An Efficient Synthesis of 2,3,4-Trisubstituted Quinolines Through Alkynylation-Cyclization at Ambient Temperature

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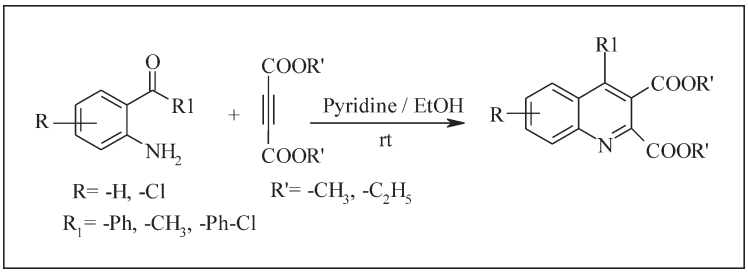

A series of 2,3,4-trisubstituted quinoline derivatives have been synthesized by reactions between 2-aminoaryl ketones and dialkyl acetylenedicarboxylate. The synthetic pathway allows for the direct construction of said quinoline derivatives in pyridine/ethanol at ambient temperature through a zwitterion intermediate.

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INTRODUCTION

Incorporation of the quinoline moiety is very important in heterocyclic chemistry as it leads to biological activity in such areas as antiplasmodial [1], intrinsic [2], cytotoxic [3], functional [4], antibacterial [5], antiproliferative [6], antimalarial [7], and anticancer activity [8]. In addition, quinolines are important synthetic materials for the preparation of nano and mesostructures [9]. In view of their remarkable significance, a number of methods have been reported for the synthesis of quinoline derivatives [10a–h]. Despite the available methods efforts have been devoted to the development of new quinoline-based structures [11] and some new synthetic methodology for their construction [12]. Among them, very few reports are available on synthesis of 2,3,4-trisubstituted quinoline derivatives by using 2-aminoaryl ketones and dimethyl acetylenedicarboxylate (DMAD) and such type of compound shows antiallergic properties [13a–e]. However, most of the reported methods have significance drawbacks such as difficulties in workup, drastic reaction conditions and lack of mechanistic details.

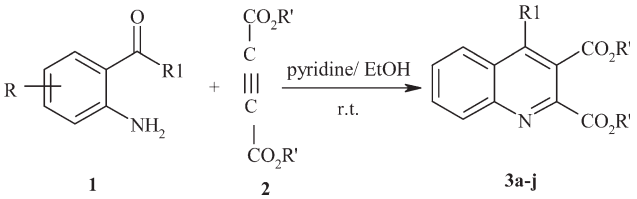
The reaction of nucleophiles with activated acetylenes has attracted the attention of organic chemists for a long time, especially from vantage point of heterocyclic synthesis. In these reaction processes, zwitterionic species are known to arise from the addition of nucleophiles such as triphenylphosphine [14], pyridine [15], dimethylsulphoxide [16], isocyanides [17], and ethanol [18] to activated acetylenes. The formed zwitterionic intermediates can be trapped by suitable substrates to give stabilized product, and this interception can either be two-component or multicomponent reaction. The 1:4 zwitterionic intermediate has been exploited in the synthesis of aminofurans [19], iminolactones [19], and 2-aminopyrroles [20].

Considering the literature background given above and in view of our general interest in synthesis of heterocyclic compounds [21], herein, we describe an efficient synthesis of 2,3,4-trisubstituted quinoline derivatives via the reaction of 2-aminoaryl ketone with dialkyl acetylenedicarboxylate in pyridine/ethanol at room temperature without using any catalyst through zwitterionic intermediates (Scheme 1).

RESULTS AND DISCUSSION

Our primary investigation was initiated with the reaction of 2-aminoacetophenone and DMAD in ethanol (5 mL) stirred at ambient temperature without any catalyst or additive gave the desired cyclization product dimethyl 4-methylquinoline-2,3-dicarboxylate **3a.** The structure of the product was assigned on the basis of spectroscopic analysis. This initial success enforced us to check the capability of the protocol by variation in 2-aminoaryl ketones and dialkyl acetylenedicarboxylate. But the limitation of the said process occurred when DMAD has been replaced by diethyl acetylenedicarboxylate (DEAD). The reaction didn't proceed even for a long time (24 h). To overcome the limitation of above reaction, we have carried out the same reaction in presence

Scheme 1. Synthesis of 2,3,4-trisubstituted quinoline derivatives.



1 2 3a-j

of pyridine (20 mol %). Surprisingly, in pyridine the reaction proceeds smoothly at room temperature to afford expected product. Pyridine is found to be effective promoting medium to complete the reaction with variations in both the substrates in shorter time with excellent yields. The results are summarized in Table 1.

Based on the experimental observations, the possible mechanism for this transformation is depicted in Scheme 2. The initial event involves the nucleophilic attack of ethanol or pyridine on dialkyl acetylenedicarboxylate form 1:4 zwitterion (I) followed by subsequent [2 + 2] cycloaddition of zwitterion to the carbonyl group of 2-aminoaryl ketone to give an unstable oxetene [22], which undergoes ring opening followed by cyclodehydration resulting in the formation of 2,3,4-trisubstituted quinolines.

CONCLUSIONS

A convenient and an efficient one-pot method for the synthesis of quinoline derivatives from readily accessible precursors have been developed. Finally, we concluded that pyridine is the most suitable promoting medium for the synthesis of 2,3,4-trisubstituted quinoline derivatives as compared with ethanol. The simplicity of the present procedure makes it an interesting alternate to other approaches. The biomedical applications of these compounds are under study.

EXPERIMENTAL

All chemicals and solvents were reagent grade and used as purchased without any further purification. Analytical thin-layer chromatography was performed on percolated silica gel 60-F 254 plates. The data found were in consistent with the proposed structure. IR spectra on KBr disks were recorded on a Shimadzu IR-470 FT-IR spectrophotometer in cm^{-1}. The routine nuclear magnetic resonance spectra were taken in $CDCl_3$ using a Bruker Spectrospin Avance II-300-MHz spectrophotometer and Jeol-400-MHz spectrophotometer with tetramethyl silane (TMS) as an internal standard. Gas chromatography mass spectrometry (GCMS) spectra analyses were done on Shimadzu QP 2010 GCMS. Melting points were determined in an open capillary tube and were found to be uncorrected.

General procedure for the synthesis of 2,3,4-trisubstituted quinoline derivatives. To DEAD (0.278 mL, 2 mmol), pyridine (20 mol %) was added at 0–10°C temperature. After 15 min stirring 2-amino-5-chlorobenzophenone (0.462 g, 2 mmol) was added, and the mixture was stirred at room temperature. The precipitate obtained was then filtered, washed with water and petroleum ether, and dried in vacuum. The crude product was recrystalized from methanol. In some cases (entry f, i, j) products were obtained by keeping the reaction mixture for several hours after completion of reaction.

Spectral data. ***Dimethyl 4-methylquinoline-2,3-dicarboxylate: (a).*** Creamish powder, mp 99–101°C; IR (KBr): 2958, 1733, 1679, 1231, 812, 785, 767 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz): δ = 2.65 (s, 3H, —CH_3), 3.75(s, 3H, —OCH_3), 3.79 (s, 3H, —OCH_3), 6.638–6.666 (dd, 1H, Ar-H), 6.994–7.045 (t, 1H, Ar-H), 7.336–7.392 (t, 1H, Ar-H), 7.821–7.852 (dd, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ 300 MHz): δ = 28.22, 51.55, 52.88, 100.24, 118.54, 121.20, 123.84, 131.55, 133.25, 141.89, 144.19, 165.46, 167.84; ms: *m/z* = 259 [M^+]. Anal. Calcd. For $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.84; H, 5.00; N, 5.37.

Dimethyl 4-phenyl-6-chloroquinoline-2,3-dicarboxylate: (b). Pale yellow powder, mp152–158°C; (lit.162.5–163°C [13a]); IR (KBr): 2954, 1727, 1441, 1220, 1054, 866, 833, 755, 702 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz): δ = 3.64 (s, 3H,—OCH_3), 4.07(s, 3H —OCH_3), 7.26–7.78(m, 7H, Ar-H), 8.26–8.29 (d, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ 300 MHz): δ = 52.56, 53.56, 99.99, 125.40, 128.43, 128.51, 129.17, 129.24, 132.18, 133.78, 135.66, 145.45, 164.09, 167.04; ms: *m/z* = 355 [M^+]. Anal. Calcd. For $C_{19}H_{14}NO_4Cl$: C, 64.14; H, 3.97; N, 3.94. Found:C, 64.11; H, 3.96; N, 3.89.

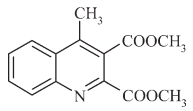
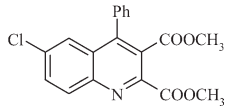
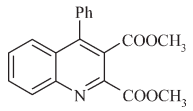
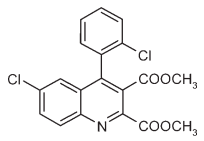
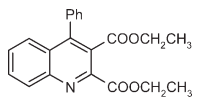
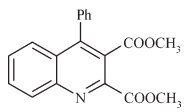
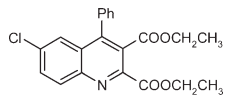
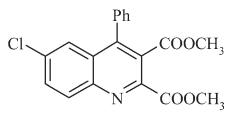
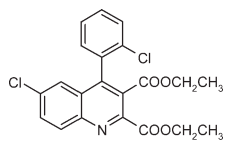
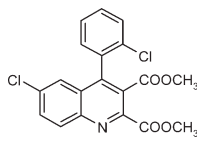
Dimethyl 4-phenylquinoline-2,3-dicarboxylate: (c). Pale yellow powder; mp 128–129°C (lit.129–130°C [13a]); IR (KBr): 3048, 2949, 1736, 1686, 1238, 819, 776, 751, 705 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz): δ = 3.76 (s, 3H,—OCH_3), 3.80 (s, 3H —OCH_3), 6.782–6.809 (dd, 1H, Ar-H) 7.028–7.053 (t, 1H, Ar-H), 7.26(s, 1H, Ar-H) 7.39–7.58 (m, 5H, Ar-H), 7.835–7.864 (dd, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ 400 MHz): δ = 51.56, 52.85, 98.56, 119.89, 121.45, 126.30, 138.08, 141.76, 145.10, 165.09, 168.46; ms: *m/z* = 321 [M^+]. Anal. Calcd. For $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.00; H, 4.67; N, 4.34.

Dimethyl 4-(2- chlorophenyl)-6-chloroquinoline-2,3-dicarboxylate: (d). Pale yellow powder; mp >300°C; IR (KBr): 2950, 1731, 1685, 1052 826, 774, 736 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz): δ = 3.78 (s, 3H —OCH_3), 3.81 (s, 3H, —OCH_3), 7.257–7.267 (d, 1H, Ar-H), 7.32–7.47 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$ 300 MHz): δ = 51.69, 53.02, 101.20, 120.45 125.53, 126.40, 126.85, 129.64, 130.24, 131.58, 131.73, 132.58, 133.43, 138.07, 141.16, 143.86, 164.85, 167.88; ms: *m/z* = 389 [M^+]. Anal. Calcd. For $C_{19}H_{13}NO_4Cl_2$: C, 58.48; H, 3.36; N, 3.59 Found: C, 58.49; H, 3.32; N, 3.56.

Diethyl 4-phenylquinoline-2,3-dicarboxylate: (e). White crystals; mp 97–102°C; IR (KBr): 2992, 1745, 1723, 1377, 1202, 1021, 860,768, 756, 704 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz): δ = 0.97–1.00 (t, *J* = 12Hz, 3H, —CH_2—CH_3) 1.44–1.48 (t, 3H, *J* =16Hz, —CH_2—CH_3), 4.06–4.10 (q, 2H, *J* = 16Hz, —CH_2—CH_3), 4.51–4.54 (q, 2H, *J* = 12Hz, —CH_2—CH_3), 7.26 (s, 2H, Ar-H), 7.36–7.37 (m, 3H, Ar-H), 7.37–7.62 (m, 3H, Ar-H), 8.32–8.34 (d, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ 400 MHz): δ = 13.69,14.29, 61.64, 62.72, 126.68, 127.14, 127.60, 128.31, 128.74, 128.82, 128.97, 129.33, 129.49, 130.74, 130.91, 130.99 134.82, 145.89, 147.16, 148.05, 165.36, 167.24; ms: *m/z* = 349 [M^+]. Anal. Calcd. For $C_{21}H_{19}NO_4$: C, 72.20; H, 5.44; N, 4.01. Found: C, 72.22; H, 5.42; N, 4.03.

Table 1

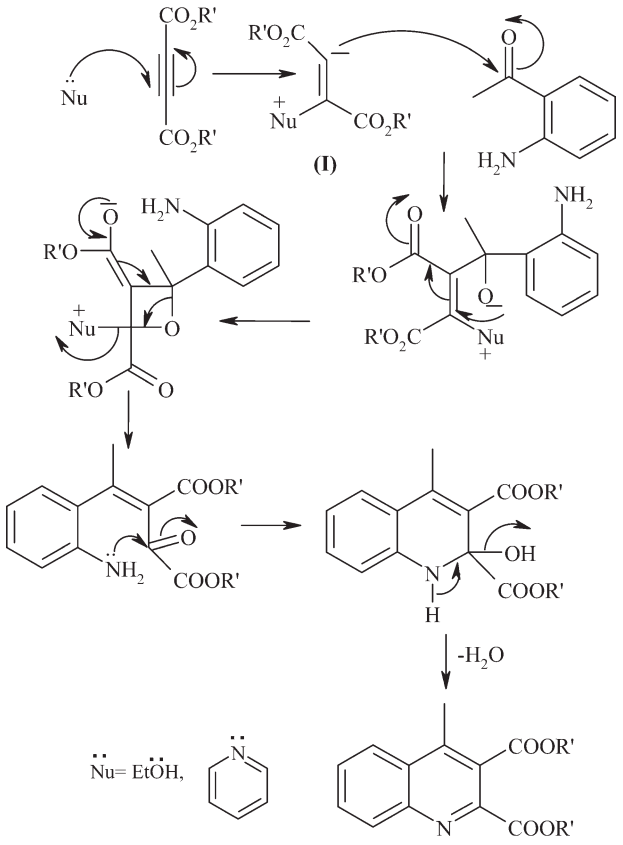
Synthesis of 2,3,4-trisubstituted quinolines at room temperature.

Entry	R	R1	R′	Medium	Product	Time/h	Yield[a]
a	—H	—CH_3	—CH_3	EtOH		20	79
b	—Cl	-Ph	—CH_3	EtOH		21	77
c	—H	-Ph	—CH_3	EtOH		23	75
d	—Cl	2-ClC_6H_4	—CH_3	EtOH		24	78
e	—H	-Ph	—CH_2CH_3	Pyridine		15	88
f	—H	-Ph	—CH_3	Pyridine		14	87
g	—Cl	-Ph	—CH_2CH_3	Pyridine		12	88
h	—Cl	-Ph	—CH_3	Pyridine		12	89
i	—Cl	2-ClC_6H_4	—CH_2CH_3	Pyridine		14	86
j	—Cl	2-ClC_6H_4	—CH_3	Pyridine		15	85

[a] Yields refers to pure isolated product.

Dimethyl 4-phenylquinoline-2,3-dicarboxylate: (f). Pale yellow crystals; mp 128°C (lit. 129–130°C [13a]); IR (KBr): 2952, 1725, 1443, 1205, 1051, 865,794, 966, 769, 605 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz): δ = 3.64 (s, 3H, —OCH_3), 4.08 (s, 3H, —OCH_3), 7.26 (s, 2H, Ar-H), 7.37–7.38(m, 3H, Ar-H), 7.50–7.63 (m, 3H Ar-H), 8.32–8.35(d, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ 400 MHz): δ = 52.50, 53.52, 100.01, 126.67, 127.24, 127.65, 128.31, 128.86, 129.29, 129.34, 130.65, 131.07,

Scheme 2. The possible mechanism for the synthesis of compounds 3a–j.



134.49, 144.83, 147.08, 148.09, 165.56, 167.67; ms: m/z = 321 [M^+]. Anal. Calcd. For $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.00; H, 4.67; N, 4.32.

Diethyl 4-phenyl-6-chloroquinoline-2,3-dicarboxylate: (g). Creamish powder; mp 255–263°C; IR (KBr): 2980, 1733, 1718, 1292, 1145, 1051, 831, 808, 753, 700 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz): δ = 0.96–1.00 (t, 3H, J = 16 Hz, —CH_2—CH_3), 1.44-1.48 (t, 3H, J = 16 Hz, —CH_2—CH_3), 4.06–4.10 (q, 2H, J = 16 Hz —CH_2—CH_3), 4.50–4.54(q, 2H, J = 16 Hz —CH_2—CH_3), 7.33–7.36 (m, 2H, Ar-H), 7.51–7.54 (t, 3H, Ar-H), 7.580–7.586 (d, 1H, Ar-H) 7.738–7.767 (dd, 1H, Ar-H) 8.256–8.281 (d, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ 400 MHz): δ = 13.68, 14.27, 61.80, 62.85, 125.44, 128.03, 128.41, 128.55, 129.17, 129.41, 132.10, 132.29, 134.09, 135.48, 145.53, 145.96, 147.26, 165.02, 166.91; ms: m/z = 383 [M^+]. Anal. Calcd. For $C_{21}H_{18}NO_4Cl$: C, 65.79, H, 4.69, N, 3.65 Found: C, 65.68; H, 4.63; N, 3.64.

Dimethyl-4-phenyl-6-chloroquinoline-2,3-dicarboxylate: (h). Pale yellow powder; mp155–160°C (lit.162.5–163°C [13a]); IR (KBr): 3065, 2954, 1741,1728, 1220, 1055, 834,755, 702, 670 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz): δ = 3.64(s, 3H —OCH_3), 4.07 (s, 3H —OCH_3), 7.33–7.36 (m, 2H, Ar-H), 7.52–7.54 (m, 3H, Ar-H), 7.596–7.604 (d, 1H, Ar-H), 7.750–7.787 (dd, 1H, Ar-H) 8.262–8.292 (d, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ 400 MHz): δ = 52.58, 53.58, 125.41, 128.44, 128.52, 129.18, 129.24, 132.18, 133.78, 135.65, 145.45, 147.29, 166.50, 167.29; ms: m/z = 355 [M^+]. Anal. Calcd. For $C_{19}H_{14}NO_4Cl$: C, 64.14; H, 3.97; N, 3.94. Found: C, 64.08; H, 3.93; N, 3.92.

Diethyl 4-(2-chlorophenyl)-6-chloroquinoline-2,3-dicarboxylate: (i). Creamish powder; mp 98–107°C; IR (KBr): 3059, 2981, 1722, 1239, 1146, 829, 812, 759, 741 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz): δ = 0.98–1.01 (t, 3H, J = 12 Hz, —CH_2—CH_3), 1.44–1.48 (t, 3H, J = 16 Hz, —CH_2—CH_3), 4.09–4.12 (q, 2H, J = 12 Hz, —CH_2—CH_3), 4.52–4.56 (q, 2H, J = 16 Hz, —CH_2—CH_3), 7.24–7.28 (m, 1H, Ar-H), 7.32–7.36 (d, 1H, Ar-H), 7.37–7.42 (m, 1H, Ar-H), 7.44–7.50 (m, 1H, Ar-H), 7.53–7.57 (d, 1H, Ar-H), 7.73–7.77 (dd, 1H, Ar-H), 8.24–8.28 (d,1H, Ar-H); ^{13}C NMR ($CDCl_3$ 400 MHz): δ = 13.66, 14.26, 61.83, 62.88, 125.00, 126.88, 127.80, 127.87, 129.82, 130.77, 131.15 132.38, 133.20, 133.68, 135.79,144.85, 145.47, 146.67,165.04, 166.27; ms: m/z- 417[M^+]. Anal. Calcd. For $C_{21}H_{17}NO_4Cl_2$: C, 60.43; H, 4.07; N, 3.35. Found: C, 60.40; H, 4.03; N, 3.32.

Dimethyl 4-(2-chlorophenyl)-6-chloroquinoline-2,3-dicarboxylate: (j). Pale yellow powder; mp > 300°C; IR (KBr): 3067, 2952,1728, 1607, 1442, 1222, 1149, 1064, 849, 813, 760, 744 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz): δ = 3.77 (s, 3H, —OCH_3), 4.10 (s, 3H, —OCH_3), 7.27–7.31 (d, 1H, Ar-H), 7.36–7.38 (d, 1H, Ar-H), 7.40–7.46 (m, 1H, Ar-H), 7.47–7.52 (m, 1H, Ar-H), 7.56–7.60 (d, 1H, Ar-H), 7.76–7.80 (dd, 1H, Ar-H), 8.26–8.31 (d, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ 400 MHz): δ = 52.79, 53.73, 125.06, 126.93, 127.98, 129.92, 130.88, 131.02, 132.36, 132.55, 132.88, 133.58, 136.07, 145.43, 165.34 166.80; ms: m/z = 389 [M^+]. Anal. Calcd. For $C_{19}H_{13}NO_4Cl_2$: C, 58.48; H, 3.96; N, 3.59. Found: C, 58.22; H, 3.76; N, 3.55.

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