Synthesis of 4-Hydroxy-3-quinolinecarboxylic Acid Derivatives by a Condensation/Cyclization Sequence between *o*-Isocyanobenzoates and Magnesium Enolates

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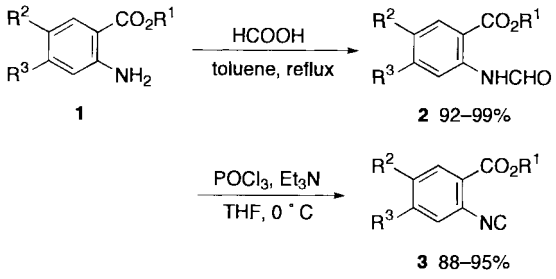
Addition of magnesium ester and amide enolates, generated using an excess amount of a magnesium amide (from diisopropylamine and ethylmagnesium bromide), to *o*-isocyanobenzoates affords 4-hydroxy-3-quinolinecarboxylic esters and amides by a tandem Claisen-type condensation/cyclization sequence.

In connection with the program we have designed to explore the utility of magnesium enolates, generated using magnesium amides,[1] in organic synthesis, we investigated reactions between *o*-isocyanobenzoate **3**[2] and magnesium ester or amide enolates toward the synthesis of 4-hydroxy-3-quinolinecarboxylic acid derivatives **5**. This class of molecules were important due to not only their biological activities[3] but also their use for the preparation of other biologically important compounds.[4] Although 4-hydroxy-3-quinolinecarboxylates have been prepared by the condensation of anilines with alkoxymethylenemalonates,[5] a few new method for the syntheses of these derivatives have recently been reported.[6] Our results, which offer an efficient new method for the preparation of 4-hydroxy-3-quinolinecarboxylic acid esters and amides, are described in this paper.

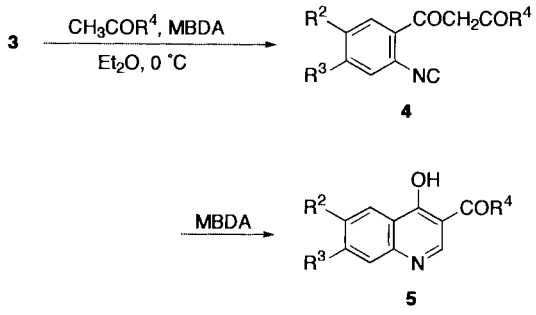
The starting 2-isocyanobenzoates **3** were prepared in good yields as shown in Scheme 1. 2-Aminobenzoates **1** were converted into the corresponding 2-(formylamino)benzoates **2** by the formylation with formic acid, which were then dehydrated with $POCl_3/Et_3N$ to give **3**. These isocyanides were isolable by column chromatography on silica gel and was somewhat unstable at room temperature. However, they were storable for several days at refrigerator temperature.[7]



a: R^1 = Me, R^2 = R^3 = H; **b**: R^1 = Et, R^2 = R^3 = H;
c: R^1 = *n*-Pr, R^2 = R^3 = H; **d**: R^1 = *n*-Bu, R^2 = R^3 = H;
e: R^1 = *n*-Pr, R^2 = Cl, R^3 = H; **f**: R^1 = *n*-Pr, R^2 = R^3 = OMe.

Scheme 1.

These isocyanobenzoates **3** were subjected to reaction with magnesium enolates, generated by treating acetates or *N*,*N*-dimethylacetamide with magnesium bis(diisopropylamide) (MBDA). The Claisen-type condensation of enolates with isocyanobenzoates gave keto ester (or amide) intermediates **4**. Cyclization with the second molar of MBDA leading to the formation of 4-hydroxy-3-quinolinecarboxylic acid esters and amides **5** was achieved by stirring the reaction mixtures for an additional 2 h (Scheme 2). As shown in Table 1, fair-to-good yields of desired products **5** were generally obtained. Exceptional is the reaction of **3a** with methyl acetate, which resulted in the formation of an intractable mixture of products (Entry 1). This may be attributable to the high self-condensation ability of methyl acetate. This methyl ester **3a** was used in the condensation with *t*-butyl acetate to give the corresponding 3-quinolinecarboxylate **5g** (Entry 7). We also found that condensation of compounds **3a** with *N*,*N*-dimethylacetamide followed by cyclization smoothly took place to give 3-quinolinecarbamide **5h** (Entry 8). The use of lithium diisopropylamide in place of MBDA gave rather poor results. For example, in the LDA-mediated reaction of **3d** with butyl acetate only up to ca. 25% yield of the desired product was detected in the reaction mixture, as judged by ^{1}H NMR. The bivalent magnesium ion, which probably stabilizes the anionic intermediate, arising from the attack of the keto enolate on the isocyano car-



Scheme 2.

Table 1. Preparation of 4-hydroxy-3-quinolinecarboxylic acid derivatives **5**

Entry	3	R^4	Product (Yield/%)[a]
1	**3a**	OMe	**5a** (0)
2	**3b**	OEt	**5b** (79)
3	**3c**	O*n*-Pr	**5c** (80)
4	**3d**	O*n*-Bu	**5d** (75)
5	**3e**	O*n*-Pr	**5e** (71)
6	**3f**	O*n*-Pr	**5f** (87)
7	**3a**	O*t*-Bu	**5g** (74)
8	**3a**	NMe_2	**5h** (63)

[a] Isolated yield after recrystallization.

bon, to promote the cyclization step, might be responsible for the success of the present reaction sequence.

A typical procedure is illustrated by the preparation of ethyl 4-hydroxy-3-quinolinecarboxylate (**5b**). To a stirred turbid solution of a magnesium amide (0 °C), generated by treating ethylmagnesium bromide (11 mmol) with diisopropylamine (11 mmol, 1.1 g) in refluxing ether (15 mL), was added ethyl acetate (3.6 mmol, 0.32 g) dropwise. After 5 min, a solution of ethyl 2-isocyanobenzoate (**2b**) (1.8 mmol, 0.31g) in diethyl ether (5 mL) was added, and stirring was continued for an additional 2 h. The resulting mixture was treated with saturated aqueous ammonium chloride and extracted with dichloromethane three times. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residual solid was triturated with hexane–diethyl ether to give the crude **5b** (0.35 g), which was recrystallized from chloroform to give pure **5b** (0.31 g, 79%).[8]

In summary, a novel and convenient synthesis of 4-hydroxy-3-quinolinecarboxylic acid derivatives has been achieved. The present method may find some value in organic synthesis, because the reaction procedure is simple and the starting materials are readily available.

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7 **3a:**[2] R_f 0.41 (1:4 AcOEt–hexane); IR (neat) 2127, 1732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.98 (3H, s), 7.4–7.6 (3H, m), 8.01 (1H, dd, *J* = 8.0, 1.6 Hz); MS *m/z* 161 (M^+, 37), 146 (53), 130 (92), 102 (100). **3b:** R_f 0.56 (1:4 AcOEt–hexane); IR (neat) 2125, 1730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.44 (3H, t, *J* = 7.3 Hz), 4.45 (2H, q, *J* = 7.3 Hz), 7.4–7.6 (3H, m), and 8.00 (1H, dd, *J* = 8.1, 1.7 Hz); MS *m/z* 175 (M^+, 29), 130 (100). **3c:** R_f 0.54 (1:4 AcOEt–hexane); IR (neat) 2125, 1731 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.06 (3H, t, *J* = 7.3 Hz), 1.75–1.9 (2H, m), 4.35 (2H, t, *J* = 6.6 Hz), 7.4–7.6 (3H, m), 8.01 (1H, dd, *J* = 7.3, 2.3 Hz); MS *m/z* 189 (M^+, 4.1), 188 (4.5), 174 (43), 130 (100). **3d:** R_f 0.54 (1:4 AcOEt–hexane); IR (neat) 2125, 1731 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.3 Hz), 1.45–1.6 (2H, m), 1.7–1.85 (2H, m), 4.39 (2H, t, *J* = 6.6 Hz), 7.4–7.6 (3H, m), 8.00 (1H, dd, *J* = 7.6, 1.7 Hz); MS *m/z* 203 (M^+, 0.42), 188 (9.3), 174 (38), 130 (83), 102 (100). **3e:** mp 58–60 °C (hexane); IR (KBr disk) 2131, 1732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.06 (3H, t, *J* = 7.3 Hz), 1.75–1.95 (2H, m), 4.36 (2H, t, *J* = 6.5 Hz), 7.42 (1H, d, *J* = 8.6 Hz), 7.53 (1H, dd, *J* = 8.6, 2.3 Hz), 7.98 (1H, d, *J* = 2.3 Hz); MS *m/z* 223 (M^+, 5.3), 208 (22), 181 (47), 164 (100). **3f:** mp 100–102 °C (hexane–Et_2O); IR (KBr disk) 2130, 1703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.06 (3H, t, *J* = 7.3 Hz), 1.75–1.95 (2H, m), 3.94 (6H, s), 4.34 (2H, t, *J* = 6.6 Hz), 6.90 (1H, s), 7.47 (1H, s); MS *m/z* 249 (M^+, 12), 207 (100).

8 **5b:** mp 267–270 °C (Et_2O) (lit.[9] 270 °C); **5c:** mp 67–69 °C (Et_2O); IR (KBr disk) 3400–2700, 1716, 1645, 1611 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.6–1.8 (2H, m), 4.13 (2H, t, *J* = 7.1 Hz), 5.75 (1H, s), 7.3–7.4 (2H, m), 7.45–7.6 (2H, m, including s at 7.54), 7.62 (1H, d, *J* = 7.9 Hz); MS *m/z* 231 (M^+, 5.8), 189 (9.6), 172 (37), 145 (100). **5d:** mp 220–225 °C (Et_2O); IR (KBr disk) 3400–2700, 1702, 1616 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 0.92 (3H, t, *J* = 7.3 Hz), 1.3–1.5 (2H, m), 1.55–1.7 (2H, m), 4.16 (2H, t, *J* = 6.6 Hz), 7.40 (1H, t, *J* = 8.2 Hz), 7.60 (1H, d, *J* = 8.2 Hz), 7.68 (1H, t, *J* = 8.2 Hz), 8.15 (1H, d, *J* = 8.2 Hz), 8.51 (1H, s), 11.23 (1H, br s); MS *m/z* 245 (M^+, 17), 171 (100). **5e:** mp 128–132 °C (Et_2O–$CHCl_3$); IR (KBr disk) 3400–2700, 1729, 1651, 1609 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.6–1.8 (2H, m), 4.12 (2H, t, *J* = 6.9 Hz), 5.70 (1H, s), 7.31 (1H, d, *J* = 8.6 Hz), 7.47 (1H, dd, *J* = 8.6, 2.3 Hz), 7.51 (1H, s), 7.58 (1H, d, *J* = 2.3 Hz); MS *m/z* 265 (M^+, 14), 223 (17), 206 (37), 179 (100). **5f:** mp 163–165 °C (Et_2O); IR (KBr disk) 3400–2700, 1699, 1642, 1612 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.00 (3H, t, *J* = 7.3 Hz), 1.6–1.8 (2H, m), 3.94 (6H, s), 4.13 (2H, t, *J* = 6.9 Hz), 5.54 (1H, s), 6.86 (1H, s), 6.94 (1H, s), 7.54 (1H, s); MS *m/z* 291 (M^+, 17), 205 (100). **5g:** mp 175–180 °C ($CHCl_3$); IR (KBr disk) 3400–2700, 1697, 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.52 (9H, s), 5.67 (1H, s), 7.3–7.4 (2H, m), 7.50 (1H, t, *J* = 7.0 Hz), 7.52 (1H, s), 7.58 (1H, d, *J* = 7.9 Hz); MS *m/z* 245 (M^+, 14), 189 (100). **5h:** mp 76–79 °C ($CHCl_3$); IR (KBr disk) 3400–2700, 1631 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.08 (6H, s), 5.97 (1H, s), 7.4–7.5 (4H, m), 7.79 (1H, dd, *J* = 7.9, 2.0 Hz); MS *m/z* 217 (11), 216 (M^+, 10), 172 (79), 116 (100).

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