A Simple Synthesis of Trisubstituted Quinolines Through Transesterification

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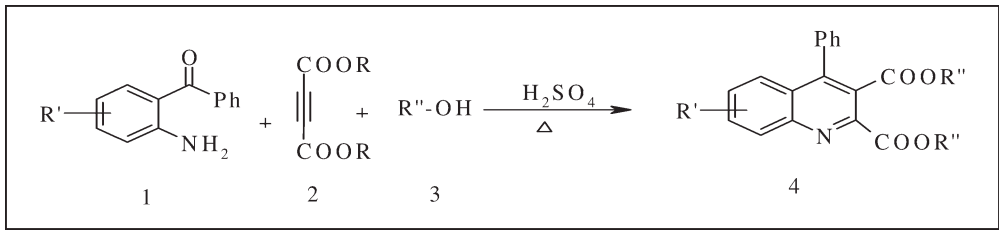

An efficient and simple method has been reported for the synthesis of 2,3,4-trisubstituted quinolines through zwitterion intermediate under reflux condition in presence of sulfuric acid. The formed dicarboxylate subsequently undergoes transesterification in various alcohols with good yields. Most of the synthesized compounds are newly reported characterized by spectroscopic method.

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INTRODUCTION

Quinoline and their derivatives are very important structural motif not only in medicinal chemistry because of their wide occurrence in numerous natural products [1] and drugs [2] but also in polymer chemistry, electronics, and optoelectronics for their excellent mechanical properties [3]. Because of their enormous importance, they have become the synthetic targets of many organic and medicinal chemistry groups [4]. The structural core of quinoline has generally been synthesized by various conventional name reactions [5]. There have been very few reports available on synthesis of 2,3,4-trisubstituted quinoline derivatives by using 2-aminoaryl ketones and dialkyl acetylenedicarboxylate, and these compounds show antiallergic properties [6,7]. However, synthetic protocols reported so far suffer from high temperatures, prolonged reaction times, harsh reaction conditions, and low yields of the products. Therefore, its important need to develop efficient method for the synthesis of said bioactive compounds so as to investigate other biological activity.

Likewise, transesterification is a potent and versatile transformation in various fields of organic synthesis in industrial and in academic laboratories. For example, the formation of methyl esters by the transesterification of naturally occurring oils and fats can be used as diesel alternatives [8]. It is applicable in the paint industry for the curing of alkyl resin [9]. It also plays significant role in polymerization [9]. Transesterification has been carried out conventionally and most frequently by the use of various Lewis acid catalysts such as boron tribromide [10], anhydrous aluminium trichloride embedded in polystyrene-divinyl benzene [11]. Bronsted acid catalysts such as hydrochloric, phosphoric, sulfonic, sulfuric, or *p*-toluenesulfonic acid [12] or basic catalysts such as metal alkoxides [13] and metal carbonates [14] also catalyze this conversion.

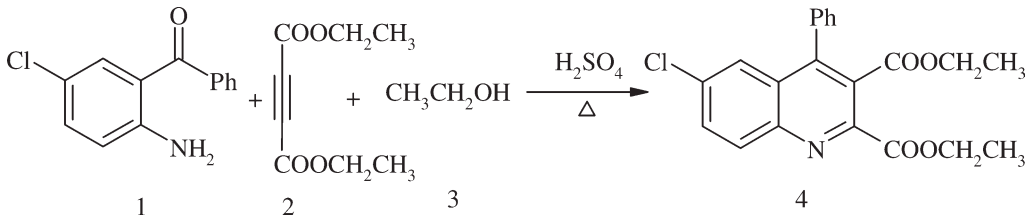
These remarkable importance of quinoline derivatives and as part of continuing efforts toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds [15] enthused us to develop new methods for quinoline synthesis.

RESULTS AND DISCUSSION

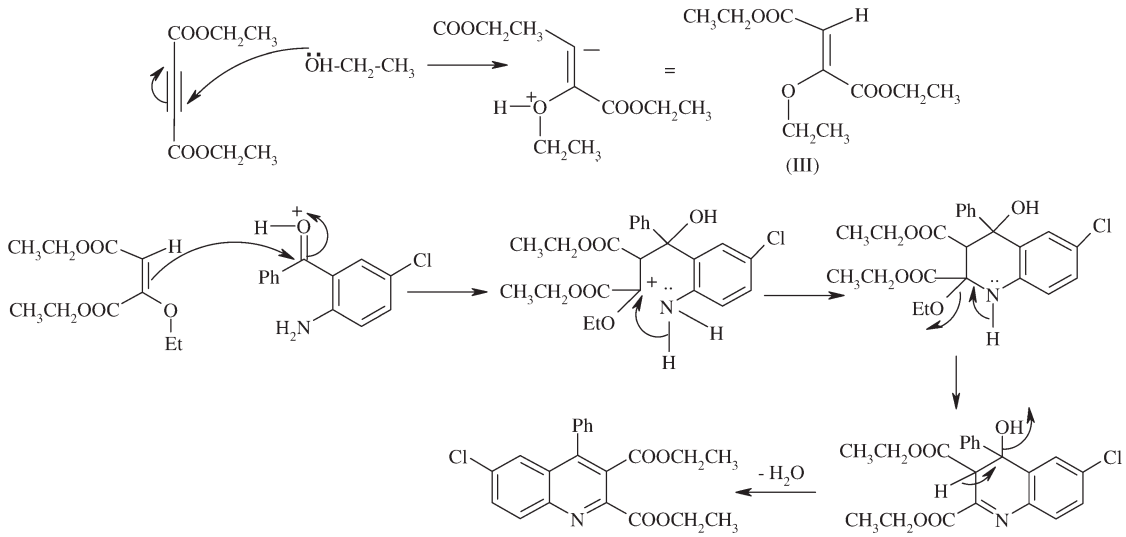
In this article, we report our results involving synthesis of 2,3,4-trisubstituted quinoline and consecutively transesterification of formed dicarboxylate using variety of alcohols in presence of sulfuric acid. As a trial case, the reaction of stoichometric amount of 5-chloro-2-aminobenzophenone with diethyl acetylenedicarboxylate (DEAD) and catalytic amount of sulfuric acid in refluxing ethanol afforded product as trisubstituted quinoline **4** in 84% yield (Scheme 1).

The structure of formed product was confirmed on the basis of spectroscopic data. The IR spectrum showed the sharp absorption bands at 1732 and 1718 cm^{-1} assigned to the two ester carbonyls. In ^{1}H-NMR spectrum, the two triplets observed at δ 0.96–1.01 and 1.45–1.49 are due to the two methyl protons of ester moiety, and the

Scheme 1



Scheme 2. Possible mechanism for synthesis of 2,3,4-trisubstituted quinolines.



two quartets resonated at δ 4.08–4.11 and 4.50–4.58 are due to the methylene protons of carbonyl ester. While in ^{13}C-NMR spectrum, the two ester carbonyls were observed at δ 164.91, 166.74. Mechanistically, the reaction may involves the initial formation of 1:4 zwitterionic intermediate between ethanol and DEAD which rearranged to form (III) which further adds to the protonated 2-aminoaryl ketone followed by cyclodehydration leads to 2,3,4-trisubstituted quinoline derivative as end product (Scheme 2).

To verify the generality of the present protocol, the same reaction was extended by replacement of DEAD with dimethyl acetylenedicarboxylate (DMAD) in ethanol. As expected two singlets for two methoxy protons in ^{1}H-NMR but interestingly it has been observed that two triplets at δ 0.96–1.01 and 1.44–1.48 while two quartets at δ 4.08–4.10 and 4.49–4.56 indicated formed trisubstituted quinoline product undergoes transesterification (Scheme 3).

In view of the interesting results obtained by above synthesis, we next focused our attention on transesterification by variety of alcohols. In most of the alcohols, we got the desired 2,3,4-trisubstituted quinolines with effective transesterification.

The reaction of 2-aminoaryl ketones with terminal dialkyl acetylenedicarboxylate and various alcohols afforded quinoline derivatives in good yields. All these results are summarized in Table 1. It have been

Scheme 3

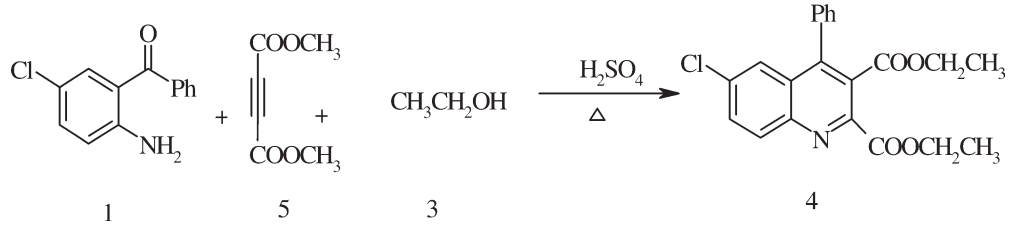
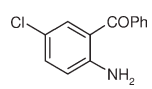
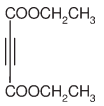
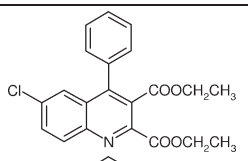
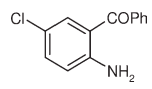
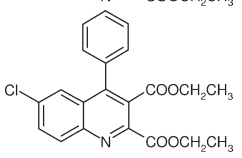
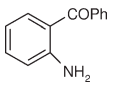
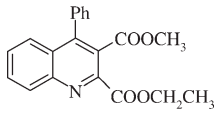
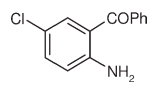
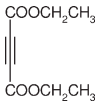
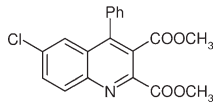
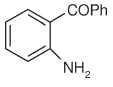
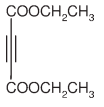
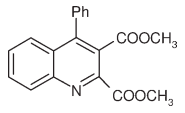
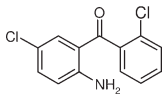
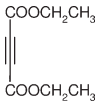
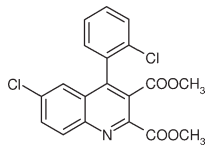
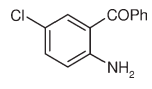
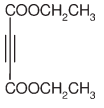
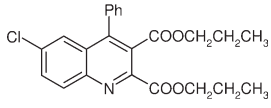
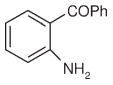
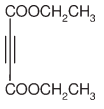
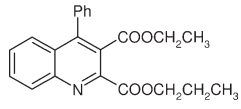
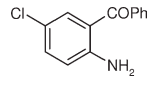
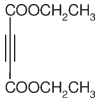
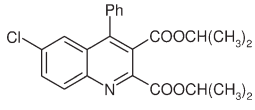
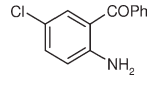
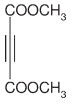
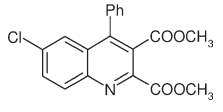
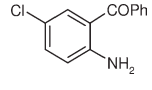
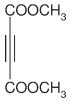
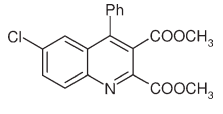
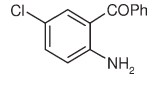
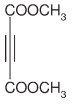
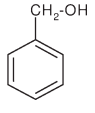
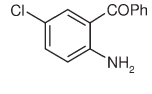
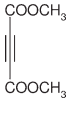
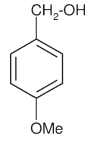


Table 1

Synthesis of 2,3,4-trisubstituted quinoline in presence of H_2SO_4 along with transesterification.

Entry	2-Aminoaryl ketones	DEAD[a]/DMAD[b]	Alcohol	Product	Yield (%)	Time (h)
a			CH_3CH_2OH		84	6
b			CH_3CH_2OH		86	6
c			CH_3CH_2OH		83	7
d			CH_3OH		92	4.5
e			CH_3OH		81	6
f			CH_3OH		89	6
g			$CH_3CH_2CH_2OH$		81	9
h			$CH_3CH_2CH_2OH$		79	5
i			$(CH_3)_2CH\text{-}OH$		80	7
j			$(CH_3)_2CH\text{-}OH$		80	12
k					84	7
l				No reaction	–	–
m				No reaction	–	–

[a]DEAD, diethyl acetylenedicarboxylate. [b] DMAD, dimethyl acetylenedicarboxylate.

noted that in case of cyclohexanol and isopropanol with DMAD transesterification product was not formed, whereas with benzyl alcohol and 4-methoxy benzyl alcohol, reactions did not proceed.

CONCLUSIONS

In conclusion, we have reported quite interesting and highly efficient strategy for the synthesis of variety of trisubstituted quinolines. The main practical importance of this reaction is that formed quinolines undergo transesterification reaction, which make it unique alternative for the synthesis of bioactive quinoline derivatives. Further investigations with other activated alkynes and alcohols are in progress.

EXPERIMENTAL

Melting points are uncorrected and were determined in an open capillary. Infrared spectra (in KBr pellets) were recorded on a Schimazdu IR-470 FT-IR spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Spectrospin Avance II-300 MHz spectrophotometer using $CDCl_3$ solvent and tetramethylsilane as an internal standard. Chemical shifts are given in the delta scale (δ) in ppm. Mass spectra were analyzed on a Shimadzu QP2010 GCMS. DMAD and DEAD were purchased from Aldrich chemicals and was used without further purification. The purity of the compounds was checked by thin layer chromatography (TLC).

Spectroscopic data of the synthesized compounds. ***Diethyl-4-phenyl-6-chloroquinoline-2,3-dicarboxylate(a).*** Yield 84%, m.p. 260–263°C; IR (KBr): 2985, 1732, 1718, 1238, 1050, 954, 830, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.96–1.01(t, 3H, —CH_2—CH_3), 1.45–1.49 (t, 3H, —CH_2—CH_3), 4.08–4.11(q, 2H, —CH_2—CH_3), 4.50–4.58 (q, 2H, —CH_2—CH_3), 7.33–7.36 (m, 2H, Ar-H), 7.51–7.54 (t, 3H, Ar-H), 7.58–7.59 (d, 1H, Ar-H), 7.73–7.77 (dd, 1H, Ar-H) 8.25–8.28 (d, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 13.57, 14.16, 61.67, 62.70, 125.34, 127.91, 128.32, 128.44, 129.05, 129.32, 131.98, 132.17, 134.04, 135.36, 145.44, 147.17, 164.91, 166.74; ms: m/z = 383 [M$^+$], 385 [M$^+$ + 2].

Diethyl-4-phenyl-6-chloroquinoline-2,3-dicarboxylate (b). Yield 86%, m.p. 259–261°C; IR (KBr): 2941, 1737, 1719, 1238, 1051, 831, 701 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.96–1.01 (t, 3H, —CH_2CH_3) 1.44–1.48 (t, 3H, —CH_2CH_3), 4.08–4.10 (q, 2H, —CH_2CH_3), 4.49–4.56 (q, 2H, —CH_2CH_3), 7.33–7.36 (m, 2H, Ar-H), 7.51–7.59 (m, 4H, Ar-H), 7.73–7.77 (m, 1H, Ar-H), 8.25–8.28 (dd, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 13.57, 14.16, 52.45, 62.69, 125.34, 125.37, 128.43, 128.49, 129.05, 129.12, 129.21, 129.32, 131.98, 132.04, 132.18, 132.22, 133.93, 134.05, 135.36. 1135.46, 145.45, 145.50, 145.71, 147.16, 147.28, 164.85, 164.92, 166.74, 167.27; ms: m/z = 383[M$^+$], 385 [M$^+$ + 2].

Ethylmethyl-4-phenylquinoline-2,3-dicarboxylate (c). Yield 83%, m.p. 98–99°C IR (KBr): 2997, 1737, 1718, 1308, 1226, 1052, 766, 704 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.45–1.49 (t, 3H, —CH_2CH_3), 3.62 (s, 3H, —OCH_3), 4.50–4.58 (q, 2H, —CH_2CH_3), 7.26–7.38 (m, 2H, Ar-H), 7.50–7.65 (m, 5H, Ar-H), 7.80–7.85 (m, 1H, Ar-H), 8.32–8.35 (m, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 14.20, 52.38, 62.66, 126.62, 127.51, 128.22, 128.27, 128.79, 129.11, 129.30, 129.41, 130.67, 130.97, 134.63, 147.14, 148.20, 165.41, 167.87; ms: m/z = 351 [M$^+$].

Dimethyl-4-phenyl-6-chloroquinoline-2,3dicarboxylate (d). Yield 92%, mp Obs. 145–152°C (lit. 162.5–163°C [6]); IR (KBr): 2954, 1726, 1605, 1246, 1054, 832, 703 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.64 (s, 3H, —OCH_3), 4.07 (s, 3H, —OCH_3), 7.34–7.37 (m, 2H, Ar-H) 7.52–7.54 (m, 3H, Ar-H), 7.59–7.60 (m, 1H, Ar-H), 7.74–7.78 (dd, 1H, Ar-H), 8.26–8.29 (dd, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 53.54, 61.78, 99.99, 125.39, 125.42, 128.47, 128.52, 129.14, 129.23, 129.33, 132.01, 132.08, 132.20, 132.24, 133.85, 135.71, 165.00, 167.55.

Dimethyl-4-phenylquinoline-2,3-dicarboxylate (e). Yield 81%, m.p. obs. 126–129°C (lit. 129–130°C [6]); IR (KBr): 2983, 1743, 1723, 1248, 1048, 768,703 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.64, (s, 3H, —OCH_3), 4.08 (s, 3H, —OCH_3), 7.35–7.38 (m, 2H, Ar-H), 7.50–7.52 (m, 3H, Ar-H), 7.60–7.67 (m, 2H, Ar-H), 7.82–7.87 (m, 1H, Ar-H), 8.36–8.38 (d 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 52.55, 53. 63.79, 126.70, 127.28, 127.73, 128.33, 128.95, 129.09 129.39, 129.43, 130.28, 131.37, 134.34, 144.52, 146.64, 148.59, 165.20, 167.46.

Dimethyl-4-(2-chlorophenyl)-6-chloroquinoline-2,3-dicarboxylate (f). Yield 89%, m.p.: obs. >300°C; IR (KBr): 2952, 1729, 1606, 1221, 830, 812, 759, 744. cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 3.64 (s, 3H, —OCH_3), 4.07 (s, 3H, —OCH_3), 7.26–7.30 (m, 1H, Ar-H) 7.37–7.40 (m, 1H, Ar-H), 7.40–7.49 (m, 2H, Ar-H), 7.51–7.59 (d, 1H, Ar-H), 7.76–7.79 (m, 1H, Ar-H), 8.26–8.30 (d, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 53.49, 61.79, 124.93, 124.97, 126.81, 127.82, 127.89, 129.74, 129.81, 130.70, 130.76, 130.93, 131.06, 132.21, 132.45, 132.37, 132.44, 132.83, 133.50, 135.96, 144.62, 145.34, 165.24, 166.80; ms: m/z = 389 [M$^+$], 391 [M$^+$ + 2].

Di-n-propyl-4-phenyl-6-chloroquinoline-2,3-dicarboxylate (g). Yield 81%, m.p. 136–138°C; IR (KBr): 2945, 1741, 1720, 1605, 1218, 1050, 813, 752 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.71–0.76 (t, 3H, —CH_2—CH_3), 1.00–1.05 (t, 2H, —CH_2—CH_3), 1.33–1.45 (m, 2H, —OCH_2—CH_2—CH_3), 1.84–1.86 (m, 2H, —OCH_2—CH_2—CH_3), 3.95–3.99 (t, 2H, —OCH_2—CH_2) 4.40–4.44 (t, 2H, —OCH_2—CH_2), 7.32–7.35 (m, 2H, Ar-H) 7.51–7.53 (m, 3H, Ar-H), 7.58–7.59 (m, 1H, Ar-H), 7.73–7.76 (dd, 1H, Ar-H), 8.25–8.28 (dd, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 10.29, 21.44, 21.93, 52.49, 68.22, 125.37, 127.71, 128.27, 128.50, 129.01, 129.13, 129.20, 129.30, 131.98, 132.17, 132.22, 133.94, 135.44, 145.42, 145.48, 145.79, 147.32, 164.99, 167.27; ms: m/z = 411[M$^+$], 413 [M$^+$ + 2].

Ethyl-n-propyl-4-phenylquinoline-2,3-dicarboxylate (h). Yield 79%, mp 82–85°C; IR (KBr): 2972, 1731, 1229, 1051, 812, 763, 705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.94–1.01 (t, 3H, —CH_2—CH_3), 1.02–1.08 (t, 3H, —CH_2—CH_3), 1.83–1.90 (m, 2H, —OCH_2—CH_2—CH_3), 4.05–4.14 (q, 2H, —OCH_2—CH_2) 4.40–4.48 (t, 2H, —OCH_2—CH_2), 7.35–7.38 (m, 2H, Ar-H), 7.49–7.51 (m, 3H, Ar-H), 7.58–7.62 (m, 2H, Ar-H), 7.81–7.82 (dd, 1H, Ar-H), 8.31–8.34 (dd, 1H, Ar-H); ^{13}C-NMR (CDCl3) δ (ppm) 10.32, 13.59, 21.94, 61.55 68.10, 100.0, 126.59, 128.22, 128.72, 129.00, 129.40, 130.66, 130.89, 147.4, 147.7, 165.5, 168.6; ms: m/z = 363 [M$^+$], 365 [M$^+$ + 2].

Diisopropyl-4-phenyl-6-chloroquinoline-2,3-dicarboxylate (i). Yield 80%, m.p. 180–185°C; IR (KBr): 2986, 1737, 1720, 1605, 1209, 830, 707 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 0.92–0.98 (m, 6H, —CH—$(CH_3)_2$), 1.42–1.44 (m, 6H, —CH—$(CH_3)_2$), 4.03–4.13 (m, 1H, —CH—$(CH_3)_2$), 5.32–5.42 (m, 1H, —CH—$(CH_3)_2$), 7.32–7.36 (m, 2H, Ar-H), 7.51–7.58 (m, 3H, Ar-H), 7.72–7.76 (m,1H, Ar-H), 8.25–8.28 (dd, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 13.53, 13.58, 21.11, 21.68, 61.69,70.68, 125.30, 125.35, 128.18, 128.44, 129.02, 129.07, 129.42, 131.92, 132.01, 132.17, 132.23, 134.17, 135.21, 145.50, 147.14, 164.50, 166.79; ms: m/z = 411[M^+], 413 [M^+ + 2].

Dimethyl-4-phenyl-6-chloroquinoline-2,3-dicarboxylate (j). Yield 80%, m.p. obs.146–148°C. (lit. 162.5–163°C[6]); IR (KBr): 3065, 2954, 1727, 1605, 1220, 1144, 1054, 833, 701cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 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), 7.59–7.60 (m, 1H, Ar-H), 7.74–7.78 (dd, 1H, Ar-H), 8.26–8.29 (dd, 1H, Ar-H).

Dimethyl-4-phenyl-6-chloroquinoline-2,3-dicarboxylate (k). Yield 84%, m.p.: Obs. 144–145°C (lit. 62.5–163°C[6]); IR (KBr): 2954, 1727, 1605, 1220, 1054, 956, 833, 701 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm) 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), 7.59–7.60 (m, 1H, Ar-H), 7.75–7.78 (dd, 1H, Ar-H), 8.26–8.29 (dd, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm) 52.59, 53.60, 100.0, 125.41, 128.44, 128.63, 129.19, 129.24, 132.18, 133.77, 135.66, 145.45, 147.29, 164.05, 167.28.

General procedure for said trisubstituted quinolines with desired transesterification. As a case study, 5-chloro-2-aminobenzophenone (2 mmol) and dimethyl acetylene dicarboxylate (DMAD) (2 mmol) in ethanol (5 mL) and sulphuric acid (0.375 mmol) were heated in oil bath under reflux condition till completion of reaction monitored by TLC. On cooling to room temperature (25°C), the reaction mixture was solidified. It was filtered off, washed with petroleum ether, and recrystalized from ethanol.

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