A New and Efficient One-pot Synthesis of Pyrido[2,1-*f*]purine-2,4-diones Starting from 6-Aminouracil Derivatives

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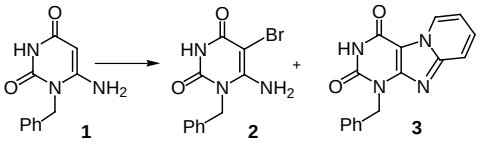
Abstract: A convenient synthesis of pyrido[2,1-*f*]purine-2,4-diones is described by reaction of 6-aminouracil derivatives with *N*-bromosuccinimide (NBS) followed by in situ reaction with pyridine or 4-substituted pyridines. A detailed study of the reaction conditions has been performed and a mechanism involving a 5,5-dibromo derivative is proposed.

Key words: heterocycles, tricyclic compounds, pyridines, halogenation, *N*-bromosuccinimide

6-Amino-5-bromouracil derivatives are interesting chemical entities both from a chemical and a pharmacological point of view. They are the reference inhibitors of an enzyme involved in the nucleoside salvage pathway, thymidine phosphorylase, nowadays profusely studied as an angiogenic agent.[1,2] Moreover, 6-amino-5-bromouracil derivatives have been used as intermediates in the synthesis of xanthine derivatives,[3,4] compounds that have been an active area of research, already for many years, due to their pharmacological properties as adenosine antagonists or phosphodiesterase inhibitors.[5]

Bromination of 6-aminouracil derivatives has been mostly performed by reaction with bromine either in acetic acid in the presence of alkali metal acetates, or in water or methanol in the presence of alkali metal carbonates or bicarbonates.[3,6] *N*-Bromosuccinimide (NBS) is a good alternative to avoid the irritating bromine as described by Pfleiderer and coworkers.[3] In the course of our research programme on thymidine phosphorylase inhibitors,[2,7] we were interested in brominating several 6-aminouracil derivatives. We chose NBS as a brominating agent, and pyridine as the solvent, considering that its basicity should favour the solubility of the 6-aminouracils. Thus, reaction of 6-amino-1-benzyluracil[3] **1** with 1.2 equivalents of NBS in pyridine at 80 ºC afforded the expected 6-amino-1-benzyl-5-bromouracil[3] **2** in 70% yield (Scheme 1). However, a second strong UV absorption product was also detected and isolated in 15% yield. This minor compound was identified as 1-benzyl-1*H*,3*H*-pyrido[2,1-*f*]purine-2,4-dione **3**. Its structure were unequivocally determined by ^{1}H NMR, ^{13}C NMR, HMQC and HMBC experiments, and its elemental composition was established by mass spectrometry and combustion analysis.[8]



Scheme 1

The only previous records that we could find of this type of structures were related to a Pfizer patent.[9] The procedure there described involved a two step synthesis starting from 6-chloro-1,3-dimethyluracil that reacted with 2-aminopyridines in the presence of NaH followed by heating with thionyl chloride. This methodology has also been employed by Gatta et al.[10] on 1,3-dipropyl-6-aminouracil. Since our reaction conditions clearly differ from the previous records on this type of structure, we considered of interest to study this reaction in detail. The results obtained are reported in this communication.

Initially, varying amounts of NBS in pyridine were assayed (Table 1). Thus, treatment of 6-amino-1-benzyluracil **1** with 0.9 equivalents of NBS in pyridine at 80 ºC (entry 1) afforded, exclusively, the 5-bromo derivative **2** in 74% yield. On the other hand, when 2.5 equivalents of NBS were employed, also in pyridine at 80 ºC (entry 2), the major compound obtained was the tricyclic derivative **3** (65%) with the 5-bromo derivative **2** being the minor compound. Alternatively, treatment of the 5-bromo derivative **2** with 1.5 equivalents of NBS in pyridine at 80 ºC (entry 3) afforded the tricyclic derivative **3** in 68% yield. It should also be mentioned that heating of the 5-bromo derivative **2** in pyridine, in the absence of NBS, even after long periods, left the 5-bromo derivative unaltered. These very simple experiments indicated that the 5-bromo derivative **2** is an intermediate for the formation of **3** in the reaction of **1** with excess NBS in pyridine. Under these reaction conditions no other intermediates could be detected, although the course of the reaction was not easy to follow due to extensive precipitation.

Table 1 Reaction of 6-Amino-1-benzyluracil Derivatives with varying Amounts of NBS in Pyridine

Entry	Substrate	Equivalents NBS	Product (Yield)
1	**1**	0.9	**2** (74%)
2	**1**	2.5	**3** (65%) + **2** (< 10%)
3	**2**	1.5	**3** (68%) + **2** (< 10%)

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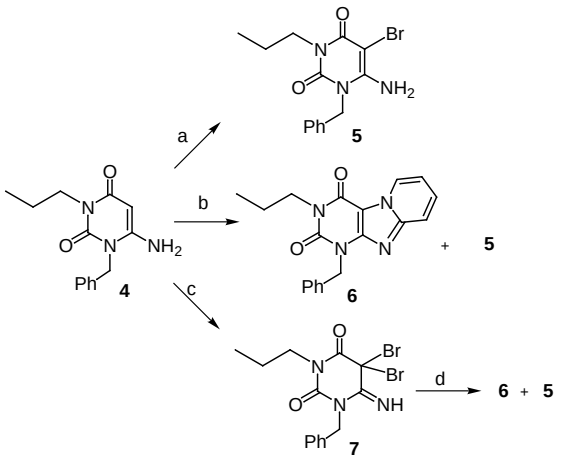
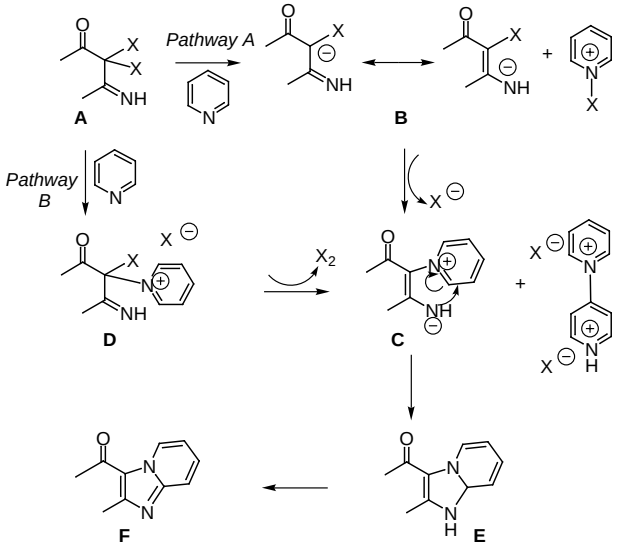
In order to increase the solubility of the substrates involved, the same reaction sequences were performed on 6-amino-1-benzyl-3-propyluracil **4**. This compound was prepared from **1** following our recently described procedure to alkylate 6-aminouracil derivatives via *N*-[(dimethylamino)methylene][6] protection.[11] Treatment of **4**[11] with 0.9 equivalents of NBS in pyridine afforded the 5-bromo derivative **5** in 77% yield[12] (Scheme 2). On the other hand, reaction of **4** with 2.5 equivalents of NBS in pyridine afforded the fused xanthine **6** (42% yield),[13] together with the 5-bromoderivative (**5**, 30% yield). So, the behaviour of **4** is quite similar to that observed for **1** under the same reaction conditions. It was also clear that in the formation of **6**, pyridine was behaving not only as the solvent but also as a reagent. Therefore, pyridine was replaced by acetonitrile as solvent. Thus, reaction of **4** with 2.5 equivalents of NBS in acetonitrile at 80 ºC afforded a new product **7**, that on TLC had R_f value higher than those of the already identified compounds **5** and **6**. Addition of pyridine (5–10 equiv) to the reaction mixture, allowed transformation of this spot **7** into the fused xanthine **6** together with the concomitant formation of the 5-bromo derivative **5**. This new product **7** could be isolated as a glassy syrup, although it tends to decompose.[14,15] The mass spectrum of **7** indicated a dibrominated compound with a quasimolecular peak pattern of 416, 418 and 420. The ^{1}H NMR spectrum of **7** showed the disappearance of the NH_2 signal at 4.88 ppm (compared to **5**) and the appearance of an NH at 9.59 ppm. The ^{13}C NMR spectrum of **7** showed a signal at 50.58 ppm, that based on long-range correlation experiments was assigned as the C-5 of the pyrimidine. The upfield shift of this carbon atom ($\Delta\delta$ = –22.6 ppm, compared to **5**) is compatible with the presence of a second bromo at position 5, therefore the amino at position 6 should now be an imine instead of an enamine as in **5**. Indeed, the ^{15}N NMR spectrum of **7** confirmed the presence of an imine by a signal shielded 145 ppm with respect to nitromethane (reference signal).



Scheme 2 a) 0.9 equiv NBS/pyridine/80 ºC, **5** (77%); b) 2.5 equiv NBS/pyridine/80 ºC, **6** (42%) and **5** (30%); c) 2.5 equiv NBS/CH_3CN/80 ºC, **7**; d) 5 equiv pyridine/80 ºC, **6** (42%) and **5** (30%)

It should be added that, when compound **4** was treated with 2.5 equivalents of *N*-chlorosuccinimide in acetonitrile, a compound with R_f value similar to **7** was detected on TLC (tentatively it should correspond to the 5,5-dichloro analogue of **7**). Addition of pyridine and heating lead to the transformation of this spot into the fused xanthine **6**, although, this transformation was slower than in the case of the 5,5-dibromo derivative **7**.

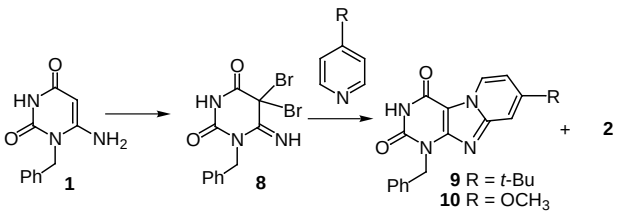
From all the described experiments above, it is clear that the tricyclic derivative **6** is obtained by reaction of the 5,5-dihaloderivative with pyridine. Upon searching for previous records on reaction of dihaloderivatives with pyridine, quite close examples were found, described by Taylor[16] and later on by Kappe,[17] on reaction of 5,5-dihalobarbituric acids with pyridine to yield ylides. Based on these precedents, a tentative mechanism, which is outlined in Scheme 3, is proposed. Following a pathway analogous to that proposed by Taylor[16] (pathway A), the reaction should be initiated by nucleophilic attack of pyridine to the dihaloderivative **A**, displacing a halonium ion and giving rise to the anion **B**, which reacts with pyridine to displace a halide ion and generate intermediate **C**. Alternatively, and following Kappe's proposal[17b] (pathway B), the first step should involve the nucleophilic substitution of one halogen atom by pyridine to generate **D**, that, by elimination of X_2, should give the same intermediate **C**. In such an intermediate **C**, the positive charge in the pyridine facilitates a nucleophilic attack in the α-position to of the pyridine to generate **E**,[19] that aromatizes to yield the final pyrido[2,1-*f*]purine-2,4-diones (**F**).



Scheme 3

Based on the mentioned results above, the experimental conditions were changed to facilitate the follow up of the reaction and isolation of the final compounds. The synthetic procedure of choice is a two-step, one-pot reaction that consists of the generation of the 5,5-dibromo compound in acetonitrile, followed by addition of pyridine and heating for 4–6 hours to generate the fused xan-

thines.[18] Following this synthetic procedure, attempts were made to extend this reaction to other pyridines. Treatment of the 5,5-dibromo compound **8**, generated in situ, with 2-methoxy, 2-cyano or 2-bromopyridine, failed to afford the corresponding fused xanthines. It could be argued that the steric demands on the 2-substituted pyridines prevent reaction at the hetero nitrogen atom.[16] However, when the reaction was performed by the addition of 4-*t*-butyl or 4-methoxypyridine, the expected fused xanthines **9** and **10** were obtained in 58% and 74% yield, respectively (Scheme 4).



Scheme 4

In summary, a simple, satisfatory and unusual synthesis of pyrido[2,1-*f*]purine-2,4-diones has been performed by reaction of 6-aminouracil derivatives with NBS in the presence of pyridine or 4-substituted pyridines. According to the results here presented, the reaction pathway involves the formation of 5,5-dibromo derivatives that further react with the corresponding pyridine. In this way, the pyrido[2,1-*f*]purine-2,4-diones are easily and smoothly obtained, and their biological evaluation is underway.

Acknowledgement

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(8) Selected data of **3**: Mp (CH_2Cl_2–MeOH): 298–299 °C. MS (EI): *m/z* = 292 [M^+]. ^{1}H NMR (DMSO-d_6): δ 5.22 (s, 2 H, CH_2Ph), 7.10–7.50 (m, 6 H, H-7, Ph), 7.66 (m, *J* = 7.1, 1.2 Hz, H-8), 7.75 (d, *J* = 9.1 Hz, 1 H, H-9), 8.94 (d, *J* = 6.6 Hz, H-6), 11.35 (br s, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ 44.92 (CH_2Ph), 101.95 (C-4a), 114.51 (C-7), 116.08 (C-9), 127.11, 127.20, 128.32, 136.71 (C-6, Ph), 130.34 (C-8), 147.08 (C-9a), 150.85 (C-10a), 151.60 (C-2), 154.53 (C-4). Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17; found: C, 65.47; H, 4.50; N, 19.35.
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(12) Selected data of **5**: MS (ES, positive mode): *m/z* = 360, [M + Na^+], showing the Br isotopic pattern. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3 H, CH_3CH$_2$), 1.72 (m, 2 H, CH$_3$CH_2), 4.00 (m, 2 H, NCH_2), 4.97 (br s, 2 H, NH_2), 5.28 (s, 2 H, CH_2Ph), 7.26–7.43 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$): δ 11.32 (CH_3CH$_2$), 21.11 (CH$_3$CH_2), 44.40 (NCH_2), 47.78 (CH_2Ph), 73.25 (C-5), 150.40, 150.93 (C-2, C-6), 158.52 (C-4).
(13) Selected data of **6**: Mp (CH_2Cl_2–MeOH): 163–165 °C. MS (EI): *m/z* = 334 [M^+]. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.69 (m, *J* = 7.5 Hz, 2 H, CH_2CH$_3$), 4.01 (pt, *J* = 7.3 Hz, 2 H, NCH_2), 5.37 (s, 2 H, CH_2Ph), 7.06 (pt, *J* = 6.1 Hz, H-7), 7.25–7.52 (m, 5 H, Ph), 7.52 (pt, *J* = 7.0 Hz, H-8), 7.65 (d, *J* = 7.0 Hz, 1 H, H-9), 9.04 (d, *J* = 6.7 Hz, 1 H, H-6). ^{13}C NMR ($CDCl_3$): δ 11.32 (CH_3CH$_2$), 21.38 (CH$_3$CH_2), 42.83 (NCH_2), 46.67 (CH_2Ph), 101.90 (C-4a), 113.90 (C-7), 116.41 (C-9), 127.48 (C-6), 129.87 (C-8), 147.63 (C-9a), 150.69 (C-10a), 151.39 (C-2), 155.01 (C-4). Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 19.76; found: C, 68.19; H, 5.12; N, 19.40.
(14) Selected data of **7**: MS (ES, positive mode): *m/z* = 416 [M + 1]$^+$, showing the isotopic 2 Br pattern. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3 H, CH_3CH$_2$), 1.67 (m, 2 H, CH$_3$CH_2), 3.90 (m, 2 H, NCH_2), 5.31 (s, 2 H, CH_2Ph), 7.28–7.49 (m, 5 H, Ph), 9.59 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 10.94 (CH_3CH$_2$), 20.68 (CH$_3$CH_2), 45.38 (NCH_2), 48.40 (CH_2Ph), 50.58 (C-5), 149.14 (C-2), 156.52 (C-6), 161.05 (C-4).
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(18) **General Experimental Procedure**: Synthesis of **3**, **9** and **10**. *N*-Bromosuccinimide (NBS) (445 mg, 2.5 mmol) was added into a suspension of 6-amino-1-benzyluracil **1** (217 mg, 1.0 mmol) in dry CH_3CN (8 mL) and the mixture was heated at 80 ºC for 1 h till all starting material was transformed into the 5,5-dibromoderivative **8**. After cooling to r.t., the corresponding pyridine (5–10 mmol) was added, and the resulting mixture was heated at 80 °C for 6 h. The resulting precipitate, that contains the target compound, was collected by filtration and washed with ethyl ether.
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