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NOVEL SYNTHESIS OF BENZOXAZOLES FROM *O*-NITROPHENOLS AND AMINES

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Abstract – *o*-Nitrophenols and *o*-nitroaniline were reacted with amines at 210-215°C to produce the corresponding benzoxazoles and benzimidazoles, respectively, in moderate yields. The reactions between *o*-nitrophenols containing a CO_2Me or OMe group on their benzene rings and *N*,*N*-diethylaniline were examined to investigate the effects of the position and electronic character of these substituents on the formation of the oxazole ring.

INTRODUCTION

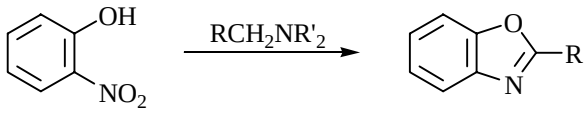
In studying the synthesis of simple 3,4-unsaturated coumarin using the Wittig reaction with salicylaldehyde in *N*,*N*-diethylaniline (Et_2NPh) under reflux, we found that 3-nitrosalicylaldehyde afforded 2-methylbenzoxazole and 8-aminocoumarin along with the expected 8-nitrocoumarin, in moderate yields.[1] We clarified that formation of the benzoxazole ring required the *o*-nitrophenol moiety and that the carbon unit introduced in the benzoxazole ring originated from the alkyl group of the solvent (amine). Moreover, the reaction temperature (210-215°C) was crucial.[1] Subsequently, we investigated the generality of benzoxazole synthesis from *o*-nitrophenol with amines, the effects of other substituent groups in *o*-nitrophenols on benzoxazole formation, and the reaction mechanism. We present those results here.

RESULTS AND DISCUSSION

This paper is dedicated to Dr. Pierre Potier on the occation of his 70th birthday.

First, we examined oxazole ring formation from *o*-nitrophenol (**1a**) and amines other than diethylaniline at high temperature. The results are summarized in Table 1. The reaction of *o*-nitroaniline (**3**) with amines under similar conditions afforded the corresponding benzimidazoles (**4**) in moderate yields, as shown in Scheme 1. As the reactions of *o*-nitrophenol (**1a**) and *o*-nitroaniline (**3**) with alkylamines yielded benzoxazoles (**2**) and benzimidazoles (**4**), respectively, the aromatic ring interaction between the amine and *o*-nitrophenol (**1a**) is nonessential, and the benzyl group transfers more easily than the ethyl group.

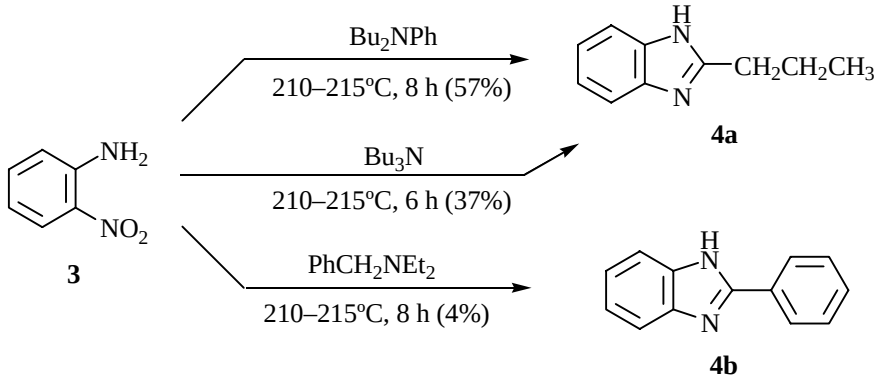
Table 1. Reactions of oxazole ring formation from *o*-nitrophenol (**1a**) and a few amines.



1a **2**

Run	Amine	Temp.(°C)	Time (h)	Yield (%)
1	EtNHPh	210-215	10	27 (R=Me: **2a**)
2	Bu_3N	210-215	8	24 (R=Pr: **2b**)
3	Me_2NPh	190	3	many spots
4	Bu_2NPh	210-215	6	22 (R=Pr: **2b**)
5	$PhCH_2NEt_2$	210-215	10	13 (R=Ph: **2c**)

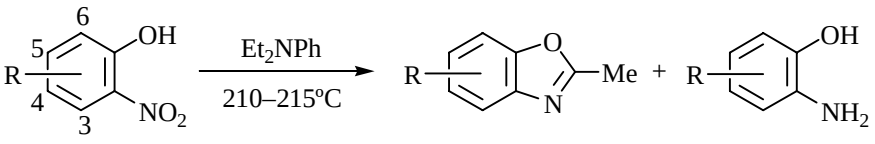
Scheme 1



In order to examine the effects of the position and electronic character of the *o*-nitrophenol substituent on the formation of the oxazole ring, we investigated the reactions of *o*-nitrophenols with electron-withdrawing (CO_2Me) (**1d-g**) or electron-donating (OMe) (**1h-k**) groups with Et_2NPh under reflux (at 210-215°C). The results are summarized in Table 2. In general, an electron-donating group (OMe) facilitated the formation of the oxazole ring regardless of the position of the substituents on the benzene ring. A C3-substituent group accelerated ring formation and a C6-substituent group retarded it regardless of its electronic character. These results seem to reflect a steric factor in ring formation. Interestingly, the reaction of 6-carbomethoxy-2-nitrophenol (**1g**) with Et_2NPh under reflux for 3 h afforded 6-carbethoxy-2-nitrophenol (**1l**) and the corresponding amine (**5l**), while the same reaction for 6 h produced 7-carbethoxy-2-methylbenzoxazole (**2l**) along with **5l** (Scheme 2). This ester-exchange is characteristic of

the salicylate moiety, as the Wittig reaction of 3-methoxycarbonylsalicylaldehyde in Et_2NPh produced 5-carbethoxycoumarin, while salicylaldehydes with a methoxycarbonyl group at a position other than C3 produced no ester-exchanged products.[2]

Table 2. The results of reaction of *o*-nitrophenol (**1**) with Et_2NPh under reflux.

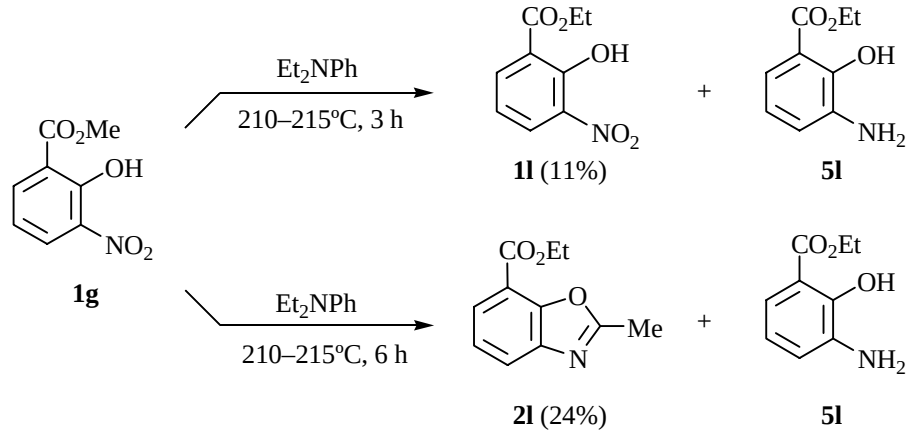


1d-l **2d-l** **5d-l**

Run	R	Time	Yield (%)[a]	
			2	**5**
1	3-CO_2Me (**1d**)	1.0 h	27 (**2d**)	48 (**5d**)
2	4-CO_2Me (**1e**)	3.0 h	75 (**2e**)	7.4 (**5e**)
3	5-CO_2Me (**1f**)	3.0 h	59 (**2f**)	17 (**5f**)
4	6-CO_2Et (**1l**)	7.0 h	21 (**2l**)	41 (**5l**)
5	3-OMe (**1h**)	20 min	75 (**2h**)	trace[b] (**5h**)
6	4-OMe (**1i**)	1.5 h	50 (**2i**)	> 6[b] (**5i**)
7	5-OMe (**1j**)	1.5 h	51 (**2j**)	>17[b] (**5j**)
8	6-OMe (**1k**)	2.0 h	42 (**2k**)	>12[b] (**5k**)

a) Isolated yield. *b*) Yields were not reliable because of instability of amines (**5**).

Scheme 2



The generation of amino-phenol (**5**) suggests that the alkyl group(s) of the amine used as the solvent is oxidized by the nitro group or air to produce an oxygenated amine, which takes part in the formation of the oxazole ring. More detailed studies of the mechanism of this reaction are underway.

EXPERIMENTAL

Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. ^1H and ^{13}C-NMR spectra were taken with a Hitachi R-1500 (60 MHz) or Varian VXR-200 (200 MHz) instrument with chemical shifts

reported as δ ppm and coupling constants given in Hertz. FAB-MS was obtained with a VG-70SE mass spectrometer. Elemental analyses were carried out on a Yanaco MT-5 CHN analyzer. Column chromatography was performed on silica gel (Merck, Silica gel 60, No. 9385).

Materials

Compounds (**1a**, **1i** and **3**) are commercially available. Compounds (**1d**[3], **1e**[4], **1f**[5], **1g**[6] and **1l**[7]) were prepared by esterification of the corresponding carboxylic acid. Compounds (**1h**[8], **1j**[9] and **1k**[10]) were prepared according to the literature.

General procedure for the reaction of *o*-nitrophenols or *o*-nitroaniline with amines

The reactions of *o*-nitrophenols or *o*-nitroaniline (500 mg) with an amine (10 mL) at 210-215°C were carried out for the times indicated in Tables 1 and 2, Schemes 1 and 2. The reaction mixtures were chromatographed on silica gel. Alkylaniline was eluted with hexane.

Methyl 2-methylbenzoxazole-4-carboxylate (2d) and methyl 2-amino-3-hydroxybenzoate (5d)

Elution with hexane-AcOEt (4:1) gave **5d**, mp 97–99˚C (lit.,[11a] mp 97-98˚C) (colorless needles from Et_2O-hexane). Further elution with the same solvent afforded **2d**, mp 74–75˚C (lit.,[11b] mp 77–79˚C) (colorless needles from hexane).

Methyl 2-methylbenzoxazole-5-carboxylate (2e) and methyl 3-amino-4-hydroxybenzoate (5e)

Elution with hexane-AcOEt (4:1) gave **2e**, mp 63–64˚C (lit.,[12] mp 66˚C) (colorless needles from hexane). Further elution with hexane-AcOEt (1:1) afforded **5e**, mp 110–111˚C (lit.,[13] mp 110–111˚C) (pale yellow sands from AcOEt-CH_2Cl_2).

Methyl 2-methylbenzoxazole-6-carboxylate (2f) and methyl 4-amino-3-hydroxybenzoate (5f)

Elution with hexane-AcOEt (3:1) gave **2f**, mp 103.5–104.5˚C (lit.,[12] mp 103–104˚C) (colorless needles from hexane). Further elution with the same solvent afforded **5f**, mp 120˚C (lit.,[13] mp 120–121˚C) (pale yellow plates from CH_2Cl_2).

Ethyl 2-methylbenzoxazole-7-carboxylate (2l) and ethyl 3-amino-2-hydroxybenzoate (5l)

Elution with hexane-AcOEt (6:1) gave **5l**, mp 41˚C (lit.,[13] mp 47˚C) (colorless needles from hexane). Further elution with the same solvent afforded **2l**. IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.45 (3H, t, *J*=7.2 Hz, CH_3), 2.72 (3H, s, 2-CH_3), 4.47, (2H, q, *J*=7.2 Hz, CH_2), 7.36 (1H, dd, *J*=7.8, 7.8 Hz, 5-H), 7.84 (1H, dd, *J*=1.4, 7.8 Hz, 6-H), 7.94 (1H, dd, *J*=1.4, 7.8 Hz, 4-H). FAB-MS *m/z*: 206 (M^++1).

4-Methoxy-2-methylbenzoxazole (2h) and 2-amino-3-methoxyphenol (5h)

Elution with hexane-AcOEt (4:1) gave **2h**, mp 57.5–59˚C (pale yellow needles from Et_2O). IR ($CHCl_3$) cm^{-1}: 1630, 1590, 1100. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.60 (3H, s, CH_3), 4.00 (3H, s, OCH_3), 6.74 (1H, dd, *J*=2.3, 7.0 Hz, 5-H), 7.00–7.23 (2H, m, 6, 7-H). FAB-MS *m/z*: 164 (M^++1). *Anal*. Calcd for $C_9H_9NO_2$:

C, 66.25; H, 5.56; N, 8.58. Found: C, 66.46; H, 5.82; N, 8.50. **5h** was recognized on TLC, but not isolated.

5-Methoxy-2-methylbenzoxazole (2i) and 2-amino-4-methoxyphenol (5i)

Elution with hexane-AcOEt (4:1) gave **2i**, mp 32–34˚C (lit.,[14] low mp.) (colorless needles from Et_2O-hexane). Further elution with hexane-AcOEt (1:1) afforded **5i**, mp 131–135˚C (lit.,[15] mp 129–132˚C) (yellow prisms from AcOEt-Et_2O).

6-Methoxy-2-methylbenzoxazole (2j) and 2-amino-5-methoxyphenol (5j)

Elution with hexane-AcOEt (6:1) gave **2j**, mp 51.5–53˚C (lit.,[16] mp 57˚C) (pale yellow needles from petr. ether). Further elution with hexane-AcOEt (1:1) afforded **5j**, mp 128–131˚C (lit.,[17] mp 128–131˚C) (pale pink prisms from Et_2O).

7- Methoxy-2-methylbenzoxazole (2k) and 6-aminoguaiacol (5k)

Elution with hexane-AcOEt (6:1) gave **2k**. IR ($CHCl_3$) cm^{-1}: 1640, 1580, 1100. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.64 (3H, s, CH_3), 4.01 (3H, s, OCH_3), 6.82 (1H, dd, *J*=2.2, 7.2 Hz, 6-H), 7.17–7.28 (2H, m, 4, 5-H). FAB-MS *m/z*: 164 (M^++1). Further elution with the same solvent afforded **5k**, mp 83–84˚C (lit.,[18] mp 83.5˚C) (pale yellow plates from Et_2O-hexane).

Ethyl 2-hydroxy-3-nitrobenzoate (1l) and ethyl 3-amino-2-hydroxybenzoate (5l)

Elution with hexane-AcOEt (6:1) gave a mixture of **1l** and **5l**. The mixture in Et_2O was chromatographed on silica gel. Elution with $CHCl_3$-hexane (20:1) gave **1l**. Further elution with the same solvent afforded **5l**.

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