Lewis Acid Catalyzed Synthesis of 4-Aminopyrrolo[1,2-*a*]quinolin-5-ol Derivatives from 2-(1-Pyrrolyl)benzaldehyde and Isocyanides

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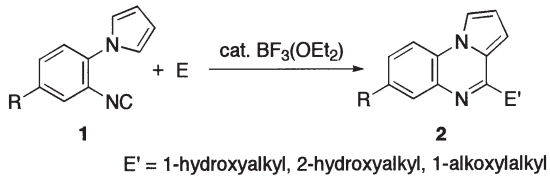
Reaction of 2-(1-pyrrolyl)benzaldehyde with isocyanides in the presence of a catalytic amount of boron trifluoride diethyl etherate was followed by treatment with acetic anhydride in pyridine to give the corresponding *O*-acetyl derivatives of 4-alkyl(or aryl)aminopyrrolo[1,2-*a*]quinolin-5-ols in moderate yields.

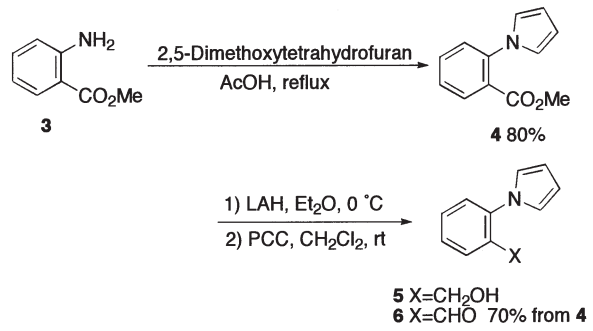
Recently, we have reported the synthesis of pyrrolo[1,2-*a*]quinoxalines carrying an oxyalkyl group at the 4-position (**2**) by boron trifluoride-catalyzed reactions of 1-(2-isocyanophenyl)-pyrroles (**1**) with aldehydes, ketones, epoxides, or acetals, as shown in Scheme 1.[1] We herein wish to report a convenient synthesis of 4-alkyl(or aryl)aminopyrrolo[1,2-*a*]quinolin-5-ol derivatives (**8**) by a boron trifluoride-catalyzed reaction of 2-(1-pyrrolyl)benzaldehyde (**6**) with isocyanides, as summarized in Scheme 3.[2] A large number of methods for the synthesis of aromatic indolizine have been reported due to their both practical and theoretical utilities.[3] Pyrrolo[1,2-*a*]quinolines are one of the benzo analogues of indolizine and of potentially importance for both practical and theoretical reasons as well. Therefore, several syntheses have recently been reported in the literature.[4]



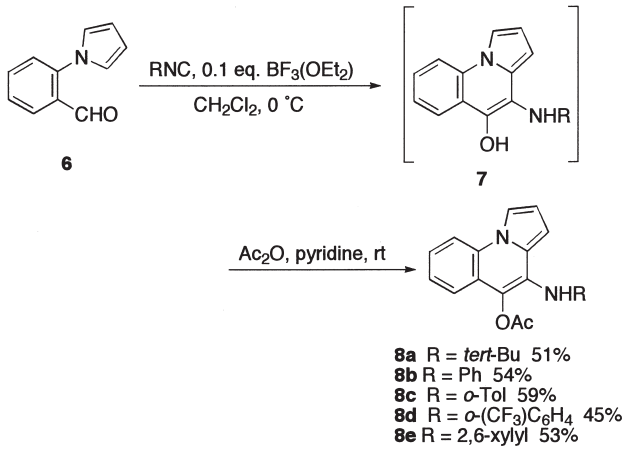
Scheme 1.

The starting compound of our synthesis, **6** was readily prepared in three steps starting from commercially available methyl 2-aminobenzoate (**3**) in good yield by the process illustrated in Scheme 2. Thus, treatment of compound **3** with 2,5-dimethoxytetrahydrofuran in refluxing acetic acid gave methyl 2-(1-pyrrolyl)benzoate (**4**) in a good yield after distillation. Reduction of **4** with LAH in diethyl ether at 0 °C gave 1-[2-(hydroxymethyl)phenyl]pyrrole (**5**), which was used without purification in PCC oxidation in dichloromethane at room temperature to afford **6** in a reasonable yield from **4** after distillation.

2-(1-Pyrrolyl)benzaldehyde (**6**) was allowed to react with aliphatic and aromatic isocyanides in the presence of a catalytic amount of boron trifluoride diethyl etherate under argon to lead to formation of 4-alkyl(or aryl)aminopyrrolo[1,2-*a*]quinolin-5-ols (**7**) as depicted in Scheme 3. Attempted isolation of these products resulted in vain because they revealed instability in air. Therefore, after rapid workup, the crude product mixtures were acetylated with acetic anhydride in pyridine at room temperature under argon to provide stable 5-acetoxy-4-alkyl(or aryl)aminopyrrolo[1,2-*a*]quinoline derivatives (**8**) in moderate yields after chromatography on silica gel. No trace of *N*-acetylation occurred during the treatment with acetic anhydride. This may be attributed to the steric bulk of *N*-substituents. The structure of this *O*-acetylated products proved by their IR spectra; each of them exhibited sharp and strong absorption bands at 3328–3422 cm^{-1} and at 1750–1764 cm^{-1} assignable to N-H and C=O stretching vibrations, respectively.



Scheme 2.

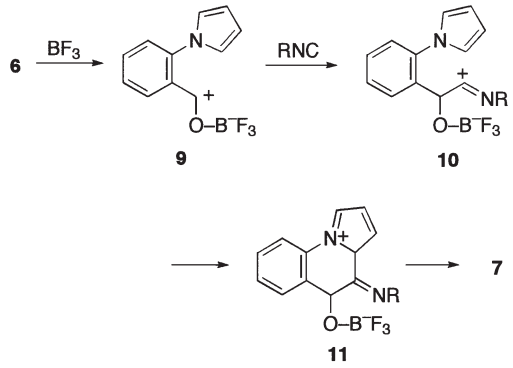


Scheme 3.

A typical procedure is illustrated by the preparation of 5-acetoxy-4-(*tert*-butylamino)pyrrolo[1,2-*a*]quinoline (**8a**). To a stirred solution of **6** (0.17 g, 1.0 mmol) and *tert*-butyl isocyanide (83 mg, 1.0 mmol) in CH_2Cl_2 (10 ml) at 0 °C under argon was added boron trifluoride diethyl etherate (14 mg, 0.10 mmol). After 5 min, saturated aqueous $NaHCO_3$ was added. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 twice (5 ml each). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. To this residue under argon were added 1.5 ml each of pyridine and acetic anhydride. These procedures were carried out as quickly as possible. The resulting mixture was stirred at room

temperature for 10 min, and the excess pyridine and acetic anhydride were removed under reduced pressure. The residue was chromatographed on silica gel (1 : 5 EtOAc-hexane) to give **8a** (0.15 g, 51%).[5]

The pathway which leads to **7** from **6** and isocyanides is outlined in Scheme 4. Thus, attack of the isocyano carbon to the activated aldehyde **9** generates the intermediate **10**. An intramolecular combination of the 2-carbon of the pyrrole and the cation center of **10** affords **11**, which gives rise to **7**.



Scheme 4.

In conclusion, we have shown that 4-alkyl(or aryl)amino-pyrrolo[1,2-*a*]quinolin-5-ol derivatives can be obtained from readily available starting materials. Application of this methodology using 2-(1-pyrrolyl)benzaldehyde and isocyanides in the synthesis of other functionalized pyrrolo[1,2-*a*]quinoline derivatives are currently under way in our laboratory and the results will be reported in due course.

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References and Notes

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5 All the stable new compounds gave satisfactory spectral data (IR, ^{1}H NMR, EIMS, and HRMS). **6**: a yellow liquid: bp 130 °C (bath temp)/0.045 Torr; IR (neat) 3140, 3103, 2856, 2759, 1691, 1599 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.39 (2H, t, J = 2.3 Hz), 6.93 (2H, t, J = 2.3 Hz), 7.43 (1H, dd, J = 7.6, 1.0 Hz), 7.49 (1H, td, J = 7.6, 1.0 Hz), 7.67 (1H, td, J = 7.6, 1.0 Hz), 7.99 (1H, dd, J = 7.6, 1.0 Hz), 9.81 (1H, s). MS m/z 171 (M^+, 58), 143 (93), 115 (100). HRMS (m/z) Found: 171.0690. Calcd for $C_{11}H_9NO$: M^+, 171.0684. **8a**: mp 125–128 °C (decomp) (hexane–Et_2O); IR (KBr disk) 3328, 1751 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (9H, s), 2.12 (3H, s), 5.51 (1H, s), 6.60 (1H, dd, J = 4.0, 1.6 Hz), 6.73 (1H, dd, J = 4.0, 3.0 Hz), 7.30 (1H, dd, J = 7.9, 1.3 Hz), 7.43 (1H, td, J = 7.3, 1.3 Hz), 7.52 (1H, ddd, J = 7.9, 7.3, 1.3 Hz), 7.79 (1H, dd, J = 3.0, 1.6 Hz), 7.83 (1H, dd, J = 7.3, 1.3 Hz); MS m/z 296 (M^+, 4), 253 (6.0), 223 (7.3), 197 (100). HRMS (m/z) Found: 296.1524. Calcd for $C_{18}H_{20}N_2O_2$: M^+, 296.1525. **8b**: mp 141–142 °C (decomp) (hexane–Et_2O); IR (KBr disk) 3362, 1751 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.04 (3H, s), 5.53 (1H, br. s), 6.41 (1H, dd, J = 3.6, 1.6 Hz), 6.69 (1H, dd, J = 3.6, 2.7 Hz), 6.85 (2H, d, J = 8.1 Hz), 6.90 (1H, t, J = 8.1 Hz), 7.24 (2H, t, J = 8.1 Hz), 7.32 (1H, t, J = 7.8 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.59 (1H, d, J = 7.8 Hz), 7.82 (1H, dd, J = 2.7, 1.6 Hz), 7.85 (1H, d, J = 7.8 Hz); MS m/z 316 (M^+, 35), 274 (100). HRMS (m/z) Found: 316.1134. Calcd for $C_{20}H_{16}N_2O_2$: M^+, 316.1212. **8c**: mp 144–145 °C (decomp) (hexane–$CHCl_3$); IR (KBr disk) 3361, 1750 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.97 (3H, s), 2.30 (3H, s), 5.30 (1H, br. s), 6.39 (1H, d, J = 3.0 Hz), 6.71 (1H, t, J = 3.0 Hz), 6.81 (1H, d, J = 7.6 Hz), 6.90 (1H, t, J = 7.6 Hz), 7.08 (1H, t, J = 7.6 Hz), 7.17 (1H, d, J = 7.6 Hz), 7.32 (1H, t, J = 7.9 Hz), 7.44 (1H, d, J = 7.9 Hz), 7.57 (1H, d, J = 7.9 Hz), 7.84 (1H, d, J = 3.0 Hz), 7.86 (1H, d, J = 7.9 Hz); MS m/z 330 (M^+, 26), 288 (79), 170 (100). HRMS (m/z) Found: 330.1370. Calcd for $C_{21}H_{18}N_2O_2$: M^+, 330.1368. **8d**: mp 172–175 °C (decomp) (hexane–CH_2Cl_2); IR (KBr disk) 3422, 1763 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.21 (3H, s), 5.95 (1H, br. s), 6.56 (1H, d, J = 3.0 Hz), 6.67 (1H, t, J = 3.0 Hz), 6.89 (1H, t, J = 7.6 Hz), 7.03 (1H, d, J = 7.6 Hz), 7.1–7.4 (4H, m), 7.5–7.65 (2H, m), 8.05 (1H, d, J = 8.1 Hz); MS m/z 384 (M^+, 25), 342 (100). HRMS (m/z) Found: 384.1105. Calcd for $C_{21}H_{15}N_2O_2F_3$: M^+, 384.1086. **8e**: mp 153–155 °C (decomp) (hexane–CH_2Cl_2); IR (KBr disk) 3385, 1764 cm^{-1}; 1H NMR (270 MHz, $CDCl_3$) d 1.68 (3H, s), 2.21 (6H, s), 5.29 (1H, br. s), 6.36 (1H, dd, J = 3.0, 1.6 Hz), 6.72 (1H, t, J = 3.0 Hz), 7.05–7.15 (3H, m), 7.2–7.4 (3H, m), 7.8–7.85 (2H, m); MS m/z 344 (M^+, 46), 301 (100). HRMS (m/z) Found: 344.1505. Calcd for $C_{22}H_{20}N_2O_2$: M^+, 344.1525.