Studies on 6-[(Dimethylamino)methylene]aminouracils: a Facile One-pot Synthesis of Pyrimido[4,5-d]pyrimidines and Pyrido[2,3-d]pyrimidines.

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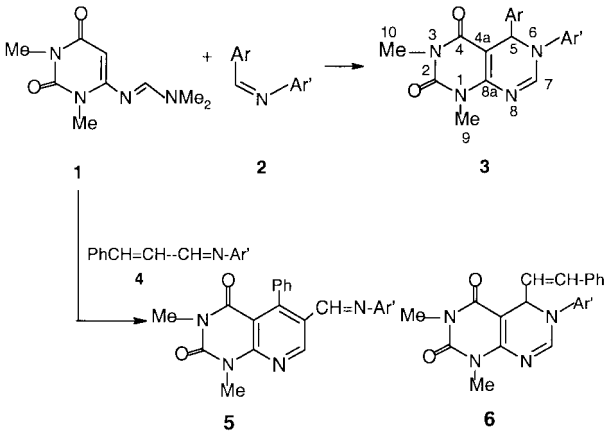
Abstract: 6-[(Dimethylamino)methylene]amino-1,3-dimethyl uracil **1** undergoes formal [4+2] cycloaddition reaction with non conjugated imines to give pyrimido[4,5-d]pyrimidines **3**. When reacted with conjugated imines and α,β-unsaturated nitro compounds cycloaddition also occurs leading to unexpected pyrido[2,3-d]pyrimidines **5** and **9**, respectively.

Key words: pyrimido[4,5-d]pyrimidines, pyrido[2,3-d]pyrimidines, imines, α,β-unsaturated nitro compounds and β−nitrostyrenes

Pyrimido[4,5-d]pyrimidines and pyrido[2,3-d]pyrimidines are an important class of annulated uracils of biological significances because of their connection with purine and pteridine systems.[1] Several patents have been reported for the preparation of these fused heterocycles, derivatives which are useful as bronchodilators,[2] vascodilators,[2] antiallergic,[2,3] antihypertensive[4] and anticancer[2] agents and recently pyrimido[4,5-d] pyrimidine analogues of folic acid have been screened for antitumor activity[5]. Therefore, for the preparation of these complex molecules, there has been remarkable interest in the synthetic manipulations of uracils.[6] Also the synthetic exploitation of the nucleophilic double bond of uracil is an undeveloped field in view of a great variety of potential products.[7] There have been reports for direct functionalisation of uracil using the C_5-C_6 double bond via thermolytic[8] and photocycloaddition reactions.[9] The heteroannulation of uracils usually require either forcing conditions[10] or relatively longer synthetic pathways.[11] In continuation of our studies on uracil analogues[12] we now want to present a new, simple and efficient preparation of novel fused pyrimidines based on [4+2] cycloaddition reaction by exploiting the 5-6 double bond of uracil in a one-pot synthesis.

A new approach to the synthesis of pyrimido[4,5-d]pyrimidines reported by Wamhoff et.al.[13] is the aza-Wittig-type reaction of iminophosphoranes of 5-aminouracils with aromatic isocyanates which leads to functionalised pyrimido[4,5-d]pyrimidines. Broom et al.[14] synthesised pyrido[2,3-d]pyrimidine from the reaction of DMAD and 6-aminouracil in protic solvent but obtained uncyclised condensed acetylenic adduct when the reaction was carried out in DMF. Also Wamhoff's group reported substituted pyrido[2,3-d]pyrimidines from 6-substituted uracil via [4+2] cycloaddition with electron-deficient olefins.[15] The main disadvantages in this method are the limitation to electron-deficient olefins and the low yield due to side reactions. Hirota et al synthesised pyrido[2,3-d]pyrimidines by the palladium-mediated C-C coupling reaction of electron-deficient olefins with uracil **1** in refluxing acetic acid,[16] but they used a stoichiometric amount of expensive $Pd(OAc)_2$ as a coupling reagent. Our synthetic strategy utilising non conjugated and conjugated imines and β-nitro styrenes with 6-[(dimethylamino)methylene]aminouracil affords an unprecedented one-pot synthesis of pyrimido[4,5-d]pyrimidines and pyrido[2,3-d]pyrimidines respectively in excellent yields.



Scheme 1

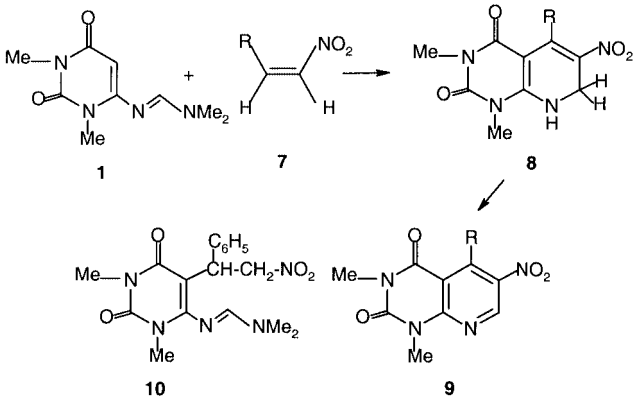
6-[(Dimethylamino)methylene]amino-1,3-dimethyl uracil **1** was readily obtained by the reaction of 6-amino-1,3-dimethylbarbituric acid with (DMF-DMA) under thermal condition in the solid state. The reaction proceeds more efficiently when carried out under microwave irradiation and takes only 3 min to complete the reaction in 90% yield. The arylidene-N-arylamines **2** and cinnamaldehyde imines **4** used were prepared from the corresponding aldehydes and amines by a published procedure.[17] Treatment of **1** with an equimolar amount of benzylidene aniline **2a** (Ar = Ph, Ar' = Ph) under reflux condition gave after elimination of dimethylamine from the 1:1 cycloadduct and tautomerisation, the pyrimido[4,5-d]pyrimidine **3a** as the only product in 95% yield[19] and there was no evidence for the formation of any other products. The structure of the compound **3a** was assigned on the basis of its spectral data and elemental analysis. The diagnostic signal for the azomethine proton at δ 8.20 was absent in the cycloadduct, whilst upfield shift of this from δ 8.20 to 6.08

showed that cycloaddition had occurred at the azomethine function. Also the ^{1}H NMR spectrum showed the absence of H-5 proton of the uracil **1** and two methyl groups from the cycloadduct **3a** and other signals appeared at δ 3.29 (s,3H, NCH_3), 3.55 (s, 3H, NCH_3), 6.08 (s, 1H, H-5), 7.07-7.79 (m, 10H, ArH), 8.12 (s, 1H, CH=N-). The mass spectrum of **3a** revealed a strong molecular ion peak at m/z 346. Similarly other pyrimido[4,5-d]pyrimidines **3b-f** were prepared in 70-95% yields and their characteristics are recorded in the Table. Interestingly, when the above reaction was carried out with a conjugated imine such as cinnamylidine aniline and refluxed in dry DMF for 6 h we obtained the pyrido[2,3-d]pyrimidine **5a** in 90% yield instead of the expected pyrimido[4,5-d]pyrimidine derivative **6a**. Here, the carbon-carbon double bond of conjugated imine reacted and the carbon-nitrogen double bond remained intact. The structure of the fused pyrimidine **5a** thus obtained is confirmed on the basis of its spectral analysis.The ^{1}H NMR spectra **5a** showed the presence of typical azomethine proton at δ 8.27 along with the N-methyls of the uracils (Scheme 1).

Table Characteristics for Pyrimido[4,5-d] and Pyrido[2,3-d]-pyrimidines.

Product	Ar	Ar'	Reaction time (h)	Yield[a] (%)	M.p. °C	M^+ (m/z)
3a	Ph	Ph	5	95	156-158	346
3b	4-ClC_6H_4	C_6H_5	8	87	212-214	380
3c	4-NO_2-C_6H_4	C_6H_5	7.5	90	203-205	391
3d	4-CH_3O-C_6H_4	C_6H_5	8	88	223-225	376
3e	4-Cl-C_6H_4	$C_2H_5OC_6H_4$	3.6	70	200-201	424
3f	4-ClC_6H_4	3-Cl-C_6H_4	12	90	230-231	414
5a	C_6H_5	C_6H_5	6	91	243-244	370
5b	C_6H_5	4-$CH_3OC_6H_4$	7	90	265-267	400
5c	C_6H_5	4-$CH_3C_6H_4$	6.5	98	199-200	384
5d	C_6H_5	α-Napthyl	7	96	208-210	420
9a	C_6H_5	-	4	91	197-198	312
9b	4-$CH_3OC_6H_4$	-	4	90	178-180	342
9c	4-CH_3-C_6H_4	-	3.5	88	219-221	326
9d	Furyl	-	4	92	170-172	302
9e	Thienyl	-	4	86	183-185	318
9f	4-ClC_6H_4	-	3.5	85	174-176	346

[a]Yields refer to the isolated pure compounds.



Scheme 2

To further investigate the synthetic scope of this cycloaddition reaction, we also reacted various α,β−unsaturated nitro compounds **7** with amidine **1** and isolated the corresponding dihydropyrido[2,3-d]pyrimidines **8**, which were readily converted into their aromatic analogues **9**, by oxidative aromatization in refluxing nitrobenzene.[18] The structure of product as pyrido[2,3-d]pyrimidine was assigned on the basis of its elemental and spectral analysis. This is in contrast to our earlier report[20] where we obtained the simple Michael adduct and failed to prepare fused pyrimidines from the reaction of α,β-unsaturated nitro compounds with 6-amino, 6-hydroxylamino and 6-hydrazino 1,3-dimethyluracils. However, with amidine **1** and β-nitrostyrene we successfully synthesised fused pyrimidines in excellent yields. The ^{1}H NMR spectrum of **9a** shows the absence of the methylene protons on the α-carbon atoms (characteristic peak for Michael adduct) and indicates the presence of −CH=N proton at δ 8.73 which rules out the formation of Michael adduct **10**. In addition to this signal, the two N-methyl protons of the uracil showed as singlets. The IR spectrum of this compound indicated a strong band at 1575 cm^{-1} which is the characteristic absorption of the NO_2 group and other bands at 1660 and 1705 cm^{-1} characteristic absorption of the uracil systems. The molecular ion peak M^+ in **9a** is at m/z 312. Similarly other β-nitrostyrenes were reacted with uracil **1** and the corresponding pyrido[2,3-d]pyrimidines **9b-f** were isolated in 85-92% yields. The high regiospecificity observed in these reactions is consistent with the electron donating effect of the dimethylamine substituent increasing the nucleophilicity of the C-5 position and the established reactivity of the olefins.

In conclusion, our results demonstrate a new, simple and efficient synthesis of novel complex pyrimido[4,5-d]pyrimidines and pyrido[2,3-d]pyrimidines 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.

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References and Notes

(1) a) Lunt, E., *Comprehensive Organic Chemistry*, Barton, D., Ollis, W. D., eds. Pergamon press, Oxford **1974**, Vol. 4, p 493; (b) Brown, J. D., *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R., Rees, C. W., Eds. Pergamon press, Oxford **1984**, Vol. 3, p 57; (c) Clercq, E. D., Beraaerts, R., *J. Biol. Chem.* **1987**, *262*, 14905.
(2) Coates, W. J., *Eur. Pat.* **1990**, 351058; *Chem. Abstr.* **1990**, *113*, 40711.
(3) Kitamura, N., and Onishi, A., *Eur. Pat.* **1984**, 163599; *Chem. Abstr.* **1984**, *104*, 186439.
(4) Raddatz, P., and Bergmann, R., *Ger. Pat.* **1988**, 3601731; *Chem. Abstr.* **1988**, *109*, 54786.

(5) Delia, T. J., Baumann, M., Bunker, A., *Heterocycles* **1993**, *35*, 1397.
(6) 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.
(7) 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., Yumuda, 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.
(8) Blank, H. V., Fox, J. J., *J. Am. Chem. Soc.* **1988**, *90*, 7175.
(9) a) Wexlar, A., Swenton, J. S., *J. Am. Chem. Soc.* **1976**, *98*, 1602; (b) Hyatt, J. A., Swenton, J. S., *J. Am. Chem. Soc.* **1972**, *94*, 7605.
(10) a) Yoneda, F., Higuichi, 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.
(11) Maki, Y., Tauta, K., Suzuki, K., *J. Chem. Soc., Chem. Commun.* **1971**, 1442.
(12) Bhuyan, P. J., Lekhok, K.C., Sandhu, J. S., *Tetrahedron Letters.* **1999**, *40*, 1793; Bhuyan, P. J., Boruah, R. C., Sandhu, J. S., *J. Org. Chem.* **1990**, *55*, 568; Baruah, B., Prajapati, D., Sandhu, J. S., Ghosh, A. C., *J. Chem. Soc., Perkin Trans 1.* **1996**, 1999.
(13) Wamhoff, H., and Muhr, J., *Synthesis* **1988**, 919.
(14) Broom, A. D., Shim, J. L., Anderson, C. L., *J. Org. Chem.* **1976**, *411*, 1095.
(15) Walsh, E. B., and Wamhoff, H., *Chem. Ber.* **1989**, *122*, 1673; Walsh, E. B., Nai-Jue, Z., Fang, G., Wamhoff, H., *Tetrahedron Letters.* **1988**, *29*, 4401.
(16) Hirota, K., Kuki, H., Maki, Y., *Heterocycles.* **1994**, *37*, 563.
(17) Singh, N., Sandhu, J. S., and Mohan, S., *Chem. Ind.,(London)* **1969**, 585.
(18) In a typical case, to a solution of 6-[(Dimethylamino)methylene]amino-1,3-dimethyluracil (0.210 g, 1 mmol) in dry DMF (15 mL), was added benzylidine aniline (0.207 g, 1 mmol) and the mixture allowed to reflux for 6 h (monitored via TLC). After completion of the reaction, the DMF was distilled off from the reaction mixture under reduced pressure. Then it was extracted with chloroform, washed with water (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and column chromatographed to give the pure product. Recrystallised from $CHCl_3$: pet.ether (40-60) (1:2), yield 95%, mp 156-158 °C (whitish solid). **3a** (Ar = Ph, Ar' = Ph): ν_{max} (KBr)/cm^{-1} 1690 and 1650 (C=O); δ_H (300 MHz, $CDCl_3$) 3.29 (s, 3H, NCH_3), 3.55 (s, 3H, NCH_3), 6.08 (s, 1H, H-5), 7.07-7.79 (m, 10H, ArH), 8.12 (s, 1H, -CH=N); δc 160.17 ((C-2), 151.48 (C-4) 151.12(C-8a), 121.72, 125.43, 126.69, 127.64, 128.03, 140.76, 140.89, 148.11 (C-7 and C-Ph), 90.16 (C-4a), 57.96 (C-5), 28.55 (C-9), 27.08 (C-10). m/z 346 (M^+); (Found: C, 69.47; H, 5.28; N, 16.29, $C_{20}H_{18}N_4O_2$ requires C, 69.36; H, 5.20; N, 16.18%). Similarly pyrido[2,3-d]pyrimidines **3b-f** and **5b-d** were prepared and characterised. **5a** m.p. 243-244 °C; ν_{max} (KBr)/cm^{-1} 1690 and 1660 (C=O); δ_H (300 MHz, $CDCl_3$) 3.35 (s, 3H, NCH_3), 3.83 (s, 3H, NCH_3), 6.68-7.82 (m, 10H, ArH), 8.27 (s, 1H, CH=N), 9.52 (s, 1H).
(19) In a typical procedure, to a solution of **1** (0.21 g, 1 mmol) in dry $CHCl_3$ (10 mL) at 0 °C, was added β-nitrostyrene (0.15 g, 1 mmol) slowly and stirred for 5 min. It was then removed from the ice bath and the reaction was allowed to stir at room temperature. The reaction immediately took a red colour, and the stiring was continued for another 1 h. A red solid was obtained which was removed and washed with chloroform and hexane repeatedly several times and a yellow solid was obtained. This was then taken in nitrobenzene (20 mL) and refluxed for 5 h. The nitrobenzene was then removed under reduced pressure and the solid thus obtained was extracted with chloroform and washed with sodium bicarbonate solution (3 × 20 mL). The organic layer was dried, distilled and purified through column chromatography to give the corresponding pyrido[2,3-d]pyrimidine **9a** in 91% yield. **9a** (R = C_6H_5): mp 197-198 °C; ν_{max} (KBr)/cm^{-1} 1575, 1705 and 1660 (NO_2, C=O). δ_H (300MHz, $CDCl_3$) 3.36 (s, 3H, NCH_3), 3.82 (s, 3H, NCH_3), 7.02-7.63 (m, 5H, ArH), 8.73 (s, 1H, -CH=N); m/z 312 (M^+) (Found: C, 57.76; H, 3.88; N, 17.80. $C_{15}H_{12}N_4O_4$ requires C, 57.69; H, 3.84; N, 17.94%). δ_c 158.27 (C-2), 152.22 (C-4), 149.73 (C-8a), 147.75 (C-5), 147.02, 142.61 (C-6, C-7), 128.65, 128.14, 125.85, 124.99 (C-Ph), 107.38 (C-4a), 28.55 (C-9), 27.08 (C-10).
(20) Prasad, A. S., Sandhu, J. S., Baruah, J. N., *J. Heterocycl. Chem.* **1984**, *21*, 1657.

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