DOI: 10.1002/cjoc.201100420

Synthesis and Cyclization of 8-Formyl-2-(phenoxymethyl)-quinoline-3-carboxylic Acids

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A facile synthesis of a series of new quinoline-8-carbaldehyde compounds, namely 8-formyl-2-(phenoxymethyl)quinoline-3-carboxylic acids (**4a**—**4h**) and 13-oxo-6,13-dihydro[1]benzoxepino[3,4-*b*]quinoline-8-carbaldehyde (**5a**—**5g**) is described, involving the one-pot synthesis reaction of ethyl 2-(chloromethyl)-8-formylquinoline-3-carboxylate (**3**) with substituted phenols followed by the intramolecular cyclization reaction via the treatment with polyphosphoric acid (PPA). Quinoline-8-carbaldehydes **4a**—**4h** and **5a**—**5g** are novel and their structures were supported by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.

Keywords benzoxepinoquinoline, quinoline-8-carbaldehyde, one-pot, polyphosphoric acid (PPA), cyclization reaction

Introduction

The quinoline ring system is one of the most ubiquitous heterocycles in nature and an important structural component in many pharmaceutical agents.[1-3] Therefore synthesis and functionalization of quinolines has been a major area of focus for synthetic organic chemists.[4-6] Many functionalized quinolines scaffold in the framework of various pharmacologically active compounds have been recognized to show a spectrum of biological activities.[7,8] Among them, quinoline aldehydes derivatives exhibit potent pharmacological activities such as antibacterial and antioxidant.[9] Moreover, quinoline aldehydes are important synthetic intermediates in the synthesis of interesting quinoline heterocycles bearing diverse bioactivities such as antimicrobial, antituberculosis, antifungal activities.[10-12] For example, 2-chloro-3-formylquinolines have been extensively used as reactive species for building chemical diversity and for various functional group interconversions.[13-15]

On the other hand, a number of benzoxepine derivatives containing a fused heterocyclic ring were known to display an important structural unit present in many biologically important molecules such as doxaminol (vasodilator and *b*-sympathomimetic agent), isoxepac (anti-inflammatory agent), oxepinac (antiinflammatory, analgesic, antipyretic agent), and have been proven to be lead compounds for psychoactive drugs for the treatment of anxiety disorder, depression, and in particular schizophrenic Psychoses.[16,17] Therefore, such benzoxepino-fused heterocycles have attracted considerable attention from both medicinal and synthetic organic chemists in recent years.[18-21]

In light of the above reports and in diversifying our work on the synthesis of new quinoline compounds,[22-25] we would like to report herein a facile and inexpensive one-pot procedure for the preparation of 8-formyl-2-(phenoxymethyl)quinoline-3-carboxylic acid derivatives and subsequent intramolecular cyclization reaction to construct benzoxepino[3,4-*b*]quinoline framework.

Experimental

Melting points were determined with a WRS-1B melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance NMR spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. The reported chemical shifts (δ values) are given downfield from tetramethylsilane (TMS) as the internal standard. The mass spectra were determined using a MSD VL ESI1 spectrometer. Elemental analyses were performed for C, H, and N using an Elementar Vario EL-III element analyzer and were within $\pm$0.4% of the calculated values. The progress of reactions was monitored by thin layer chromatography (TLC) on silica gel GF254 using ethyl acetate as mobile phase.

Procedure for the preparation of ethyl 2-(chloromethyl)-8-formylquinoline-3-carboxylate (3)

A mixture of 2-aminobenzaldehyde (1 mmol, 0.121 g) and ethyl 4-chloroacetoacetate (1 mmol, 0.165 g) was added into Vilsmeier reagent (11 mL). The reaction

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Received September 28, 2011; accepted November 29, 2011; published online May 7, 2012.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc201100420 or from the author.

mixture was magnetically stirred at 90 ℃ for 1 h. After completion of the reaction (TLC), the mixture was cooled to room temperature, poured into ice-water and filtered to give the crude product. The resulting crude was recrystalized from 95% ethanol to afford ethyl 2-(chloromethyl)-8-formylquinoline-3-carboxylate (**3**) as a brown solid in 58% yield. m.p. 113—115 ℃; ^{1}H NMR (DMSO-d_6, 600 MHz) δ: 1.48 (t, J=6.6 Hz, 3H, CH_3), 4.49 (q, J=7.2 Hz, 2H, CH_2), 5.28 (s, 2H, Cl-CH_2-Ar), 7.62 (t, J=7.8 Hz, 1H, ArH), 7.83 (t, J=6.6 Hz, 1H, ArH), 7.91 (d, J=8.4 Hz, 1H, ArH), 8.12 (d, J=8.4 Hz, 1H, ArH), 8.82 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 14.20, 46.58, 61.87, 123.18, 126.66, 127.87, 128.47, 129.31, 132.05, 140.89, 148.30, 155.67, 165.66; IR (KBr) v: 3048, 2985, 1715 (C=O), 1617 (C=O) cm^{-1}; EI-MS *m/z* (%): 277.1 (M^+). Anal. calcd for $C_{14}H_{12}ClNO_3$: C 60.55, H 4.36, N 5.04; found C 60.53, H 4.32, N 4.98.

General procedure for the preparation of 8-formyl-2-(phenoxymethyl)quinoline-3-carboxylic acid derivatives (4a—4h)

A mixture of ethyl 2-(chloromethyl)-8-formylquinoline-3-carboxylate (**3**) (1 mmol, 0.278 g), each phenol (1 mmol) and K_2CO_3 (2.5 mmol, 0.346 g) was stirred in refluxing CH_3CN (15 mL). The conversion was monitored by TLC. After the reaction was complete, CH_3CN was evaporated to dryness. 60% Ethanolic potassium hydroxide solution (15 mL) was added to the reaction mixture and continued to reflux for 1 h, cooled, and acidified with 1 mol/L HCl solution. The resulting crude product was recrystallized from ethanol to afford the corresponding products **4**. Yields and melting points are indicated in Table 1.

8-Formyl-2-(phenoxymethyl)quinoline-3-carboxylic acid (4a)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 5.60 (s, 2H, OCH_2), 6.95 (t, J=7.2 Hz, 1H, ArH), 7.02 (d, J=8.4 Hz, 2H, ArH), 7.29 (t, J=7.2 Hz, 2H, ArH), 7.71 (t, J=7.8 Hz, 1H, ArH), 7.89—7.91 (m, 1H, ArH), 8.06 (d, J=8.4 Hz, 1H, ArH), 8.17 (d, J=7.8 Hz, 1H, ArH), 8.91 (s, 1H, CHO), 13.45 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 70.52, 114.79, 120.85, 125.03, 126.46, 127.75, 128.66, 128.98, 129.52, 131.94, 139.61, 147.35, 155.27, 158.73, 167.50; IR (KBr) v: 3450 (OH), 1703 (C=O), 1658 (C=O) cm^{-1}; ESI-MS *m/z*: 307.1 (M^+). Anal. calcd for $C_{18}H_{13}NO_4$: C 70.35, H 4.26, N 4.56; found C 70.42, H 4.18, N 4.52.

8-Formyl-2-[(4-methylphenoxy)methyl]quinoline-3-carboxylic acid (4b)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 2.22 (s, 3H, CH_3), 5.56 (s, 2H, OCH_2-Ar), 6.90 (d, J=8.4 Hz, 2H, ArH), 7.08 (d, J=8.4 Hz, 2H, ArH), 7.71 (t, J=7.8 Hz, 1H, ArH), 7.88—7.91 (m, 1H, ArH), 8.06 (d, J=8.4 Hz, 1H, ArH), 8.16 (d, J=7.8 Hz, 1H, ArH), 8.90 (s, 1H, CHO), 13.44 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 20.15, 70.63, 114.67, 125.06, 126.43, 127.71, 128.66, 128.95, 129.50, 129.83, 131.89, 139.52, 147.33, 155.39, 156.63, 167.52; IR (KBr) v: 3435 (OH), 1706 (C=O), 1614 (C=O) cm^{-1}; ESI-MS *m/z*: 321.1 (M^+). Anal. calcd for $C_{19}H_{15}NO_4$: C 71.02, H 4.71, N 4.36; found C 70.92, H 4.80, N 4.32.

8-Formyl-2-[(3-methylphenoxy)methyl]quinoline-3-carboxylic acid (4c)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 2.27 (s, 3H, CH_3), 5.56 (s, 2H, OCH_2-Ar), 6.76 (d, J=7.8 Hz, 1H, ArH), 6.80 (dd, J=8.4, 2.4 Hz, 1H, ArH), 6.84 (s, 1H, ArH), 7.16 (t, J=7.8 Hz, 1H, ArH), 7.71 (t, J=7.2 Hz, 1H, ArH), 7.89—7.91 (m, 1H, ArH), 8.07 (d, J=8.4 Hz, 1H, ArH), 8.17 (d, J=7.8 Hz, 1H, ArH), 8.90 (s, 1H, CHO), 13.42 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 21.18, 70.46, 111.67, 115.49, 121.61, 125.09, 126.45, 127.74, 128.65, 128.96, 129.24, 131.92, 138.97, 139.54, 147.32, 155.29, 158.73, 167.49; IR (KBr) v: 3400 (OH), 1703 (C=O), 1693 (C=O) cm^{-1}; ESI-MS *m/z*: 321.1 (M^+). Anal. calcd for $C_{19}H_{15}NO_4$: C 71.02, H 4.71, N 4.36; found C 71.19, H 4.56, N 4.40.

8-Formyl-2-[(2-methylphenoxy)methyl]quinoline-3-carboxylic acid (4d)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 2.13 (s, 3H, CH_3), 5.58 (s, 2H, OCH_2-Ar), 6.84 (t, J=7.2 Hz, 1H, ArH), 7.05 (d, J=8.4 Hz, 1H, ArH), 7.13 (t, J=6.6 Hz, 2H, ArH), 7.72 (t, J=7.8 Hz, 1H, ArH), 7.89—7.92 (m, 1H, ArH), 8.07 (d, J=8.4 Hz, 1H, ArH), 8.17 (d, J=8.4 Hz, 1H, ArH), 8.88 (s, 1H, CHO), 13.41 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 15.99, 70.75, 111.56, 120.46, 125.40, 126.02, 126.50, 126.95, 127.76, 128.67, 128.93, 130.44, 131.87, 139.35, 147.21, 155.39, 156.72, 167.72; IR (KBr) v: 3425 (OH), 1714 (C=O), 1628 (C=O) cm^{-1}; ESI-MS *m/z*: 321.1 (M^+). Anal. calcd for $C_{19}H_{15}NO_4$: C 71.02, H 4.71, N 4.36; found C 71.21, H 4.62, N 4.34.

8-Formyl-2-((3-methoxyphenoxy)methyl)quinoline-3-carboxylic acid (4e)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 3.72 (s, 3H, OCH_3), 5.58 (s, 2H, OCH_2-Ar), 6.52 (dd, J=7.8, 1.8 Hz, 1H, ArH), 6.58—6.60 (m, 2H, ArH), 7.18 (t, J=8.4 Hz, 1H, ArH), 7.71 (t, J=7.2 Hz, 1H, ArH), 7.90 (t, J=7.2 Hz, 1H, ArH), 8.07 (d, J=8.4 Hz, 1H, ArH), 8.17 (d, J=8.4 Hz, 1H, ArH), 8.91 (s, 1H, CHO), 13.45 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 70.52, 116.63, 124.16, 24.42, 126.65, 127.43, 128.55 129.04, 129.45, 132.21, 132.36, 139.67, 147.00, 154.40, 158.62, 167.74; IR (KBr) v: 3429 (OH), 1773 (C=O), 1705 (C=O) cm^{-1}; ESI-MS *m/z*: 337.1 (M^+). Anal. calcd for $C_{19}H_{15}NO_5$: C 67.65, H 4.48, N 4.15; found C 67.72, H 4.39, N 4.21.

2-((4-Chlorophenoxy)methyl)-8-formylquinoline-3-carboxylic acid (4f)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 5.61 (s, 2H, OCH_2-Ar), 7.04 (d, J=8.4 Hz, 2H, ArH), 7.32 (d, J=9.0 Hz, 2H, ArH), 7.71 (t, J=7.8 Hz, 1H, ArH),

7.88—7.91 (m, 1H, ArH), 8.04 (d, J=8.4 Hz, 1H, ArH), 8.17 (d, J=8.4 Hz, 1H, ArH), 8.93 (s, 1H, CHO), 13.47 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 70.82, 116.59, 124.50, 124.74, 126.44, 127.78, 128.65, 129.00, 129.25, 132.01, 139.79, 147.35, 154.94, 157.61, 167.36; IR (KBr) v: 3446 (OH), 1761 (C=O), 1697 (C=O) cm^{-1}; ESI-MS m/z: 341.1 (M^+). Anal. calcd for $C_{18}H_{12}ClNO_4$: C 63.26, H 3.54, N 4.10; found C 63.37, H 3.41, N 4.06.

2-((4-Bromophenoxy)methyl)-8-formylquinoline-3-carboxylic acid (4g)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 5.60 (s, 2H, OCH_2-Ar), 6.97—6.99 (m, 2H, ArH), 7.43—7.46 (m, 2H, ArH), 7.69—7.73 (m, 1H, ArH), 7.88—7.91 (m, 1H, ArH), 8.04 (d, J=8.4 Hz, 1H, ArH), 8.17 (d, J=7.8 Hz, 1H, ArH), 8.93 (s, 1H, CHO), 13.46 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 70.74, 112.21, 117.13, 124.74, 126.44, 127.79, 128.65, 129.01, 132.02, 132.14, 139.79, 147.34, 154.92, 158.06, 167.35; IR (KBr) v: 3428 (OH), 1780 (C=O), 1695 (C=O) cm^{-1}; ESI-MS m/z: 384.9 (M^+). Anal. calcd for $C_{18}H_{12}BrNO_4$: C 55.98, H 3.13, N 3.63; found C 55.86, H 3.26, N 3.59.

8-Formyl-2-((2-nitrophenoxy)methyl)quinoline-3-carboxylic acid (4h)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 5.83 (s, 2H, OCH_2-Ar), 7.10—7.13 (m, 1H, ArH), 7.48 (d, J=8.4 Hz, 1H, ArH), 7.60—7.63 (m, 1H, ArH), 7.70—7.73 (m, 1H, ArH), 7.87—7.91 (m, 2H, ArH), 7.99 (d, J=8.4 Hz, 1H, ArH), 8.18 (d, J=7.8 Hz, 1H, ArH), 8.98 (s, 1H, CHO), 13.45 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 71.74, 115.81, 120.78, 124.13, 124.94, 126.47, 127.86, 128.61, 129.10, 132.16, 134.34, 139.85, 140.34, 147.34, 151.71, 154.43, 166.90; IR (KBr) v: 3438 (OH), 1711 (C=O), 1630 (C=O) cm^{-1}; ESI-MS m/z: 351.9 (M^+). Anal. calcd for $C_{18}H_{12}N_2O_6$: C 61.37, H 3.43, N 7.95; found C 61.15, H 3.53, N 7.82.

General procedure for the preparation of 13-oxo-6,13–dihydro[1]benzoxepino[3,4-*b*]quinoline-8-carbaldehyde derivatives (5a—5g)

Quinolinic acids **4a—4g** (1 mmol) and 12 g PPA were added to 25 mL round flask and stirred at 125 ℃ for 3 h. Then the reaction mixture was poured slowly with stirring into an icy saturated sodium carbonate solution. The crude product was obtained after filtration and washed with water. The pure products **5a—5g** were obtained by recrystalization from 95% ethanol. Yields and melting points are indicated in Table 2.

13-Oxo-6,13–dihydro[1]benzoxepino[3,4-*b*]quinoline-8-carbaldehyde (5a)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 5.56 (s, 2H, OCH_2-Ar), 7.22 (d, J=8.4 Hz, 1H, ArH), 7.28 (t, J=7.8 Hz, 1H, ArH), 7.65—7.68 (m, 1H, ArH), 7.74 (t, J=7.2, 1H, ArH), 7.94—7.96 (m, 1H, ArH), 8.14 (d, J=8.4 Hz, 1H, ArH), 8.21 (dd, J=8.4, 1.8 Hz, 1H, ArH), 8.24 (d, J=7.8 Hz, 1H, ArH), 8.95 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 76.25, 120.94, 122.93, 125.34, 127.13, 127.88, 128.66, 129.69, 131.59, 132.29, 132.53, 136.12, 139.65, 148.35, 154.59, 160.96, 187.73; IR (KBr) v: 1701 (C=O), 1641 (C=O) cm^{-1}; ESI-MS m/z: 289.3 (M^+). Anal. calcd for $C_{18}H_{11}NO_3$: C 74.73, H 3.83, N 4.84; found C 74.84, H 3.71, N 4.80.

2-Methyl-13-oxo-6,13-dihydro[1]benzoxepino[3,4-*b*]-quinoline-8-carbaldehyde (5b)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 2.36 (s, 3H, CH_3), 5.51 (s, 2H, OCH_2-Ar), 7.11 (d, J=8.4 Hz, 1H, ArH), 7.47 (dd, J=8.4, 1.8 Hz, 1H, ArH), 7.74 (t, J=7.2 Hz, 1H, ArH), 7.93—7.96 (m, 1H, ArH), 7.99 (d, J=1.2 Hz, 1H, ArH), 8.13 (d, J=8.4 Hz, 1H, ArH), 8.24 (d, J=7.8, 1H, ArH), 8.94 (s, 1H, CHO); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 20.1, 76.33, 120.87, 125.03, 127.15, 127.87, 128.65, 129.68, 131.10, 131.99, 132.26, 137.00, 139.70, 148.33, 154.80, 159.11, 187.69; IR (KBr) v: 1689 (C=O), 1629 (C=O) cm^{-1}; ESI-MS m/z: 303.3 (M^+). Anal. calcd for $C_{19}H_{13}NO_3$: C 75.24, H 4.32, N 4.62; found C 75.36, H 4.29, N 4.58.

3-Methyl-13-oxo-6,13-dihydro[1]benzoxepino[3,4-*b*]-quinoline-8-carbaldehyde (5c)

^{1}H NMR ($CDCl_3$, 600 MHz) δ: 2.39 (s, 3H, CH_3), 5.48 (s, 2H, OCH_2-Ar), 6.96 (s, 1H, ArH), 7.01 (d, J=8.4 Hz, 1H, ArH), 7.63 (t, J=7.2 Hz ,1H, ArH), 7.84 (t, J=7.8 Hz, 1H, ArH), 7.98 (d, J=7.8 Hz, 1H, ArH), 8.14 (d, J=8.4 Hz, 1H, ArH), 8.22 (d, J=8.4 Hz, 1H, ArH), 8.83 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 21.51, 120.98, 123.36, 124.17, 127.59, 129.15, 129.19, 132.01, 132.07, 132.69, 139.85, 147.37, 148.96, 154.59, 161.53, 187.98; IR (KBr) v: 1709 (C=O), 1629 (C=O) cm^{-1}; ESI-MS m/z: 303.3 (M^+). Anal. calcd for $C_{19}H_{13}NO_3$: C 75.24, H 4.32, N 4.62; found C 75.18, H 4.40, N 4.57.

4-Methyl-13-oxo-6,13-dihydro[1]benzoxepino[3,4-*b*]-quinoline-8-carbaldehyde (5d)

^{1}H NMR ($CDCl_3$, 600 MHz) δ: 2.33 (s, 3H, CH_3), 5.52 (s, 2H, OCH_2-Ar), 7.08 (t, J=7.8 Hz, 1H, ArH), 7.42 (d, J=7.2 Hz, 1H, ArH), 7.62 (t, J=7.8 Hz, 1H, ArH), 7.84 (t, J=7.8 Hz, 1H, ArH), 7.97 (d, J=7.8 Hz, 1H, ArH), 8.14 (dd, J=8.4, 4.2 Hz, 2H, ArH), 8.81 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 16.54, 122.25, 125.79, 127.58, 129.14, 129.19, 129.78, 129.93, 132.01, 132.69, 136.72, 139.69, 148.99, 154.73, 159.79, 188.98; IR (KBr) v: 1716 (C=O), 1643(C=O) cm^{-1}; ESI-MS m/z: 303.3 (M^+). Anal. calcd for $C_{19}H_{13}NO_3$: C 75.24, H 4.32, N 4.62; found C 75.28, H 4.27, N 4.55.

3-Methoxy-13-oxo-6,13-dihydro[1]benzoxepino[3,4-*b*]quinoline-8-carbaldehyde (5e)

^{1}H NMR (DMSO-d_6, 600 MHz) δ: 3.84 (s, 3H, OCH_3); 5.51 (s, 2H, OCH_2-Ar), 6.70 (d, J=9.0 Hz, 1H, ArH), 6.85 (dd, J=9.0, 2.4 Hz, 1H, ArH), 7.70—7.73 (m, 1H, ArH), 7.91—7.94 (m, 1H, ArH), 8.11 (d, J=8.4 Hz, 1H, ArH), 8.16 (d, J=9.0 Hz, 1H, ArH), 8.22 (d, J=7.8 Hz, 1H, ArH), 8.92 (s, 1H, CHO); ^{13}C NMR

(DMSO-d_6, 150 MHz) δ: 56.02, 76.39, 103.80, 111.23, 118.86, 127.22, 127.83, 128.64, 129.62, 132.40, 133.49, 139.58, 148.24, 154.49, 163.06, 165.48, 185.94; IR (KBr) v: 1695 (C=O), 1598 (C=O) cm^{-1}; ESI-MS *m/z*: 319.3 (M^+). Anal. calcd for $C_{19}H_{13}NO_4$: C 71.47, H 4.10, N 4.39; found C 71.36, H 4.23, N 4.42.

2-Chloro-13-oxo-6,13-dihydro[1]benzoxepino[3,4-*b*]-quinoline-8-carbaldehyde (5f)

^{1}H NMR ($CDCl_3$, 600 MHz) δ: 5.49 (s, 2H, OCH_2-Ar), 7.12 (d, J=9.0 Hz, 1H, ArH), 7.48 (dd, J=8.4, 1.8 Hz, 1H, ArH), 7.65 (t, J=7.8 Hz, 1H, ArH), 7.86 (t, J=7.2 Hz, 1H, ArH), 7.99 (d, J=7.8 Hz, 1H, ArH), 8.15 (d, J=8.4 Hz, 1H, ArH), 8.28 (d, J=2.4 Hz, 1H, ArH), 8.83 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 122.82, 126.59, 127.52, 127.84, 128.38, 129.23, 129.27, 131.24, 132.01, 132.37, 135.49, 140.19, 149.14, 154.07, 160.05, 187.18; IR (KBr) v: 1675 (C=O), 1645 (C=O) cm^{-1}; ESI-MS *m/z*: 323.7 (M^+). Anal. calcd for $C_{18}H_{10}ClNO_3$: C 66.78, H 3.11, N 4.33; found C 66.70, H 3.20, N 4.30.

2-Bromo-13-oxo-6,13-dihydro[1]benzoxepino[3,4-*b*]-quinoline-8-carbaldehyde (5g)

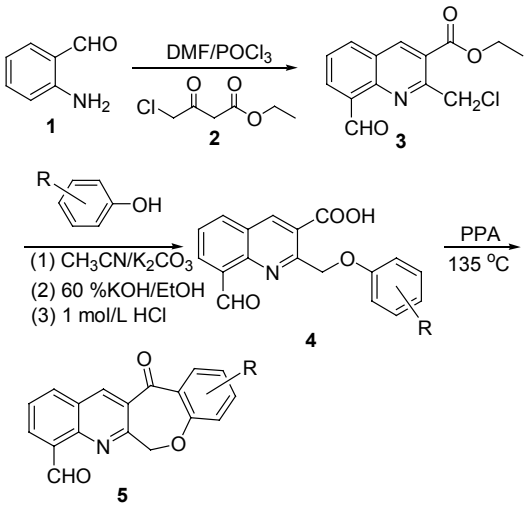
1H NMR ($CDCl_3$, 600 MHz) δ: 5.49 (s, 2H, OCH_2-Ar), 7.06 (d, J=8.4 Hz, 2H, ArH), 7.61 (d, J=8.4 Hz, 1H, ArH), 7.65 (t, J=7.2 Hz, 1H, ArH), 7.87 (t, J=7.2 Hz, 1H, ArH), 7.99 (d, J=8.4 Hz, 1H, ArH), 8.15 (d, J=8.4 Hz, 1H, ArH), 8.43 (s, 1H, ArH), 8.83 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 115.59, 123.13 126.99, 127.53, 127.85, 129.24, 129.27, 132.05, 132.38, 134.32, 138.33, 140.14, 149.15, 153.99, 160.54, 187.14; IR (KBr) v: 1679 (C=O), 1643 (C=O) cm^{-1}; ESI-MS *m/z*: 366.9 (M^+). Anal. calcd for $C_{18}H_{10}BrNO_3$: C 58.72, H 2.74, N 3.80; found C 58.86, H 2.68, N 3.76

Results and Discussion

The synthetic route developed in our laboratory for the preparation of 8-formyl-2-(phenoxymethyl) quinoline-3-carboxylic acid derivatives **4a**—**4h** and subsequent intramolecular Friedel-Crafts cyclization reaction to synthesize quinoline-fused 13-oxo-6,13-dihydro[1]-benzoxepino[3,4-*b*]quinoline-8-carbaldehyde derivatives **5a**—**5h** is summarized in Scheme 1.

Recently, our laboratory has reported a one-pot two-step reaction of bromomethyl- or chloromethyl-quinolines with substituted salicylaldehydes to give the corresponding quinoline carboxylic acid ethers as key precursors for heterocycle-fused quinoline compounds.[23,24] In order to continue our interest in the development of bioactive quinoline alkaloids, the objective of the present work is to extend the reaction of ethyl 2-(chloromethyl)-8-formylquinoline-3-carboxylates (**3**) with some substituted phenols, in which the presence of alhedhyde functional group may provide opportunity for further manipulation. The starting material **3** was prepared according to the method of literature.[26,27]

Scheme 1 Synthesis of the title compounds **4** and **5**



Chloromethylquinoline **3** was first subjected to the Williamson reaction with substituted phenols. Because the reaction product does not interfere with further hydrolysis reaction, purification at this stage is unnecessary. Thus, we simply added 60% aqueous ethanolic potassium hydroxide solution 15 mL to this reaction mixture under reflux. After the reaction was complete and acidified with 1 mol/L HCl, the major product was identified as 8-formyl-2-(phenoxymethyl) quinoline-3-carboxylic acid derivatives (**4a**—**4h**) as expected. For example, their ^{1}H NMR spectra showed the presence of a carboxylic OH signal at δ 13.41—13.47, which disappeared with the addition of D_2O. The singlet resonance at δ 8.88—8.93 was assigned to aldehyde proton (it did not disappear with the addition of D_2O). Moreover, the proposed structures of **4a**—**4h** were also confirmed by their ^{13}C NMR spectra, which revealed the presence of carboxyl carbon, formyl carbon, and methylene carbon besides the signals due to quinoline and benzene ring carbons. Further, the structures assigned for this reaction products were fully supported by their mass spectra, which showed the molecular ion (M^+) peak matching the expected molecular weight. Moreover, the obtained elemental analysis values were also in agreement with theoretical data. This novel one-pot procedure provides quick and easy access to the incorporation of quinoline acid with good yields and simple workup.

The next step involves the construction of the benzoxepinoquinolines from quinoline-3-carboxylic acids **4a**—**4h** as outlined in Scheme 1. The synthetic sequence employed in our laboratories for the preparation of the 13-oxo-6,13-dihydro[1]benzoxepino[3,4-*b*]-quinoline-8-carbaldehyde derivatives **5a**—**5h** mainly relied on the intramolecular Friedel-Crafts acylation reaction of **4**. Of the commonly available cyclization agents screened for the intramolecular cyclization (*e.g.* H_2SO_4, *p*-TsOH, $TiCl_4$, and P_2O_5), the use of polyphosphoric acid (PPA) was found to be the most suitable for this reaction as shown in Table 1.

In the reaction with concentrated H_2SO_4 (Entry 1),

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Table 1 Synthesis of **5a** using various cyclization agents

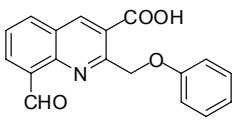
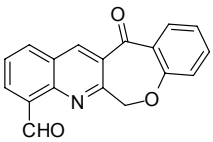
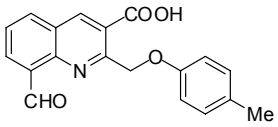
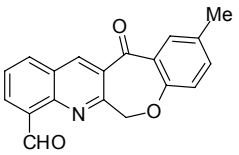
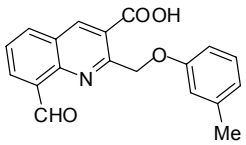
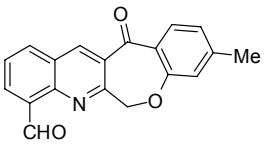
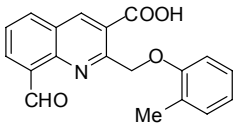
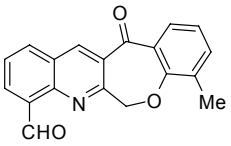
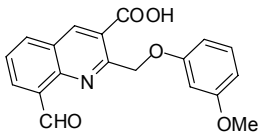
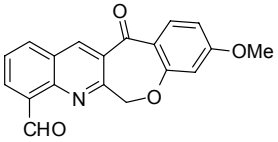
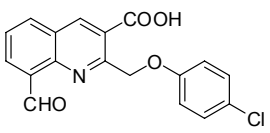
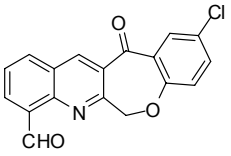
Entry	Agent	Time/h	Yield[a,b]/%
1	H_2SO_4	10	26
2	*p*-TsOH	10	17
3	$TiCl_4$	10	Trace
4	P_2O_5	10	20
5	PPA	3	67

[a] Isolated yields. [b] Reaction temperature at 125 ℃.

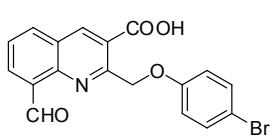
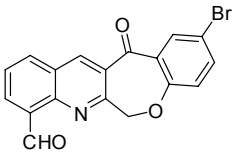
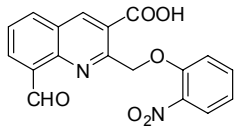
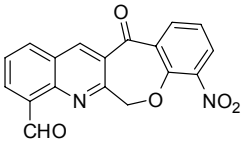
the cyclized product **5a** was obtained in a rather low yield (26%) after 10 h. Unfortunately, the yield could not be further improved when using either *p*-TsOH (Entry 2) or P_2O_5 (Entry 4), for which the desired product was isolated in lower yields of 17% and 20%, respectively. The reaction with $TiCl_4$ (Entry 3) was also found to be ineffective and only trace amounts of the product was observed. Moreover, in the cases of Entries 1—4, we could not further improve the yield by increasing the amount of the cyclization agent, reaction temperature or reaction time. Comparatively, upon using PPA as the cyclization reagent (Entry 5), the reaction was complete within 3 h as observed on TLC with the advantages of good yield, short reaction time, and high purity as well. In addition, there was no further improvement in the yield upon increasing the reaction time. As far as the amount of PPA is concerned, the use of 12 g PPA to 1 mmol of **4a** was found most suitable to provide maximum yield and there was no further improvement in the yield with increasing the amount of PPA. Some representative results are summarized in Table 2. The resulting 13-oxo-6,13-dihydro[1]benzo-xepino-[3,4-*b*]quinoline-8-carbaldehyde deriveatives **5a**—**5g** are novel and their structures were established based on spectral data and elemental analyses. All data were fully consistent with the assigned molecular structure (see Experimental Section).

As seen in Table **2**, the electronic nature of the substituents on phenols has no significant effect on the one-pot synthesis of 8-formyl-2-(phenoxymethyl) quinoline-3-carboxylic acids (**4a**—**4h**); all the 8-formyl-quinoline-3-carboxylic acid derivatives with electron-donating (Entries 2—5) or electron-withdrawing groups (Entries 6—8) were obtained in good yields, showing little distinction. On the other hand, as regards the cyclized quinoline-fused products 13-oxo-6,13-dihydro[1]benzo-

Table 2 Yields and physical properties of the compounds **4a**—**4h** and **5a**—**5h**

Entry	Compound **4**		Yield[a]/%	m.p./℃	Compound **5**		Yield[a]/%	m.p./℃
1		**4a**	71	166—167		**5a**	67	188—189
2		**4b**	77	165—166		**5b**	73	189—190
3		**4c**	80	164—165		**5c**	78	210—211
4		**4d**	69	173—174		**5d**	72	169—170
5		**4e**	74	182—184		**5e**	76	199—200
6		**4f**	86	232—233		**5f**	72	192—194

Continued

Entry	Compound **4**		Yield[a]/%	m.p./℃	Compound **5**		Yield[a]/%	m.p./℃
7		**4g**	66	264—265		**5g**	77	196—198
8		**4h**	71	174—175		**5h**	0	—

[a] Isolated yield.

xepino-[3,4-*b*]quinoline-8-carbaldehye (**5a**—**5h**), it seems that the effect of substitution groups of the precursors compounds **4a** — **4g** on the intramolecular Friedel-Crafts acylation reaction is not very strong; both the electron-donating (*e.g.*, Me, OMe) (Entries 2—5) and slightly electron-withdrawing (*e.g.*, Cl, Br) (Entries 6 and 7) groups worked well, showing little distinction. However, the intramolecular Friedel-Crafts acylation reaction failed when the strong electron-withdrawing groups such as nitro group were present (**4h**), and no formation of the expected cyclized product **5h** was detected, albeit the reaction temperature was enhanced and the reaction time was prolonged. A possible reason is that the presence of the strong electron-withdrawing group might render the benzene ring highly electron-deficient and retard reaction process. The ease of isolation of all the products was notable. After simple aqueous workup and recrystallization from ethanol, the corresponding products were isolated in analytically pure.

Conclusions

In conclusion, the present method offered a facile synthetic route to a variety of functionalized quinoline compounds 8-formyl-2-(phenoxymethyl)quinoline-3-carboxylic acid (**4a**—**4h**) and cyclized quinoline-fused products 13-oxo-6,13-dihydro[1]benzoxepino-[3,4-*b*]-quinoline-8-carbaldehye (**5a**—**5g**), which would provide new leads in the search for future drug candidates. Readily availability of starting material, short reaction times, experimental simplicity and satisfactory yields contribute to the usefulness of this method. Possible biological activity of the described compounds possessing the fused quinoline skeletons remains to be studied. In addition, due to the presence of aldehyde functional group, all the newly synthesized products represent potentially useful synthetic building blocks in medicinal chemistry.

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