Efficient Synthesis of Novel Six-Member Ring-Fused Quinoline Derivatives via the Friedländer Reaction

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ABSTRACT: Novel quinolines fused with a six-member ring 5a–j were prepared in high yields (75–95%) via the Friedländer reaction of dimethoxy-substituted o-aminobenzaldehydes of 3a or 3b with cyclic ketones 4, respectively. The structures of 5a–j were determined by IR, 1H NMR, MS, and elemental analysis.

INTRODUCTION

As a potential drug candidate, quinoline derivatives have recently attracted increasing interest because of their broad range of biological activities [1]. For example, quinoline derivatives have been found to be potent, selective, and orally bioavailable inhibitors for the platelet-derived growth factor receptor [2a] and an effective inhibitor for the replication of the severe acute respiratory syndrome coronavirus in vitro [2b]. Moreover, quinoline analogues were reported to display promising antibacterial [3], anticancer and antiplatelet [4], antiasthmatic [5], anti-inflammatory [6], and antihypertensive [7] activities. In addition, quinoline’s derivatives have been widely utilized as ligands for preparing metal complexes [8] and as useful materials for organic synthesis [9].

Among these quinoline derivatives, we are particularly interested in six-member ring-fused quinolines due to their promising antitumor activity [10].

RESULTS AND DISCUSSION

The starting materials, dimethoxy-substituted o-aminobenzaldehydes, 3a,b, were prepared in two steps as outlined in Scheme 2.

Dimethoxy-substituted o-nitrobenzaldehydes of 2a and 2b were prepared by nitration of the corresponding dimethoxy-substituted benzaldehydes 1a,b, respectively. Because of the electron-withdrawing effects and less stability of the
aldehyde group in the strong acidic conditions, compounds 1a,b were found to give the expected products 2a,b in poor yields (less than 40%) at room temperature by using 70% nitric acid, the classic nitration method, as described in the literature [12]. We found that using nitric acid and acetic anhydride as solvent the yields of compounds 2a,b were remarkably improved (73–80%). The reaction of 1a under this condition gave compound 2a (73%) as yellow needles, whereas that of 1b gave a mixture of 2,5-dimethoxy-4-nitrobenzaldehyde (14%) and 3,6-dimethoxy-2-nitrobenzaldehyde 2b [13] (80%), which were separated and purified through a flash silica gel chromatographic column using petroleum ether/ethyl acetate (1:1, v/v) as solvent.

To selectively reduce the nitro group in 2a and 2b in the amino group, reagents, described in the literature such as Na2S2O4 [14], and FeSO4·7H2O–NH3·H2O [15], had been first attempted. However, we found that all reactions gave products in poor yields. It is worth to point out that, when FeSO4·7H2O–NH3·H2O was used, the reaction produced large amount of semisolid inorganic wastes and made the filtration process very difficult. We then attempted to use iron powder, which was able to selectively reduce the nitro group of 2a and 2b to give the corresponding amino products 3a (62%) and 3b (76%), respectively.

The condensation reaction of the dimethoxy-substituted aminoaldehydes 3a,b with cyclic ketones 4 in anhydrous ethanol, in the presence of catalytic amount of sodium ethoxide, yielded the expected six-member ring-fused quinolines 5a–j in high yields (Scheme 3; Table 1). Their structures were fully characterized by IR, 1H NMR, MS, and elemental analysis (see the Experimental).

**CONCLUSION**

We have reported an efficient method for the synthesis of novel quinoline derivatives 5a–j through the condensation reaction of dimethoxy-substituted aminoaldehydes 3a,b with cyclic ketones 4 via the Friedländer reaction. The experimental procedure is very simple. Our protocol can be applied to a wide range of substrates. These methods not only afford significant improvements in the reaction rates and yields but also present a more straightforward and easy work-up procedure. The anticancer activities of the new quinoline derivatives are currently under evaluation.

**EXPERIMENTAL**

**General**

Melting points were determined on a microscopic melting point apparatus (Kofler, Guangzhou, PRC) and were uncorrected. The IR spectra were recorded on a Perkin-Elmer 1730 FT-IR spectrometer using KBr films. The 1H NMR spectra were recorded on a Varian Inova 500 MHz in CDCl3 solutions using TMS as an internal standard. The mass spectra were obtained on a Shimadzu Qp5050A spectrometer. Elemental analysis was performed on an elemental Varioel spectrometer. 3,4-Dimethoxybenzaldehyde, 2,5-dimethoxybenzaldehyde, cyclic ketones, and
TABLE 1  Physical Data of Compounds 5a–j

| Compounds | R′′ | X     | Time (h) | Melting Point (°C) | Yield (%) |
|-----------|-----|-------|----------|-------------------|-----------|
| 5a        | H   | CH₃O  | NCOOCH₂CH₃ | 2               | 139–141   | 90        |
| 5b        | H   | CH₃O  | NCH₃     | 2               | 138–140   | 95        |
| 5c        | H   | CH₃O  | NCOCE₆H₅ | 1.5             | 135–138   | 75        |
| 5d        | H   | CH₃O  | S        | 1.5             | 117–119   | 90        |
| 5e        | H   | CH₃O  | O        | 2               | 140–142   | 90        |
| 5f        | CH₃O | H     | NCOOCH₂CH₃ | 2—               | 8         | 5         |
| 5g        | CH₃O | H     | NCH₃     | 2               | 145–146   | 90        |
| 5h        | CH₃O | H     | NCOC₆H₅ | 1.5             | 141–143   | 70        |
| 5i        | CH₃O | H     | S        | 2               | 134–136   | 95        |
| 5j        | CH₃O | H     | O        | 2               | 160–161   | 95        |

Preparation of 3,6-Dimethoxy-2-aminobenzaldehyde (3b). Compound 3b was prepared by following the same experimental procedure described for 3a. 3b was recrystallized from 95% ethanol, and a yellow solid 3b (1.60 g, yield 76%, mp 67–68°C (Lit. 67–68°C) [16]) was obtained. 1H NMR (500 MHz, CDCl₃), δ (ppm): 10.32 (s, 1H, CHO), 6.69 (d, 1H, J₄,₅= 8.7 Hz, H₄), 6.8–6.5 (br s, 2H, NH₂), 5.90 (d, 1H, H₅), 3.74 (s, 6H, OCH₃).

Preparation of 7,8-Dimethoxy-3,4-dihydro-1H-benzo[b][1,6]-naphthyridine-2-carboxylic Acid Ethyl Ester (5a). The compound was purified by flash silica gel chromatographic column (ethyl acetate/petroleum ether = 3:1, v/v) to give 5a as a white solid in yield of 90%. It has Rᵢ 0.30 (ethyl acetate/petroleum ether = 3/1, v/v), and mp 139–141°C. IR (KBr), ν (cm⁻¹): 2958, 1695, 1500, 1434, 1395, 893, 850. 1H NMR (500 MHz, CDCl₃), δ (ppm): 2.12 (t, J = 7.0 Hz, 3H, CH₃), 3.16 (t, J = 6.0 Hz, 2H, CH₂), 3.87 (t, J = 6.0 Hz, 2H, CH₂), 4.00 (s, 3H, OCH₃), 4.01 (s, 3H, OCH₃), 4.22–4.60 (m, J = 7.0 Hz, 2H, CH₂), 4.78 (s, 2H, CH₂), 6.98 (s, 1H, H-6), 7.34 (s, 1H, H-3), 7.72 (s, 1H, H-10). MS (m/z, %): 316 (M⁺, 18), 287 (100), 243 (19).
7,8-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-benzo-[b][1,6]napthyridine ([5b]). The compound was purified by flash chromatographic column (dichloromethane/ethanol = 4:1, v/v) to give 5b as a white solid in yield of 95%. It has \( R_t 0.40 \) (dichloromethane/ethanol = 4:1, v/v) and mp 138–140 °C. IR (KBr), \( \nu \) (cm\(^{-1}\)): 2938, 1624, 1503, 1464, 1395, 1251, 850. \(^1\)H NMR (500 MHz, CDCl\(_3\)), \( \delta \) (ppm): 2.53 (s, 3H, CH\(_3\)), 2.88 (t, \( J = 6.5 \) Hz, 2H, CH\(_2\)), 3.22 (t, \( J = 6.5 \) Hz, 2H, CH\(_2\)), 3.74 (s, 2H, CH\(_2\)), 4.00 (s, 3H, OCH\(_3\)), 4.02 (s, 3H, OCH\(_3\)), 6.96 (s, 1H, H-6), 7.33 (s, 1H, H-3), 7.63 (s, 1H, H-10). MS (m/z, %): 258 (M\(^+\), 60), 257 (100), 215 (44), 128 (23).

Anal. Calcld for C\(_{15}\)H\(_{20}\)N\(_2\)O\(_4\) (316.14), C, 64.54; H, 6.37; N, 8.86. Found: C, 64.16; H, 6.51; N, 8.58.

6,9-Dimethoxy-3,4-dihydro-1H-benzo[b][1,6]napthyridine-2-carboxylic Acid Ethyl Ester ([5f]). The compound was purified by flash chromatographic column (ethyl acetate/petroleum ether = 3:1, v/v) to give 5f as a yellow oil in yield of 85%. It has \( R_t 0.39 \) (ethyl acetate/petroleum ether = 3:1, v/v). IR (KBr), \( \nu \) (cm\(^{-1}\)): 2936, 1697, 1479, 1435, 1262, 1097, 725. \(^1\)H NMR (500 MHz, CDCl\(_3\)), \( \delta \) (ppm): 1.29 (t, \( J = 7.0 \) Hz, 3H, CH\(_3\)), 2.32 (t, \( J = 6.0 \) Hz, 2H, CH\(_2\)), 3.86 (t, \( J = 6.0 \) Hz, 2H, CH\(_2\)), 3.86 (s, 3H, OCH\(_3\)), 4.03 (s, 3H, OCH\(_3\)), 4.21–4.60 (m, \( J = 7.0 \) Hz, 2H, CH\(_2\)), 4.83 (s, 2H, CH\(_2\)), 6.70 (d, \( J = 8.5 \) Hz, 1H, H-10). 1H NMR (500 MHz, CDCl\(_3\)), \( \delta \) (ppm): 1.29 (t, \( J = 7.0 \) Hz, 3H, CH\(_3\)), 2.32 (t, \( J = 6.0 \) Hz, 2H, CH\(_2\)), 3.86 (t, \( J = 6.0 \) Hz, 2H, CH\(_2\)), 3.86 (s, 3H, OCH\(_3\)), 4.03 (s, 3H, OCH\(_3\)), 4.21–4.60 (m, \( J = 7.0 \) Hz, 2H, CH\(_2\)), 4.83 (s, 2H, CH\(_2\)), 6.70 (d, \( J = 8.5 \) Hz, 1H, H-10). 1H NMR (500 MHz, CDCl\(_3\)), \( \delta \) (ppm): 1.29 (t, \( J = 7.0 \) Hz, 3H, CH\(_3\)), 2.32 (t, \( J = 6.0 \) Hz, 2H, CH\(_2\)), 3.86 (t, \( J = 6.0 \) Hz, 2H, CH\(_2\)), 3.86 (s, 3H, OCH\(_3\)), 4.03 (s, 3H, OCH\(_3\)), 4.21–4.60 (m, \( J = 7.0 \) Hz, 2H, CH\(_2\)), 4.83 (s, 2H, CH\(_2\)), 6.70 (d, \( J = 8.5 \) Hz, 1H, H-10).

Anal. Calcld for C\(_{17}\)H\(_{20}\)N\(_2\)O\(_4\) (316.14), C, 64.54; H, 6.37; N, 8.86. Found: C, 64.53; H, 6.64; N, 8.56.

Anal. Calcld for C\(_{18}\)H\(_{20}\)N\(_2\)O\(_4\) (348.15), C, 72.40; H, 6.06; N, 8.56.
1622, 1479, 1435, 1264, 1077, 725. 1H NMR (500 MHz, CDCl₃), δ (ppm): 3.33 (s, 2H, CH₂), 3.95 (s, 2H, CH₂), 4.03 (s, 6H, 2OCH₃), 5.09 (s, 2H, CH₂), 6.72 (d, J = 8.5 Hz, 1H, H-1), 6.90 (d, J = 8.5 Hz, 1H, H-2). 7.44–7.47 (m, 5H, C₆H₅), 8.20 (s, 1H, H-10). MS (m/z, %): 349 (11), 348 (M⁺, 49), 333 (53), 213 (23), 200 (13), 105 (79), 77 (100).

Anal. Calcd for C₂₃H₂₂N₃O₈ (384.45), C, 64.34; H, 6.16; N, 5.71. Found: C, 63.87; H, 6.36; N, 5.55.

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