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One-Pot Synthesis of 4-Amino-1,2-dihydro-3-quinolinecarboxylic Acid Derivatives

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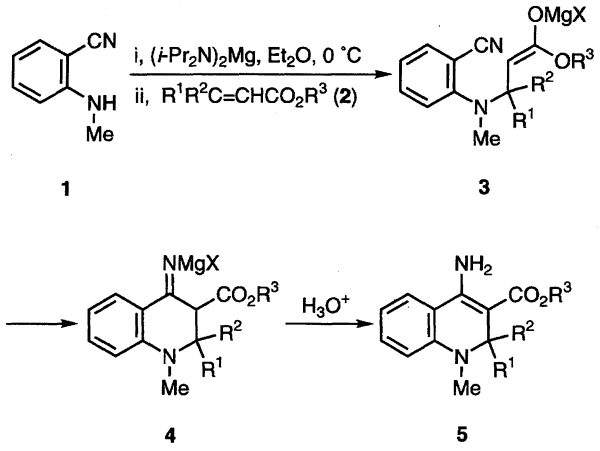
When 2-(methylamino)benzonitrile was treated successively with magnesium bis(diisopropylamide), generated in situ from the reaction of ethylmagnesium bromide and diisopropylamine, and α,β-unsaturated carboxylic acid esters in diethyl ether at 0 °C, conjugate addition and enolate–nitrile coupling proceeded sequentially to give the corresponding 4-amino-1,2-dihydro-3-quinolinecarboxylates in isolated yields ranging from 36 to 79%.

The synthetic efficiency of *o*-aminobenzonitriles has made them attractive for constructing a variety of heterocyclic compounds.[1] Recently, a number of methods for preparing biologically important 4-aminoquinoline derivatives[2] have been reported,[2,3] most of which rely on condensation reactions of *o*-aminobenzonitriles with carbonyl compounds, such as ketones, lactones, and 1,3-dicarbonyls. On the other hand, partially hydrogenated heterocycles are currently of industrial and medical interest as potential antioxidants.[4] However, only a few reports on the preparation of 1,2-dihydro-4-aminoquinoline derivatives can be found in the literature.[5] We therefore decided to establish conditions for preparing 4-amino-1,2-dihydro-3-quinolinecarboxylates from *o*-aminobenzonitriles and α,β-unsaturated carboxylates, and envisaged that a conjugate addition/nitrile–enolate coupling sequence[6] using these starting materials could be mediated by an appropriate base to afford the desired products in a one-pot procedure. We herein wish to report in full on the results of our investigation, which illustrate the realization of this envisagement and provide a general approach to this class of molecules. To the best of our knowledge, this is the first report concerning the construction of this skeleton.[7]

2-(Methylamino)benzonitrile (**1**)[8] and *t*-butyl (*E*)-2-butenoate (**2a**) were chosen as model substrates, and reactions of these substrates using various bases, such as bis(diisopropylamide) (MBDA),[9] ethylmagnesium bromide, sodium hydride, butyllithium, and lithium diisopropylamide (LDA), were examined. It was found that MBDA works most efficiently in the sequence depicted in Scheme 1; the nitrile **1** was treated successively with 2 molar amounts each of MBDA and **2a** in diethyl ether to give *t*-butyl 4-amino-1,2-dimethyl-1,2-dihydro-3-quinolinecarboxylate (**5a**) in good isolated yield.[10] Substantial decreases in the yields were observed in the case of using ethylmagnesium bromide or sodium hydride. When the reaction was carried out with butyllithium or LDA, the starting material **1** was recovered



1 3 4 5

Scheme 1.

almost quantitatively. It can be assumed that the bivalent magnesium ion, which probably stabilizes the intermediate **4** to promote the coupling step, is responsible for the success of the present reaction sequence.[11]

In order to explore the generality of this procedure, the reactions of **1** with a range of α,β-unsaturated carboxylates were tested under the MBDA conditions described above. Table 1 summarizes the yields of the 4-amino-1,2-dihydro-3-quinolinecarboxylates **5** prepared. As shown in Entry 3, ethyl (*E*)-3-phenylpropenoate (**2c**) also worked well to give the expected product **5c** in a somewhat lower yield than that for the corresponding *t*-butyl ester, most probably due to a competing self-condensation of the initially formed adduct **3**. β,β-Disubstituted acrylates proved to be usable in this procedure; the reaction of **1** with *t*-butyl 2-cyclopentylideneacetate (**2e**)[12] gave the spiro derivative **5e** in satisfactory yield (Entry 5). The use of *t*-butyl acrylate (**2f**) also led to the formation of the expected product **5f**, though the yield was rather poorer (Entry 6). This can probably be attributable to the highly polymerizable property of this ester. The aminodihydroquinoline derivatives prepared in this study were

Table 1. Preparation of 4-Amino-1,2-dihydro-3-quinolinecarboxylates **5**

Entry	**2**	**5** (Yield/%)[a]
1	**2a** (R^1=Me, R^2=H, R^3=*t*-Bu)	**5a** (79)
2	**2b** (R^1=Ph, R^2=H, R^3=*t*-Bu)	**5b** (75)
3	**2c** (R^1=Ph, R^2=H, R^3=Et)	**5c** (52)
4	**2d** (R^1=R^2=Me, R^3=*t*-Bu)	**5d** (65)
5	**2e** (R^1=R^2=$-(CH_2)_4-$, R^3=*t*-Bu)	**5e** (68)
6	**2f** (R^1=R^2=H, R^3=*t*-Bu)	**5f** (36)

a) Isolated yields after purification by preparative TLC on SiO_2.

all isolated by preparative TLC on silica gel, and little or no hydrolysis of the enamine moiety occurred during the isolation procedure. Each of them fluoresces light yellow.

It should be noted that the attempted reaction of 2-aminobenzonitrile with *t*-butyl (*E*)-2-butenoate under the MBDA conditions resulted in the formation of an intractable mixture of products. The reaction of **1** with an α,β-unsaturated carbonitrile, such as 2-butenenitrile, also gave an intractable mixture of products.

In conclusion, we have demonstrated that the present magnesium amide-mediated reaction between 2-(methylamino)benzonitriles and α,β-unsaturated carboxylic acid esters can serve as an efficient method for a general preparation of 4-amino-1,2-dihydro-3-quinolinecarboxylic acid derivatives, which are of interest because of their potential biological activities. Simple manipulations and milder reaction conditions as well as the ready availability of the starting materials make it attractive.

Experimental

General. The mps were recorded with a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were determined with a Perkin–Elmer 1600 Series FT IR spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference with either a JEOL JNX-PMX 60 NMR spectrometer operating at 60 MHz in CCl_4 or a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in $CDCl_3$. Mass spectra were recorded with a JEOL AUTOMASS 20 spectrometer (Center for Cooperative Research and Development, this University). TLC was carried out on a Merck Kieselgel 60 PF_{254}. All of the solvent used were dried over appropriate drying agents and distilled under argon prior to use.

Starting Materials. 2-(Methylamino)benzonitrile (**1**) was prepared by the reported procedure.[8] *t*-Butyl 3-methyl-2-butenoate (**2d**)[13] was prepared by the treatment of 3-methyl-2-butenoyl chloride with *t*-butyl alcohol in the presence of *N,N*-dimethylaniline. All other organic chemicals were commercially available.

***t*-Butyl 2-Cyclopentylideneacetate (2e):**[12] To a stirred solution of LDA (10 mmol), generated from diisopropylamine and *n*-BuLi by the standard method, in dry THF (50 ml) under argon at −78 °C was added *t*-butyl acetate (1.2 g, 10 mmol). After the resulting mixture was stirred for 20 min, cyclopentanone (0.84 g, 10 mol) was added. The mixture was then allowed to slowly warm to 0 °C over 1 h, and was then quenched with saturated aqueous NH_4Cl. The organic product 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 distilled by Kugelrohr to give *t*-butyl 2-(1-hydroxycyclopentyl)-acetate (1.8 g, 91%): bp 150 °C (bath temp)/2666.44 Pa (lit,[14] bp 71—72 °C/133.322 Pa).

A solution of the foregoing hydroxy ester (1.8 g, 9.1 mmol) and acetic anhydride (1.9 g, 18 mmol) in benzene (25 ml) containing *p*-toluenesulfonic acid monohydrate (50 mg, 0.46 mmol) was heated under reflux for 30 min. The cooled reaction mixture was poured into iced water, and 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 distilled by Kugelrohr to give *t*-butyl 2-(1-acetoxycyclopentyl)acetate (1.6 g, 98%) as a colorless liquid: bp 150 °C (bath temp)/2666.44 Pa; IR (neat) 1732 cm^{-1}; ^{1}H NMR (60 MHz) δ = 1.46 (9H, s), 1.55—2.05 (11H, m including s at 1.90), and 2.81 (2H, s).

To a stirred solution of *t*-BuOK (0.96 g, 8.5 mmol) in *t*-BuOH (10 ml) at 0 °C was added dropwise the forgoing acetoxy ester (1.0 g, 5.7 mmol). After 30 min, aqueous NH_4Cl was added and the 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, distillation of the residue by Kugelrohr gave **2e** (0.50 g, 47%): bp 100 °C (bath temp)/2666.44 Pa (lit,[12] bp 65 °C/2133.152 Pa).

***t*-Butyl 4-Amino-1,2-dimethyl-1,2-dihydro-3-quinolinecarboxylate (5a). Typical Procedure.** The following procedure is typical. To a stirred solution of EtMgBr (4.0 mmol) in Et_2O (6 ml) at 0 °C in an atmosphere of argon was added diisopropylamine (0.40 g, 4.0 mmol); the mixture was heated under reflux for 1 h. The resulting turbid mixture was cooled to 0 °C, and compounds **1** (0.13 g, 1.0 mmol) and **2a** (0.28 g, 2.0 mmol) were added successively. After 20 min, aqueous NH_4Cl was added, and the organic products were extracted with Et_2O three times. After the combined extracts were washed with first water and then brine, they were dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by PLC to give **5a** (0.20 g, 72%) as a pale-yellow solid: R_f 0.46 (1 : 5 EtOAc–hexane); mp 126—129 °C (hexane–CH_2Cl_2); IR (KBr disk) 3472, 3320, 1659, and 1621 cm^{-1}; ^{1}H NMR (270 MHz) δ = 1.00 (3H, d, *J* = 6.2 Hz), 1.53 (9H, s), 2.92 (3H, s), 4.31 (1H, q, *J* = 6.2 Hz), 6.29 (2H, br. s), 6.56 (1H, d, *J* = 8.3 Hz), 6.72 (1H, t, *J* = 7.6 Hz), and 7.2—7.35 (2H, m); MS *m/z* (%) 274 (M^+; 0.62), 259 (13), and 203 (100). Found: C, 69.85; H, 8.18; N, 10.11%. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.05; H, 8.08; N, 10.21%.

***t*-Butyl 4-Amino-1-methyl-2-phenyl-1,2-dihydro-3-quinolinecarboxylate (5b):** R_f 0.31 (1 : 5 EtOAc–hexane); IR (neat) 3478, 3316, 1656, and 1621 cm^{-1}; ^{1}H NMR (270 MHz) δ = 1.41 (9H, s), 2.81 (3H, s), 5.23 (1H, s), 6.46 (1H, d, *J* = 8.3 Hz), 6.50 (2H, br. s), 6.73 (1H, dd, *J* = 7.7 and 7.3 Hz), 7.15 (5H, s), 7.23 (1H, ddd, *J* = 8.1, 7.3 and 1.3 Hz), and 7.33 (1H, dd, *J* = 7.7 and 1.3 Hz); MS *m/z* (%) 336 (M^+; 2.2), 259 (19), and 203 (100). Found: C, 74.75; H, 7.48; N, 8.62%. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19 N, 8.33%.

Ethyl 4-Amino-1-methyl-2-phenyl-1,2-dihydro-3-quinolinecarboxylate (5c): R_f 0.33 (1 : 5 EtOAc–hexane); mp 109—112 °C (hexane–Et_2O); IR (KBr disk) 3444, 3317, 1657, and 1620 cm^{-1}; ^{1}H NMR (270 MHz) δ = 1.17 (3H, t, *J* = 7.3 Hz), 2.76 (3H, s), 4.06 (2H, q, *J* = 7.3 Hz), 5.24 (1H, s), 6.41 (1H, d, *J* = 8.3 Hz), 6.50 (2H, br. s), 6.66 (1H, dd, *J* = 7.6 and 7.3 Hz), 7.09 (5H, s), 7.19 (1H, dd, *J* = 8.3 and 7.3 Hz), and 7.27 (1H, d, *J* = 7.6 Hz); MS *m/z* (%) 308 (M^+; 4.2) and 231 (100). Found: C, 73.85; H, 6.54; N, 9.01%. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08%.

***t*-Butyl 4-Amino-1,2,2-trimethyl-1,2-dihydro-3-quinolinecarboxylate (5d):** R_f 0.36 (1 : 5 EtOAc–hexane); IR (neat) 3471,

3314, 1655, and 1615 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.52$ (6H, s), 1.55 (9H, s), 2.81 (3H, s), 6.07 (2H, br. s), 6.61 (1H, d, $J = 8.1$ Hz), 6.69 (1H, t, $J = 7.3$ Hz), and 7.15—7.25 (2H, m); MS *m/z* (%) 288 (M^+; 1.1), 287 (5.3), 231 (24), and 173 (100). Found: C, 70.87; H, 8.20; N, 9.99%. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71%.

***t*-Butyl 4-Amino-1-methyl-1,2-dihydroquinoline-2-spiro-1′-cyclopentane-3-carboxylate (5e):** R_f 0.54 (1 : 5 EtOAc–hexane); IR (neat) 3427, 3310, 1656, and 1607 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.51$ (9H, s), 1.9—2.05 (4H, m), 2.2—2.3 (4H, m), 2.81 (3H, s), 6.44 (2H, br. s), 6.55 (1H, d, $J = 8.4$ Hz), 6.67 (1H, t, $J = 7.4$ Hz), and 7.35—7.45 (2H, m); MS *m/z* (%) 314 (M^+; 0.75), 242 (61), and 213 (100). Found: C, 72.36; H, 8.63; N, 9.16%. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91%.

***t*-Butyl 4-Amino-1-methyl-1,2-dihydro-3-quinolinecarboxylate (5f):** R_f 0.36 (1 : 5 EtOAc–hexane); IR (neat) 3433, 3309, 1660, and 1627 cm^{-1}; ^1H NMR (270 MHz) $\delta = 1.52$ (9H, s), 2.84 (3H, s), 3.88 (2H, s), 6.2—6.4 (2H, br), 6.62 (1H, d, $J = 7.3$ Hz), 6.74 (1H, t, $J = 7.3$ Hz), and 7.2—7.3 (2H, m); MS *m/z* (%) 245 [$(M - CH_3)^+$; 5.4], 202 (41), and 170 (100). Found: C, 68.92; H, 7.73; N, 11.03%. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76%.

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