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A NEW METHOD FOR THE SYNTHESIS OF PYRROLO[1,2-*a*]QUINOLINES BASED ON BORON TRIFLUORIDE-MEDIATED CYCLIZATION OF 1-(2-OXIRANYLPHENYL)PYRROLES

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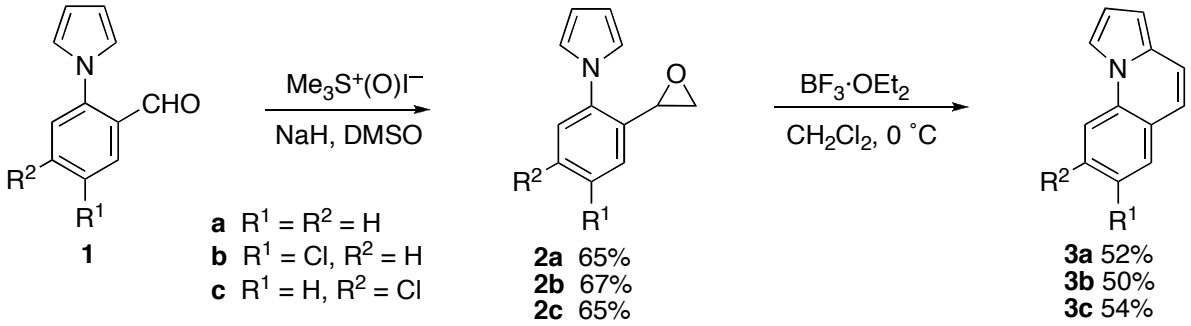
Abstract - A simple synthesis of pyrrolo[1,2-*a*]quinolines carrying no substituent at all of the 1- to 5-positions based on boron trifluoride-mediated cyclization of 1-(2-oxiranylphenyl)pyrroles, which can be easily prepared from 2-(pyrrol-1-yl)benzaldehydes, is described.

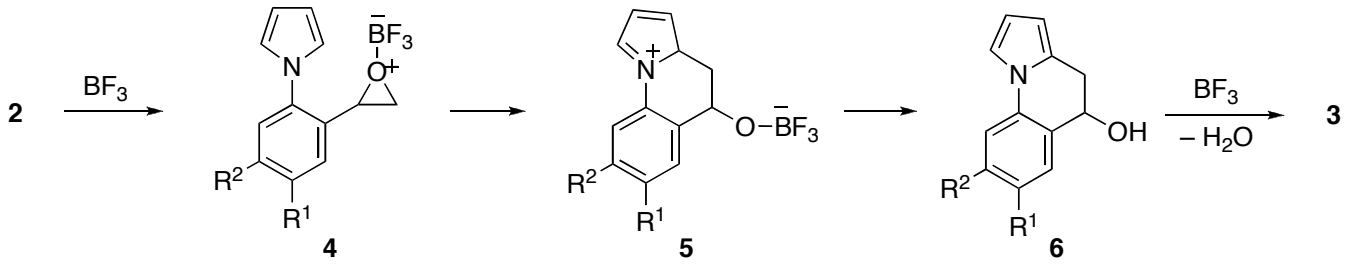
We previously described a boron trifluoride catalyzed synthesis of 3-aminopyrrolo[1,2-*a*]quinolin-4-ol derivatives from 2-(pyrrol-1-yl)benzaldehydes and isocyanides.[1] In addition, we demonstrated that 3,4-diaminopyrrolo[1,2-*a*]quinoline derivatives could be obtained by reactions of 2-(pyrrol-1-yl)benzaldehydes with secondary amine hydrochlorides in the presence of isocyanides,[2] or by boron trifluoride catalyzed reactions of 2-(pyrrol-1-yl)benzaldimines with isocyanides.[3] We became interested in the development of a new and facile method for preparing pyrrolo[1,2-*a*]quinolines carrying no substituent at all of the 1- to 5-positions. Although a number of syntheses of pyrrolo[1,2-*a*]quinoline derivatives have recently been reported,[4] there have been only a few reports on the synthesis of this class of pyrrolo[1,2-*a*]quinolines,[5] The methods involve multi-step sequences and/or rare metal-catalyzed reactions. For example, in 1976 Vomero and coworkers described a synthesis of pyrrolo[1,2-*a*]quinoline from 2-(pyrrol-1-yl)benzyl alcohol in five steps via formylation of [2-(pyrrol-1-yl)phenyl]acetonitrile as the key step.[5c] Recently, Fürster and coworkers have synthesized pyrrolo[1,2-*a*]quinoline by a platinum chloride catalyzed cyclization reaction of 1-(2-alkynylphenyl)pyrrole.[5d] In this paper, we wish to describe the results of our investigation, which provide a convenient method to prepare pyrrolo[1,2-*a*]quinolines (**3**) by boron trifluoride-mediated reactions of 1-(2-oxiranylphenyl)pyrroles (**2**), easily obtainable from 2-(pyrrol-1-yl)benzaldehydes (**1**). Pyrrolo[1,2-*a*]quinolines are known to be of potentially importance for both practical and theoretical utilities as one of the benzo analogues of indolizines.[6]

The transformation of 2-(pyrrol-1-yl)benzaldehydes (**1**) into the pyrroloquinolines (**3**) were accomplished via 1-(2-oxiranylphenyl)pyrroles (**2**), as outlined in Scheme 1. Thus, 2-(pyrrol-1-yl)benzaldehydes (**1**) were allowed to react with trimethylsulfoxonium iodide in the presence of sodium hydride to give the



Scheme 1

oxiranes (**2**) in fair yields. We found that a stoichiometric amount of boron trifluoride diethyl etherate was successfully employed for the cyclization of these oxiranes (**2**) to afford the desired products (**3**) in moderate yields. Best results in regard to yield were obtained when the reactions were carried out at 0 ˚C. Higher temperatures gave more complex mixtures of products, and considerable amounts of starting materials were recovered at lower temperatures. When the reactions were carried out with a catalytic amount of boron trifluoride, they did not complete and desired products were formed in rather lower yields and considerable amounts of starting materials were recovered. Using other Lewis acids, such as $SnCl_4$ or $ZnCl_2$, the conversion of **2** into **3** was not successful, and no more than a trace amount of desired product was obtained from an intractable mixture of products in each case.



Scheme 2

The conversion of **2** into **3** is thought to proceed as shown in Scheme 2. Thus, the attack of the 2-position of the pyrrole ring upon the activated epoxy moiety of the intermediates (**4**) results in the formation of 4,5- dihydropyrrolo[1,2-*a*]quinolin-5-ol derivatives (**6**), via the intermediates (**5**). Subsequent dehydration of these alcohols (**6**) with boron trifluoride gives rise to **3**. No trace of **6** was isolated in each case, and any pyrrolo[1,2-*a*]indole derivatives were not obtained. These results may be ascribed to the aromaticity of pyrrolo[1,2-*a*]quinoline.

In summary, a simple procedure for the preparation of pyrrolo[1,2-*a*]quinoline derivatives has been developed using boron trifluoride-mediated cyclization of 1-(2-oxiranylphenyl)pyrroles, which can be easily obtained by epoxidation of 2-(pyrrol-1-yl)benzaldehyde. As the starting materials are readily

available and the manipulations are very simple, this new approach may be efficient and advantageous.

EXPERIMENTAL

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz. *J* values are given in Hz. The ^{13}C NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz in $CDCl_3$. Low-resolution mass spectra (EI) were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm).

Starting Materials. 2-(Pyrrol-1-yl)benzaldehyde (**1a**),[1,2] 5-chloro-2-(pyrrol-1-yl)benzaldehyde (**1b**),[2] and 4-chloro-2-(pyrrol-1-yl)benzaldehyde (**1c**)[7] were prepared by the procedure previously reported by us. Other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of (Oxiranylphenyl)pyrrole Derivatives 2. 1-(2-Oxiranylphenyl)pyrrole (2a). To a stirred suspension of NaH (60%; 0.27 g, 6.8 mmol) in DMSO (5 mL) and THF (10 mL) at rt was added dropwise a solution of trimethylsulfoxonium iodide (1.5 g, 6.8 mmol) in DMSO (15 mL) over 15 min. After stirring for 5 min, 2-(pyrrol-1-yl)benzaldehyde (0.58 g, 3.4 mmol) was added to the mixture over 5 min, and stirring was continued for an additional 20 min. Water was added and the mixture was extracted with Et_2O twice. The combined extracts were washed with water 10 times and then brine, and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure the residue was subjected to column chromatography on silica gel (1:5 EtOAc–hexane) to give **2a** (0.49 g, 65%) as an yellow oil; R_f 0.57 ; IR (neat) 3051, 1504 cm^{-1}; δ_H 2.77 (1H, dd, *J* 5.6, 2.6), 3.11 (1H, dd, *J* 5.6, 4.3), 3.72 (1H, dd, *J* 4.3, 2.6), 6.34 (2H, dd, *J* 2.3, 2.0), 6.89 (2H, dd, *J* 2.3, 2.0), 7.25–7.4 (4H, m). Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.75; H, 6.04; N, 7.54.

1-(4-Chloro-2-oxiranylphenyl)pyrrole (2b): R_f 0.47 (1:2 THF–hexane); IR (neat) 3050, 1501 cm^{-1}; δ_H 2.76 (1H, dd, *J* 5.6, 2.6), 3.12 (1H, dd, *J* 5.6, 4.3), 3.69 (1H, dd, *J* 4.3, 2.6), 6.34 (2H, dd, *J* 2.3, 2.0), 6.85 (2H, dd, *J* 2.3, 2.0), 7.23 (1H, d, *J* 8.2), 7.25-7.45 (2H, m). Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.49; H, 4.79; N, 6.09.

1-(5-Chloro-2-oxiranylphenyl)pyrrole (2c): R_f 0.45 (1:1 hexane–CH_2Cl_2); IR (neat) 3055, 1603, 1501 cm^{-1}; δ_H 2.75 (1H, dd, *J* 5.6, 2.6), 3.12 (1H, dd, *J* 5.6, 4.3), 3.71 (1H, dd, *J* 4.3, 2.6), 6.34 (2H, dd, *J* 2.3, 2.0), 6.87 (2H, dd, *J* 2.3, 2.0), 7.2–7.35 (3H, m). Anal. Calcd for $C_{12}H_{10}ClNO$: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.52; H, 4.62; N, 6.37.

Typical Procedure for the Preparation of Pyrrolo[1,2-*a*]quinolines 3. Pyrrolo[1,2-*a*]quinoline (3a).

To a stirred solution of **2a** (0.13 g, 0.70 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added dropwise $BF_3{\cdot}OEt_2$ (0.10 g, 0.71 mmol). After 10 min stirring, the mixture was washed with saturated aqueous $NaHCO_3$ and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (1:3 CH_2Cl_2–hexane) to give **3a** (60 mg, 52%) as a white solid; mp 110–111 °C (lit.,[5a] 108–108.5 °C). The spectral (IR, ^1H and ^{13}C NMR, MS) data were identical to those reported previously.[5d]

7-Chloropyrrolo[1,2-*a*]quinoline (3b): mp 99–100 °C (hexane–Et_2O); IR (KBr) 3134, 1614 cm^{-1}; δ_H 6.53 (1H, dd, *J* 3.6, 1.3), 6.78 (1H, dd, *J* 3.6, 2.3), 6.88 (1H, d, *J* 9.2), 7.32 (1H, d, *J* 9.2), 7.42 (1H, dd, *J* 8.9, 2.3), 7.60 (1H, d, *J* 2.3), 7.75–7.85 (2H, m); δ_C 103.39, 112.23, 113.06, 115.57, 117.54, 120.22, 125.11, 127.62, 127.66, 128.74, 130.85, 131.86; MS *m/z* 201 (M^+, 100). Anal. Calcd for $C_{12}H_8ClN$: C, 71.47; H, 4.00; N, 6.95. Found: C, 71.22; H, 4.01; N, 6.91.

8-Chloropyrrolo[1,2-*a*]quinoline (3c): mp 92–93 °C (hexane–Et_2O); IR (KBr) 3142, 1603 cm^{-1}; δ_H 6.52 (1H, dd, *J* 3.6, 1.3), 6.79 (1H, dd, *J* 3.6, 3.0), 6.92 (1H, d, *J* 9.2), 7.26 (1H, d, *J* 8.2), 7.28 (1H, d, *J* 9.2), 7.54 (1H, d, *J* 8.2), 7.76 (1H, dd, *J* 3.0, 1.3), 7.86 (1H, d, *J* 1.6); δ_C 103.24, 112.12, 113.26, 114.32, 117.91, 119.16, 122.26, 123.87, 129.63, 131.00, 133.18, 133.95; MS *m/z* 201 (M^+, 100). Anal. Calcd for $C_{12}H_8ClN$: C, 71.47; H, 4.00; N, 6.95. Found: C, 71.38; H, 4.24; N, 6.95.

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