A Novel One-Pot Synthesis of Substituted Quinolines

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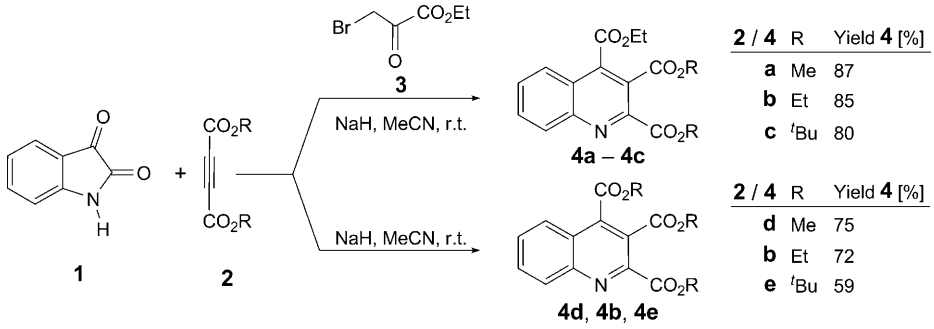
A synthesis of quinoline derivatives is described *via* reaction between ethyl bromopyruvate (=ethyl 3-bromo-2-oxopropanoate), acetylenedicarboxylate, and isatin (=1*H*-indole-2,3-dione) in the presence of NaH as a base. Also, these reactions were performed without ethyl bromopyruvate. The reaction in the presence of ethyl bromopyruvate provides regioselectively a quinoline with the ethyl ester group in 4-position. In the absence of ethyl bromopyruvate, the reaction leads to functionalized quinolines with the same ester groups in 2-, 3-, and 4-positions.

Introduction. – Heterocyclic aromatic aza compounds, especially quinoline derivatives, are widely present in several natural compounds (*e.g.*, *Cinchona* alkaloids) [1–3] and pharmacologically active substances displaying a broad range of biological activity [4–6]. Quinoline compounds have been found to possess antiasthmatic, antibacterial, anti-inflammatory, and antihypertensive properties [7–9]. In addition to the medicinal applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes [10]. Quinolines are also known for their formation of conjugated molecules and polymers that combine enhanced electronic, optoelectronic, or nonlinear optical properties with excellent mechanical properties [11]. A number of methods have been reported for the synthesis of quinolines involving a variety of metal catalysts and *Lewis* acids [12–15]. Especially the *Pfitzinger* reaction [16] of isatins with α-methylidene carbonyl compounds is widely used for the synthesis of physiologically active derivatives of substituted quinoline-4-carboxylic acids [17]. However, many of these procedures are not fully satisfactory with regard to operational simplicity, cost of the reagent, drastic reaction conditions, and relatively low yield. Therefore, a simple, general, and efficient procedure is still in demand for the preparation of these important heterocyclic compounds.

Results and Discussion. – In this article, as part of our ongoing studies on the multicomponent reactions [18–20], we present our results of a novel synthesis of quinoline derivatives, using commercially available starting materials. Thus, the reaction of isatin (=1*H*-indole-2,3-dione; **1**), and acetylenedicarboxylates **2** with ethyl bromopyruvate (=ethyl 3-bromo-2-oxopropanoate; **3**), in the presence of NaH at room temperature and MeCN as a solvent, gave quinoline derivatives **4** in good yields (*Scheme 1*).

Scheme 1



The structures of compounds **4a**–**4c** were assigned by consideration of their IR, ^{1}H- and ^{13}C-NMR, and MS data. For example, the ^{1}H-NMR spectrum of **4a** exhibited characteristic signals for the MeO (δ(H) 3.97, 4.06) and EtO groups (1.45 and 4.55), along with four signals (7.75 (*t*, *J* = 8.3), 7.90 (*t*, *J* = 8.5), 8.09 (*d*, *J* = 8.5), and 8.29 (*d*, *J* = 8.5)) for the aromatic H-atoms. In the ^{13}C-NMR spectrum, the signals corresponding to the ester C=O groups of **4a** were observed at δ(C) 165.3, 165.7, and 165.8 ppm. The mass spectrum of **4a** displayed the molecular ion peak at *m*/*z* 317. The ^{1}H- and ^{13}C-NMR spectra of **4b** and **4c** are similar to those of **4a** except for the ester moieties at C(2) and C(3) of quinoline, which exhibited characteristic resonances in appropriate regions of the spectrum (see *Exper. Part*). The position of the different ester groups in **4** are confirmed by nuclear *Overhauser* effect measurements. Thus, when the *d* at 8.29 ppm, which belongs to H–C(5), was irradiated, the *t* at 1.44 ppm was enhanced by *ca.* 7%, while the MeO signals remained unchanged. This result is in agreement with the proposed structure for **4a**.

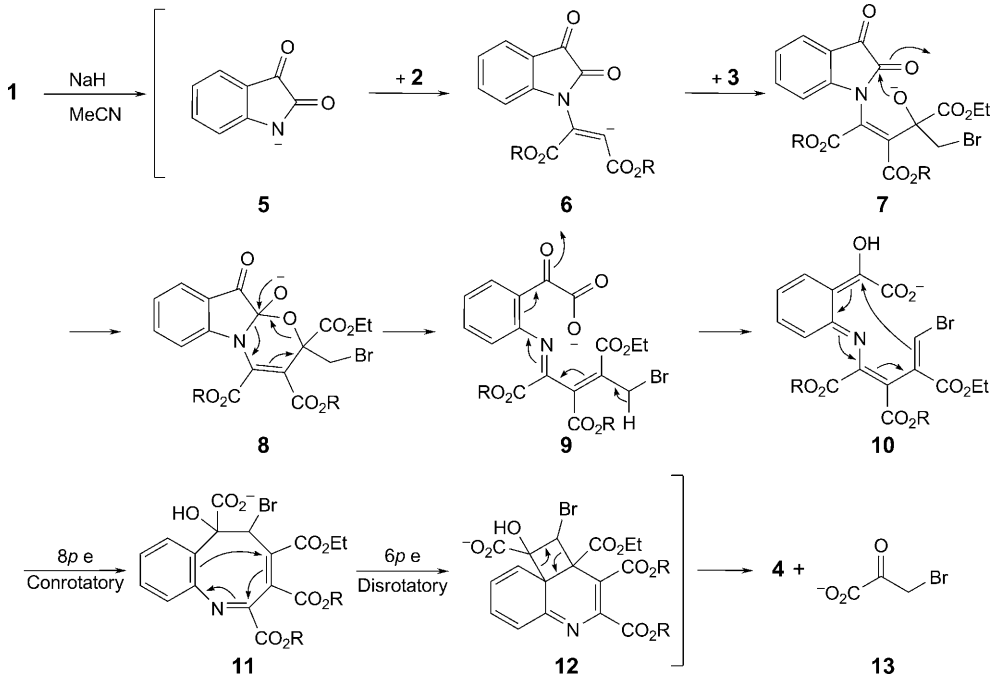
Although the mechanistic details of the reaction are not known, a rationalization may be proposed to explain the product formation (*Scheme 2*). From the reaction of deprotonated isatin (**5**) and **2**, intermediate **6** is formed, which, subsequently, reacts with **3** to produce the anionic species **7** and **8**. Intermediate **8**, then, undergoes a rearrangement to give **9**, from which intermediate **10** may be generated by a H-atom shift. Electrocyclic processes could lead to **11** and **12** [21], and an aromatization of the latter is achieved by loss of the carboxylate **13**.

Under similar conditions, the reaction between acetylenedicarboxylates **2** and isatin as a 'pronucleophile' leads to functionalized quinolines with three equal ester groups in good yields (*Scheme 1*).

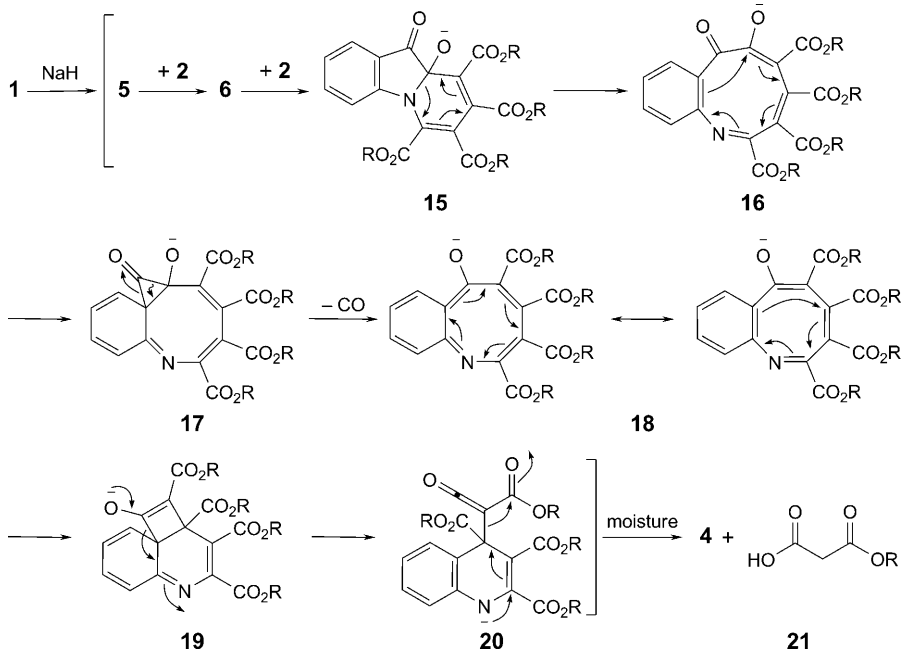
The ^{1}H-NMR spectrum of **4d** exhibited three *singlet*s for MeO groups at δ(H) 3.96, 4.05, and 4.06 ppm, together with characteristic signals for the aromatic moiety. The ^{13}C-NMR spectrum of **4d** showed distinct resonances in agreement with the proposed structure. The mass spectrum of **4d** displayed the molecular ion peak at *m*/*z* 303.

Mechanistically, the reaction can be considered to proceed *via* reaction of **5** with two equivalents of the acetylenic compounds to produce intermediate **15**. The following intermediates **16** and **17** may be formed by pericyclic reactions, followed by elimination of CO to give **18** [22]. Subsequent pericyclic reactions could lead to **19**, which then undergoes rearrangement and aromatization *via* **20** to generate **4** and **21** (*Scheme 3*).

Scheme 2



Scheme 3



In summary, we have described a convenient route to functionalized quinolines from ethyl bromopyruvate (**3**), acetylenedicarboxylate **2**, and isatin (**1**) in the presence of NaH. The reactions provide regioselectively a quinoline with the ethyl ester group at C(4). In the absence of ethyl bromopyruvate, the reaction leads to functionalized quinolines with the same ester groups in 2-, 3-, and 4-positions. The advantage of the present procedure is that the reaction is performed under convenient conditions by simple mixing of the starting materials.

Experimental Part

General. Compounds **1**, **2**, and **3** were obtained from *Merck* and were used without further purification. IR Spectra: *Shimadzu IR-460* spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker DRX-500 AVANCE* instrument, in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. MS: *Finnigan-MAT-8430* mass spectrometer, at 70 eV; in m/z. Elemental analyses (C,H,N): *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **4a**–**4c**. To a stirred soln. of dialkyl but-2-ynedioate **2** (2 mmol), and ethyl 3-bromo-2-oxopropanoate (**3**; 0.39 g, 2 mmol), in 10 ml of MeCN was added a mixture of isatin (=1*H*-indole-2,3-dione; **1**; 0.298 g, 2 mmol) and NaH (0.048 g, 2 mmol) in MeCN at r.t. The mixture was stirred for 12 h. Then, the solvent was removed under reduced pressure, and the viscous residue was purified by CC (SiO_2; 230–240 mesh, *Merck*) using hexane/AcOEt 8:1 as eluent to afford the pure product.

These reactions were also performed without **3**, leading to compounds **4b**, **4d**, and **4e**. For these reactions, corresponding **2** was added slowly to a mixture of isatin (**1**; 0.298 g, 2 mmol) and NaH (0.048 g, 2 mmol) in 10 ml of MeCN at r.t. The mixture was stirred for 12 h. Then, the solvent was removed under reduced pressure, and the viscous residue was purified by the conditions mentioned above to afford the pure product.

4-Ethyl 2,3-Dimethyl Quinoline-2,3,4-tricarboxylate (**4a**). Yield: 0.55 g (87%). Yellow oil. IR (KBr): 1734, 1719, 1717, 1554, 1431, 1304, 1244. ^1H-NMR: 1.45 (*t*, ^3J = 7.2, Me); 3.97 (*s*, Me); 4.06 (*s*, Me); 4.55 (*q*, ^3J = 7.2, CH_2O); 7.75 (*t*, ^3J = 8.3, CH); 7.90 (*t*, ^3J = 8.5, CH); 8.09 (*d*, ^3J = 8.5, CH), 8.29 (*d*, ^3J = 8.5, CH). ^{13}C-NMR: 14.0 ($MeCH_2$); 52.5, 53.3 (2 MeO); 62.7 (CH_2O); 123.8 (C); 124.4 (C); 125.6, 129.6, 130.5, 132.1 (4 CH); 140.2, 147.6, 147.8 (3 C); 165.3, 165.7, 165.8 (3 C=O). EI-MS: 317 (20), 287 (65), 272 (54), 258 (85), 246 (60), 129 (100), 71 (54), 59 (60). Anal. calc. for $C_{16}H_{15}NO_6$ (317.29): C 60.22, H 4.96, N 4.41; found: C 60.14, H 5.05, N 4.29.

Triethyl Quinoline-2,3,4-tricarboxylate (**4b**). Yield: 0.58 g (85%). Yellow oil. IR (KBr): 1736, 1725, 1723, 1603, 1555, 1456, 1374, 1300, 1220, 1016. ^1H-NMR: 1.37 (*t*, ^3J = 7.2, Me); 1.42 (*t*, ^3J = 7.2, Me); 1.47 (*t*, ^3J = 7.2, Me); 4.40 (*q*, ^3J = 7.2, CH_2O); 4.50 (*q*, ^3J = 7.2, CH_2O); 4.53 (*q*, ^3J = 7.2, CH_2O); 7.69 (*t*, ^3J = 7.9, CH); 7.84 (*t*, ^3J = 8.5, CH); 8.01 (*d*, ^3J = 8.5, CH); 8.25 (*d*, ^3J = 8.5, CH). ^{13}C-NMR: 13.9, 14.0, 14.1 ($MeCH_2$); 62.4, 62.6, 62.7 (3 CH_2O); 122.7 (C); 123.7 (C); 125.6, 129.7, 130.5, 131.9 (4 CH); 140.5, 147.6, 147.8 (3 C); 165.3, 165.5, 165.6 (3 C=O). EI-MS: 345 (20), 274 (54), 216 (54), 129 (66), 71 (48). Anal. calc. for $C_{18}H_{19}NO_6$ (345.35): C 62.60, H 5.55, N 4.06; found: C 62.27, H 5.35, N 4.01.

*2,3-Di-(*tert*-butyl) 4-Ethyl Quinoline-2,3,4-tricarboxylate* (**4c**). Yield: 0.64 g (80%). Yellow oil. IR (KBr): 1732, 1731, 1653, 1510, 1372, 1124. ^1H-NMR: 1.44 (*t*, ^3J = 7.2, Me); 1.61 (*s*, 3 Me); 1.66 (*s*, 3 Me); 4.54 (*q*, ^3J = 7.2, CH_2O); 7.67 (*t*, ^3J = 8.4, CH); 7.81 (*t*, ^3J = 8.4, CH); 7.90 (*d*, ^3J = 8.4, CH); 8.21 (*d*, ^3J = 8.4, CH). ^{13}C-NMR: 14.1 ($MeCH_2$); 27.9 (3 Me); 28.0 (3 Me); 62.4 (CH_2O); 83.4, 83.6, 123.4, 124.2 (4 C); 125.3, 129.2, 130.5, 131.4 (4 CH); 140.1, 147.4, 150.6 (3 C); 164.3, 165.2, 165.9 (3 C=O). Anal. calc. for $C_{22}H_{27}NO_6$ (401.45): C 65.82, H 6.43, N 3.49; found: C 65.34, H 6.35, N 3.42.

Trimethyl Quinoline-2,3,4-tricarboxylate (**4d**). Yield: 0.45 g (75%). Yellow oil. IR (KBr): 1721, 1719, 1717, 1549, 1431, 1308, 1265, 1230, 1195. ^1H-NMR: 3.96, 4.05, 4.06 (3*s*, 3 MeO); 7.74 (*t*, ^3J = 8.2, CH); 7.88 (*t*, ^3J = 8.3, CH); 8.05 (*d*, ^3J = 8.3, CH); 8.28 (*d*, ^3J = 8.5, CH). ^{13}C-NMR: 53.2, 53.3, 53.4 (3 MeO); 123.1 (C); 123.8 (C); 125.7, 130.1, 130.6, 132.1 (4 CH); 140.1, 147.7, 147.9 (3 C); 165.7, 165.8, 165.9 (3 C=O). EI-MS: 303 (30), 273 (85), 244 (75), 187 (80), 129 (100), 59 (45). Anal. calc. for $C_{15}H_{13}NO_6$ (303.26): C 59.41, H 4.32, N 4.62; found: C 59.35, H 4.36, N 4.60.

Triethyl Quinoline-2,3,4-tricarboxylate (**4b**). Yield: 0.49 g (72%). Yellow oil. Anal. calc. for $C_{18}H_{19}NO_6$ (345.35): C 62.60, H 5.55, N 4.06; found: C 62.59, H 5.54, N 4.07.

*Tri-(*tert*-butyl) Quinoline-2,3,4-tricarboxylate* (**4e**). Yield: 0.49 g (59%). Yellow oil. IR (KBr): 1731, 1725, 1720, 1653, 1510, 1372, 1124. ^{1}H-NMR: 1.26 (*s*, 3 Me); 1.61 (*s*, 3 Me); 1.67 (*s*, 3 Me); 7.67 (*t*, $^3J = 9.2$, CH); 7.82 (*t*, $^3J = 8.4$, CH); 7.92 (*d*, $^3J = 9.2$, CH); 8.24 (*d*, $^3J = 8.4$, CH). ^{13}C-NMR: 27.9 (3 Me); 28.1 (3 Me); 29.7 (3 Me); 83.4, 83.5, 83.6, 123.1, 123.5 (5 C); 125.3, 129.2, 130.5, 131.4 (4 CH); 140.1, 147.4, 150.6 (3 C); 164.4, 165.2, 165.9 (3 C=O). EI-MS: 345 (10), 274 (54), 216 (54), 129 (66), 71 (48). Anal. calc. for $C_{24}H_{31}NO_6$ (429.51): C 67.11, H 7.27, N 3.26; found: C 67.09, H 7.11, N 3.19.

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Received August 26, 2009