Quinoline-3-carboxylates as potential antibacterial agents

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Abstract The ethyl-2-chloroquinoline-3-carboxylates, **4**, were achieved from *o*-aminobenzophenones in two steps. i.e. initially, the ethyl-2-oxoquinoline-3-carboxylates, **3**, were obtained by base-catalyzed Friedlander condensations of *o*-aminobenzophenones, **1**, and diethylmalonate, **2**. The 2-chloroquinoline-3-carboxylates, **4**, were then obtained by the reaction with POCl₃ in good yields. The chemical structures were confirmed by FTIR, mass and ¹H-NMR spectroscopic techniques. All the synthesized compounds were tested for their in vitro antibacterial activity against *Bacillus subtilis* and *Vibrio cholera* and found to possess moderate activity.

Keywords Quinolines · Friedlander synthesis · Antibacterial activity

Introduction

Quinoline heterocycles occur widely among medicinally important natural products. Several natural products possessing quinoline moiety exhibit interesting biological and pharmacological properties, such as antimalarial [1, 2], antibacterial [3], anti-asthmatic, antihypertensive, anti-inflammatory [4], immunosuppressive activity [5], antileishmanial activity [6], and anticancer [7] properties. In addition, quinolines have been employed in the study of bioorganic and bioorganometallic processes [8]. These properties turn quinolines into very interesting targets for organic chemists, and several strategies for their synthesis have been developed including Skraup [9],

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Doebner-Von Miller [10], Friedlander [11, 12], Pfitzinger [13], Conard–Limpach [14] and Combes [15] methods. Among these methods, the Friedlander approach, involving an aromatic o-aminoaldehyde or ketone and a carbonyl compound containing reactive α -methylene functionality, is the most efficient one.

A number of methods involving metal salts, Lewis acids, and Brønsted acid catalysts [16, 17] have been commonly employed for the quinolines following Friedlander synthesis. However, the above procedures are unsatisfactory with regard to cost of the reagent, drastic reaction conditions, operational simplicity, and very low yield. Friedländer reactions are generally carried out by refluxing an alcoholic solution or an organic solvent. Therefore, a general and efficient method is still needed for the preparation of these important quinolines and and the search continues to find a better and improved methodology.

In recent decades, chemists have focused much attention on environmentally friendly reactions. In continuation of our interest in carbon–carbon and carbon–nitrogen bond formation reaction [18–24] and environmentally benign reactions, in the present study the titled compounds were obtained in excellent yields by the Friedlander approach and chlorination method. However, in this paper, solvent-free neat reaction under catalytic amounts of piperidine as a base catalyst is reported. The experimental results indicate the formation of the corresponding quinolines with good to excellent yields.

Results and discussion

The 2-chloro-3-carboxylatequinolines were synthesized in two steps involving different *o*-amino arylaldehydes or ketones. Initially, when *o*-amino arylaldehyde or ketone reacted with diethylmalonate formed keto esters (**3a**–**f**) (Table 1) by Friedlander annulations. Purified keto esters (**1a**–**f**) were then allowed to react with phosphorous oxychloride to give the corresponding 2-chloro-3-carboxylatequinolines (**4a**–**f**) (Table 2). The 2-chloro-3-carboxylatequinolines has been achieved by a simple and an efficient route in good yields. Products of the reaction have been isolated, purified, and characterized by various spectral techniques such as IR, HRMS, ¹H NMR, and ¹³C NMR techniques. Antibacterial screening was carried out for all the synthesized compounds. The screened compounds showed moderate activity against the *Bacillus subtilis* and *Vibrio cholera*.

The HRMS of compounds **3** and **4** showed a molecular ion peak M^+ in the positive mode. The molecular ion peak for **3a** was observed at m/z = 326.8033. This was evidenced from HRMS analysis of other compounds, **3b–f**. In the IR spectrum, the initially formed keto esters **3a–f** gave the ester carbonyl frequencies, 1,743–1,715 cm⁻¹ and carbonyl frequencies around 1,650 cm⁻¹, the NH group of keto esters appeared at 3,452–3,413 cm⁻¹, whereas in chloroesters, **4a–f** obtained from **3a–f** gave IR frequencies corresponding to ester carbonyls around 1,730 cm⁻¹ confirming the reaction between the keto carbonyl group of **3a–f** and POCl₃ with the formation of 2-chloroquinolines. In ¹H NMR compound **3a–f**, the NH peak appears as singlet between 12.32 and 12.88 ppm which disappears in **4a–f**, and in ¹³C NMR

$\begin{array}{c} R'' \\ R' \\ N_{1} \\ N_{2} \end{array} + \begin{array}{c} COOC_{2}H_{5} \\ COOC_{2}H_{5} \end{array}$		$\begin{array}{c} \text{Piperidine} \\ \hline 180 \text{ °C} \\ \hline R \\ R \\$		0C₂H₅
1	2		3	
R	R′	R″	Yield ^a % 3	mp °C
Н	Cl	C_6H_5	90	215-218
Н	Н	CH ₃	70	228-230
Н	Cl	2-Cl-C ₆ H ₄	80	195–198
Н	Cl	2-F-C ₆ H ₄	80	178-180
Br	Br	Н	85	229–232
Н	Cl	4-F-C ₆ H ₄	88	203-206
		$ \begin{array}{c} $	$\begin{array}{c} R'' \\ R \\ R \\ R' \\ R'' \\ R'' \\ \hline R \\ R' \\ R'$	$\begin{array}{c} R'' \\ R \\ R$

 Table 1
 Friedlander reaction of o-aminoarylcarbonyls and diethylmalonate in the formation of ethyl-2-oxoquinoline-3-carboxylate, 3

1 (1 mmol), 2 (1.2 mmol), piperidine two drops, reflux at 180 °C

^a Isolated yield of 3

Table 2Conversion of ethyl-2-oxoquinoline-3-carboxylate, 3into ethyl-2-chloroquinoline-3-carboxylate, 3ylate, 4

$\begin{array}{c} R' \\ R' \\ \downarrow \\ R \\ R \\ R \\ \end{array}$	POCl ₃ R' reflux	$R'' COOC_2H_5$ $N CI$ R 4
Product	Yield ^a %	mp °C
4a	85	98–100
4b	50	78–80
4c	60	98–101
4d	70	108–110
4e	80	>300
4f	80	108–111

3 (1 mmol), $POCl_3$, reflux in water bath

^b Isolated yield of 4

spectra, compound **3a–f**, the cyclic amide carbonyl peaks appeared between δ at 158.2–158.6 ppm which was shifted upfield region δ at 147.9–148.6 ppm after chorination which is confirmed the formation of the products.

Almost all the compounds showed moderate activity against both *B. subtilis* and *V. cholera*. The activity data generated are tabulated in Table 3.

Titled compounds organisms	Microorganisms zone of inhibition (mm)		
	Bacillus subtilis	Vibrio cholera	
3a	15	15	
3b	7	13	
3c	11	7	
3d	15	8	
3e	17	11	
3f	13	10	
4a	16	16	
4b	9	12	
4c	12	12	
4d	8	14	
4e	12	15	
4f	10	13	
Streptomycin	31	26	

Experimental section

Materials and methods

Chemicals were purchased from Aldrich Chemical (India) and used as such without further purification. Completion of the reaction was performed by thin layer chromatography. Melting points were taken in open capillary tubes and corrected with benzoic acid as reference. IR spectra of compounds (KBr pellets) were recorded on Nucon Infrared spectrophotometer. ¹H NMR (300, 400, and 500 MHz) and ¹³C NMR (75, 100, and 125 MHz) spectra were recorded on a different Bruker NMR spectrometer, respectively, in CDCl₃.

Synthesis of 2-oxo-3-carboxylatequinoline derivatives (3a-f)

A mixture of 2-amino-5-chlorobenzophenone **1a** (231 mg, 1 mmol) and diethylmalonate **2** (192 mg, 1.2 mmol) and catalytic amount of piperidine were taken into the RB-flask. The mixture was heated under reflux at 180 °C and the reaction was monitored by TLC. After completion, the reaction mixture was poured into the water, and extracted with ethyl acetate, concentrated under reduced pressure. The crude product was then purified by silica gel column (using petroleum ether and ethyl acetate) as eluant. The desired product, **3a**, obtained was characterized by IR, HRMS, ¹H and ¹³C NMR techniques. The reaction of substituted 2-aminoarylketones **1a–f** with diethylmalonate **2** gave the product of 2-chloro-3-carboxylatequinolines, **3a–f** (Table 1).

The spectral data of compounds, 3a-f, is given below

Table 3Antibacterialactivity of 3a-f and 4a-f

Ethyl 6-chloro-1,2 -dihydro-2-oxo-4-phenylquinoline-3-carboxylate **3a**). Pale yellow, mp 215–218 °C; IR (film) 3,445 (NH), 1,743 (COOEt), 1,650 (CO), 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.42 (t, 3H, J = 7 Hz), 4.51 (q, 2H, J = 7 Hz), 7.10–8.00 (m, 8H), 12.35 (s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 158.7, 147.8, 137.9, 133.8, 131.9, 129.6, 129.5, 129.1, 129.0, 128.8, 128.1, 126.7, 126.2, 120.1, 118.3, 61.2, 13.97. HRMS [EI, M⁺] calcd for C₁₈H₁₄ClNO₃ *m*/*z* 327.7617 found 326.8033.

Ethyl 1,2-dihydro-4-methyl-2-oxoquinoline-3-carboxylate (**3b**). Pale brown, mp 225–230 °C; IR (film) 3,452 (NH), 1,732 (COOEt), 1,651 (CO), cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (t, 3H, J = 7 Hz), 1.7 (s, 3H), 4.39 (q, 2H, J = 7 Hz), 7.2–7.6 (m, 4H), 12.32 (s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.9, 158.2, 146.9, 129.2, 128.4, 127.8, 126.3, 125.6, 120.7, 117.8, 61.7, 14.1, 13.94. HRMS [EI, M⁺], calcd for C₁₃H₁₃NO₃ *m/z* 231.0895 found 231.0892.

Ethyl 6-chloro-4-(2-chlorophenyl)-1,2-dihydro-2-oxoquinoline-3-carboxylate (**3c**). Pale yellow, mp 193–198 °C, IR (film) 3,439 (NH), 1,715 (COOEt), 1,653, 757, 605 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.43 (t, 3H, J = 7 Hz), 4.32 (q, 2H, J = 7 Hz), 7.05–7.81 (m, 7H), 12.88 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 165.4, 158.2, 147.3, 137.5, 132.9, 132.1, 129.9, 129.3, 128.7, 128.6, 128.1, 127.6, 126.9, 126.3, 120.5, 117.9, 61.6, 14.0 ppm. HRMS [EI, M⁺] calcd for C₁₈H₁₃Cl₂NO₃ *m*/*z*.361.0272 found 361.0268.

Ethyl 6-chloro-4-(2-fluorophenyl)-1,2-dihydro-2-oxoquinoline-3-carboxylate (**3d**). Pale yellow, mp 174–180 °C; IR (film) 3,413 (NH), 1,715 (COOEt), 1,652, 1,092, 758 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.12 (t, 3H, J = 7 Hz), 4.28 (q, 2H, J = 7 Hz), 6.92–7.80 (m, 7H), 12.45 (s, 1H) ppm; ¹³C NMR (125 MHz, CDCl3) δ 165.1, 158.6, 147.8, 137.9, 133.1, 132.7, 130.1, 129.8, 128.9, 128.4, 128.1, 127.4, 126.6, 126.2, 120.3, 118.3, 61.1, 14.0 ppm. HRMS [EI, M⁺] calcd for C₁₈H₁₃ClFNO₃ *m/z* 345.0568 found 345. 0498.

Ethyl 6,8-dibromo-1,2-dihydro-2-oxoquinoline-3-carboxylate (**3e**). Pale yellow, mp 228–232 °C, IR (film) 3413 (NH), 1715 (COOEt), 1652, 1092, 758 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.08 (t, 3H, J = 7 Hz), 4.21 (q, 2H, J = 7 Hz), 7.28 (s, 1H), 7.46 (s, 1H), 8.12 (s, 1H), 12.80 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 165.7, 158.6, 147.2, 137.9, 132.3, 132.6, 129.7, 129.2, 120.7, 117.6, 61.2, 13.89 ppm. HRMS [EI, M⁺] calcd. for C₁₂H₉Br₂NO₃ *m/z* 374.8949 found 374.8929.

Ethyl 6-chloro-4-(4-fluorophenyl)-1,2-dihydro-2-oxoquinoline-3-carboxylate (**3f**). White solid, mp 204–206 °C, IR (film) 3,413 (NH), 1,715 (COOEt), 1,652, 1,092, 758 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.02 (t, 3H, J = 7 Hz), 4.12 (q, 2H, J = 7 Hz), 7.10–7.60 (m, 7H), 12.80 (s, 1H) ¹³C NMR (75 MHz, CDCl₃) δ 165.3, 158.4, 147.5, 137.5, 133.3, 132.9, 130.4, 129.4, 128.7, 128.7, 128.2, 127.8, 126.8, 126.3, 120.6, 117.9, 61.3, 13.96 ppm. HRMS [EI, M +] calcd for C₁₈H₁₃ClFNO₃ *m/z*, calculated 345.0568 found 345.0632.

Synthesis of ethyl-2-chloroquinoline-3-carboxylate derivatives (4a-f)

A mixture of ethyl-6-chloro-1,2-dihydro-2-oxo-4-phenylquinoline-3-carboxylate **3a** (327 mg, 1 mmol) and POCl₃ (93 μ l, 1 mmol) was taken in a RB flash and refluxed in water bath for 5–7 h. The reaction complection was monitored by TLC using

petroleum ether and ethylacetate mixture as eluent. The reaction mixture was allowed to cool, poured into a crushed ice taken in a beaker stirred well for 15 min and then filtered to get the products 4a-f (Table 2).

Ethyl 2, 6-*dichloro-4-phenylquinoline-3-carboxylate* (**4a**). White solid, mp 98–100 °C; IR (film) 1,736, 1,556, 1,483, 1,386, 1,214, 1,145, 761, 713 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.94 (t, 3H, J = 7 Hz), 4.10 (q, 2H, J = 7 Hz), 7.42–7.45 (m, 3H), 7.59–7.61 (m, 2H), 7.95–7.98 (m, 2H), 8.1 (d, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) d 165.8 (C=O), 148.1 (C–Cl), 147.3, 138.6, 136.6, 131.8 × 2, 129.4 × 2, 125.5 × 2, 124.3 × 2, 123.8, 122.9 × 2, 62.1 (CH₂), 13.6 (CH₃) ppm.;. HRMS [EI, M⁺] calcd for C₁₈H₁₃Cl₂NO₂ *m/z* 345.0323, found 346.1923.

Ethyl 2-chloro-4-methylquinoline-3-carboxylate (**4b**). Brown solid, mp 78–80 °C; IR (film) 1,723, 1,619, 1,573, 1,453, 1,390, 1,243, 755 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.14 (t, 3H, J = 7 Hz), 2.3 (s, 3H), 4.24 (q, 2H, J = 7 Hz), 7.5–7.8 (m, 3H), 8.09 (d, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) d 165.1 (C=O), 147.9 (C–Cl), 147.5, 136.4, 130.8, 125.8, 124.7, 123.4, 122.7, 62.4 (CH₂), 16.4 (CH₃), 13.2 (CH₃) ppm.; HRMS [EI, M⁺] calcd for C₁₃H₁₂ClNO₂ m/z 249.6929, found 248.8972.

Ethyl 2,6-*dichloro-4*-(2-*chlorophenyl*)*quinoline-3-carboxylate* (**4c**). White solid, mp 98–101 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.09 (t, 3H, J = 7 Hz), 4.17 (q, 2H, J = 7 Hz), 7.2–7.3 (m, 2H), 7.5–7.6 (m, 2H), 7.8 (m, 2H), 8.1 (d, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃)) d 164.9 (C=O), 148.6 (C–Cl), 147.9, 138.4, 136.7, 131.6 × 2, 129.7 × 2, 125.6 × 2, 124.6 × 2, 123.7, 122.5 × 2, 62.4 (CH₂), 13.9 (CH₃) ppm; HRMS [EI, M⁺] calcd for C₁₈H₁₂Cl₃NO₂ *m/z* 378.9934, found 378.6372.

Ethyl 2,6-*dichloro-4-(2-fluorophenyl)quinoline-3-carboxylate* (**4d**). White solid, mp 108–110 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.14 (t, 3H, J = 7 Hz), 4.26 (q, 2H, J = 7 Hz), 7.2–7.6 (m, 6H); 8.1 (m, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) d 164.4 (C=O), 148.2 (C–Cl), 147.4, 138.7, 136.3, 131.5 × 2, 129.3 × 2, 125.9 × 2, 124.3 × 2, 123.9, 122.2 × 2, 62.7 (CH₂), 13.6 (CH₃) ppm; HRMS [EI, M⁺] calcd for C₁₈H₁₂Cl₂FNO₂ *m/z* 363.0229, found 362.0724.

Ethyl 6,8-*dibromo-2-chloroquinoline-3-carboxylate* (4e). White solid, mp > 300 °C; IR (film) 1,711, 1,634, 1,573, 1,487, 1,408, 1,242, 1,031, 748 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.11 (t, 3H, J = 7 Hz), 4.21 (q, 2H, J = 7 Hz), 8.1 (s, 1H), 8.7 (s. 1H), 9.2 (s, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) d 165.1 (C=O), 147.9 (C–Cl), 147.5, 138.4, 136.4, 130.8, 125.8, 124.7, 123.4, 122.7, 62.4 (CH₂), 13.2 (CH₃) ppm.; HRMS [EI, M⁺] calcd for C₁₂H₈Br₂ClNO₂ *m*/ *z* 390.8610, found 390.8112.

Ethyl 2-chloro-4-(4-fluorophenyl)-3-quinolinecarboxylate (**4f**). White solid, mp 108–111 °C; IR (film) 1,722, 1,605, 1,557, 1,492, 1,400, 1,227, 1,024, 768 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.09 (t, 3H, J = 7 Hz), 4.17 (q, 2H, J = 7 Hz), 7.2–7.3 (m, 2H), 7.3–7.4 (m, 2H), 7.5–7.6 (m, 2H), 7.8 (m, 1H), 8.1 (m, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) d 165.5 (C=O), 163.1 (C–F), 147.9 (C–Cl), 147.5, 145.8, 131.4, 131.2, 130.3, 128.9 × 2, 127.8, 127.7, 126.4, 125.7, 115.6 × 2, 62.0 (CH₂), 13.7 (CH₃) ppm. HRMS [EI, M⁺] calcd for C₁₈H₁₃ClFNO₂ *m/z* 329.0619, found 329.0612.

Antibacterial activity

Antibacterial activity of all these compounds was determined by agar well diffusion method, as recommended by the National Committee for Clinical Laboratory Standards against *B. subtilis* (Gram-positive) and *V. cholera* (Gram-negative) micro organisms at 100 μ g/mL concentration, using dimethyl sulfoxide (DMSO) as solvent. The bacterial were sub-cultured on Mueller–Hinton agar medium. Standard Streptomycin was also screened under similar conditions at a concentration of 100 μ g/mL for comparison. Solvent condition also maintained under similar conditions.

Conclusions

In conclusion, a simple and efficient procedure for the synthesis of 2-chloro-3carboxylatequinoline derivatives (**4a–f**), using piperidine as a base catalyst via Friedlander annulations is reported. The advantage of this method includes the use of inexpensive reagents and catalyst, and operational simplicity. All the synthesized compounds were tested for their in vitro antibacterial activity. These compounds showed moderate activity against some bacteria such as *B. subtilis* and *V. cholera*.

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