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Studies on 6-[(dimethylamino)methylene]aminouracil: a facile one-pot synthesis of novel pyrimido[4,5-*d*]pyrimidine derivatives

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Abstract—The reactions of 6-[(dimethylamino)methylene]aminouracil **1**, with various heterocumulenes such as aryl isocyanates and isothiocyanates give rise to novel pyrimido[4,5-*d*]pyrimidines in excellent yields, after elimination of dimethylamine from the (1:1) cycloadducts and tautomerisation. This procedure provides a convenient method for direct synthesis of pyrimido[4,5-*d*]pyrimidine derivatives under thermal conditions.

Pyrimidines and fused pyrimidines represent a broad class of compounds, which have received considerable attention due to their wide range of biological activities.[1–4] Among them, the pyrimido[4,5-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines are an important class of annulated uracils with biological significance because of their connection with purine pteridine systems.[5] Several patents have been reported for the preparation of these fused heterocycles, derivatives of which are useful as bronchodilators,[6] vasodilators,[2] antiallergic,[6,7] antihypertensive[8] and anticancer[6] agents. Most of these preparations rely on cyclocondensation reactions from pyrimidine or pyridine intermediates. However this type of stepwise synthetic strategy limits the synthetic flexibility. Recently pyrimido[4,5-*d*]pyrimidine analogues of folic acid have been screened for antitumour activity.[9] Therefore, with the aim of the preparation of these complex molecules, there has been remarkable interest in the synthetic manipulations of uracils,[10] although the synthetic exploitation of the nucleophilic double bond of uracil is an undeveloped field in view of a great variety of potential products.[11] An approach to the synthesis of pyrimido[4,5-*d*]pyrimidines reported by Wamhoff and Muhr[12] is the aza-Wittig type reaction of iminophosphoranes of 5-aminouracils leading to functionalised pyrimido[4,5-*d*]pyrimidines. Our synthetic strategy utilizing aromatic isocyanates and isothiocyanates with 6-[(dimethylamino)methylene]aminouracil affords an unprecedented one-pot synthesis of novel pyrimido[4,5-*d*]pyrimidines in excellent yields in refluxing nitrobenzene in 45–70 min based on a [4+2] cycloaddition strategy. In the past a cycloaddition approach has had little appeal since the dienophilic nature of the pyrimidine ring is rather limited, and the diene properties of vinylpyrimidines had not been established.[13] It was postulated that if a vinylpyrimidine system were appropriately substituted with strongly electron-donating groups, cycloaddition might occur with electron deficient dienophiles. It has been reported that the dienyl-character of furan is enhanced by incorporation of a dimethylhydrazino group[14] and as 1-(dimethylamino)-3-methyl-2-azabutadiene[15] functions as an azadiene, perhaps the dienic character of vinylpyrimidines would be increased by similar substituents. This is also supported by HOMO calculations.[16] It is notable that although the chemistry of isothiocyanates greatly resembles that of isocyanates, the cycloaddition reactions of isothiocyanates have received little attention. In addition to their widely known nucleophilic substitution reactions, isothiocyanates react with suitable substrates to form 1,2-, 1,3- and 1,4-cycloadducts.[17a] With isocyanates, reactions occur almost exclusively across the C=N bond, while with the isothiocyanates, the C=S bond often participates in the cycloaddition reactions. Perhaps the best example of the interaction across the C=S bond is the dimerisation of sulfonyl isothiocyanates to afford the symmetric dimers.[17b] In a recent report[18] various isocyanates were reacted with

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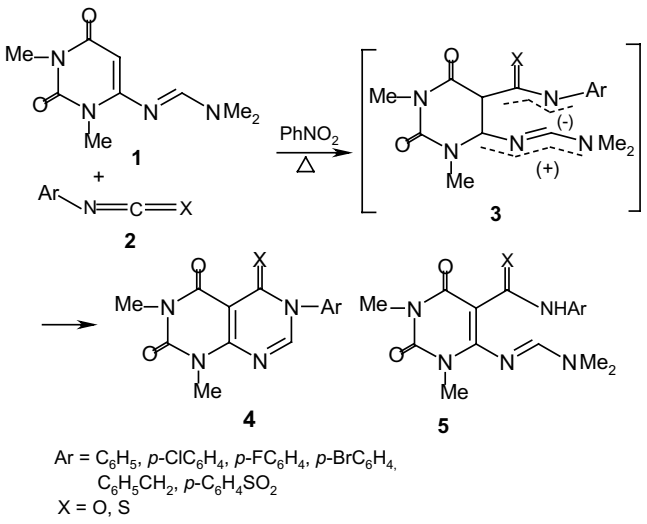

Scheme 1.

6-hydrazino-uracils in refluxing ethanol and the corresponding pyrazolo[3,4-*d*]pyrimidines were obtained in excellent yields. We have now found that the C=N bond of isocyanates and isothiocyanates react with uracil amidine **1**, yielding novel pyrimido[4,5-*d*]pyrimidine derivatives in excellent yields, leaving the C=S bond of isothiocyanates intact (Scheme 1).

Treatment of 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil **1**, with an equimolar amount of aryl isocyanate **2a** (Ar = C_6H_5, X = O) in nitrobenzene (10 mL) under reflux conditions gave, after elimination of dimethylamine from the 1:1 cycloadduct, the pyrimido[4,5-*d*]pyrimidine **4a** as the only product (yellowish solid) mp 209–210 °C in an 86% yield.[19] The 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil **1**, was readily obtained by the reaction of 6-amino-1,3-dimethyl barbituric acid with (DMF–DMA) under thermal conditions in the solid state. The reaction proceeds more efficiently when carried out under microwave irradiation and it takes only 3 min to complete the reaction in 90% yield. The structure of product **4a** as a pyrimido[4,5-*d*]pyrimidine derivative was assigned on the basis of its elemental and spectral analyses. The diagnostic signal for the isocyanate at 2275 cm^{-1} in the IR was absent in the cycloadduct whilst the appearance of peak at 1610 cm^{-1} showed that the cycloaddition had occurred at the C=N bond of the isocyanate. Also, the ^1H NMR spectrum showed the absence of the H-5 proton of the uracil **1** and the presence of two methyl groups from the cycloadduct **4a** at δ 3.35 (s, 3H, CH_3) and at 3.68 (s, 3H, NCH_3), and other peaks at 6.98–7.54 (m, 5H, ArH) and 8.62 (s, 1H, CH=N–). Similarly, other pyrimido[4,5-*d*]pyrimidines **4b–d** were prepared in 80–86% yields (Table 1). To investigate further the synthetic scope of this cycloaddition reaction, we reacted various aromatic isothiocyanates **2e–i** with amidine **1** in refluxing nitrobenzene (45–70 min) and isolated the corresponding pyrimido[4,5-*d*]pyrimidine derivatives, after elimination of dimethylamine from the 1:1 cycloadducts. The ^1H NMR spectrum showed the absence of the H-5 proton of the uracil **1** and the presence of two methyl groups for the cycloadduct **3e** at δ 3.32 (s, 3H, NCH_3) and 3.60 (s, 3H, NCH_3). Also, the characteristic isothiocyanate peak at 2120 cm^{-1} was absent in the IR spectrum of the cycloadduct whilst the appearance of peak at 1600 cm^{-1} showed that the cycloaddition had occurred at the C=N bond of the isothiocyanate. However, we did not observe the formation of any Michael type products **5**. This finding is in contrast to an earlier report[20] where Sandhu et al. have obtained simple Michael adducts and failed to prepare fused pyrimidines from the reactions of α,β-unsaturated nitro compounds with 6-amino, 6-hydroxylamino and 6-hydrazino-1,3-dimethyluracils. However, with amidine **1** and aryl isocyanates or aryl isothiocyanates, we successfully synthesised fused pyrimidines in excellent yields. The high regiospecificity observed in these reactions is consistent with the electron donating effect of the dimethylamino substituent increasing the nucleophilicity of the C-5 position. Although, we could not isolate any intermediates from the reaction mixture, a reasonable mechanism for the formation of the product would involve initial electrophilic attack of the aryl isocyanate at the C-5 position of the amidine **1** to give the Michael adduct **3**, which suffers a subsequent nucleophilic attack on the imino carbon atom eliminating dimethylamine to give product **4**. However further work is in progress to understand the mechanism in detail.

In conclusion, our results demonstrate a new, simple and efficient synthesis of novel complex pyrimido[4,5-*d*]pyrimidine derivatives of biological significance in almost quantitative yields. These results also illustrate that the title compound **1** is a useful substrate for the generation of an array of fused nitrogen heterocycles.

Table 1. Characteristics of pyrimido[4,5-*d*]pyrimidines **4a–i**

Product	Ar	X	Reaction time (min)	Yield[a] (%)	Mp (°C)
4a	C_6H_5	O	45	86	209–210
4b	*p*-BrC_6H_4–	O	60	82	171–173
4c	*p*-ClC_6H_4–	O	50	83	300–302
4d	*p*-$MeC_6H_4SO_2$–	O	70	80	335–337
4e	C_6H_5	S	65	85	279–281
4f	*p*-BrC_6H_4–	S	70	80	176–178
4g	*p*-FC_6H_4–	S	60	81	271–272
4h	*p*-ClC_6H_4–	S	65	85	273–275
4i	$C_6H_5CH_2$–	S	50	84	191–192

[a] Yields refer to the isolated pure compounds.

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References and notes

1. Castle, R. N.; Philips, S. D. In Katritzky, Rees, Eds.; Comprehensive Heterocyclic Chemistry; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 329ff; Melik-Ogandzhanyan, R. G.; Khachatryan, V. E.; Gapoyan, A. S. *Russ. Chem. Rev.* **1985**, *54*, 262.
2. Taylor, E. C.; Knopf, R. J.; Meyer, R. F.; Holmes, A.; Hoefle, M. L. *J. Am. Chem. Soc.* **1960**, *82*, 5711; Figueroa-Villar, J. D.; Carneiro, C. L.; Cruz, E. R. *Heterocycles* **1992**, *34*, 891.
3. Campaigne, E.; Ellis, R. L.; Bradford, M.; Ho, J. *J. Med. Chem.* **1996**, *12*, 339.
4. Blume, F.; Arndt, F.; Ress, R. Ger. Patent 3712782, 1988; *Chem. Abstr*. **1989**, *110*, 154312e.
5. (a) Lunt, E. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1974; Vol. 4, p 493; (b) Brown, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, p 57; (c) Clercq, E. D.; Beraaerts, R. *J. Biol. Chem.* **1987**, *262*, 14905.
6. Coates, W. J. Eur. Patent 351058, 1990; *Chem. Abstr*. **1990**, *113*, 40711; Ramsey, A. A. U.S. Patent 3830812, 1974; FMC Corp, *Chem. Abstr*. **1974**, *81*, 136174.
7. Kitamura, N.; Onishi, A. Eur. Pat. 163599, 1984; *Chem. Abstr*. **1984**, *104*, 186439.
8. Raddatz, P.; Bergmann, R. Ger. Pat. 360731, 1988; *Chem. Abstr*. **1988**, *109*, 54786.
9. Delia, T. J.; Baumann, M.; Bunker, A. *Heterocycles* **1993**, *35*, 1397.
10. (a) Hirota, K.; Kitade, Y.; Senda, S.; Halat, M. J.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 846; (b) Su, T. L.; Huang, J. T.; Burchanal, J. H.; Watanabe, K. A.; Fox, J. J. *J. Med. Chem.* **1986**, *29*, 709; (c) Prajapati, D.; Sandhu, J. S. *Synthesis* **1988**, 342.
11. (a) Taylor, E. C.; Sawinski, F. *J. Org. Chem.* **1974**, *39*, 907; (b) Wamhoff, H.; Winfried, S. *J. Org. Chem.* **1986**, *51*, 2787; (c) Hirota, K.; Benno, K.; Yamada, Y.; Senda, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1137; (d) Sasaki, T.; Minamoto, T.; Suzuki, T.; Suguira, T. *J. Am. Chem. Soc.* **1978**, *100*, 2248.
12. Wamhoff, H.; Muhr, J. *Synthesis* **1988**, 919.
13. Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3478; Thiellier, H. P. M.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1977**, *33*, 1493, 2603, 2609; Senda, S.; Asao, T.; Sugiyama, I.; Hirota, K. *Tetrahedron Lett.* **1980**, *21*, 531.
14. Potts, K. T.; Walsh, E. B. *J. Org. Chem.* **1988**, *53*, 1199.
15. Demoulin, A.; Gorissen, H.; Hesbain Frisque, A.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 4409.
16. Streitwieser, A. *Molecular Orbital Theory for Organic Chemists*; Wiley: New York, 1961; p 115.
17. (a) Ulrich, U. *Cycloaddition Reactions of Heterocumulenes*; Academic: New York, 1967; pp 8–253; (b) Dickore, K.; Kuhle, E. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 430; (c) Dickore, K.; Kuhle, E. Ger. Pat. 1,183,492, 1964; *Chem. Abstr*. **1965**, *62*, 7691.
18. Bhuyan, P. J.; Borah, H. N.; Sandhu, J. S. *Tetrahedron Lett.* **2002**, *43*, 895.
19. *Typical reaction of uracil amidine* **1** *with aromatic isocyanates and isothiocyanates*: To a solution of 6-[(dimethylamino)methylene]-1,3-dimethyl uracil **1** (0.210 g, 1 mmol) in redistilled nitrobenzene (10 mL), phenyl isocyanate **2a** (Ar = C_6H_5, X = O, 0.12 g, 1 mmol) was added and the resulting mixture allowed to reflux for 45 min (monitored by TLC). After completion of the reaction, the nitrobenzene was distilled off from the reaction mixture under reduced procedure. The crude, so obtained, was subjected to column chromatography to afford the corresponding pyrimido[4,5-*d*]pyrimidine **4a** in 86% yield, mp 209–210 °C, recrystallised from chloroform–petroleum ether (40–60) (3:1). To generalize this reaction we reacted various aryl isocyanates and isothiocyanates **2** with uracil amidine **1** and isolated the corresponding pyrimido[4,5-*d*]pyrimidines in 80–86% yields. The structure of the fused pyrimidines **4** thus obtained were confirmed on the basis of their spectral and elemental analyses. Compound **4a**: (yellowish solid), IR ν_{max}/KBr/cm^{-1}: 1660, 1720 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$) at δ 3.35 (s, 3H, CH_3), 3.68 (s, 3H, NCH_3), 6.98–7.54 (m, 5H, ArH), 8.62 (s, 1H, CH=N–); δ_c 28.0 (NMe), 29.6 (NMe), 90.9 (C-4a), 127.6 (C-2′), 129.2 (C-4′), 130.4 (C-3′), 139.9 (C-1′), 151.6 (C-8a), 157.4 (C-2), 158.0 (C-7), 158.3 (C-4), 158.6 (C-5). MS *m*/*z* 284 (M^+). Anal. Calcd for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.23; N, 19.72. Found: C, 59.22; H, 4.28; N, 19.65%. Compound **4b**: (yellowish solid), IR ν_{max}/KBr/cm^{-1}: 1674, 1719 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$) δ 3.22 (s, 3H, NMe), 3.42 (s, 3H, NMe), 7.02-7.70 (m, 4H, ArH), 8.12 (s, 1H, CH=N–); δ_c 27.7 (NMe), 29.4 (NMe), 90.9 (C-4a), 126.9 (C-2′), 127.4 (C-6′), 128.8 (C-4′), 129.8 (C-5′), 133.3 (C-3′), 133.9 (C-4′), 150.4 (C-8a), 157.5 (C-2), 158.0 (C-7, C-4), 158.6 (C-5). MS *m*/*z* 363 (M^+). Anal. Calcd for $C_{14}H_{11}N_4O_3Br$: C, 46.28; H, 3.03; N, 15.43. Found: C, 55.22; H, 4.28; N, 19.65%. Compound **4c**: (whitish solid), IR ν_{max}/KBr/cm^{-1}: 1680, 1736 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$) δ 3.32 (s, 3H, NMe), 3.63 (s, 3H, NMe), 7.06–7.66 (m, 4H, ArH), 8.10 (s, 1H, CH=N–); δ_c 27.6 (NMe), 29.9 (NMe), 91.3 (C-4a), 121.7, 126.1, 128.0, 130.1, 133.9, 134.3, 150.7, 156.7, 157.7, 158.6. MS *m*/*z* 318 (M^+). Anal. Calcd for $C_{14}H_{11}N_4O_3Cl$: C, 52.83; H, 3.46; N, 17.61. Found: C, 52.89; H, 3.53; N, 17.53%. Compound **4d**: (yellowish solid), IR ν_{max}/KBr/cm^{-1}: 1660, 1722 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ 2.28 (C–Me), 3.25 (s, 3H, NMe), 3.46 (s, 3H, NMe), 6.98 (d, 2H, *J* = 9, ArH), 7.48 (d, 2H, *J* = 9, ArH), 8.22 (s, 1H, CH=N–); δ_c 21.4 ($PhCH_2$), 28.0 (NMe), 30.1 (NMe), 91.8 (C-4a), 127.6, 130.0, 130.8, 139.4, 151.8, 157.1, 158.4, 158.9. MS *m*/*z* 362 (M^+). Anal. Calcd for $C_{15}H_{14}N_4O_5S$: C, 49.72; H, 3.87; N, 15.47. Found: C, 49.81; H, 3.92; N, 15.39%. Compound **4e**: IR ν_{max}/KBr/cm^{-1}: 1663, 1713 (C=O), 1600 (C=N); ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3H, NMe), 3.69 (s, 3H, NMe), 7.27–7.30 (m, 2H, ArH), 7.53–7.57 (m, 3H, ArH), 8.32 (s, 1H, CH=N–); δ_c 28.8 (NMe), 30.5 (NMe), 91.3 (C-4a), 127.6, 128.1, 130.0, 140.2, 151.7, 157.5, 1580, 159.2. MS *m*/*z* 300 (M^+). Anal. Calcd for $C_{14}H_{12}N_4O_2S$: C, 56.00; H, 4.00; N, 18.67. Found: C, 56.10; H, 4.06; N, 18.59%. Compound **4f**: IR ν_{max}/KBr/cm^{-1}: 1680, 1710 (C=O), 1599 (C=N); ^{1}H NMR ($CDCl_3$) δ 3.20 (s, 3H, NMe), 3.38 (s, 3H, NMe), 7.10–7.75 (m, 4H, ArH), 8.12 (s, 1H, CH=N–); MS *m*/*z* 379 (M^+). Anal. Calcd for $C_{14}H_{11}N_4O_2SBr$: C, 44.33; H, 2.90; N, 14.78. Found: C, 44.40; H, 2.98; N, 14.69%. Compound **4g**: IR ν_{max}/KBr/cm^{-1}: 1670, 1715 (C=O), 1596 (C=N); ^{1}H NMR ($CDCl_3$) δ 3.34 (s, 3H, NMe), 3.54 (s, 3H, NMe), 7.12–7.76 (m, 4H, ArH), 8.10 (s, 1H, CH=N–); MS *m*/*z* 318 (M^+). Anal. Calcd for $C_{14}H_{11}N_4O_2SF$: C, 52.83; H, 3.46; N, 17.61. Found: C, 52.89; H, 3.52; N, 17.53%. Compound **4h**: IR ν_{max}/KBr/cm^{-1}: 1675, 1712 (C=O),

1598 (C=N); ^{1}H NMR ($CDCl_3$) δ 3.16 (s, 3H, NMe), 3.32 (s, 3H, NMe), 7.06–7.71 (m, 4H, ArH), 8.16 (s, 1H, CH=N–); MS *m*/*z* 334 (M^+). Anal. Calcd for $C_{14}H_{11}N_4O_2SCl$: C, 50.30; H, 3.29; N, 1677. Found: C, 50.24; H, 3.36; N, 16.86%. Compound **4i**: IRν_{max}/KBr/cm^{-1}: 1670, 1715 (C=O), 1600 (C=N); ^{1}H NMR ($CDCl_3$). MS *m*/*z* 298 (M^+). Anal. Calcd for $C_{15}H_{14}N_4O_2S$: C, 60.40; H, 4.70; N, 18.79. Found: C, 60.48; H, 4.80; N, 18.68%.

20. Prasad, A. S.; Sandhu, J. S.; Baruah, J. N. *J. Heterocycl. Chem.* **1984**, *21*, 1657.