A Facile One-Pot Synthesis of Substituted Quinolines via New Multicomponent Reaction

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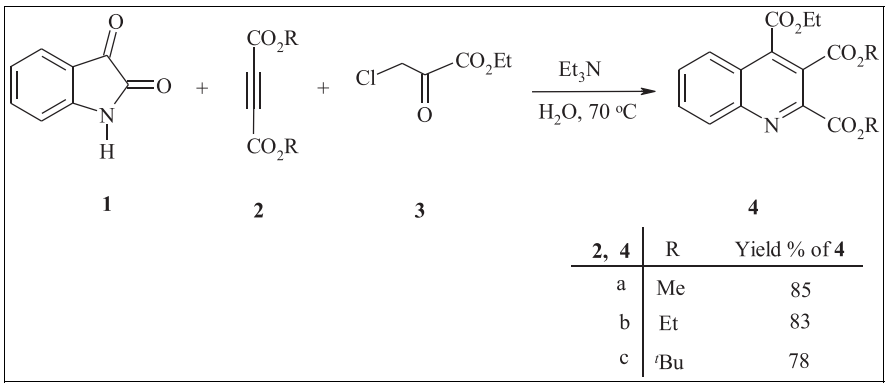

2, 4	R	Yield % of 4
a	Me	85
b	Et	83
c	^{t}Bu	78

An efficient synthesis of quinoline derivatives is described *via* the reaction between ethyl chloropyruvate or alkyl 4-chloroacetoacetate and activated acetylenic compounds in the presence of nucleophilic form of isatin in water as the solvent. Nucleophilic form of isatin is produced from the reaction of isatin and triethylamin.

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INTRODUCTION

Quinolines are important groups of heterocyclic compounds, several derivatives of which have been found to possess useful biological activity such as antimalarial, antibacterial, antiasthmatic, antihypertensive, and anti-inflammatory [1–4]. In addition, quinolines are valuable synthons for the preparation of nano- and meso-structures with enhanced electronic and photonic functions [5–7]. Because of their importance as substructures in a broad range of natural and designed products, significant effort continues to be directed toward the development of new quinoline-based structures and new methods for their construction [8–11]. A number of methods have been reported for the synthesis of quinolines involving a variety of metal catalysts and Lewis acids [12–15]. In this article, as part of our ongoing studies on the multicomponent area, we present herein our results of a novel discovery involving synthesis of quinoline derivatives, using commercially available starting materials in excellent yields. Thus, the reaction of isatin **1**, activated acetylenes **2** and ethyl chloropyruvate **3** or alkyl 4-chloroacetoacetate, at 70°C in water as the solvent, produced quinoline derivatives **4** [15] in good yields (Scheme 1).

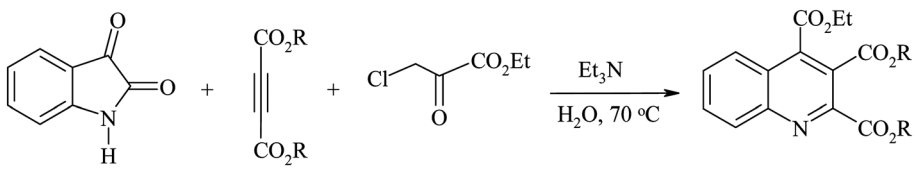
RESULT AND DISCUSSION

The structures of compounds **4a–c** were assigned by a consideration of their IR, ^{1}H NMR, ^{13}C NMR spectroscopic and mass spectrometric data. For example, the ^{1}H NMR spectrum of **4a** exhibited characteristic signals for the methoxy (δ = 3.97, 4.06), ethoxy (δ = 1.45 and 4.55) along with multiplets (δ = 7.45–8.29) for the aromatic protons. In the ^{13}C NMR spectrum, the signals corresponding to ester carbonyl groups of **4a** were observed at δ = 165.3, 165.7 and 165.8 ppm. The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 317.

Under similar conditions, the reaction of alkyl 4-chloroacetoacetate and acetylenic compounds, with isatin as a pronucleophile leads to functionalized quinolines (Scheme 2).

A tentative mechanism for this transformation is proposed in Scheme 3 [15]. Intermediate **7** is formed from the reaction of anionic species of isatin and acetylenic compound **2**, which react with ethyl chloropyruvate to produce anionic species of **8** and **9**. Intermediate **9**, then undergoes a rearrangement to produce **10**. Intermediate **12** may be produced by hydrogen elimination from **10** and, intramolecular nucleophilic substitution reaction. Aromatization of quinoline ring is achieved by loss of salt **15**.

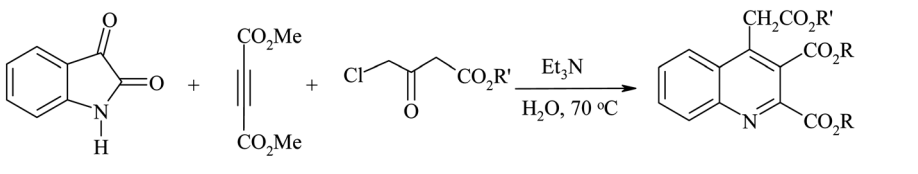
Scheme 1. Three-component reactions of isatin, acetylenic compounds, and ethyl chloropyruvate.



1 **2** **3** **4**

2, 4	R	Yield % of 4
a	Me	85
b	Et	83
c	^{t}Bu	78

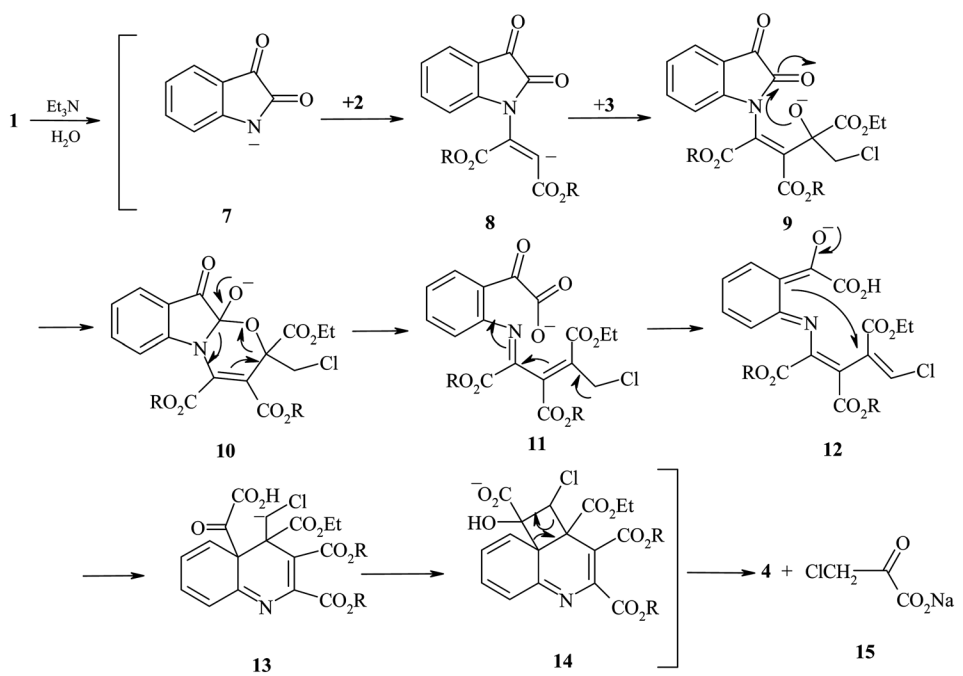
Scheme 2. Three-component reactions of isatin, acetylenic compounds, and alkyl 4-chloroacetoacetate.



1 **2** **5** **6**

5, 6	R	R'	Yield % of 6
a	Me	Me	87
b	Me	Et	85

Scheme 3. Possible mechanism for the formation of products **4**.



7 **8** **9** **10** **11** **12** **13** **14** **15**

In conclusion, the reaction between ethyl chloropyruvate or alkyl 4-chloroacetoacetate and acetylenic compounds, with isatin as a pronucleophile leads to functionalized quinolines and with the regioselectivity on the quinoline accompanied by esteric groups in excellent yields. This procedure has the advantage that the reaction is performed under simple conditions, and the starting materials can be used without any purification or modification.

EXPERIMENTAL

All the chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal-9100 apparatus. IR spectra were recorded with a *Shimadzu IR-460* spectrometer. ^{1}H, and ^{13}C NMR spectra were measured with a *BRUKER DRX-500 AVANCE* spectrometer at 500.1 and 125.7 MHz, respectively. ^{1}H, and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ using TMS or 85% H_3PO_4 as external standard.; δ in parts per million, *J* in hertz. EIMS (70 eV): Mass spectra were obtained with a *Finnigan-MAT-8430* mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were obtained with a *Heraeus CHN-O-Rapid* analyzer.

General procedure for preparation of compounds 4a-c and 6a-b. Ethyl chloropyruvate or alkyl 4-chloroacetoacetate (2 mmol) and **3** was added slowly to a mixture of isatin (0.298 g, 2 mmol) and triethylamine (2 mmol) in 10 mL of H_2O at 70°C temperature. The reaction mixture was stirred for 12 h. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3:1), the organic phase of reaction mixture was extracted with ethyl acetate (3 × 10 mL). The solvent was removed under reduced pressure, and the residue was purified by silica gel (Merck 230–240 mesh) column chromatography using 4:1 *n*-hexane-EtOAc mixture as eluent to afford the pure product.

4- Ethyl 2,3-dimethyl 2,3,4-quinolinetricarboxylate (4a). Yellow Oil, yield (85%). IR (KBr) (ν_{max}/cm^{-1}): 1734, 1719, 1717, 1554, 1431, 1304, 1244. ^{1}H NMR: 1.45 (3 H, t, ^3J = 7.2, Me), 3.97 (3 H, s, Me), 4.06 (3 H, s, Me), 4.55 (2 H, q, ^3J = 7.2, OCH_2), 7.75 (1 H, t, ^3J = 8.3, CH), 7.90 (1 H, t, ^3J = 8.5, CH), 8.09 (1 H, d, ^3J = 8.5, CH), 8.29 (1 H, d, ^3J = 8.5, CH). ^{13}C NMR: 14.0 (Me), 52.5 (Me), 53.3 (Me), 62.7 (OCH_2), 123.8 (C), 124.4 (C), 125.6 (CH), 129.6 (CH), 130.5 (CH), 132.1 (CH), 140.2 (C), 147.6 (C), 147.8 (C), 165.3 (C═O), 165.7 (C═O), 165.8 (C═O). EI-MS: 317 (M^+, 20), 287 (65), 272 (54), 258 (85), 246 (60), 129 (100), 71 (54), 59 (60). Anal. Calcd for $C_{16}H_{15}NO_6$ (317.29): C, 60.57; H, 4.76; N, 4.41; found: C, 60.14; H, 5.05; N, 4.29%.

Triethyl 2,3,4-quinolinetricarboxylate (4b). Yellow Oil, yield (83%). IR (KBr) (ν_{max}/cm^{-1}): 1736, 1725, 1723, 1603, 1555, 1456, 1374, 1300, 1220, 1016. ^{1}H NMR: 1.37 (3 H, t, ^3J = 7.1, Me), 1.42 (3 H, t, ^3J = 7.2, Me), 1.47 (3 H, t, ^3J = 7.2, Me), 4.40 (2 H, q, ^3J = 7.2, OCH_2), 4.50 (2 H, q, ^3J = 7.2, OCH_2), 4.53 (2 H, q, ^3J = 7.2, OCH_2), 7.69 (1 H, t, ^3J = 7.9, 1 CH), 7.84 (1 H, t, ^3J = 8.5, CH), 8.01 (1 H, d, ^3J = 8.5, CH), 8.25 (1 H, d, ^3J = 8.5, CH). ^{13}C NMR: 13.9 (Me), 14.0 (Me), 14.1 (Me), 62.4 (OCH_2), 62.6 (OCH_2), 62.7 (OCH_2), 122.7 (C), 123.7 (C), 125.6 (CH), 129.7 (CH), 130.5 (CH), 131.9 (CH), 140.5 (C), 147.6 (C), 147.8 (C), 165.3 (C═O), 165.5 (C═O), 165.6 (C═O). EI-MS: 345 (M^+, 20), 274 (54), 216 (54), 129 (66), 71 (48). Anal. Calcd for $C_{18}H_{19}NO_6$ (345.35): C, 62.60; H, 5.55; N, 4.06; found: C, 61.86; H, 5.35; N, 4.01%.

2,3-Di(*tert*-butyl) 4- ethyl-2,3,4-quinolinetricarboxylate (4c). Yellow Oil, yield (78%). IR (KBr) (ν_{max}/cm^{-1}): 1732, 1731, 1653, 1510, 1372, 1124. ^{1}H NMR: 1.44 (3 H, t, ^3J = 7.2, Me), 1.61 (9 H, s, 3 Me), 1.66 (9 H, s, 3 Me), 4.54 (2 H, q, ^3J = 7.2, OCH_2), 7.67 (1 H, t, ^3J = 8.4, 1 CH), 7.81 (1 H, t, ^3J = 8.4, CH), 7.90 (1 H, d, ^3J = 8.4, CH), 8.21 (1 H, d, ^3J = 8.4, CH). ^{13}C NMR: 14.1 (Me), 27.9 (3 Me), 28.0 (3 Me), 62.4 (OCH_2), 83.4 (C), 83.6 (C), 123.4 (C), 124.2 (C), 125.3 (CH), 129.2 (CH), 130.5 (CH), 131.4 (CH), 140.1 (C), 147.4 (C), 150.6 (C), 164.3 (C═O), 165.2 (C═O), 165.9 (C═O). Anal. Calcd for $C_{22}H_{27}NO_6$ (401.45): C, 65.82; H, 6.78; N, 3.49; found: C, 64.54; H, 6.35; N, 3.42%.

Dimethyl 4-(2-methoxy-2-oxoethyl)-2,3-quinolinedicarboxylate (6a). Yellow Oil, yield (87%). IR (KBr) (ν_{max}/cm^{-1}): 1728, 1717, 1710, 1537, 1482, 1315. ^{1}H NMR: 3.78 (3 H, s, MeO), 3.82 (3 H, s, MeO), 3.87 (3 H, s, MeO), 4.02 (2 H, s, CH_2), 7.74 (1 H, t, ^3J = 7.9, CH), 7.82 (1 H, t, ^3J = 8.0, CH), 8.07 (1 H, d, ^3J = 8.0, CH), 8.27 (1 H, d, ^3J = 8.0, CH). ^{13}C NMR: 41.3 (CH_2), 52.3 (MeO), 52.8 (MeO), 53.2 (MeO), 121.8 (C), 122.4 (C), 123.5 (CH), 124.8 (CH), 130.8 (CH), 132.6 (CH), 141.0 (C), 145.8 (C), 148.5 (C), 163.8 (C═O), 164.2 (C═O), 164.6 (C═O). Anal. Calcd for $C_{16}H_{15}NO_6$ (317.29): C, 60.57; H, 4.77; N, 4.41; found: C, 60.42; H, 4.65; N, 4.35%.

Dimethyl 4-(2-ethoxy-2-oxoethyl)-2,3-quinolinedicarboxylate (6b). Yellow Oil, yield (85%). IR (KBr) (ν_{max}/cm^{-1}): 1730, 1725, 1715, 1548, 1452, 1325. ^{1}H NMR: 1.34 (3 H, t, ^3J = 7.4, Me), 3.75 (3 H, s, MeO), 3.85 (3 H, s, MeO), 3.95 (2 H, s, CH_2), 4.28 (2 H, q, ^3J = 7.4, OCH_2), 7.72 (1 H, t, ^3J = 8.0, CH), 7.87 (1 H, t, ^3J = 8.2, CH), 8.12 (1 H, d, ^3J = 8.3, CH), 8.25 (1 H, d, ^3J = 8.3, CH). ^{13}C NMR: 14.1 (Me), 41.2 (CH_2), 52.3 (Me), 53.0 (Me), 62.5 (OCH_2), 120.2 (C), 121.5 (C), 123.4 (CH), 125.6 (CH), 131.2 (CH), 132.7 (CH), 140.6 (C), 146.8 (C), 148.2 (C), 164.2 (C═O), 164.8 (C═O), 165.3 (C═O). Anal. Calcd for $C_{17}H_{17}NO_6$ (331.32): C, 61.63; H, 5.17; N, 4.23; found: C, 61.52; H, 5.04; N, 4.12%.

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