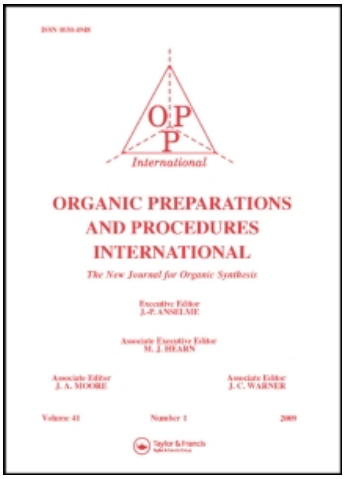

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4(1*H*)-Quinolinones by a Tandem Reduction-Addition-Elimination Reaction

Richard A. Bunce[a]; Baskar Nammalwar[a]
[a] Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma, USA

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4(1*H*)-Quinolinones by a Tandem Reduction-Addition-Elimination Reaction

Richard A. Bunce and Baskar Nammalwar

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma, USA

Compounds incorporating the 4(*1H*)-quinolinone ring system are commonly found in drug chemistry and express a broad spectrum of biological activities.[1–13] Thus, they have become attractive targets for synthesis. In this paper, we report simple and efficient syntheses of 4(1*H*)-quinolinone (**3**), 2,4(1*H*,3*H*)-quinolinedione (**8**) and ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylate (**10**) using an adaptation of the Leimgruber-Batcho indole synthesis.[14–17]

Numerous methods have been described for the synthesis of **3**. In the most practical routes, aniline was reacted with Meldrum's acid[18,19] or methyl propiolate[20] to form an adduct that underwent thermal cyclization to give the target heterocycle. Another useful approach involved the condensation of 2′-nitroacetophenone with *N*,*N*-dimethylformamide dimethyl acetal to give an enaminone followed by reduction and cyclization in refluxing ethanol containing cyclohexene and 10% Pd/C.[21] Though this reaction is similar to our procedure, we were not able to achieve the yield reported for the preparation of **3**. Finally, palladium-catalyzed coupling of 2′-bromoacetophenone with formamide followed by intramolecular cyclization using sodium *tert*-butoxide also provided access to this ring system.[22] A disadvantage of this procedure was the expensive catalyst required for the initial coupling reaction.

There are also many reported preparations for 2,4(1*H*,3*H*)-quinolinedione (**8**). In the classical synthesis, 2-aminobenzoic acid was condensed with urea in a high-boiling solvent.[23–27] This method appears to be the most viable approach since it is simple, inexpensive and scalable. Other preparations have been reported from 2-aminobenzamide,[28] 2-aminobenzonitrile,[29,30] methyl 2-bromobenzoate[31] and 1*H*-indole-2,3-dione.[32] While elegant, most of these approaches used expensive or hazardous reagents that would not be practical on a large scale.

Approaches to the synthesis of ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylate (**10**) are more limited. All of the methods involved the addition of aniline to diethyl 2-(ethoxymethylene)propanedioate[7,9,33–35] followed by thermally induced ring closure. The drawbacks of this process were the high temperature conditions (>200°C) for the final

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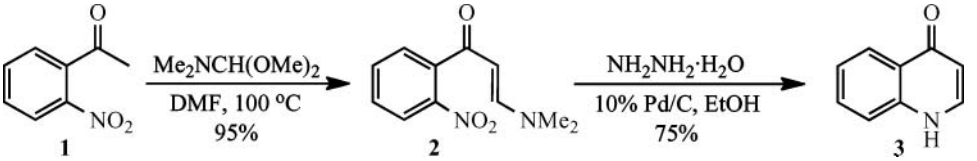
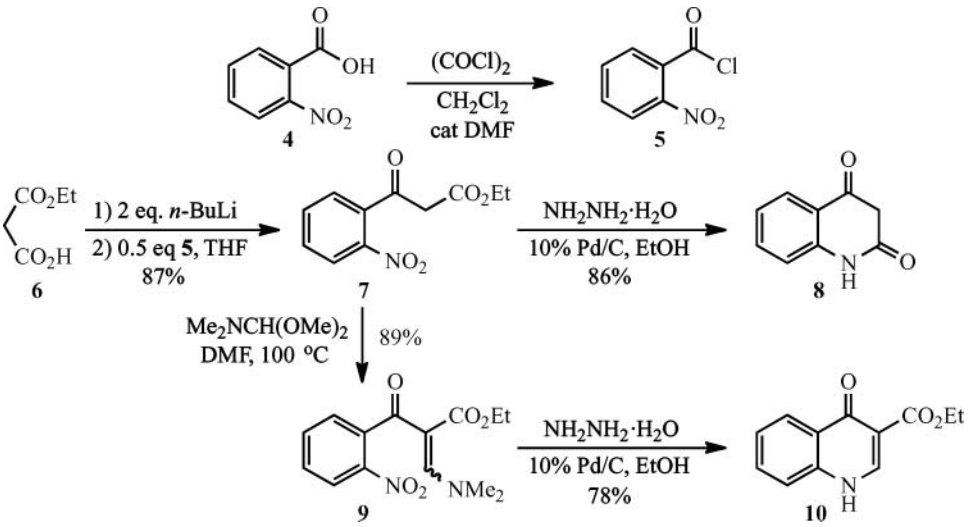
Address correspondence to Richard A. Bunce, Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078-3071, USA. E-mail: rab@okstate.edu

cyclization and the requirement of removing a high-boiling solvent (usually diphenyl ether) from the product.

Our syntheses of 4(1*H*)-quinolinone (**3**), 2,4(1*H*,3*H*)-quinolinedione (**8**) and ethyl 1,4-dihydroquinoline-4-oxo-3-carboxylate (**10**) are outlined in Schemes 1 and 2. The strategy is an adaptation of the Leimgruber-Batcho reaction, which is normally used to prepare indoles.[14–17] The synthesis of **3** was achieved *via* a two-step sequence in 71% overall yield. The first step involved heating 2′-nitroacetophenone (**1**) with *N*,*N*-dimethylformamide dimethyl acetal in DMF at 100°C for 45 min to give (*E*)-3-(dimethylamino)-1-(2-nitrophenyl)-2-propen-1-one (**2**) in 95% yield. Treatment of enaminone **2** with hydrazine hydrate and 10% Pd/C in ethanol at 23°C for 60 min then initiated a tandem sequence involving reduction of the nitro function, addition of the resulting amino group to the enaminone double bond, and elimination of dimethylamine to give 4(1*H*)-quinolinone (**3**) in 75% yield.



Scheme 1
Synthesis of 4(1*H*)-quinolinone (**3**).



Scheme 2
Synthesis of 2,4(1*H*,3*H*)-quinolinedione (**8**) and ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylate (**10**).

The preparation of **8** and **10** was readily achieved from 3-(2-nitrophenyl)-3-oxopropanoate (**7**). To prepare **7**,[36] ethyl hydrogen malonate (**6**) was converted to its dianion, using *n*-butyllithium in THF, and reacted with 0.5 equivalents of 2-nitrobenzoyl chloride (**5**), prepared from 2-nitrobenzoic acid using oxalyl chloride in the presence of catalytic

DMF. This gave ketoester **7** in 87% yield. Treatment of **7** with 85% hydrazine hydrate and 10% Pd/C in ethanol at 23°C for 20 min then gave dione **8** in 86% yield. The conversion of **7** to **10** was analogous to the procedure used to prepare **3**. Ketoester **7** was converted to enaminone **9** in 89% yield by reaction with *N*,*N*-dimethylformamide dimethyl acetal in DMF at 100 °C for 30 minutes. Though the double bond geometry of **9** was unclear, the compound was used as isolated. Treatment of **9** with hydrazine hydrate and 10% Pd/C in ethanol at 23°C for 30 min then effected the reduction-cyclization sequence to give **10** in 78% yield.[37] Both **8** and **10** were easily purified by recrystallization.

We have developed a simple and efficient method for the syntheses of quinolinones **3** and **10** and quinolinedione **8** using inexpensive starting materials. The yields are comparatively higher than previous methods. These ring systems can serve as building blocks for the synthesis of a number of pharmaceutically active drug compounds.

Experimental Section

All reactions were run under dry N_2 in oven-dried glassware. Commercial anhydrous *N,N*-dimethylformamide (DMF) was stored under N_2 and transferred by syringe into reactions where it was used. Tetrahydrofuran (THF) was dried over KOH pellets and distilled from lithium aluminum hydride under N_2. Other reagents and solvents were used as received. Reactions were monitored by thin layer chromatography (TLC) on silica gel GF plates (Analtech 21521). Preparative separations were performed using flash column chromatography[38] (FC) on silica gel (Grade 62, 60–200 mesh) mixed with UV-active phosphor (Sorbent Technologies, UV-5); band elution was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks. ^{1}H and ^{13}C NMR spectra were measured at 300 MHz and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (*J*) are reported in Hz. Low-resolution mass spectra (EI/DP) were run at 30 eV.

(E)-3-(Dimethylamino)-1-(2-nitrophenyl)-2-propen-1-one (2)

The procedure of Koskinen and coworkers[21] was modified. In a one-necked round-bottomed flask, equipped with a magnetic stirrer and a N_2 inlet, 5.00 g (30.2 mmol) of 2′-nitroacetophenone (**1**) was dissolved in 25 mL of dry DMF. The solution was heated to 100°C (oil bath), 3.60 g (30.2 mmol) of *N*,*N*-dimethylformamide dimethyl acetal was added and heating was continued at 100°C for 45 min. The crude reaction mixture was quenched with ice water, stirred for 5 min, and then extracted with ether (2 × 150 mL). The aqueous layer was saturated with NaCl and extracted one final time with ether (1 × 75 mL). The combined ether layers were washed with saturated NaCl, dried ($MgSO_4$) and concentrated under vacuum. Further drying under high vacuum for 30 min gave 6.30 g (95%) of **2** as a yellow solid, mp 119–121°C, which was used directly in the next step. IR: 1645, 1556, 1527, 1355 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96 (d, $J = 7.0$ Hz, 1 H), 7.62 (apparent t, $J \approx 7.5$ Hz, 2 H), 7.49 (m, 2 H), 5.27 (d, $J = 12.6$ Hz, 1 H), 3.10 (s, 3 H), 2.87 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 188.5 (br), 154.8 (br), 147.2, 138.5 (br), 133.0, 129.3, 128.8, 124.0, 95.0 (br), 45.1, 37.1; MS: *m/z* 220 (M^+).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.45; N, 12.72. Found: C, 59.93; H, 5.40; N, 12.81.

*4(***1H***)-Quinolinone (3)*

A 100 mL two-necked round-bottomed flask, equipped with a reflux condenser, a magnetic stirrer and a N_2 inlet, was charged with a solution of 2.00 g (9.10 mmol) of **2** in 15 mL of ethanol and 0.27 g (0.26 mL, 5.44 mmol, 0.6 eq) of 85% hydrazine monohydrate. To this solution, stirred under N_2, was cautiously added 15 mg of 10% Pd/C and the reaction mixture was stirred at 23°C until TLC indicated the reaction was complete (*ca* 60 min). During the reaction, much of the product precipitated from the solution. To remove the Pd/C, the solution was heated to dissolve the precipitate, the hot solution was filtered through Celite® and the solvent was removed under vacuum. The crude product was purified by FC on a 20 cm × 2 cm silica gel column eluted with 50–80% ether in hexanes to give 0.99 g (75%) of **3** as a white solid, mp 208–210°C [*lit.*[20] mp 209–211°C]. IR: 3600–2410, 1613, 1587, 1507 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.81 (br s, 1 H), 8.12 (d, $J = 8.2$ Hz, 1 H), 7.93 (t, $J = 6.3$ Hz, 1 H), 7.65 (td, $J = 8.2$, 1.3 Hz, 1 H), 7.57 (d, $J = 8.4$ Hz, 1 H), 7.33 (td, $J = 6.8$, 1.3 Hz, 1 H), 6.07 (d, $J = 7.4$ Hz, 1 H); ^{13}C NMR (DMSO-d_6): δ 176.9, 140.0, 139.4, 131.6, 125.8, 124.9, 123.1, 118.3, 108.7.

Ethyl 3-(2-Nitrophenyl)-3-oxopropanoate (7)

The procedure of Domagala and coworkers was modified.[36] A 250 mL one-necked round-bottomed flask, equipped with a magnetic stirrer, a condenser and a N_2 inlet, was charged with 3.01 g (18.0 mmol) of 2-nitrobenzoic acid (**4**) and 100 mL of dichloromethane. The resulting suspension was stirred and 2.76 g (1.84 mL, 21.7 mmol) of oxalyl chloride was added dropwise over a period of 20 min followed by 5 drops of dry DMF. The reaction was stirred at 23°C for 12 h during which time gas evolution subsided and the acid completely dissolved into the dichloromethane. The crude mixture was then concentrated under vacuum to give 2-nitrobenzoyl chloride (**5**), which was used without further purification.

In a three-necked round-bottomed flask, equipped with a strong magnetic stirrer, 4.17 g (31.6 mmol) of ethyl hydrogen malonate (**6**) was dissolved in 125 mL of THF and 10 mg of bipyridyl was added as an internal indicator. The mixture was cooled to −30°C and 16.0 mL of 2.0 *M* *n*-butyllithium in hexanes (32.0 mmol) was added dropwise over 20 min. The reaction mixture was then warmed to −5°C and a second 16.0 mL portion of 2.0 *M* *n*-butyllithium (32.0 mmol) was added until a red color persisted for 5 min. The mixture was cooled to −78°C, and a solution of **5** (from above) in 15 mL of THF was added dropwise over 25 min. [**Note**: The reaction became a thick yellow suspension and stirring was a problem with a weak magnetic stirrer]. The solution was kept at −78°C for 30 min and then slowly warmed to −30°C and stirred for another 30 min. The reaction mixture was poured into ice water containing 20 mL of concentrated HCl and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with water, 5% $NaHCO_3$ and 1 *N* HCl. The dichloromethane layer was finally washed with saturated NaCl, dried ($MgSO_4$) and concentrated under vacuum to give 3.70 g (87%) of **3** as a thick yellow oil. The ketoester was used directly in the next reaction. An analytical sample (0.25 g) was obtained as a *ca* 90:10 keto-enol mixture by FC of on a 20 cm × 2 cm

silica gel column eluted with 5–10% ether in hexanes. IR: 1740, 1708, 1531, 1348 cm^{-1}; ^1H NMR (keto form, $CDCl_3$): δ 8.16 (d, $J = 8.4$ Hz, 1 H), 7.77 (t, $J = 7.6$ Hz, 1 H), 7.65 (td, $J = 7.6$, 1.2 Hz, 1 H), 7.53 (dd, $J = 7.6$, 1.3 Hz, 1 H), 4.16 (q, $J = 7.1$ Hz, 2 H), 3.83 (s, 2 H), 1.23 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (keto form, $CDCl_3$): δ 194.6, 166.5, 144.5, 134.5, 132.6, 130.9, 128.1, 124.2, 61.6, 49.0, 13.9; MS: *m/z* 237 (M^+).

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.64; N, 5.91. Found: C, 55.96; H, 4.66; N, 5.83 for the keto-enol mixture.

2,4(1H,3H)-Quinolinedione (8)

The procedure used to prepare **3** was followed to convert 1.00 g (4.22 mmol) of **7** to **8**. The reaction was complete in 20 min, but no precipitate was observed in this case. Filtration through Celite® and concentration under vacuum gave a viscous oil to which 10 mL of ether was added to give a solid precipitate. The product was collected and washed with ether and chloroform to give 0.59 g (86%) of **10** as a white solid. An analytical sample was obtained by recrystallization from dioxane, mp 315–317°C (dec) [*lit.*[29] mp 320°C (dec) (dioxane)]. IR: 3620–2360, 1657, 1630, 1508 cm^{-1}. The ^1H and ^{13}C NMR data (in DMSO-d_6) matched those reported previously.[29]

Ethyl 3-(Dimethylamino)-2-(2-nitrobenzoyl)acrylate (9)

A 100 mL single-necked round-bottomed flask, equipped with a reflux condenser, a magnetic stirrer and a N_2 inlet, was charged with 1.00 g (4.22 mmol) of **7** and 5 mL of DMF. The resulting solution was heated to 100°C (oil bath), 0.51 g (0.57 mL, 4.22 mmol) of *N*,*N*-dimethylformamide dimethyl acetal was added and heating was continued at 100°C for 30 min. The crude reaction mixture was quenched with ice water, stirred for 5 min and extracted with ether (2 × 50 mL). The aqueous solution was saturated with NaCl and extracted one final time with ether (1 × 50 mL). The combined ether layers were washed with saturated NaCl, dried ($MgSO_4$) and concentrated under vacuum. The resulting oil solidified to give 1.10 g (89%) of **8** as a yellow solid, mp 122–124°C. IR: 1682, 1633, 1570, 1526, 1377, 1349 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05 (d, $J = 8.2$ Hz, 1 H), 8.00 (s, 1 H), 7.62 (t, $J = 7.6$ Hz, 1 H), 7.48 (td, $J = 7.4$, 0.8 Hz, 1 H), 7.36 (d, $J = 7.6$ Hz, 1 H), 3.83 (q, $J = 7.1$ Hz, 2 H), 3.38 (s, 3 H), 3.09 (s, 3 H), 0.82 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 188.6, 166.7, 159.9, 146.3, 140.1, 133.3, 128.6, 127.7, 123.6, 100.2, 59.7, 48.2, 42.7, 13.6; MS: *m/z* 292 (M^+).

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.48; N, 9.59. Found: C, 57.71; H, 5.57; N, 9.46.

The double bond geometry of this product was unclear, but the compound was used directly in the next step.

Ethyl 1,4-Dihydro-4-oxo-3-quinolinecarboxylate (10)

The procedure used to prepare **3** was followed to convert 1.00 g (3.42 mmol) of **9** to **10**. The reaction was complete in 30 min and much of the product precipitated from the solution. After heating to dissolve the product, filtration through Celite® and concentration gave a tan solid. Recrystallization using chloroform-ether yielded 0.58 g (78%) of **10** as an off-white solid, mp 268–269°C [*lit.*[1] mp 270–272°C]. IR: 3424, 1642 cm^{-1}; ^1H NMR

(DMSO-d_6): δ 12.33 (br s, 1 H), 8.56 (s, 1 H), 8.16 (dd, $J = 8.2$, 1.0 Hz, 1 H), 7.71 (td, $J = 7.5$, 1.4 Hz, 2 H), 7.63 (d, $J = 8.2$ Hz, 1 H), 7.42 (td, $J = 7.5$, 1.0 Hz, 1 H), 4.22 (q, $J = 7.1$ Hz, 2 H), 1.29 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (DMSO-d_6): δ 173.4, 164.8, 144.9, 138.9, 132.4, 127.2, 125.6, 124.7, 118.8, 109.7, 59.5, 14.3; MS: *m/z* 217 (M^+).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07; N, 6.45. Found: C, 66.34; H, 5.08; N, 6.40.

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