

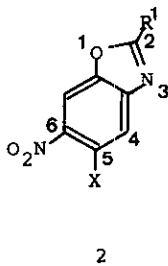
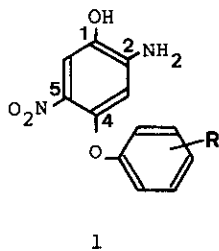
2-t-BUTYL-5-CHLORO-6-NITROBENZOXAZOLE: A PRACTICAL SYNTHETIC
INTERMEDIATE FOR 4-ARYLOXY-5-NITRO-2-AMINOPHENOLS

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Abstract--- On the examination of the anomalous reactivities
of several nitrobenzoxazole derivatives 2a-e toward acids and
bases it has been found that 2-t-butyl-5-chloro-6-nitrobenz-
oxazole 2c serves as one of the most convenient and practical
synthetic intermediates for 4-aryloxy-5-nitro-2-aminophenols.

Although 4-aryloxy-5-nitro-2-aminophenols 1 are useful compounds, particularly for
preparing colour photographic materials,¹ chelating dyes,² thermal-transfer-record-
ing materials,³ and bactericides,⁴ any standard procedure leading to 1 has not been
reported in the literature. In order to develop a practical synthetic intermediate
for 1, 2-substituted 5-chloro-6-nitrobenzoxazoles 2a-e were prepared,⁵ and both in-
troduction reaction of the aryloxy group and hydrolysis of the oxazole ring were
examined. The results are presented in this communication.

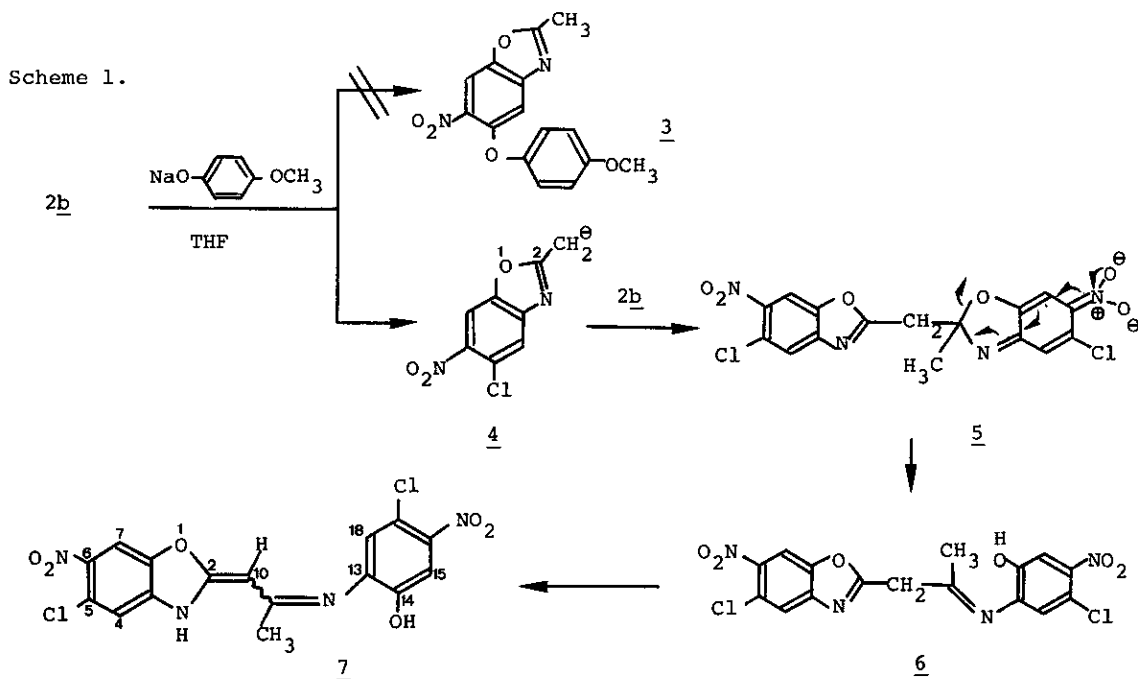


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|--|---------------------------------|
| 2a: R ¹ = H, X = Cl | e: R ¹ = o-Cl-phenyl |
| mp 88-89°C | X = Cl, |
| b: R ¹ = CH ₃ , X = Cl | mp 172°C |
| mp 138°C | f: R ¹ = o-Cl-phenyl |
| c: R ¹ = <i>t</i> -C ₄ H ₉ , X = Cl | X = H |
| mp 78-81°C | |
| d: R ¹ = phenyl, X = Cl | |
| mp 199-201°C | |

Nucleophilic aromatic substitution of 2

The behavior of 2 in the S_NAr reaction with aryloxy anions was dependent on the
nature of the substituent at the C-2 position of 2. For instance, treatment of 2a
and 2b with sodium *p*-methoxyphenoxide in DMF gave a complex mixture, no expected

p-methoxyphenoxy derivative 3 being detected. The same treatment, in the case of 2e, resulted in the reduction on chlorine atom at the C-5 position, giving 2f in 62 % yield. Moreover, 2b when treated with sodium p-methoxyphenoxide in THF at room temperature for several minutes and then quenched with diluted HCl afforded the dimer 7 as orange crystals (mp 238-240 °C) in 81% yield. The structure was assigned on the basis of the following spectral data: MS: m/z 425 (M+1) and 423 (M-1); IR (Nujol) 3360, 1645, 1615, 1600, and 1270 cm^{-1} ; UV/VIS λ_{max} (EtOH) 418 nm ($\epsilon=31200$); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 2.42 (s, 3H, CH_3), 5.67 (s, 1H, C-10-H), 7.63 (s, 1H, C-4-H), 7.67 (s, 1H, C-18-H), 7.87 (s, 1H, C-7-H), 8.48 (s, 1H, C-15-H), and 10.73 (s, 1H, OH). Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{N}_4\text{O}_6\text{Cl}_2$: C, 45.20; H, 2.37; N, 13.18; Cl, 16.68%; Found: C, 45.06; H, 2.30; N, 13.07; Cl, 16.53%. A plausible pathway leading to the dimer 7 is depicted in Scheme 1: The unstable intermediate 5 would be formed by the initial attack of the anion 4 to the C-2 position of the oxazole ring, and the subsequent ring cleavage would produce 6, which underwent a double bond isomerization to afford 7.



In view of general reactivity of the oxazole ring toward weak bases (nucleophiles) without any special electrophilic assistance,⁶ these phenomena are unusual⁷ and interesting. As shown in Table 1, successful introduction of the aryloxy group at the C-5 position of 2 was observed only in the case of 2c possessing *t*-butyl

substituent on the C-2 position.

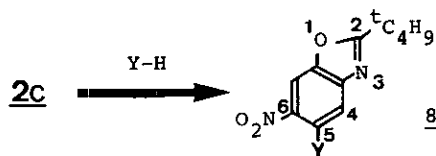
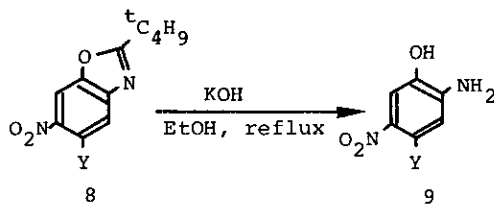


Table 1

Run	Y	Conditions	Yield of <u>8</u>	Run	Y	Conditions	Yield of <u>8</u>
1		NaOH (1.0 equiv.) DMF/toluene/80 °C 3 h.	92%	5		NaOH (1.0 equiv.) CuCl (0.5 equiv.) DMF/toluene/80 °C 4 h.	36%
2		NaOH (1.0 equiv.) DMF/toluene/120 °C 3 h.	88%	6		NaOH (1.0 equiv.) DMF/toluene/140 °C 4 h.	89%
3		KOH (1.0 equiv.) CuCl (0.5 equiv.) DMF/80 °C/4 h	60%	7		DMF/100 °C/4 h	93%
4		KOH (1.0 equiv.) CuCl (0.5 equiv.) DMF/100 °C/4 h	40%	8		NaOH (1.0 equiv.) toluene/115 °C 3 h.	75%

Hydrolysis of the oxazole ring of 8

In the subsequent hydrolysis of the oxazole ring of 8, contrary to the expectation, all attempted usual acidic cleavage⁸ [(a) HBr / EtOH, reflux (b) aq. CF₃SO₃H, reflux (c) H₂SO₄ / AcOH, reflux (d) H₂SO₄, reflux] failed. However, treatment of 8 (1.0 equiv.) with KOH (4.0 equiv.) in EtOH under reflux for several hours effected hydrolysis of 8 to give the corresponding aminophenol derivatives 9 in 85-93% yield.



In order to estimate this unexpected pH dependence in the hydrolysis of 8, the pseudo-first order rate constants (k_1 and k_2) were determined in the hydrolytic cleavage of model compounds 10 and 11. The pH dependence of the hydrolysis of 10 and 11 in buffered 50% aqueous 2-propanol over the pH range 2.5-12.5 are plotted in Fig. 1 and 2. The pH-rate (k_1) profiles for 10c-d indicate that the formation of amidophenols 11c-d is enhanced in rather higher alkaline region, respectively.

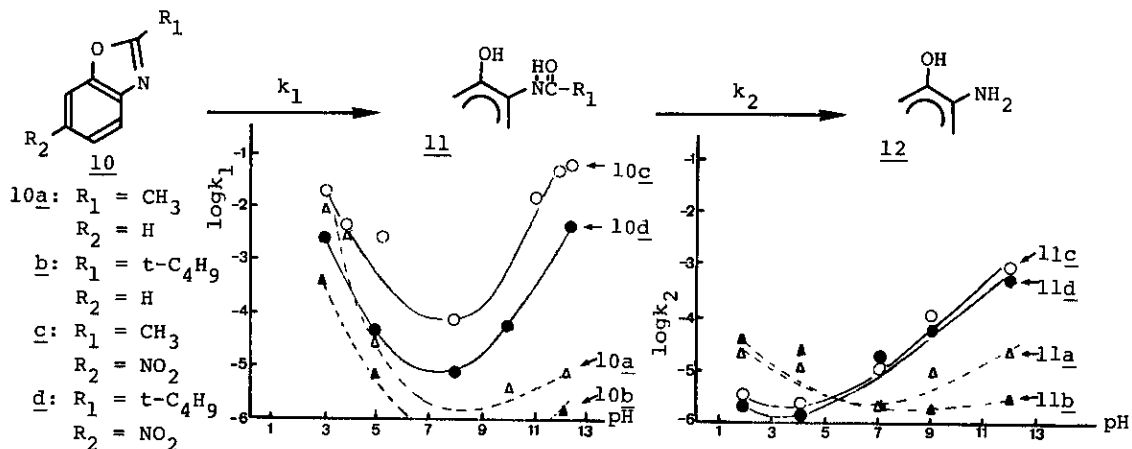


Fig. 1 Logarithmic plot of the pseudo-first order rate constants (k_1) as a function of the pH of the buffer solution. (80°)

Fig. 2 Logarithmic plot of the pseudo-first order rate constants (k_2) as a function of the pH of the buffer solution. (80°)

Furthermore, those (k_2) for 11 in Fig. 2 clearly show the presence of the nitro substituent in 11c-d serves to enhance the hydrolytic cleavage of the amide group by approximately 100-fold at higher alkaline region relative to lower acidic one. These observations are consistent with the result obtained in the case of 8 and in striking contrast with those in the case of usual oxazoles⁸ and amidophenols (e.g. 10a-b and 11a-b). Thus, we have shown 2-*t*-butyl-5-chloro-6-nitrobenzoxazole 2c serves as a practical synthetic intermediate for 1 on the examination of the anomalous reactivities of 2-substituted 6-nitrobenzoxazole derivatives.⁹

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