Synthesis of 3-Methoxycarbonylmethyl Derivatives of Dihydroquinolone and Dihydrochromenone

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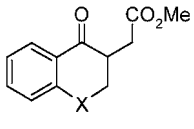
Recently, we required the 3-substituted dihydroquinolone compounds **1a** and **1b**.[1] Unfortunately, a search

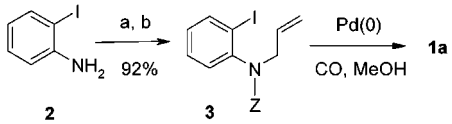


1a X = NZ
1b X = NH
1c X = O
1d X = CH_2

of the literature revealed no facile method for their preparation. All previous approaches to 3-carbomethoxymethyl-2,3-dihydro-4-quinolones required at least six steps and proceeded in 7−25% yield.[2] These approaches first involved an annulation to construct a 2,3-dihydro-4-quinolone ring system[3,4] and then relied upon either Stork enamine[2] or Mannich chemistry[2a] to introduce the required acetate side-chain. We believed that a more efficient preparation could be accomplished by the application of a palladium-catalyzed carbonylative cyclization reaction to *simultaneously* construct the 2,3-dihydroquinolone and install the 2-acetate side-chain (e.g., **3** → **1a**, Scheme 1). Although the carbocyclic analogue **1d** has previously been synthesized via this methodology by Negishi,[5−7] no analogous heterocyclic examples have been reported.

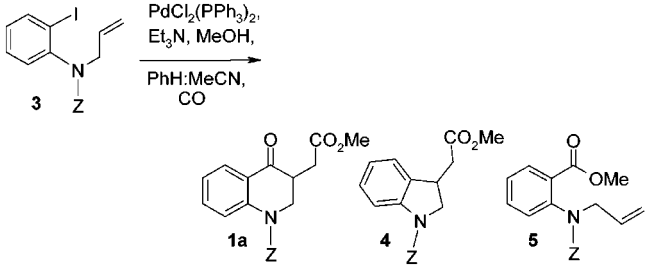
To examine the viability of the palladium-mediated carbonylative cyclization protocol for the synthesis of **1a** (Scheme 1), we prepared **3** in two steps from 2-iodoaniline (**2**).[8] When the conditions reported by Negishi to form carbocycle **1d** were applied to aniline derivative **3**,[5] only a modest amount of the desired compound **1a** was observed (Table 1, entry 1). The dominant product observed was the indoline **4**, where intramolecular carbopalladation had occurred faster than the desired CO insertion.[9] We therefore repeated the reaction using a higher pressure of CO with the hopes of favoring the formation of **1a**. Indeed, doubling the CO pressure more than doubled the relative amount of desired product **1a** (entry 2).[10] Unfortunately, a significant amount of indoline **4** was still observed. We found that lowering the reaction temperature significantly attenuated the rate

Scheme 1[a]



[a] Conditions: (a) $NaOH_{(aq)}$, ZCl; (b) NaH, allyl bromide, THF.

Table 1. Conditions for the Formation of 1a from 3 via a Palladium-Catalyzed Carbonylative Cyclization[a]



entry	pressure CO (psi)	*T* (°C)	equiv of MeOH	relative product distribution[b] (%) (isolated yield, %) 1a	4	5
1	600	100	4	21	49	
2	1200	100	4	50	42	
3	1200	80	4	62	34	
4	1200	60	4	67 (47)	22	4
5	1200	50	4	67 (46)	16	8
6	1600	60	4	76 (46)	19	4
7	1600	60	20	70 (60)	18	8
8	1600	60	40	66 (57)	18	12

[a] All reactions were performed in a high-pressure minireactor ("bomb") with 1 mmol of **3**, 2 equiv of Et_3N, MeOH (4 equiv except in entries 7 and 8), 5 mol % $PdCl_2(PPh_3)_2$, 10 mL of PhH and 10 mL of MeCN. [b] Obtained from integration of ^1H NMR of unpurified reaction products.

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(9) Product ratio determined by ^1H NMR of unpurified product.

(10) The insertion of CO into a carbon−palladium bond is believed to be a reversible process. For more information see ref 7a.

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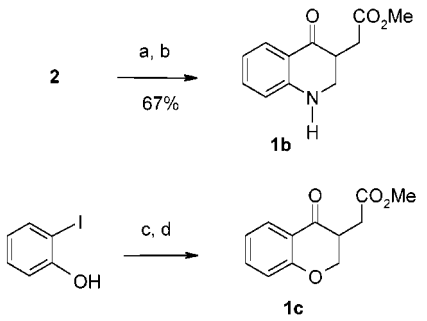
Scheme 2[a]

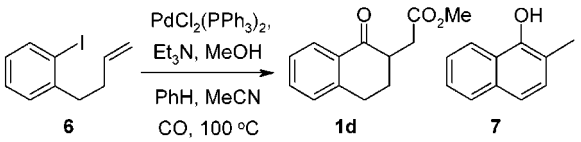


[a] Conditions: (a) LDA, allyl bromide, THF, 98%; (b) $PdCl_2(PPh_3)_2$, Et_3N, MeOH, PhH, MeCN, CO (1450 psi), 60 °C, 68%; (c) K_2CO_3, allyl bromide, DMF, 72%; (d) conditions b with CO (1200 psi) and 130 °C, 51%.

of undesired carbopalladation leading to **4** (entries 3−5), but even at 60 °C (entry 4) a disappointing 47% yield of **1a** was obtained.[11] Performing the reaction at 1600 psi failed to improve the isolated yield, but did improve the proportion of desired product observed by ^{1}H NMR. We felt that the unexpectedly low isolated yield of **1a** may be due to polymerization of a late-stage intermediate.[12] To diminish this potential polymerization, we studied the effect of increasing methanol concentration on the observed product ratios and isolated yields (entries 7 and 8). Although higher concentrations of methanol increased the quantity of benzoate **5** observed, we also realized an improved yield of **1a**. The best chemical yield obtained utilized 20 equiv of methanol (0.9 M final concentration) and produced a 60% isolated yield of desired compound **1a** (entry 7).[13,14]

With a good procedure for the formation of **1a** in hand, we turned our attention to the formation of the analogous heterocycles **1b** and **1c** (Scheme 2). Subjection of the *N*-allyl derivative of 2-iodoaniline[15] to the palladium-catalyzed carbonylative cyclization conditions generated an impressive yield of 67% for the two-step formation of **1b**. Although allylation of 2-iodophenol proceeded as previously reported,[16] attempts to form **1c** at low temperature (60 °C) or lower pressure (600 psi) resulted in predominantly formation of methyl salicylate. Performing the palladium-catalyzed carbonylative cyclization at 130 °C with a CO pressure of 1200 psi resulted in a 51% isolation yield of the desired annulated product **1c**.

Considering that optimum formation of **1a**−**c** required higher CO pressures and greater equivalents of methanol than the carbocyclic example (**1d**) reported by Negishi and co-workers,[5b] we decided to investigate the conversion of **6** to **1d** (reaction 1). When **6** was subjected to the reaction conditions previously reported by Negishi (600 psi CO pressure, 4 equivalents methanol, 100 °C)[17] in a high-pressure minireactor ("bomb"), the main product obtained was the naphthol **7**. Only a 14% yield of **1d** was isolated after purification. If, however, the CO pressure was increased to 1200 psi and the methanol concentration[18] was increased (20 equivalents, 0.9 M) product **1d** was obtained in a similar chemical yield (55%) to that previously reported.



In summary, we have successfully developed facile syntheses of **1a** (55% yield, three steps), **1b** (67% yield, two steps), and **1c** (37% yield, two steps) by application of a palladium-catalyzed carbonylative cyclization as the key transformation. For these reactions, we found that CO pressure (greater than 1200 psi), temperature, and methanol concentration are all important factors in optimizing production of the desired γ-ketoester products. It is interesting to note that the chromanone **1c** and the tetralone **1d** required higher reaction temperatures (100 and 130 °C) to obtain good yields than did the quinolone substrates **1a** and **1b** (60 °C).

Experimental Section

General Methods. Proton and carbon magnetic resonance spectra were recorded in $CDCl_3$ at 300 and 75.5 MHz, respectively, and are reported in ppm on the δ scale. Infrared spectra, mass spectra, and combustion analysis were determined by Structural and Analytical Chemistry, Pharmacia Corp. Anhydrous THF was distilled prior to use from sodium metal/benzophenone ketyl. Dry benzene, DMF, and acetonitrile were purchased from Aldrich in Sure-Seal bottles. For the high-pressure carbon monoxide reactions, a stainless steel 100 mL high-pressure minireactor or "bomb" (Parr Instrument Company, Series 4560) equipped with a thermocouple, gas inlet, gas outlet, pressure gauge (to 2000 psi), and mechanical stirrer was used. Unless otherwise noted, all nonaqueous reactions were carried out under a nitrogen atmosphere using oven-dried glassware.

***N*-Benzyloxycarbonyl-2-iodoaniline.**[8a] To 2-iodoaniline (20.0 g, 91.3 mmol) was added a 1.0 N aqueous sodium hydroxide solution (91.3 mL, 91.3 mmol). The resulting suspension was stirred vigorously as benzyl chloroformate (19.6 mL, 137 mmol) was added slowly from an addition funnel. The temperature was maintained close to room temperature by cooling as needed. The progress of the reaction was followed by loss of starting material by TLC. When the 2-iodoaniline was completely consumed (~0.5 h), the reaction mixture was poured into ethyl acetate. The ethyl acetate layer was separated and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was purified on a Waters Prep 500 (1:20 ethyl acetate−*n*-heptane) to give *N*-benzyloxycarbonyl-2-iodoaniline (31.9 g, 90.3 mmol, 99% yield) as a white solid: mp 61.1−61.7 °C; IR (drift) 3380, 1739, 1587, 1526, 1432 cm^{-1}; ^{1}H NMR δ 8.09 (d, J = 8 Hz, 1 H), 7.77 (dd, J = 1, 8 Hz, 1 H), 7.46−7.32 (m, 6 H), 7.04 (bs, 1H), 6.81 (dt, J = 1, 8 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR δ 153.1, 138.8, 138.2, 135.7, 129.2, 128.6, 128.3, 128.3, 125.1, 120.3, 88.8, 67.2; MS (EI) *m*/*z* 353 (M^+). Anal. Calcd for $C_{14}H_{12}INO_2$: C, 47.61; H, 3.42; N, 3.97. Found: C, 47.96; H, 3.46; N, 3.89.

(11) Attempts to use DMF or benzene as the solvent under identical conditions to entry 5 (Table 1) failed to improve the isolated yield.

(12) Drent, E.; Budzelaar, P. H. M. *Chem. Rev.* **1996**, *96*, 663.

(13) Different palladium sources and phosphine ligands were also investigated using identical conditions to entry 7 (Table 1), but none provided a better isolated yield for **1a**. Other sources (5 mol %) and ligands tried included the following: $PdCl_2(Po\text{-}tol_3)_2$, 29% yield; $PdCl_2$-BINAP, 31%; $Pd(PPh_3)_4$, 51%; $Pd(dba)_2$, 28%; $Pd(OAc)_2$, 32%; $Pd(OAc)_2$ with 5 mol % dppp, 20%; and $Pd(OAc)_2$ with 10 mol % P(*t*-Bu)$_3$, 36%.

(14) Benzene can be replaced by toluene in the benzene: acetonitrile solvent mixture. This chemistry has been performed on a 15 g scale with the toluene/acetonitrile mixture resulting in a 54% isolated yield of **1a**.

(15) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171.

(16) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050.

(17) Negishi and co-workers used a different apparatus (i.e., an autoclave). See ref 5b for more details.

(18) In scaling up the reaction of **3a** to **1a**, we have observed that the concentration of methanol appears to be more important for obtaining high yields than the number of equivalents.

***N*-Allyl-*N*-benzyloxycarbonyl-2-iodoaniline (3).** *N*-Benzyloxycarbonyl-2-iodoaniline (15.3 g, 43.2 mmol) was dissolved in 100 mL anhydrous THF and the solution was cooled to 0 °C. Sodium hydride (60% dispersion, 1.90 g, 47.5 mmol) was added portionwise. **Caution: hydrogen gas evolved**. Upon cessation of gas evolution, the ice bath was removed and the suspension was stirred at room temperature for 15 min. and then recooled to 0 °C. Allyl bromide (4.49 mL, 51.8 mmol) was added and the reaction mixture was slowly warmed to room-temperature overnight (~19 h). The reaction was quenched by the addition of water (**Caution: hydrogen gas evolved**) followed by ethyl acetate. The ethyl acetate layer was separated and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting cloudy oil was subjected to silica gel column chromatography (1:20 ethyl acetate−*n*-heptane; the sample was loaded as a solution in chloroform) resulting in the isolation of **3** (15.8 g, 40.1 mmol, 93% yield) as a clear, colorless oil: IR (liquid) 1710, 1472, 1440 cm^{-1}; ^1H NMR δ 7.89 (d, $J = 8$ Hz, 1 H), 7.44−7.16 (m, 7 H), 7.02 (t, $J = 8$ Hz, 1 H), 5.97−5.90 (m, 1 H), 5.28−5.08 (m, 4 H), 4.60 (dd, $J = 7$, 15 Hz, 1 H), 3.81 (dd, $J = 7$, 15 Hz, 1 H); ^{13}C NMR δ 154.6, 143.3, 139.4, 136.3, 132.9, 129.9, 129.1, 128.8, 128.1, 127.6, 127.4, 118.3, 100.3, 67.2, 52.7; MS (EI) *m*/*z* 393 (M^+). Anal. Calcd for $C_{17}H_{16}INO_2$: C, 51.93; H, 4.10; N, 3.56. Found: C, 51.84; H, 4.04; N, 3.54.

General Procedure for Palladium-Catalyzed Carbonylative Cyclization. The aryl iodide (1.00 mmol), benzene (10 mL), acetonitrile (10 mL), triethylamine (2 equiv), methanol (4−40 equiv), and the palladium catalyst (0.05 equiv.) were placed in a 100 mL bomb. The apparatus was assembled, stirring was commenced, and the bomb was purged thoroughly with CO before charging to the required pressure. **Caution: carbon monoxide is highly toxic.** The bomb was warmed to the reaction temperature (50−130 °C) using a Parr temperature controller (Model 4841) and bomb support and stirrer drive system. As the reaction temperature increased, small quantities of gas were released to maintain the desired pressure (600−1600 psi). After the reaction had been maintained at the desired pressure and temperature for 18 h it was cooled, depressurized, and poured into water. The resulting mixture was extracted three times with ethyl acetate. The ethyl acetate layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The ^1H NMR of this crude product gave the product ratios. The desired γ-ketoester was purified by silica gel column chromatography.

Benzyl 3-(2-Methoxy-2-oxoethyl)-4-oxo-3,4-dihydro-1(2*H*)-quinolinecarboxylate (1a). Compound **1a** was synthesized using the general procedure described above. The reaction was run at a temperature of 65 °C and a CO pressure of 1600 psi with the following quantities: **3**, 356 mg (0.905 mmol); benzene, 10 mL; acetonitrile, 10 mL; triethylamine, 0.252 mL (1.81 mmol); methanol, 0.733 mL (0.87 M final concetration, 20 equiv.); $Pd(PPh_3)_2Cl_2$, 30.8 mg (0.0439 mmol). The crude product was purified by silica gel column chromatography (1:5 ethyl acetate−*n*-heptane, the sample was loaded as a solution in chloroform) producing **1a** (192 mg, 0.543 mmol, 60% yield) as a light orange viscous oil which solidified upon standing: mp 70.6−74.6 °C; IR (mull) 1737, 1709, 1690, 1483, 1403 cm^{-1}; ^1H NMR δ 8.01 (dd, $J = 2$, 8 Hz, 1 H), 7.86 (d, $J = 8$ Hz, 1 H), 7.52 (dt, $J = 2$, 7 Hz, 1 H), 7.44−7.34 (m, 5 H), 7.19 (dt, $J = 1$, 8 Hz, 1 H), 5.33 (d, $J = 12$ Hz, 1 H), 5.27 (d, $J = 12$ Hz, 1 H), 4.64 (dd, $J = 5$, 13 Hz, 1 H), 3.79 (dd, $J = 12$, 13 Hz, 1 H), 3.69 (s, 3 H), 3.27−3.17 (m, 1 H), 2.88 (dd, $J = 5$, 17 Hz, 1 H), 2.57 (dd, $J = 8$, 17 Hz, 1 H); ^{13}C NMR δ 194.3, 171.6, 153.5, 143.3, 135.5, 134.1, 128.5, 128.3, 128.0, 127.5, 124.2, 124.1, 123.1, 68.1, 51.8, 48.3, 44.0, 31.7; MS (EI) *m*/*z* 353 (M^+); HRMS (FAB) calcd for $C_{20}H_{19}NO_5 + Na_1$ 376.1161, found 376.1177. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.76; H, 5.53; N, 3.98.

Methyl 2-(4-Oxo-1,2,3,4-tetrahydro-3-quinolinyl)acetate (1b). Compound **1b** was synthesized using the general procedure described above. The reaction was run at a temperature of 65 °C and a CO pressure of 1400 psi with the following quantities: *N*-allyl-2-iodoaniline,[15] 250 mg (0.965 mmol); benzene, 10 mL; acetonitrile, 10 mL; triethylamine, 0.269 mL (1.93 mmol); methanol, 0.782 mL (0.93 M final concentration, 20 equiv); $Pd(PPh_3)_2Cl_2$, 33.9 mg (0.0482 mmol). The crude product was purified by radial column chromatography (2 mm plate, 1:2 ethyl acetate−*n*-heptane, the sample was loaded onto the column as a solution in chloroform) producing **1b** (144 mg, 0.657 mmol, 68% yield) as a light brown solid: mp 146.6−147.2 °C; IR (drift) 3386, 1727, 1671, 1611, 1512 cm^{-1}; ^1H NMR δ 7.78 (dd, $J = 1$, 8 Hz, 1 H), 7.25 (dt, $J = 2$, 7 Hz, 1 H), 6.67 (t, $J = 8$ Hz, 1 H), 6.66 (dd, $J = 1$, 8 Hz, 1 H), 4.67 (bs, 1 H), 3.68 (s, 3 H), 3.58 (dd, $J = 5$, 12 Hz, 1 H), 3.34 (t, $J = 13$ Hz, 1 H), 3.17−3.08 (m, 1 H), 2.91 (dd, $J = 5$, 17 Hz, 1 H), 2.36 (dd, $J = 8$, 17 Hz, 1 H); ^{13}C NMR δ 193.9, 172.4, 151.7, 135.0, 127.5, 118.1, 117.6, 115.7, 51.7, 46.3, 42.7, 31.5; MS (EI) *m*/*z* 219 (M^+); HRMS (FAB) calcd for $C_{12}H_{13}NO_3 + H_1$ 220.0974, found 220.0971. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.61; H, 5.94; N, 6.38.

Methyl 2-(4-Oxo-3,4-dihydro-2*H*-chromen-3-yl)acetate (1c). Compound **1c** was synthesized using the general procedure described above. The reaction was run at a temperature of 130 °C and a CO pressure of 1200 psi with the following quantities: 2-iodophenyl allyl ether,[16] 247 mg (0.950 mmol); benzene, 10 mL; acetonitrile, 10 mL; triethylamine, 0.265 mL (1.90 mmol); methanol, 0.769 mL (0.91 M final concentration, 20 equiv.); $Pd(PPh_3)_2Cl_2$, 33.3 mg (0.0475 mmol). The only modification to the general procedure was acidification of the water layer during the aqueous/organic partitioning. The crude product was purified by radial column chromatography (2 mm plate, 1:5 ethyl acetate−*n*-heptane, the sample was loaded as a solution in chloroform) producing **1c** (107 mg, 0.487 mmol, 51% yield) as a light orange oil. The characterization data obtained for **1c** matched that previously reported.[19]

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(19) For the synthesis of **1c** via a different route, see: Ciganek, E. *Synthesis* **1995**, 1311.