Efficient Synthesis of *N*-3-Substituted 6-Aminouracil Derivatives via N^6-[(Dimethylamino)methylene] Protection

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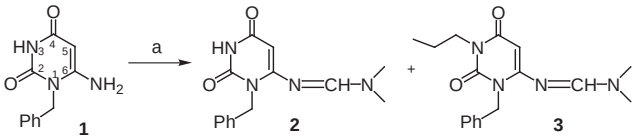
Abstract: A convenient synthetic procedure has been developed to introduce different functional groups at position 3 of 6-amino-1-benzyl- or 6-amino-1-methyluracil based on N^6-[(dimethylamino) methylene] protection. This method allows for the smooth substitution at *N*-3 even when base-labile or heat sensitive halide reagents are employed.

Key words: alkylations, heterocycles, protecting groups, nucleobases



a) $CH_3CH_2CH_2I/K_2CO_3$/DMF, 80 ºC, **2** (8%) and **3** (35%)

Scheme 1

6-Aminouracils are key intermediates in the synthesis of different families of heterocyclic compounds.[1] Their key role in the synthesis of xanthines and analogues, compounds that show well established biological activities as adenosine receptor antagonists, diuretics, antiinflammatory agents, etc. is well known.[2] Despite the versatility of 6-aminouracils in heterocyclic chemistry, most of the reactions described have been performed on 1,3-dimethyl-6-aminouracil, and this, somehow, limits the interest of the final heterocyclic compounds for biological evaluation. This can be partially explained by the difficulties encountered to alkylate the *N*-3 position of 6-aminouracil, especially when the *N*-1 position is already substituted. The classical approach of 15% NaOH in refluxing EtOH,[3] affords, in general, low yields of the *N*-3 substituted compound and cannot be employed with basic labile or heat sensitive alkylating agents, such as propargyl bromide. Attempts to increase the reactivity of 6-amino-1-methyluracil by silylation, an approach that has afforded good results in the free base,[4] gave only low yields of the desired 6-amino-1-methyl-3-propragyluracil.[5]

In the course of our research on purines, we were interested in introducing different substituents at the *N*-3 position of 6-amino-1-benzyluracil (**1**) under smooth conditions. Thus, we tried the alkylation of **1** with propyl iodide in the presence of K_2CO_3 in different solvents at 80 ºC. Among the solvents tested (acetone, acetonitrile, DMF, or nitromethane) only DMF allowed significant transformation of the starting material into two new products (Scheme 1). However, to our surprise, when these two new compounds were characterized, their ^{1}H NMR spectra showed the absence of the 6-NH_2 signal, and the presence of two new singlets at 3.03 ppm and 3.10 ppm, respectively, each of them corresponding to three H-atoms, and an extra singlet at 7.62 ppm. These two compounds were finally identified as the formamidino derivatives **2** and **3**.

The fact that the *N*-3 alkylated product **3** showed concomitant transformation of the 6-amino function into the formamidino, led us to consider whether "masking" the exocyclic amino function with a (dimethylamino)methylene moiety could favor the alkylation at position 3. Therefore, we decided to study this reaction in detail and here we report our results on the functionalization at position 3 of 1-substituted-6-aminouracils via N^6-[(dimethylamino)methylene] protection. This procedure represents a smooth alternative to previously described methods for *N*-3 substitution of 6-aminouracil derivatives. Despite its common use as a protecting group in the purine chemistry,[6] to the best of our knowledge a [(dimethylamino)methylene] moiety has not been used with this purpose on 6-aminouracil.[7]

As starting materials, we chose either 6-amino-1-benzyluracil[3,8] (**1**) or 6-amino-1-methyluracil[3,9] (**4**) (Scheme 2) which were quantitatively transformed into the corresponding formamidines **2** or **5**, respectively, by reaction with DMF-dimethyl acetal (DMF-DMA) in DMF at 40 ºC. This reaction can be easily followed by TLC. Then, addition of K_2CO_3 and the corresponding alkyl halide and heating to 80 ºC, gave the corresponding *N*-3 alkyl derivatives **3**, **6**–**9** in good to excellent yields. (Table, entries 1–5). In this reaction no deprotection of the formamidino moiety was observed and the only side product detected was the protected starting material **2** or **5**. Moreover, no *O*-4 alkylated derivatives were detected. It should be emphasised that this strategy allows the reaction with base-labile alkylating agents such as 4-(methoxycarbonyl)butyl bromide (Table, entries 3 and 4) or *N*-(3-bromopropyl)phthalimide (Table, entry 5), substituents that could not be introduced under the classical vigorous ethanolic sodium hydroxide conditions.[3]

From these experiments it was clear that the (dimethylamino)methylene protection causes a marked increase in the 3-*N*-alkylation of 1-substituted-6-aminouracils. Next, and in order to prove the validity of this approach, it was

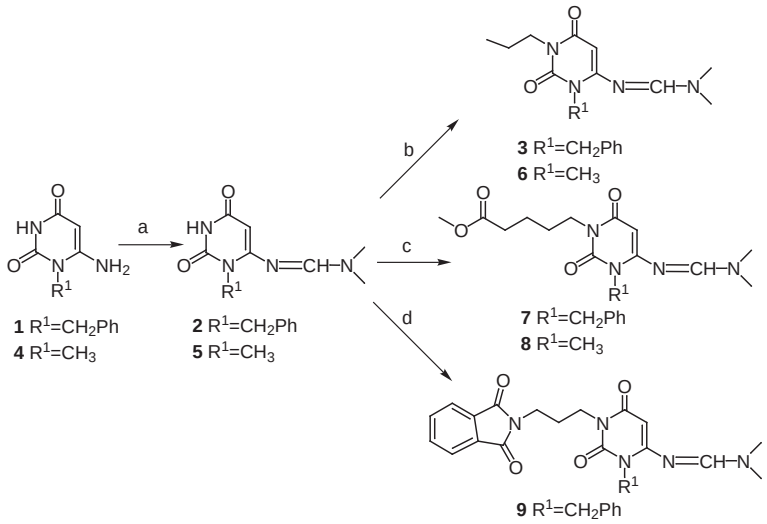
Table Synthesis of 3-Substituted 6-[(Dimethylamino)methylene]aminouracil Derivatives

Entry	Substrate	Halide Reagent	Reaction Conditions	Product	Yield (%)	mp (°C)
1	**2**	$CH_3CH_2CH_2I$	DMF/DMF-DMA/K_2CO_3; 80 ºC	**3**	69	119
2	**5**	$CH_3CH_2CH_2I$	DMF/DMF-DMA/K_2CO_3; 80 ºC	**6**	68	110
3	**2**	$MeO_2C(CH_2)_4Br$	DMF/DMF-DMA/K_2CO_3; 80 ºC	**7**	72	134
4	**5**	$MeO_2C(CH_2)_4Br$	DMF/DMF-DMA/K_2CO_3; 80 ºC	**8**	71	126
5	**2**	$PhtN(CH_2)_3Br$	DMF/DMF-DMA/K_2CO_3; 80 ºC	**9**	97	245
6	**2**	$HC{\equiv}CCH_2Br$	DMF/DMF-DMA/K_2CO_3; 80 ºC	**13**	15[b]	
7[a]	**2**	$HC{\equiv}CCH_2Br$	DMF/K_2CO_3/TBAI; r.t.	**13**	15	
8[a]	**2**	$HC{\equiv}CCH_2Br$	acetone/K_2CO_3/I_2; r.t.	**13**	37	
9[a]	**2**	$HC{\equiv}CCH_2Br$	MeCN/DBU; 80 ºC	**13**	62	166
10	**2**	*p*-$MeOC_4H_6CH_2Cl$	DMF/DMF-DMA/K_2CO_3/I_2; 80 ºC	**16**	30	
11[a]	**2**	*p*-$MeOC_4H_6CH_2Cl$	MeCN/DBU; 80 ºC	**16**	68	136

[a] The excess of DMF-DMA was distilled off in vacuo previous to the addition of the alkylating agent.
[b] Compound **14** was also obtained in 20% yield.

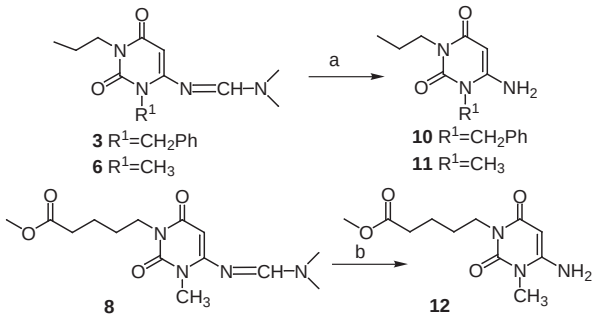
imperative to efficiently remove the *N*,*N*-dimethylaminomethylene moiety under conditions that do not affect the substituents. Thus, removal of the formamidino moiety in compounds **3** and **6** was performed by treatment with aqueous ammonia in methanol at room temperature,[6] affording the desired 6-amino derivatives **10** and **11**[3] in 92% and 94% yields, respectively (Scheme 3). On the other hand, compound **8** was deprotected by treatment with $ZnCl_2$ in refluxing methanol[6,10] in order to avoid transformation of the methoxycarbonyl group into the corresponding amide. Thus, the 6-amino-3-(4-methoxycarbonyl)butyl derivative **12** was obtained in 90% yield.

Particularly interesting compounds are 6-amino-3-propargyluracils, key intermediates in the synthesis of 1-propargyl xanthines, compounds that show important pharmacological properties, but have proven to be difficult to obtain.[11] These facts led us to assay our strategy for the introduction of the propargyl moiety. Following an analogous procedure to that described above, that is, protection of the exocyclic amino function with DMF-DMA, followed by in situ reaction with K_2CO_3 and propargyl bromide (Table, entry 6), the desired 3-propargyl deriva-



a) DMF-DMA/DMF, 40 ºC; b) $CH_3CH_2CH_2I/K_2CO_3$, 80 ºC, **3** (69%), **6** (68%); c) $CH_3O_2C(CH_2)_4Br/K_2CO_3$, 80 ºC, **7** (72%), **8** (71%); d) $PhtN(CH_2)_3Br/K_2CO_3$, 80 ºC, **9** (97%)

Scheme 2

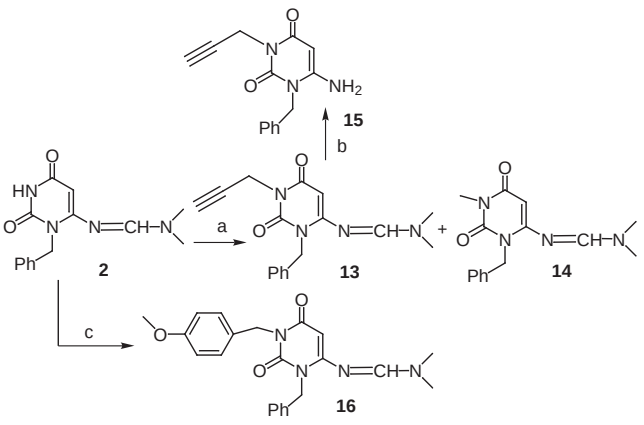


a) NH_3 (aq)/MeOH, r.t., **10** (92%), **11** (94%); b) $ZnCl_2$/MeOH, reflux, **12** (90%)

Scheme 3

tive **13** was isolated in a 15% yield, together with a second compound that was identified as the *N*-3 methyl derivative **14** (Scheme 4). It seems that the excess of the protective reagent DMF-DMA present in the reaction media, under basic conditions (K_2CO_3), behaves as a methylating agent.[12,13] Therefore, to avoid this undesired methylation, the excess of DMF-DMA was removed prior to treatment with the carbonate. Reaction of the crude protected derivative **2** with propargyl bromide and K_2CO_3 in acetone/DMF led to a poor transformation into the propargyl derivative **13**, even in the presence of a phase-transfer catalyst (Bu_4NI) (Table, entry 7). Addition of iodine (Table, entry 8) allowed a slight increase in the yield of the 3-propargyl derivative (37%). Finally, when different basic conditions were tested, it was found that treatment of **2** with DBU in acetonitrile (Table, entry 9) gave the best results allowing a 62% yield of the desired 1-benzyl-3-propargyl-6-formamidino derivative **13**. Deprotection with aqueous ammonia in methanol afforded the 6-amino-derivative **15** in 75% yield.

Finally, we decided to extend the reaction to benzyl substituents. Treatment of **2** in the DMF-DMA medium (Table, entry 10), with 4-methoxybenzyl chloride and K_2CO_3 at 80 ºC gave only a poor yield of the 3-*N*-(4-methoxybenzyl) derivative **16**, even after addition of iodine (Scheme 4). However, treatment of the crude protected **2** with DBU in acetonitrile (Table, entry 11), afforded the desired 4-methoxybenzyl derivative **16** in 68% yield.



a) See Table, entries 6−9; b) NH_3(aq)/MeOH; r.t., **15** (75%); c) See Table, entries 10 and 11

Scheme 4

In conclusion, protection of 1-substituted 6-aminouracils with a N^6-[(dimethylamino)methylene] moiety allows the introduction of a variety of functional groups at position 3 under smooth conditions in good to excellent yields. The present method offers an alternative over the previously described procedures that required either harsh conditions[3] or resulted in poor yields.[4] Therefore, the present synthetic procedure could be of interest to obtain heterocyclic compounds, including pharmacologically active xanthine derivatives. Moreover, the here described compounds can be useful scaffolds for combinatorial chemistry.

Melting points were obtained on a Reichert-Jung Kofler apparatus and are uncorrected. Microanalyses were obtained with a Heraeus CHN-O-RAPID instrument. Electrospray mass spectra were measured on a quadrupole mass spectrometer equipped with an electrospray source (Hewlett-Packard, LC/MS HP 1100). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini operating at 200 MHz (^{1}H) and 50 MHz (^{13}C), respectively, on a Varian INOVA 300 operating at 299 MHz (^{1}H) and 75 MHz (^{13}C), respectively, and Varian INOVA-400 operating at 399 MHz (^{1}H) and 99 MHz (^{13}C), respectively. Monodimensional ^{1}H and ^{13}C spectra were obtained using standard conditions. 2D inverse proton detected heteronuclear one-bond shift correlation spectra were obtained using the Pulsed Field Gradient HSQC pulse sequence. Data were collected in a 2048 × 512 matrix with a spectral width of 3460 Hz in the proton domain and 22500 Hz in the carbon domain, and processed in a 2048 × 1024 matrix. The experiment was optimized for one bond heteronuclear coupling constant of 150 Hz. 2D inverse proton detected heteronuclear long range shift correlation spectra were obtained using the Pulsed Field Gradient HMBC pulse sequence. The HMBC experiment was acquired under the same conditions that of HSQC experiment and optimized for long range coupling constants of 7 Hz. Analytical TLC was performed on silica gel 60 F_{254} (Merck) precoated plates (0.2 mm). Spots were detected under UV light (254 nm) and/or by charring with phosphomolybdic acid. Separations on silica gel were performed by preparative centrifugal circular thin-layer chromatography (CCTLC) on a Chromatotron® (Kiesegel 60 PF_{254} gipshaltig (Merck)), layer thickness (1 or 2 mm), flow rate (4 or 8 mL/min, respectively). Flash column chromatography was performed with silica gel 60 (230−400 mesh) (Merck).

Reaction of 6-Amino-1-benzyluracil with Propyl Iodide in DMF

To a suspension of **1** (217 mg, 1.0 mmol) in anhyd DMF (8 mL) were added K_2CO_3 (208 mg, 1.50 mmol) and propyl iodide (0.14 mL, 1.50 mmol), and the mixture was heated at 80 ºC for 4 h. Volatiles were removed in vacuo and the residue was treated with EtOAc (50 mL) and filtered through Celite. Evaporation of the filtrate followed by purification by CCTLC on the Chromatotrom (mixtures of CH_2Cl_2/MeOH) afforded 22 mg (8%) of **2** and 110 mg (35%) of **3**.

1-Benzyl-6-(dimethylaminomethylene)aminouracil (2)

Mp 213 ºC.

MS (ES, positive mode): m/z = 273 $(M + 1)^+$, 295 $(M + Na)^+$.

^{1}H NMR ($CDCl_3$): δ = 3.03, 3.10 [2 s, 6 H, $N(CH_3)_2$], 4.98 (s, 1 H, H-5), 5.19 (s, 2 H, *N*-1-CH_2), 7.22−7.33 (m, 5 H, C_6H_5), 7.62 (s, 1 H, N=CH), 8.11 (br s, 1 H, NH-3).

1-Benzyl-6-(dimethylaminomethylene)amino-3-propyluracil (3)

Mp 119 ºC.

MS (ES, positive mode): *m*/*z* = 315 $(M + 1)^+$.

^{1}H NMR ($CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.66 (m, 2 H, CH_2CH_3), 3.03, 3.08 [2 s, 6 H, $N(CH_3)_2$], 3.89 (t, *J* = 7.0 Hz, 2 H, *N*-3-CH_2), 5.05 (s, 1 H, H-5), 5.22 (s, 2 H, *N*-1-CH_2), 7.24−7.34 (m, 5 H, C_6H_5), 7.62 (s, 1 H, N=CH).

^{13}C NMR ($CDCl_3$): δ = 11.31 (CH_2CH_3), 21.11 (CH_2CH_3), 34.98, 40.81 [$N(CH_3)_2$], 42.65 (*N*-3-CH_2), 46.03 (*N*-1-CH_2), 83.73 (C-5), 127.08, 127.68, 128.30, 138.17 (C_6H_5), 152.46 (C-2), 154.08 (N=CH), 159.01 (C-6), 163.48 (C-4).

3-*N*-Alkyl-6-(dimethylaminomethylene)amino-1-benzyl or -1-methyluracil (3, 6-9); General Procedure

A suspension containing 6-amino-1-benzyl (**1**) or 6-amino-1-methyluracil (**4**) (0.5 mmol) in anhyd DMF (2.5 mL) and DMF-DMA (0.27 mL, 2.0 mmol) was warmed at 40 ºC till disappearance of starting material (typically 45-60 min; TLC: CH_2Cl_2/MeOH, 10:1). Then K_2CO_3 (104 mg, 0.75 mmol) and the corresponding alkyl halide (0.75 mmol) were added and the mixture was heated to 80 ºC. After 4 h, solvents were removed, the residue was dissolved in EtOAc (50 mL) and filtered through Celite. The filtrate was evaporated and purified by CCTLC on the Chromatotron using CH_2Cl_2/MeOH (20:1).

1-Benzyl-6-(dimethylaminomethylene)amino-3-propyluracil (3)

Following this general procedure and starting from **1** (100 mg), 100 mg (69%) of **3** was obtained.

6-(Dimethylaminomethylene)amino-1-methyl-3-propyluracil (6)

Starting from **4** (150 mg), 172 mg (68%) of **6** was obtained as a white solid; mp (see Table).

MS (ES, positive mode): *m*/*z* = 239.1 $(M + 1)^+$.

^{1}H NMR ($CDCl_3$): δ = 0.91 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.65 (m, 2 H, CH_2), 3.05, 3.10 [2 s, 6 H, $N(CH_3)_2$], 3.37 (s, 3 H, *N*-1-CH_3), 3.86 (m, 2 H, *N*-3-CH_2), 5.01 (s, 1 H, H-5), 7.63 (s, 1 H, N=CH).

^{13}C NMR ($CDCl_3$): δ = 11.30 (CH_3), 21.11 (CH_2), 29.93 (*N*-1-CH_3), 34.85, 40.77 [$N(CH_3)_2$], 42.58 (*N*-3-CH_2), 83.72 (C-5), 152.58 (C-2), 153.89, 159.36 (N=CH, C-6), 163.52 (C-4).

1-Benzyl-6-(dimethylaminomethylene)amino-3-[4-(methoxycarbonyl)butyl]uracil (7)

Starting from **1** (100 mg), 128 mg (72%) of **7** was obtained as a white solid; mp (see Table).

MS (ES, positive mode): *m*/*z* = 387.1 $(M + 1)^+$.

^{1}H NMR ($CDCl_3$): δ = 1.69 [m, 4 H, $(CH_2)_2$], 2.33 (m, 2 H, CH_2CO), 3.04, 3.10 [2 s, 6 H, $N(CH_3)_2$], 3.95 (m, 2 H, *N*-3-CH_2), 5.06 (s, 1 H, H-5), 5.22 (s, 2 H, *N*-1-CH_2), 7.25−7.32 (m, 5 H, C_6H_5), 7.64 (s, 1 H, N=CH).

^{13}C NMR ($CDCl_3$): δ = 22.30, 27.34 (CH_2), 33.77 (CH_2CO), 34,98, 40.83 [$N(CH_3)_2$], 40.50 (*N*-1-CH_2), 46.01 (*N*-3-CH_2), 51.41 (OCH_3), 83.63 (C-5), 127.08, 127.63, 128.29, 138.05 (C_6H_5), 152.37 (C-2), 154.04, 159.03 (N=CH, C-6), 163.34 (C-4), 173.91 (CO_2CH_3).

6-(Dimethylaminomethylene)amino-3-[4-(methoxycarbonyl)butyl]-1-methyluracil (8)

Starting from **4** (100 mg), 128 mg (72%) of **8** was obtained as a white solid; mp (see Table).

MS (ES, positive mode): *m*/*z* = 311.2 $(M + 1)^+$, 333.3 $(M + Na)^+$.

^{1}H NMR ($CDCl_3$): δ = 1.65−1.72 [m, 4 H, $(CH_2)_2$], 2.35 (t, 2 H, *J* = 7.0 Hz, CH_2CO), 3.07, 3.12 [2 s, 6 H, $N(CH_3)_2$], 3.39 (s, 3 H, N-1-CH_3), 3.65 (s, 3 H, OCH_3), 3.96 (t, 2 H, *J* = 7.0 Hz, N-3-CH_2), 5.02 (s, 1 H, H-5), 7.65 (s, 1 H, N=CH).

^{13}C NMR ($CDCl_3$): δ = 22.29, 27.34 (CH_2), 29.95 (N-1-CH_3), 33.78 (CH_2CO), 34.86, 40.42, 40.84 [$N(CH_3)_2$, N-3-CH_2], 51.43 (OCH_3), 83.56 (C-5), 152.46 (C-2), 153.90 (N=CH), 159.42, 163.42 (C-4, C-6), 173.95 (CH_3O_2).

1-Benzyl-6-(dimethylaminomethylene)amino-3-(3-phthalimidopropyl)uracil (9)

Starting from **1** (100 mg), 205 mg (97%) of **9** was obtained as a white solid; mp (see Table).

MS (ES, positive mode): m/*z* = 460.1 $(M + H)^+$, 482.1 $(M + Na)^+$.

^{1}H NMR ($CDCl_3$): δ = 2.04 (q, *J* = 7.0 Hz, 2 H, CH_2), 3.02, 3.08 [2 s, 6 H, $N(CH_3)_2$], 3.75 (t, *J* = 7.2 Hz, 2 H, NPht-CH_2), 4.02 (t, *J* = 7.0 Hz, 2 H, *N*-3-CH_2), 5.03 (s, 1 H, H-5), 5.20 (s, 2 H, *N*-1-CH_2), 7.23 (m, 5 H, C_6H_5), 7.62 (s, 1 H, N=CH), 7.68 (m, 2 H, C_6H_4), 7.82 (m, 2 H, C_6H_4).

^{13}C NMR ($CDCl_3$): δ = 27.30 (CH_2), 35.01 [$N(CH_3)_2$], 36.06 (*N*Pht-CH_2), 38.87 (*N*-3-CH_2), 40.87 [$N(CH_3)_2$], 46.06 (*N*-1-CH_2), 83.66 (C-5), 123.16, 127.08, 127.52, 128.35, 132.21, 133.76, 138.02 (C_6H_4, C_6H_5), 152.34 (C-2), 154.06, 159.15 (N=CH, C6), 163.27 (C-4), 168.29 (COPht).

Removal of the Formamidino Group; Synthesis of 10 and 11; General Procedure

A solution of the corresponding formamidino derivative (0.3 mmol) in MeOH (2 mL) was treated with aq ammonia (4 mL) at r.t. for 1 to 3 days. Solvents were evaporated and the resulting residue was purified by CCTLC on the Chromatotron eluting with CH_2Cl_2/MeOH (15:1).

6-Amino-1-benzyl-3-propyluracil (10)

Starting from **3** (94 mg), 76 mg (92%) of **10** was obtained as a white solid.

Mp 169 ºC.

^{1}H NMR (DMSO-d_6): δ = 0.79 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.46 (m, 2 H, CH_2CH_3), 3.66 (t, *J* = 6.8 Hz, 2 H, N-3-CH_2), 4.69 (s, 1 H, H-5), 5.04 (s, 2 H, *N*-1-CH_2), 7.17 (br s, 2 H, NH_2), 7.23−7.34 (m, 5 H, C_6H_5).

6-Amino-1-methyl-3-propyluracil (11)

Starting from **6** (72 mg), 57 mg (94%) of **11** was obtained.

Mp 80 ºC.

MS (ES, positive mode): *m*/*z* = 184.1 $(M + 1)^+$, 206.0 $(M + Na)^+$.

^{1}H NMR (acetone-d_6): δ = 0.84 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.49−1.61 (m, 2 H, CH_2), 3.38 (s, 3 H, *N*-1-CH_3), 3.75 (t, *J* = 7.5 Hz, 2 H, *N*-3-CH_2), 4.82 (s, 1 H, H-5), 6.13 (br s, 2 H, NH_2).

^{13}C NMR (acetone-d_6): δ = 11.52 (CH_3), 21.90 (CH_2), 29.03 (*N*-1-CH_3), 42.58 (*N*-3-CH_2), 77.05 (C-5), 152.58 (C-2), 155.78 (C-6), 162.61 (C-4).

6-Amino-3-[4-(methoxycarbonyl)butyl]-1-methyluracil (12)

To a solution of **8** (60 mg, 0.19 mmol) in MeOH (3 mL) was added $ZnCl_2$ (111mg, 0.81 mmol), and the mixture was refluxed for 2 d. Then the mixture was partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, evaporated, and the resulting residue was purified by CCTLC on the Chromatotron using CH_2Cl_2/MeOH (15:1) to yield 45 mg (90%) of **12** as white solid; mp 165 ºC.

MS (ES, positive mode): *m*/*z* = 256.1$(M + 1)^+$, 278.0 $(M + Na)^+$.

^{1}H NMR (DMSO-d_6): δ = 1.44−1.48 [m, 4 H, $(CH_2)_2$], 2.29 (t, J = 7.0 Hz, 2 H, CH_2CO), 3.22 (s, 3 H, N-1-CH_3), 3.55 (s, 3 H, OCH_3), 3.69 (t, 2 H, J = 7.0 Hz, N-3-CH_2), 4.66 (s, 1 H, H-5), 6.75 (br s, 2 H, NH_2).

^{13}C NMR (DMSO-d_6): δ = 21.71, 26.98 (CH_2), 29.10 (N-1-CH_3), 32.86 (CH_2CO), 40.75 (N-3-CH_2), 51.02 (OCH_3), 74.95 (C-5), 151.31 (C-2), 154.85 (C-6), 161.15 (C-4), 173.09 (C=O).

1-Benzyl-6-(dimethylaminomethylene)amino-3-propargyluracil (13).

A suspension containing 6-amino-1-benzyluracil (**1**) (108 mg, 0.5 mmol) in dry DMF (2.5 mL) and DMF-DMA (0.27 mL, 2.0 mmol) was warmed at 40 ºC till disappearance of starting material (TLC: CH_2Cl_2/MeOH, 10:1). It was cooled to r.t. and volatiles were removed by distillation in vacuo. The crude residue containing **2** was dissolved in anhyd MeCN (4 mL) and DMF (0.5 mL), and then treated with DBU (0.30 mL, 1 mmol) and propargyl bromide (0.10 mL, 0.9 mmol). The mixture was heated at 80 ºC for 4 h. Then it was cooled and neutralized by the addition of AcOH. Solvents were removed, and the residue was treated with aq $NaHCO_3$ solution (20 mL) and EtOAc (30 mL). The aqueous phase was further extracted with EtOAc (2 × 30 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by flash column chromatography using CH_2Cl_2/acetone (6:1) as eluent to yield 96 mg (62%) of **13** as a white solid; mp (see Table).

MS (ES, positive mode): m/z = 311 $(M + 1)^+$, 333 $(M + Na)^+$.

^{1}H NMR ($CDCl_3$): δ = 2.17 (t, 1 H, J = 2.6 Hz, C≡CH), 3.07, 3.13 [2 s, 6 H, $N(CH_3)_2$], 4.73 (d, 2 H, N-3-CH_2), 5.12 (s, 1 H, H-5), 5.26 (s, 2 H, N-1-CH_2), 7.26−7.36 (m, 5 H, C_6H_5), 7.67 (s, 1 H, N=CH).

^{13}C NMR ($CDCl_3$): δ = 30.17 (N-3-CH_2), 35.06, 40.91 [$N(CH_3)_2$], 46.14 (N-1-CH_2), 69.99 (C≡*C*H), 78.95 (*C*≡CH), 83.28 (C-5), 127.18, 127.82, 128.28, 138.79 (C_6H_5), 151.81 (C-2), 154.29 (N=CH), 159.46 (C-6), 162.23 (C-4).

6-Amino-1-benzyl-3-propargyluracil (15)

Following the general procedure for the removal of the formamidino group, compound **13** (93 mg, mmol) was treated with aq ammonia in MeOH. Filtration of the reaction mixture and washing with MeOH afforded 58 mg (75%) of **13** as a white solid; mp 225 ºC.

MS (ES, positive mode): m/z = 256.1 $(M + 1)^+$, 274.1 $(M + Na)^+$.

^{1}H NMR (DMSO-d_6): δ = 3.20 (s, 1 H, HC≡C), 4.45 (d, 2 H, J = 2.2 Hz, N-3-CH_2), 4.74 (s, 1 H, H-5), 5.08 (s, 2 H, N-1-CH_2), 6.95 (s, 2 H, NH_2), 7.18−7.36 (m, 5 H, C_6H_5).

^{13}C NMR (DMSO-d_6): δ = 29.29 (N-3-CH_2), 44.77 (N-1-CH_2), 72.47 (HC≡C), 74.85 (HC≡*C*), 80.14 (C-5), 126.40, 127.31, 128.57, 136.30 (C_6H_5), 151.04 (C-2), 154.68(C-6), 160.22 (C-4).

1-Benzyl-6-(dimethylaminomethylene)amino-3-(4-methoxybenzyl)uracil (16)

Starting from **1** (100 mg, 0.46 mmol), and following an analogous procedure to that described for the synthesis of **13**, compound **16** (123 mg, 68%) was obtained after purification by CCTLC in the Chromatotron using CH_2Cl_2/MeOH (25:1) as eluent; mp (see Table).

MS (ES, positive mode): m/z = 393.1 $(M + 1)^+$; 415.0 $(M + Na)^+$.

^{1}H NMR ($CDCl_3$): δ = 3.01, 3.08 [2 s, 6 H, $N(CH_3)_2$], 3.76 (s, 3 H, OCH_3), 5.05 (s, 2 H, N-3-CH_2), 5.07 (s, 1 H, H-5), 5.19 (s, 2 H, N-1-CH_2), 6.81 (d, J = 8.4 Hz, 2 H, C_6H_4), 7.24−7.41 (m, 5 H, C_6H_5), 7.43 (d, J = 8.4 Hz, 2 H, C_6H_4) 7.61 (s, 1 H, N=CH).

^{13}C NMR ($CDCl_3$): δ = 34.96, 40.81 [$N(CH_3)_2$], 43.54 (N-3-CH_2), 46.05 (N-1-CH_2), 55.18 (OCH_3), 83.71 (C-5), 113.57, 130.04, 130.27, 158.74 (C_6H_4), 127.06, 127.58, 128.28, 138.03 (C_6H_5), 152.46 (C-2), 154.03 (N=CH), 159.09 (C-6), 163.31 (C-4).

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