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6-[(DIMETHYLAMINO)METHYLENE]AMINO-1,3-DIMETHYLURACIL: A VERSATILE AZA-DIENE SUBSTRATE FOR CYCLOADDITION AND MICHAEL-TYPE REACTIONS[1]

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Summary: 6-[(Dimethylamino)methylene]amino-1,3-dimethyluracil **1** undergoes formal [4+2] cycloaddition reactions with electron deficient olefins to give pyrido[2,3-d]pyrimidines. With DMAD or azodicarboxylates Michael addition occurs leading to pyrrolo[3,4-c]pyridines (X-ray analysis) and theophylline derivatives.

Fused pyrido-pyrimidines have long been of interest for their potential biological activities. As such, a large volume of work has been published on these compounds with syntheses usually involving cyclocondensation reactions of appropriate pyridine or pyrimidine intermediates[2]. Now we want to present a new, simple, and efficient preparation of these fused heterocycles based on a [4+2] cycloaddition reaction.

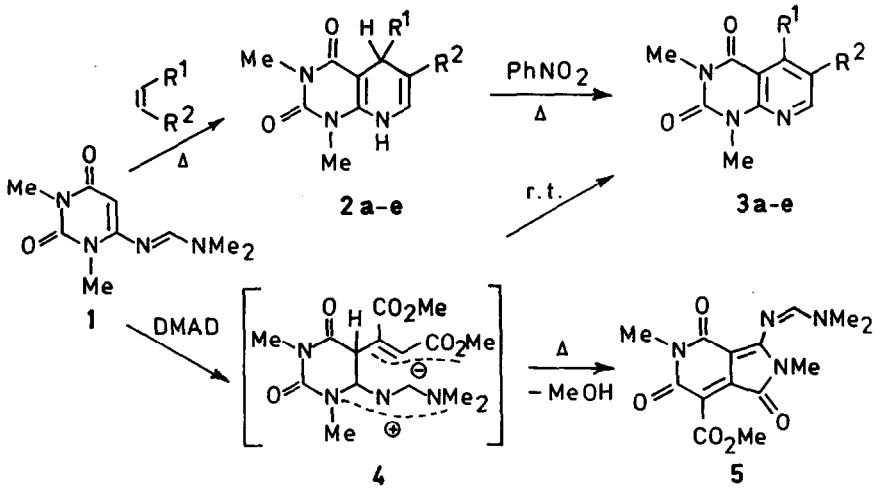
We have found that 6-[(dimethylamino)methylene]amino-1,3-dimethyluracil **1** behaves as a reactive diene with electron deficient olefins, addition occuring across the aza-diene moiety[3], providing substituted pyrido[2,3-d]pyrimidines. With dimethyl acetylenedicarboxylate or azadicarboxylates, Michael adducts were obtained leading to pyrrolo[3,4-c]pyridines and theophylline derivatives.

The title compound **1** was conveniently prepared in high yields by reaction of 6-amino-1,3-dimethyluracil with DMF-dimethylacetal. Treatment of **1** with an equimolar amount of methyl vinyl ketone, methyl acrylate or acrylonitrile (toluene, 110°C, 12 h) gave, after elimination of dimethylamine from the 1:1 cycloadduct and tautomerization, the 5,8-dihydropyrido[2,3-d]pyrimidinediones **2a-c** as the only products [**2a**, 62%, mp 237-238°C; **2b**, 54%, mp 258-260°C; **2c**, 33%, mp 236-237°C]. The high regiospecifity observed in these reactions is consistent with the electron donating effect of the dimethylamine substituent increasing the nucleophilicity of the C-5 position[4] and, the established reactivity of the olefins.

The dihydroadducts **2a-c** were readily converted into their aromatic analogous **3a-c** by oxidative aromatization in refluxing nitrobenzene [**3a**, 81%, mp 162-163°C; **3b**, 73%, mp 126-127°C; **3c**, 70%, mp 182-183°C].

Reaction of **1** with dimethyl fumarate, diethyl fumarate, and diethyl maleate also resulted in the isolation of the pyrido[2,3-d]pyrimidines **2d,e** [**2d**, 55%, mp 236-238°C; **2e**,

65%, mp 211-212°C]. However, while refluxing **2d** in nitrobenzene afforded **3d** [50%, mp 160-161°C] similar treatment of **2e** gave **3e** [45%, mp 144-146°C] by thermal elimination of ethyl formate. Reaction of **1** with fumaronitrile (MeCN, 82°C, 12 h) afforded **3c** directly. This is presumably due to the extremely facile elimination of HCN in addition to dimethylamine from the 1:1 cycloadduct.



2a-e **3a-e** **1** **4** **5**

2,3 a: R^1 = H; R^2 = $COCH_3$ **2,3 d**: R^1 = CO_2CH_3; R^2 = CO_2CH_3
b: R^1 = H; R^2 = CO_2CH_3 **2e**: R^1 = $CO_2C_2H_5$; R^2 = $CO_2C_2H_5$
c: R^1 = H; R^2 = CN **3e**: R^1 = H; R^2 = $CO_2C_2H_5$

Treatment of **1** with DMAD (MeCN, r.t., 36 h) afforded a mixture of products **3d** and the pyrrolo[3,4-c]pyridine **5** in a 1:2 ratio separable by column chromatography (silica gel, EtOAc) [**3d**, 9.6%; **5**, 19.7%, mp 301-302°C]. The formation of both **3d** and **5** in this reaction suggests a common intermediary whereby the resulting terminal carbanion from initial Michael addition **4** either attacks the imino carbon atom eliminating dimethylamine to give **3d** or, attacks competitively the 2-carbonyl group of the uracil moiety and with subsequent rearrangement and condensation of methanol yields **5**[6]. When the reaction was carried out in boiling toluene (6 h) or chloroform (8 h), **5** was obtained exclusively in 70% yield. The structure of **5** was established unambiguously by single crystal X-ray analysis (cf. Figure).

The proposed Michael addition between **1** and DMAD, and the abilities of 6-amino and 6-alkylamino uracils to undergo Michael additions with azodicarboxylates[8], prompted us to examine analogous reactions of **1**. Treatment of **1** with 4-phenyl-1,2,4-triazoline-3,5-dione (4-Ph-TAD)[9] (MeCN, r.t., 1 h) , or diethyl and diphenyl azodicarboxylates (toluene, 110°C, 8 h) gave the 5-hydrazinopyrimidines **6a-c** in 35-70% yields. These Michael adducts are key intermediates in the formation of theophylline derivatives by thermal cyclization reactions[10]. Thus, heating **6a-c** above 230°C or in refluxing nitrobenzene results in the for-

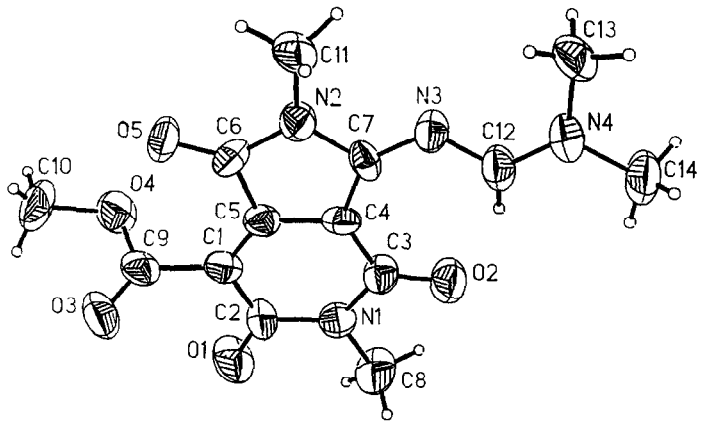
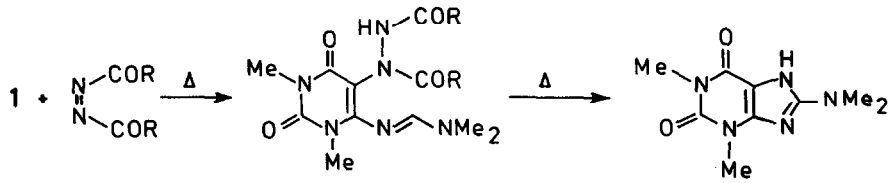


Figure 1. The molecular structure of **5**. Selected bond lengths (Å) and angles (°) are as follows: C(1)-C(5) 1.347(13), C(4)-C(5) 1.429(12), C(3)-C(4) 1.413(12), C(3)-N(1) 1.421(11), C(2)-N(1) 1.414(12), C(1)-C(2) 1.416(14), C(5)-C(6) 1.477(14), C(6)-N(2) 1.383(11), C(7)-N(2) 1.394(12), C(4)-C(7) 1.433(11), C(12)-N(3) 1.321(13), C(12)-N(4) 1.302(12); C(4)-C(3)-N(1) 114.5(7), C(2)-C(1)-C(5) 120.4(8), C(2)-N(1)-C(3) 126.3(8), C(6)-N(2)-C(7) 112.0(7), C(5)-C(6)-N(2) 105.7(8), N(3)-C(12)-N(4) 118.9.

mation of 8-dimethylaminotheophylline **7**[10,11].



6a: >N-Ph
b: OC_2H_5
c: OPh

These results illustrate the extreme ease at which the title compound **1** enters into both cycloaddition and Michael-type reactions. As such, it is a useful substrate for the generation of an array of fused nitrogen heterocycles. Further investigations of related vinyluracils will be the subject of a forthcoming publication.

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