The Chemistry of 2*H*-3,1-Benzoxazine-2,4-(1*H*)-dione (Isatoic Anhydride); 13[1]. Facile Preparation of 4-Oxoquinoline-2-acetic Acid Derivatives

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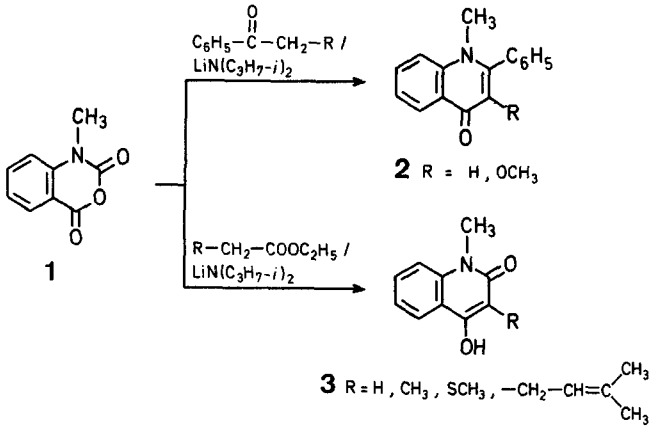
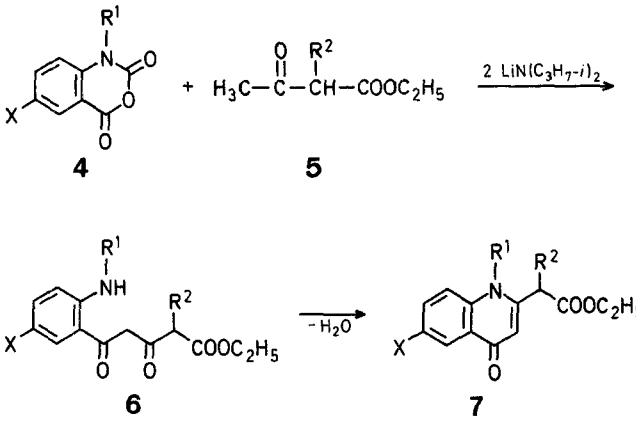
Functionalized 2- and 4-quinolinones are interesting compounds possessing a broad spectrum of pharmacological activities[2-7]. The nature of the substituent and its location on the quinoline nucleus dictates the biological profile of the molecule.



In previous reports[8-15] we have shown that a wide variety of quinolines are readily accessible from the reaction of isatoic anhydrides with sodium salts of active methylene derivatives in dimethylacetamide at elevated temperatures (80–120°C). However, it has recently been found that *N*-methylisatoic anhydride (**1**) reacts smoothly at low temperatures (20° to −65°C) in tetrahydrofuran with either ketone enolates[16] to give 4-quinolinones **2** or with ester enolates[17] to produce 2-quinolinones **3**.



In an effort to examine the scope of this reaction, the interaction of isatoic anhydrides with β-ketoester dianions was investigated. Polymetallated derivatives of β-ketoesters are easily generated[19]. The mixed dianion can be prepared by sequential treatment of β-ketoesters **5** with sodium hydride followed by *n*-butyllithium, whereas the dilithiated species is readily formed with two equivalents of lithium diisopropylamide[20]. When *N*-alkylisatoic anhydrides **4** are added to solutions of dilithiated ethyl acetoacetate derivatives at −65°C an almost instantaneous reaction occurs. Complete consumption of both starting materials is observed within 2 min after the addition of **4**. Quenching the reaction with saturated ammonium chloride gives a two-phase mixture with an intensely yellow organic phase. A thin layer chromatogram of the organic solution exhibits a spot less polar than **4**. When the solvent is removed from the organic solution the yellow color fades. Thin layer analysis indicates the disappearance of the original product and the formation of a new spot more polar than **4**.

Table. 4-Oxo-1,4-dihydroquinoline-2-acetic Acid Ethyl Esters **7** prepared

Product No.	R^1	R^2	X	Yield [%]	m.p. [°C][a]	Molecular formula[b]	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
7a	H_3C	H	H	64	127–129°	$C_{14}H_{15}NO_3$ (245.3)	1730, 1620, 1600	1.25 (t, 3 H, J=7 Hz); 3.70 (s, 3 H); 3.75 (s, 2 H); 4.20 (q, 2 H, J=7 Hz); 6.20 (s, 1 H); 7.15–7.85 (m, 3 H); 8.4 (m, 1 H)
7b	H_3C	H	Cl	47	128–130°	$C_{14}H_{14}ClNO_3$ (279.7)	1732, 1620	1.25 (t, 3 H, J=7 Hz), 3.65 (s, 3 H), 3.75 (s, 2 H), 4.22 (q, 2 H, J=7 Hz), 6.18 (s, 1 H), 7.24–7.55 (m, 2 H), 8.32 (m, 1 H).
7c	H_3C—$COOCH_2CH_2$—	H	H	41	93–95°	$C_{17}H_{19}NO_5$ (317.3)	1732, 1622	1.30 (t, 3 H, J=7 Hz), 2.08 (s, 3 H), 3.90 (s, 2 H), 4.25 (q, 2 H, J=7 Hz), 4.48 (m, 4 H), 6.31 (s, 1 H), 7.23–7.80 (m, 3 H), 8.47 (m, 1 H).
7d	4-F—C_6H_4—CH_2	H	H	46	154–157°	$C_{20}H_{18}FNO_3$ (339.4)	1730, 1621	1.23 (t, 3 H, J=7 Hz), 3.65 (s, 2 H), 4.11 (q, 2 H, J=7 Hz), 5.48 (s, 2 H), 6.37 (s, 1 H), 6.95–7.68 (m, 7 H), 8.49 (m, 1 H).
7e	H_3C	H_3C	H	61	83–86°	$C_{15}H_{17}NO_3$ (259.3)	1730, 1620	1.21 (t, 3 H, J=7 Hz), 1.60 (d, 3 H, J=7 Hz), 3.75 (s, 3 H), 4.0 (m, 1 H), 4.19 (q, 2 H, J=7 Hz), 6.30 (s, 1 H), 7.17–7.86 (m, 3 H), 8.40 (m, 1 H).

[a] All products were crystallized from dichloromethane/ether.

[b] Satisfactory microanalyses obtained: C ±0.4; H ±0.4.

Isolation and characterization of this new product shows it to be a 4-oxoquinoline-2-acetic acid ethyl ester **7**.

Probably, the initial product formed in the reaction is the acyclic derivative **6**. The yellow color observed for solutions of **6** is characteristic for systems of this type and has been reported for similar intermediates formed in analogous reactions of isatoic anhydrides with ester enolates[17]. Dehydrative cyclization during the work-up process then furnishes the quinolinones **7**.

1-Substituted 4-Oxo-1,4-dihydroquinoline-2-acetic Acid Ethyl Esters 7; General Procedure:

To a solution of diisopropylamine (8.0 g, 0.08 mol) in dry tetrahydrofuran (160 ml) at 0°C, under a blanket of nitrogen, is added *n*-butyllithium (5.12 g, 0.08 mol as a 1.6 molar solution). To this is added dropwise a solution of the β-keto ester **5** (0.04 mol) in tetrahydrofuran (25 ml) and the resulting yellow solution is stirred at 0°C for 1 h. After cooling to −65°C, a solution of **4**[8] (0.02 mol) in tetrahydrofuran (80 ml) is added slowly and the mixture is stirred at −65°C for 20 min. The mixture is quenched with saturated ammonium chloride solution (100 ml) and the organic phase is separated. The aqueous phase is extracted with dichloromethane (2 × 100 ml), the organic solutions are combined, and dried with sodium sulfate. The solvent is removed under reduced pressure and the residue is chromatographed on silica gel using methanol/chloroform (5/95) as eluent.

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