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Convenient Synthesis of 4-Hydroxy-1,2-dihydroquinoline-3-carboxylate Derivatives and 4-Oxo-1,2,3,4-tetrahydroquinoline-3-carboxylates

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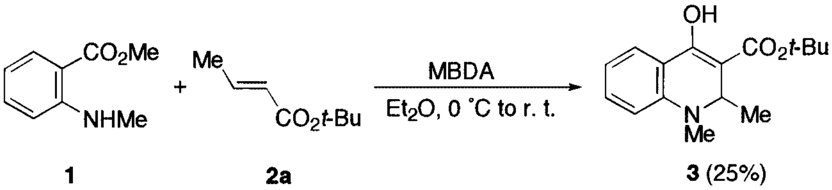
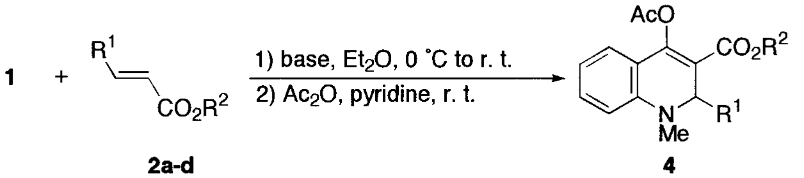
A magnesium amide-induced sequential conjugate addition/Claisen-type condensation between methyl 2-(methylamino)benzoate and α,β-unsaturated carboxylates has been found to provide convenient access to 4-hydroxy-1,2-dihydroquinoline-3-carboxylate derivatives and 4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylates.

Recently, studies by our group demonstrated that 2-(methylamino)benzonitrile was treated successively with magnesium bis(diisopropylamide) (MBDA), generated in situ from the reaction of ethylmagnesium bromide and diisopropylamine, and α,β-unsaturated carboxylates to give the corresponding 4-amino-1,2-dihydroquinoline-3-carboxylates via a conjugate addition/enolate-nitrile coupling sequence,[1] and that a magnesium amide-induced sequential conjugate addition/aldol-type condensation reaction between 2-(alkylamino)phenyl ketones and α,β-unsaturated carboxylates, followed by simple dehydration, gave 1,2-dihydroquinoline-3-carboxylates.[2] In this paper, we wish to describe the results of our extensive investigation of these magnesium amide-induced reactions, which provide a convenient method to prepare 4-acetoxy-1,2-dihydroquinoline-3-carboxylates **4**[3] and 4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylates **5**,[4] via a sequence of conjugate addition and Claisen-type condensation between methyl 2-(methylamino)benzoate (**1**)[5] and α,β-unsaturated carboxylates **2**.

We initiated our investigation by reacting **1** with *t*-butyl crotonate (**2a**) in the presence of MBDA under conditions similar to those reported previously by us.[1,2] Thus, compound **1** was treated successively with an equimolar amount of MBDA and 2 molar amounts of **2a**[6] at 0 °C. The reaction was found to proceed smoothly to produce *t*-butyl 4-hydroxy-1,2-dimethyl-1,2-dihydroquinoline-3-carboxylate (**3**) (tautomerized with the keto-ester form in $CDCl_3$; ca. 4:1), as outlined in Scheme 1. However, it is important to note that this product was rather unstable toward air and/or silica gel, though we have no explanation for the instability of this compound, which could not be isolated in a pure form or in good yield. A variety of additional products were observed by TLC, but could not be cleanly isolated or characterized. Thus, we attempted the isolation of **3** as a protected from. Thus, the crude product was treated with acetic anhydride in pyridine at room temperature in an atmosphere of argon, as depicted in Scheme 2. Following purification by preparative TLC on silica gel, *t*-butyl 4-acetoxy-1,2-dimethyl-1,2-dihydroquinoline-3-carboxylate (**4a**) was isolated in good yield (Table 1, entry 1). Using three other α,β-unsaturated carboxylates **2b–d**, the corresponding 4-acetoxy-1,2-dihydroquinoline-3-carboxylates **4b–d** could be obtained in good yields (Table 1, entries 5–7). Several other bases were examined in the reaction of **1** with **2a**. The use of LDA (entry 2) or *n*-BuLi (entry 3) instead of MBDA proved to give very low yields of **4a**, after acetylation. Using NaH as a base, no formation of the desired product was observed (entry 4). These results indicate that the use of MBDA was essential for the satisfactory production of the desired product. The bivalent magnesium ion, which probably stabilizes the intermediate after Claisen-type condensation, is responsible for



Scheme 1.



Scheme 2.

Table 1. Preparation of 4-Acetoxy-1,2-dihydroquinoline-3-carboxylates **4**

Entry	**2**	Base	**4** (Yield/%)[a)]
1	**2a**	MBDA	**4a** (77)
2	**2a**	LDA	**4a** (15)
3	**2a**	*n*-BuLi	**4a** (10)
4	**2a**	NaH	**4a** (0)
5	**2b** (R^1 = R^2 = Me)	MBDA	**4b** (74)
6	**2c** (R^1 = Ph, R^2 = Me)	MBDA	**4c** (70)
7	**2d** (R^1 = 2-furyl, R^2 = *t*-Bu)	MBDA	**4d** (73)

a) Isolated yields.

the success of this sequence.[1,2]

We next turned our attention to the reaction of **1** with methacrylates **2e** and **2f** in the presence of the magnesium amide. The sequential conjugate addition/Claisen-type condensation smoothly occurred under the same conditions described above to give 3-methyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylates **5a** or **5b**, as a single diastereomer in the latter case, in good yields. These results are illustrated in Scheme 3. The stereochemistry of **5b** was unambiguously confirmed by NOE experiments. Thus, irradiation of the signal at δ 1.38, assignable to 3-Me, resulted in a strong enhancement (27%) of the signals at δ 3.96, assignable to 2-H.

In summary, we have developed a convenient method for preparing 4-acetoxy-1,2-dihydroquinoline-3-carboxylates and 4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylates via a conjugate addition/Claisen-type condensation sequence between **1** and α,β-unsaturated carboxylates. Since the method employs readily available starting materials, and is operationally simple, it may be of value in organic synthesis.

Experimental

General. The melting points were determined on a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1600 Series FT IR spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in $CDCl_3$. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). High-resolution mass spectra were performed on a JEOL JMS-AX505 HA spectrometer (Faculty of Agriculture, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use. All of the reactions were carried out under argon.

Starting Materials. *t*-Butyl 3-(2-furyl)propenoate (**2d**) was prepared by a procedure reported previously by us.[2] All of the other chemicals used in this study were commercially available.

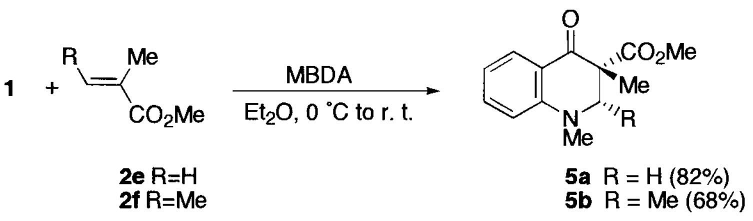
Reaction of 1 with *t*-Butyl Crotonate (2a) in the Presence of the Bis(diisopropylamido)magnesium Reagent. To a stirred solution (0 °C) of a magnesium amide, generated in situ by treating EtMgBr (2.0 mmol) with *i*-Pr_2NH (0.20 g, 2.0 mmol) in Et_2O (6 mL) at reflux temperature for 1 h, was added **1** (0.17 g, 1.0 mmol) and **2a** (0.28 g, 2.0 mmol). The mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with Et_2O three times. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was separated by preparative TLC on SiO_2 to give *t*-butyl 4-hydroxy-1,2-dimethyl-1,2-dihydroquinoline-3-carboxylate (**3**) (69 mg, 25%; a yellow oil): R_f 0.62 (1:5 EtOAc–hexane); IR (neat) 3300–2500, 1731, 1682, 1645, and 1623 cm^{-1}; ^{1}H NMR (tautomerized with the keto-ester form; ca. 4:1) δ 1.09 (2.4H, d, $J = 6.8$ Hz), 1.18 (0.6H, d, $J = 6.8$ Hz), 1.31 (1.8H, s), 1.54 (7.2H, s), 2.91 (2.4H, s), 2.99 (0.6H, s), 3.19 (0.2H, d, $J = 2.4$ Hz), 4.06 (0.2H, qd, $J = 6.8$ and 2.4 Hz), 4.31 (0.8H, q, $J = 6.8$ Hz), 6.45–6.75 (2H, m), 7.2–7.45 (1H, m), 7.63 (0.8H, dd, $J = 7.9$ and 1.6 Hz), 7.88 (0.2H, dd, $J = 7.9$ and 1.6 Hz), and 12.31 (0.8 H, br s); MS *m*/*z* (%) 275 (M^+, 1.2), 175 [$(M - C_4H_8 - CO_2)^+$, 28], and 160 (100). Found: *m*/*z* 275.0140. Calcd for $C_{16}H_{21}NO_3$: M, 275.0145.

***t*-Butyl 4-Acetoxy-1,2-dimethyl-1,2-dihydroquinoline-3-carboxylate (4a):** A crude product, obtained from the reaction of **1** and **2a** in the presence of MBDA under the same reaction conditions as described above and the subsequent workup, was treated with 0.5 mL each of pyridine and acetic anhydride overnight at room temperature. The resulting mixture was concentrated under reduced pressure, and the residual solid was recrystallized from hexane to give **4a** (0.24 g, 77%) as a yellow solid; mp 84–86 °C; IR (KBr disk) 1775, 1685, and 1634 cm^{-1}; ^{1}H NMR δ 1.15 (3H, d, $J = 6.8$ Hz), 1.50 (9H, s), 2.34 (3H, s), 2.92 (3H, s), 4.49 (1H, q, $J = 6.8$ Hz), 6.49 (1H, d, $J = 7.9$ Hz), 6.65 (1H, td, $J = 7.9$ and 1.1 Hz), 7.16 (1H, dd, $J = 7.9$ and 1.1 Hz), and 7.21 (1H, td, $J = 7.9$ and 1.1 Hz); MS *m*/*z* (%) 317 (M^+, 3.9), 302 (6.8), 260 (9.8), 204 (84), and 186 (100). Found: C, 68.10; H, 7.16; N, 4.28%. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41%.

Compounds **4b**–**d** were prepared according to the procedure described above for the preparation of **4a**.

Methyl 4-Acetoxy-1,2-dimethyl-1,2-dihydroquinoline-3-carboxylate (4b): A yellow solid; mp 77–81 °C (hexane); IR (KBr disk) 1766, 1702, and 1633 cm^{-1}; ^{1}H NMR δ 1.16 (3H, d, $J = 6.8$ Hz), 2.35 (3H, s), 2.94 (3H, s), 3.77 (3H, s), 4.56 (1H, q, $J = 6.8$ Hz), 6.50 (1H, d, $J = 7.9$ Hz), 6.66 (1H, td, $J = 7.9$ and 1.1 Hz), and 7.15–7.3 (2H, m); MS *m*/*z* (%) 275 (M^+, 3.2), 260 (5.4), 218 (76), and 186 (100). Found: C, 65.56; H, 6.34; N, 4.97%. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09%.

Methyl 4-Acetoxy-1-methyl-2-phenyl-1,2-dihydroquinoline-3-carboxylate (4c): A yellow solid; mp 155–157 °C (hexane);



Scheme 3.

IR (KBr disk) 1763, 1682, and 1635 cm^{-1}; ^{1}H NMR δ 2.37 (3H, s), 2.82 (3H, s), 3.66 (3H, s), 5.53 (1H, s), 6.39 (1H, d, $J = 7.9$ Hz), 6.67 (1H, td, $J = 7.9$ and 1.1 Hz), 7.2–7.5 (5H, m), and 7.3–7.4 (2H, m); MS m/z (%) 337 (M$^+$, 5.3) and 265 (100). Found: C, 71.20; H, 5.63; N, 4.13%. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15%.

***t*-Butyl 4-Acetoxy-2-(2-furyl)-1-methyl-1,2-dihydroquinoline-3-carboxylate (4d):** A yellow solid; mp 105–107 °C (hexane); IR (KBr disk) 1770, 1703, and 1636 cm^{-1}; ^{1}H NMR δ 1.41 (9H, s), 2.39 (3H, s), 3.02 (3H, s), 5.52 (1H, s), 6.19 (1H, br. s), 6.29 (1H, br. s), 6.48 (1H, d, $J = 7.9$ Hz), 6.69 (1H, t, $J = 7.9$ Hz), and 7.2–7.3 (3H, m); MS m/z (%) 369 (M$^+$, 4.1), 312 (65), and 186 (100). Found: C, 68.06; H, 6.46; N, 3.69%. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79%.

Compounds **5a** and **5b** were prepared under conditions similar to those described above for the preparation of **3**.

Methyl 1,3-Dimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (5a): A yellow solid; mp 127–130 °C (hexane); IR (KBr disk) 1735, 1681, and 1607 cm^{-1}; ^{1}H NMR δ 1.44 (3H, s), 3.01 (3H, s), 3.30 (1H, d, $J = 12.1$ Hz), 3.67 (3H, s), 3.83 (1H, d, $J = 12.1$ Hz), 6.69 (1H, d, $J = 7.9$ Hz), 6.78 (1H, td, $J = 7.9$ and 1.1 Hz), 7.40 (1H, td, $J = 7.9$ and 1.6 Hz), and 7.95 (1H, dd, $J = 7.9$ and 1.6 Hz); MS m/z (%) 233 (M$^+$, 100). Found: C, 67.11; H, 6.22; N, 6.00%. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00%.

Methyl *trans*-1,2,3-Trimethyl-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (5b): A lemon-yellow oil; R_f 0.20 (hexane–EtOAc 5:1); ^{1}H NMR δ 1.06 (3H, d, $J = 6.9$ Hz), 1.38 (3H, s), 2.95 (3H, s), 3.61 (3H, s), 3.96 (1H, q, $J = 6.9$ Hz), 6.58 (1H, d, $J = 7.9$ Hz), 6.72 (1H, td, $J = 7.9$ and 0.9 Hz), 7.37 (1H, td, $J = 7.9$ and 1.7 Hz), and 7.89 (1H, dd, $J = 7.9$ and 1.7 Hz); MS m/z (%) 247 (M$^+$, 34) and 188 (100). Found: C, 67.95; H, 7.13; N, 5.54%. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66%.

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6 When the reaction was carried out with an equimolar amounts of **2a**, a small amount (ca. 20 %) of the starting material **1** was recovered.