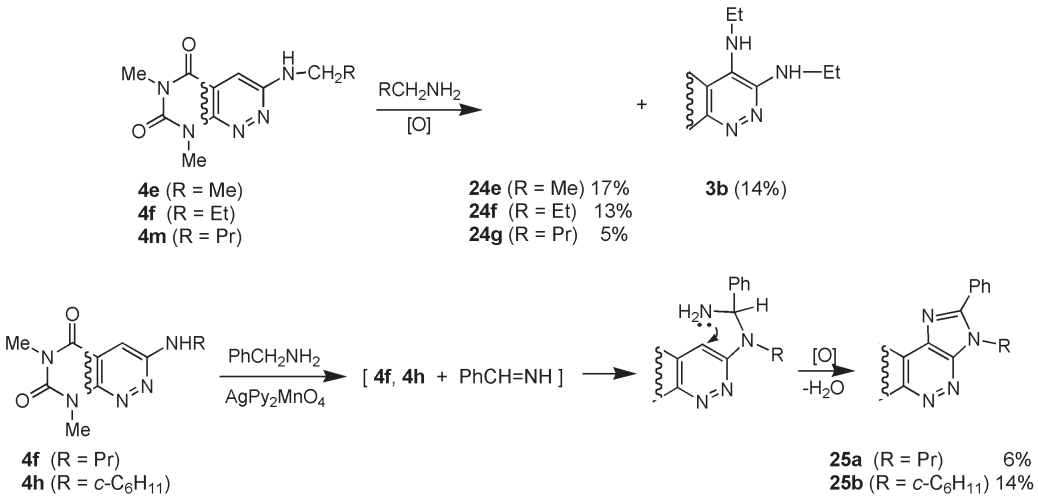
Scheme 14



The 3-alkylamino derivatives **4e,f,m** were converted under the same conditions into imidazoles **24e,f,g** though the yields were quite small. In one instance, the double amination product **3b** was also isolated. The interaction of 3-alkylaminopyridazines **4f,h** with benzylamine led to isomeric imidazoles **25a,b** (Scheme 15). Evidently, in the latter case the benzylamine is firstly oxidized into benzylidenimine reacting as shown in Scheme 15.

From above it follows that a course of the reactions of 3-alkylaminopyridazinouracils with primary alkylamines mainly depends on the relative ease of external amine and 3-NHR-group oxidation. Both benzylamine and 3-benzylamino group possess the largest ability to transformation into imines. In the absence of benzylamino groups, the cyclohexylamino group is oxidized first and the reaction proceeds via cyclohexanone imine intermediate. In those cases, when the reagents do not content benzylamino and

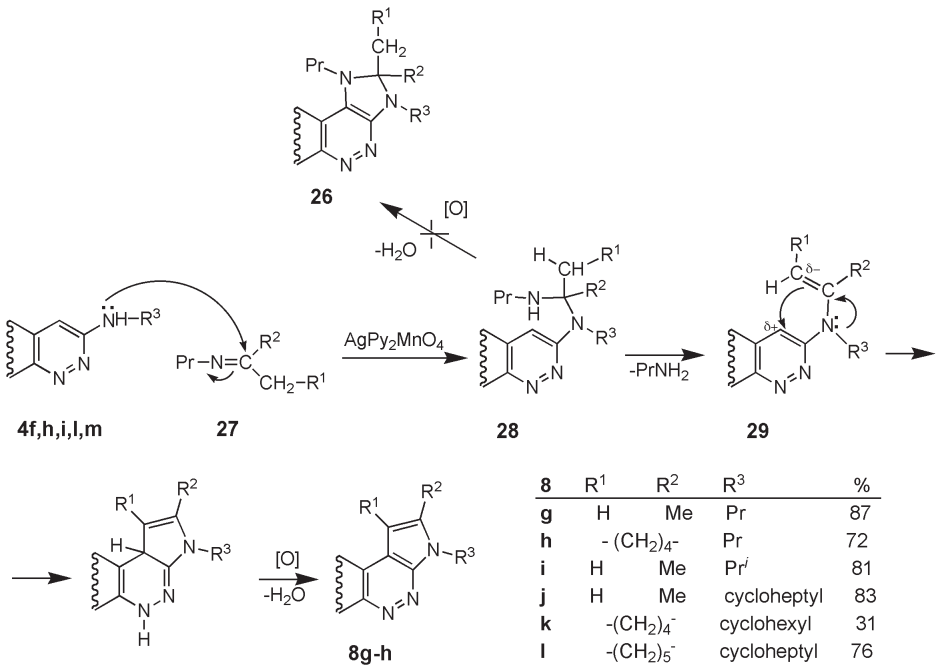
Scheme 15



cyclohexylamino functions, the reaction starts with oxidation of the 3-alkylamino group. All these transformations represent a novel approach to construction of condensed imidazoles and imidazolines.

Next we suggested that an alternative way to the imidazolines and imidazoles might consist in the reaction of the 3-alkylaminopyridazines with specially prepared ketone imines. However, the treatment of **4f,h,i,l,m** with N-propylimines **27** in the presence of an oxidant afforded not imidazolines **26** but the condensed pyrroles **8g-n** as single products in 31-87% yield (Scheme 16). Apparently, the intermediates **28** are not inclined into imidazoline cyclization because of their insufficient stability and steric effects. Instead, they lose a propylamine molecule yielding enam ines **29** which are cyclized into pyrroles.

Scheme 16



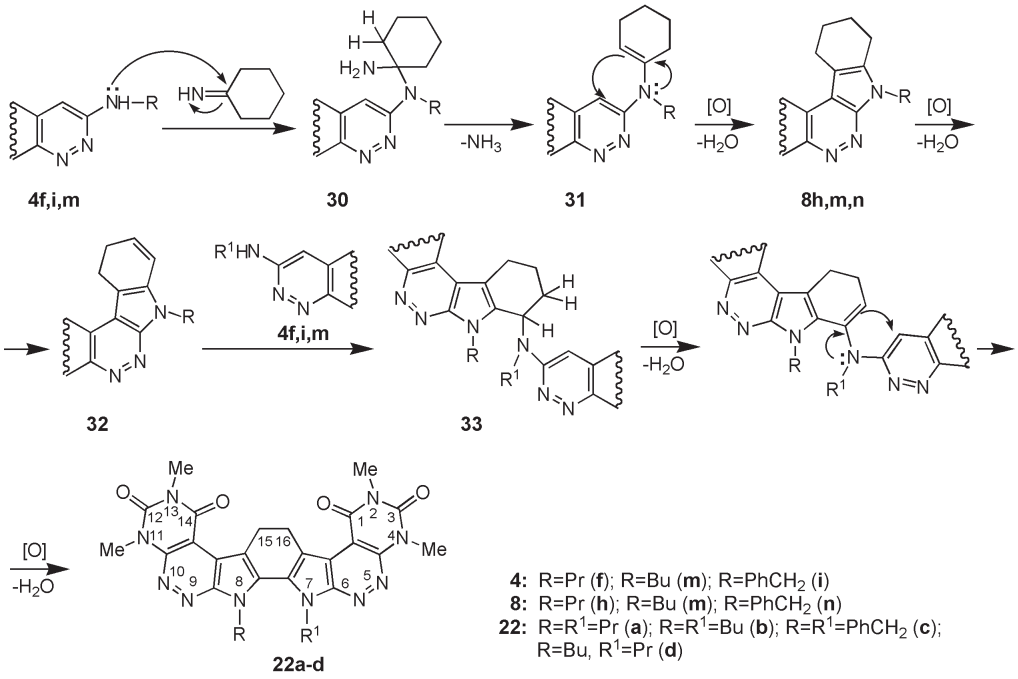
8	R^1	R^2	R^3	%
g	H	Me	Pr	87
h	-$(CH_2)_4$-		Pr	72
i	H	Me	Pr^i	81
j	H	Me	cycloheptyl	83
k	-$(CH_2)_4$-		cyclohexyl	31
l	-$(CH_2)_5$-		cycloheptyl	76
m	-$(CH_2)_4$-		Bu	56
n	-$(CH_2)_4$-		$PhCH_2$	25

Let us turn now to the seven-membered condensed pyridazines **22** which are formed in 5-10% yields in some reactions with participation of cyclohexylamine [20]. These compounds are highly melted (mp >340ºC) red substances (λ_{max} 512-520 nm), rather insoluble in most organic solvents. We have assumed that their formation occurs in accordance with Scheme 17 and starts from the addition of 3-alkylamino derivatives across the C=N bond of cyclohexanone imine. The departure of ammonia from the resulted *gem*-diamine **30** furnishes enamine **31**, which is cyclized into the corresponding pyrrole **8h,m,n**. Its oxidation affords the key intermediate **32**, reacting with the starting molecule **4** to produce adduct **35**. The subsequent oxidation and pyrrole-ring closure produce the compound **22**.

3-propylaminopyridazine **4f** to give asymmetrically substituted **22d**. On the whole, the formation of compounds **22** looks as a cascade process with repeating stages of oxidation, nucleophilic addition of amino groups across C=N bonds and nucleophilic substitution of the ring hydrogen atoms.

As expected, compounds **22** can be easily oxidized (*e.g.* by MnO_2) into derivatives of fully conjugated heterocyclic system **34** (in a trace amount they are usually present in the crude **22**) (Scheme 18). The latter represent 30π-electron analogues of yet unknown polycyclic hydrocarbon dibenzo[*a*,*o*]pycene **35**. Compounds **34** have a deep red colour (λ_{max} 520-534 nm) and reveal in ^{1}H NMR spectra a downfield singlet of two aromatic protons at δ 9.6 (Figures 2, 3). The chloroform solutions

Scheme 17

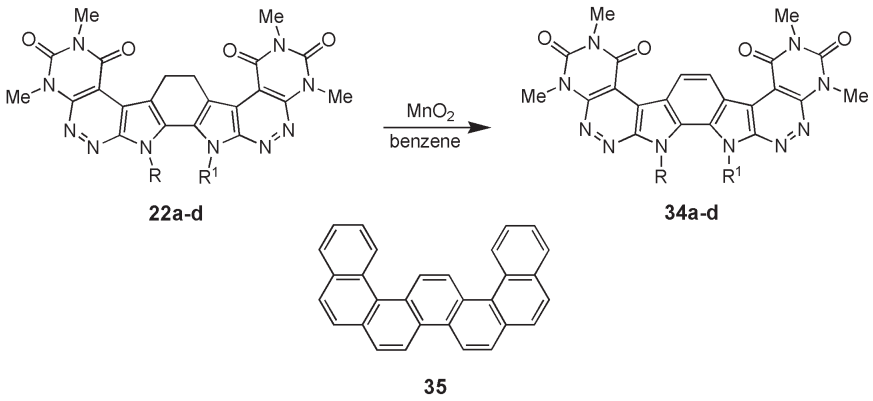


This mechanism was substantiated by the fact that treatment of the authentic pyrrole **8h** with one equivalent of 3-propylaminopyridazine **4f** in cyclohexylamine-oxidant system resulted in its complete conversion into **22a**. Under the same conditions pyrrole **8m** reacted with

of both polycycles **22** and **34** demonstrate yellow and dark-red fluorescence with the Stokes shift equal in average 25 and 75 nm, respectively.

We have also interested in preparation of other cycloalkane-based analogues of compounds **22.** A

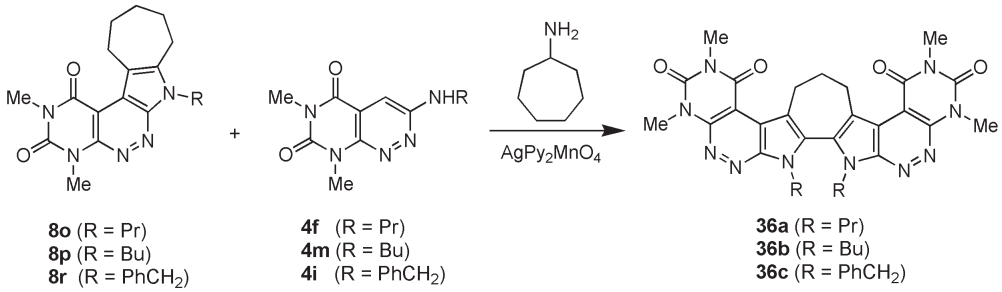
Scheme 18



22, 34 R=R^1=Pr (**a**); R=R^1=Bu (**b**); R=R^1=PhCH$_2$ (**c**); R=Bu, R^1=Pr (**d**)

number of them, **36a-c**, have been obtained in 25-30% yield on treatment the cyclohepthano[b]pyrroles **8o,p,r** with the corresponding 3-alkylaminopyridazinouracils **4f,m,i** in cyclohepthylamine media (Scheme 19) [21]. They are yellow-coloured (λ_{max} ~450 nm)) high-melted substances, NMR ^{1}H spectra of which demonstrate an equivalence of the two uracil moieties but non-equivalence of the methylene protons attached to pyrrole rings. The latter circumstance seems to be originated from helicene-like structure of the polycyclic system **36**.The assignment of all signals in NMR ^{1}H spectra followed from analysis of COSY spectra. Currently we are studying synthesis of the similar cyclopentane- and cyclooctane-based multinuclear compounds.

Scheme 19



In summary, one can conclude that nucleophilic displacement of hydrogen can be of importance not only for simple functionalizations but also for complex sequential processes and pyridazines are especially convenient substrates for this purpose.

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REFERENCES AND NOTES

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[1] A. E .Chichibabin and O. A. Zeide, *Zhur. Russ. Phys.-Khim. Obshch*. **46**, 1216 (1914); *Chem. Abstr.*, **9**, 1901 (1915).

[2] A. F. Pozharskii, A. M. Simonov and V. N. Doron'kin, *Uspekhi Khimii*, **47**, 1933 (1978).

[3] C. K. McGill and A. Rappa, *Adv. Heterocycl. Chem*., **44**, 1 (1988).

[4] H.Hara and H.C. van der Plas, *J. Heterocycl. Chem*., **19**, 1285 (1982).

[5] H.C. van der Plas, *Khim. Geterotsikl. Soedin*., 1011 (1987)

[6] O. N. Chupakhin, V. N. Charushin and H. C. van der Plas, Nucleophilic Aromatic Substitution of Hydrogen, Academic Press, San Diego, 1994.

[7] H. C. van der Plas, in Chemistry and Biological Activity of Oxygen- and Sulfur-Containing Heterocycles (keynote lectures), Interbioscreen, Moscow, 2003, pp. 128-188

[8] A. T. M. Marcelis, H.Tondyes and H. C. van der Plas, *J. Heterocycl. Chem*., **25**, 831 (1988).

[9] N. A. Buluchevskaya, A. V. Gulevskaya and A. F. Pozharskii, *Chem. Heterocycl. Comp*. (Engl. Transl.) **39**, 87 (2003).

[10] D. V. Paul and H.J.Rodda, *Austral. J. Chem*., **22**, 1745 (1969).

[11] M. F.Budyka, P. B. Terent'ev, A. N. Kost, *Khim. Geterotsikl. Soedin*., 1554 (1977); C.A. , **89**, 129466 (1978).

[12] A. V. Gulevskaya, D. V. Besedin and A. F. Pozharskii, *Russ. Chem. Bull., Int Ed*., **4**8, 1150-1153 (1999).

[13] The dipyridine silver permanganate complex is a reagent of choice in these cases because of better than $KMnO_4$ solubility in alkylamines; for its synthesis see H. Firousbadi, M. Vessal, M. Naderi, *Tetrahedron Lett*., **23**, 1843 (1982).

[14] D. V. Besedin, A. V. Gulevskaya and A. F. Pozharskii, *Mendeleev Commun*., **10**, 150 (2000).

[15] O. N. Chupakhin, D. N. Beresnev, *Uspekhi Khimii*, **71**, 803 (2002).

[16] A. V. Gulevskaya, D. V. Besedin, A. F. Pozharskii and Z. A. Starikova, *Tetrahedron Lett*., **42**, 5981 (2001).

[17] V. V. Gorunenko, A. V. Gulevskaya and A. F. Pozharskii, *Russ. Chem. Bull., Int. Ed*., **2004** (in print).

[18] V. V. Gorunenko, A. V. Gulevskaya and A. F. Pozharskii, *Russ. Chem. Bull., Int. Ed*., **52**, 441 (2004)

[19] A. V. Gulevskaya, A. F. Pozharskii, D. V. Besedin, O. V. Serduke and Z. A. Starikova, *Mendeleev Commun*., **12**, 157 (2002).

[20] A. V. Gulevskaya, O. V. Serduke, A. F. Pozharskii and D. V. Besedin, *Tetrahedron*, **59**, 7669 (2003).

[21] O. V. Serduke, A. V. Gulevskaya and A. F. Pozharskii, Unpublished results.