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A convenient method for N-1 arylation of uracil derivatives

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Abstract—1-(4-Nitrophenyl)- and 1-(2,4-dinitrophenyl)uracil derivatives have been obtained by direct arylation of uracil and its 5-substituted derivatives using 1-fluoro-4-nitrobenzene or 1-fluoro-2,4-dinitrobenzene in the presence of a base. The application of the newly obtained uracil derivatives in further synthesis is also presented.

Many N-substituted uracil derivatives possess biological activity.[1] N-Glycosides of substituted uracils are widely used in therapy, mainly as antiviral and antineoplastic agents. The most prominent representatives are 5-fluorouracil and thymine derivatives.[2,3] Uramustine, 5-[*N*,*N*′-bis(2′-chloroethyl)amino]uracil, is used orally in the treatment of several leukemias,[4] and 5-nitrouracil derivatives exhibit macrophage growth inhibition.[5] 1-Aryl-5-substituted uracils are also useful intermediates in the synthesis of other uracil derivatives.[6–8] 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, when treated with different N-centered nucleophiles readily undergo ring transformation according to the ANRORC type reaction.[6–8] The 1-(4-nitrophenyl)-5-substituted uracils were obtained using known condensation methods. 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).[9] A similar procedure was used for the synthesis of 5-cyano-3-methyl-1-(4-nitrophenyl)uracil.[7] In both cases, the final products were obtained in moderate yields. The other 1-aryluracils have been synthesized from substituted ureidopropanoic acids or 1-acryloyl-3-arylureas.[10] 6-Methyl-1,3-oxazine-2,4(3*H*)-dione when treated with an excess of arylamines was transformed into the appropriate 1-aryl-6-methyluracils.[11] Uracil derivatives, in reaction with diaryliodonium salts, gave the appropriate N-mono- and N,N′-diarylation products with high regioselectivity.[12,13] The reaction of pyridin-2(1*H*)-one with triphenylbismuth or tris(3-methoxyphenyl)bismuth gave the appropriate *N*-aryl derivatives in moderate yields.[14] Attempts at direct N-arylation of uracil derivatives have also been reported.[15,16]

As a part of our research interest in the synthetic applications of 1,5-disubstituted uracil derivatives, the direct arylation of 5-substituted uracils with activated fluorobenzene derivatives under basic conditions was investigated to achieve N-monoarylation with high yields and regioselectivity. The 5-substituted uracils are weak *NH*-acids with pK_as in the range of 7.93–9.75, except for the 5-nitrouracil having a pK_a of 5.66.[17] In most cases, potassium carbonate should be a strong enough base to deprotonate uracils. In a typical procedure, uracils **1a**–**f** were dissolved in DMSO at room temperature, followed by the addition of a base and a 1-fluorobenzene derivative (**2a** or **2b**).[18] When 1-fluoro-4-nitrobenzene **2a** was used as the arylating agent, the best conversions were obtained when the reaction was performed at an elevated temperature (70–80 °C, oil bath) for a period of 6–48 h. The more reactive 1-fluoro-2,4-dinitrobenzene reacted at room temperature, and usually after 1–2 h the complete consumption of the starting **2b** was observed (TLC, MeOH–$CHCl_3$, 5:95, v/v). Under these

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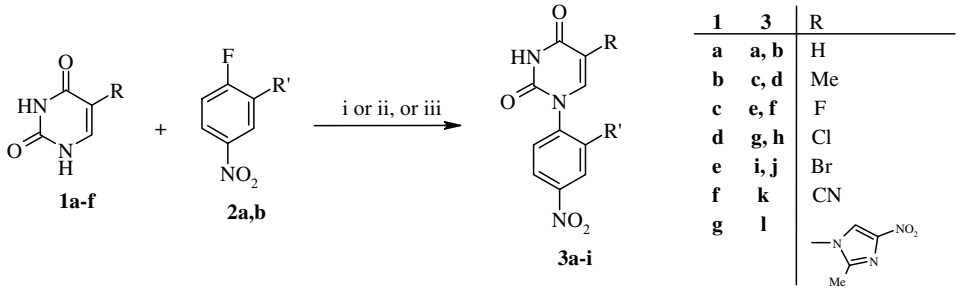
conditions the formation of only the desired products was observed. The products **3a–l** were isolated as precipitates by pouring the reaction mixture onto ice and were obtained in satisfactory yields (Scheme 1, Table 1). Crystallization from ethyl acetate or methanol gave analytically pure compounds.[18] Additional products (approx 10%) could be isolated from post-crystallization liquors using column chromatography.

The arylation of unsubstituted uracil **1a** using 1-fluoro-2,4-dinitrobenzene has been performed in the presence of triethylamine as a base.[19] However, in the presence of potassium carbonate the formation of a bisarylation product was observed.

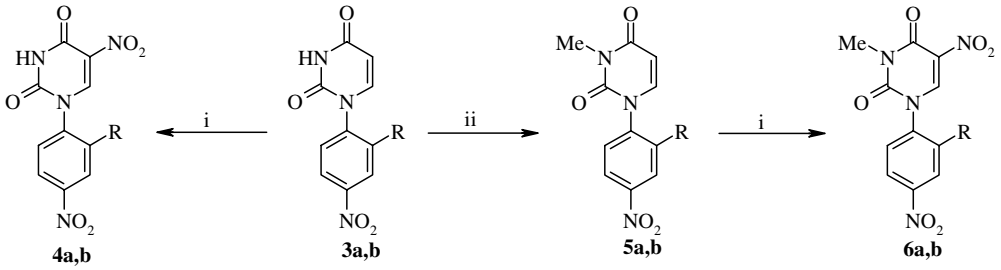
In the case of 5-nitrouracil, the anion of which is less nucleophilic, the direct arylation failed. Examination of the reaction mixture indicated the presence of unreacted substrates and traces of 4-nitrophenol. 1-(4-Nitrophenyl)-5-nitrouracil **4a** was obtained by nitration of **3a** using a nitrating mixture (fuming nitric acid and sulfuric acid (98%) in the volume ratio 1:2) at 0 °C in 86% yield (Scheme 2). The position of uracil arylation was confirmed by the conversion of **3a** into the known 3-methyl-5-nitro-1-(4-nitrophenyl)uracil[20] **6a** by methylation at N-3, followed by nitration at C-5 of the uracil ring. The same procedure was applied for the conversion of **3b** into **6b**. The structures of all the compounds obtained were confirmed on the basis of elemental analysis and NMR spectroscopy (Table 2). It should be mentioned that the formation of neither N-3 nor O-arylation products was detected. In the case of uracil and thymine arylations, inspection of TLC plates indicated the presence of a by-product. We separated these substances in



Scheme 1. **2a**: R′ = H, **2b**: R′ = NO_2. Reagents and conditions: (i) R = H, Me, F, Cl, Br, (1) DMSO, K_2CO_3, 80 °C, 0.5 h, (2) **2a**, 6–48 h; (ii) R = H, Me, (1) DMSO, Et_3N, 50 °C, 15 min, (2) **2b**, 25 °C, 1 h; (iii) R = F, Cl, Br, (1) DMSO, K_2CO_3, 25 °C, ca. 10 min, (2) **2b**, 1–2 h.

Table 1. Yields and properties of 1,5-disubstituted uracil derivatives

Entry	Product	R	R′	Yield (%)	Mp (°C)
1	**3a**	H	H	87	306–308
2	**3b**	H	NO_2	62	221–222
3	**3c**	CH_3	H	51	283–284
4	**3d**	CH_3	NO_2	66	276–277
5	**3e**	F	H	70	244–245
6	**3f**	F	NO_2	68	248–249
7	**3g**	Cl	H	74	257–258
8	**3h**	Cl	NO_2	69	243–244
9	**3i**	Br	H	60	269–270
10	**3j**	Br	NO_2	52	270–271
11	**3k**	CN	NO_2	93	260–261
12	**3l**	2-Methyl-4-nitroimidazol-1-yl	NO_2	50	300–302

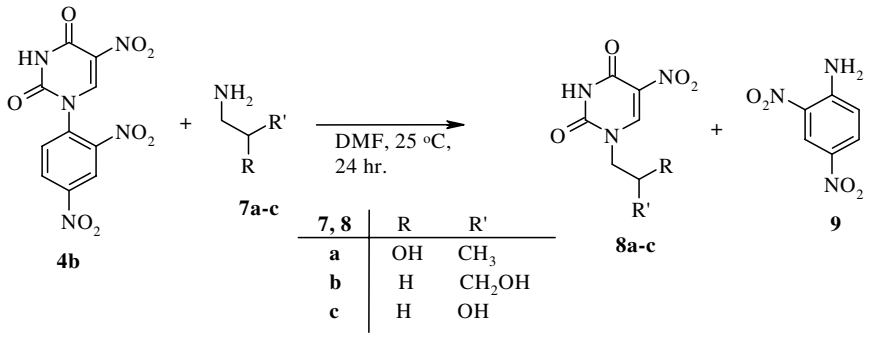


Scheme 2. **a**: R = H, **b**: R = NO_2. Reagents and conditions: (i) concd HNO_3, concd H_2SO_4, (1) 0 °C, 30 min, (2) 25 °C, 4 h; (ii) (1) DMF, NaH, 30 min, (2) CH_3I, 20 °C, 2.5 h.

Table 2. ^{1}H NMR and ^{13}C NMR data[a] for compounds **3a–l**

Compound	^{1}H NMR (300 MHz)	^{13}C NMR (75 MHz)
3a	5.77 (d, 1H, $J = 7.9$ Hz, H-5), 7.75 (d, 2H, $J = 8.9$ Hz, Ar), 7.81 (d, 1H, $J = 7.9$ Hz, H-6), 8.34 (d, 2H, $J = 8.9$ Hz, Ar), 11.55 (br s, 1H, NH)	102.55, 124.28 (2C), 127.97 (2C), 144.11, 144.44, 146.46, 150.00, 163.52
3b	5.89 (d, 1H, $J = 8.0$ Hz, H-5), 7.92 (d, 1H, $J = 8.0$ Hz, H-6), 8.03 (d, 1H, $J = 8.7$ Hz, H-6′), 8.73 (dd, 1H, $J = 2.6$, 8.7 Hz, H-5′), 8.85 (d, 1H, $J = 2.6$ Hz, H-3′), 11.78 (br s, 1H, NH)	103.14, 120.71, 129.21, 131.50, 136.09, 143.69, 145.08, 146.97, 149.59, 163.25
3c	1.84 (d, 3H, $J = 0.9$ Hz, CH_3), 7.72 (d, 1H, $J = 0.9$ Hz, H-6), 7.75 (d, 2H, $J = 9.0$ Hz, Ar), 8.33 (d, 2H, $J = 9.0$ Hz, Ar), 11.60 (1H, NH)	11.89 (CH_3), 110.33, 124.26 (2C), 127.82 (2C), 140.01, 144.27, 146.23, 149.93, 164.14
3d	1.87 (s, 3H, CH_3), 7.85 (s, 1H, H-6), 8.02 (d, 1H, $J = 8.7$ Hz, H-6′), 8.71 (dd, 1H, $J = 2.7$, 8.7 Hz, H-5′), 8.83 (d, 1H, $J = 2.7$ Hz, H-3′), 11.80 (s, 1H, NH)	11.96 (CH_3), 111.06, 120.71, 129.15, 131.22, 136.21, 139.20, 145.05, 146.73, 149.54, 163.99
3e	7.76 (d, 2H, $J = 9.3$ Hz, Ar), 8.32 (d, 1H, $^{3}J_{H-F} = 6.9$ Hz, H-6), 8.34 (d, 2H, 9.3 Hz, Ar), 12.09 (s, 1H, NH)	124.25 (2C), 128.10 (2C), 129.35 (d, $^{2}J_{C-F} = 36$ Hz, C-6), 140.70 (d, $^{1}J_{C-F} = 232$ Hz, C-5), 143.72, 146.47, 148.76 (C-2), 157.45 (d, $^{2}J_{C-F} = 26$ Hz, C-4)
3f	8.04 (d, 1H, $J = 8.7$ Hz, H-6′), 8.49 (d, 1H, $^{3}J_{H-F} = 6.6$ Hz, H-6), 8.75 (dd, 1H, $J = 2.7$, 8.7 Hz, H-5′), 8.86 (d, 1H, $J = 2.7$ Hz, H-3′), 12.36 (s, 1H, NH)	120.80, 128.72 (d, $^{2}J_{C-F} = 35$ Hz, C-6), 129.24, 131.70, 135.53, 140.8 (d, $^{1}J_{C-F} = 233$ Hz, H-5), 145.17, 147.06, 148.40 (C-2), 157.29 (d, $^{2}J_{C-F} = 26$ Hz, C-4)
3g	7.77 (d, 2H, $J = 6.9$ Hz, Ar), 8.32 (s, 1H, H-6), 8.34 (d, 2H, $J = 6.9$ Hz, Ar), 12.09 (s, 1H, NH)	108.16, 124.24 (2C), 128.33 (2C), 141.75, 143.52, 146.70, 149.28, 159.45
3h	8.08 (d, 1H, $J = 8.7$ Hz, H-6′), 8.50 (s, 1H, H-6), 8.74 (dd, 1H, $J = 2.7$, 8.7 Hz, H-5′), 8.87 (d, 1H, $J = 2.7$ Hz, H-3′), 12.36 (s, 1H, NH)	108.83, 120.78, 129.29, 131.96, 135.41, 140.95, 144.98, 147.23, 148.91, 159.22
3i	7.78 (d, 2H, $J = 9.0$ Hz, Ar), 8.34 (d, 2H, $J = 9.0$ Hz, Ar), 8.36 (s, 1H, H-6), 12.05 (s, 1H, NH)	96.83, 124.21 (2C), 128.32 (2C), 143.48, 143.90, 146.69, 149.48, 159.59
3j	8.08 (d, 1H, $J = 8.7$ Hz, H-6′), 8.54 (s, 1H, H-6), 8.75 (dd, 1H, $J = 2.4$, 8.7 Hz, H-5′), 8.76 (d, 1H, $J = 2.4$ Hz, H-3′), 12.31 (s, 1H, NH)	97.38, 120.73, 129.25, 131,98, 135.39, 143.10, 144.90, 147.20, 149.12, 159.38
3k	8.10 (d, 1H, $J = 9.0$ Hz, H-6′), 8.81(dd, 1H, $J = 2.7$, 9.0 Hz, H-5′), 8.91 (d, 1H, $J = 2.7$ Hz, H-3′), 9.03 (s, 1H, H-6), 12.59 (s, 1H, NH)	89.97 (CN), 113.50, 120.96, 129.61, 132.09, 134.79, 144.77, 147.75, 148.44, 153.15, 160.02
3l[b]	2.40 (s, 3H, $CH_{3\,imidazoyl}$), 8.23 (d, 1H, $J = 8.7$ Hz, H-6′), 8.25 (s, 1H, H-$5_{imidazoyl}$), 8.73 (s, 1H, H-6), 8.83 (dd, 1H, $J = 2.4$, 8.7 Hz, H-5′), 8.97 (d, 1H, $J = 2.4$ Hz, H-3′), 12.34 (s, 1H, NH)	13.11 (CH_3), 113.96, 121.62, 123.78, 129.95, 132.49, 136.56, 143.72, 146.21, 146.92, 147.32, 148.50, 149.75, 160.23

[a] Chemical shift (δ) in ppm, DMSO-d_6 as a solvent.
[b] Acetone-d_6.



7, 8	R	R'
a	OH	CH_3
b	H	CH_2OH
c	H	OH

Scheme 3.

amounts not exceeding 2% (as calculated based on starting **1a** and **1b**) and on the basis of NMR spectra we assigned the structures as 1,3-diarylation products.

It has been demonstrated that 3-methyl-5-nitro-1-(4-nitrophenyl)uracil **6a** when treated with primary amines undergoes ring transformation according to the ANRORC mechanism.[6] 1-(2,4-Dinitrophenyl)-5-nitrouracil **4b** possessing an additional nitro group on the benzene ring should be a more efficient nucleofuge in the ANRORC type reaction. In initial trials, **4b** was subjected to reaction with amino alcohols **7a**–**c** (Scheme 3), in anhydrous DMF at room temperature. The desired products **8a**–**c** were obtained in satisfactory yields after purification by column chromatography.[21] The 2,4-dinitroaniline **9**, a side product formed in this reaction, was isolated and identified by comparison with an authentic sample (mp and ^{1}H NMR).[22]

All newly synthesized compounds were subjected to primary bioactivity assays as inhibitors against *Mycobacterium tuberculosis*; compound **4b** exhibited an inhibition ability of 93%.

In conclusion, an effective method for the introduction of 4-nitrophenyl and 2,4-dinitrophenyl groups on the N-1 nitrogen atom of uracil is described. The conditions applied provided products with high regioselectivity in good yields. The hitherto unknown 1-(2,4-dinitrophenyl)-5-nitrouracil can be used as a substrate in nucleophilic substitution reactions of the ANRORC type. This is the first example when a 5-nitrouracil derivative unsubstituted at N-3 has been used as substrate in an ANRORC type reaction. The results obtained with derivative **4b** have encouraged us to prepare other nitrouracil derivatives, the synthesis of which will be published in due time.

Acknowledgements

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18. Synthesis of 1-(4-nitrophenyl)- or 1-(2,4-dinitrophenyl)-5-substituted uracil derivatives **3** (general procedure): To a solution of 5-substituted uracil (2.1 mmol) in anhydrous DMSO (6 ml), potassium carbonate was added (1 mmol). After 10 min, **2a** or **2b** (2 mmol) was added in one portion.

The resulting yellow-red solution was stirred until the substrate had been consumed and was then poured into ice–water (25 g/25 ml). The precipitate formed was filtered off and after drying in air was crystallized from methanol or ethyl acetate–methanol (1:3).

1-(4-Nitrophenyl)uracil **3a**: Anal. Calcd for $C_{10}H_7N_3O_4$ (233.18): C, 51.51; H, 3.03; N, 18.02. Found: C, 51.39; H, 2.97; N, 17.89.

5-Chloro-1-(2,4-dinitrophenyl)uracil **3h**: Anal. Calcd for $C_{10}H_5ClN_4O_6$ (312.63): C, 38.42; H, 1.61; N, 17.92. Found: C, 38.45; H, 1.35; N, 17.93.

1-(2,4-Dinitrophenyl)-5-nitrouracil **4b**: To a suspension of **3b** (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 the 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%), mp 267–269 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 8.16 (d, 1H, $J = 8.4$ Hz, H-6′), 8.81 (dd, 1H, $J = 2.4$, 8.4 Hz, H-5′), 8.95 (d, 1H, $J = 2.4$ Hz, H-3′), 9.50 (s, 1H, H-6), 12.63 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 120.88, 126.71, 129.65, 132.60, 134.72, 144.90, 147.92, 148.24, 148.66, 154.73. 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.

19. Synthesis of 1-(2,4-dinitrophenyl)uracil **3b**: Uracil **1a** (10 mmol) was dissolved in DMSO (10 ml) at 50 °C, triethylamine was added dropwise while stirring and the temperature was cooled to rt. To this solution, 1-fluoro-2,4-dinitrobenzene (1.8 g, 9.7 mmol) in DMSO (1 ml) was added. The reaction mixture was stirred for 30 min and poured onto crushed ice (100 g). The precipitate was filtered off, washed with water and dried. The crude product (2.25 g) was crystallized from glacial acetic acid. 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.
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21. Synthesis of 5-nitro-1-substituted uracils **8a**–**c** from 1-(2,4-dinitrophenyl)-5-nitrouracil (general procedure): To a solution of amino alcohol (1.5 mmol) dissolved in DMF (5 ml), 1-(2,4-dinitrophenyl)-5-nitrouracil (1.0 mmol) was added at room temperature while stirring. After consumption of the starting material (24 h, TLC MeOH–$CHCl_3$, 20:80), the solvent was evaporated under reduced pressure and the oily residue was purified on a silica gel column using a mixture of MeOH and $CHCl_3$ in a ratio of 10:90. The isolated product was crystallized from aqueous methanol (30% H_2O v/v).

Compound **8a**: (±)-1-(2-Hydroxypropyl)-5-nitrouracil: Yield 0.18 g (85%); mp 233–234 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.09 (d, 3H, $J = 6.3$ Hz, H-3′), 3.35 (dd, 1H, $J = 8.7$, 12.9 Hz, H-1′$_a$), 3.80–3.92 (m, 1H, H-2′), 3.95 (dd, 1H, $J = 2.7$, 12.9 Hz, H-1′$_b$), 4.58 (d, 1H, $J = 4.5$ Hz, OH), 9.07 (s, 1H, H-6), 12.02 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 20.56, 55.63, 63.51, 124.37, 149.39, 151.39, 155.04. Anal. Calcd for $C_7H_9N_3O_5$ (215.17): C, 39.08; H, 4.22; N, 19.53. Found: C, 39.10; H, 4.36; N, 19.15.

Compound **8b**: 1-(3-Hydroxypropyl)-5-nitrouracil: Yield 0.11 g (52%), mp 185–187 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.79 (p, 2H, $J = 6.5$ Hz, H-2′), 3.47 (dt, 2H, $J = 5.1$, 5.7 Hz, H-3′), 3.92 (t, 2H, $J = 6.5$ Hz, H-1′), 4.58 (t, 1H, $J = 5.1$ Hz, OH), 9.20 (s, 1H, H-6), 11.98 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 30.94, 47.28, 57.81, 124.66, 149.29, 150.97, 155.00. Anal. Calcd for $C_7H_9N_3O_5$ (215.17): C, 39.08; H, 4.22; N, 19.53. Found: C, 39.08; H, 4.26; N, 19.26.

Compound **8c**: 1-(2-Hydroxyethyl)-5-nitrouracil: Yield 0.1 g (50%), mp 239–241 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.61 (t, 2H, $J = 4.9$ Hz, H-2′), 4.92 (t, 2H, $J = 4.9$ Hz, H-1′), 5.02 (br s, 1H, OH), 9.12 (s, 1H, H-6), 12.03 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 51.42, 58.04, 124.44, 149.32, 151.36, 155.11. Anal. Calcd for $C_6H_7N_3O_5$ (201.14): C, 35.83; H, 3.51; N, 20.89. Found: C, 35.91; H, 3.62; N, 20.47.
22. 2,4-Dinitroaniline **9**; mp 177–179 °C (mp of authentic sample 176–178 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.12 (d, 1H, $J = 9.0$ Hz, H-6), 8.01 (br s, 2H, NH_2), 8.11 (dd, 1H $J = 2.7$, 9.0 Hz, H-5), 9.00 (d, 1H, $J = 2.7$ Hz, H-3).