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From N-n-butyl-2,6-dinitroaniline to a Fused Heterocyclic N-oxide

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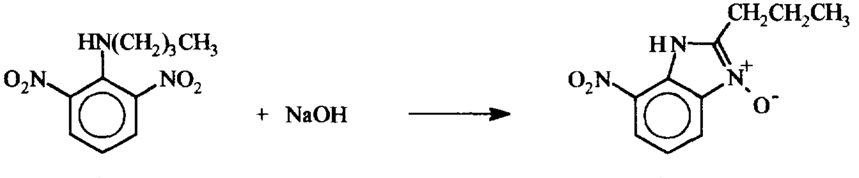
Abstract. The reaction of N-n-butyl-2,6-dinitroaniline with NaOH in 60% dioxane-water at reflux gives 7-nitro-2-n-propylbenzimidazole-3-oxide quantitatively.

Syntheses of fused heterocyclic N-oxides from o-nitroaniline derivatives having electron withdrawing substituents β to the amino group have been prevviously described.[1,2,3] Other benzimidazole or benzimidazole N-oxide derivatives were also obtained by photolysis in aqueous methanolic hydrochloric acid of 1-amino-2-nitrobenzene and 1-amino-4-chloro-2-nitrobenzene with pyrrolidine, piperidine or morpholine as the amino group.[4]

We found that the reaction of N-n-butyl-2,6-dinitroaniline **1a** with NaOH 0.1 to 1 M in 10% dioxane-water at 25° C gives 2,6-dinitrophenol and 7-nitro-2-n-propylbenzimidazole-3-oxide **2a** in ratios depending on the HO⁻ concentration. When the reaction was carried out at reflux in 60% dioxane-water with 0.2 M NaOH, **2a** was quantitatively formed, as shown in the equation below:



1a **2a**

A solution of 25 mg of **1a**[5] in 25 mL of 60% dioxane-water with 0.2 M NaOH was heated at reflux for 20 min. The solution was cooled to room temperature and $NaPO_4H_2$ buffer was added to bring the pH down to 6. The sample was evaporated to dryness in a rotavapor and extracted in a Soxhlet with acetone. After evaporation of the solvent we obtain 22 mg (95.6%) of **2a**.

The spectrum of **1a** in 10% dioxane-water shows an absorption band at 442 nm. The spectrum of the product changes with the pH of the solution as shown in Fig. 1. Spectrophotometric titration gave two inflection points at pH 2.36 and 7.33; these values are similar to those reported for 5-nitrobenzimidazole-3-oxide and 6-nitrobenzimidazole-1-oxide.[2]

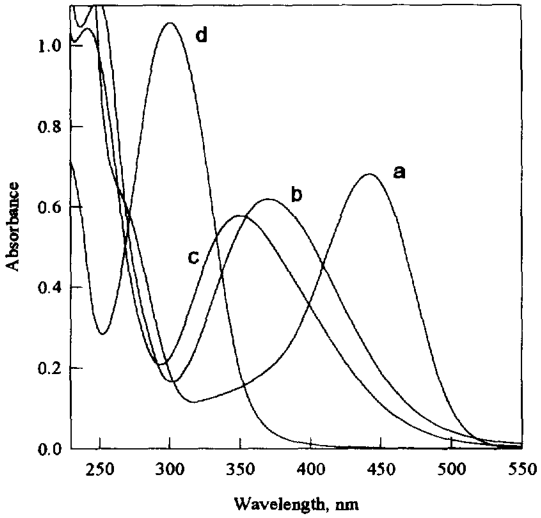
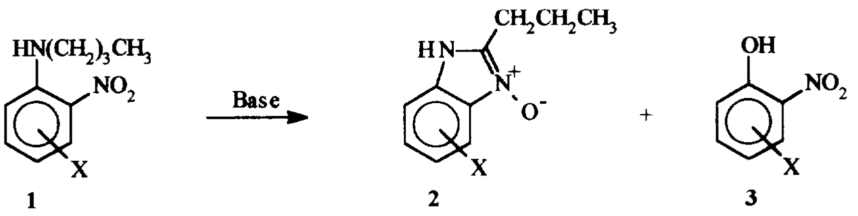


Fig. 1. (a) Spectrum of **1a** in 10% dioxane-water at pH 7.24 ($NaPO_4H_2$ buffer) $[1]_0 = 1 \times 10^{-4}$ M. Spectra of **2a** in 10% dioxane-water at different pH, $[2]_0 = 1 \times 10^{-4}$ M; (b) pH 13.42 (NaOH 0.1 M); (c) pH 7.24 ($NaPO_4H_2$ buffer); (d) pH 1.12 (HCl 0.1 M).

The product was identified as **2a** by ^{1}H and ^{13}C-NMR, IR, mass spectrometry and high resolution mass spectrometry. IR υ_{N-H} 3467 cm^{-1}; υ_{N-O} 1249 cm^{-1} (characteristic of N-oxides). ^{1}H-NMR (200 MHz) ($(CD_3)_2SO$) δ 0.98 (t, 3H, $-CH_3$), 1.88 (sex., 2H, $-CH_2CH_3$), 2.91 (t, 2H, $-CH_2CH_2CH_3$), 7.4 (t, 1H, H(5)), 7.88 (d, 1H, H(4)), 8 (d, 1H, H(6)), 12.1 (s, 1H, -NH). ^{13}C-NMR (200 MHz) ($(CD_3)_2SO$) δ 13.7 (C(3')), 20.1 (C(2')), 27.4 (C(1')), 115.3 (C(4)), 116.2 (C(6)), 121.2 (C(5)), 131 (C(7a)), 134.7 (C(7)), 137.7 (C(3a)), 155 (C(2)). MS e/z (%) M$^+$ 221 (17.66), 205 (8), 193 (24.13) ($M^+ - CH_2CH_2$), 191 (3.10), 190 (15.03), 178 (4.41), 177 (88.11), 163 (3.39), 75 (16.43), 71 (100) ($CH_3CH_2CH_2C{=}N^+H_2$), 51 (7.12), 46 (1.28), 43 (99.30), 41 (20.45). HRMS calcd for $C_{10}H_{11}N_3O_3$ (M) 221,080041, found 221,080151.

We examine our method of synthesis with other 2-nitroanilines derivatives **1b-d** [6,7] with different results. The general reaction is shown in the Scheme below and the results are summarized in Table 1.



a X = 6-NO_2
b X = H
c X = 4-NO_2
d X = 4,6-diNO_2

Table 1. Products of Reactions of 2-Nitroanilines **1a-d** at Reflux in 60% Dioxane-Water.

Nitroaniline	[NaOH]	Reaction time	**2**	**3**	Unreacted **1**	Recovery 1+ **2** + **3**
1a	0.20 M	20 min	95.6 %	---	---	95.6 %
1b	0.20 M	65 h	a	---	98 %	98%
1b	0.20 M	4 h[b]	---	---	100 %	c
1c	0.20 M	4 h	---	100 %	---	c
1c	0.01 M	24 h	---	100 %	---	c
1d	0.20 M	5 h	---	100 %	---	c
1d	0.01 M	18 h	46.3 %	10.4 %	---	60.9 %[d]

[a] An unknown product whose UV-visible spectrum is different from that of **1b** or **3b** and changes with pH remains in solution. [b] The reaction mixture was irradiated with two Phillips model HPT lamps emitting at 350 nm. [c] Product quantification was made by spectrophotometry. [d] 4.2% of an unidentified product was recovered.

Compound **2d** was identified by IR, ^1H and ^{13}C-NMR, mass spectrometry and high resolution mass spectrometry. IR: υ_{N-H} 3450 cm^{-1}; υ_{N-O} 1543 cm^{-1} (-NO_2); υ_{N-O} 1249 cm^{-1} (characteristic of N-oxides). ^1H-NMR (200 MHz) ($(CD_3)_2SO$) δ 1.00 (t, 3H, -CH_3), 1.80 (sex., 2H, -CH_2CH_3), 3.00 (t, 2H, -$CH_2CH_2CH_3$), 8.60 (d, 1H, H(4)), 8.90 (d, 1H, H(6)), 12.7 (s, 1H, -NH). ^{13}C-NMR (200 MHz) ($(CD_3)_2SO$) δ 13.62 (C(3')), 19.85 (C(2')), 27.61 (C(1')), 110.48 (C(4)), 13.83 (C(6)), 134.39 (C(7)); 136.48 (C(5)), 140.77 (C(7a)), 160.25 (C(3a)), 166.65 (C(2)). MS e/z (%) M^+ 266 (2.69); 250 (2.08); 238 (13.98); 222 (19.48); 71 (65.63); 43 (100). HRMS calcd for $C_{10}H_{10}N_4O_5$ (M) 266,06512, found 266,06512.

The results show that the two nitro groups ortho to the amine are needed for the reaction to occur. The formation of N-oxide competes with substitution of the amine by HO^- and straightforward substitution takes place at high base concentration while cyclization predominates at low base concentration. Compounds with only one nitro group are too unreactive under our reaction conditions and neither substitution nor cyclization takes place even at $[HO^-]$ as low as 0.01 M. In the case of compound **3c** that is highly activated for substitution by the presence of three nitro groups, cyclization can only compete at low base concentrations.

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4. Fielden, R.; Meth-Cohn, O.; Suschitzky, H. *Tetrahedron Lett.* **1970**, *15*, 1229-1234.
5. This substrate was synthesized as described previously in de Vargas, E. B.; de Rossi, R. H. *J. Org. Chem.* **1984**, *49*, 3978-3983. mp 39-40° C.
6. Substrate **1b** was obtained as an orange oil by the method described in Chiacchiera, M. S.; Singh, J. O.; Anunziata, J. D.; Silber, J.J. *J. Chem. Soc. Perkin Trans 2* **1987**, 987-993, and was identified by IR and ^{1}H-NMR.
7. Substrates **1c** and **1b** were synthesized by the same method used for substrate **1a**, mp 88-89°C and 100-101°C respectively.

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