Studies on Uracils: Synthesis of Novel Uracil Analogues *via* 1,5- and 1,6-Intramolecular Cycloaddition Reactions

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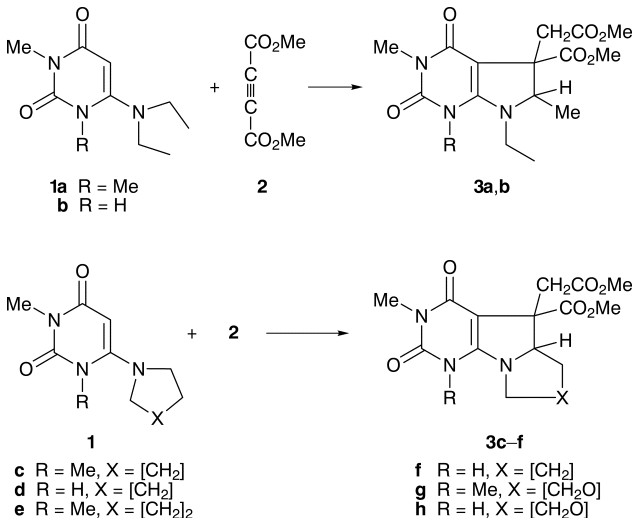
6-(Tertiary amino)uracils **1** react with dimethyl acetylenedicarboxylate (DMAD) to afford 5,6-dihydropyrrolo[2,3-*d*]-pyrimidines **3a** and **3b** and the tricyclic analogues **3c**–**f** *via* 1,5-electrocyclisation in excellent yields, whereas suitably functionalized uracil derivatives **5** undergo intramolecular 1,6-cycloaddition reactions to afford 5,6,7,8-tetrahydro-pyrido[2,3-*d*]pyrimidines **6a** and **6b** and the tricyclic analogues **6c**–**h** in high yields.

α-Cyclization of tertiary amines is a mechanistically intriguing and synthetically useful cyclization. Suchitzky and Meth-Cohn[1] have coined the term 'tertiary amine effect' to describe such processes which have been further developed by Reinhoudt and Verboom.[2]

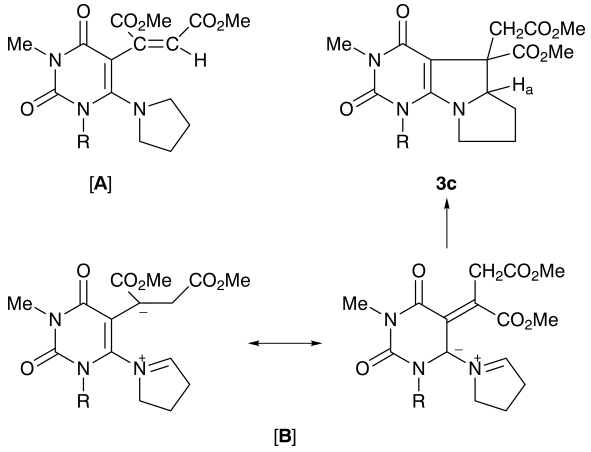
Uracil derivatives continue to be of great interest due to their wide range of biological activities.[4] Preparation of naturally occuring complex molecules containing a uracil ring pose significant synthetic challenges.[5] In this regard, the synthetic exploitation of the nucleophilic double bond of 6-aminouracils is an important strategy for synthesis of complex molecules. The present report describes the full account of our studies[9] of tertiary amine effect in 6-amino-uracils and thus establishes a novel method for the synthesis of complex uracils *via* 1,5- and 1,6-electrocyclizations.

Our synthetic strategy utilizing activated acetylenes, *viz*. dimethyl acetylenedicarboxylate **2**,[10] with 6-(tertiary amino)uracils **1** in refluxing ethanol afforded an un-precedented one-pot synthesis of 5,6-dihydropyrrolo[2,3-*d*]-pyrimidines **3a** and **3b** and their fused tricyclic analogues **3c**–**f** in excellent yields as shown in Scheme 1 (see Table 1).

A reasonable mechanism for the formation of **3** could be explained *via* initial Michael addition of DMAD at C_5 of the uracil ring to give an aminodiene system [**A**], which on subsequent heating, undergoes a 1,6-hydride shift to generate the 1,5-dipole [**B**] and finally cyclizes to give the adduct. Isolation of the intermediate Michael adduct from the reaction of 6-cyclic aminouracil **1c** with DMAD at room temperature (see Scheme 2) provides evidence for this mechanism.

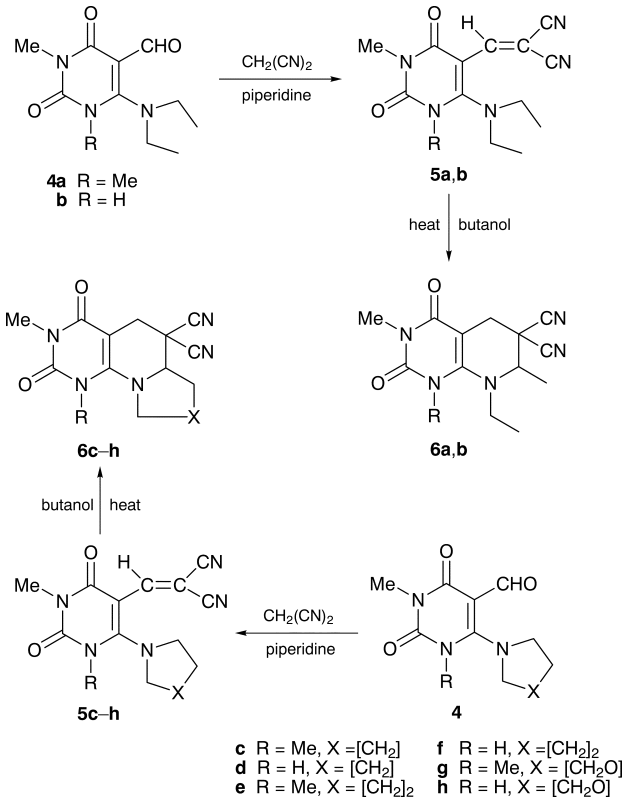


Scheme 1



Scheme 2

In order to study the effect of electron-withdrawing substituents at the vinyl group of the intermediate aminodiene, we prepared a series of 6-(tertiary amino)uracil derivatives **5** by Knoevenagel condensation of the

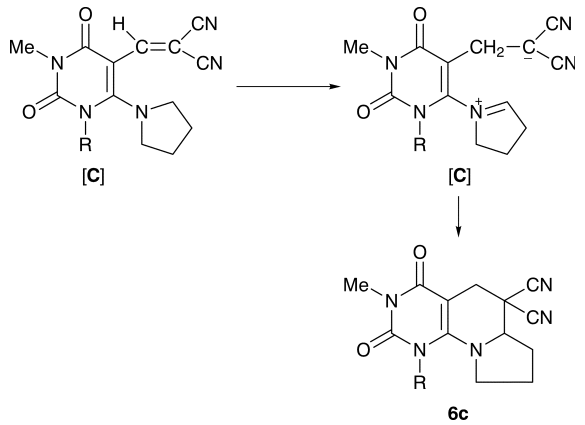


Scheme 3

*To receive any correspondence.

Table 1 Some pertinent data for uracils **3a**–**f** and **6a**–**h**

Compd.	Molecular formula	Analytical data: calc. (found)		
		C	H	N
3a	$C_{16}N_3O_6H_{23}$	54.39(54.36)	6.51(6.48)	11.89(11.85)
3b	$C_{15}N_3O_6H_{21}$	53.09(53.06)	6.19(6.16)	12.38(12.35)
3c	$C_{16}N_3O_6H_{21}$	54.70(54.66)	5.98(5.95)	11.96(11.93)
3d	$C_{15}N_3O_6H_{19}$	53.41(53.38)	5.63(5.60)	12.46(12.42)
3e	$C_{17}N_3O_6H_{23}$	55.89(55.85)	6.30(6.26)	11.50(11.46)
3f	$C_{16}N_3O_6H_{21}$	54.70(54.66)	5.98(5.94)	11.96(11.92)
6a	$C_{14}N_5O_2H_{17}$	58.53(58.50)	5.92(5.89)	24.39(24.36)
6b	$C_{13}N_5O_2H_{15}$	57.14(57.10)	5.49(5.45)	25.64(25.60)
6c	$C_{14}N_5O_2H_{15}$	58.94(58.90)	5.26(5.22)	24.56(24.52)
6d	$C_{13}N_5O_2H_{13}$	57.56(57.53)	4.79(4.76)	25.83(25.80)
6e	$C_{15}N_5O_2H_{17}$	60.20(60.16)	5.68(5.64)	23.41(23.37)
6f	$C_{14}N_5O_2H_{15}$	58.94(58.90)	5.26(5.22)	24.56(24.52)
6g	$C_{14}N_5O_3H_{15}$	55.81(55.78)	4.98(4.95)	23.25(23.22)
6h	$C_{13}N_5O_3H_{13}$	54.35(54.31)	4.52(4.48)	24.39(24.35)



Scheme 4

corresponding 5-formyl-6-(tertiary amino)uracils **4**[11] with malononitrile at room temperature. The condensed intermediate on refluxing in *n*-butanol furnished 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines **6a** and **6b** and their tricyclic analogues **6c**–**h** in excellent yields as shown in Scheme 3 (see Table 1). Contrary to the mechanism already described, in the present case a 1,5-hydride shift occurs under thermolytic conditions to generate a 1,6-dipole, which finally cyclizes intramolecularly to give the 1,6-cycloadduct (Scheme 4).

In conclusion our results demonstrate that 6-(tertiary amino)uracils are interesting precursors for the facile preparation of complex uracil analogues.

Techniques used: ^{1}H NMR, MS, IR

References: 12

Schemes: 4

Tables: 1

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