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Synthesis and Antibacterial Activity of Substituted Quinoline Derivatives

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An efficient and convenient method is reported for the synthesis of various substituted quinolines through the condensation of *o*-amino aryl carbonyls with ketones containing an active methylene group in the presence of $CuSO_4 \cdot 5H_2O$ as catalyst at room temperature to yeild substituted quinolines (**3a-l**). All the synthesized compounds were fully characterized and screened for their antibacterial activities.

Keywords: Substituted quinolines, Antibacterial activity, *o*-Aminoarylketone.

INTRODUCTION

Quinoline is a common structural unit found in many natural products with remarkable pharmacological properties. Members of this family have wide applications in medicinal chemistry [1-3]. The classical methods for the synthesis of quinolines, such as Scrup, Doebner-von Miller, Doebner, Combes, Pfitzinger quinoline syntheses, require harsh reaction conditions and the yields are unsatisfactory in most cases. The Friedlander annulations are the simplest, most straightforward synthetic method for the synthesis of quinoline derivatives, especially for the highly substituted 3-quinoline carboxylic esters [4,5]. This method usually involves acid- or base-catalyzed or thermal (up to 250 °C) condensation between a 2-aminoaryl ketone or aldehyde and a secondary carbonyl compound possessing a reactive α-methylene group, followed by cyclodehydration.

Friedlander reported quinoline synthesis in 1882 by the condensation of *o*-aminobenzaldehyde with acetaldehyde in the presence of sodium hydroxide. Acid catalysts such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid and phosphoric acids are widely used for this conversion. However, many of these classical methods require high temperatures, prolonged reaction times and drastic conditions and the yields reported are unsatisfactory due to the formation of several side products [6-9]. Therefore, new catalytic systems are being continuously explored in search of improved efficiencies and cost effectiveness. However in recent times iodine, Lewis acids such as $ZnCl_2$ and $AuCl_3 \cdot 3H_2O$, a combination of acidic catalysts [*e.g.*, $NaAuCl_4$, $Bi(OTf)_3$, $Nd(NO_3)_3 \cdot 6H_2O$] and microwave Even some of these methods also suffer from harsh reaction conditions, low yields, high temperature, tedious work-up and the use of stoichiometric and relatively expensive reagents [10-15]. As a part of our continuing efforts towards the development of useful synthetic methodologies, we planned to develop a new method for the synthesis of quinolines and its novel derivatives *via* Friedlander annulation approach catalyzed by copper sulphate. We observed high efficiency of $CuSO_4 \cdot 5H_2O$ (20 mol %) in sequential condensation/annulation reactions of *o*-aminoaryl carbonyls and ketones containing an active methylene group for the synthesis of substituted quinolines.

EXPERIMENTAL

All the used reactants, reagents and solvents were obtained from commercial sources and were of analytical grade. Melting points were determined by open capillary method. ^{1}H NMR (DMSO-d_6 300, 500 MHz) and ^{13}C NMR (DMSO-d_6, 300 MHz) were recorded on spectrometer TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument.

General procedure for the synthesis of ethyl 2-methyl-4-phenylquinoline-3-carboxylate (3a): A mixture of 2-amino-5-chlorobenzophenone (0.231 g, 1.00 mmol), ethyl 4-chloro-3-oxobutanoate (0.164 g, 1.00 mmol) and $CuSO_4 \cdot 5H_2O$ (0.049 g, 0.2 mmol, 20 mol %) in ethanol (10 mL) was stirred at room temperature for 3-4 h. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under vacuum. EtOAc (40 mL), was added to the crude product and washed with water (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using EtOAc:hexane (1:10) to

afford the pure product **3a** as a pale yellow coloured solid (0.294 g, 82 %). m.p. 100-103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J* = 6.79 Hz), 2.79 (s, 3H), 4.07 (q, 2H, *J* = 6.79 Hz), 7.33-7.53 (m, 6H), 7.59 (dd, 1H, *J* = 8.30 Hz, *J* = 1.51 Hz), 7.67-7.78 (m, 1H), 8.08 (d, 1H, *J* = 8.30 r Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.5, 23.7, 61.2, 125.0, 126.3, 126.4, 127.3, 128.1, 128.3, 128.7, 129.2, 130.1, 135.6, 146.1, 147.6, 154.5, 168.3; ESI-MS: *m/z* 292 (M^++H); HRMS calculated for $C_{19}H_{17}NO_2$ (M^++H) 292.1332, found 292.1323.

9-Phenyl-3,4-dihydroacridin-l(2*H*)-one (3b): m.p. 152-154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20-2.30 (m, 2H), 2.70 (t, 2H, *J* = 5.99 Hz), 3.38 (t, 2H, *J* = 5.99 Hz), 8.12 (d, 2H, *J* = 5.99 Hz), 7.36-7.57 (m, 5H), 7.71-7.81 (m, 1H), 8.06 (d, 1H, *J* = 8.99 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.31, 34.53, 40.57, 126.37, 127.42, 127.48, 127.94, 128.02, 128.17, 128.37, 131.69, 137.57, 148.57, 151.39, 162.18, 197.94; ESI-MS: *m/z* 296 (M^++Na), 274 (M^++H); HRMS (ESI) calculated for $C_{19}H_{16}NO$ (M^++H) 274.1226, found 274.1227.

1-(2-Methyl-4-phenylquinolin-3-yl)ethanone (3c): m.p. 110-112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.67 (s, 3H), 7.31-7.71 (m, 8H), 8.03 (d, 1H, *J* = 9.06 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.81, 31.86, 124.98, 126.08, 126.44, 128.64, 128.82, 129.98, 134.77, 135.15, 143.85, 147.48, 153.47, 205.56; ESI-MS: *m/z* 284 (M^++Na), 262 (M+H); HRMS (ESI) calculated for $C_{18}H_{15}NONa$ (M^++Na) 284.1045, found 284.1055 and calculated for $C_{18}H_{16}NO$ (M^++H) 262.1226, found 262.1235.

Ethyl 2-(chloromethyl)-4-phenylquinoline-3-carboxylate (3d): m.p. 105-106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.17 Hz), 4.05 (q, 2H, *J* = 7.17 Hz), 5.03 (s, 2H), 7.32-7.42 (m, 2H), 7.44-7.58 (m, 4H), 7.60-7.68 (m, 1H), 7.73-7.83 (m, 1H), 8.15 (d, 1H, *J* = 8.30 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.38, 45.64, 61.67, 125.31, 126.95, 128.44, 128.64, 128.83, 129.10, 131.14, 131.66, 133.79, 134.89, 145.63, 147.29, 153.31, 167.25; ESIMS: *m/z* 348 (M^++Na), 326 (M^++H); HRMS calculated for $C_{19}H_{16}NO_2Cl$ Na (M^++Na) 348.0761, found 348.0777.

3,3-Dimethyl-9-phenyl-3,4-dihydroacridin-l(2*H*)-one (3e): m.p. 192-194 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 6H), 2.58 (s, 2H), 3.28 (s, 2H), 7.13-7.24 (m, 2H), 7.35-7.61 (m, 5H), 7.71-7.82 (m, 1H), 8.07 (d, 1H, *J* = 8.30 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.27, 32.17, 48.30, 54.13, 122.61, 126.36, 127.33, 127.44, 127.95, 128.04, 128.18, 128.43, 131.58, 137.50, 148.91, 150.93, 161.07, 197.87; ESI-MS: *m/z* 324 (M^++Na), 302 (M^++H); HRMS (ESI) calculated for $C_{21}H_{19}NONa$ (M^++Na) 324.1358, found 324.1368, $C_{21}H_{20}NO$ (M^++H) calculated 302.1539 found 302.1551.

Ethyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (3f): m.p. 103-105 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J* = 7.55 Hz), 2.78 (s, 3H), 4.07 (q, 2H, *J* = 7.55 Hz), 7.32-7.41(m, 2H), 7.45-7.58 (m, 4H), 7.61-7.70 (m, 1H), 8.02 (d, 1H, *J* = 9.06 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.59, 23.67, 61.43, 125.15, 125.90, 128.13, 128.39, 128.71, 129.22, 130.45, 131.07, 132.29, 134.95, 145.36, 146.01, 154.95, 168.03; ESI-MS: *m/z* 326 (M^++H); HRMS (ESI) calculated for $C_{19}H_{16}O_2NClNa$ (M^++Na) 348.07618, found 348.0775, $C_{19}H_{17}O_2NCl$ (M+H) calculated 326.0942 found 326.0957.

Methyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (3g): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.76 (s, 3H), 3.57 (s, 3H), 7.30-7.37 (m, 2H), 7.45-7.57 (m, 4H), 7.61-7.68 (m, 1H), 8.00 (d, 1H, *J* = 8.92 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.61, 52.16, 125.12, 125.73, 127.91, 128.38, 128.69, 129.02, 130.41, 131.08, 132.27, 134.81, 145.43, 145.98, 154.79, 168.52; ESI-MS: *m/z* 312 (M^++H); HRMS calculated for $C_{18}H_{15}O_2NCl$ (M^++H) 312.0785, found 312.0799.

1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (3h): m.p. 150-152 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.00 (s, 3H), 2.68 (s, 3H), 7.30-7.40 (m, 2H), 7.49-7.61 (m, 4H), 7.66 (dd, 1H, *J* = 9-06 Hz, *J* = 2.26 Hz), 8.02 (d, 1H, *J* = 9.06 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.81, 31.86, 124.98, 126.08, 126.44, 128.64, 128.82, 129.98, 134.77, 135.15, 143.85, 147.48, 153-47, 205.56; ESI-MS: *m/z* 296 (M^++H); HRMS (ESI) calculated for $C_{18}H_{15}ONC1$ (M^++H) 296.0836, found 296.0847.

Ethyl 2,4-dimethylquinoline-3-carboxylate (3i): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H, *J* = 7.17 Hz), 2.65 (s, 3H), 2.71 (s, 3H), 4.48 (q, 2H, *J* = 7.17 Hz), 7.47-7.62 (m, 1H), 7.65-7.79 (m, 1H), 7.93-8.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.17, 15.57, 23.69, 61.56, 123.89, 125.71, 126.21, 127.93, 129.20, 129.93, 141.33, 147.05, 154.25, 169.09; ESI-MS: *m/z* 230 (M^++H); HRMS (ESI) calculated for $C_{14}H_{15}NO_2Na$ (M^++Na) 252.0995, found 252.1008, $C_{14}H_{16}NO_2$ (M^++H) calculated 230.1175 found 230.1182, 179.0176, 157.0357.

Methyl 2,4-dimethylquinoline-3-carboxylate (3j): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H), 2.70 (s, 3H), 4.00 (s, 3H), 7.49-7.60 (m, 1H), 7.67-7.78 (m, 1H), 7.94-8.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.73, 23.73, 52.42, 123.93, 126.61, 126.25, 127.62, 129.13, 130.03, 141.61, 147.02, 154.27, 169.60; ESI-MS: *m/z* 216 (M^++H); HRMS calculated for $C_{13}H_{13}NO_2Na$ (M^++Na) 238.0838, found 238.0846, $C_{13}H_{14}NO_2$ (M^++H) calculated 216.1019 found 216.1026, 179.0177.

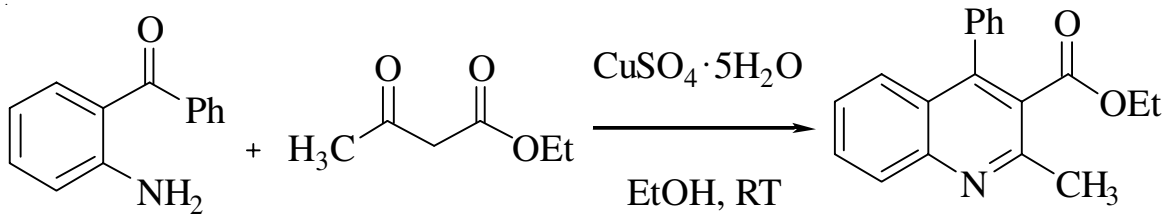
1-(2,4-Dimethylquinolin-3-yl)ethanone (3k): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H), 2.57 (s, 3H), 2.62 (s, 3H), 7.46-7.58 (m, 1H), 7.63-7.74 (m, 1H), 7.88-7.97 (m, 1H), 8.01 (d, 1H, *J* = 8.30 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.02, 23.21, 32.44, 123.43, 125.68, 126.17, 128.85, 129.61, 135.43, 138.48, 146.53, 152.33, 206.44; ESI-MS: *m/z* 200 (M^++H).

Ethyl 6-chloro-2-(chloromethyl)-4-phenylquinoline-3-carboxylate (3l): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.17 Hz), 4.05 (q, 2H, *J* = 7.17 Hz), 5.00 (s, 2H), 7.30-7.41 (m, 2H), 7.47-7.57 (m, 3H), 7.59 (d, 1H, *J* = 2.07 Hz), 7.71 (dd, 1H, *J* = 8.87 Hz, *J* = 2.26 Hz), 8.09 (d, 1H, *J* = 8.87 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.38, 45.64, 61.67, 125.31, 126.95, 128.44, 128.64, 128.83, 129.10, 131.14, 131.66, 133.79, 134.89, 145.63, 147.29, 153.31, 167.25; ESI-MS: 360 (M^++H).

RESULTS AND DISCUSSION

Twelve novel compounds (**3a-l)** in good yields (Table-1) have been synthesized *via* 2-amino-5-chloro benzophenones by employing the reaction sequences as shown in **Scheme-I**.

The synthesis of substituted qinolines primarily is due to an appropriate Cu(II) salt as Lewis acid activator and finding out right conditions that would favour dehydration. To this end, copper sulfate pentahydrate was considered an attractive



1a-c **2a-f** **3a-l**

Reaction conditions: *o*-Aminoarylketone (1 mmol), -methyleneketone (1 mmol), $CuSO_4 \cdot 5H_2O$ (20 mol %), ethanol 10 mL)

Scheme-I: Synthesis of substituted quinolines (**3a-l**)

catalyst in view of its attenuated Lewis acidity, ability to coordinate with hydroxy group and excellent performance as an alcohol dehydration catalyst. Herein, we reveal a simple, inexpensive, mild and efficient method for the condensation of *o*-aminoaryl carbonyls with ketones containing an active methylene group by using catalytic amount of $CuSO_4 \cdot 5H_2O$ (20 mol %) at room temperature to afford the polysubstituted quinolines **(3a-l)** in high yields (**Scheme-I**). ^{1}H NMR spectrum of ethyl 2-methyl-4-phenylquinoline-3-carboxylate **3a** δ 0.95 (t, 3H, *J* = 6.79 Hz), 2.79 (s, 3H), 4.07 (q, 2H, *J* = 6.79 Hz), 7.33-7.53 (m, 6H), 7.59 (dd, 1H, *J* = 8.30 Hz, *J* = 1.51 Hz), 7.67-7.78 (m, 1H), 8.08 (d, 1H, *J* = 8.30 r Hz) and ^{13}C NMR spectrum of ethyl 2-methyl-4-phenylquinoline-3-carboxylate δ 13.5, 23.7, 61.2, 125.0, 126.3, 126.4, 127.3

Antibacterial activity: All the newly prepared compounds **(3a-l)** were screened for the antibacterial activity is performed according to the paper disc method [16,17]. The antibacterial screening data showed that almost all the compounds **3a-l** are active and showing moderate to good antibacterial activity. Among the screened **3b**, **3e, 3f, 3j** and **3j** in which respectively showed high activity against all the micro-organism employed. The activities of these compounds are almost equal to the standards and the remaining compounds showed moderate to good antibacterial activity (Table-2).

TABLE-1
SYNTHESIZED SUBSTITUTED QUINOLINES

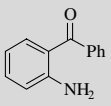
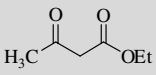
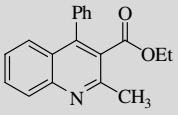
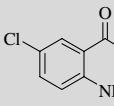
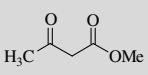
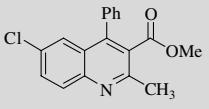
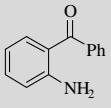
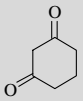
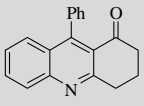
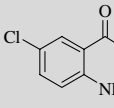
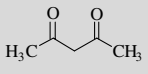
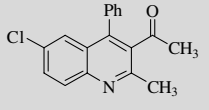
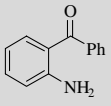
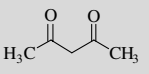
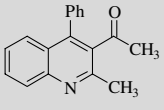
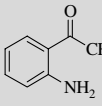
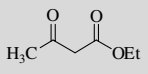
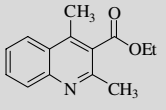
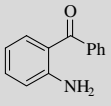
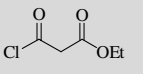
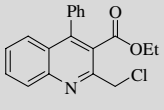
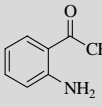
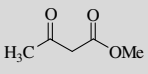
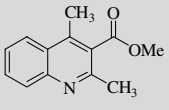
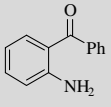
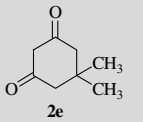
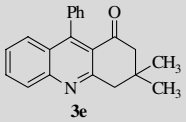
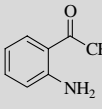
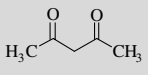
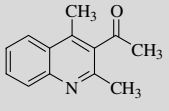
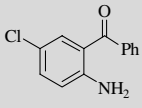
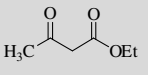
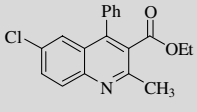
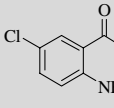
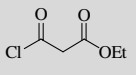
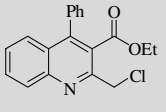
S. No.	*o*-Amino-ketone	Ketone	Product	Yield (%)	S. No.	*o*-Amino-ketone	Ketone	Product	Yield (%)
1	 **1a**	 **2a**	 **3a**	95	7	 **1b**	 **2f**	 **3g**	95
2	 **1a**	 **2b**	 **3b**	85	8	 **1b**	 **2c**	 **3h**	80
3	 **1a**	 **2c**	 **3c**	93	9	 **1c**	 **2a**	 **3i**	95
4	 **1a**	 **2d**	 **3d**	82	10	 **1c**	 **2f**	 **3j**	92
5	 **1a**	 **2e**	 **3e**	80	11	 **1c**	 **2c**	 **3k**	83
6	 **1b**	 **2a**	 **3f**	94	12	 **1b**	 **2d**	 **3l**	85

TABLE-2
ANTIBACTERIAL ACTIVITY OF SUBSTITUTED QUINOLINES (**3a-l**)

Compounds	*Escherichia coli* (Gram-negative) (conc. µg/mL)			*Staphylococcus aureus* (Gram-positive) (conc. µg/mL)		
	200	100	50	200	100	50
3a	20	20		12	21	9
3b	12	14	12	31	24	22
3c	11	13	8	-	14	7
3d	**14**	-	11	18	-	11
3e	18	19	30	28	19	23
3f	12	12	22	23	32	22
3g	23	19	17	11	19	17
3h	11	15	17	22	15	15
3i	22	11	17	13	11	17
3j	13	-	11	14	-	11
3k	14	11	11	26	29	19
3l	12	6	8	3	6	8
Ciprofloxacin (100 µg/disc)		20			21	

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