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Studies on uracils: a facile one-pot synthesis of pyrazolo[3,4-*d*]pyrimidines

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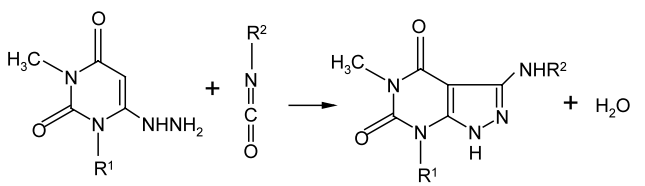
Abstract—The reaction of 6-hydrazino uracils **1** with isocyanates **2** gave access to an efficient one-pot synthesis of pyrazolo[3,4-*d*]pyrimidines **3** in excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

The importance of uracil and its annelated derivatives is well recognised by synthetic[1] as well as biological[2] chemists. Pyrazolo[3,4-*d*]pyrimidines are a class of naturally occurring fused uracils that possess a wide range of biological activity.[3] Allopurinol (6-dehydroxy-pyrazolo[3,4-*d*]pyrimidine), an effective xanthine oxidase inhibitor,[4] is in clinical use for controlling gout and related metabolic disorders.[5] Furthermore, the allopurinol 1-ribo-nucleotide-like 6-azauridine-5′-phosphate is a potential antiviral and antitumor agent.[6] Several reports are available which suggest that 4-aminopyrazolo[3,4-*d*]pyrimidine nucleosides and related compounds may function as substrates for anabolic and catabolic enzymes.[7] The discovery of strong antiparasitic properties shown by allopurinol, its 1-β-D-ribose derivative and related compounds has resulted in extensive work in this area, which has been reviewed.[8] However, a literature survey revealed only a few reports on the synthesis of the parent pyrazolo[3,4-*d*]pyrimidine moiety, which usually requires drastic conditions, long reaction times and complex synthetic pathways.

Synthetic exploitation of the nucleophilic double bond of uracils is an important field in view of a great variety[9] of potential products. Recently, we reported[10] a novel method for the synthesis of pyrimido[4,5-*c*]pyridazines from the reaction of 6-hydrazino uracils and acetylene dicarboxylates at room temperature. In the present communication we describe the results of our study of the reaction of 6-hydrazino uracils and isocyanates, which gives access to an efficient one-pot synthesis of pyrazolo[3,4-*d*]pyrimidines and thus a novel class of 3-amino-pyrazolo[3,4-*d*]pyrimidines in excellent yields.

A previous synthesis of pyrazolo[3,4-*d*]pyrimidine reported by Yoneda et al.[11a,b] involved the cycloaddition of the azahexatriene obtained from the reaction of an arylaldehyde and a 6-uracil hydrazone. One disadvantage of this approach is the concomitant arylation of the pyrazolo moiety. Earlier this class of compounds was synthesised by fusion of 6-uracil hydrazones at 300°C.[11c] Another synthesis reported by Maki et al.[12] required the cycloaddition of an arylhydrazone with 6-chloro-5-nitro uracil, which involved several steps. Further, Kanazawa et al.[13] synthesised pyrazolo[3,4-*d*]pyrimidines by the reaction of 6-aryledinehydrazinouracils with NBS (*N*-bromosuccinimide) in acetic acid under refluxing conditions, which yielded triazino and pyridazinouracils in addition to the pyrazolo[3,4-*d*]pyrimidines (Scheme 1).

Our synthetic strategy utilising 6-hydrazinouracils **1** and isocyanates **2** affords an unprecedented one-pot



Scheme 1.

Keywords: uracil; pyrazolo[3,4-*d*]pyrimidine; phenyl isocyanate.

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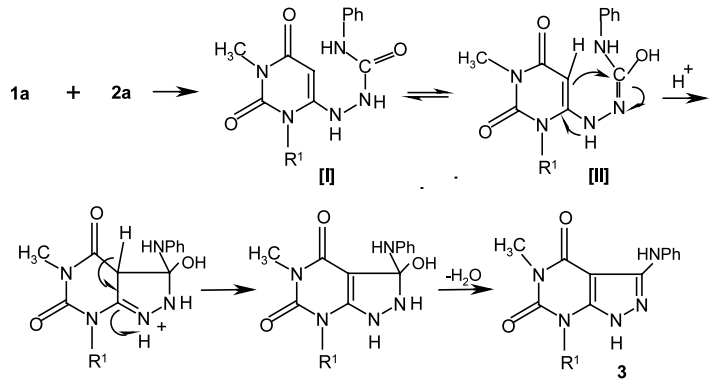

Scheme 2.

synthesis of pyrazolo[3,4-*d*]pyrimidines **3** in excellent yields.

In a very simple experimental procedure an equimolar amount of 1,3-dimethyl-6-hydrazino uracil[14] **1a** (0.170 g, 1 mmol) was added quickly to phenyl isocyanate **2a** (0.119 g, 1 mmol) at room temperature. An exothermic reaction occurred. After 10 min the reaction mixture was refluxed in ethanol (10 ml) for 20 min. On cooling the thick precipitate of the product, which appeared in the reaction mixture was filtered, washed with a small amount of ethanol and dried. A 95% yield (0.257 g) of the compound was obtained and confirmed as **3a** from spectroscopic data and elemental analysis, mp 246°C. ^{1}H NMR 90 MHz ($CDCl_3$+TFA) δ 2.95 (s, 3H), 3.30 (s, 3H), 6.75–7.20 (m, 5H). ^{13}C NMR 75 MHz ($CDCl_3$+TFA) δ 28.0 (N^3-CH_3); 28.5 (N^1-CH_3); 107.0 (4a); (112.2, 114.2, 120.0, 123.7 aromatic); 129.6 (C-5); 158.0 (C-7a); 158.4 (C-2); 160.0 (C-4). IR 3220, 3202, 1700 cm^{-1}. MS 271 M$^+$. CHN analyses (calcd %) C, 57.56; H, 4.80; N, 25.83; (found %) C, 57.52; H, 4.75; N, 25.85. The IR spectrum showed the involvement of the hydrazine group and the absence of the C-5 proton of the uracil moiety in the ^{1}H NMR spectrum evidenced in the cyclisation process in the reaction. Similarly, compounds **3b–d** were prepared and the structures confirmed by spectroscopic data and elemental analyses. **3b**: mp 242°C. ^{1}H NMR 90 MHz ($CDCl_3$+TFA) δ 2.95 (s, 3H), 6.80–7.25 (m, 5H). ^{13}C NMR 75 MHz ($CDCl_3$+TFA) δ 28.8 (N^3-CH_3); 107.2 (4a); (111.7, 115.5, 120.2, 124.6 aromatic); 128.9 (C-5); 158.0 (C-7a); 158.5 (C-2); 160.0 (C-4). IR 3250, 3205, 3125, 1700 cm^{-1}. MS 257 M$^+$. CHN analysis (calcd %) C, 56.03; H, 4.28; N, 27.24; (found %) C, 56.10; H, 4.29; N, 27.20. **3c**: mp 253°C. ^{1}H NMR 90 MHz ($CDCl_3$+TFA) δ 3.00 (s, 3H), 3.25 (s, 3H), 4.20 (s, 2H), 6.75–7.20 (m, 5H). ^{13}C NMR 75 MHz ($CDCl_3$+TFA) δ 28.5 (N^3-CH_3); 28.9 (N^1-CH_3); 41.0 (CH_2Ph); 107.4 (4a); (124.0, 125.2, 126.4, 127.0 aromatic); 129.2 (C-5); 158.0 (C-7a); 159.2 (C-2); 160.0 (C-4). IR 3220, 3210, 1700 cm^{-1}. MS 285 M$^+$. CHN analysis (calcd %) C, 58.94; H, 5.26; N, 24.56; (found %) C, 58.95; H, 5.20; N, 24.55. **3d**: mp 262°C. ^{1}H NMR 90 MHz ($CDCl_3$+TFA) δ 3.00 (s, 3H), 4.25 (s, 2H), 6.70–7.25 (m, 5H). ^{13}C NMR 75 MHz ($CDCl_3$+TFA) δ 28.2 (N^3-CH_3); 41.5 (CH_2Ph); 107.4 (4a); (123.4, 124.2, 125.1, 125.6 aromatic); 130.2 (C-5); 158.8 (C-7a); 159.4 (C-2); 160.2 (C-4). IR 3230, 3220, 3205, 1700 cm^{-1}. MS 271 M$^+$. CHN analyses (calcd %) C, 57.56; H, 4.80; N, 25.83; (found %) C, 57.50; H, 4.85; N, 25.80.

Although we could not isolate any intermediates from the reaction mixture a reasonable mechanism for the formation of the product is outlined in Scheme 2. The reaction occurs via a nucleophilic attack of the hydrazine group onto the carbon atom of the isocyanate to give compound [**I**]. The imine [**II**], which might have been formed during the reaction suffers another nucleophilic attack by the C-5 atom of the uracil, followed by elimination of a water molecule to yield the product.

It was interesting to note that the reaction occurred immediately after the addition of the 6-hydrazino uracils to the isocyanates and a low yield of the cyclised product was found (in carefully observed TLC) in the reaction mixture. The intermediate which could not be isolated from the reaction mixture due to solubility problems, cyclised completely on heating in ethanol.

Further study of this effective synthetic method is in progress. In conclusion, our results demonstrate a very simple and efficient method for the synthesis of well functionalised pyrazolo[3,4-*d*]pyrimidines of biological importance in excellent yields. Heteroannulation on the nucleophilic double bond of uracil, which is an important developing field for synthetic manipulation, usually requires either forcing conditions or relatively long and complex synthetic pathways. Our results delineated above have demonstrated that heteroannulation on the double bond of uracil is possible under simple and moderate conditions using suitable organic reagents such as isocyanates.

References

1. (a) Bradshaw, T. K.; Hutchison, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43; (b) Lunt, E. In *Comprehensive Organic Chemistry*; Barton, D. H. R.; Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 4, p. 493; (c) Brown, D. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p.

57; (d) Sasaki, T.; Minamoto, K.; Suzuki, T.; Yamashita, S. *Tetrahedron* **1980**, *36*, 865; (e) Prajapati, D.; Bhuyan, P. J.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 607; (f) Bhuyan, P. J.; Borah, H. N.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3083.

2. (a) Marumoto, R.; Furukawa, Y. *Chem. Pharm. Bull.* **1977**, *25*, 2974; (b) Griengl, H.; Wanck, E.; Schwarz, W.; Streicher, W.; Rosenwirth, B.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 1199; (c) De Clercq, E.; Bernaerts, R. *J. Biol. Chem.* **1987**, *262*, 14905; (d) Jones, A. S.; Sayers, J. R.; Walker, R. T.; De Clercq, E. *J. Med. Chem.* **1988**, *31*, 268; (e) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533; (f) Pontikis, R.; Monneret, C. *Tetrahedron Lett.* **1994**, *35*, 4351.
3. Sutcliffe, E. Y.; Zee-Cheng, K. Y.; Cheng, C. C.; Robins, R. K. *J. Med. Chem.* **1962**, *5*, 588.
4. (a) Elion, G. B.; Callahan, S. W.; Nathan, H.; Bieber, S.; Rundles, R. W.; Hilching, G. H. *Biochem. Pharmacol.* **1963**, *12*, 85; (b) Rundles, R. W.; Wyngarden, J. W.; Hilching, G. H.; Elion, G. B.; Silbermann, H. R. *Trans. Assoc. Am. Physicians* **1963**, *76*, 126.
5. Elion, G. B.; Hand, B. *Exp. Pharmacol.* **1978**, *51*, 48f.
6. (a) Fyfe, J. A.; Miller, R. L.; Krenitsky, T. A. *J. Biol. Chem.* **1973**, *248*, 3801; (b) Trant, T. W.; Jones, M. E. *Biochem. Pharmacol.* **1977**, *26*, 2291.
7. (a) Bennett, L. L., Jr.; Allan, P. W.; Smithers, D.; Vail, M. H. *Biochem. Pharmacol.* **1969**, *18*, 725; (b) Hecht, S. M.; Frye, R. B.; Werner, D.; Fukui, T.; Hawrelak, S. D. *Biochemistry* **1976**, *15*, 1005.
8. Hups, D. J. *Annu. Rep. Med. Chem.* **1986**, *21*, 247.
9. (a) Taylor, E. C.; Sowinski, F. *J. Org. Chem.* **1974**, *39*, 907; (b) Yoneda, F.; Kawamura, M.; Matsumoto, S.; Higuichi, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2285; (c) Wamhoff, H.; Winfried, S. *J. Org. Chem.* **1986**, *51*, 2787; (d) Hirota, K.; Banno, K.; Yumuda, Y.; Senda, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1137; (e) Sasaki, T.; Minamoto, T.; Suzuki, T.; Suguira, T. *J. Am. Chem. Soc.* **1978**, *100*, 2248; (f) Prajapati, D.; Sandhu, J. S. *Synthesis* **1988**, 342; (g) Bhuyan, P. J.; Sandhu, J. S.; Ghosh, A. C. *Tetrahedron Lett.* **1996**, *37*, 1853.
10. Bhuyan, P. J.; Lekhok, K. C.; Sandhu, J. S. *Tetrahedron Lett.* **1999**, *40*, 1793.
11. (a) Yoneda, F.; Higuchi, M.; Nagamatsu, T. *J. Am. Chem. Soc.* **1974**, *96*, 5607; (b) Yoneda, F.; Nagamatsu, T.; Senga, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 765; (c) Yoneda, F.; Nagamatsu, T. *Synthesis* **1973**, 300.
12. Maki, Y.; Izuka, K.; Suzuki, M. *J. Chem. Soc., Chem. Commun.* **1971**, 1442.
13. Kanazawa, H.; Nishigaki, S.; Senga, K. *J. Heterocycl. Chem.* **1984**, *21*, 969.
14. Pfleiderer, W.; Ferch, H. *Annalen* **1958**, *52*, 615.