Synthesis of Pyrrolo[1,2-*a*]quinoxaline and Its 4-(1-Hydroxyalkyl) Derivatives by Lewis Acid-Catalyzed Reactions of 1-(2-Isocyanophenyl)pyrrole

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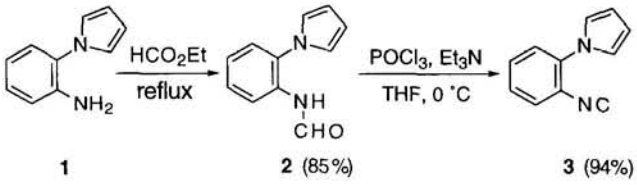
When 1-(2-isocyanophenyl)pyrrole was treated with a catalytic amount of boron trifluoride, pyrrolo[1,2-*a*]quinoxaline was obtained almost quantitatively. The reaction in the presence of aldehydes or ketones gave the corresponding 4-(1-hydroxyalkyl)pyrrolo[1,2-*a*]quinoxalines in moderate to good isolated yields.

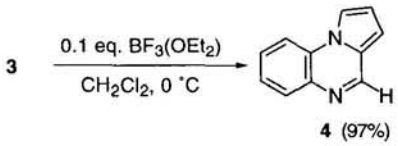
Pyrrolo[1,2-*a*]quinoxaline derivatives have held considerable interest for not only organic but also medicinal chemists because of their enzyme inhibitory,[1a] antiallergic,[1b,c] antagonistic,[1d,e,f] and other biological activities.[1c] Although a number of methods have been reported to prepare this class of molecules,[1,2] most of them involves either multi-steps and/or incomplete generality. For these reasons we embarked upon development of a new and efficient method for synthesizing substituted pyrrolo[1,2-*a*]quinoxalines. In this paper, we wish to report a boron trifluoride-catalyzed reaction of 1-(2-isocyanophenyl)pyrrole (**3**) with a variety of ketones or aldehydes,[3] which involves two C–C bond formations in one-pot and allows rapid access to 4-(1-hydroxyalkyl)pyrrolo[1,2-*a*]quinoxalines **5**.

The starting isocyanide **3** was prepared according to the sequence outlined in Scheme 1. Thus, *N*-formylation of commercially available 1-(2-aminophenyl)pyrrole (**1**) in refluxing ethyl formate gave 1-(2-formylaminophenyl)pyrrole (**2**)[2a] in good yield, which was dehydrated with phosphorous oxychloride and triethylamine in THF to afford **3** in excellent yield as pale-yellow needles after recrystallization from pentane (mp 42–43 °C). This isocyanide is rather stable and storable at refrigerator temperature under argon for several weeks.



1 **2** (85%) **3** (94%)

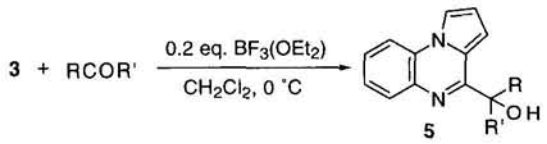
Scheme 1.



4 (97%)

Scheme 2.

Treatment of the isocyanide **3** with 0.1 molar amount of $BF_3(OEt_2)$ under mild conditions (in CH_2Cl_2, 0 °C) resulted in smooth (1 h) and almost quantitative conversion to pyrrolo[1,2-*a*]quinoxaline (**4**), whose spectral data (IR and ^1H NMR) and melting point were in agreement with literature values (Scheme 2).[2a]



5

Scheme 3.

Table 1. Preparation of 4-(1-hydroxyalkyl)pyrrolo[1,2-*a*]quinoxalines **5**

Entry	Ketone or aldehyde	Product (Yield/%)[a]
1	EtCHO	**5a** (89)
2	*i*-PrCHO	**5b** (85)
3	PhCHO	**5c** (81)
4	2-Furancarbaldehyde	**5d** (49)
5	Me_2CO	**5e** (76)
6	cyclohexanone	**5f** (78)
7	PhCOMe	**5g** (59)
8	$MeCOCO_2Et$	**5h** (84)
9	$MeCO(CH_2)_2CO_2Et$	**5i** (74)

[a]Isolated yields after purification by column chromatography on silica gel.

We next examined the boron trifluoride-catalyzed reactions in the presence of ketones or aldehydes. The reactions also proceeded under conditions similar to those described above for the preparation of **4** to give the corresponding 4-(1-hydroxyalkyl)pyrrolo[1,2-*a*]quinoxalines **5**, although the yields were low (Scheme 3). For example, the reaction of **3** with propanal gave the expected product **5a** only in 32% yield, and the starting isocyanide was recovered (56%). The reaction using equimolar amount of the catalyst resulted in the formation of somewhat increased yield of **5a** (36%) together with fairly large quantities of **4** (48%). The use of other Lewis acids gave much inferior results; $TiCl_4$ and $SnCl_4$ gave **5a** in about 5% yields, and $ZnCl_2$ and $AlCl_3$ gave no more than a trace amount of **5a**. However, we found that the yield of **5a** was considerably improved (89%) by adding two portions of 0.1 molar amount each of $BF_3(OEt_2)$ at a 20 min interval. The reactions using four aldehydes and five ketones were carried out under these conditions. The results are summarized in Table 1. The yields of the products are generally good, except that the reactions using 2-furancarbaldehyde and acetophenone gave the desired products **5d** and **5g** in modest yields (Entries 4 and 7). These results may be ascribable to the susceptibility of the furan ring of 2-furancarbaldehyde to acidic degradation and the lower reactivity

of acetophenone. When keto esters, such as ethyl pyruvate and ethyl levulinate, were used, the corresponding pyrrroloquinoxalyl hydroxy esters **5h** and **5i** could be obtained in satisfactory yields (Entries 8 and 9).

Typical experimental procedure is illustrated for the preparation of 4-(1-hydroxylpropyl)pyrrolo[1,2-*a*]quinoxaline (**5a**). To a stirred solution of the isocyanide **3** (1 mmol, 0.17 g) and EtCHO (58 mg, 1.0 mmol) in CH_2Cl_2 (20 ml) at 0 °C under argon was added dropwise $BF_3(OEt_2)$ (14 mg, 0.1 mmol). After 20 min, another portion of the catalyst (14 mg, 0.1 mmol) was added, and the resulting mixture was stirred for an additional 20 min at the same temperature before it was quenched by adding aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was subjected to column chromatography on SiO_2 to afford **5a** (0.20 g, 89%).[4]

In summary, we have shown that the boron trifluoride-catalyzed α-hydroxyalkylative cyclization of 1-(2-isocyanophenyl)pyrrole with aldehydes or ketones provides an efficient method to prepare 4-(1-hydroxyalkyl)pyrrolo[1,2-*a*]quinoxalines. Since the method employs readily available starting materials and is experimentally simple, it may be of value in heterocyclic synthesis. Work on investigating the reactions using other electrophiles is currently in progress in our laboratory, and the results will be reported in due course.

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References and Notes

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4 All new compounds gave satisfactory spectral [IR (neat or KBr), ^{1}H NMR (270 MHz, $CDCl_3$), and LR-MS] and analytical data. Spectral data for the products follow. **3:** ν/cm^{-1} 2122; δ_H 6.39 (2H, t, J = 2.1 Hz), 7.02 (2H, t, J = 2.1 Hz), 7.3–7.55 (4H, m); *m/z* 168 (M$^+$, 100%). **5a**: ν/cm^{-1} 3395, 3158, 1613, 1365, 756; δ_H 1.03 (3H, t, J = 7.4 Hz), 1.75–1.9 (1H, m), 2.1–2.2 (1H, m), 4.82 (1H, d, J = 6.3 Hz), 5.0–5.1 (1H, m), 6.85–6.9 (2H, m), 7.4–7.6 (2H, m), 7.87 (1H, dd, J = 8.4, 1.6 Hz), 7.9–8.0 (2H, m); *m/z* 226 (M$^+$, 37%), 198 (100). **5b**: ν/cm^{-1} 3400, 3136, 1614; δ_H 0.75 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.9 Hz), 2.3–2.4 (1H, m), 4.68 (1H, br. s), 4.94 (1H, d, J = 3.2 Hz), 6.85–6.9 (2H, m), 7.44 (1H, td, J = 7.9, 1.6 Hz), 7.52 (1H, td, J = 7.9, 1.6 Hz), 7.86 (1H, dd, J =7.9, 1.6 Hz), 7.9-8.0 (2H, m); *m/z* 240 (M$^+$, 15%), 223 (29), 197 (100). **5c**: ν/cm^{-1} 3334, 3133, 1613, 1368, 763; δ_H 5.9–5.95 (2H, m), 6.64 (1H, dd, J = 4.2, 1.1 Hz), 6.75 (1H, dd, J = 4.2, 2.6 Hz), 7.25–7.35 (3H, m), 7.45–7.6 (4H, m), 7.85 (1H, dd, J = 7.9, 1.6 Hz), 7.89 (1H, dd, J = 2.6, 1.1 Hz), 8.05 (1H, dd, J = 7.9, 1.6 Hz); *m/z* 274 (M$^+$, 28%), 257 (100). **5d:** ν/cm^{-1} 3352, 3138, 1365, 755; δ_H 5.79 (1H, br. s), 6.05 (1H, br. s), 6.34 (1H, dd, J = 4.3, 1.1 Hz), 6.42 (1H, d, J = 4.3, 1.1 Hz), 6.73 (1H, dd, J = 4.3, 2.6 Hz), 6.80 (1H, dd, J = 4.3, 2.6 Hz), 7.45–7.6 (2H, m), 7.86 (1H, dd, J = 8.1, 1.7 Hz), 7.9–8.0 (2H, m), 8.02 (1H, dd, J = 7.7, 1.7 Hz); *m/z* 264 (M$^+$, 1.5%), 262 (49), 234 (100). **5e:** ν/cm^{-1} 3355, 3123, 1612, 1362, 749; δ_H 1.75 (6H, s), 6.24 (1H, s), 6.90 (1H, dd, J = 4.2, 2.6 Hz), 7.00 (1H, dd, J = 4.2, 1.6 Hz), 7.45 (1H, td, J = 7.4, 1.6 Hz), 7.54 (1H, td, J=7.4, 2.1 Hz), 7.87 (1H, dd, J = 7.4, 1.6 Hz), 7.9–8.0 (2H, m); *m/z* 226 (M$^+$, 42), 211 (100). **5f:** ν/cm^{-1}; 3302, 3146, 1611, 1368, 738; δ_H 1.5–2.05 (8H, m), 2.25-2.4 (2H, m), 6.10 (1H, s), 6.90 (1H, dd, J = 4.2, 2.6 Hz), 7.12 (1H, dd, J = 4.2, 1.6 Hz), 7.4–7.55 (2H, m), 7.86 (1H, d, J = 7.9 Hz), 7.94 (1H, dd, J = 7.9, 1.6 Hz), 7.96 (1H, dd, J = 2. 6, 1.6 Hz); *m/z* 266 (M$^+$, 46%), 211 (100). **5g:** ν/cm^{-1} 3293, 3135, 1610, 1363, 756; δ_H 2.12 (3H, s), 2.61 (1H, s), 6.43 (1H, dd, J = 4.2, 2.6 Hz), 6.69 (1H, dd, J = 4.2, 1.6 Hz), 7.25–7.35 (3H, m), 7.45–7.6 (4H, m), 7.84 (1H, dd, J = 7.4, 1.6 Hz), 7.86 (1H, dd, J = 2.6, 1.6 Hz), 8.04 (1H, dd, J = 7.9, 1.6 Hz); *m/z* 288 (M$^+$, 38%), 271 (82), 168 (100). **5h:** ν/cm^{-1} 3356, 3136, 1736, 1613, 1361, 758; δ_H 1.16 (3H. t, J = 7.4 Hz), 1.95 (3H, s), 4.1–4.25 (2H, m), 6.27 (1H, s), 6.88 (1H, dd, J = 4.2, 2.6 Hz), 7.03 (1H, dd, J = 4.2, 1.6 Hz), 7.46 (1H, td, J = 7.9, 1.0 Hz), 7.46 (1H, td, J = 7.9, 1.6 Hz), 7.87 (1H, dd, J = 7.9, 1.0 Hz), 7.95–8.05 (2H, m); *m/z* 284 (M$^+$, 30%), 211 (100). **5i:** ν/cm^{-1} 3340, 3135, 1731, 1621, 1375, 761; δ_H 1.15 (3H, t, J = 6.8 Hz), 1.84 (3H, s), 2.09 (1H, ddd, J = 15.8, 11.1, 5.3 Hz), 2.35–2.6 (3H, m), 2.72 (1H, ddd, J = 15.8, 10.0, 5.3 Hz), 3.95–4.1 (2H, m), 7.17 (1H, dd, J = 4.2, 2.6 Hz), 7.40 (1H, dd, J = 4.2, 1.0 Hz), 7.61 (1H, td, J = 7.9 and 1.0 Hz), 7.72 (1H, td, J = 7.9, 1.0 Hz), 8.00 (1H, dd, J = 7.9, 1.0 Hz), 8.26 (1H, dd, J = 2.6, 1.0 Hz), 8.41 (1H, dd, J = 7.9 and 1.0 Hz); *m/z* 266 [(M-EtOH)$^+$, 35%], 195 (100).