NEW SYNTHESIS OF NAPHTHO- AND BENZOXAZOLES: DECOMPOSITION OF NAPHTHO- AND BENZOXAZINONES WITH KOH

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ABSTRACT

A method that allows the synthesis of 4 different heterocyclic systems of fused aryl oxazoles, i.e., naphtho[1,2-d], naphtho[2,1-d], naphtho[2,3-d], and benzo[d]oxazoles in reasonable yield is described. This method consists of the decomposition of naphtho- and benzoxazinones with KOH.

Benzoxazoles have been obtained by heating *o*-aminophenols and carboxylic acids in the presence of polyphosphoric acid (1,2). The novel antibacterial agent Boxazomicyn B has been synthesized by this method (3). Other options are the Beckmann rearrangement of *o*-acylphenol oximes using zeolite catalysts (4) and, more recently, treatment of N,O-diacylated 2-aminophenols with *p*-toluenesulfonic acid under reflux in xylenes or toluene (5), or oxidative intramolecular cyclization

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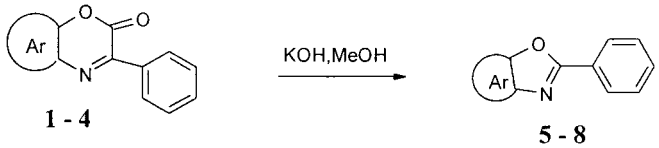
of phenolic Schiffs bases using iodobenzene diacetate as an oxidant (6), or manganese triacetate, a relatively benign oxidizing reagent (7). On the other hand, naphthoxazoles have been obtained, by cycloaddition of azomethine ylides (from thermal cleavage of aziridines) to 1-nitroso-2-naphthol (8,9); by treatment of an equimolecular mixture of 1-nitroso-2-naphthol and phenacyl piridinium bromide with NaOH solution at −30°C (10); by cycloaddition of masked azomethine ylide, generated from 2-*p*-methoxyphenyl-4-phenyl-2-oxazolin-5-one, with 1-nitroso-2-naphthol (11), and by reaction of 1,3-dipole, proceeding from 3-aroyl aziridines cleavage, with 2-nitroso-1-naphthol. In this last reaction, naphthodiazepine is obtained besides naphthoxazole (12). Some methods to obtain either benzo- or naphthoxazoles have been described: palladium-catalyzed condensation of aryl halides with *o*-amino phenols or naphthols, followed by dehydrative cyclization (13); and cycloaddition of *o*-hydroxy anilides by heating with aqueous HCl at 150°C, (anilide can be prepared in situ heating the corresponding *o*-substituted aniline with carboxylic acid, anhydride or acid chloride (14)). As an example, the benzoxazole ring of the antibiotic Calcymicin (15) and the anti-inflammatory Benoxaprofen (16) have been obtained by these methods. Reduction of the suitable 2-nitrophenyl, 2-nitro-1-naphthyl or 1-nitro-2-naphthyl-benzoates or 4-nitrobenzoates with Sn-HCl (17) is another suitable method, and 2-arylnaphtho[1,2-d]oxazoles have been prepared by condensation of 1-amino-2-naphthol derivatives with aromatic aldehydes in the presence of pyridine in BuOH (18).

Most of the existing methods referred to above consist of oxidative reactions using uncommon oxidizing reagents, or they are cycloaddition reactions where more than one product is obtained. The importance of the method we describe lies on the easy and rapid way that these heterocyclic system are available. Both substrate and product are heterocycles, the last readily obtained by decomposition of the first.

In this work, the transformation of 2-phenyl-3H-naphtho[2,1-b][1,4]-oxazin-3-one (**1**), 3-phenyl-2H-naphtho[1,2-b][1,4]oxazin-2-one (**2**), 3-phenyl-2H-naphtho[2,3-b][1,4]-oxazin-2-one (**3**), and 3-phenyl-2H-benzo[b][1,4]oxazin-2-one (**4**) on heating with KOH in MeOH to their corresponding naphtho- and benzoxazoles: 2-phenylnaphtho[1,2-d]oxazole (**5**), 2-phenylnaphtho[2,1-d]oxazole (**6**), 2-phenyl naphtho[2,3-d]oxazole (**7**) and 2-phenylbenzo[d]oxazole (**8**), is described (Scheme 1).

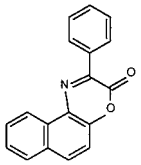
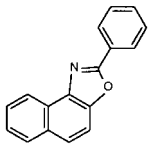
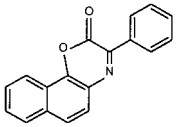
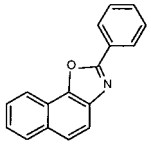
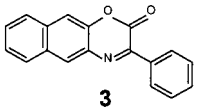
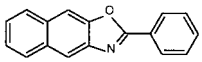
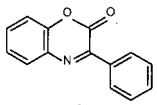
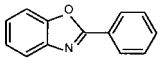


1 - 4 **5 - 8**

Ar = 1,2-benzo-, 1-,2-naphtho-, 2,1-naphtho, 2,3-naphtho-

Scheme 1.

Table 1. Conversion of Aryl Oxazinones **1–4** into Aryloxazoles **5–8**

Entry	Substrate	Product	Yield (%)
1	 **1**	 **5**	75
2	 **2**	 **6**	68
3	 **3**	 **7**	76
4	 **4**	 **8**	81

The oxazinones **1–4** were obtained, in satisfactory yields through a modification of the Moffet's method (19), which heats at 120°C for 1.5 h an equimolecular mixture of the respective *o*-aminophenol and -naphthol or their chlorohydrate with the corresponding α-keto ester in pyridine as solvent.

We herein describe a rapid method that allows the synthesis of four different heterocyclic systems of fused aryl oxazoles: naphtho[1,2-d]; naphtho[2,1-d]; naphtho[2,3-d]; and benzo[d]oxazoles in reasonable yields (Table 1), thus complementing the existing methods to obtain these heterocyclic systems.

EXPERIMENTAL

Melting points were determined on a hot-stage apparatus and are uncorrected. Spectra were recorded using the following instruments: IR, FT-IR Bruker IFS 55; UV, ATI-UNICAM; ^{1}H and ^{13}C-NMR, Bruker DRX-300 (300 and 75 MHz), using tetramethylsilane as internal reference. Microanalyses were

determinated using Fisons EA 1108 analizer and were performed in CEPEDEQ (Centro Para el Desarrollo de la Química), Facultad de Ciencias Químicas y Farmaceúticas, Universidad de Chile. Column chromatography was performed on Merck silica gel 60, 230–400 mesh, and TLC- on Merck silica gel G.

General Procedure for Preparation of Naphtho- and Benzoxazinones 1 to 4

A Modification of the Moffet's Method

The required *o*-aminophenol and -naphthol, or their chlorohydrate and methyl benzoyl formate, were mixed in pyridine as solvent under nitrogen and the mixture was heated at 120°C during 1.5–2 h. After this time, the reaction mixture was poured into ice water. The precipitate was collected by filtration, washed with water, and purified by column chromatography (chloroform) on silica gel.

All compounds gave satisfactory spectroscopic and analytical data. Representative data for select compounds follows. Compounds **1** and **5** were fully characterized by concerted use of one- and two-dimensional NMR techniques in our previous paper (20).

2-Phenyl-3H-naphto[2,1-b] l,4-oxazin-3-one (1) was obtained in 95% yield (crude) and 71% (purified). Recrystallization from carbon tetrachloride gave yellow pales m.p 174°–175°C. Lit.[19] 177°–178°C. ^{1}H NMR ($CDCl_3$) δ: 8.86 (d, J_d 8.3 Hz, 1H), 8.53 (m, 2H), 7.93 (d, J_d 8.78 Hz, 1H), 7.86 (d, J_d 8.78 Hz, 1H), 7.71 (d, J_d 8.78 Hz,1H), 7.58 (dd, 1H), 7.55 (m, 3H), 7.39 (d, J_d 9.0 Hz,1H), ^{13}C NMR ($CDCl_3$) δ: 152.67, 148.28, 144.22, 134.50, 132.35, 131.31, 131.02, 130.45, 129.48, 128.40, 128.22, 128.03, 126.67, 126.30, 122.84, 115.64.

3-Phenyl-2H-naphto[1,2-b] l,4-oxazin-2-one (2) was obtained in 85% yield (crude). Recrystallization from carbon tetrachloride gave yellow pales m.p. 166°–167°C ^{1}H NMR ($CDCl_3$) δ: 8.48 (m, 2H), 8.42 (m, 2H), 7.89 (m, 1H), 7.83 (d, J_d 8.78 Hz, 1H), 7.77 (d,J_d 8.81 Hz, 1H), 7.65 (m, 2H), 7.53 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 152.41, 150.04, 142.62, 134.35, 134.26, 131.34, 129.34, 128.72, 128.43, 128.02, 127.90, 127.30, 125.63, 125.46, 126.30, 122.55, 122.13, 115.65. IR (Kbr) ν/cm^{-1}: 1724 (C═O), 1639 (C═N). Anal. Calcd. for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. Found: C, 79.04; H, 4.06; N, 5.21.

3-Phenyl-2H-naphtho[2,3-d] l,4-oxazin-2-one (3) was obtained in 60% yield (crude). Recrystallization from acetonitrile gave yellow pales m.p. 201°–203°C. ^{1}H NMR ($CDCl_3$) δ: 8.37 (m, 2H), 8,34 (s,1H), 8.12 (d, J_d 7.93 Hz; 1H), 7.88 (d, J_d 7.96 Hz, 1H), 7.67 (s, 1H), 7.56 (m, 5H). ^{13}CNMR ($CDCl_3$) δ: 152.15, 151.02, 144.20, 134.24, 139.95, 131.48, 130.95, 130.82, 129.57, 129.21, 128.87,

128.44, 128.41, 127.41, 126.03, 125.89, 112.27. IR (Kbr) ν/cm^{-1}: 1724 (C═O), 1639 (C═N). Anal. Calcd. for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. Found: C, 78.99; H, 4.03; N, 5.40.

3-Phenyl–2H-benzo[d]-l,4-oxazin-2-one (4) was obtained in 85% yield. Recrystallization from methanol gave light yellow pales m.p. 118–119°C ^{1}H NMR ($CDCl_3$) δ: 8.34 (dd, J_d S. 17; J_d 2.09 Hz, 2H), 7.85 (dd, J_d 7.90; J_d 1.55 Hz, 1H), 7.52 (m, 4H), 7.39 (td, J 7.70; J 7.62; J 1.30 Hz, 1H); 7.33 (dd, J_d 8.17; J_d 1.25 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 152.26, 150.85, 146.47, 134.13, 131.66, 131.41, 131.11, 129.44, 128.37, 125.87, 116.16.

Typical Procedure for Transformation of Naphtho- and Benzoxazinones in Naphtho- and Benzoxazoles 5 to 8

-Phenyl-3H-naphtho[2,1-b] l,4-oxazinone (40 mg, 0.146 mmol) and 10% KOH solution (2mL) were refluxed in MeOH for 30 min. Immediately, the solution became an intense brownish red. The mixture was left overnight and then neutralizad with acetic acid (10%). The precipitate was collected by filtration, washed with water, and purified by column choromatography (chloroform) on silica gel.

2-Phenylnaphtho[1,2-d]oxazole (5) Recrystallization from ligroin gave white needles, m.p. 122°–123°C. Lit. (9) 125°–130°C, Lit. (21) 131°C. See Abbady (21) for synthesis of **5**; however, nmr data were not reported. ^{1}H-RMN ($CDCl_3$) δ 8.63 (d, J_d 8.20 Hz, 1H), 8.37 (m, 2H), 8.01 (d, J_d 8.20 Hz, 1H), 7.84 (d, J_d 8.90 Hz, 1H), 7.76 (d, J_d 8.90 Hz, 1H), 7.71 (m, 1H), 7.58 (m, 4H). ^{13}C-RMN ($CDCl_3$) δ: 162.25, 148.09, 137.66, 130.96, 128.80, 128.48, 127.48, 127.27, 126.87, 126.64, 125.91, 125.27, 122.21, 110.53.

2-Phenylnaphtho[2,1-d]oxazole (6) m.p. 122°C. ^{1}H-RMN ($CDCl_3$) δ: 8.30 (m, 3H), 7.96 (d, J_d 8.24 Hz, 1H), 7.91 (d, J_d 8.73 Hz, 1H), 7.78 (d, J_d 8.74 Hz, IH), 7.63 (td, J 9.0; J 9,0; J 1.14 Hz, 1H) (m, 1H), 7.54 (m, 4H). ^{13}C-RMN ($CDCl_3$) δ: 162.43, 146.45, 138.60, 131.7, 131.14, 128.92, 128.68, 127.41, 127.29, 126.82, 125.62, 125.40, 125.03, 124.51, 119.98, 110.53.

2-Phenylnaphtho[2,3-d]oxazole (7) m.p. 203°–205°C. ^{1}H-RMN ($CDCl_3$) δ: 8.34 (m, 2H), 8.20 (s, 1H), 7.99 (m, 2H), 7.95 (s, 1H), 7.55 (m, 3H), 7.49 (m, 2H). ^{13}C-RMN ($CDCl_3$) δ: 165.04, 149.73, 142.07, 132.08, 131.77, 131.56, 128.97, 128.53, 128.14, 127.91, 126.96, 125.47, 124.69, 117.33, 106.35.

2-Phenylbenzo [d]oxazole (8) m.p. 100°–102°C Lit (7) 101°C. ^{1}H-RMN ($CDCl_3$) δ: 8.24 (m, 2H), 7.77 (m, 1H), 7.54 (m, 1H), 7.49 (m, 3H), 7.32 (m, 2H). ^{13}C-RMN ($CDCl_3$,) δ: 162.96, 150.71, 142.10, 131.43, 128.83, 127.57, 127.14, 125.03, 124.51, 119.98, 110.53.

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