Synthesis of Hetaryl-Substituted Benzoxazoles *via* Oxidative Cyclization of Phenolic Schiff's Bases

Kadri G. Ozokan, Mustafa K. Gumus, Seniz Kaban*

Department of Chemistry, Yildiz Technical University, Istanbul 34220, Turkey
skaban29@yahoo.com
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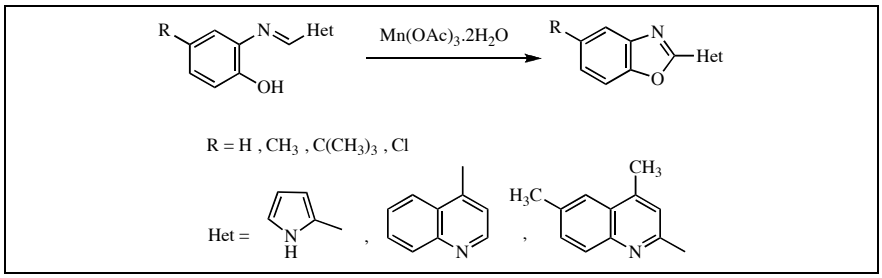

2-(1*H*-Pyrrol-2-yl)benzo[*d*]oxazoles, 4-(benzo[*d*]oxazol-2-yl)quinoline and 2-(benzo[*d*]oxazol-2-yl)-4,6-dimethylquinolines were obtained in good yield by the oxidative intramolecular ring closing reactions of phenolic Schiff's bases with the effect of manganese triacetate.

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INTRODUCTION

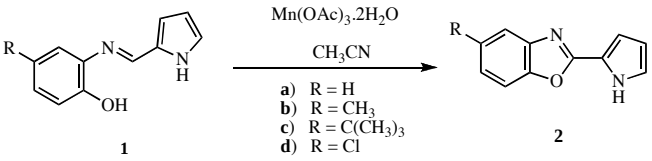
Heterocycles constitute one of the largest group of organic compounds and are becoming ever more important in all aspects of pure and applied chemistry. Oxazole derivatives have gained great interest in heterocyclic chemistry because of their biological and analytical properties and their applications in both industry and agriculture [1]. For instance, the benzoxazole ring system has been a key part of the antitumor metabolite, UK-1, produced by *Streptomyces sp.* 517-06 [2]. In spite of the various preparative methods of 2-substituted benzoxazoles [3-8], oxidative intramolecular cyclization of phenolic Schiff's bases using reagents such as manganese triacetate, lead tetraacetate, barium manganate, nickel peroxide, copper chloride and thianthrene perchlorate has seemed to be a general method [9-11]. However, manganese triacetate has been rapidly evolving as a new and exceptionally versatile reagent in organic synthesis [12].

Herein, we report the synthesis of 2-hetaryl-1,3-benzoxazoles (**2a-h**), as novel bicyclic compounds containing pyrrole or quinoline cores *via* oxidative ring closing reactions of phenolic Schiff's bases by using manganese triacetate. However, two different preparation methods of the 2-(1*H*-pyrrol-2-yl)-1,3-benzoxazole (**2a**) are being presented in the literature, by using *N*-ethoxycarbonylthioamide [13] and by using PCC [14].

RESULTS AND DISCUSSION

Treatment of (*E*)-2-[(1*H*-pyrrol-2-yl)methyleneamino]-phenols (**1a-d**) with 2 equivalents of manganese triacetate dihydrate in refluxing acetonitrile yielded 2-(1*H*-pyrrol-2-yl)benzo[*d*]oxazoles (**2a-d**) (Scheme I).

Scheme I

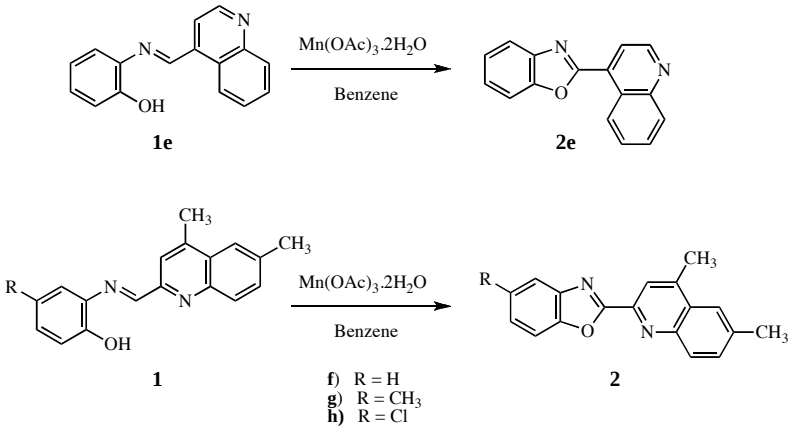


In fact, various reaction conditions were applied in order to find an optimum and convenient procedure for the formation of these benzoxazole derivates (**2a-d**): 1) Toluene (or benzene), 1 eq. of **1**, 1 or 2 eq. of $Mn(OAc)_3.2H_2O$: trace amount of the product formation (GC–MS). 2) Ethanol, 1 eq. of **1**, 1 or 2 eq. of $Mn(OAc)_3.2H_2O$: no product formation. 3) Acetic acid, 1 eq. of **1**, 1 or 2 eq. of $Mn(OAc)_3.2H_2O$: no product formation. 4) Finally the highest yields (64-86%) were achieved by using of 1 eq. of **1a-d**, 2 eq. of $Mn(OAc)_3.2H_2O$ and acetonitrile as solvent.

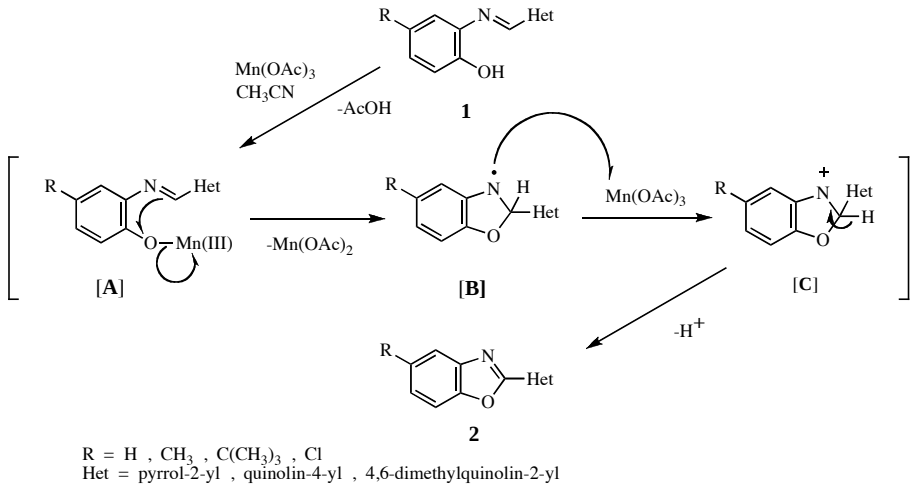
In addition, reactions of (*E*)-2-(quinolin-4-ylmethyl-eneamino)phenol (**1e**) and (*E*)-2-[(4,6-dimethylquinolin-2-yl)methyleneamino]phenols (**1f-h**) with 2 equivalents of manganese triacetate dihydrate in refluxing benzene gave 4-(benzo[*d*]oxazol-2-yl)quinoline and 2-(benzo[*d*]oxazol-2-yl)-4,6-dimethylquinolines (**2e-h**) (Scheme II).

We agree with Varma and Kumar [1] that the mechanism involves the enolization of Schiff's base (**1a-h**), to give Mn (III) enolate, [**A**], which loses $Mn(OAc)_2$ to provide nitrogen radical, [**B**], that subsequently undergoes oxidation by a second equivalent of $Mn(OAc)_3$ to afford nitrogen cation, [**C**]. Eventually, [**C**] loses a proton to form benzoxazoles (**2a-h**). This mechanism is in accordance with the experimental results because of the

Scheme II



Scheme III



consumption of two equivalents of manganese triacetate to complete the reaction (Scheme III).

In the uv spectra, 1,3-benzoxazoles (**2a-h**) gave characteristic maximum absorption bands in the region of 240-249 nm and 312-336 nm. The sharp -OH absorption band which appears at the area of 3412-3336 cm^{-1} in the ir spectra of phenolic azomethines (**1a-h**) was not observed in the spectra of 1,3-benzoxazoles. This was evidence that the ring-closing reactions have taken place. In addition, N-H stretching vibration band of pyrrole core, which is at the 2-position of the compounds **2a-d**, appeared in the region of 3234–3131 cm^{-1}.

The ^{1}H- and ^{13}C nmr spectra of compounds **2a-h** showed typical signals corresponding to the 1,3-benzoxazole skeleton. Besides, the proton on the nitrogen atom of the pyrrole unit resonated as a broad singlet, which was observed in the range of 10.20–11.02 ppm in the pmr spectra of **2a-d**. In the ^{13}C nmr spectra of compounds **2a-h**, the resonances at approximately 143, 150, 161 ppm correspond to C9, C8, and C2, respectively, which were unequivocally characteristic for the products.

The mass spectra of the compounds **2a-h** displayed peaks for their molecular ions as *m/z* 184, 198, 240, 218, 246, 274, 288 and 308, respectively. The $[N{\equiv}C{-}pyrrolyl]^{+}$ ion was observed at *m/z* 92 was an important fragment for **2a-d**; and loss of the HCN from the molecular ions was a proof for the pyrrole moiety.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus in open capillary tubes. Ultraviolet spectra were performed on a Philips PU 8700 UV/VIS spectrophotometer. The ir spectra were measured on a Jasco FT/IR-5300 instrument as potassium bromide pellets. The nmr spectra were run on a Varian 200 MHz Gemini spectrometer. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ units. Mass spectra were taken on a Schimadzu GC/MS QP 2000 A machine. Elemental analyses were obtained

on a Thermo Electron CHNS-O Analyzer. Reactions were monitored by thin layer chromatography, carried out on silica gel 60 F-254 (Merck) plates.

(*E*)-2-[(1*H*-Pyrrol-2-yl)methyleneamino]phenols (**1a-d**) [15-18] **and (*E*)-2-(quinolinylmethyleneamino)phenols** (**1e-h**) [19, 20] were synthesized according to literature procedures. Quinolinecarboxaldehydes used in the synthesis of **1e-h** were prepared by the oxidation of 4-methylquinoline [21] and 2,4,6-trimethylquinoline [22] with selenium dioxide in the medium of 1,4-dioxane. Pyrrole-2-carbaldehyde and 4-methylquinoline are commercially available; but 2,4,6-trimethylquinoline was prepared by a reported procedure [23].

General procedure I for the synthesis of 2-(1*H*-Pyrrol-2-yl)benzo[*d*]oxazoles (**2a-d**). A mixture of 1.0 mmole of (*E*)-2-[(1*H*-pyrrol-2-yl)methyleneamino]phenol (**1a-d**) and 2.0 mmoles of manganese triacetate dihydrate in 10 mL of acetonitrile was heated under reflux for 4 h. The progress of the reaction was monitored by tlc using *n*-hexane/ethyl acetate (2/1) as eluent. The precipitated manganese diacetate was then separated by filtration and the solvent was removed under reduced pressure. The crude product was crystallized from aqueous ethanol.

2-(1*H*-Pyrrol-2-yl)benzo[*d*]oxazole (**2a**). This compound was obtained from **1a** and $Mn(OAc)_3.2H_2O$ according to the general procedure I; beige tiny crystals, 0.16 g (86%), mp 141-142 °C (lit: mp 149 °C [13], 144-146 °C [14]); uv (chloroform): λ_{max} 240 and 312 nm; ir (potassium bromide): 3131 (NH), 3029 (aromatic, =C–H), 1625 (C=N), 1574, 1523 and 1446 (C=C and C–N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.37-7.13 (m, 3H, 3'-, 4'- and 5'-H), 7.29-7.70 (m, 4H, 4-, 5-, 6- and 7-H), 10.45 (br.s, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): δ 111.24-125.46 (C4, C5, C6, C7, C2', C3', C4' and C5'), 142.78 (C9), 151.11 (C8), 159.00 (C2) ppm; ms (70 eV): m/z 185 (M+1, 13), 184 (M^+, 100), 157 (M^+ –HCN, 8), 92 (N≡C–pyrrolyl$^+$, 14). *Anal*. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.79; H, 4.36; N, 15.26.

5-Methyl-2-(1*H*-pyrrol-2-yl)benzo[*d*]oxazole (**2b**). This compound was obtained from **1b** and $Mn(OAc)_3.2H_2O$ according to the general procedure I; beige tiny crystals, 0.16 g (81%), mp 129-130 °C; uv (chloroform): λ_{max} 240 and 318 nm; ir (potassium bromide): 3182 (NH), 3055 (aromatic, =C–H), 2957 and 2856 (CH_3), 1625 (C=N), 1600, 1523 and 1472 (C=C and C–N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.46 (s, 3H, CH_3), 6.38 (br.s, 1H, 3'-H), 7.04 (br.s, 1H, 4'-H), 7.10 (br.s, 1H, 5'-H), 7.11 (d, 1H, 6-H, $^3J_{6,7}$=8.0 Hz), 7.41 (d, 1H, 7-H), 7.45 (br.s, 1H, 4-H), 11.02 (br.s, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): δ 21.75 (CH_3), 109.97-125.61 (C4, C6, C7, C2', C3', C4' and C5'), 134.66 (C5), 142.08 (C9), 148.57 (C8), 158.70 (C2) ppm; ms (70 eV): m/z 199 (M+1, 14), 198 (M^+, 100), 171 (M^+ –HCN, 3), 92 (N≡C–pyrrolyl$^+$, 5). *Anal*. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.77; H, 5.06; N, 14.17.

5-*tert*-Butyl-2-(1*H*-pyrrol-2-yl)benzo[*d*]oxazole (**2c**). This compound was obtained from **1c** and $Mn(OAc)_3.2H_2O$ according to the general procedure I and the crude product was purified by extraction with boiling petroleum ether to yield **2c** as viscous oil; 0.20 g (83%); uv (chloroform): λ_{max} 241 and 316 nm; ir (potassium bromide): 3234 (NH), 3040 (aromatic, =C–H), 2953 and 2927 [$C(CH_3)_3$], 1625 (C=N), 1600, 1573 and 1472 (C=C and C–N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.39 (s, 9H, $C(CH_3)_3$), 6.37 (br.s, 1H, 3'-H), 6.99-7.46 (m, 4H, 4'-, 5'-, 6- and 7-H), 7.68 (br.s, 1H, 4-H), 10.53 (br.s, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): δ 32.73 ($C(\mathbf{C}H_3)_3$), 35.86 ($\mathbf{C}(CH_3)_3$), 110.34-123.90 (C4, C6, C7, C2', C3', C4' and C5'), 142.39 (C9), 148.99 (C5), 149.10 (C8), 159.20 (C2) ppm; ms (70 eV): m/z 241 (M+1, 11), 240 (M^+, 64), 225 (M^+ –CH_3, 100), 92 (N≡C–pyrrole$^+$, 2). *Anal*. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.89; H, 6.79; N, 11.70.

5-Chloro-2-(1*H*-pyrrol-2-yl)benzo[*d*]oxazole (**2d**). This compound was obtained from **1d** and $Mn(OAc)_3.2H_2O$ according to the general procedure I; beige tiny crystals, 0.14 g (64%), mp 127-128 °C; uv (chloroform): λ_{max} 242 and 321 nm; ir (potassium bromide): 3208 (NH), 3029 (aromatic, =C–H), 1625 (C=N), 1574, 1523 and 1446 (C=C and C–N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.19 (br.s, 1H, 3'-H), 6.86 (br.s, 1H, 4'-H), 6.90 (br.s, 1H, 5'-H), 7.06 (d, 1H, 6-H, $^3J_{6,7}$=8.0 Hz), 7.23 (d, 1H, 7-H), 7.40 (br.s, 1H, 4-H), 10.20 (br.s, 1H, NH) ppm; ^{13}C nmr (deuteriochloroform): δ 110.34-125.16 (C4, C6, C7, C2', C3', C4' and C5'), 130.03 (C5), 142.90 (C9), 148.71 (C8), 159.37 (C2) ppm; ms (70 eV): m/z 220 (M+2, 32), 219 (M+1, 14), 218 (M^+, 100), 191 (M^+ –HCN, 6), 92 (N≡C–pyrrolyl$^+$, 3). *Anal*. Calcd. for $C_{11}H_7ClN_2O$: C, 60.43; H, 3.23; N, 12.81. Found: C, 60.54; H, 3.32; N, 12.82.

General procedure II for the synthesis of 4-(Benzo[*d*]-oxazol-2-yl)quinoline (**2e**) **and 2-(Benzo[*d*]oxazol-2-yl)-4,6-dimethylquinolines** (**2f-h**). To a stirred solution of imine compound (**1e-h)** (1.0 mmol) in dry benzene (20 mL), manganese triacetate dihydrate (2.0 mmoles) was added and the mixture was refluxed for 4 h by stirring. After elimination of the residual manganese diacetate by filtration, most of the solvent was distilled out under reduced pressure. The crude product so obtained was purified by recrystallization from methanol.

4-(Benzo[*d*]oxazol-2-yl)quinoline (**2e**). This compound was obtained from **1e** and $Mn(OAc)_3.2H_2O$ according to the general procedure II; honey-coloured rod crystals, 0.19 g (77%), mp 113-114 °C; uv (chloroform): λ_{max} 249 and 307 nm; ir (potassium bromide): 3080 and 3029 (aromatic, =C–H), 1579 (C=N), 1543, 1498 and 1452 (aromatic and heteroaromatic, C=C and C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.41 - 9.52 (m, 10H, aromatic) ppm; ^{13}C nmr (deuteriochloroform): δ 112.85 – 133.21 (11C, aromatic carbons), 144.12 (C9), 151.16 (C8), 151.89 (C2'), 152.29 (C9'), 162.57 (C2) ppm; ms (70 eV): m/z 247 (M+1, 16), 246 M^+, 100), 245 (M–1, 85), 128 (quinolinyl$^+$, 8). *Anal*. Calcd. for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.38. Found: C, 78.02; H, 4.05; N, 11.42.

2-(Benzo[*d*]oxazol-2-yl)-4,6-dimethylquinoline (**2f**). This compound was obtained from **1f** and $Mn(OAc)_3.2H_2O$ according to the general procedure II; beige tiny crystals, 0.13 g (47%), mp 193-194 °C; uv (chloroform): λ_{max} 246, 260, 287 and 334 nm; ir (potassium bromide): 3055 (aromatic, =C–H), 2978, 2902 and 2851(CH_3), 1591 (C=N), 1545, 1498 and 1452 (aromatic and heteroaromatic, C=C and C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.59 (s, 3H, 6'–CH_3), 2.79 (s, 3H, 4'–CH_3), 7.42 - 9.29 (m, 8H, aromatic) ppm; ms (70 eV): m/z 276 (M+2, 3), 275 (M+1, 25), 274 (M^+, 100), 273 (M–1, 15), 156 ((4,6-dimetylquinolinyl)$^+$, 4). *Anal*. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.79; H, 5.20; N, 10.29.

4,6-Dimethyl-2-(5-methylbenzo[*d*]oxazol-2-yl)quinoline (**2g**). This compound was obtained from **1g** and $Mn(OAc)_3.2H_2O$ according to the general procedure II; beige tiny crystals, 0.18 g (63%), mp 220-221 °C; uv (chloroform): λ_{max} 248, 264, 285 and 336 nm; ir (potassium bromide): 3029 (aromatic, =C–H), 2978, 2902 and 2851 (CH_3), 1594 (C=N), 1543 and 1440 (aromatic and heteroaromatic, C=C and C=N) cm^{-1}; ^1H nmr

(deuteriochloroform): δ 2.48 (s, 3H, 5–CH_3), 2.54 (s, 3H, 6'–CH_3), 2.74 (s, 3H, 4'–CH_3), 7.17 - 8.22 (m, 7H, aromatic) ppm; ^{13}C nmr (deuteriochloroform): δ 20.59 (5–CH_3), 23.37 (6'–CH_3), 23.86 (4'–CH_3), 112.66-146.65 (12C, aromatic carbons), 146.77 (C9), 148.67 (C8), 151.71 (C2'), 164.18 (C2) ppm; ms (70 eV): m/z 290 (M+2, 4), 289 (M+1, 24), 288 (M^+, 100), 287 (M–1, 16), 156 (4,6-dimetylquinolinyl$^+$, 5). *Anal*. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.19; H, 5.64; N, 9.79.

2-(5-Chlorobenzo[*d*]oxazol-2-yl)-4,6-dimethylquinoline (**2h**). This compound was obtained from **1h** and $Mn(OAc)_3.2H_2O$ according to the general procedure II; beige rod crystals, 0.17 g (55%), mp 217-218 °C; uv (chloroform): λ_{max} 248, 264 and 334 nm; ir (potassium bromide): 3055 (aromatic, =C–H), 2927 and 2851 (CH_3), 1593 (C=N), 1543 and 1501 (aromatic and heteroaromatic, C=C and C=N) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.61 (s, 3H, 6'–CH_3), 2.80 (s, 3H, 4'–CH_3), 7.38-8.26 (m, 7H, aromatic) ppm; ms (70 eV): m/z 311 (M+3, 6), 310 (M+2, 35), 309 (M+1, 25), 308 (M^+, 100), 307 (M–1, 9), 156 (4,6-dimetylquinolinyl$^+$, 5). *Anal*. Calcd. for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07. Found: C, 70.05; H, 4.31; N, 9.11.

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