Chlorotrimethylsilane-Mediated Friedländer Synthesis of 2-(α-Chloroalkyl)quinoline Derivatives

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Abstract: Condensation of 2-aminoacetophenone and 2-aminobenzophenone with ethyl 4-chloro-3-oxobutanoate in the presence of excess chlorotrimethylsilane was shown to give ethyl 2-chloromethyl-3-quinoline carboxylates in high yields. A similar reaction with 1,3-dichloroacetone and 2-chlorocyclohexanone led to the 3-chloro-2-(chloromethyl)quinolines and 4-chloro-1,2,3,4-tetrahydroacridines, respectively.

Key words: condensation, heterocycles, nitriles, quinolines, ring closure

Of late 2-(α-chloroalkyl)quinolines are important semiproducts in medicinal chemistry. Thus, they were reported to be key substances in the syntheses of several prospective analgesics,[1] anti-inflammatories,[2] tachykinin receptor[3] and peripheral benzodiazepine receptor[4] agonists. Moreover, Takeda Pharmaceutical has recently introduced a new potent antirheumatic drug referred as TAK-603,[5] the preparation of which also included a 2-chloromethylquinoline derivative as the key precursor. TAK-603 is required in bulk amounts on account of being in the final steps of clinical evaluation. So, the optimized procedure for its preparation together with the synthesis of the appropriate precursor in multi-kilogram scale has been developed.[5a] In light of these facts, elaboration of novel approaches to 2-(α-chloroalkyl)quinolines providing high yields and cheap starting materials becomes a very important task.

The known methods for the preparation of the title compounds can be divided into two principal subgroups. The first one includes introduction of the halogen into alkyl or alkenyl side chain of quinoline derivatives.[4b,6,7] Both direct halogenation[4b,6] and oxidation with further transformation of oxygen containing functionality into haloalkyl moiety[7] were described. The second group is based on quinoline ring formation from the suitable acyclic precursors bearing haloalkyl substituents.[1,2,4a,5,8–10] Among these methods, the Friedländer synthesis with ethyl 4-chloro-3-oxobutanoate (**1**; Figure 1) was the most frequently used.[2,4a,5,8] Furthermore, a cyclodimerization of 2-chloro-*N*-arylacetamides upon treatment with $POCl_3$ or PCl_5 should be mentioned.[9] Finally, an interesting recyclization

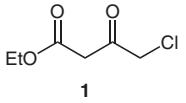

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Figure 1

of 2-(α-chloroalkyl)-3,1-benzoxazin-4-ones with lithiated acetamides was reported.[1,10]

Nevertheless, the Friedländer reaction with α-chloroketones remains the simplest and the most promising approach. However, its main drawback is, in fact, the single suitable and available reagent, the mentioned compound **1**. Hence, it would be interesting to find a way to extend the scope of the reaction to other chloroketones. In our previous work,[11] the chlorotrimethylsilane (TMSCl) was employed to carry out several unusual condensations including those with participation of α-chloroketones. Continuing the research in the field, we have now examined the application of TMSCl for the synthesis of 2-(α-chloroalkyl)quinolines, and the results obtained are reported herein.

To begin with, the condensation of aminoacetophenone **2a** and benzophenones **2b**,**c** with ethyl 4-chloro-3-oxobutanoate (**1**) in the presence of 4-fold excess TMSCl was performed. It was shown to give the expected quinoline hydrochloride **3a** and the known compounds **3d**,**f**[4a,8b] in 78–90% yields (Table 1). The yields of derivatives **3d**,**f** achieved in this reaction were 25–30% higher than those reported through the typical procedure.[4a,8b] So, prompted by this success we have studied the reactions of compounds **2** with 1,3-dichloroacetone and 2-chlorocyclohexanone, which have never been used previously in the Friedländer synthesis. In anhydrous DMF and in the presence of excess TMSCl, the reactions of both the chloroketones were found to proceed smoothly affording the quinoline hydrochlorides **3c**,**e**,**g** and the tetrahydroacridine derivatives **4a–c** in 75–85% yields. Moreover, in most cases, the products isolated from the reaction mixture were analytically pure and did not require further purification. The structures of the prepared compounds **3**,**4** were confirmed by ^1H and ^{13}C NMR spectroscopy. The spectral data observed for the derivatives **3d**,**f** were in complete agreement with the reported data.[4a,8b]

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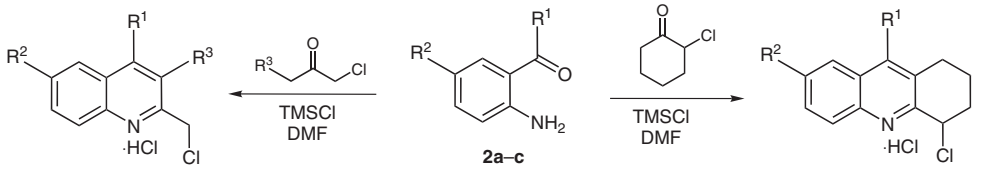
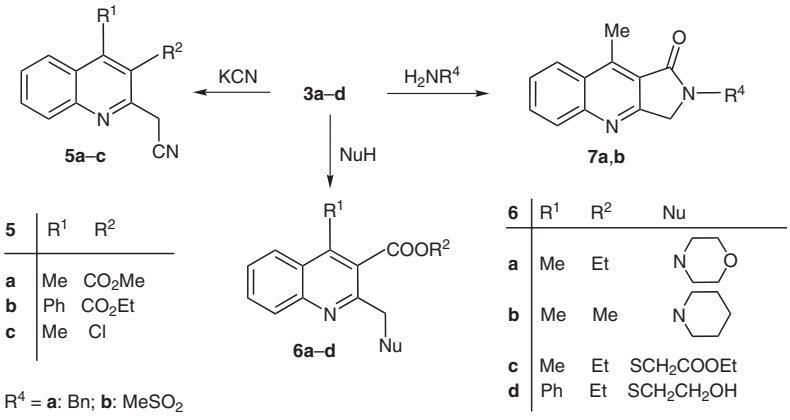
Table 1 R-Group Assignments for Compounds **2–4**



Compd	R^1	R^2	R^3	Yield (%)
2a	Me	H	–	–
2b	Ph	H	–	–
2c	Ph	Cl	–	–
3a	Me	H	CO_2Et	78
3b	Me	H	CO_2Me	79
3c	Me	H	Cl	82
3d	Ph	H	CO_2Et	95
3e	Ph	H	Cl	80
3f	Ph	Cl	CO_2Et	87
3g	Ph	Cl	Cl	84
4a	Me	H	–	75
4b	Ph	H	–	76
4c	Ph	Cl	–	78

The possibility of easy nucleophilic substitution of the chlorine in the derivatives **3** was demonstrated by several examples (Scheme 1). Thus, the nitriles **5a–c** were prepared by the reaction of compounds **3a–c** with potassium cyanide. Treatment of the derivatives **3a–d** with secondary amines and mercaptanes yielded the corresponding quinolines **6a–d**. Finally, reaction of the chloroesters **3a**,**b** with the nucleophiles containing primary amino group afforded the expected lactams **7a**,**b**. All these substitution reactions occurred in almost quantitative yields.

In summary, the present investigation has resulted in the simple and convenient procedure for the synthesis of 2-(α-chloroalkyl)quinolines. Application of the chlorotrimethylsilane as acidic catalyst and water scavenger in the Friedländer reaction allowed to extend its scope to certain α-chloroketones for the first time. In the case of ethyl 4-chloro-3-oxobutanoate (**1**) the use of TMSCl increased the yields significantly. The reported method provides access to new chloroalkylquinolines improving the preparation of the known compounds and is a useful tool in the field.



5	R^1	R^2
a	Me	CO_2Me
b	Ph	CO_2Et
c	Me	Cl

6	R^1	R^2	Nu
a	Me	Et	N O
b	Me	Me	N
c	Me	Et	SCH_2COOEt
d	Ph	Et	SCH_2CH_2OH

Scheme 1

All starting materials were commercially available. Commercial TMSCl was distilled. Commercial DMF was kept over P_2O_5 overnight and then distilled under reduced pressure. Other reagents were used without additional purification. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UNITYplus 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in DMSO-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si. *J* values are in Hz. The purity of all compounds obtained was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

Quinoline Hydrochlorides 3a–g and Acridine Hydrochlorides 4a–c; General Procedure

TMSCl (30.4 g, 0.28 mol) was added carefully in one portion to a stirred solution of compound **2a–c** (0.074 mol) and the appropriate chloroketone (0.074 mol) in DMF (20 mL). After the initial exothermic reaction had ceased, the mixture was heated for 1 h at 60–80 °C. Upon cooling, the mixture separated into two layers; the upper one, the hexamethyldisiloxane, was decanted. H_2O (15 mL) was added to the residue and the mixture was refrigerated. The solid precipitate was filtered and washed with cold *i*-PrOH to give the pure derivatives **3a**–**g** and **4a**–**c** (Table 1). If necessary, compounds **3**,**4** could be additionally purified by recrystallization from *i*-PrOH.

2-Chloromethyl-4-methyl-3-quinolinecarboxylic Acid Ethyl Ester Hydrochloride (3a)

Mp 144 °C (*i*-PrOH).

^{1}H NMR: δ = 1.43 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.89 (s, 3 H, CH_3), 4.47 (q, *J* = 7.2 Hz, 2 H, OCH_2), 4.94 (s, 2 H, CH_2Cl), 7.72 (t, *J* = 8.4 Hz, 1 H, 7-H), 7.85 (t, *J* = 8.4 Hz, 1 H, 6-H), 8.07 (d, *J* = 8.4 Hz, 1 H, 5-H), 8.20 (d, *J* = 8.4 Hz, 1 H, 8-H), 10.86 (br s, 1 H, N·HCl).

^{13}C NMR: δ = 15.5 (CH_3), 16.4 (CH_3), 46.1 (CH_2Cl), 62.6 (OCH_2), 125.7(6-C), 126.9 (7-C), 127.0 (5-C), 128.9 (4a-C), 129.3 (3-C), 132.1 (8-C), 145.7 (4-C), 145.9 (8a-C), 152.7 (2-C), 167.5 (COO).

Anal. Calcd for $C_{14}H_{14}ClNO_2$·HCl: C, 56.02; H, 5.04; N, 4.67; Cl, 23.62. Found: C, 56.10; H, 5.24; N, 4.60; Cl, 23.61.

2-Chloromethyl-4-methyl-3-quinolinecarboxylic Acid Methyl Ester Hydrochloride (3b)

Mp 149 °C (*i*-PrOH).

^{1}H NMR: δ = 2.72 (s, 3 H, CH_3), 4.00 (s, 3 H, OCH_3), 4.91 (s, 2 H, CH_2Cl), 7.71 (dd, *J* = 8.4, 7.6 Hz, 1 H, 7-H), 7.84 (dd, *J* = 8.0, 7.6 Hz, 1 H, 6-H), 8.03 (d, *J* = 8.0 Hz, 1 H, 5-H), 8.19 (d, *J* = 8.4 Hz, 1 H, 8-H), 10.46 (br s, 1 H, N·HCl).

^{13}C NMR: δ = 16.5 (CH_3), 46.4 (CH_2Cl), 53.6 (OCH_3), 125.7 (6-C), 126.6 (7-C), 126.9 (5-C), 128.9 (4a-C), 129.4 (3-C), 132.1 (8-C), 145.6 (4-C), 146.1 (8a-C), 152.8 (2-C), 168.1 (COO).

Anal. Calcd for $C_{13}H_{12}ClNO_2$·HCl: C, 54.57; H, 4.58; N, 4.89; Cl, 24.78. Found: C, 54.48; H, 4.43; N, 4.80; Cl, 24.70.

3-Chloro-2-chloromethyl-4-methylquinoline Hydrochloride (3c)

Mp 101–102 °C (*i*-PrOH).

^{1}H NMR: δ = 2.92 (s, 3 H, CH_3), 4.95 (s, 2 H, CH_2Cl), 7.81 (dd, *J* = 8.4, 7.2 Hz, 1 H, 7-H), 7.96 (dd, *J* = 8.0, 7.2 Hz, 1 H, 6-H), 8.30 (d, *J* = 8.0 Hz, 1 H, 5-H), 8.43 (d, *J* = 8.4 Hz, 1 H, 8-H), 10.51 (br s, 1 H, N·HCl).

^{13}C NMR: δ = 16.8 (CH_3), 46.8 (CH_2Cl), 125.4 (5-C), 125.7 (6-C), 127.3 (4a-C), 128.7 (7-C), 129.0 (8-C), 132.1 (3-C), 143.4 (4-C), 144.6 (8a-C), 156.0 (2-C).

Anal. Calcd for $C_{11}H_9Cl_2N$·HCl: C, 50.32; H, 3.84; N, 5.33; Cl, 40.51. Found: C, 50.40; H, 3.96; N, 5.17; Cl, 40.32.

2-Chloromethyl-4-phenyl-3-quinolinecarboxylic Acid Ethyl Ester Hydrochloride (3d)

Mp 75 °C (*i*-PrOH) (Lit.[8b] mp 75–76 °C).

The spectral data were in agreement with those reported.[8b]

3-Chloro-2-chloromethyl-4-phenylquinoline Hydrochloride (3e)

Mp 143–144 °C (*i*-PrOH).

^{1}H NMR: δ = 5.03 (s, 2 H, CH_2Cl), 7.34 (d, *J* = 6.8 Hz, 2 H, C_6H_5, 2,6-H), 7.40 (d, *J* = 8.4 Hz, 1 H, 5-H), 7.53–7.62 (m, 4 H, 7-H + C_6H_5, 3,4,5-H), 7.79 (t, *J* = 8.4 Hz, 1 H, 6-H), 8.09 (d, *J* = 8.4 Hz, 1 H, 8-H), 9.84 (br s, 1 H, N·HCl).

^{13}C NMR: δ = 46.7 (CH_2Cl), 126.4 (6-C), 126.8 (5-C), 128.2 (4a-C), 129.2 (7-C), 129.4 (C_6H_5, 4-CH), 129.5 (C_6H_5, 2,6-CH), 129.7 (C_6H_5, 3,5-CH), 129.8 (8-C), 131.0 (C_6H_5, 1-C), 135.2 (3-C), 145.8 (4-C), 147.4 (8a-C), 154.0 (2-C).

Anal. Calcd for $C_{16}H_{11}Cl_2N$·HCl: C, 59.20; H, 3.73; N, 4.31; Cl, 32.76. Found: C, 59.30; H, 3.51; N, 4.35; Cl, 32.79.

6-Chloro-2-chloromethyl-4-phenyl-3-quinolinecarboxylic Acid Ethyl Ester Hydrochloride (3f)

Mp 108–109 °C (*i*-PrOH) (Lit.[8b] mp 110 °C).

The spectral data were in agreement with those reported.[8b]

3,6-Dichloro-2-chloromethyl-4-phenylquinoline Hydrochloride (3g)

Mp 122–123 °C (*i*-PrOH).

^{1}H NMR: δ = 5.02 (s, 2 H, CH_2Cl), 7.29 (s, 1 H, 5-H), 7.34 (d, *J* = 6.8 Hz, 2 H, C_6H_5, 2,6-H), 7.61 (m, 3 H, C_6H_5, 3,4,5-H), 7.76 (d, *J* = 8.8 Hz, 1 H, 7-H), 8.10 (d, *J* = 8.8 Hz, 1 H, 8-H), 10.56 (br s, 1 H, N·HCl).

^{13}C NMR: δ = 46.5 (CH_2Cl), 124.9 (5-C), 128.0 (4a-C), 128.6 (7-C), 129.0 (C_6H_5, 4-CH), 129.6 (C_6H_5, 2,6-CH), 129.8 (8-C), 131.5 (C_6H_5, 3,5-CH), 132.0 (C_6H_5, 1-C), 133.7 (6-C), 134.5 (3-C), 144.3 (4-C), 146.7 (8a-C), 154.7 (2-C).

Anal. Calcd for $C_{16}H_{10}Cl_3N$·HCl: C, 53.52; H, 3.09; N, 3.90; Cl, 39.49. Found: C, 53.50; H, 3.15; N, 3.73; Cl, 39.65.

4-Chloro-1,2,3,4-tetrahydro-9-methylacridine Hydrochloride (4a)

Mp 114–115 °C (*i*-PrOH).

^{1}H NMR: δ = 2.13 (m, 1 H, 2-H), 2.26 (m, 1 H, 3-H), 2.38 (m, 2 H, 2,3-H), 2.80 (s, 3 H, CH_3), 2.90 (m, 1 H, 1-H), 3.21 (m, 1 H, 1-H), 6.00 (m, 1 H, 4-H), 7.82 (dd, *J* = 8.4, 7.6 Hz, 1 H, 6-H), 7.99 (dd, *J* = 8.4, 7.6 Hz, 1 H, 7-H), 8.37 (d, *J* = 8.4 Hz, 1 H, 8-H), 8.46 (d, *J* = 8.4 Hz, 1 H, 5-H), 10.47 (br s, 1 H, N·HCl).

^{13}C NMR: δ = 16.0 (CH_3), 16.7 (2-CH_2), 25.5 (1-CH_2), 30.1 (3-CH_2), 55.4 (4-CHCl), 123.0 (7-C), 125.8 (8a-C), 128.0 (6-C), 129.6 (9a-C), 129.7 (8-C), 133.6 (5-C), 138.6 (9-C), 151.5 (10a-C), 154.9 (4a-C).

Anal. Calcd for $C_{14}H_{14}ClN$·HCl: C, 62.70; H, 5.64; N, 5.22; Cl, 26.44. Found: C, 62.56; H, 5.73; N, 5.30; Cl, 26.22.

4-Chloro-1,2,3,4-tetrahydro-9-phenylacridine Hydrochloride (4b)

Mp 182–183 °C (*i*-PrOH).

^{1}H NMR: δ = 1.91 (m, 1 H, 2-H), 2.14 (m, 1 H, 3-H), 2.4 (m, 2 H, 2,3-H), 2.73 (m, 2 H, 1-CH_2), 5.91 (m, 1 H, 4-CHCl), 7.25 (d, *J* = 6.0 Hz, 1 H, 8-H), 7.36 (dd, *J* = 6.8, 6.0 Hz, 1 H, 7-H), 7.42 (m, 1 H, C_6H_5, 4-H), 7.59 (m, 4 H, C_6H_5, 2,3,5,6-H), 7.89 (dd, *J* = 7.6, 6.8 Hz, 1 H, 6-H), 8.38 (d, *J* = 7.6 Hz, 1 H, 5-H), 10.17 (br s, 1 H, N·HCl).

^{13}C NMR: δ = 17.2 (2-CH_2), 27.0 (1-CH_2), 31.0 (3-CH_2), 57.1 (4-CHCl), 124.8 (7-C), 125.4 (8-C), 126.7 (8a-C), 127.9 (6-C), 129.1 (C_6H_5, 2,6-CH), 129.4 (C_6H_5, 4-CH), 129.6 (C_6H_5, 3,5-CH), 129.8 (9a-C), 132.6 (C_6H_5, 1-C), 135.3 (5-C), 141.5 (9-C), 153.6 (10a-C), 153.8 (4a-C).

Anal. Calcd for $C_{19}H_{16}ClN$·HCl: C, 69.10; H, 5.19; N, 4.24; Cl, 21.47. Found: C, 68.93; H, 5.18; N, 4.49; Cl, 21.57.

4,7-Dichloro-1,2,3,4-tetrahydro-9-phenylacridine Hydrochloride (4c)

Mp 171–172 °C (*i*-PrOH).

^{1}H NMR: δ = 1.87 (m, 1 H, 2-H), 2.14 (m, 1 H, 3-H), 2.37 (m, 2 H, 2,3-H), 2.66 (m, 2 H, 1-CH_2), 5.59 (s, 1 H, 4-CHCl), 7.19 (s, 1 H, 8-H), 7.39 (d, *J* = 7.0 Hz, 2 H, C_6H_5, 2,6-H), 7.60 (m, 3 H, C_6H_5, 3,4,5-H), 7.76 (d, *J* = 8.4 Hz, 1 H, 6-H), 8.10 (d, *J* = 8.4 Hz, 1 H, 5-H), 10.45 (br s, 1 H, N·HCl).

^{13}C NMR: δ = 17.5 (2-CH_2), 27.3 (1-CH_2), 31.8 (3-CH_2), 60.1 (4-CHCl), 123.1 (8-C), 124.6 (8a-C), 128.3 (6-C), 129.3 (C_6H_5, 2.6-CH), 129.4 (C_6H_5, 4-CH), 129.7 (C_6H_5, 3,5-CH), 130.6 (9a-C), 131.0 (C_6H_5, 1-C), 132.7 (7-C), 135.5 (5-C), 143.8 (9-C), 148.5 (10a-C), 156.2 (4a-C).

Anal. Calcd for $C_{19}H_{15}Cl_2N$·HCl: C, 62.57; H, 4.42; N, 3.84; Cl, 29.16. Found: C, 62.50; H, 4.51; N, 3.85; Cl, 29.35.

2-Quinolineacetonitriles 5a–c; General Procedure

Powdered KCN (0.5 g, 8.7 mmol) was added to a solution of **3a–c** (4 mmol) in DMF (10 mL) and the resulting mixture was stirred for 3 h at 45 °C. The inorganic materials were removed by filtration and the solvent was evaporated to dryness in vacuo. The residue was treated with H_2O (30 mL), filtered, and recrystallized from *i*-PrOH to yield derivatives **5a–c**.

2-Cyanomethyl-4-methyl-3-quinolinecarboxylic Acid Methyl Ester (5a)

Yield: 0.94 g (98%); mp 101–102 °C (*i*-PrOH).

^{1}H NMR: δ = 2.72 (s, 3 H, CH_3), 4.00 (s, 3 H, OCH_3), 4.18 (s, 2 H, CH_2), 7.71 (dd, *J* = 8.4, 7.6 Hz, 1 H, 7-H), 7.84 (dd, *J* = 8.0, 7.6 Hz, 1 H, 6-H), 8.03 (d, *J* = 8.0 Hz, 1 H, 5-H), 8.19 (d, *J* = 8.4 Hz, 1 H, 8-H).

^{13}C NMR: δ = 16.3 (CH_3), 26.6 (CH_2), 53.6 (OCH_3), 118.1 (CN), 125.7 (6-C), 126.2 (4a-C), 126.6 (7-C), 128.5 (5-C), 129.8 (3-C), 132.0 (8-C), 145.1 (4-C), 147.0 (8a-C), 148.4 (2-C), 168.3 (COO).

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.90; H, 4.87; N, 11.60.

2-Cyanomethyl-4-phenyl-3-quinolinecarboxylic Acid Ethyl Ester (5b)

Yield: 1.20 g (95%); mp 90–91 °C (*i*-PrOH).

^{1}H NMR: δ = 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.99 (q, *J* = 7.2 Hz, 2 H, OCH_2), 4.45 (s, 2 H, CH_2CN), 7.34 (d, *J* = 6.0 Hz, 1 H, 5-H), 7.53–7.56 (m, 5 H, 6,7-H + C_6H_5), 7.84 (m, 2 H, C_6H_5), 8.11 (d, *J* = 8.4 Hz, 1 H, 8-H).

^{13}C NMR: δ = 13.9 (CH_3), 23.3 (CH_2), 62.0 (OCH_2), 118.4 (CN), 126.1 (C_6H_5, 2,6-CH), 126.5 (5-C), 127.0 (4a-C), 129.1 (C_6H_5, 4-CH), 129.2 (6-C), 129.4 (7-C), 129.6 (C_6H_5, 3,5-CH), 129.7 (8-C), 132.0 (C_6H_5, 1-C), 135.6 (3-C), 147.2 (4-C), 148.5 (8a-C), 153.1 (2-C), 167.3 (COO).

Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.71; H, 5.05; N, 9.02.

3-Chloro-4-methyl-2-quinolineacetonitrile (5c)

Yield: 0.84 g (97%); mp 107–108 °C (*i*-PrOH).

^{1}H NMR: δ = 2.92 (s, 3 H, CH_3), 4.45 (s, 2 H, CH_2), 7.81 (dd, *J* = 8.4, 7.2 Hz, 1 H, 7-H), 7.96 (dd, *J* = 8.0, 7.2 Hz, 1 H, 6-H), 8.30 (d, *J* = 8.0 Hz, 1 H, 5-H), 8.43 (d, *J* = 8.4 Hz, 1 H, 8-H).

^{13}C NMR: δ = 15.7 (CH_3), 26.6 (CH_2), 117.4 (CN), 124.5 (6-C), 126.6 (7-C), 127.6 (4a-C), 128.0 (5-C), 129.5 (8-C), 130.4 (3-C), 142.8 (4-C), 144.9 (8a-C), 149.1 (2-C).

Anal. Calcd for $C_{12}H_9ClN_2$: C, 66.52; H, 4.19; N, 12.93; Cl, 16.36. Found: C, 66.50; H, 4.13; N, 12.86; Cl, 16.40.

2-(Aminomethyl)quinolines 6a,b; General Procedure

A solution of compound **3a**,**b** (0.016 mol) and the corresponding amine (0.05 mol) in DMF (20 mL) was stirred for 4 h at 50 °C. The solvent was removed in vacuo and the residue was treated with H_2O (20 mL) to give an oily material which slowly solidified over the course of a day. It was filtered and recrystallized from an appropriate solvent to afford derivatives **6a**,**b**.

4-Methyl-2-(4-morpholinylmethyl)-3-quinolinecarboxylic Acid Ethyl Ester (6a)

Yield: 4.02 g (80%), mp 153 °C (*i*-PrOH).

^{1}H NMR: δ = 1.43 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.50 (m, 4 H, NCH_2), 3.95 (m, 4 H, OCH_2), 4.47 (q, *J* = 7.2 Hz, 2 H, OCH_2), 4.75 (s, 2 H, CH_2N), 7.75 (dd, *J* = 8.4, 7.6 Hz, 1 H, 7-H), 7.92 (dd, *J* = 8.4, 7.6 Hz, 1 H, 6-H), 8.12 (d, *J* = 8.4 Hz, 1 H, 5-H), 8.25 (d, *J* = 8.4 Hz, 1 H, 8-H).

^{13}C NMR: δ = 14.4 (CH_3), 16.3 (CH_3), 52.5 (NCH_2), 58.1 (2-CH_2), 62.7 (OCH_2), 63.7 (2 OCH_2), 125.5 (6-C), 125.9 (7-C), 126.4 (4a-C), 128.5 (5-C), 129.5 (3-C), 131.8 (8-C), 145.2 (4-C), 145.9 (8a-C), 147.5 (2-C), 167 (COO).

Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.83; H, 6.85; N, 9.14.

4-Methyl-2-(1-piperidinylmethyl)-3-quinolinecarboxylic Acid Methyl Ester (6b)

Yield: 4.19 g (88%); mp 75 °C (MeOH).

^{1}H NMR: δ = 1.41–1.48 (m, 6 H, 3 CH_2), 2.30 (m, 4 H, NCH_2), 2.68 (s, 3 H, CH_3), 3.79 (s, 2 H, CH_2N), 3.94 (s, 3 H, OCH_3), 7.70 (dd, *J* = 8.5, 8.0 Hz, 1 H, 7-H), 7.84 (dd, *J* = 8.5, 8.0 Hz, 1 H, 6-H), 8.03 (d, *J* = 8.5 Hz, 1 H, 5-H), 8.20 (d, *J* = 8.5 Hz, 1 H, 8-H).

^{13}C NMR: δ = 15.6 (CH_3), 24.1 (CH_2), 25.7 (2CH_2), 52.0 (OCH_3), 54.2 (2 NCH_2), 64.9 (2-CH_2N), 125.3 (6-C), 126.5 (3-C), 126.9 (4a-C), 127.0 (7-C), 130.0 (5-C), 130.7 (8-C), 142.2 (4-C), 146.4 (8a-C), 156.9 (2-C), 168.8 (COO).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.46; H, 7.50; N, 9.46.

2-[(2-Ethoxy-2-oxoethyl)thio]methyl-4-methyl-3-quinolinecarboxylic Acid Ethyl Ester (6c)

Powdered K_2CO_3 (31 g, 0.22 mol) was added to a solution of compound **3a** (30 g, 0.10 mol) and ethyl mercaptoacetate (14 g, 0.10 mol) in DMF (70 mL) and the resulting mixture was stirred for 4 h at 40 °C. The solvent was removed in vacuo and the residue was treated with H_2O (50 mL) to give an oil. It was taken into $CHCl_3$ (50 mL), and the $CHCl_3$ layer was washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and evaporated to dryness in vacuo to yield the pure compound **6c** as an oil; yield: 32.96 g (95%).

^{1}H NMR: δ = 1.21 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.44 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 3.37 (s, 2 H, CH_2), 4.10 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.18 (s, 2 H, CH_2), 4.47 (q, *J* = 7.2 Hz, 2 H, OCH_2), 7.55 (t, *J* = 7.8 Hz, 1 H, 7-H), 7.70 (t, *J* = 7.8 Hz, 1 H, 6-H), 8.00 (m, 2 H, 5,8-H).

^{13}C NMR: δ = 14.2 (CH_3), 14.3 (CH_3), 15.9 (CH_3), 33.7 (SCH_2), 37.4 (SCH_2), 61.0 (OCH_2), 62.0 (OCH_2), 124.5 (6-C), 126.0 (7-C),

126.2 (4a-C), 127.3 (3-C), 129.5 (5-C), 130.6 (8-C), 143.4 (4-C), 146.4 (8a-C), 154.0 (2-C), 168.0 (COO), 170.1 (COO).

Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03; S, 9.23. Found: C, 62.08; H, 6.10; N, 4.10; S, 9.26.

2-[(2-Hydroxyethyl)thio]methyl-4-phenyl-3-quinolinecarboxylic Acid Ethyl Ester (6d)

Powdered K_2CO_3 (2.3 g, 0.016 mol) was added to a solution of compound **3d** (3.0 g, 0.008 mol) and mercaptoethanol (0.55 mL, 0.008 mol) in DMF (10 mL), and the resulting mixture was stirred for 3 h at 80 °C. The solvent was removed in vacuo, the residue was treated with H_2O (30 mL), filtered, and recrystallized from *i*-PrOH to give **6d**; yield: 2.88 g (98%); mp 100 °C (*i*-PrOH).

^{1}H NMR: δ = 0.81 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.57 (t, *J* = 7.2 Hz, 2 H, SCH_2), 3.51 (m, 2 H, CH_2OH), 3.99 (q, *J* = 7.2 Hz, 2 H, OCH_2), 4.12 (s, 2 H, CH_2S), 4.77 (t, *J* = 3.5 Hz, 1 H, OH), 7.34 (d, *J* = 6.0 Hz, 1 H, 5-H), 7.53–7.56 (m, 5 H, 6,7-H + C_6H_5), 7.84 (m, 2 H, C_6H_5), 8.11 (d, *J* = 8.4 Hz, 1 H, 8-H).

^{13}C NMR: δ = 14.0 (CH_3), 34.5 (SCH_2), 37.0 (SCH_2), 61.1 (OCH_2), 61.6 (OCH_2), 125.5 (5-C), 126.5 (2,6-C_{R1}), 126.9 (3-C), 128.2 (C_6H_5, 3,5-CH), 129.0 (6-C), 129.3 (7-C), 129.6 (4a-C), 129.7 (C_6H_5, 4-CH), 131.6 (C_6H_5, 1-C), 135.9 (8-C), 147.2 (4-C), 147.8 (8a-C), 156.1 (2-C), 167.9 (COO).

Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.64; H, 5.76; N, 3.81; S, 8.73. Found: C, 68.80; H, 5.56; N, 3.72; S, 8.51.

Pyrrolo[3,4-*b*]quinolin-1-ones 7a,b; General Procedure

Powdered K_2CO_3 (2.3 g, 0.016 mol) was added to a solution of compound **3a** or **3b** (0.0075 mol) and benzylamine (0.8 g, 0.0075 mol) or methanesulfonamide (0.7 g, 0.0075 mol) in DMF (10 mL). The resulting mixture was stirred for 4 h at 100 °C. The solvent was evaporated in vacuo, the residue was treated with H_2O (20 mL), filtered, and recrystallized from *i*-PrOH to yield **7a**,**b**.

2-Benzyl-2,3-dihydro-9-methyl-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (7a)

Yield: 1.79 g (83%); mp 149 °C (*i*-PrOH).

^{1}H NMR: δ = 3.03 (s, 3 H, CH_3), 4.36 (s, 2 H, CH_2), 4.75 (s, 2 H, CH_2), 7.27 (m, 1 H, C_6H_5, 4-H), 7.32 (m, 4 H, C_6H_5, H), 7.61 (t, *J* = 7.5 Hz, 1 H, 6-H), 7.79 (t, *J* = 7.5 Hz, 1 H, 7-H), 7.97 (d, *J* = 7.5 Hz, 1 H, 8-H), 8.19 (d, *J* = 7.5 Hz, 1 H, 5-H).

^{13}C NMR: δ = 12.1 (CH_3), 46.0 (CH_2), 50.6 (CH_2), 120.6 (8a-C), 125.7 (7-C), 127.0 (6-C), 127.8 (8-C), 128.1 (C_6H_5, 4-CH), 128.5 (C_6H_5, 3,5-CH), 129.4 (C_6H_5, 2,6-CH), 129.6 (5-C), 131.5 (C_6H_5, 1-C), 137.7 (9a-C), 145.5 (9-C), 148.7 (4a-C), 160.9 (3a-C), 167.2 (1-CO).

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.71. Found: C, 79.20; H, 5.40; N, 9.49.

2,3-Dihydro-9-methyl-2-methylsulfonyl-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (7b)

Yield: 1.80 g (87%); mp 245–246 °C (*i*-PrOH).

^{1}H NMR: δ = 3.12 (s, 3 H, CH_3), 3.47 (s, 3 H, CH_3), 4.90 (s, 2 H, CH_2), 7.75 (t, *J* = 8.5 Hz, 1 H, 6-H), 7.78 (t, *J* = 8.5 Hz, 1 H, 7-H), 8.10 (d, *J* = 8.5 Hz, 1 H, 8-H), 8.38 (d, *J* = 8.5 Hz, 1 H, 5-H).

^{13}C NMR: δ = 12.7 (CH_3), 41.0 (SO_2CH_3), 50.8 (CH_2), 119.3 (8a-C), 126.4 (7-C), 127.6 (6-C), 127.7 (8-C), 129.8 (5-C), 133.0 (9a-C), 149.2 (9-C), 149.8 (4a-C), 159.9 (3a-C), 166.8 (1-C=O).

Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.50; H, 4.40; N, 10.18; S, 11.43.

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