

A Convenient Preparation of 1,4-Dihydro-1-methyl-4-oxo-2-quinolinecarboxaldehyde from *N*-Methylisatoic Anhydride

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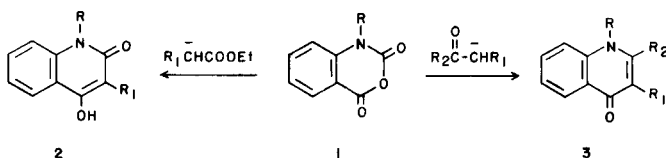
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The dianion of hydroxyacetone is readily generated with LDA in THF at -65° . This dianion reacts rapidly with *N*-methylisatoic anhydride (**6**) at -65° to furnish 2-hydroxymethyl-1-methylquinolin-4(1*H*)-one (**12**). The alcohol is oxidized to aldehyde **4** with manganese dioxide, and is subsequently converted to α,β -unsaturated ester **5** under Horner-Emmons conditions.

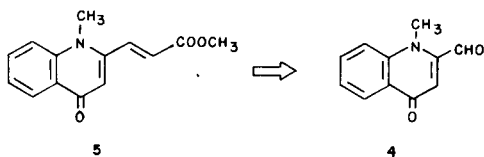
J. Heterocyclic Chem., **23**, 1717 (1986).

For the past 10 years, our laboratory has been concerned with the functionalization of quinolines with the aim that they can be developed into useful intermediates for the synthesis of biologically active compounds.

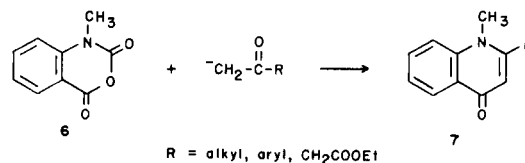
An important heterocycle which we have found useful for the construction of quinolines is the isatoic anhydride ring system **1**. Reaction of **1** with carbanions derived from active methylene compounds allows a wide variety of functional groups to be placed around the periphery of the quinoline nucleus [1,2,3].



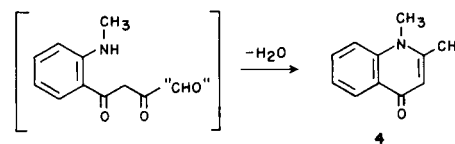
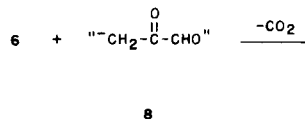
A project in our laboratory required the preparation of the α,β -unsaturated ester **5**. It appeared that the easiest method to fabricate this molecule with the correct olefin stereochemistry would be to employ the Horner-Emmons version of the Wittig reaction on an intermediate aldehyde such as **4**.



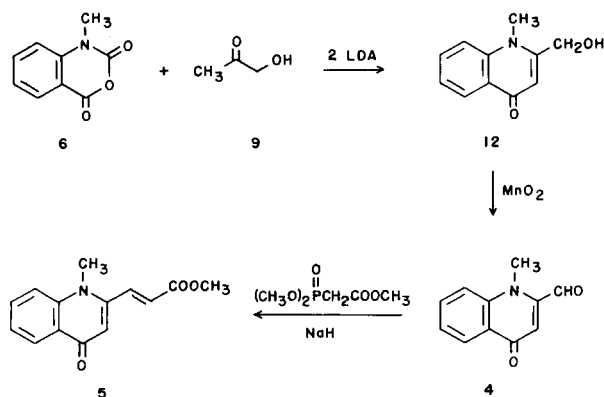
Drawing upon previous experience from this laboratory, it has been shown that 2-substituted-4-quinolones **7** are easily accessible from the reaction of *N*-methylisatoic anhydride (**6**) with methyl ketone enolates [4,5,6]. The transformation takes place by initial attack of the anion on the carbonyl in the 4-position of the benzoxazine ring where subsequent loss of carbon dioxide followed by dehydrative ring closure affords the product.



With this in mind one can envision constructing **4** in a quick and efficient manner by an analogous hetero ring opening reaction of **6** with a 2-ketopropionaldehyde anion equivalent (**8**).



A suitable candidate for **8**, which differs only in oxidation state, is hydroxyacetone (acetol) (**9**). This inexpensive commercially available material, when treated with two equivalents of LDA at -65° , smoothly forms the dilithiated species $\text{CH}_2=\text{C}(\text{OLi})\text{CH}_2\text{OLi}$. This dianion reacts rapidly with **6** at -65° [7] to consume the anhydride within 20 minutes. After quenching the reaction mixture with saturated ammonium chloride solution, a deep yellow color develops which is indicative for the presence of a β -diketone species believed to be **11** [7]. Colors of this type have been consistently observed, and in some instances the intermediate characterized, in previous investigations [8,9]. In this case, the intermediate **11** could not be characterized due to spontaneous ring closure upon removal of the solvent from the reaction mixture. Consequently, the desired product **12** was isolated directly in a single operation in a yield of 50%.



Oxidation of the alcohol function of **12** to the requisite aldehyde **4** is cleanly accomplished with activated manganese dioxide in refluxing methylene chloride. A 1:4 (wt/wt) ratio of substrate to oxidizing agent provides an optimal isolated yield of about 50%. This moderate yield is primarily due to the propensity of the product **4** to be adsorbed on the surface of the manganese dioxide. An almost linear relationship in reduction of yield versus quantity of manganese dioxide can be observed. For example, if the ratio of manganese dioxide is increased to 1:7 the yield of **4** is reduced to 24%. A ratio of 1:10 further reduces the yield to 8%. On the other hand, reducing the ratio of manganese dioxide:**12** to 1:1 increases the mass balance of organic material to 80%, however, this consists of a 56:44 mixture of aldehyde **4** and unreacted alcohol **12**.

Methods of oxidation of **12** to **4** are limited to those which occur exceptionally clean, and do not require chromatographic purification. Aldehyde **4** has a tendency towards hydration, and exposure to silica gel is sufficient to cause it to hydrate and adhere to it.

Conversion of **4** to the α,β -unsaturated ester **5** proceeds without incident under Horner-Emmons conditions using trimethylphosphonoacetate and sodium hydride. The nmr spectrum of **5** exhibits the olefin protons as the expected two sets of doublets each centered at δ 7.75 and δ 6.47 respectively, and shows a *trans* coupling of 15.7 Hz for both of the doublets.

In summary, 2-functionalized-4-quinolones are easily accessible from the reaction of an isatoic anhydride with the lithio dianion of hydroxyacetone. As far as the author is aware, this is the first time that the dianion of hydroxyacetone has been generated and used synthetically. Other synthetic applications of this dianion are presently being investigated.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on either Perkin-Elmer Model 257 and 457, or Analect FX-6200 spectro-

photometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on EM-360 and Jeol FX-90-Q spectrometers using TMS as an internal reference. Chemical shifts are quoted in parts per million (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet).

Enolate generating reactions were conducted under a nitrogen atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. No attempt has been made to optimize the yields of the described reactions.

2-Hydroxymethyl-1-methylquinolin-4(1H)-one (**12**).

To a solution of 12.1 g (0.12 mole) of diisopropylamine in 300 ml of tetrahydrofuran (at -30°) was added 7.8 g (0.122 mole) of *n*-butyllithium (1.6M in hexane). After cooling to -65° , a solution of 4.5 g (0.06 mole) of hydroxyacetone in 75 ml of tetrahydrofuran was added dropwise, and the mixture was stirred at -65° for 45 minutes. To this was added slowly a solution of 5.3 g (0.03 mole) of **6** in 120 ml of tetrahydrofuran. Stirring was continued for 20 minutes during which time a precipitate formed. The mixture was quenched with saturated ammonium chloride, and the yellow mixture was extracted into methyl *t*-butyl ether (1 x) and methylene chloride (2 x). After drying the organic solutions over sodium sulfate, the solvent was removed under reduced pressure to give 5.3 g of the crude product. Crystallization from methanol/ethylacetate furnished 2.8 g (50% yield) of **12**, mp 203-204°; ir (potassium bromide): 3206, 1625, 1601 cm^{-1} ; nmr (DMSO- d_6): δ 8.16 (dd, 1H), 7.79-7.61 (m, 2H), 7.47-7.22 (m, 1H), 6.23 (s, 1H), 5.68 (t, 1H, OH), 4.59 (d, 2H, *J* = 5.7 Hz), 3.75 (s, 3H, N-CH₃).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{NO}_2$: C, 70.6; H, 4.8; N, 7.5. Found: C, 70.7; H, 4.8; N, 7.4.

1,4-Dihydro-1-methyl-4-oxo-2-quinolinecarboxaldehyde (**4**).

A mixture of 1.5 g of **12** and 6.0 g of activated manganese dioxide in 250 ml of methylene chloride was refluxed for 24 hours. The manganese dioxide was filtered from the reaction mixture, and the solvent was removed under reduced pressure to give 905 mg of a solid. Refluxing the filtered manganese dioxide cake in methylene chloride (200 ml) for 24 hours did not afford any further appreciable quantity of product. The isolated solid was crystallized from methylene chloride/methyl *t*-butyl ether to give 730 mg (49% yield) of **4**, mp 176-179°; ir (chloroform): 1715, 1625, 1609 cm^{-1} ; nmr (deuteriochloroform): δ 9.75 (s, 1H, CHO), 8.41 (dd, 1H), 7.9-7.3 (m, 3H), 6.75 (s, 1H), 4.08 (s, 3H).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{NO}_2$: C, 70.6; H, 4.8; N, 7.5. Found: C, 70.7; H, 4.8; N, 7.4.

3-(1,4-Dihydro-1-methyl-4-oxo-2-quinolin-2-yl)-2-propenoic Acid Methyl Ester (**5**).

To a suspension of 145 mg of sodium hydride (pentane washed) in 30 ml of tetrahydrofuran was added dropwise a solution of 550 mg of trimethyl phosphonoacetate in 10 ml of tetrahydrofuran. The mixture was stirred at room temperature for 3 hours during which time a white precipitate formed. To this was added dropwise a solution of 460 mg of **4** in 20 ml of tetrahydrofuran, and stirring was continued at room temperature for 18 hours. The mixture was poured into water and was extracted into methyl *t*-butyl ether (1 x) and methylene chloride (2 x). The organic solutions were combined and dried over sodium sulfate. After removing the solvent under reduced pressure, the residue was chromatographed on a Waters Prep-500 apparatus using 5% methanol/ethyl acetate to elute the product, 190 mg (32% yield) of **5**, mp 159-162°; ir (chloroform): 1725, 1645, 1625 cm^{-1} ; nmr (deuteriochloroform): δ 8.41 (dd, 1H), 7.75 (d, 1H, *J* = 15.7 Hz), 7.80-7.25 (m, 3H), 6.47 (d, 1H, *J* = 15.7 Hz), 6.41 (s, 1H), 3.88 (s, 3H), 3.78 (s, 3H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_3$: C, 69.1; H, 5.4; N, 5.7. Found: C, 69.3; H, 5.3; N, 5.4.

Acknowledgments.

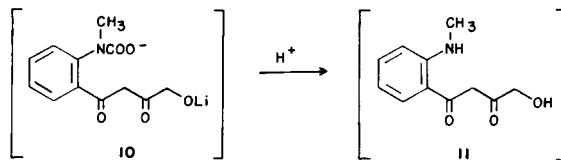
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