INSIGHT INTO NOVEL CYCLIZATION REACTIONS USING ACETIC ANHYDRIDE IN THE PRESENCE OF 4-DIMETHYLAMINOPYRIDINE

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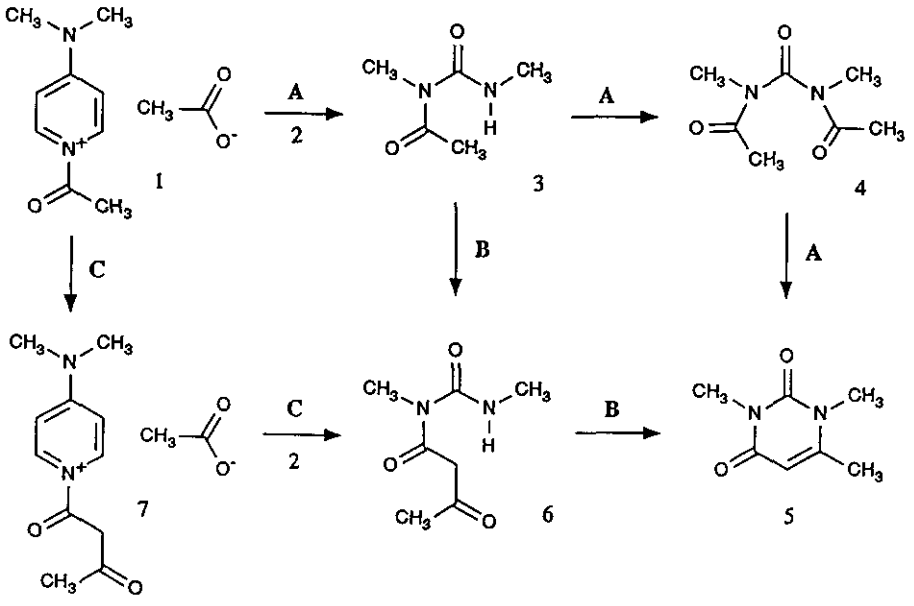
Abstract - Reactions of acetic anhydride in the presence of 4-dimethylamino-pyridine with 1,3-disubstituted ureas and hydrazobenzenes gave uracils and pyrazolinones respectively. Unsymmetrical 1,3-disubstituted ureas react regioselectively.

Since almost two decades 4-dimethylaminopyridine (DMAP) is known as a very effective catalyst greatly facilitating difficult acylations and related reactions of sterically hindered and other deactivated compounds.[1,2] The superiority of DMAP over comparable bases as catalyst is attributed to the donor ability of the 4-dimethyl-amino group, which exerts a stabilizing effect on *N*-acyl pyridinium species thought to be the reactive intermediates in these reactions. Moreover, there were found several reactions, which do not occur in the absence of DMAP. For instance, Burke and coworkers[3] described a decarboxylative dimerization by heating 4-methyl-6-hydroxy-2-pyrone with a catalytic amount of DMAP yielding a coumarochromanone.

In previous papers[4,5] we reported DMAP-catalyzed reactions of bifunctional compounds with carboxylic acid anhydrides leading to heterocycles, which in part can not be obtained by other methods. We have now investigated scope, limitation and mechanism of this new procedure. In this study, we examined the behaviour of a variety of compounds containing two nucleophilic nitrogen atoms towards acetic anhydride in the presence of DMAP, i.e. mono- and 1,3-disubstituted ureas, mono- and 1,2-disubstituted hydrazines, 1,3-disubstituted sulfuryldiamides, *N,N'-dialkyl oxalic acid diamides and N,N'-dialkyl-1,2-phenylendiamines*. It was found that this cyclization method, which in every case requires one equivalent of the catalyst, is successfull only with compounds containing secondary nitrogen atoms of rather low nucleophilicity. Compounds with primary

nitrogen atoms are either acetylated or, in the case of urea derivatives, decomposed to *N*-substituted acetic acid amides. In the case of compounds with secondary N atoms low nucleophilicity is required for cyclization, as it is observed with 1,3-dialkylureas and hydrazobenzenes. In contrast, stronger nucleophiles such as 1,2-dialkylhydrazines, 1-alkyl-2-arylhydrazines and *N,N'*-dialkyl-1,2-phenylendiamines are acetylated exclusively. With weaker nucleophiles, for instance oxalic acid *N,N'*-dimethyldiamide and 1,3-dimethylsulfuryldiamide, either no reaction or slow acetylation occurs. In these cases, autocondensation of acetic anhydride is the main reaction.

As reaction mechanism, formally three different pathways can be taken into consideration, which are outlined in Scheme 1 for 1,3-dimethylurea (**2**): Generally, these reaction are started by the formation of 1-acetyl-4-(dimethylamino)pyridinium acetate (**1**). In a mechanism *via* path A, **1** reacts with **2** forming 1-acetyl-1,3-dimethylurea (**3**) and 1,3-diacetyl-1,3-dimethylurea (**4**) respectively, which by condensation affords 1,3,6-trimethyluracil (**5**). In Path B, the intermediate (**3**) is acetylated by **1** to 1-acetoacetyl1,3-dimethylurea (**6**), leading again to **5** upon ring closure. In Path C, first **1** reacts with a second molecule of acetic anhydride yielding 1-acetoacetyl-4-dimethylaminopyridinium acetate (**7**), which transforms **2** directly into **6**.



Scheme 1

It was easy to show that paths A and B must not be considered, as the monoacetyl derivative (**3**) is not an intermediate on the way to **5**. When **3**, which is obtained by reacting **2** with acetic anhydride in pyridine, is treated with an excess of acetic anhydride in the presence of one equivalent DMAP, no **5** can be isolated. Under

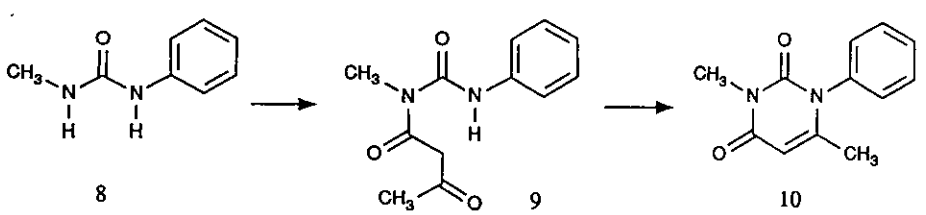
these conditions, most of **2** remains unchanged and can be recovered from the dark brown reaction mixture, which contains several autocondensation products of acetic anhydride.

Consequently, path C seems to be quite certain. This brings about the answer to the unsolved problems, why one equivalent of DMAP and low reactivity of the *N*-nucleophile are essential: In principle, 1-acetyl-4-dimethylaminopyridinium acetate (**1**), which is thought to be the first reactive intermediate, has two possibilities to react: either with the *N*-nucleophile, furnishing an acetyl derivative, or with acetic anhydride, furnishing **7**. Which one of these two reactions does predominate, is depending on the strength of the two competing nucleophiles. With a highly reactive *N*-nucleophile, the former is the main reaction, leading rapidly to acetylated products. With a weaker *N*-nucleophile, showing the optimum of nucleophilicity mentioned above, the latter reaction is prevalent. Obviously, the extent to which **7** is generated, is proportional to the amount of DMAP added. In a subsequent reaction, the weak *N*-nucleophile is acetoacetylated by **7** leading to **6** and finally to the uracil (**5**). If the reactivity of the *N*-nucleophile is very low, autocondensation of acetic anhydride is the only process observed, leading to complex mixtures of polymerization products.

For these reactions, stoichiometrically three equivalents of acetic anhydride are required: two equivalents to give **7**, one further equivalent to bind the water formed in the course of the cyclization. Generally, best results are obtained when 3.3 equivalents of acetic anhydride are used.

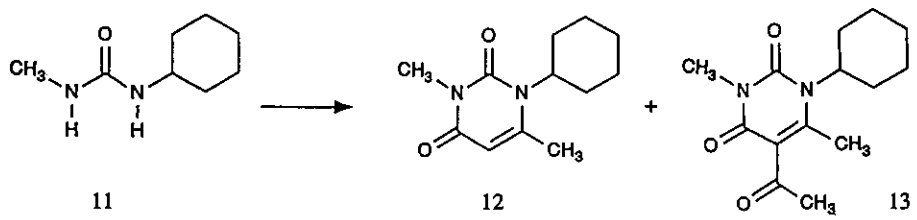
In accordance with this mechanism, unsymmetrical 1,3-disubstituted urea derivatives with nitrogens of different nucleophilicity and/or substituents of different steric demand, react regioselectively with acetic anhydride in the presence of DMAP, at the more nucleophilic or less sterically hindered N-atom.

For example, 1-methyl-3-phenylurea (**8**) is converted exclusively to the predicted isomer 3,6-dimethyl-1-phenyluracil (**10**). Very likely, in the first step the more nucleophilic, methylated N is acetoacetylated affording the intermediate (**9**), which easily cyclizes to **10** (Scheme 2). The structure of **10** was confirmed by comparison with data provided by Senda et al.[6] who obtained **10** by treatment of 6-methyl-1-phenyluracil with dimethyl sulfate.



Scheme 2

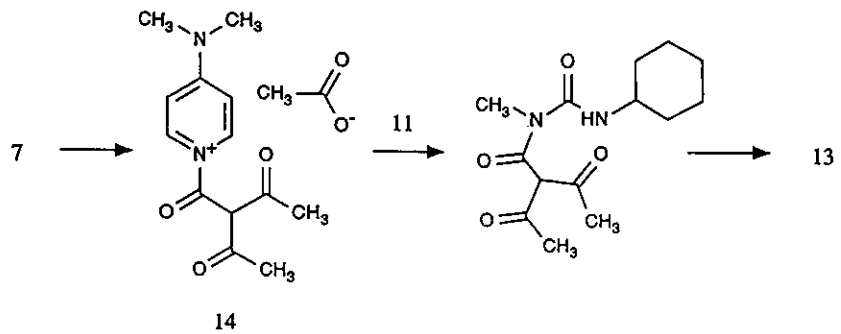
Similarly, from 1-cyclohexyl-3-methylurea (**11**) the known 1-cyclohexyl-3,6-dimethyluracil (**12**)[6] is obtained as the expected isomer, together with 5-acetyl-1-cyclohexyl-3,6-dimethyluracil (**13**) (Scheme 3).



11 12 13

Scheme 3

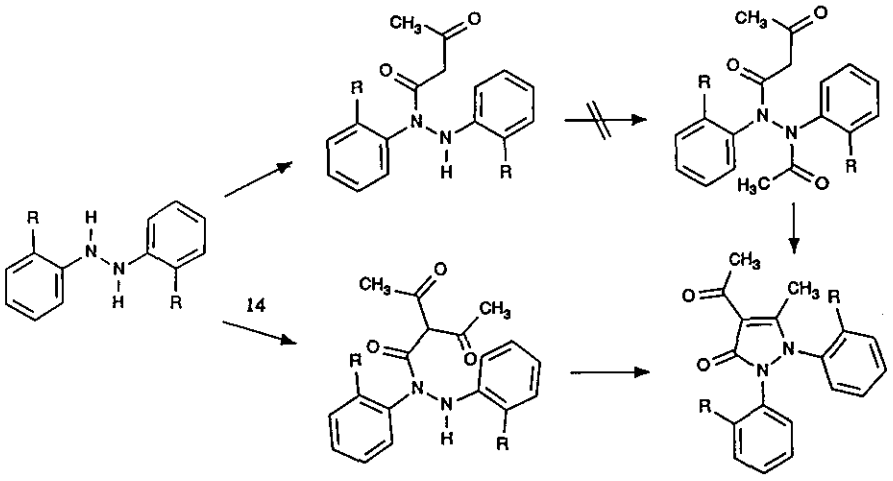
The formation of **13** can be attributed to steric hindrance exerted by the cyclohexyl group, which decreases essentially the reaction rate. This prompts enhanced autocondensation of acetic anhydride, which apparently leads to the trimerization product (**14**). When **11** is acylated by **14**, an intermediate is formed, which by cyclization yields **13** (Scheme 4). The ratio of products (**12**) and (**13**) is not influenced by the amount of acetic anhydride used.



14

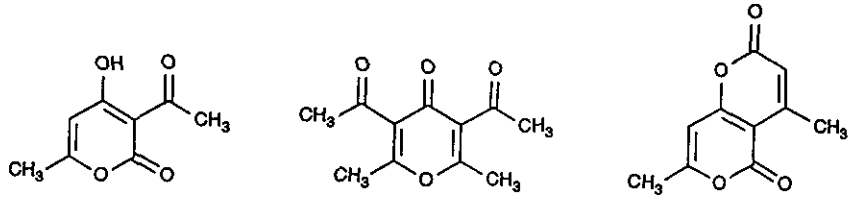
Scheme 4

This mechanism is contradictory to the one we published previously[5] in order to explain the generation of 4-acetyl-1,2-diaryl-1,2-dihydro-5-methyl-3*H*-pyrazol-3-ones. In that paper, we postulated á mechanism involving an acetoacetyl species, which after acetylation of the second N and dehydration should afford the pyrazolone derivative. Now we found, that this can not be true, as acetoacetylhydrazobenzene derivatives, obtained from hydrazobenzenes and diketene, do not react in this way, when treated with acetic anhydride in the presence of DMAP (Scheme 5). Thus, this cyclization also seems to proceed *via* **14**.



Scheme 5

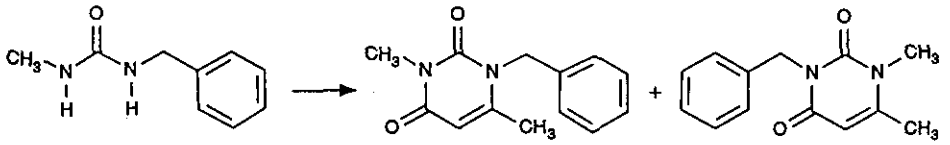
The occurrence of branched chain intermediates, as **14**, in the course of the autocondensation of acetic anhydride catalyzed by DMAP is plausible and can be evidenced by the findings of Vorbrüggen and Bennua.[7] They noticed that mixtures of equimolar amounts of acetic anhydride and DMAP come to boiling and darkening. From these reaction mixtures, several cyclic products such as dehydracetic acid (**15**), 3,5-diacetyl-2,6-dimethylpyran-4-one (**16**) and 4,7-dimethylpyrano[4,3-*b*]pyran-2,5-dione (**17**) (Scheme 6), were isolated and are likely to be formed *via* **14**.



15 16 17

Scheme 6

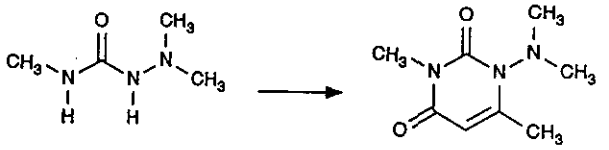
As one can anticipate, the reaction of 1-benzyl-3-methylurea (**18**) yielded both isomers. In accordance with the difference in the nucleophilicity of the *N*-methyl and the *N*-benzyl group, presumably following the basicity order of the corresponding amines, an approximately 3:2 mixture of 1-benzyl-3,6-dimethyluracil (**19**) and 3-benzyl-1,6-dimethyluracil (**20**) was obtained (Scheme 7). Products (**19**) and (**20**) were separated by medium pressure lc and characterized by comparison with data from the literature.[6,8]



18 19 20

Scheme 7

In contrast, from 1,1,4-trimethylsemicarbazide (**21**) just one isomer was obtained, which by elemental analysis and spectroscopic data, especially NOE difference spectroscopy, was identified as 1-dimethylamino-3,6-dimethyluracil (**22**) (Scheme 8).



21 22

Scheme 8

EXPERIMENTAL

Melting points: uncorrected, Reichert-Kofler hot-stage microscope. Ir spectra (KBr; cm^{-1}): Shimadzu IR-470; only selected absorptions are reported. ^1H Nmr spectra: Jeol JMN-PMX 60; δ-values in ppm using TMS as internal standard, J in Hz.

General Procedure

Acetic anhydride (3.37 g, 33 mmol) was added to a solution of 10 mmol of the appropriate disubstituted urea and DMAP in 10 ml dry pyridine under ice cooling and stirring. The mixture was kept at room temperature for 12 h, then poured into 100 ml 2N HCl and extracted three times with 50 ml portions of methylene chloride each. The combined methylene chloride extract was evaporated under reduced pressure and the resulting residue was either separated by medium pressure lc[9] on silica (Kieselgel Merck, corn size 0.040-0.063 mm, eluting agents given below) or purified by recrystallization.

3,6-Dimethyl-1-phenyluracil (10)

Yield 1.28 g (59%); mp 301°C (chloroform/hexane) (lit.,[6] mp 300°C). Ir: 1690 and 1660 (C=O); nmr ($CDCl_3$): 7.5-7.2 (m, 5H, aromat.), 5.50 (s, 1H, H-5), 3.30 (s, 3H, 3-CH_3), 1.80 (s, 3H, 6-CH_3).

1-Cyclohexyl-3,6-dimethyluracil (12) and 5-Acetyl-1-cyclohexyl-3,6-dimethyluracil (13)

Eluting agent: Methylene chloride

12: Yield 0.33 g (15%); mp 214°C (methanol) (lit.,[6] mp 211-213°C). Ir: 1700 and 1660 (C=O); nmr ($CDCl_3$): 5.50 (s, 1H, H-5), 3.85 (m, 1H, cyclohexyl), 3.22 (s, 3H, 3-CH_3), 2.20 (s, 3H, 6-CH_3), 1.80-1.25 (m, 10H, cyclohexyl).

13: Yield 0.37 g (14%); mp 165-168°C (methanol). Ir: 1700 and 1660 (C=O); nmr ($CDCl_3$): 4.03 (m, 1H, cyclohexyl), 3.26 (s, 3H, 3-CH_3), 2.50 (s, 3H, CH_3CO), 2.20 (s, 3H, 6-CH_3), 1.80-1.25 (m, 10H, cyclohexyl). Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.62; H, 7.75; N, 10.57.

1-Benzyl-3,6-dimethyluracil (19) and 3-Benzyl-1,6-dimethyluracil (20)

Eluting agent: Ethyl acetate

19: Yield 0.66 g (29%); mp 83-84°C (ether) (lit.,[8] mp 84-85°C). Ir: 1695 and 1660 (C=O); nmr ($CDCl_3$): 7.5-7.0 (m, 5H, aromat.), 5.64 (s, 1H, H-5), 5.10 (s, 2H, CH_2), 3.37 (s, 3H, 3-CH_3), 2.13 (s, 3H, 6-CH_3).

20: Yield 0.44 g (19%); mp 166-167°C (methanol) (lit.,[6] mp 165°C). Ir: 1700 and 1660 (C=O); nmr ($CDCl_3$): 7.6-7.2 (m, 5H, aromat.), 5.62 (s, 1H, H-5), 5.07 (s, 2H, CH_2), 3.35 (s, 3H, 1-CH_3), 2.20 (s, 3H, 6-CH_3).

1-Dimethylamino-3,6-dimethyluracil (22)

Yield 0.36 g (20%); mp 170°C (chloroform/hexane). Ir: 1700 and 1660 (C=O); nmr ($CDCl_3$): 5.50 (s, 1H, H-5), 3.29 (s, 3H, 3-CH_3), 2.92 (s, 6H, dimethylamino), 2.20 (s, 3H, 6-CH_3). Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.50; H, 7.19; N, 22.83.

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