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New approach for the synthesis of 1-aryl- and 1-heteroaryl-5-nitrouracil derivatives

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Abstract—1-(2,4-Dinitrophenyl)-5-nitrouracil and its 3-methyl derivatives were synthesized and used as substrates in reaction with aromatic amines and amino pyridines. In the reaction of aniline with 1-(2,4-dinitrophenyl)-5-nitrouracil, only the acyclic adduct was isolated. When 1-(2,4-dinitrophenyl)-3-methyl-5-nitrouracil was treated with aniline and other aromatic amines or amino pyridines, the desired 1-aryl-5-nitrouracil derivatives were obtained in satisfactory yield. The influence of the free H-3 proton present in the uracil ring on the course of the reaction is discussed.

1. Introduction

Pyrimidines are especially intriguing azine compounds due to their importance as the constituents of nucleic acids and useful biological properties. Many *N*-substituted uracil derivatives possess biological activity.[1,2] *N*-Glycosides of substituted uracil are widely used in therapy, mainly as antiviral and antineoplastic agents. The most prominent representatives are 5-fluorouracil and thymine derivatives.[2–4] Uramustine, 5-[*N*,*N*′-bis(2′-chloroethyl)amino]uracil is used orally in the treatment of several leukemias[5] and stavudine (D4T) inhibits the replication of HIV. Lamivudine [(−)-β-L-(2*R*,5*S*)-1,3-oxathiolanylcytosine], a reverse transcriptase inhibitor, is currently being investigated for therapy of chronic HBV infection.[1]

On the other hand, uracil derivatives show interesting reactivity. The uracil is susceptible to attack by either electrophiles (nitrogen and oxygen atoms, carbon C-5) or nucleophiles (carbon C-6, or C-5 in 6-substituted uracil derivatives), giving different products depending on the applied reactant. We have paid a special attention to 1-aryl-5-substituted uracils as useful intermediates in the synthesis of other uracil derivatives. It has been demonstrated that 3-methyl-1-(4-nitrophenyl)uracil derivatives possessing an electron-withdrawing group such as nitro, cyano, or carbamoyl group at the 5-position readily undergo ring transformation according to the *ANRORC* type reaction when treated with different *N*-centred nucleophiles.[6,7] The most available routes for the synthesis of 1-aryl- or 1-heteroaryl-5-substituted uracil derivatives involve condensation reactions. Thus, 3-methyl-5-nitro-1-(4-nitrophenyl)uracil was obtained by the condensation of 1-phenylurea with methyl 3,3-dimethoxypropanoate and subsequent ring closure under acidic conditions followed by *N*-3 methylation and nitration, which occurred on both rings (at C-5 of the uracil ring and C-4 of the benzene ring).[8] A similar procedure was used for the synthesis of a 1-(2-pyridyl)uracil derivative.[9] In both cases, the final products were obtained in moderate yield. Other 1-aryluracils have been synthesized from substituted ureidopropanoic acids or 1-acrylyl-3-arylureas.[10,11] 6-Methyl-1,3-oxazine-2,4(3*H*)-dione was transformed into the appropriate 1-aryl-6-methyluracils when treated with an excess of arylamines.[12] Uracil derivatives, in reaction with diaryliodonium salts, gave the appropriate *N*-mono- and *N*,*N*′-diarylation product with high regioselectivity.[13,14] Attempts at direct N-arylation of uracil derivatives have also been reported.[15–17]

2. Results and discussion

In this paper, we describe a simple and effective method for replacement of the 1-(2,4-dinitrophenyl) substituent by other substituted benzene or pyridine rings under *ANRORC* reaction conditions. Formally, this process can be considered as a transarylation reaction.

The substrates **4** and **6** were obtained by *N*-1 arylation.[17] An unsubstituted uracil **1** was treated with 1-fluoro-2,4-dinitrobenzene **2** in the presence of triethylamine as a base. 1-Aryl derivative **3** was subsequently nitrated using nitrating

Keywords: 1-(2,4-Dinitrophenyl)-5-nitrouracil; 1-Aryl-5-nitrouracil; 3-Methyl-1-(pyridyl)-5-nitrouracil; ANRORC type reaction; Nucleophilic aromatic substitution.
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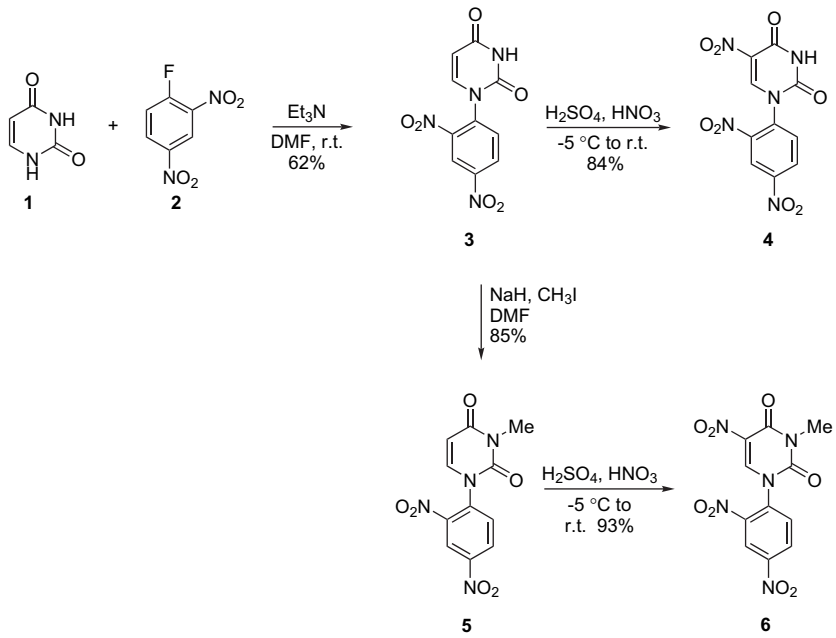


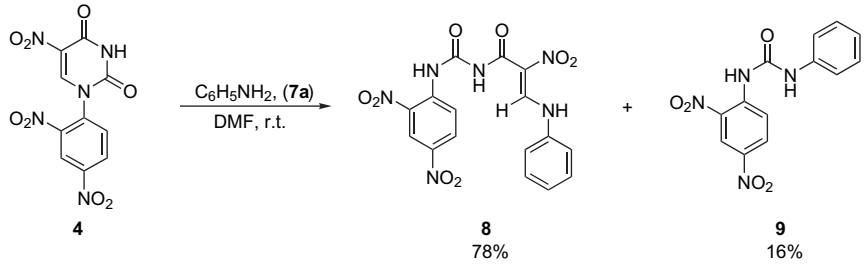
Scheme 1.

mixture (fuming nitric acid and sulfuric acid (98%) in the volume ratio 1:2) and gave **4**, or methylated at *N*-3 using methyl iodide in the presence of sodium hydride, followed by nitration of **5** using the same nitrating mixture as above, gave **6** (Scheme 1).

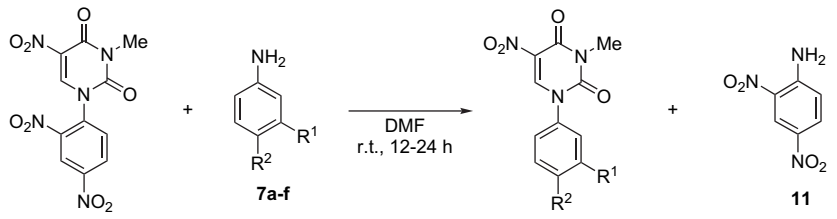
The position of uracil arylation was confirmed on the basis of NMR spectroscopy. Thus, the ^{1}H NMR spectrum of **3** indicated the presence of two conjugated protons of the uracil ring at 5.89 and 7.92 ppm, respectively, with a coupling constant of 8.0 Hz. The protons of the benzene ring were observed in the following order: the uncovered proton H-3′ appears at 8.85 ppm as a doublet (*J* 2.6 Hz) coupled with the proton H-5′ (dd, 1H, *J* 2.6 Hz, *J* 8.7 Hz). The H-5′ proton showed a coupling constant of 8.7 Hz with proton H-6′ (8.03 ppm). The signal of the H-3 proton of the uracil ring was observed at 11.78 ppm as a broad singlet. After the methylation reaction, this signal was not observed in the ^{1}H NMR spectrum. In compound **6**, the proton H-6 of the uracil ring appeared as a sharp singlet at 9.56 ppm. It should be mentioned that neither *N*-3 nor *O*-arylation products were detected. The signals of two carbonyl groups in the ^{13}C NMR spectrum at 163 and 149 ppm exclude the possibility of O-arylation.

According to reported data, 3-methyl-1-(4-nitrophenyl)-5-nitrouracil undergoes ring transformation when treated with compounds bearing primary amino group.[16,17] In the course of this reaction, *N*-1 nitrogen atom connected to 4-nitrophenyl group is replaced by nitrogen atom present in attacking nucleophile. During this transformation, the C–N bond in the molecule of nucleophile is retained and as a second product the 4-nitroaniline is isolated. The aromatic amines are non-reactive under the applied conditions.[18] It can be assumed that introduction of the 2,4-dinitrophenyl group on the *N*-1 nitrogen atom of 5-nitrouracil could accelerate the transformation reaction due to the better nucleofuge properties of the latter and enable the reaction with aromatic amines. In primary trials, the nitro derivative **4** was treated with aniline **7**. When the solution of **4** was mixed with aniline, the reaction mixture changed colour and in a couple of minutes yellow precipitation appeared. After 24 h at room temperature from the post-reaction mixture, two compounds were isolated: 1-(2,4-dinitrophenyl)-3-[(*E*)-2-nitro-3-phenylamino-acryloyl]urea **8** and 1-(2,4-dinitrophenyl)-3-phenylurea **9** in 78% and 16% yield, respectively (Scheme 2).

The isolated solid was stable and did not cyclize to the expected product of ring transformation. It is opposite to the results obtained in reaction of **4** with amino alcohols where the product of ring transformation was isolated in satisfactory yield.[17] When instead of compound **4**, 1-(2,4-dinitrophenyl)-3-methyl-5-nitrouracil **6** has been used in



Scheme 2.



6 7a-f 10a-f 11

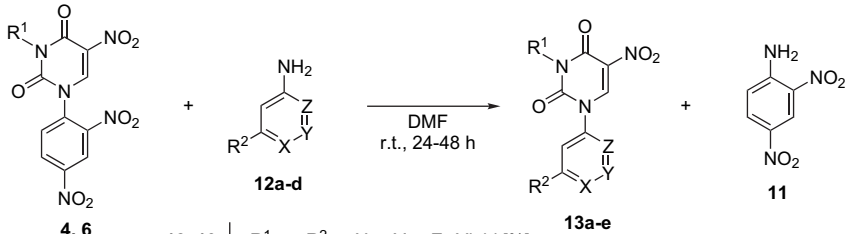
7,10	R^1	R^2	Yield [%]
a	H	H	56
b	$N(Et)_2$	H	45
c	OMe	OMe	45
d	OMe	H	86
e	OH	H	68
f	Me	H	77

Scheme 3.

reaction with aniline, the formation of a yellow adduct was observed, however after 24 h the TLC indicated the disappearance of the adduct and formation of a new substance. From the post-reaction mixture, the desired product **10a** was isolated in moderate yield and identified on the basis of NMR spectra and elemental analysis (Scheme 3). 2,4-Dinitroaniline **11**, a side product formed in this reaction, was isolated and identified by comparison with an authentic sample (mp and ^{1}H NMR spectroscopy). A similar behaviour was exhibited by the other investigated anilines **7b–f**. This transformation was next explored using the amino pyridines **12a–d**; they react smoothly at room temperature with uracil derivative **6** giving the appropriate 1-pyridyl substituted derivatives **13a–d** in satisfactory yield (Scheme 4). It is the first example of direct introduction of a pyridyl moiety at the *N*-1 nitrogen atom of the uracil ring.

When **6** was replaced by unsubstituted uracil derivative **4**, the reaction became more complicated. The TLC indicated the presence of the acyclic adduct together with several unidentified compounds. The moderate rate of formation of the desired product **13e** was obtained when the reaction was conducted in refluxing DMF.

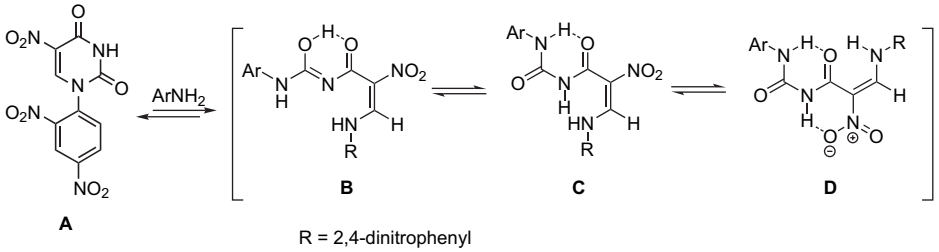
These results suggest that the unsubstituted H-3 proton of the uracil ring influences somehow the reaction rate in the case of such weak nucleophiles as aromatic amines. After addition of the nucleophile (aromatic amine) and ring opening, the acyclic adduct is stabilized by the formation of hydrogen bonds (e.g., in forms of **B**–**D**, Scheme 5). Several of these mesomeric structures may be derived from the lactim form of uracil, which are probably more stable and able to retard the recyclization. The solvatation effects created by polar



4, 6 12a-d 13a-e 11

12, 13	R^1	R^2	X	Y	Z	Yield [%]
a	CH_3	H	C	N	C	73
b	CH_3	H	C	C	N	62
c	CH_3	H	N	C	C	26
d	CH_3	CH_3	C	C	N	67
e	H	H	C	N	C	57

Scheme 4.



Scheme 5.

DMF, used as a solvent, can also stabilize the **B**–**D** forms but these effects are difficult to estimate.

3. Conclusion

In conclusion, an effective method for the regioselective introduction of a substituted benzene or pyridine ring on the *N*-1 nitrogen atom of uracil is described. The hitherto unknown 1-(2,4-dinitrophenyl)-3-methyl-5-nitrouracil can be considered as a convenient substrate in nucleophilic substitution reactions of the *ANRORC* type. The proposed method establishes a versatile route for the preparation of 1-aryl-substituted uracil, where the benzene ring contains electron donating groups.

4. Experimental

4.1. General

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR on a Varian Inova 300 MHz in DMSO-d_6 solution; δ-values are in parts per million relative to tetramethylsilane as an internal standard. Elemental analyses were obtained using a Perkin–Elmer 240C apparatus. All used reagents were purchased from Lancaster. TLC $60F_{254}$ plates and silica gel 60 (0.040–0.063 mm) were purchased from Merck.

4.1.1. 1-(2,4-Dinitrophenyl)uracil (3). To a solution of uracil (1.12 g, 10 mmol) in anhydrous DMSO (10 mL) at 50 °C, triethylamine (1.01 g, 10 mmol) was added dropwise while stirring. After 10 min, the solution was cooled down to room temperature and the solution of 1-fluoro-2,4-dinitrobenzene **2** (1.8 g, 9.7 mmol) in DMSO (1 mL) was added dropwise. The resulting yellow-reddish solution was stirred until the substrate had been consumed (approx. 30–60 min TLC, 10% v/v MeOH/$CHCl_3$) and was then poured into ice-water (50 g/50 mL). The precipitate formed was filtered off and after drying in air was crystallized from glacial acetic acid. Yield 1.75 g (62%), a yellow solid, mp 220–222 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 11.78 (br s, 1H, NH), 8.85 (d, 1H, $J_{3'-5'}$ 2.6 Hz, H-3′), 8.73 (dd, 1H, $J_{3'-5'}$ 2.6 Hz, $J_{5'-6'}$ 8.7 Hz, H-5′), 8.03 (d, 1H, $J_{5'-6'}$ 8.7 Hz, H-6′), 7.92 (d, 1H, J_{5-6} 8.0 Hz, H-6), 5.89 (d, 1H, J_{5-6} 8.0 Hz, H-5). ^{13}C NMR (DMSO-d_6) δ (ppm) 163.2, 149.6, 147.0, 145.1, 143.7, 136.1, 131.5, 129.2, 120.7, 103.1. Anal. Calcd for $C_{10}H_6N_4O_6$ (278.18): %C, 43.18; %H, 2.17; %N, 20.14. Found: %C, 42.96; %H, 2.21; %N, 19.89.

4.1.2. 1-(2,4-Dinitrophenyl)-5-nitrouracil (4). To a suspension of **3** (2.13 g, 7.67 mmol) in concentrated sulfuric acid (d=1.83 g/mL, 7.0 mL) cooled in an ice bath to 0 °C, fuming nitric acid (d=1.5 g/mL, 3.5 mL) was added dropwise at a temperature below 5 °C while stirring. After addition of nitric acid, the ice bath was removed and stirring was continued for 4 h at room temperature. Then, the reaction mixture was poured into ice-water (200 g, 1:1). The precipitated product was filtered off, rinsed with cold water to pH neutral and then with cold methanol (5 mL). Yield 2.03 g (84%), a yellow powder, mp 267–269 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ (ppm) 12.63 (br s, 1H, NH), 9.50 (s, 1H, H-6), 8.95 (d, 1H, $J_{3'-5'}$ 2.4 Hz, H-3′), 8.81 (dd, 1H, $J_{3'-5'}$ 2.4 Hz, $J_{5'-6'}$ 8.4 Hz, H-5′), 8.16 (d, 1H, $J_{5'-6'}$ 8.4 Hz, H-6′). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.7, 148.7, 148.2, 147.9, 144.9, 134.7, 132.6, 129.6, 126.7, 120.9. Anal. Calcd for $C_{10}H_5N_5O_8$ (323.18): %C, 37.17; %H, 1.56; %N, 21.67. Found: %C, 37.31; %H, 1.72; %N, 21.69.

4.1.3. 1-(2,4-Dinitrophenyl)-3-methyluracil (5). To the solution of **4** (3.0 g, 10.8 mmol) in anhydrous DMF (10 mL) at room temperature, sodium hydride (80% immersion in a mineral oil, 0.36 g, 12 mmol) was added in small portions while stirring. After 30 min methyl iodide (1.7 g, 0.75 mL, 12 mmol) was added dropwise. After decay of substrate (3 h, TLC, 20% MeOH/$CHCl_3$), reaction mixture was poured into ice-water (50 g/50 g). The formed precipitation was filtered off, washed with cold water and dried on air. Crystallization from methanol gives pure compound. Yield 2.68 g (85%), a yellow solid, mp 170–172 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 8.88 (d, 1H, $J_{3'-5'}$ 2.4 Hz, H-3′), 8.74 (dd, 1H, $J_{3'-5'}$ 2.4 Hz, $J_{5'-6'}$ 9.0 Hz, H-5′), 8.03 (d, 1H, $J_{5'-6'}$ 9.0 Hz, H-6′), 7.96 (d, 1H, J_{5-6} 8.1 Hz, H-6), 6.03 (d, 1H, J_{5-6} 8.1 Hz, H-5), 3.18 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 162.1, 150.1, 147.1, 145.1, 142.1, 136.4, 131.7, 129.3, 120.8, 102.2, 27.4. Anal. Calcd for $C_{11}H_8N_4O_6$ (292.21): %C, 45.22; %H, 2.76; %N, 19.17. Found: %C, 45.39; %H, 2.31; %N, 18.98.

4.1.4. 1-(2,4-Dinitrophenyl)-3-methyl-5-nitrouracil (6). To a suspension of **5** (2.07 g, 7.1 mmol) in concentrated sulfuric acid (d=1.83 g/mL, 6.0 mL) cooled in an ice bath to 0 °C, fuming nitric acid (d=1.5 g/mL, 3.0 mL) was added dropwise at a temperature below 5 °C while stirring. After addition of nitric acid, the ice bath was removed and stirring was continued for 4 h at room temperature. Then, the reaction mixture was poured into ice-water (200 g, 1:1). The precipitated product was filtered off, rinsed with cold water to pH neutral and then with cold methanol (5 mL). Yield 2.21 g (93%), a yellow powder, mp 125–127 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.56 (s, 1H, H-6), 8.88 (d, 1H, $J_{3'-5'}$ 2.4 Hz, H-3′), 8.74 (dd, 1H, $J_{3'-5'}$ 2.4 Hz, $J_{5'-6'}$ 8.4 Hz, H-5′), 8.14 (d, 1H, $J_{5'-6'}$ 8.4 Hz, H-6′), 3.26 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 162.1, 150.1, 147.1, 145.1, 142.1, 136.4, 131.7, 129.3, 120.8, 102.2, 27.4. Anal. Calcd for $C_{11}H_7N_5O_8$ (337.21): %C, 39.18; %H, 2.09; %N, 20.77. Found: %C, 39.56; %H, 2.15; %N, 21.03.

4.1.5. 1-(2,4-Dinitrophenyl)-3-[(*E*)-2-nitro-3-phenylaminoacryloyl]urea (8) and 1-(2,4-dinitrophenyl)-3-phenylurea (9). To the solution of aniline **7** (0.10 g, 1.1 mmol) in DMF (3 mL) **4** (0.32 g, 1.0 mmol) was added while stirring. After approx. 15 min yellow solid starts precipitating. The resulting suspension was stirred until the substrate had been consumed (24 h, TLC, 5% v/v MeOH/$CHCl_3$) and poured into cold methanol (10 mL). The solid **8** was filtered off, washed with cold methanol and dried in air. Yield 0.32 g (78%), a yellow powder. The residue after filtration and washing was concentrated in vacuum and recrystallized from methanol. The solid **9** was filtered off, washed with cold methanol and dried in air. Yield 0.05 g (16%), a yellow powder.

4.1.5.1. Compound 8. Mp 210–211 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 12.48 (br s, 1H, NH), 11.83 (br s, 1H,

NH), 11.10 (s, 1H, C=*CH*), 7.64 (d, 2H, $J_{o'-m'}$ 7.8 Hz, H-2Ar′, H-6Ar′), 8.89 (d, 1H, J_{3-5} 2.7 Hz, H-3Ar), 8.81 (d, 1H, J_{5-6} 9.5 Hz, H-6Ar), 8.70 (br s, 1H, NH), 8.59 (dd, 1H, J_{3-5} 2.7 Hz, J_{5-6} 9.5 Hz, H-5Ar), 7.50 (m, 2H, H-3Ar′, H-5Ar′), 7.35 (t, 1H, $J_{m'-p'}$ 7.4 Hz, H-4Ar′). Anal. Calcd for $C_{16}H_{12}N_6O_8$ (416.31): %C, 46.16; %H, 2.91; %N, 20.19. Found: %C, 46.21; %H, 2.15; %N, 20.13.

4.1.5.2. Compound 9. ^{1}H NMR (DMSO-d_6) δ (ppm) 10.20 (s, 1H, NH), 10.08 (s, 1H, NH), 8.83 (d, 1H, J_{3-5} 2.7 Hz, H-3Ar), 8.81 (d, 1H, J_{5-6} 9.6 Hz, H-6Ar), 7.51 (d, 2H, $J_{o'-m'}$ 8.4 Hz, H-2Ar′, H-6Ar′), 8.49 (dd, 1H, J_{3-5} 2.7 Hz, J_{5-6} 9.6 Hz, H-5Ar), 7.33 (m, 2H, Hz, H-3Ar′, H-5Ar′), 7.06 (t, 1H, $J_{m'-p'}$ 7.4 Hz, H-4Ar′).

4.2. Typical preparation procedure of 10a–f

To the stirred solution of an appropriate aniline **7a–f** (1.1 mmol) in DMF (3 mL) 1-(2,4-dinitrophenyl)-3-methyl-5-nitrouracil **6** (0.32 g, 1.0 mmol) was added. When the TLC (AcOEt/*n*-hexane 1:1 v/v, 12–24 h) indicated the consumption of substrate **6**, the solvent was evaporated under reduced pressure. The residue was dissolved in methanol, decolourized with charcoal and after partial concentration left for crystallization.

4.2.1. 3-Methyl-5-nitro-1-phenyluracil (10a). Yield 0.14 g (56%), a yellow solid, mp 231–233 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.14 (s, 1H, H-6), 7.55–7.50 (m, 5H, Ph), 3.25 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.6, 149.4, 147.8, 138.2, 129.4, 129.2 (2C), 127.1 (2C), 125.6, 28.4. Anal. Calcd for $C_{11}H_9N_3O_4$ (247.21): %C, 53.45; %H, 3.67; %N, 17.00. Found: %C, 53.06; %H, 3.72; %N, 16.66.

4.2.2. 1-(4-Diethylaminophenyl)-3-methyl-5-nitrouracil (10b). Yield 0.14 g (45%), orange needles, mp 162–163 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 8.99 (s, 1H, H-6), 7.24 (d, 2H, J_{o-p} 9.0 Hz, H-2′, H-6′), 6.71 (d, 2H, J_{o-p} 9.0 Hz, H-3′, H-5′), 3.38 (q, 4H, $J_{1''-2''}$ 6.9 Hz, CH_2–CH_3), 3.24 (s, 3H, NCH_3), 1.11 (t, 6H, $J_{1''-2''}$ 6.9 Hz, CH_2–CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.6, 149.8, 148.4, 147.7, 127.6 (2C), 125.9, 110.8 (2C), 43.8 (2C), 28.4, 12.3 (2C). Anal. Calcd for $C_{15}H_{18}N_4O_4$ (318.34): %C, 56.60; %H, 5.70; %N, 17.60. Found: %C, 56.58; %H, 5.61; %N, 17.63.

4.2.3. 1-(3,4-Dimethoxyphenyl)-3-methyl-5-nitrouracil (10c). Yield 0.14 g (45%), a dark olive solid, mp 194–195 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.08 (s, 1H, H-6), 7.16 (d, 1H, $J_{2'-6'}$ 1.8 Hz, H-2′), 7.10–7.02 (m, 2H, H-5′, H-6′), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.25 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.6, 149.5, 149.3, 148.7, 148.2, 131.0, 125.2 119.3, 111.1, 55.8, 55.7, 28.4. Anal. Calcd for $C_{13}H_{13}N_3O_6$ (307.27): %C, 50.82; %H, 4.26; %N, 13.68. Found: %C, 50.62; %H, 4.21; %N, 13.69.

4.2.4. 1-(4-Methoxyphenyl)-3-methyl-5-nitrouracil (10d). Yield 0.24 g (86%), yellow plates, mp 215–217 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.08 (s, 1H, H-6), 7.43 (d, 2H, J_{o-p} 9.0 Hz, H-2′, H-6′), 7.07 (d, 2H, J_{o-p} 9.0 Hz, H-3′, H-5′), 3.81 (s, 3H, OCH_3), 3.24 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 159.6, 154.6, 149.6, 148.2, 131.0, 128.3 (2C), 125.4, 114.3 (2C), 55.5, 28.4. Anal. Calcd for $C_{12}H_{11}N_3O_5$ (277.24): %C, 51.99; %H, 4.00; %N, 15.16. Found: %C, 51.97; %H, 4.02; %N, 5.08.

4.2.5. 1-(4-Hydroxyphenyl)-3-methyl-5-nitrouracil (10e). Yield 0.21 g (68%), a brownish solid, mp 286–288 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.91 (s, 1H, OH), 9.03 (s, 1H, H-6), 7.29 (d, 2H, J_{o-p} 8.7 Hz, H-2′, H-6′), 6.86 (d, 2H, J_{o-p} 8.7 Hz, H-3′, H-5′), 3.24 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 158.1, 154.6, 149.7, 148.2, 129.6, 128.2 (2C), 125.3, 115.5 (2C), 28.4. Anal. Calcd for $C_{11}H_9N_3O_5$ (263.21): %C, 50.20; %H, 3.45; %N, 15.96. Found: %C, 50.19; %H, 3.44; %N, 15.74.

4.2.6. 1-(4-Methylphenyl)-3-methyl-5-nitrouracil (10f). Yield 0.20 g (77%), a yellow solid, mp 193–194 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.08 (s, 1H, H-6), 7.39 (d, 2H, J_{o-p} 8.4 Hz, H-2′, H-6′), 7.34 (d, 2H, J_{o-p} 8.4 Hz, H-3′, H-5′), 3.24 (s, 3H, NCH_3), 2.38 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.6, 147.9, 139.1, 135.8, 129.6 (2C), 126.8 (2C), 125.5, 28.5, 20.7. Anal. Calcd for $C_{12}H_{11}N_3O_4$ (261.24): %C, 55.17; %H, 4.24; %N, 16.08. Found: %C, 55.19; %H, 4.25; %N, 16.08.

4.3. Preparation of 3-methyl-5-nitro-1-(pyridin-*X*-yl)uracils 13a–d

To stirred solution of *X*-aminopyridine **12a–d** (0.031 g, 0.33 mmol) in DMF (1 mL) 3-methyl-1-(2,4-dinitrophenyl)-5-nitrouracil **6** (0.1 g, 0.29 mmol) was added. The reaction mixture was stirred at room temperature until the decay of **6** was observed (24–48 h, TLC 3% v/v MeOH/$CHCl_3$). The solvent was removed under reduced pressure and the residue was resolved in appropriate solvent (discussed below are the details of synthesis) and left for crystallization at 0 °C. The precipitated solid was filtered off and dried in air.

4.3.1. 3-Methyl-5-nitro-1-(pyridin-3-yl)uracil (13a). 3-Aminopyridine **(12a)** (0.031 g, 0.33 mmol) was stirred with **6** (0.1 g, 0.29 mmol) for 48 h; crystallization from the solution of ethyl acetate and methanol (1:10 v/v). Yield 0.053 g (73%), a brownish powder, mp 220–222 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.34 (s, 1H, H-6), 8.73–8.68 (m, 2H, H-2′, H-6′), 7.98 (ddd, 1H, $J_{4'-6'}$ 1.5 Hz, $J_{2'-4'}$ 2.5 Hz, $J_{4'-5'}$ 8.2 Hz, H-4′), 7.61 (ddd, 1H, $J_{2'-5'}$ 0.6 Hz, $J_{5'-6'}$ 4.8 Hz, $J_{4'-5'}$ 8.2 Hz, H-5′), 3.26 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.6, 150.1, 149.5, 147.9, 147.8, 135.2, 134.9, 126.0, 124.0, 28.5. Anal. Calcd for $C_{10}H_8N_4O_4$ (243.17): %C, 48.39; %H, 3.25; %N, 22.57. Found: %C, 48.41; %H, 3.25; %N, 22.65.

4.3.2. 3-Methyl-5-nitro-1-(pyridin-2-yl)uracil (13b). The reaction was continued for 48 h, after work-up crystallization from solution of acetone and methanol (1:1 v/v). Yield 0.088 g (62%), brown crystals; mp 204–205 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.41 (s, 1H, H-6), 8.63 (ddd, 1H, $J_{3'-6'}$ 0.7 Hz, $J_{4'-6'}$ 1.8 Hz, $J_{5'-6'}$ 4.8 Hz, H-6′), 8.07 (dt, 1H, $J_{4'-6'}$ 1.8 Hz, $J_{4'-3'(5')}$ 7.8 Hz, H-4′), 7.79 (td, 1H, $J_{3'-5'(6')}$ 0.7 Hz, $J_{4'-3'(5')}$ 7.8 Hz, H-3′), 7.58 (ddd, 1H, $J_{3'-5'}$ 0.7 Hz, $J_{5'-6'}$ 4.8 Hz, $J_{4'-3'(5')}$ 7.8 Hz, H-5′), 3.27 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.28, 149.10, 148.94, 148.88, 145.50, 138.90, 126.29, 124.63, 121.36,

28.44. Anal. Calcd for $C_{10}H_8N_4O_4$ (243.17): %C, 48.39; %H, 3.25; %N, 22.57. Found: %C, 48.37; %H, 3.29; %N, 22.70.

4.3.3. 3-Methyl-5-nitro-1-(pyridin-4-yl)uracil (13c). The reaction time was 48 h, crystallization from acetone. Yield 0.019 g (26%), a white solid, mp 263–264.5 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ (ppm) 9.27 (s, 1H, H-6), 8.77 (d, 2H, $J_{2'(6')-3'(5')}$ 3.9 Hz, H3′, H-5′), 7.60 (d, 2H, $J_{2'(6')-3'(5')}$ 3.9 Hz, H-2′, H-6′), 3.26 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.4, 150.9, 148.8, 147.0 (2C), 145.2, 126.3, 121.8 (2C), 28.4. Anal. Calcd for $C_{10}H_8N_4O_4$ (243.17): %C, 48.39; %H, 3.25; %N, 22.57. Found: %C, 48.35; %H, 3.23; %N, 22.61.

4.3.4. 3-Methyl-1-(4′-methylpyridin-2-yl)-5-nitrouracil (13d). The reaction time was 24 h; crystallization from solution of ethyl acetate. The product precipitated in amounts of 0.036 g; the additional crop of **13d** (0.015 g) was obtained by column chromatography (silica gel, 3% v/v MeOH/$CHCl_3$). Total yield 0.051 g (67%), a yellow solid, mp 198–200 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 9.37 (s, 1H, H-6), 8.47 (d, 1H, $J_{5'-6'}$ 5.1 Hz, H-6′), 7.61 (s, 1H, H-3′), 7.41 (d, 1H, $J_{5'-6'}$ 5.1 Hz, H-5′), 3.26 (s, 3H, CH_3), 2.43 (s, 3H, CH_3-Py). ^{13}C NMR (DMSO-d_6) δ (ppm) 154.3, 150.1, 149.2, 148.5, 148.8, 145.6, 126.2, 125.5, 121.6, 28.4, 20.6. Anal. Calcd for $C_{11}H_{10}N_4O_4$ (262.23): %C, 50.38; %H, 3.84; %N, 21.37. Found: %C, 50.35; %H, 3.87; %N, 21.41.

4.3.5. 5-Nitro-1-(pyridin-3-yl)uracil (13e). The solution of 3-aminopyridine (**12a**) (0.101 g, 1.1 mmol) and **4** (0.323 g, 1.0 mmol) in DMF (5 mL) was refluxed for 1 h, then solvent was removed in vacuum. The residue was triturated with hot ethyl acetate to separate the 2,4-dinitroaniline and other side products. The residual crude product (0.166 g) was dissolved in hot 1 M HCl, decolorized with charcoal, neutralized to pH ~ 5 and cooled to room temperature. The precipitate of **13e** was filtered off, washed with water and dried in air. Yield 0.133 g (57%), a brownish solid, mp 241–242 °C. ^{1}H NMR (DMSO-d_6) δ (ppm) 12.32 (s, 1H, NH), 9.28 (s, 1H, H-6), 8.73 (d, 1H, $J_{2'-4'}$ 2.5 Hz, H-2′), 8.64 (dd, 1H, $J_{4'-6'}$ 1.5 Hz, $J_{5'-6'}$ 4.8 Hz, H-6′), 8.00 (ddd, 1H, $J_{4'-6'}$ 1.5 Hz, $J_{2'-4'}$ 2.5 Hz, $J_{4'-5'}$ 8.2 Hz, H-4′), 7.60 (ddd, 1H, $J_{2'-5'}$ 0.6 Hz, $J_{5'-6'}$ 4.8 Hz, $J_{4'-5'}$ 8.2 Hz, H-5′). ^{13}C NMR (DMSO-d_6) δ (ppm) 155.18, 149.97, 149.84, 149.03, 147.92, 135.29, 134.45, 126.25, 123.93. Anal. Calcd for $C_9H_6N_4O_4$ (234.17): %C, 46.16; %H, 2.58; %N, 23.93. Found: %C, 45.94; %H, 2.53; %N, 23.98.

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