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Tertiary amine effect: synthesis of some novel spirosubstituted pyrido[2,3-*d*]pyrimidines

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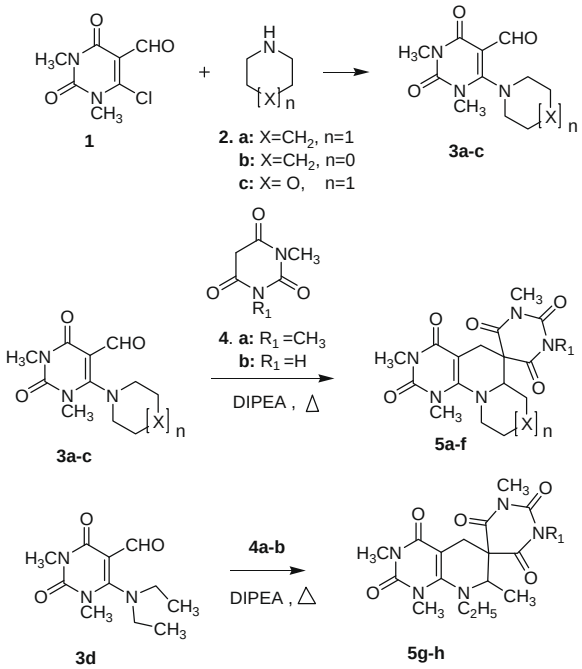
ABSTRACT

5-Formyl-6-tertiaryamino uracils **3** prepared from 6-chloro-5-formyl uracil derivative **1** react with barbituric acids **4** in the presence of base catalyst to afford a novel class of spirosubstituted pyrido[2,3-*d*]pyrimidines **5** via 1,6-electro-cyclisation in excellent yields.

The importance of uracil and its annelated derivatives is well recognised by synthetic as well as by biological chemists.[1] The preparation of naturally occurring complex molecules containing a uracil ring poses significant synthetic challenges.[2] In this regard, the synthetic exploitation of the nucleophilic double bond of uracil is an important strategy for the synthesis of a variety of potential products.[3] Pyrido[2,3-*d*]pyrimidines represent a broad class of annelated uracils of natural occurrence, which has received considerable attention over the past years due to its wide range of biological activities. Compounds with this ring system have diverse pharmacological activity such as antibacterial,[4] antitumour,[5] cardiotonic,[6] hepatoprotective,[6a] antihypertensive[6a] and antibronchitics.[7] Some of them exhibit antiallergic,[8] antimalarial[9] and analgesic[10] properties, and also act as inhibitors of adenosine kinase.[11] Hence, for the preparation of these molecules, there has been growing interest in the synthetic manipulation of uracils.[12]

α-Cyclisation of tertiary amines is a mechanistically intriguing and synthetically useful cyclisation process, which has not received much attention. Certain tertiary anilines or enamines and enamine esters undergo such cyclisation leading to annelated pyrrolidines. Suschitzky and Meth-Cohn have coined the term 'tertiary amine effect' for such a process,[13] which has been further developed by Reinhoudt and Verboom.[14]

In one of our earlier studies, we synthesised some novel pyrrolizino[2,3-*d*]pyrimidines from the reaction of 6-tertiaryamino uracils with dimethylacetylenedicarboxylate (DMAD) via α-cyclisation of tertiary amines.[15] In our continued interest in uracils and the synthesis of diverse heterocyclic compounds of biological importance,[16] we report here the synthesis of some novel classes of spirosubstituted pyrido[2,3-*d*]pyrimidines by exploring the tertiary amine effect reaction strategy (Scheme 1).



Scheme 1.

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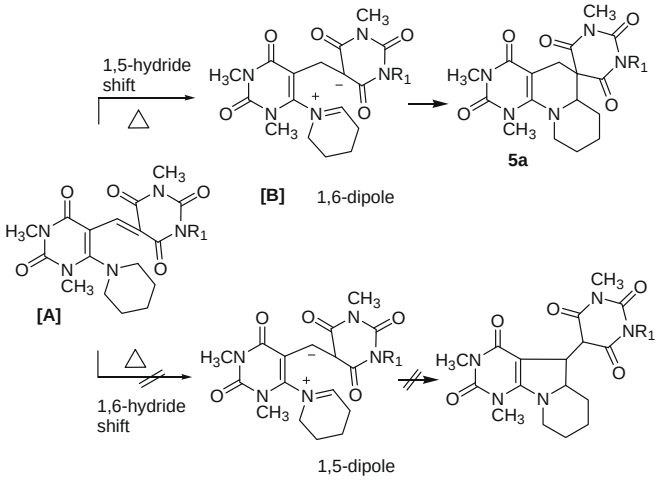
2-Chloro-3-formyl-*N*,*N*-dimethyl uracils **1** were prepared from *N*,*N*-dimethyl-6-hydroxy uracil by following our own reported method,[17] which on treatment with piperidine **3a** afforded the 5-formyl-6-pipiridino uracil derivative **3a**.[18] The compound **3a** on treatment with *N*,*N*-dimethyl barbituric acid **4a** in the presence of diisopropylethylamine (DIPEA) under stirring conditions in ethanol at room temperature and then under refluxing conditions afforded after work up the spirosubstituted pyrido[2,3-*d*]pyrimidine **5a** in excellent yield.[19] The structure of the compound was ascertained from the spectroscopic data and elemental analysis. The ^{1}H NMR spectra showed the absence of the aldehyde proton and splitting of the protons of the tertiary amino group. It showed the presence of two additional *N*-Me groups at δ 3.35 and 3.45 and the presence of two isolated protons at δ 3.79 as a singlet. Moreover, one triplet appeared at δ 1.89 for a single proton. The mass spectra showed the molecular ion peak at 390.3 $(M+H)^+$.

The generality of the reaction was established by synthesising various cyclic and acyclic tertiary amino uracil derivatives **2a**–**d** from **1**, and utilising them with *N*,*N*-dimethylbarbituric acid/*N*-methylbarbituric acid **4a**–**b** under thermal conditions using ethanol as solvent and diisopropylethylamine as base, which afforded the diverse annelated spirosubstituted pyrido[2,3-*d*]pyrimidines **5b**–**h** in good to excellent yield. The structure of the compounds was determined from the spectroscopic data and elemental analysis. Our observations are recorded in Table 1. In our study, it is observed that the reactivity of 6-pyrrolidino uracils are comparatively high, and the yields of the products are also very good. On the other hand, 6-morpholino uracils are the least reactive, and the yields of the products are not good. Moreover, the reactivity of *N*,*N*-dimethylbarbituric acid **4a** is much better than that of *N*-methylbarbituric acid **4b**.

Table 1
Synthesis of novel spirosubstituted pyrido-[2,3-*d*]pyrimidines **5**

Product	$[X]_n$	R_1	Time (h)	Yield (%)	(Appearance)[a] mp °C
5a	$[CH_2]_1$	Me	4	70	(orange) 267–269
5b	$[CH_2]_0$	Me	3	75	(yellow) 274–275
5c	$[O]_1$	Me	4	60	(yellow) 281–283
5d	$[CH_2]_1$	H	5	50	(orange) 312–315
5e	$[CH_2]_0$	H	5	58	(yellow) 325–327
5f	$[O]_1$	H	5	40	(yellow) 342–345
5g	—	Me	3	70	(yellow) 237–239
5h	—	H	5	50	(yellow) 295–297

[a] All are crystalline compounds.



Scheme 2.

A plausible mechanism for the cyclisation step is outlined in Scheme 2. The Knoevenagel condensation of **3a** with **4a** gives an aminodiene system **[A]**, which under thermolytic conditions undergoes an internal redox process to generate a 1,6-dipole through a 1,5-hydride shift (sigmatropic shift), and is subsequently cyclised to give the product **5a**. Contrary to our earlier report,[15] where a 1,5-dipole formed via a 1,6-hydride shift, in the present case a 1,6-dipole formed via a 1,5-hydride shift. This can be explained by the fact that the 1,6-sigmatropic shift is not possible in the present case to generate the 1,5-dipole. Moreover, the carbanion formed in the present case is stabilised by the adjacent carbonyl groups. Thus, we obtained selectively the pyrido[2,3-*d*]pyrimidine ring system during the cyclisation process.

Further study of the reaction is in progress. In conclusion, we have reported the synthesis of some novel classes of spirosubstituted pyrido[2,3-*d*]pyrimidines by exploring the 'tertiary amine effect' reaction strategy under thermal conditions. A suitable mechanism is given for the cyclisation process. This reaction, which can be further explored for the synthetic manipulation of many heterocyclic compounds of biological significance, is a valuable addition to the chemistry of heterocyclic compounds in general and uracils in particular.

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18. Equimolar amounts of **1** (2 mmol, 400 mg), piperidine **2a** (2 mmol, 170 mg) and triethyl amine (2 mmol, 200 mg) were treated at room temperature for 4 h using dichloromethane as solvent. The solvent was evaporated under reduced pressure, and the compound obtained was purified by preparative TLC using ethyl acetate-petroleum ether (3:2) as eluent. The product **3a** was obtained in 80% yield (400 mg) as light brown crystalline. mp 123–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ, 1.74 (br s, 6H), 3.21 (s, 3H), 3.34 (s, 3H), 3.68 (br s, 4H), 9.93 (s, 1H); IR ν_{max} 1690, 1655 cm^{-1}. MS (EI) 252.2 $(M+H)^+$.Similarly compounds **3b–d** were synthesised and characterised.
19. Equimolar amounts of **3a** (1.4 mmol, 350 mg) and *N,N*-dimethyl barbituric acid **4a** (1.4 mmol, 220 mg) were refluxed in ethanol in the presence of a catalytic amount of diisopropylamine. The solvent was evaporated under reduced pressure, and the compound obtained was purified by preparative TLC using ethyl acetate-petroleum ether (7:3) as eluent. The product **5a** was obtained in 70% yield (270 mg) as orange crystalline compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ, 1.49 (m, 4H, $-CH_2-CH_2-$), 1.78 (m, 2H, $-CH_2-$), 1.89 (t, 1H), 2.87 (m, 2H, $-CH_2-$), 3.23 (s, 3H, >NMe), 3.28 (s, 3H, >NMe), 3.35 (s, 3H, >NMe), 3.45 (s, 3H, >NMe), 3.79 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ, 23.10, 27.69, 27.84, 28.85. 28.96, 31.25, 35.05, 36.20, 47.30, 52.14, 65.30, 88.54, 150.23, 150.51, 152.19, 161.53, 168.33, 170.14; IR ν_{max} 1690, 1681, 1629 cm^{-1}. MS (EI) 390.3 $(M+H)^+$. Anal. Calcd for $C_{18}H_{23}N_5O_5$: C, 55.52; H, 5.95; N, 17.98. Found: C, 55.47; H, 5.89; N, 17.93.
Similarly compounds **5b–h** were synthesised and characterised.