(±)-2-Aryl-2,3-dihydro-4(1*H*)-quinolinones by a Tandem Reduction–Michael Addition Reaction

Richard A. Bunce* and Baskar Nammalwar

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078-3071
*E-mail: rab@okstate.edu

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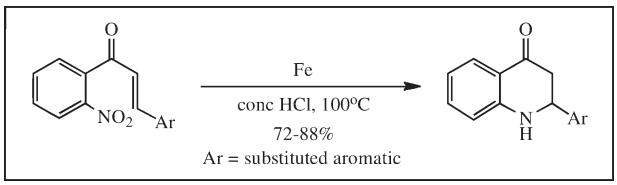

An efficient synthesis of (±)-2-aryl-2,3-dihydro-4(1*H*)-quinolinones has been developed from chalcones prepared from 2′-nitroacetophenone and a series of substituted benzaldehydes. The cyclization sequence is initiated by reduction of the nitro group under dissolving metal conditions using iron powder in concentrated hydrochloric acid. Milder conditions, using acetic acid or acetic acid–phosphoric acid as the reaction medium, were less satisfactory. Procedural details as well as a mechanistic discussion and reaction optimization studies are presented.

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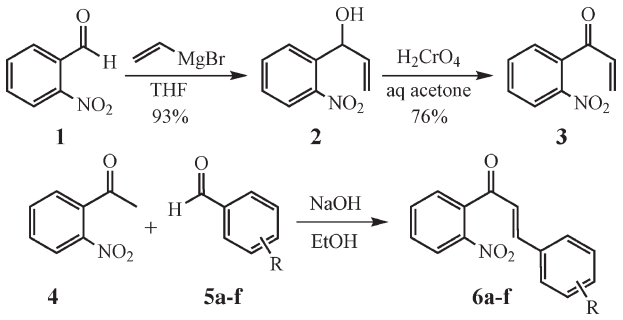
INTRODUCTION

Over the past several years, we have described a number of tandem reaction approaches to nitrogen heterocycles initiated by dissolving metal reduction of nitroarenes [1]. In this project, we sought to extend this strategy to the synthesis of 2,3-dihydro-4(1*H*)-quinolinone as well as several (±)-2-aryl-2,3-dihydro-4(1*H*)-quinolinones by reductive cyclization of 1-(2-nitrophenyl)-2-propen-1-one derivatives. Dihydroquinolinones, similar to those prepared in this study, have attracted considerable interest as potential antimalarial [2] and anticancer drugs [3].

The title compounds have been common targets for synthesis, and numerous approaches have been reported, primarily from 2′-aminochalcone derivatives. In the original synthesis [4], 2′-aminochalcone was treated with sodium ethoxide to give (±)-2,3-dihydro-2-phenyl-4(1*H*)-quinolinone in a modest 45% yield. Work by others [5a,6] described the cyclization of anions derived by treatment of *N*-acylated 2′-aminochalcones with base, and the yields improved to 50–60%. Further studies [5b,6] revealed that similar yields could be achieved by cyclizing 2′-aminochalcones with 1:1 acetic acid–phosphoric acid. More recently, montmorillonite K-10 under microwave irradiation [7] and Lewis acids on silica or alumina [8] have been used to promote this cyclization in 60–90% yields. Additionally, the ring closure of 2′-aminochalcones has also been performed in 80–90% yields by heating in PEG-400 solvent at 130°C with no additives [9]. Using an alternative strategy, metathesis of 2-alkynylanilines with aldehydes in the presence of an antimony pentafluoride-methanol catalyst gave (±)-2,3-disubstituted-2,3-dihydro-4(1*H*)-quinolinones [10] as cis–trans mixtures in 25–95% yields. Finally, condensation of 2′-aminoacetophenone with various benzaldehydes in the presence of L-proline was reported as a potential route to chiral 2-aryldihydroquinolinones [11], and although yields were in the 79–93% range, the asymmetric induction was poor (less than 10% enantiomeric excess). To date, there have been few reports detailing the synthesis of 2-aryldihydroquinolinones from 2′-nitrochalcones [12], and this is the route we sought to exploit.

RESULTS AND DISCUSSION

The synthesis of the cyclization substrates is shown in Figure 1. To prepare the precursor to 2,3-dihydro-4(1*H*)-quinolinone, vinylmagnesium bromide was added to 2-nitrobenzaldehyde (**1**) in tetrahydrofuran (THF) to give alcohol **2**, which was further oxidized to 1-(2-nitrophenyl)-2-propen-1-one (**3**) in 71% overall yield [13]. The 2′-nitrochalcones **6a–f** for the preparation of the (±)-2-aryl-2,3-dihydro-4(1*H*)-quinolinones were prepared in 92–97% yields from 2′-nitroacetophenone (**4**) and a series of benzaldehyde derivatives (**5a–f**) using standard conditions with sodium hydroxide in ethanol. It should be noted that only substrates derived from benzaldehydes bearing resonance electron-donating substituents were examined. This was due to the fact that many electron-withdrawing groups, such as ester and cyano, would degrade under the basic conditions used to prepare the chalcones and others, such as nitro, would be reduced in the cyclization reaction.

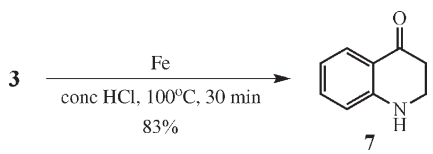


	R in **5**	Yield of **6** (%)
a	H	95
b	4-CH_3	97
c	4-CH_3O	93
d	3,4-$(CH_3O)_2$	95
e	3,4-OCH_2O	94
f	2-Cl	92

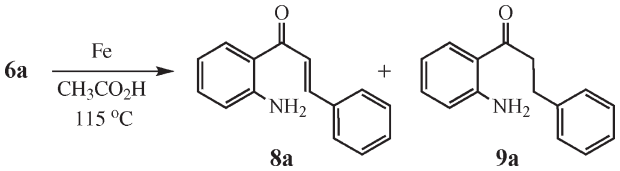
Figure 1. Synthesis of cyclization substrates.

The cyclization of **3** to the parent 2,3-dihydro-4(1*H*)-quinolinone (**7**) was initially attempted using iron powder in acetic acid, because these conditions had been successful in our earlier work [1]. Unfortunately, this protocol gave a complex mixture of products containing a significant amount of polymeric material. Literature reports by others [5b,6] suggested that stronger acid conditions might facilitate the final cyclization. Thus, the reaction was repeated in 1:1 v/v acetic acid–phosphoric acid, and the desired product was isolated in 72% yield after chromatography. During the course of this conversion, however, a heavy insoluble precipitate was formed that disrupted stirring and hampered isolation of the product. To circumvent this problem, we decided to rerun the reaction in concentrated hydrochloric acid, because this had proven effective in one of our earlier reductive cyclizations [1c]. When the reaction was performed using iron powder in concentrated hydrochloric acid at 100°C, the reaction was complete in 30 min, and the target heterocycle was produced in 83% yield after chromatography. Critical to the success of the reaction was the addition of the iron to the hot solution, which minimized the formation of side products (see Scheme 1).

Scheme 1. Reductive cyclization of **3** with iron in concentrated hydrochloric acid.



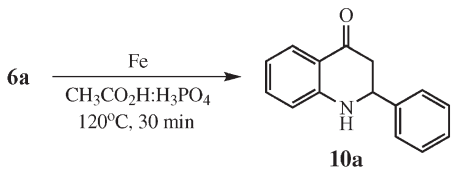
Scheme 2. Reduction of **6a** with iron in acetic acid.



We began our study on the conversion of 2′-nitrochalcone **6a** to (±)-2,3-dihydro-2-phenyl-4(1*H*)-quinolinone by attempting to effect the cyclization using iron powder in acetic acid as above [1]. These conditions, however, yielded only mixtures of 2′-aminochalcone (**8a**) and its double-bond reduction product **9a** (see Scheme 2). None of the desired 2,3-dihydro-2-phenyl-4(1*H*)-quinolinone was observed. Similar results were obtained with substrates **6e** and **6f**.

We also explored the use of iron powder in various mixtures of acetic acid and phosphoric acid, because this had been successful for the ring closure of **3**. Under these conditions, the reaction proceeded to give the reductive cyclization product in 24–78% yield. The best result was achieved using a 70:30 ratio of acetic acid–phosphoric acid. Higher proportions of phosphoric acid led to the formation of an intractable precipitate that decreased product recovery (see Fig. 2).

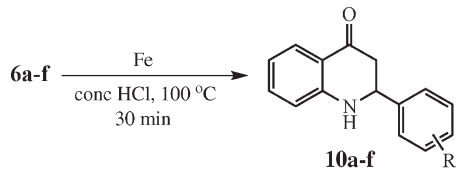
On the basis of the enhanced conversion of **3** to **7** in stronger acid, we decided to explore the use of iron powder in concentrated hydrochloric acid for the cyclization of 2′-nitrochalcones **6** and found that the yields improved to 72–88%. The optimized conditions involved treating 1 equiv of **6** with 4 equiv of iron powder in concentrated hydrochloric acid at 100°C for 30 min. Again, it was important to add the iron to the hot mixture to achieve optimum results. Surprisingly, no cleavage of any of the ether groups was observed. After quenching with ice water, extractive workup, and recrystallization, the 2-aryldihydroquinolinones **10** were



CH_3CO_2H:H_3PO_4 (v/v)	Yield of **10a** (%)
100:0	3 [a]
90:10	24
80:20	50
70:30	78

[a] Yield estimated from ^{1}H NMR

Figure 2. Reductive cyclization of **6a** with various v/v mixtures of acetic acid and phosphoric acid.



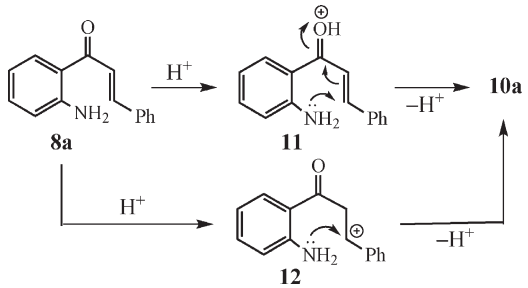
	R	Yield of **10** (%)
a	H	88
b	4-CH_3	85
c	4-CH_3O	82
d	3,4-$(CH_3O)_2$	72
e	3,4-OCH_2O	83
f	2-Cl	80

Figure 3. Reductive cyclization of **6** with iron in concentrated hydrochloric acid.

isolated in nearly pure form. Chromatography was generally not necessary because all reactions went to completion and gave highly crystalline products. Our results are summarized in Figure 3.

Following reduction of the nitro group in **6a**, two mechanistic pathways can be envisoned for the ring closure of aminochalcone **8a**. Iron does not appear to play a significant role in the cyclization because **8a** has been successfully cyclized to **10a** using 1:1 v/v acetic acid–phosphoric acid [6] and concentrated hydrochloric acid (this study) without iron. In the first mechanistic scenario, strong acid would protonate the enone carbonyl in **8a** to give **11**, which would be activated toward conjugate addition by the amino group. Because the amine function in **8a** is part of a vinylogous amide, it is not as basic as a typical aniline nitrogen, and thus, some of the unprotonated form should be present to add to the activated enone system. Alternatively, strong acid conditions could also protonate the enone double bond to give the benzylic carbocation **12**, which would then be attacked by the nucleophilic aniline nitrogen. These mechanistic possibilities for the cyclization of **8a** to **10a** are outlined in Scheme 3.

Scheme 3. Mechanistic possibilities for ring closure of 2′-aminochalcone in concentrated hydrochloric acid.



CONCLUSION

We have successfully developed a synthesis of 2,3-dihydro-4(1*H*)-quinolinone from 1-(2-nitrophenyl)-2-propen-1-one and a series of (±)-2-aryl-2,3-dihydro-4(1*H*)-quinolinones from 2′-nitrochalcones. Reductive cyclization of these derivatives using iron powder in concentrated hydrochloric acid gave the best results, affording the target heterocycles in 72–88% yields. The products were obtained in good yields without the need for extensive purification. This synthetic approach is limited to chalcone substrates bearing electron-donating groups on the C3 aromatic ring, as these are most stable to the base used in their preparation and the reductive conditions used for the final cyclization.

EXPERIMENTAL

All reactions were run under dry nitrogen or air in oven-dried glassware. THF was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride under nitrogen. All other commercial reagents and solvents were used as received. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No 21521) using UV detection. Preparative separations were performed using flash chromatography [14] on silica gel (Grade 62, 60–200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies No UV-05) or preparative thin layer chromatography on 20-cm × 20-cm silica gel GF plates (Analtech No 02015); band elution for both methods was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on sodium chloride disks. Unless otherwise specified, ^{1}H- and ^{13}C-NMR spectra were measured in deuteriochloroform at 300 and 75 MHz, respectively; coupling constants (*J*) are reported in Hertz. Low-resolution mass spectra (direct probe/electron impact) were obtained at 30 or 70 eV as indicated.

1-(2-Nitrophenyl)-2-propen-1-ol (2). The general procedure of Danishefsky and coworkers [13] was used. A 250-mL three-necked round-bottomed flask, equipped with a rubber septum, a reflux condenser, a nitrogen inlet, and a magnetic stirrer, was charged with 50 mL of dry THF and 3.00 g (19.9 mmol) of 2-nitrobenzaldehyde (**1**). The resulting solution was cooled to −78°C, and 29.5 mL of 1.0 *M* vinylmagnesium bromide (29.5 mmol) was added dropwise *via* syringe over a period of 20 min. The reaction was stirred for 2 h at −78°C at which time thin layer chromatography indicated the reaction was complete. The reaction mixture was poured into 75 mL of 1 *M* hydrochloric acid, stirred for 10 min, and extracted with 50 mL of ether. The aqueous layer was then saturated with sodium chloride and extracted with additional ether (2 × 50 mL). The combined ether layers were washed with saturated sodium chloride solution, dried (magnesium sulfate), and concentrated under vacuum to yield 3.32 g (93%) of **2** as a viscous yellow oil. This product was spectroscopically pure and was used in the next step without further purification. IR: 3415, 1639, 1609, 1524, 1349 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.90 (d, 1H, *J* = 7.7), 7.76 (d, 1H, *J* = 7.7), 7.64 (t, 1H, *J* = 7.9), 7.44 (t, 1H, *J* = 7.9), 6.07 (ddd, 1H, *J* = 17.2, 10.4, 5.3),

5.79 (d, 1H, J = 5.3), 5.41 (d, 1H, J = 17.2), 5.25 (d, 1H, J = 10.4), 2.82 (br s, 1H); ^{13}C-NMR (100 MHz): δ 148.2, 138.0, 137.6, 133.5, 128.8, 128.4, 124.5, 116.1, 69.9; ms (30 eV): m/z 179 (M^+). Anal. Calcd. for $C_9H_9NO_3$: C, 60.34; H, 5.03; N, 7.82. Found: C, 60.51; H, 5.07; N, 7.69.

1-(2-Nitrophenyl)-2-propen-1-one (3). A 100-mL two-necked round-bottomed flask, fitted with an addition funnel, a reflux condenser, a nitrogen inlet, and a magnetic stirrer, was charged with 3.00 g (16.8 mmol) of **2** and 20 mL of acetone. To the resulting solution was slowly added 8.5 mL of 2.97 *M* Jones reagent (25.2 mmol) over a period of 25 min at 23°C. [Note: The addition was done very slowly. Faster addition led to significant heating, loss of solvent, and a reduced yield.] After 1 h at 23°C, thin layer chromatography indicated that the reaction was complete. Excess Jones reagent was quenched with saturated sodium bisulfite solution (*ca*. 3 mL), and the crude reaction mixture was extracted with 50 mL of ether. The aqueous layer was then saturated with sodium chloride and extracted with additional ether (2 × 50 mL). The combined ether layers were washed with saturated sodium chloride, then dried (magnesium sulfate), and concentrated under vacuum. The crude product was purified by flash chromatography on a 20-cm × 2-cm silica gel column using increasing concentrations of ether in hexanes to give 2.26 g (76%) of **3** as a yellow oil. IR: 1672, 1613, 1527, 1347 cm^{-1}; ^{1}H-NMR: δ 8.16 (dd, 1H, J = 8.2, 1.3), 7.75 (td, 1H, J = 7.5, 1.3), 7.65 (ddd, 1H, J = 8.2, 7.5, 1.5), 7.45 (dd, 1H, J = 7.5, 1.5), 6.65 (dd, 1H, J = 17.6, 10.6), 6.05 (d, 1H, J = 10.6), 5.85 (d, 1H, J = 17.6); ^{13}C-NMR: δ 193.4, 146.8, 136.5, 135.4, 134.1, 131.2, 130.7, 128.8, 124.4; ms: m/z 177 (M^+). Anal. Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.95; N, 7.91. Found: C, 61.12; H, 3.98; N, 7.83.

Representative aldol condensation: (2*E*)-1-(2-Nitrophenyl)-3-phenyl-2-propen-1-one (6a). A 100-mL two-necked round-bottomed flask, equipped with an addition funnel, a nitrogen inlet, and a magnetic stirrer, was charged with 800 mg (4.85 mmol) of 2′-nitroacetophenone (**4**) and 15 mL of ethanol, and the resulting solution was cooled to 0°C. Stirring was begun and 232 mg (5.80 mmol, 1.2 equiv) of sodium hydroxide powder was added and allowed to dissolve. To this mixture was slowly added a solution of 540 mg (5.09 mmol, 1.05 equiv) of benzaldehyde (**5a**) in 5 mL of ethanol. The reaction was stirred for 3 h at 0°C during which time the product crystallized from the mixture. The product was filtered, and the crystals were washed thoroughly with ice-cold ethanol to give 1.16 g (95%) of **6a** as a white solid, mp 125–127°C (lit. [15] mp 128°C). IR: 1652, 1608, 1527, 1347 cm^{-1}; ^{1}H-NMR (400 MHz): δ 8.18 (dd, 1H, J = 8.2, 1.1), 7.77 (td, 1H, J = 7.6, 1.1), 7.66 (td, 1H, J = 7.6, 1.1), 7.53–7.46 (complex, 3H), 7.42–7.34 (complex, 3H), 7.24 (d, 1H, J = 16.2), 7.01 (d, 1H, J = 16.2); ^{13}C-NMR (100 MHz): δ 192.9, 146.7, 146.3, 136.3, 134.0, 133.9, 131.0, 130.5, 129.0, 128.8, 128.5, 126.2, 124.5; ms: m/z 253 (M^+).

(2*E*)-3-(4-Methylphenyl)-1-(2-nitrophenyl)-2-propen-1-one (6b). This compound (1.25 g, 97%) was prepared from 800 mg (4.85 mmol) of **4** and 611 mg (5.09 mmol) of 4-methylbenzaldehyde (**5b**) and isolated as a pale yellow solid, mp 133–135°C (lit. [15] mp 134–135°C). IR: 1652, 1599, 1528, 1348 cm^{-1}; ^{1}H-NMR: δ 8.16 (dd, 1H, J = 7.7, 1.1), 7.76 (td, 1H, J = 7.7, 1.1), 7.65 (td, 1H, J = 7.7, 1.1), 7.50 (dd, 1H, J = 7.7, 1.1), 7.39 (d, 2H, J = 8.2), 7.21 (d, 1H, J = 15.9), 7.18 (d, 2H, J = 8.2), 6.97 (d, 1H, J = 15.9), 2.37 (s, 3H); ^{13}C-NMR: δ 193.0, 146.52, 146.49, 141.7, 136.4, 133.9, 131.2, 130.4, 129.7, 128.8, 128.6, 125.3, 124.5, 21.5; ms: m/z 267 (M^+).

(2*E*)-3-(4-Methoxyphenyl)-1-(2-nitrophenyl)-2-propen-1-one (6c). This compound (1.27 g, 93%) was prepared from 800 mg (4.85 mmol) of **4** and 692 mg (5.09 mmol) of 4-methoxybenzaldehyde (**5c**) and isolated as an off-white solid, mp 101–103°C (lit. [16] mp 105°C). IR: 2840, 1645, 1600, 1528, 1348 cm^{-1}; ^{1}H-NMR (400 MHz): δ 8.16 (dd, 1H, J = 8.2, 1.2), 7.75 (dt, 1H, J = 7.5, 1.2), 7.64 (ddd, 1H, J = 8.2, 7.5, 1.4), 7.50 (dd, 1H, J = 7.5, 1.4), 7.45 (d, 2H, J = 8.8), 7.24 (d, 1H, J = 16.2), 6.90 (d, 1H, J = 16.2), 6.87 (d, 2H, J = 8.8), 3.83 (s, 3H); ^{13}C-NMR (100 MHz): δ 192.9, 162.0, 146.6, 146.3, 136.5, 133.9, 130.40, 130.38, 128.8, 126.6, 124.5, 123.9, 114.4, 55.4; ms: m/z 283 (M^+). Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59; N, 4.95. Found: C, 67.88; H, 4.62; N, 4.87.

(2*E*)-3-(3,4-Dimethoxyphenyl)-1-(2-nitrophenyl)-2-propen-1-one (6d). This compound (1.44 g, 95%) was prepared from 800 mg (4.85 mmol) of **4** and 845 mg (5.09 mmol) of 3,4-dimethoxybenzaldehyde (**5d**) and isolated as a yellow solid, mp 120–122°C (lit. [16] mp 124°C]. IR: 2839, 1645, 1594, 1512, 1347 cm^{-1}; ^{1}H-NMR: δ 8.18 (d, 1H, J = 7.7), 7.76 (td, 1H, J = 7.7, 1.1), 7.65 (td, 1H, J = 7.7, 1.6), 7.51 (dd, 1H, J = 7.7, 1.1), 7.19 (d, 1H, J = 15.9), 7.10–7.01 (complex, 2H), 6.89 (d, 1H, J = 15.9), 6.85 (d, 1H, J = 7.7), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C-NMR: δ 192.8, 151.8, 149.3, 146.6, 146.5, 136.5, 133.9, 130.4, 128.8, 126.7, 124.5, 124.2, 123.6, 111.0, 109.8, 56.0, 55.9; ms: m/z 313 (M^+). Anal. Calcd. for $C_{17}H_{15}NO_5$: 65.18; H, 4.79; N, 4.47. Found: C, 65.23; H, 4.78; N, 4.44.

(2*E*)-3-(1,3-Benzodioxol-5-yl)-1-(2-nitrophenyl)-2-propen-1-one (6e). This compound (1.36 g, 94%) was prepared from 800 mg (4.85 mmol) of **4** and 764 mg (5.09 mmol) of piperonal (**5e**) and isolated as a pale yellow solid, mp 128–130°C (lit. [12b] mp 128–130°C). IR: 1650, 1599, 1528, 1384 cm^{-1}; ^{1}H-NMR: δ 8.17 (d, 1H, J = 8.2), 7.76 (td, 1H, J = 7.7, 1.1), 7.64 (td, 1H, J = 8.2, 1.1), 7.51 (dd, 1H, J = 7.7, 1.6), 7.17 (d, 1H, J = 15.9), 7.03 (d, 1H, J = 1.6), 6.96 (dd, 1H, J = 7.7, 1.1), 6.84 (d, 1H, J = 15.9), 6.79 (d, 1H, J = 8.2), 6.02 (s, 2H); ^{13}C-NMR: δ 192.7, 150.3, 148.5, 146.7, 146.1, 136.5, 133.9, 130.4, 128.8, 128.4, 125.5, 124.5, 124.2, 108.6, 106.7, 101.7; ms: m/z 297 (M^+). Anal. Calcd. for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.70; N, 4.71. Found: C, 64.71; H, 3.73; N, 4.66.

(2*E*)-3-(2-Chlorophenyl)-1-(2-nitrophenyl)-2-propen-1-one (6f). This compound (1.28 g, 92%) was prepared from 800 mg (4.85 mmol) of **4** and 715 mg (5.09 mmol) of 2-chlorobenzaldehyde (**5f**) and isolated as a pale yellow solid, mp 87–88°C (lit. [15] mp 88–89°C). IR: 1657, 1605, 1527, 1347 cm^{-1}; ^{1}H-NMR: δ 8.20 (d, 1H, J = 7.7), 7.79 (t, 1H, J = 7.1), 7.75–7.60 (complex, 3H), 7.53 (d, 1H, J = 7.1), 7.42–7.23 (complex, 3H), 6.97 (d, 1H, J = 16.5); ^{13}C-NMR: δ 192.8, 146.7, 141.8, 136.0, 135.2, 134.1, 132.2, 131.7, 130.7, 130.2, 128.9, 128.6, 127.8, 127.2, 124.5; ms: m/z 287, 289 (*ca*. 3:1, M^+).

2,3-Dihydro-4(1*H*)-quinolinone (7). A 100-mL two-necked round-bottomed flask, equipped with a reflux condenser, a drying tube, and a magnetic stirrer, was charged with 400 mg (2.26 mmol) of **3** and 10 mL of concentrated hydrochloric acid, and the mixture was heated to 80–85°C (oil bath). The heat was briefly removed and 630 mg (1.13 mmol, 5 equiv) of

iron powder (>100 mesh) was added. [Caution! The addition was sufficiently exothermic to boil the mixture and some frothing occurred as the iron was added. The reaction flask should be at least 10 times the volume of the reactants at this scale.] Heating was resumed at 100°C until thin layer chromatography indicated the reaction was complete (*ca*. 1 h). The reaction mixture was cooled, poured into ice water, and extracted with 50 mL of ether. The aqueous layer was then saturated with sodium chloride and extracted again with ether (1 × 50 mL) and ethyl acetate (1 × 50 mL). The combined organic layers were washed with saturated sodium chloride solution, dried (magnesium sulfate), and concentrated under vacuum. The resulting oil was flash chromatographed on a 20-cm × 2-cm silica gel column eluted with increasing concentrations of ether in hexanes to give 276 mg (83%) of **7** as a yellow solid, mp 42–44°C (lit. [17] mp 43–44.5°C). IR: 3347, 1659, 1611 cm^{-1}; ^{1}H-NMR: δ 7.84 (dd, 1H, J = 8.2, 1.1), 7.29 (td, 1H, J = 7.7, 1.1), 6.74 (t, 1H, J = 7.7), 6.67 (d, 1H, J = 8.2), 4.43 (br s, 1H), 3.58 (t, 2H, J = 6.6), 2.70 (t, 2H, J = 6.6); ^{13}C-NMR: δ 193.7, 152.0, 135.1, 127.6, 119.4, 117.9, 115.8, 42.3, 38.1; ms: *m*/*z* 147 (M^+). Anal. Calcd. for C_9H_9NO: C, 73.47; H, 6.12; N, 9.52. Found: C, 73.51; H, 6.11; N, 9.47.

This same reductive cyclization was carried out using 5 equiv of iron powder in 1:1 v/v acetic acid–phosphoric acid, but the product yield was only 72% because of the formation of a heavy insoluble precipitate during the heating period. When the reaction was carried out using iron in acetic acid without a stronger acid, a complex mixture of products containing a significant amount of polymeric material was isolated.

Attempted reductive cyclization of 6a with iron powder in acetic acid: (2*E*)-1-(2-Aminophenyl)-2-propen-1-one (8a) and 1-(2-aminophenyl)-1-propanone (9a). A 100-mL two-necked round-bottomed flask, equipped with a reflux condenser, a nitrogen inlet, and a magnetic stirrer, was charged with 500 mg (1.98 mmol) of **6a** and 10 mL of acetic acid, and the solution was heated to 100°C (oil bath). The heat was briefly removed and 440 mg (7.88 mmol) of iron powder (>100 mesh) was added. [Caution! The addition was sufficiently exothermic to boil the mixture and some frothing occurred as the iron was added. The reaction flask should be at least 10 times the volume of the reactants at this scale.] Heating was resumed at 115°C until thin layer chromatography indicated the reaction was complete (*ca*. 10 min). The reaction mixture was cooled, poured into ice-cold water, and extracted with ether (3 × 25 mL). The combined ether layers were washed with saturated sodium bicarbonate (three times) and saturated sodium chloride (one time), then dried (magnesium sulfate), and concentrated under vacuum. The crude product was purified by flash chromatography on a 40-cm × 2-cm silica gel column eluted with increasing concentrations of ether in hexanes to give 220 mg (50%) of **8a** as a yellow solid, mp 70–71°C (lit. [6] mp 71–72°C), and 169 mg (38%) of **9a** as a yellow solid, mp 85–86°C. The spectral data for **8a** were as follows: IR: 3471, 3334, 1645, 1614 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.85 (dd, 1H, J = 8.4, 1.4), 7.74 (d, 1H, J = 15.6), 7.62 (d, 1H, J = 15.6). 7.60 (obscured signal, 1H), 7.43–7.33 (complex, 4H), 7.28 (ddd, 1H, J = 8.4, 7.2, 1.6), 6.69 (overlapping d and t, 2H, $J \approx 8.0$), 6.34 (br s, 2H); ^{13}C-NMR (100 MHz): δ 191.6, 150.9, 142.8, 135.2, 134.3, 130.9, 130.0, 128.8, 128.2, 123.0, 118.9, 117.2, 115.8; ms: *m*/*z* 223 (M^+).

The spectral data for **9a** were as follows: IR: 3475, 3346, 1647, 1614 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.73 (dd, 1H, J = 6.6, 8.2), 7.33–7.16 (complex, 6H), 6.65 (d, 1H, J = 7.2), 6.63 (td, 1H, J = 7.7, 1.0), 6.26 (br s, 2H), 3.28 (t, 2H, J = 7.4), 3.04 (t, 2H, J = 7.4); ^{13}C-NMR (100 MHz): δ 201.5, 150.3, 141.5, 134.3, 131.0, 128.5, 128.4, 126.0, 117.8, 117.3, 115.8, 41.0, 30.6; ms: *m*/*z* 225 (M^+). Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.00; H, 6.67; N, 6.22. Found: C, 79.93; H, 6.69; N, 6.17.

(2*E*)-1-(2-Aminophenyl)-3-(1,3-benzodioxol-5-yl)-2-propen-1-one (8e) and 1-(2-aminophenyl)-3-(1,3-benzodioxol-5-yl)-1-propanone (9e). Reduction of 500 mg (1.68 mmol) of **6e** using 375 mg (6.72 mmol) of iron powder gave 207 mg (46%) of **8e** as a yellow solid, mp 110–112°C, and 171 mg (40%) of **9e** as a yellow solid, mp 85–87°C. The spectral data for **8e** were as follows: IR: 3468, 3339, 1643, 1614 cm^{-1}; ^{1}H-NMR: δ 7.85 (dd, 1H, J = 8.2, 1.1), 7.67 (d, 1H, J = 15.4), 7.45 (d, 1H, J = 15.4), 7.29 (dt, 1H, J = 8.2, 1.6), 7.16 (d, 1H, J = 1.6), 7.11 (dd, 1H, J = 8.2, 1.6), 6.84 (d, 1H, J = 8.2), 6.70 (m, 2H), 6.31 (br s, 2H), 6.02 (s, 2H); ^{13}C-NMR: δ 191.6, 150.9, 149.5, 148.3, 142.8, 134.1, 130.9, 129.7, 124.7, 121.1, 119.2, 117.3, 115.8, 108.6, 106.6, 101.5; ms: *m*/*z* 267 (M^+). Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.87; N, 5.24. Found: C, 71.98; H, 4.89; N, 5.15.

The spectral data for **9e** were as follows: IR: 3468, 3352, 1645, 1614 cm^{-1}; ^{1}H-NMR: δ 7.72 (d, 1H, J = 7.7), 7.26 (t, 1H, J = 7.7), 6.78–6.59 (complex, 5H), 6.27 (br s, 2H), 5.92 (s, 2H), 3.23 (t, 2H, J = 7.6), 2.96 (t, 2H, J = 7.6); ^{13}C-NMR: δ 201.4, 150.3, 147.6, 146.3 135.3, 134.2, 131.0, 121.1, 117.8, 117.3, 115.8, 108.9, 108.2, 100.8, 41.2, 30.3; ms: *m*/*z* 269 (M^+). Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.38; H, 5.58; N, 5.20. Found: C, 71.44; H, 5.61; N, 5.14.

(2*E*)-1-(2-Aminophenyl)-3-(2-chlorophenyl)-2-propen-1-one (8f) and 1-(2-aminophenyl)-3-(2-chlorophenyl)-1-propanone (9f). Reduction of 500 mg (1.74 mmol) of **6f** using 389 mg (6.96 mmol) of iron gave 235 mg (53%) of **8f** as a yellow solid, mp 87–89°C, and 156 mg (34%) of **9f** as a yellow solid, mp 86–87°C. The spectral data for **8f** were as follows: IR: 3464, 3338, 1644, 1615 cm^{-1}; ^{1}H-NMR: δ 8.11 (d, 1H, J = 15.4), 7.84 (d, 1H, J = 8.2), 7.73 (m, 1H), 7.59 (d, 1H, J = 15.4), 7.43 (m, 1H), 7.36–7.25 (complex, 3H), 6.70 (d, 1H, J = 7.7), 6.69 (t, 1H, J = 7.7), 6.37 (br s, 2H); ^{13}C-NMR: δ 191.3, 151.1, 138.7, 135.2, 134.5, 133.6, 131.1, 130.7, 130.2, 127.7, 127.0, 125.8, 118.8, 117.3, 115.8; ms: *m*/*z* 257, 259 (*ca*. 3:1, M^+). Anal. Calcd. for $C_{15}H_{12}ClNO$: C, 69.90; H, 4.66; N, 5.44. Found: C, 69.97; H, 4.67; N, 5.39.

The spectral data for **9f** were as follows: IR: 3478, 3348, 1647, 1615 cm^{-1}; ^{1}H-NMR: δ 7.73 (d, 1H, J = 8.2), 7.38–7.12 (complex, 5H), 6.64 (d, 1H, J = 8.2), 6.62 (t, 1H, J = 7.7), 6.28 (br s, 2H), 3.27 (m, 2H), 3.14 (m, 2H); ^{13}C-NMR: δ 201.2, 150.3, 139.0, 134.3, 133.9, 131.0, 130.6, 129.5, 127.6, 126.9, 117.7, 117.3, 115.8, 39.0, 28.7; ms: *m*/*z* 259, 261 (*ca*. 3:1, M^+). Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.39; N, 5.39. Found: C, 69.45; H, 5.44; N, 5.30.

Attempted reductive ring closure with iron powder in acetic acid–phosphoric acid mixtures: (±)-2,3-Dihydro-2-phenyl-4(1*H*)-quinolinone (10a). Using the procedure given for the reduction of **6a** with iron and acetic acid above, 500 mg (1.97 mmol) of **6a** and 440 mg (7.88 mmol) of iron powder (>100 mesh), with 10 mL of each acetic acid–phosphoric acid mixture given in Figure 2, were reacted for 30 min at

120°C. Workup and purification afforded **10a**. The yield for each run is given in Figure 2.

Representative reductive ring closure using iron powder in concentrated hydrochloric acid: (±)-2,3-Dihydro-2-phenyl-4(1*H*)-quinolinone (10a). Using the procedure given for the preparation of **7**, a mixture of 500 mg (1.97 mmol) of **6a** and 10 mL of concentrated hydrochloric acid in a 100-mL two-necked round-bottomed flask was heated to 80–85°C. The heat was briefly removed and 440 mg (7.88 mmol, 4 equiv) of iron powder (>100 mesh) was added. [Caution! The addition was sufficiently exothermic to boil the mixture and some frothing occurred as the iron was added. The reaction flask should be at least 10 times the volume of the reactants at this scale.] Heating was resumed at 100°C until thin layer chromatography indicated the reaction was complete (*ca*. 30 min). Workup and purification by flash chromatography on a 20-cm × 2-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 386 mg (88%) of **10a** as a pale yellow solid, mp 149–151°C (lit. [3a] mp 149–150°C). IR: 3326, 1661, 1608, 1482 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.87 (dd, 1H, J = 8.0, 1.5), 7.45 (dd, 2H, J = 7.6, 1.5), 7.42–7.31 (complex, 4H), 6.78 (t, 1H, J = 7.6), 6.71 (d, 1H, J = 8.2), 4.74 (dd, 1H, J = 13.8, 3.7), 4.55 (br s, 1H), 2.87 (dd, 1H, J = 16.2, 13.8), 2.77 (dm, 1H, J = 16.2); ^{13}C-NMR (100 MHz): δ 193.3, 151.5, 141.0, 135.4, 128.9, 128.4, 127.6, 126.6, 119.0, 118.4, 115.9, 58.4, 46.4; ms: *m*/*z* 223 (M^+).

(±)-2,3-Dihydro-2-(4-methylphenyl)-4(1*H*)-quinolinone (10b). Reductive cyclization of 415 mg (1.87 mmol) of **6b** with 418 mg (7.48 mmol) of iron gave 378 mg (85%) of **10b** as an off-white solid, mp 147–149°C (lit. [8c] mp 148–149°C). IR: 3331, 1655, 1608 cm^{-1}; ^{1}H-NMR: δ 7.87 (d, 1H, J = 7.7), 7.35 (d, 2H, J = 7.7), 7.34 (obscured signal, 1H), 7.21 (d, 2H, J = 7.7), 6.79 (t, 1H, J = 7.7), 6.70 (d, 1H, J = 8.2), 4.72 (dd, 1H, J = 13.7, 3.7), 4.47 (br s, 1H), 2.88 (dd, 1H, J = 16.2, 13.7), 2.75 (dd, 1H, J = 16.2, 3.7), 2.37 (s, 3H); ^{13}C-NMR: δ 193.4, 151.6, 138.3, 138.0, 135.3, 129.6, 127.6, 126.5, 119.0, 118.4, 115.9, 58.2, 46.5, 21.1; ms: *m*/*z* 237 (M^+). Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.91. Found: 80.94; H, 6.32; N, 5.85.

(±)-2,3-Dihydro-2-(4-methoxyphenyl)-4(1*H*)-quinolinone (10c). Reductive cyclization of 415 mg (1.76 mmol) of **6c** with 393 mg (7.04 mmol) of iron gave 365 mg (82%) of **10c** as a yellow solid, mp 147–148°C (lit. [8c] mp 147°C). IR: 3329, 2836, 1660, 1608 cm^{-1}; ^{1}H-NMR (400 MHz): δ 7.87 (dd, 1H, J = 8.0, 1.6), 7.37 (d, 2H, J = 8.6), 7.33 (td, 1H, J = 7.7, 1.2), 6.92 (d, 2H, J = 8.6), 6.78 (t, 1H, J = 7.7), 6.70 (d, 1H, J = 8.2), 4.69 (dd, 1H, J = 13.8, 3.7), 4.48 (br s, 1H), 3.82 (s, 3H), 2.87 (dd, 1H, J = 16.2, 13.8), 2.74 (dd, 1H, J = 16.2, 3.7); ^{13}C-NMR (100 MHz): δ 193.5, 159.6, 151.6, 135.3, 133.0, 127.8, 127.6, 119.0, 118.3, 115.9, 114.2, 57.9, 55.3, 46.5; ms: *m*/*z* 253 (M^+). Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93; N, 5.53. Found: C, 75.83; H, 5.94; N, 5.49.

(±)-2,3-Dihydro-2-(3,4-dimethoxyphenyl)-4(1*H*)-quinolinone (10d). Reductive cyclization of 426 mg (1.59 mmol) of **6d** and 355 mg (6.36 mmol) of iron gave 326 mg (72%) of **10d** as a white solid, mp 145–147°C. IR: 3348, 2836, 1660, 1611 cm^{-1}. ^{1}H-NMR: δ 7.87 (d, 1H, J = 7.7), 7.35 (t, 1H, J = 7.1), 7.00 (s, 1H), 6.99 (d, 1H, J = 7.7), 6.87 (d, 1H, J = 8.2), 6.80 (t, 1H, J = 7.7), 6.72 (d, 1H, J = 8.2), 4.70 (dd, 1H, J = 13.7, 3.7), 4.51 (br s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.88 (dd, 1H, J = 15.9, 13.7), 2.75 (dd, 1H, J = 15.9, 3.7); ^{13}C-NMR: δ 193.4, 151.5, 149.3, 149.0, 135.3, 133.5, 127.6, 119.0, 118.9, 118.4, 115.9, 111.2, 109.4, 58.3, 55.97, 55.94, 46.7; ms: *m*/*z* 283 (M^+). Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.11; H, 6.02; N, 4.91.

(±)-2-(1,3-Benzodioxol-5-yl)-2,3,dihydro-4(1*H*)-quinolinone (10e). Reductive cyclization of 423 mg (1.68 mmol) of **6e** and 375 mg (6.72 mmol) of iron gave 374 mg (83%) of **10e** as an off-white solid, mp 128–130°C (lit. [12b] mp 118–119°C). IR: 3328, 1663, 1610 cm^{-1}; ^{1}H-NMR: δ 7.86 (d, 1H, J = 7.7), 7.34 (td, 1H, J = 7.7, 1.6), 6.97 (d, 1H, J = 1.1), 6.89 (dd, 1H, J = 8.0, 1.6), 6.79 (overlapping d and t, 2H, $J \approx$ 8.2), 6.71 (d, 1H, J = 8.2), 5.98 (s, 2H), 4.65 (dd, 1H, J = 13.4, 3.7), 4.49 (br s, 1H), 2.83 (dd, 1H, J = 16.2, 13.4), 2.71 (dd, 1H, J = 16.2, 3.7); ^{13}C-NMR: δ 193.3, 151.5, 148.0, 147.6, 135.4, 134.9, 127.6, 120.1, 119.0, 118.4, 115.9, 108.5, 106.9, 101.2, 58.3, 46.6; ms: *m*/*z* 267 (M^+). Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.87; N, 5.24. Found: C, 71.92; H, 4.89; N, 5.22.

(±)-2-(2-Chlorophenyl)-2,3-dihydro-4(1*H*)-quinolinone (10f). Reductive cyclization of 399 mg (1.73 mmol) of **6f** and 386 mg (6.92 mmol) of iron gave 357 mg (80%) of **10f** as a yellow solid, mp 126–128°C. IR: 3429, 1659, 1609 cm^{-1}. ^{1}H-NMR: δ 7.88 (d, 1H, J = 7.7), 7.68 (dd, 1H, J = 7.1, 1.6), 7.44–7.23 (complex, 4H), 6.81 (t, 1H, J = 7.1), 6.74 (d, 1H, J = 8.2), 5.27 (dd, 1H, J = 12.1, 3.7), 4.52 (br s, 1H), 2.96 (ddd, 1H, J = 16.2, 3.7, 1.5), 2.78 (dd, 1H, J = 16.2, 12.1); ^{13}C-NMR: δ 192.7, 151.5, 138.3, 135.4, 132.8, 130.0, 129.3, 127.6, 127.5, 127.4, 119.1, 118.7, 116.0, 54.2, 44.0; ms: *m*/*z* 257, 259 (*ca*. 3:1, M^+). Anal. Calcd. for $C_{15}H_{12}ClNO$: C, 69.90; H, 4.66; N, 5.44. Found: C, 69.97; H, 4.69; N, 5.39.

Cyclization of 8a using concentrated hydrochloric acid: (±)-2,3-Dihydro-2-phenyl-4(1*H*)-quinolinone (10a). Using the procedure for the conversion of **6a** to **10a**, a mixture of 150 mg (0.67 mmol) of **8a** and 6 mL of concentrated hydrochloric acid was treated at 85°C with 150 mg (2.69 mmol, 4 equiv) of iron powder and then heated at 100°C for 30 min. Workup and purification by preparative thin layer chromatography eluted with 30% ether in hexanes yielded 128 mg (85%) of **10a** as a pale yellow solid. The physical properties and spectral data matched those reported above. The cyclization of **8a** to **10a** can also be carried out in the same fashion without iron.

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REFERENCES AND NOTES

[1] (a) Bunce, R. A.; Herron, D. M.; Ackerman, M. L. J Org Chem 2000, 65, 2847; (b) Bunce, R. A.; Randall, M. H.; Applegate, K. G. Org Prep Proced Int 2002, 34, 493; (c) Bunce, R. A.; Nammalwar, B. J Heterocycl Chem 2009, 46, 172; (d) Bunce, R. A.; Nammalwar, B. J Heterocycl Chem 2009, 46, 854.

[2] Ibrahim, E.-S.; Montgomerie, A. M.; Sneddon, A. H.; Proctor, G. R.; Green, B. Eur J Med Chem 1988, 23, 183.

[3] (a) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. J Med Chem 1998, 41, 1155; (b) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T.

Org Lett 2005, 7, 5317; (c) Choi, S.; Jung, K.; Ryu, J. Arch Pharm Res 2006, 29, 369.

[4] (a) Mannich, C.; Dannehl, M. Chem Ber B 1938, 71, 1899; no yield reported; (b) Tökés, A. L.; Szilágyi, L. Synth Commun 1987, 17, 1235; a yield of 45% was reported.

[5] (a) Kundu, N. G.; Mahanty, J. S.; Das, P.; Das, B. Tetrahedron Lett 1993, 34, 1625; (b) Tokes, A. L.; Janzsó, G. Synth Commun 1989, 19, 3159.

[6] Donnelly, J. A.; Farrell, D. F. J Org Chem 1990, 55, 1757.

[7] Varma, R. S. J Heterocycl Chem 1999, 36, 1565.

[8] (a) Kumar, K. H.; Muralidharan, D.; Perumal, P. T. Synthesis 2004, 63; (b) Ahmed, N.; van Lier, J. E. Tetrahedron Lett 2006, 47, 2725; (c) Kumar, K. H.; Perumal, P. T. Can J Chem 2006, 84, 1079; (d) Ahmed, N.; van Lier, J. E. Tetrahedron Lett 2007, 48, 13; (e) Lee, J. I.; Youn, J. S. Bull Korean Chem Soc 2008, 29, 1853.

[9] Kumar, D.; Patel, G.; Mishra, B. G.; Varma, R. S. Tetrahedron Lett 2008, 49, 6974.

[10] Saito, A.; Kasai, J.; Odaira, Y.; Fukaya, H.; Hanzawa, Y. J Org Chem 2009, 74, 5644.

[11] Chandrasekhar, S.; Vijeender, K.; Sridhar, Ch. Tetrahedron Lett 2007, 48, 4935.

[12] (a) Tollari, S.; Cenini, S.; Ragaini, F.; Cassar, L. J Chem Soc Chem Commun 1994, 1741; (b) Annunziata, R.; Cenini, S.; Palmisano, G.; Tollari, S. Synth Commun 1996, 26, 495.

[13] Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. J Org Chem 1993, 58, 611.

[14] Still, W. C.; Kahn, M.; Mitra, A. J Org Chem 1978, 43, 2923.

[15] Barnes, R. P.; Graham, J. H.; Qureshi, M. A. S. J Org Chem 1963, 28, 2890.

[16] Sahasrabudhe, A. B.; Kamath, H. V.; Bapat, B. V.; Kulkarni, S. N. Indian J Chem B 1980, 19, 230.

[17] Johnson, W. S.; Woroch, E. L.; Buell, B. G. J Am Chem Soc 1949, 71, 1901.