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SCIENCE DIRECT®

Tetrahedron 59 (2003) 747–754

TETRAHEDRON

Unexpected products from the Fp_2-catalyzed reductive cyclization of nitroaromatics bearing pendant unsaturation

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Received 28 August 2002; revised 12 December 2002; accepted 12 December 2002

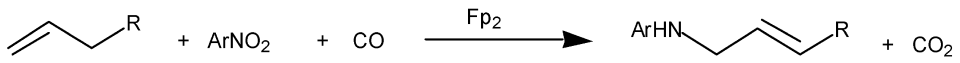
Abstract—A representative *o*-nitroenone (Z=O) was cyclized by reduction with CO and $[CpFe(CO)_2]_2$ (Fp_2) as the catalyst to give the corresponding 4-quinolone. In contrast, Baylis–Hillman adducts derived from *o*-nitrobenzaldehydes were cyclized to *N*-formylindolines and indoles under the same conditions. © 2003 Published by Elsevier Science Ltd.

1. Introduction

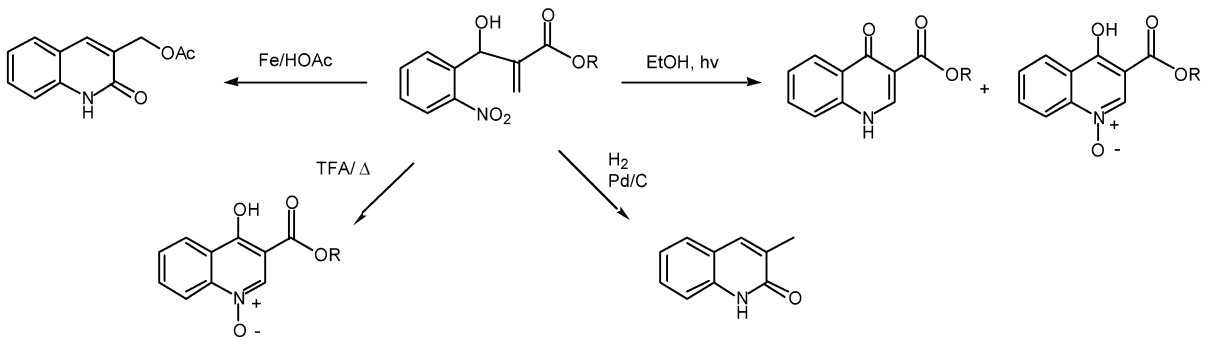
The transition metal-catalyzed cyclization of anilines bearing pendant unsaturation is a well established route to important heterocycles.[1,2] Several groups have also focused upon the reduction of the corresponding *o*-nitro compounds with concomitant cyclization. These aromatic nitro group deoxygenations, pioneered by Cadogan and Sundberg's phosphine and phosphite chemistry,[3,4] have also been effected by carbon monoxide, catalyzed by Pd complexes,[5–7] Se,[8] and Group 8 transition metal carbonyls,[9] affording a variety of heterocycles, including indoles, quinolones and quinolines.

In an ongoing effort to discover new amination reactions, we have used the cyclopentadienyliron dicarbonyl dimer (Fp_2) to catalyze the intermolecular reductive reaction of nitroarenes with alkenes to give allylamines (Scheme 1).[10] We have now sought to examine the efficacy of this protocol in an intramolecular reaction, to prepare 4-quinolone derivatives, an important class of chemotherapeutic agents.[11]

We also wanted to investigate the transition metal catalyzed carbonylative cyclization of the Baylis–Hillman (B–H) adducts of 2-nitrobenzaldehydes and methylacrylate, again in an effort to prepare 4-quinolone derivatives. The Baylis–Hillman reaction is a powerful carbon–carbon bond forming reaction between an aryl aldehyde and a Michael-acceptor, catalyzed by a non-nucleophilic base, giving a 2-functionalized allylic alcohol.[12–14] The synthesis and subsequent elaboration of such adducts has thus received increasing attention. Several groups have targeted the B–H



Scheme 1.



Scheme 2.

Keywords: cyclization; hydrogenation; indoles.

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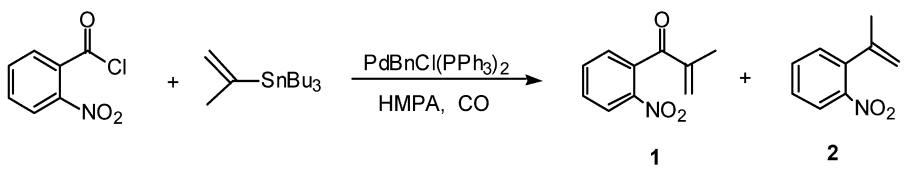
0040–4020/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
PII: S0040-4020(02)01627-7

adducts of 2-nitrobenzaldehyde as precursors to nitrogen heterocycles (Scheme 2). Recently Basavaiah has reported the synthesis of 2-quinolones by reduction of these compounds with Fe/AcOH.[15] Kim and coworkers were able to synthesize the 4-quinolones and 4-quinolone-*N*-oxides through irradiation of the B–H adducts, as well as synthesis of the later by treatment with TFA.[16,17] Kaye et. al. have used catalytic hydrogenation of B–H adducts to produce 2-quinolones.[18]

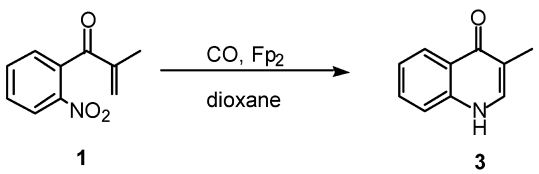
2. Results and discussion

Our initial studies focused on the reaction of the nitroenone **1**, which could be obtained by Stille coupling[19] of 2-nitrobenzoyl chloride with 2-propenyltributyltin under CO pressure using a catalytic amount of $Pd(CH_2Ph)Cl(PPh_3)_2$ (Scheme 3). When CO was bubbled through the reaction mixture the major product was the (decarbonylated) 2-nitrostyrene **2**. It has been found previously that aroyl halides can be used in place of aryl halides in Pd-catalyzed coupling reactions, readily decarbonylating to give the intermediate aryl-Pd(II) species.[20]

A pressure of 300 psi was required to nearly completely suppress the formation of **2** and give **1** in 35% yield. 2-Nitrostyrenes have been reductively cyclized to give indoles under a variety of conditions.[3–9] Indeed, when **2** was heated at 150°C with 10 mol% Fp_2 at 750 psi CO, 3-methylindole (skatole) was formed as the primary product (40% GC yield). Given the relatively large number of such indole-forming reactions and the instability of the styrene precursors, a more extensive study of these reactions was not carried out. Instead, we focused our attention upon the nitroenone **1** that could produce the corresponding 4-quinolone. To our delight when **1** was heated in dioxane with 5 mol% Fp_2 under CO (800 psi), 3-methylquinolin-4(1*H*)-one **3** was obtained in 76% yield (Scheme 4).



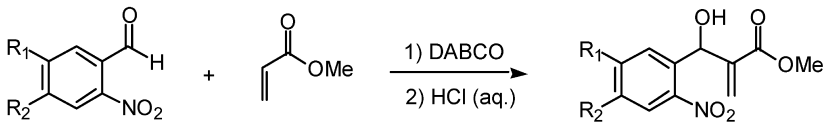
Scheme 3.



Scheme 4.

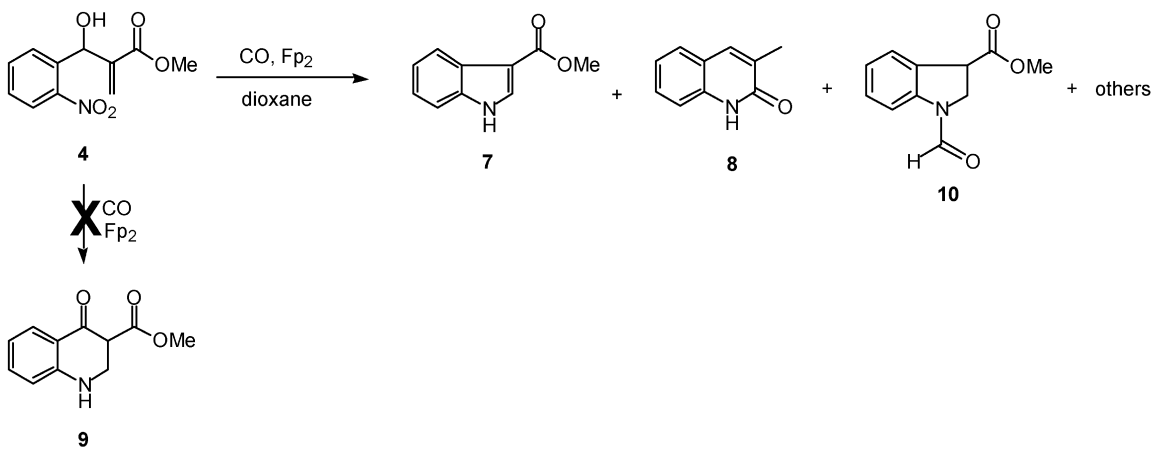
Next we turned our attention to the easily prepared Baylis–Hillman adducts, hoping to produce, by analogy, dihydro-4-quinolones. Compounds **4**–**6** were prepared in excellent yield by reaction of the appropriate aldehyde with DABCO in methyl acrylate (Scheme 5).

The Baylis–Hillman adduct **4** was heated (150°C) in



4 R_1,R_2=H ; R_3=Me 99%
5 R_1=Cl; R_2=H; R_3=Me 93%
6 R_1=CH_2O-CH_2=R_2 95%

Scheme 5.



Scheme 6.

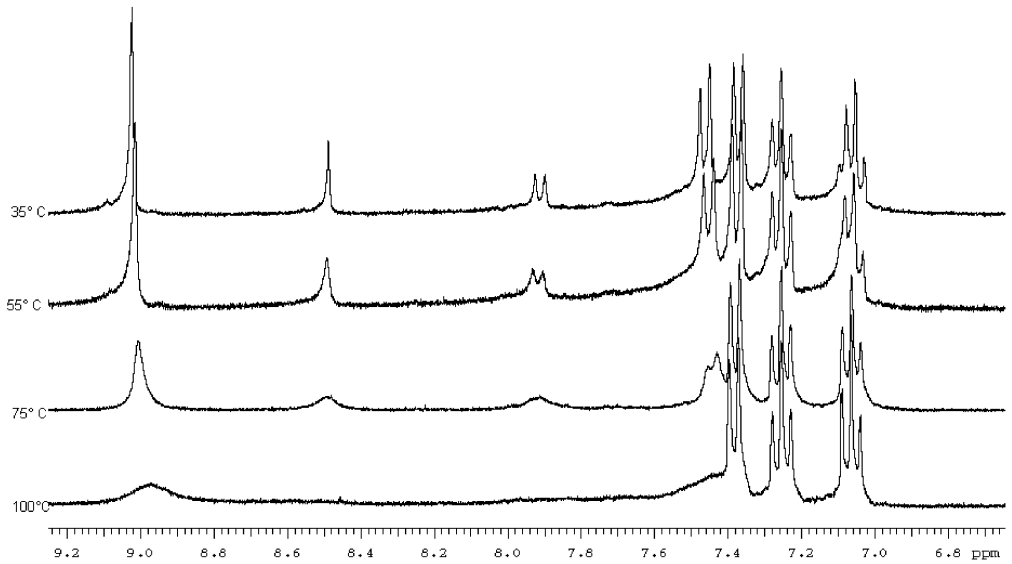


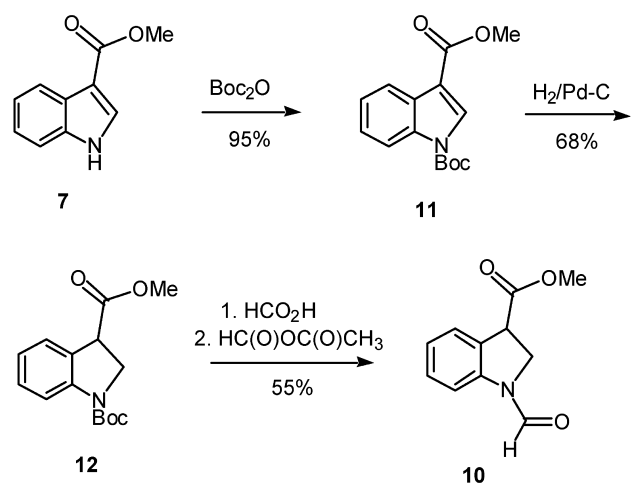
Figure 1. Temperature-dependent ^{1}H NMR spectra of **10**.

dioxane with 10 mol% of Fp_2 under 750 psi CO (Scheme 6). Chromatography of the product mixture gave two major products, one of apparent mass 175 and another with *m/e* 205, a few minor products, and some tar, which accounts for a poor mass balance. As Smith noted in his review of related deoxygenations, 'cyclizations of *o*-nitrostyrenes that take place in low yields are usually accompanied by extensive tar formation'.[21] The *m/e* 175 product (17% yield), remarkably, is the result of the loss of one carbon (as CO, CH_2O?) from the precursor **4**. It was identified as methyl 3-indolecarboxylate **7** and was spectroscopically identical to commercial material. Also detected was the known 2-quinolone **8** (4%), arising from apparent ester aminolysis, reduction and dehydration.[18]

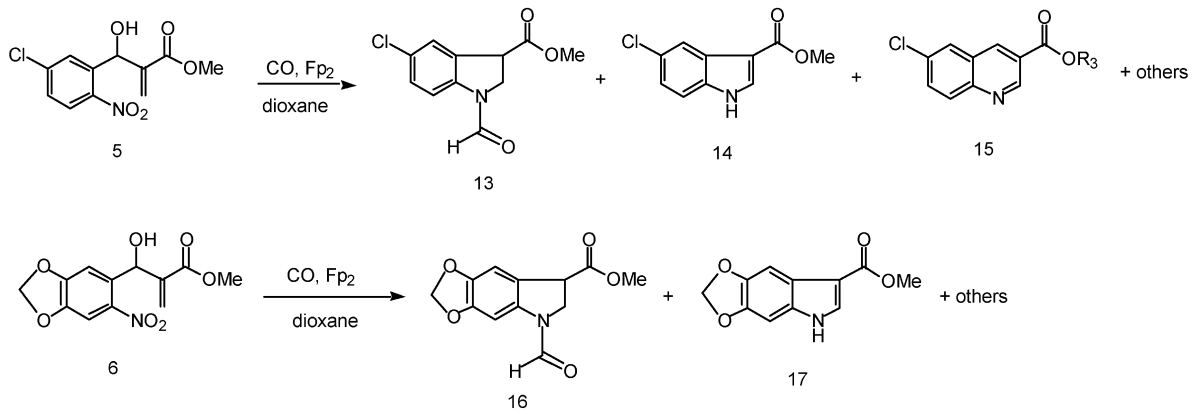
The other major product (20%, *m/e* 205) corresponded formally to the removal of two oxygen atoms, consistent with the expected dihydroquinolone **9**. The ^{1}H NMR spectrum of this compound in *d*6-DMSO was temperature-dependent, the low field portion of which is shown in Figure 1. The two singlets at 8.45 and 9.0 ppm (approximately 3:1 ratio at 20°C) and two doublets at 7.5 and 7.9 ppm coalesced at 100°C; the original spectrum was restored upon cooling to room temperature. The NMR results suggested that two isomers of the compound were in equilibrium. Although this could be explained by the existence of a keto-enol tautomeric mixture for **9**, the sharpness of the low field resonances, the differing melting point of the compound compared to that reported for **9**,[22] and other data (vide infra) pointed to an alternative structure for the *m/e* 205 product.

When this compound was subjected to oxidation with MnO_2, it gave a product with *m/e* 203 (loss of 2H) and a small amount of the indole **7**. We thus turned our attention to prospective structures that could be oxidized to indoles. Examination of the literature of *N*-formylindolines,[23] revealed ^{1}H NMR spectra strikingly similar to those we obtained, with temperature-dependent spectra arising from the slowly interconverting *N*-formyl rotamers. Ultimately, we assigned the structure of the *m/e* 205 compound to be the *N*-formylindoline **10**. To verify this assignment, we applied standard reaction protocols to synthesize **10** from the commercially available indole **7** (Scheme 7). Thus **7** was protected as the *N*-Boc derivative **11**,[24] followed by catalytic hydrogenation to give *N*-Boc-indoline **12**.[25] A one pot deprotection/formylation[26] using formic acid, followed by treatment with formic acetic anhydride, gave the *N*-formylindoline **10** which was spectroscopically identical to that formed through our cyclization.

Regardless of the efficiency of this transformation, formation of the indole **7** and the *N*-formylindoline **10** is remarkable. In a control experiment reaction of **4** with Fp_2 (35 mol%) in the absence of CO also gave the indole **7**, albeit in 7% yield, as the sole identifiable product. Additionally, when either the indole **7** or the indoline **10** were subjected to the catalytic cyclization conditions, they were recovered unchanged after several days. This result indicates that both **7** and **10** are primary products of the cyclization reaction. It is also worth noting that heating the Baylis–Hillman adduct **4** to 150°C under 750 psi CO



Scheme 7.



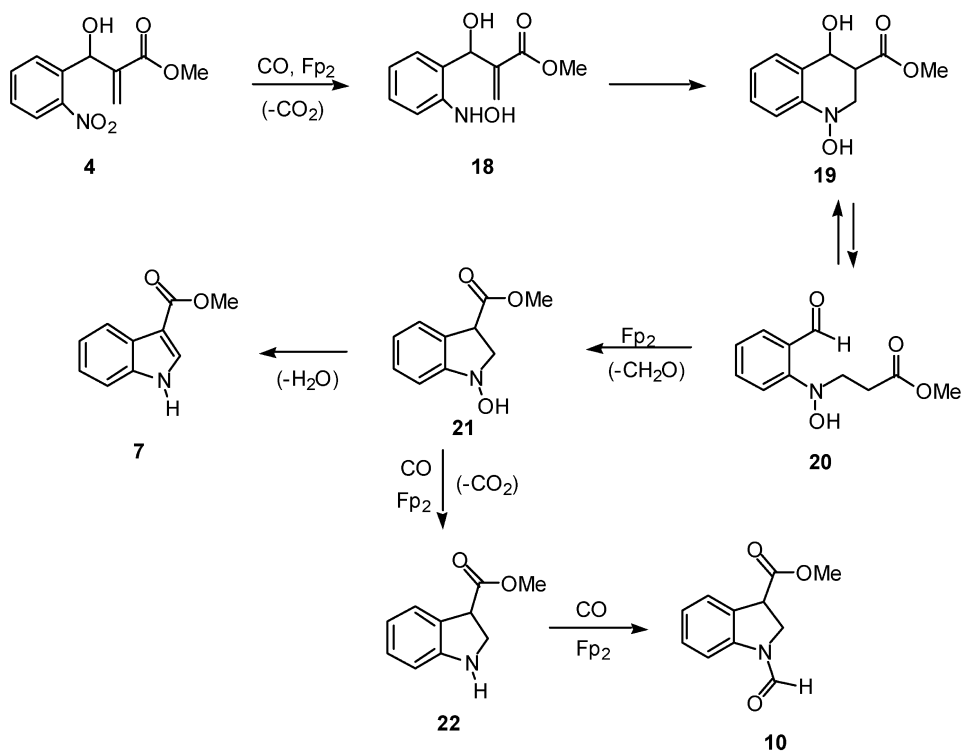
Scheme 8.

without Fp_2 for several days did not produce any of the products mentioned above.

We also compared these results to corresponding reactions using other CO-based reduction methods, specifically the $PdCl_2(PPh_3)/SnCl_2/CO$ system of Watanabe[6] and the $Se/NEt_3/CO$ combination employed by Sonoda.[8] In both cases the reduction of **4** was incomplete after prolonged reaction times and the product mixtures were extremely complex. In neither case was the *N*-formylindoline **10** detected; however, the indole **7** was formed in trace amounts.

The cyclization of the other two B–H adducts, **5** and **6**, gave similar results, as shown in Scheme 8. The 5-chloro-2-nitrobenzaldehyde adduct **5** provided a 13% yield of *N*-formylindoline **13** and 8% of the methyl 5-chloro-indole-3-carboxylate **14**; a small amount of the 6-chloro-quinoline **15** was also isolated. Similarly, the adduct of the 2-nitropiperonal **6** gave the *N*-formylindoline **16** (8%) and the indole **17** (5%). Each of the *N*-formyl indolines apparently exists as a rotomeric mixture, judging from the appearance of two formyl proton resonances in their ^1H NMR spectra as well as the presence of multiple pairs of resonances in their ^{13}C NMR spectra.

An admittedly speculative, but precedented, mechanistic outline is suggested in Scheme 9. Initial Fp_2-promoted reduction of the nitro group of **4** to the hydroxylamine **18** would be followed by Michael addition to the terminal olefinic carbon.[27] Intermediate **19** could then undergo reversible retro-aldol reaction to generate aldehyde **20**. Deformylation of **20** could be effected by seventeen electron $CpFe(CO)_2$,[28] either by a radical[29,30] or an organometallic pathway,[31] to generate an aryl-iron or aryl radical intermediate, which then could cyclize to indoline **21** by addition to the ester enol. The *N*-hydroxyindoline **21** could then dehydrate to give the indole **7** or be further reduced to the indoline **22**, which could be re-carbonylated to



Scheme 9.

produce the *N*-formylindoline **10**. The *N*-carbonylation of amines to formamides by group 8 transition metal complexes and carbon monoxide is also established.[32]

3. Conclusions

Entry to the 4-quinolone ring system has been demonstrated by the Fp_2-catalyzed reductive cyclization of an *o*-acryloyl nitroarene derivative. In contrast to other reductions of Baylis–Hillman adducts the Fp_2–CO system gives markedly different products, the formation of indole and *N*-formylindolines being quite unusual. Further studies are underway to improve product selectivity, to expand the range of substrates, and to elucidate the mechanistic details.

4. Experimental

4.1. General

Unless specified otherwise all reactions were carried out under an atmosphere of nitrogen with magnetic stirring, using dried, freshly distilled solvents and oven dried glassware. High pressure reactions were carried out in Parr stainless steel reaction vessels. All reagents and $[CpFe(CO)_2]_2$ were purchased from US suppliers. TLC was performed using ANALTECH HPTLC with fluorescent indicator. Flash chromatography was performed using silica gel 230–400 mesh (Merck). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Varian spectrometer; TMS was used as an internal standard for all spectra taken in acetone. Melting points are uncorrected.

4.1.1. 2-Methyl-1-(2-nitrophenyl)prop-2-en-1-one (1). $(PPh_3)_2Pd(CH_2Ph)Cl$[33] (64 mg, 0.090 mmol) was sealed in a glass vial which was scored to ensure breakage. This vial along with 2-nitrobenzoyl chloride (1.67 g, 9.00 mmol), isopropenyltributyltin[34] (3.40 g, 10.3 mmol), and HMPA (4 mL) were added to a 120 mL glass-lined Parr reaction vessel equipped with a large magnetic stirrer. The vessel was flushed three times with CO (fume hood) and finally charged to 300 psi. The vessel was manually shaken until the vial containing the catalyst was broken, after which the reaction was stirred at 70°C for 10 h. After cooling and venting of CO (fume hood), the reaction mixture was diluted with ether and stirred with saturated aqueous KF (30 mL) for 1 day. The ether layer was separated and filtered to remove a white precipitate (Bu_3SnCl), and washed with brine (3×20 mL). Solvent was removed in vacuo and the residue was purified by flash chromatography (Et_2O/hexanes, 1:4) to give the product slightly contaminated with Bu_3SnCl. Recrystallization from Et_2O/hexanes gave pale yellow prisms of the nitroenone **1** (0. 60 g, 35%); mp 61.5–63°C; R_f=0.5 (1:1, Et_2O/hexanes); IR (KBr) 3321, 3097, 3027, 2957, 1660, 1521, 1436, 1343, 1189 cm^{-1}. ^1H NMR (300 MHz; d_6-DMSO) 1.96 (dd, *J*=1.2, 0.3 Hz, 3H), 5.35 (d, *J*=0.9 Hz, 1H), 5.99 (q, *J*=1.2 Hz, 1H), 7.57 (ddd, *J*=7.12, 1.2, 0.3 Hz 1H), 7.77 (tdd, *J*=8.1, 1.2, 0.6 Hz, 1H), 7.88 (td, *J*=7.5, 1.2 Hz, 1H), 8.20 (dd, *J*=8.25, 1.2 Hz, 1H); ^{13}C NMR (75.45 MHz; d_6-DMSO) 17.8, 125.1, 129.5, 129.6, 131.9, 135.4, 134.8, 143.7, 146.1, 194.5; MS (ESI) 192 (M+H, 30), 214 (M+Na, 100), 405 (M_2+Na, 11.4); Anal. calcd: C 62.82, H 4.74, N 7.33; found: C 62.52, H 4.79, N 7.27.

4.1.2. 3-Methylquinolin-4(1*H*)-one (3).[35] In a glass-lined 15 mL Parr reaction vessel the nitroenone **1** (75 mg, 0.39 mmol) and Fp_2 (7 mg, 0.02 mmol) were combined in dioxane (10 mL). The vessel was purged thrice with CO (fume hood) and charged to 800 psi. The vessel was then stirred at 200°C for 8.5 h. After cooling and venting of the CO (fume hood), the reaction mixture was filtered to remove insoluble material and concentrated. Preparative TLC, eluting with EtOAc/hexanes (1:1), gave the quinolone **3**, R_f=0.1 (48 mg, 76%). ^1H NMR (300 MHz; d_6-DMSO) 1.95 (s, 3H), 7.23 (td, *J*=7.5, 1.2 Hz, 1H), 7.46 (dd, *J*=6.6, 0.6 Hz, 1H), 7.55 (td, *J*=7.7, 1.5 Hz, 1H), 7.85 (s, 1H), 8.07 (dd, *J*=8.1, 1.2 Hz, 1H), 8.29 (s, 1H); ^{13}C NMR (d_6-DMSO) 13.6, 116.2, 117.8, 122.3, 123.8, 124.7, 130.8, 136.5, 139.5, 176.4; IR (KBr) 3460, 2865, 1630 cm^{-1}; MS (EI) 159 (83), 130 (100), 104 (10), 92 (5), 77 (18), 63 (8), 51(8); HRMS (ESI) calcd for $C_{10}H_9NONa$ (M+Na) 182.0582; found: 182.0591.

4.1.3. Methyl 2-[hydroxy(2-nitrophenyl)methyl]acrylate (4).[36] 2-Nitrobenzaldehyde (2.00 g, 13.2 mmol) was dissolved in methyl acrylate (20 mL), DABCO (1.48 g, 13.2 mmol) was added slowly over 5 min upon which the mixture became a dark orange-red. The mixture was stirred at room temperature for 5 days. The methyl acrylate was removed in vacuo, and the residue was dissolved in Et_2O, washed with 1 M HCl (3×20 mL), and then with water (2×10 mL). The ether extract was concentrated on a rotary evaporator and then chromatographed over silica gel (Et_2O/hexanes, 1:1) to give **4** (R_f=0.28) as a straw colored oil (3.1 g, 99%), which crystallized from cold ether. Mp 28–29°C; IR (film) 3445, 2946, 1699, 1537 cm^{-1}; ^1H NMR (300 MHz; d_6-acetone) 3.64 (s, 3H), 5.1 (br s, 1H), 5.81 (d, *J*=1.2 Hz, 1H), 6.26 (m, 2H), 7.52 (td, *J*=8.1, 1.8 Hz, 1H), 7.69 (td, *J*=7.8, 1.2 Hz, 1H), 7.76 (dd, *J*=7.8, 1.8 Hz, 1H), 7.9 (dd, *J*=8.1, 1.2 Hz, 1H); ^{13}C NMR (75.45 MHz; d_6-acetone) 51.7, 66.4, 124.4, 124.6, 128.9, 129.2, 133.2, 137.3, 143.1, 148.8, 165.8; MS (EI) 220 (M+ –OH, 10), 191 (M+ –NO_2, 100), 160 (40), 132 (146), 117 (38), 117 (38), 104 (40), 77 (42), 51 (28); HRMS (ESI) calcd for $C_{11}H_{11}NO_5Na$ (M+Na) 260.0535; found: 260.0463.

4.1.4. Methyl 2-[(5-chloro-2-nitrophenyl)(hydroxy)-methyl]acrylate (5). 5-Chloro-2-nitrobenzaldehyde (1.00 g, 5.3 mmol), sold as a mixture from Aldrich of at least 77% purity, was dissolved in 15 mL of methyl acrylate. DABCO (0.60 g, 5.4 mmol) was then added over 5 min after which the mixture darkened. The mixture was stirred at room temperature for 4 days, followed by the workup described for compound **4**. Chromatography on silica gel with Et_2O/hexanes (gradient elution: 1:5 to 1:1) gave 1.0 g (93% yield based upon the purity of the starting material) of the Baylis–Hillman adduct **5** as a yellow solid, mp 63–65°C, R_f=0.40 (1:1, Et_2O/hexanes). IR (KBr) 3475, 1722, 1529, 1367, 1297 cm^{-1}; ^1H NMR (300 MHz; d_6-acetone) 3.69 (s, 3H), 5.38 (d, *J*=5.1 Hz, 1H), 5.81 (d, *J*=0.9 Hz, 1H), 6.29 (m, 2H), 7.59 (dd, *J*=8.7, 2.4 Hz, 1H), 7.79 (d, *J*=2.4 Hz, 1H), 8.0 (d, *J*=8.7 Hz, 1H); ^{13}C NMR (75.45 MHz; d_6-acetone) 52.2, 66.8, 125.7, 127.0, 129.3, 129.6, 139.5, 140.5, 143.2, 147.5, 166.1; MS (EI) 254 (M+ –OH, 1), 227

(30), 225 (M+ $-NO_2$, 100), 194 (20), 166 (15), 138 (6); HRMS (ESI) calcd for $C_{11}H_{10}NO_5Na$ (M+Na) 294.0145; found: 294.0103.

4.1.5. Methyl 2-[hydroxy(6-nitro-1,3-benzodioxol-5-yl)methyl]acrylate (6). 2-Nitropiperonal (3.00 g, 15.4 mmol) was dissolved in methyl acrylate (20 mL), DABCO (1.72 g, 15.4 mmol) was added slowly over 5 min upon which the mixture became a dark orange-red. The mixture was stirred at room temperature for 7 days; after one day a yellow precipitate formed. After the above described workup, chromatography on silica gel using a gradient elution with Et_2O/hexanes (20–50% Et_2O) gave 4.10 g (95%) of **6**, R_f=0.2 (1:1, Et_2O/hexanes); mp 122–123.5°C; IR (KBr) 3494, 1712, 1637, 1531, 1482, 1343, 1256, 1030, 879, 822 cm^{-1}; ^1H NMR (300 MHz; CD_3CN) 3.71 (s, 3H), 4.02 (br s, 1H), 5.67 (d, J=0.9 Hz, 1H), 6.15 (m, 3H), 7.17 (s, 1H), 7.49 (s, 1H); ^{13}C NMR (75.45 MHz; CD_3CN) 52.6, 67.3, 104.5, 105.7, 108.2, 125.5, 135.2, 142.2, 143.4, 148.2, 153.0, 166.8; MS (EI) 235 (M+ $-NO_2$, 20), 221 (32), 204 (76), 188 (64), 176 (100), 160 (26), 148 (18), 135 (9), 120 (7), 104 (4), 77 (3), 53 (8); HRMS (ESI) calcd for $C_{12}H_{11}NO_7Na$ (M+Na) 304.0433; found: 304.0412; Anal. calc: C 51.25, H 3.94, N 4.98; found: C 51.25, H 3.99, N 4.86.

4.2. Cyclization of Baylis–Hillman adduct 4

Compound **4** (0.20 g, 0.84 mmol) and Fp_2 (30 mg, 0.085 mmol) were placed in a glass-lined, stainless steel Parr reaction vessel with dioxane (10 mL). The vessel was flushed three times with CO (fume hood) and charged to 800 psi. The mixture was the heated to 150°C with stirring for 14 h. After cooling and venting of CO (fume hood), the resulting brown solution was filtered to remove insoluble material, concentrated and then chromatographed on silica gel with a gradient elution of Et_2O/hexanes (1:5–9:1) to give the following compounds:

4.2.1. Methyl 1-formylindoline-3-carboxylate (10). 34 mg (20%); R_f=0.20 (Et_2O/hexanes, 3:1); mp 84–85.5°C; IR (KBr) 1732, 1665, 1594, 1497, 1367, 1283, 1220, 1174 cm^{-1}; ^1H NMR (300 MHz; d_6-DMSO) 3.69 (s, 3H), 4.0–4.5 (m, 3H), 7.09 (m, 1H), 7.26 (m, 1H), 7.37 (d, J=7.8 Hz, 1H), 7.48 (d, J=8.1 Hz, 0.7H, major isomer), 7.91 (d, J=7.8 Hz, 0.3H, minor), 8.50 (s, 0.3H, minor), 9.04 (s, 0.7H, major); ^{13}C NMR (75.45 MHz; d_6-DMSO) 44.0, 44.5, 46.9, 48.9, 52.5, 110.2, 115.6, 123.7, 124.1, 125.3, 125.9, 128.5, 128.6, 128.8, 129.4, 140.8, 158.3, 160.0, 171.2, 171.3; MS (EI) 205 (M^+, 60), 177 (8),145 (35), 118 (100), 91 (17); Anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.45; H, 5.47; N, 6.74.

4.2.2. Methyl 1*H*-indole-3-carboxylate (7). 25 mg (17%); R_f=0.25 (Et_2O/hexanes, 1:1); spectroscopically identical to material purchased from Aldrich.

4.2.3. 3-Methylquinolin-2(1*H*)-one (8). 6 mg (4%); R_f=0.26 (Et_2O/hexanes, 3:1); identical to literature compound.[37]

4.3. Cyclization of Baylis–Hillman adduct 5

The Baylis–Hillman adduct **5** (0.24 g, 0.89 mmol) and Fp_2 (35 mg, 0.10 mmol) were placed in a glass-lined, stainless steel 15 mL Parr reaction vessel with benzene (10 mL). The vessel was flushed thrice with CO (fume hood) and charged to 800 psi. The mixture was heated to 150°C while stirring for 18 h. After cooling and venting the CO (fume hood), the resulting dark brown solution was filtered to remove insoluble material, the filtrate concentrated, and then chromatographed on silica gel with a gradient elution of Et_2O/hexanes (1:5–9:1) giving the following compounds:

4.3.1. Methyl 5-chloro-1-formylindoline-3-carboxylate (13).[37] 30 mg (13%); R_f=0.13 (Et_2O/hexanes, 3:1); IR (KBr) 3452, 2975, 1738, 1684, 1491, 1367, 1321, 819 cm^{-1}; ^1H NMR (300 MHz; CD_3CN) 3.72 (s, 3H), 4.05–4.15 (m, 1H), 4.24–4.47 (m, 2H), 7.26 (m, 2H), 7.41 (m, 0.7H), 7.93 (d, J=8.7 Hz, 0.3H, minor isomer), 8.42 (s, 0.3H, minor), 8.86 (s, 0.7H, major); ^{13}C NMR (75.45 MHz; CD_3CN) 45.1, 45.6, 48.1, 50.2, 53.2, 111.8, 117.6, 126.0, 126.3, 127.1, 128.8, 129.3, 131.7, 158.5, 160.5, 171.7; MS (EI) 241 (M^+, 15), 239 (50), 211 (16), 180 (31), 154 (32), 152 (100), 117 (78), 89 (14); Anal. calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 54.91; H, 4.33; N, 5.54.

4.3.2. Methyl 5-chloro-1*H*-indole-3-carboxylate (14). 23 mg (11%); mp 110–112°C; R_f=0.18 (Et_2O/hexanes, 1:1); IR (KBr) 3250, 1680, 1524, 1443; ^1H NMR (300 MHz; CD_3CN) 3.87 (s, 3H), 7.23 (dd, J=8.8, 2.1 Hz, 1H), 7.51 (d, J=8.7 Hz, 1H), 7.97 (s, 1H), 8.07 (d, J=2.1 Hz, 1H), 10.06 (br s, 1H); ^{13}C NMR (75.45 MHz; CD_3CN) 51.4, 114.3, 120.8, 123.6, 133.8, 165.4; MS (EI) 211 (15), 209 (50), 178 (100), 150 (24), 123 (8); HRMS (ESI) calcd for $C_{10}H_8ClNO_2Na$ (M+Na) 232.0141; found: 232.0080.

4.3.3. Methyl 6-chloroquinoline-3-carboxylate (15). 8 mg (4%); R_f=0.2 (Et_2O/hexanes, 1:3), mp 170–172°C; IR (KBr) 3066, 2950, 1722, 1491, 1436, 1336, 1267, 1097, 819 cm^{-1}. ^1H NMR (300 MHz; d_6-acetone) 4.00 (s, 3H), 7.89 (dd, J=9.0, 2.4 Hz, 1H), 8.12 (d, J=9.0 Hz, 1H), 8.24 (d, J=2.1 Hz, 1H), 8.93 (d, J=1.5 Hz, 1H), 9.35 (d, J=2.1 Hz, 1H); ^{13}C NMR (75.45 MHz; $CDCl_3$) 52.7, 132.7, 127.5, 130.9, 132.7, 133.3, 137.7, 148.0, 150.0, 165.3; MS (EI) 221 (M^+, 100), 190 (95), 162 (70), 127 (27), 99 (16), 74 (5); HRMS (ESI) calcd for $C_{11}H_8ClNO_2Na$ (M+Na) 244.0141; found: 244.0092.

4.4. Cyclization of Baylis–Hillman adduct 6

The Baylis–Hillman adduct **6** (200 mg, 0.71 mmol) and Fp_2 (27 mg, 0.08 mmol) were placed in a glass-lined, 15 mL stainless steel Parr reaction vessel with dioxane (10 mL). The vessel was flushed thrice with CO (fume hood) and charged to 800 psi. The mixture was heated to 150°C while stirring for 24 h. After cooling and venting of CO (fume hood) the resulting dark brown solution was filtered to remove insoluble material, concentrated, and then chromatographed on silica gel with a gradient elution of Et_2O/hexanes (1:5 to 9:1) giving the following compounds:

4.4.1. Methyl 5-formyl-6,7-dihydro-5*H*-[1,3]dioxolo[4,5-*f*]-indole-7-carboxylate (16). 14 mg (8%); R_f=0.25 (Et_2O/hexanes, 3:1); IR (KBr) 2973, 2919, 1730, 1669, 1483, 1297, 1220, 1035 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) 3.76

(s, 3H), 4.10–4.24 (m, 2H), 4.40–4.58 (m, 1H), 5.95 (m, 2H), 6.69 (s, 0.7H, major isomer), 6.86 (s, 0.3H, minor isomer), 6.88 (s, 0.7H, major), 7.69 (s, 0.3H), 8.41 (s, 0.3H, minor), 8.74 (s, 0.7H, major); ^{13}C NMR (75.45 MHz; $CDCl_3$) 44.5, 44.9, 47.9, 49.7, 52.8, 92.2, 99.3, 101.6, 105.4, 106.4, 120.5, 130.7, 156.5, 158.2, 171.1; MS (EI) 249 (M^+, 65), 190 (100), 160 (40), 132 (60), 104 (40), 77 (10); HRMS (ESI) calcd for $C_{12}H_{11}ClNO_5Na$ (M+Na) 272.0535; found: 272.0551.

4.4.2. Methyl 5*H*-[1,3]dioxolo[4,5-*f*]indole-7-carboxylate (17). 8 mg (5%); R_f=0.20 (Et_2O/hexanes, 1:1); IR (KBr) 3351, 2950, 1676, 1545, 1467, 1297, 1197, 1081, 1027, 942, 819. ^{1}H NMR (300 MHz; d_6-acetone) 3.7 (s, 3H), 5.96 (s, 2H), 6.98 (s, 3H), 7.45 (s, 1H), 7.85 (s, 1H), 10.81 (br s, 1H); ^{13}C NMR (75.45 MHz; d_6-acetone) 50.3, 92.8, 99.6, 101.1, 108.0, 120.7, 130.1, 131.6, 144.5, 145.5, 165.0; MS (EI) 219 (100), 188 (80), 160 (27), 130 (5), 103 (6), 74 (10); HRMS (ESI) calcd for $C_{11}H_9NO_4Na$ (M+Na) 242.0429; found: 242.0483.

4.4.3. Methyl 1-(2,2-dimethylpropanoyl)-1*H*-indole-3-carboxylate (11). The indole **7** (3.00 g, 17.1 mmol) was placed in a 50 mL round bottom flask with NaH (0.54 g, 22.3 mmol) and cooled with an ice bath. THF (20 mL) was added with stirring, and gas evolution was observed. After 5 min Boc_2O (4.86 g, 22.2 mmol) was added and a solid precipitated. The mixture was stirred overnight. The solution was then quenched with sat. NH_4Cl (20 mL), diluted with ether and washed with water (3×20 mL). The ethereal solution was then dried with $MgSO_4$ concentrated under vacuum, and chromatographed with Et_2O/hexanes (1:10) to give a 4.5g (95%) of a white solid. Mp 125–127°C; R_f=0.25 (1:20, Et_2O/hexanes); IR (KBr) 3166, 2981, 1745, 1714, 1560, 1451, 1374, 1150, 726 cm^{-1}; ^{1}H NMR (300 MHz; d_6-acetone) 1.71 (s, 9H), 3.89 (s, 3H), 7.32–7.44 (m, 2H), 8.12–8.21 (m, 2H), 8.23 (s, 1H); ^{13}C NMR (75.45 MHz; d_6-acetone) 28.1, 51.5, 85.8, 112.4, 115.8, 122.0, 124.4, 125.7, 128.1, 132.3, 136.1, 149.3, 164.3; MS (EI) 275 (M^+, 11), 175 (100), 144 (63), 116 (10); HRMS (ESI) calcd for $C_{15}H_{17}NO_4Na$ (M+Na) 298.1055; found: 298.1144.

4.4.4. Methyl 1-(2,2-dimethylpropanoyl)indoline-3-carboxylate (12). The *N*-Boc indole **11** (2.25 g, 8.20 mmol) was placed in Fischer–Porter bottle with 5% Pd/C (0.50 g), MeOH (10 mL) and EtOAc (30 mL). The bottle was purged thrice with H_2 (fume hood) and charged to 110 psi. After stirring for 3 days at room temperature the vessel was recharged with H_2 to 110 psi and an additional 300 mg of 5% Pd/C was added. After another 2 days of stirring the reaction was stopped and the solution was filtered through Celite and concentrated. Chromatography on silica gel with Et_2O/hexanes (gradient elution 1:20–1:10) gave 1.54 g (68%) of a white solid with R_f=0.1 (1:20, Et_2O/hexanes) and an undetermined amount of recovered starting material. Mp 53–54°C. IR (KBr, cm^{-1}) 2981, 1745, 1699, 1491, 1398, 1004, 741; ^{1}H NMR (300 MHz; d_6-acetone) 1.58 (s, 9H), 3.75 (s, 3H), 4.12 (m, 3H), 4.31 (m, 2H), 6.96 (td, J=7.4, 1.2 Hz, 1H), 7.23 (tdd, J=7.7, 1.5, 0.6 Hz, 1H), (ddd, J=8.0, 1.5, 0.6 Hz), 7.84 (br s, 1H); ^{13}C NMR (75.45 MHz; d_6-acetone) 29.5, 50.5, 52.6, 65.9, 115.1, 122.6, 125.5, 129.1, 152.1, 172.0; MS (EI) 277 (M+, 20), 221 (80), 177 (100), 118 (58), 89 (8); HRMS (ESI) calcd for $C_{15}H_{19}NO_4Na$ (M+Na) 300.1212; found: 300.1252.

4.5. One pot deprotection and formylation of *N*-Boc indoline 12

The *N*-Boc indoline **12** (0.730 g, 2.64 mmol) was stirred in formic acid (8 mL) for 1 h at rt. Acetic formic anhydride, preformed by the addition of acetic acid (0.5 mL) to formic acid (1.0 mL) with stirring for 1 h, was then added. The mixture was stirred at room temperature for 4 h. Formic acid was removed in vacuo, the residue was dissolved in ether (20 mL) and then extracted with aqueous saturated $NaHCO_3$ (3×15 mL). The ether extract was dried with $MgSO_4$, concentrated, and chromatographed using Et_2O/hexanes (gradient elution 1:1–9:1) to give 0.295 g (55%) of the previously described *N*-formyl-indoline **10** and an undetermined amount of starting material.

Acknowledgements

We are grateful for financial support provided by the National Science Foundation and for an O.U. Graduate Alumni Fellowship. We also thank Professor S. Blechert of T.U. Berlin for stimulating discussions.

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