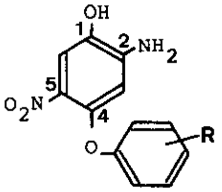
HETEROCYCLES, Vol 27, No 4, 1988

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

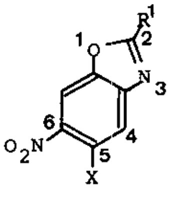
Mitsunori Ono*, Katsuyoshi Yamakawa, Hidetoshi Kobayashi, and Isamu Itoh
Research Laboratories, Ashigara, Fuji Photo Film Co., Ltd.,
Minami-ashigara, Kanagawa 250-01, Japan

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-nitrobenzoxazole 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-recording 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 introduction reaction of the aryloxy group and hydrolysis of the oxazole ring were examined. The results are presented in this communication.



1



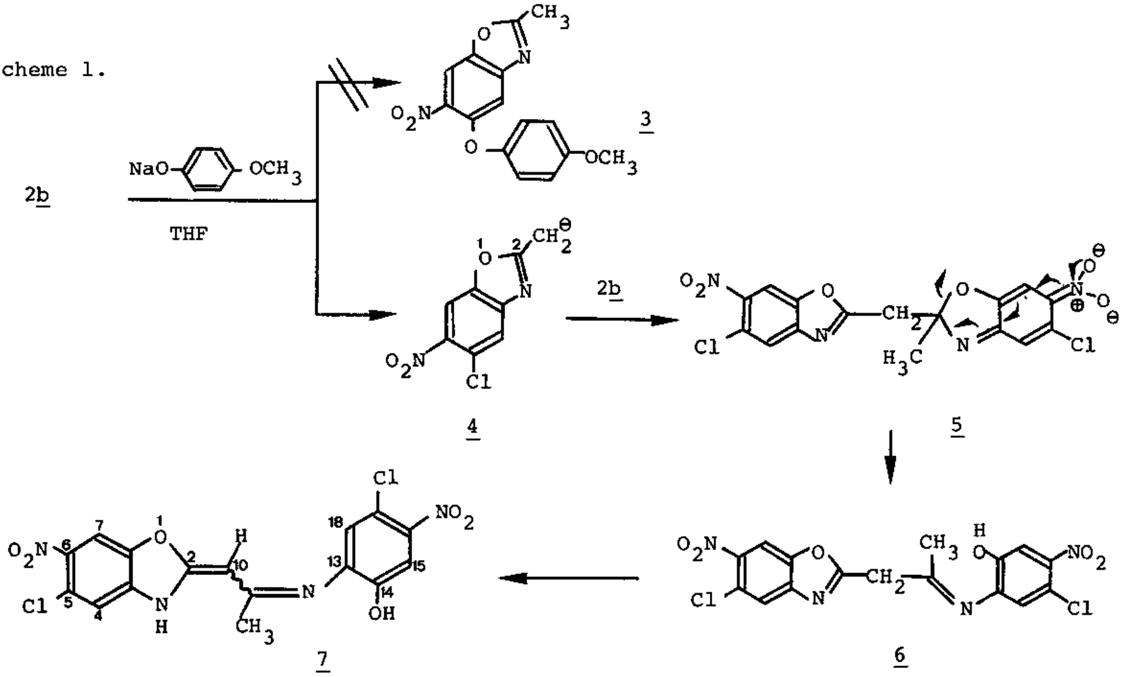
2

2a: R^1 = H, X = Cl
mp 88-89°C
b: R^1 = CH_3, X = Cl
mp 138°C
c: R^1 = t-C_4H_9, X = Cl
mp 78-81°C
d: R^1 = phenyl, X = Cl
mp 199-201°C
e: R^1 = o-Cl-phenyl
X = Cl,
mp 172°C
f: R^1 = o-Cl-phenyl
X = H

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 (ε=31200); ^{1}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 $C_{16}H_{10}N_4O_6Cl_2$: 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.

Scheme 1.



In view of general reactivity of the oxazole ring toward weak bases (nucleophiles) without any special electrophilic assistance,[6] these phenomena are unusual[7] 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.

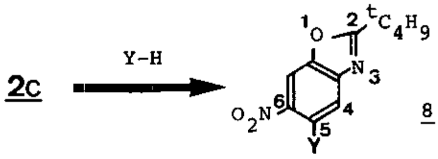
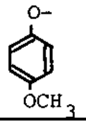
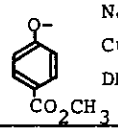
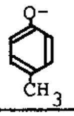
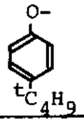
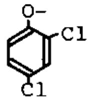
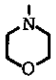
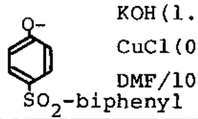
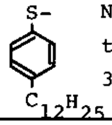
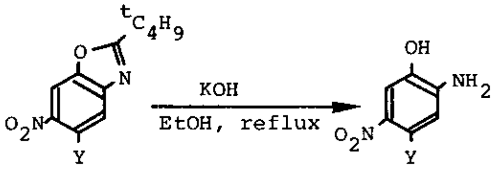


Table 1

Run	Y	Conditions	Yield of 8	Run	Y	Conditions	Yield of 8
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%

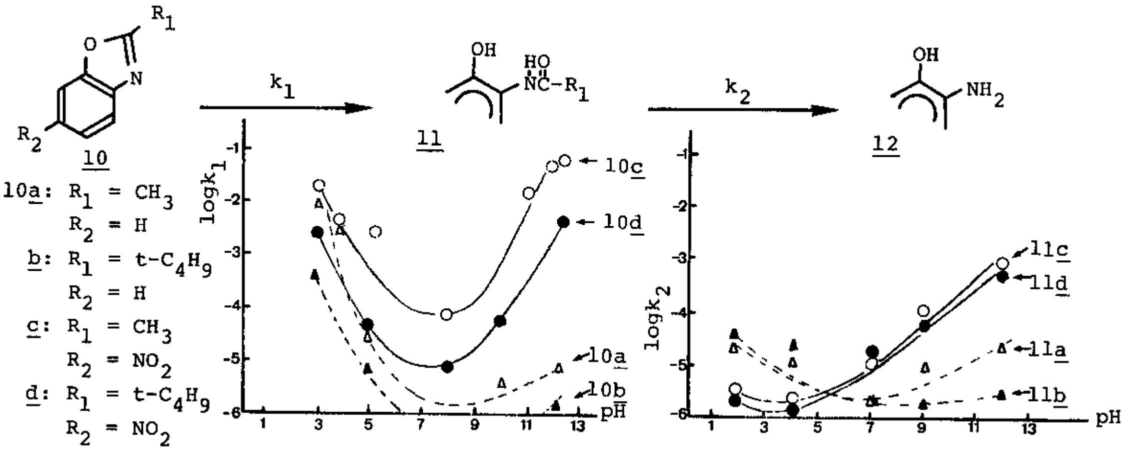
Hydrolysis of the oxazole ring of 8

In the subsequent hydrolysis of the oxazole ring of 8, contrary to the expectation, all attempted usual acidic cleavage[8] [(a) HBr / EtOH, reflux (b) aq. CF_3SO_3H, reflux (c) H_2SO_4 / AcOH, reflux (d) H_2SO_4, 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.



8 9

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.



10a: R_1 = CH_3
R_2 = H
b: R_1 = t-C_4H_9
R_2 = H
c: R_1 = CH_3
R_2 = NO_2
d: R_1 = t-C_4H_9
R_2 = NO_2

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 oxazoles[8] 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]

REFERENCES AND NOTE

1. I. Itoh and H. Kobayashi, Japan Kokai, 61-65241 (1986).
2. L. S. Hegedus, R. R. Odle, P. M. Winton, and P. P. Weider, J. Org. Chem., 47, 2607 (1982).
3. T. Niwa, Y. Murata, and S. Maeda, Japan Kokai, 60-180889 (1985).
4. B. Loev, H. Jones, R. E. Brown, F. C. Huang, A. Khandwala, J. Mitchell, P. Somnino-Goldman, J. Med. Chem., 28, 24 (1985).
5. L. E. Beavers, P. T. S. Lau, and I. F. Salminen, Japan Kokai, 47-21139 (1972).
6. E. J. Corey and D. L. Boger, Tetrahedron Lett., 1978, 5; S. Florio, Tetrahedron, 40, 5089 (1984).
7. P. F. Jackson, K. J. Morgan, and A. M. Turner, J. Chem. Soc., Perkin II, 1972, 1582.
8. A. Bruylants and E. Feytmants-de Medicis, "The Chemistry of the Carbon-Nitrogen Double Bond," S. Patai ed, John Wiley & Sons, 1970.
9. The authors wish to thank Miss Haruko Shimizu for carrying out the kinetic determinations.

Received, 16th December, 1987