A Convenient Synthesis of 3-(1-Aminoalkyl)quinolin-2(1*H*)-one Derivatives

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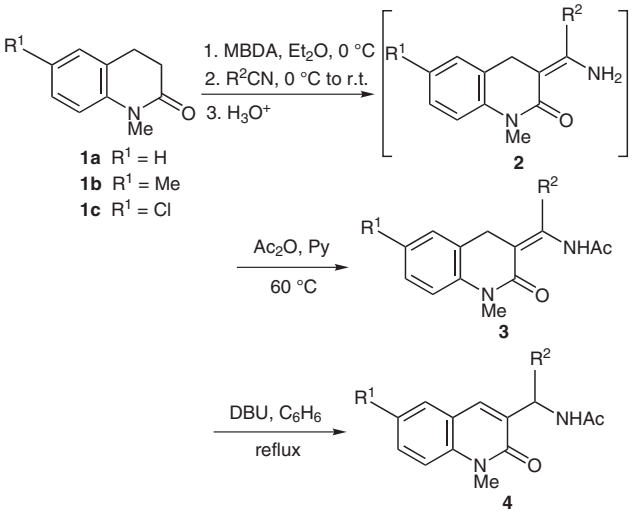
Abstract: Treatment of magnesium enolates of 1-methyl-3,4-dihydroquinolin-2(1*H*)-ones with nitriles, followed by N-acetylation of the resulting vinylogous urea derivatives with acetic anhydride/pyridine and double bond migration with 1,8-diazabicyclo[5.3.0]undec-7-ene, affords 3-[1-(acetylamino)alkyl]-1-methylquinolin-2(1*H*)-one derivatives in reasonable overall yields.

Key words: carbanion, lactams, magnesium, nitriles, quinolines

Substituted quinolin-2(1*H*)-one derivatives are an important class of molecules because of their biological activities.[1] We are interested in developing a simple and general synthetic method of 3-(1-aminoalkyl)quinolin-2(1*H*)-one derivatives, which are also of potential interest from a biological point of view. While quinolin-2(1*H*)-one derivatives bearing various kind of substituents have been prepared, there have been only few reports on the synthesis of quinolin-2(1*H*)-one derivatives bearing a 1-aminoalkyl substituent at the 3-position, though 3-(dialkylamino)methyl-4-hydroxyquinolin-2(1*H*)-ones have been prepared from 4-hydroxyquinolin-2(1*H*)-one by the Mannich method.[2] We now report on the preparation of 3-[1-(acetylamino)alkyl]-1-methylquinolin-2(1*H*)-one derivatives **4** from readily available starting materials, 1-methyl-3,4-dihydroquinolin-2(1*H*)-ones **1**.

Transformation of **1** into **4** was conducted as illustrated in Scheme 1. In previous papers we reported that magnesium enolates of carboxylic esters[3] or tertiary amides,[4] generated by treatment with magnesium bis(diisopropylamide) (MBDA) from diisopropylamine and ethylmagnesium bromide, coupled efficiently with a range of nitriles to afford the corresponding vinylogous urethanes or ureas, respectively.[5] The reaction of magnesium enolates of **1** with nitriles, yielding the corresponding vinylogous urea derivatives **2**, is the key reaction of the present sequence. It should be noted that only a trace amount of the corresponding coupling product could be obtained by using LDA in the reaction of **1a** with benzonitrile. The bivalent magnesium ion is responsible for the success of the present reaction as described before.[3–5] The products **2** were unstable under purification conditions using silica gel, and the amino group was then acetylated using acetic anhydride in pyridine at 60 °C without any purification to give (*Z*)-3-[1-(acetylamino)alkylidene]-3,4-dihydroquinolin-2(1*H*)-one derivatives **3** in fair to good yields based on **1** as summarized in Table 1. Nitriles bearing an α-hydrogen, such as 2-methylpropanenitrile and cyclohexanecarbonitrile, proved to be usable in this sequence to afford the desired products **3c** and **3d**, respectively, in fair yields (entries 3 and 4). Then, in order to investigate the scope of the sequence, the reactions using propanenitrile and 2,2-dimethylpropanenitrile were carried out. The reaction of magnesium enolate of **1a** with the former nitrile resulted in the formation of an intractable mixture of products, including a Thorpe condensation product of the nitrile. The reaction with the latter nitrile proceeded sluggishly, probably due to its bulkiness, to give only very low yield of the desired product.



Scheme 1

Table 1 Conversion of **1** into **4**, via **2** and **3**

Entry	**1**	R^2	**3** Yield (%)[a]	**4** Yield (%)[a]
1	**1a**	Ph	**3a** (84)	**4a** (88)
2	**1a**	2-FC_6H_4	**3b** (69)	**4b** (84)
3	**1a**	*i*-Pr	**3c** (60)	**4c** (78)
4	**1a**	*c*-Hex	**3d** (60)	**4d** (80)
5	**1b**	Ph	**3e** (78)	**4e** (83)
6	**1c**	Ph	**3f** (79)	**4f** (82)

[a] Isolated yields.

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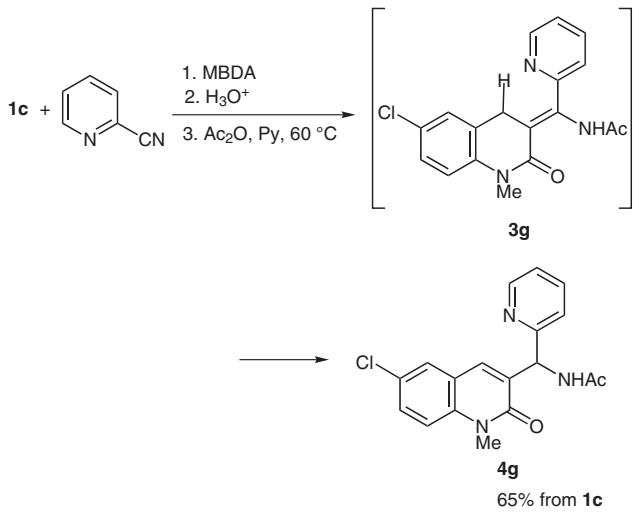
While two stereoisomers were possible in the formation of **3**, in fact only one isomer was isolated in each case. The stereochemistry of **3** was determined to be *Z*, because it is thermodynamically stable. This is ascribed to the hydrogen bonding between the quinolone carbonyl and the NH proton. The stereochemistry of **3c** was unambiguously confirmed by NOE experiments. Thus, irradiation of the signal at δ = 1.07, assignable to isopropyl methyls, resulted in an enhancement (10%) of the signal at δ = 3.43, assignable to 4-protons.

We conceived that treatment of **3** with 1,8-diazabicyclo[5.3.0]undec-7-ene (DBU) would allow them to undergo double bond migration to give the desired products **4**. Thus, the migration proceeded smoothly by heating **3** in benzene at reflux temperature in the presence of an equimolar amount of DBU to give **4** in good yields.

It is particularly noteworthy that the direct conversion of the coupling product of 6-chloro-1-methylquinolin-2(1*H*)-one (**1c**) with pyridine-2-carbonitrile into 3-[(acetylamino)(pyridin-2-yl)methyl]-6-chloro-1-methylquinolin-2(1*H*)-one (**4g**) was accomplished under the N-acetylating conditions described above, without isolating the corresponding intermediate **3g**. It is thought that this easy formation of **4g** is attributable to the feasible deprotonation of 4-hydrogen of **3g** by pyridine-nitrogen, which is the initial step of the double bond migration, as shown in Scheme 2.



Scheme 2

We attempted the direct conversion of **2a**–**2f** into **4a**–**4f** using acetic anhydride and DBU at 80 °C. The results, however, were not so good; rather complicated mixtures of products were obtained and only 30–35% yields of the desired products were isolated.

In summary, we have developed an efficient synthetic route to 3-(1-aminoalkyl)quinolin-2(1*H*)-one derivatives. The present method may find some value in organic synthesis because of simple manipulations as well as the ready availability of the starting materials.

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded using KBr disks (unless stated otherwise) on a Shimadzu FTIR-8300 spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference in $CDCl_3$ with a Jeol ECP500 FT NMR spectrometer operating at 500 MHz. Low-resolution mass spectra were recorded on a Jeol Automass 20 spectrometer (Center for Joint Research and Development, this University). 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.

1-Methyl-3,4-dihydroquinolin-2(1*H*)-ones 1a–c

These compounds were prepared by N-methylation of the corresponding 3,4-dihydroquinolin-2(1*H*)-ones[6] with NaH/MeI in THF at room temperature.

1a[7]

Yield: 95%; colorless oil; bp 120 °C (bath temp)/0.15 Torr.

IR (neat): 1673 cm^{-1}.

The ^{1}H NMR data for this compound was identical to those reported previously.[8]

1b

Yield: 94%; white solid; mp 63–65 °C (hexane–Et_2O).

IR (KBr): 1664 cm^{-1}.

^{1}H NMR: δ = 2.31 (3 H, s), 2.63 (2 H, t, *J* = 6.8 Hz), 2.86 (2 H, *J* = 6.8 Hz), 3.34 (3 H, s), 6.87 (1 H, d, *J* = 8.2 Hz), 6.98 (1 H, br s), 7.05 (1 H, dd, *J* = 8.2, 1.4 Hz).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.32; H, 7.50; N, 8.00.

1c

Yield: 96%; white solid; mp 77–78 °C (hexane–Et_2O–CH_2Cl_2).

IR (KBr): 1670 cm^{-1}.

^{1}H NMR: δ = 2.65 (2 H, *J* = 6.9 Hz), 2.89 (2 H, t, *J* = 6.9 Hz), 3.34 (3 H, s), 6.89 (1 H, d, *J* = 8.2 Hz), 7.15 (1 H, d, *J* = 2.7 Hz), 7.22 (1 H, dd, *J* = 8.2, 2.7 Hz).

Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.24; H, 5.20; N, 7.05.

All other chemicals used in this study were commercially available.

(*Z*)-3-(1-Acetylaminoalkylidine)-3,4-dihydroquinolin-2(1*H*)-one Derivatives 3; (*Z*)-3-(1-Acetylamino-1-phenylmethylene)-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (3a); Typical Procedure

To a turbid solution of MBDA (1.0 mmol), which was prepared by treatment of *i*-Pr_2NH (0.20 g, 2.0 mmol) with EtMgBr (2.0 mmol, 3.0 M in Et_2O) in Et_2O (5 mL) at reflux temperature for 1 h, was added a solution of **1a** (0.15 g, 0.96 mmol) in Et_2O (5 mL) with stirring at 0 °C. After 5 min, PhCN (98 mg, 0.98 mmol) was added and the mixture was stirred for 40 min at r.t. Sat. aq NH_4Cl (10 mL) was added to quench the reaction and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 5 mL) and the combined organic layers were washed with brine. After drying and evaporation of the solvent the residue was dissolved in a mixture of pyridine and Ac_2O (1 mL, 1:1). The mixture was heated at 60 °C for 10 h, after which excess pyridine and Ac_2O were removed under reduced pressure. The residue was separated by preparative TLC on SiO_2 (hexane–THF, 3:1) to give **3a** (0.26 g, 84%); white solid; mp 162–164 °C (hexane–THF) (Table 1).

IR (KBr): 3343, 1709, 1632 cm^{-1}.

^{1}H NMR: δ = 2.05 (3 H, s), 3.39 (3 H, s), 3.43 (2 H, s), 6.95–7.45 (9 H, m), 11.63 (1 H, s).

MS: *m*/*z* (%) = 306 (6.4, [M$^+$]), 263 (100).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.28; H, 6.00; N, 9.05.

(*Z*)-3-[1-Acetylamino-1-(2-fluorophenyl)methylene]-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (3b)
Yield: 69%; white solid; mp 143–145 °C (hexane–CH_2Cl_2).

IR (KBr): 3256, 1709, 1641 cm^{-1}.

^{1}H NMR: δ = 2.07 (3 H, s), 3.34 (1 H, d, *J* = 16.5 Hz), 3.37 (1 H, d, *J* = 16.5 Hz), 3.44 (3 H, s), 6.97–7.00 (3 H, m), 7.14 (1 H, t, *J* = 8.7 Hz), 7.19–7.25 (3 H, m), 7.38–7.43 (1 H, m), 11.83 (1 H, br s).

MS: *m*/*z* (%) = 324 (2.7, [M$^+$]), 281 (100).

Anal. Calcd for $C_{19}H_{17}FN_2O_2$: C, 70.36; H, 5.28; N, 8.64. Found; C, 70.14; H, 5.29; N, 8.64.

(*Z*)-3-(1-Acetylamino-2-methylpropylidene)-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (3c)
Yield: 60%; white solid; mp 196–198 °C (hexane–CH_2Cl_2).

IR (KBr): 3321, 1697, 1651 cm^{-1}.

^{1}H NMR: δ = 1.07 (6 H, d, *J* = 6.9 Hz), 2.21 (3 H, s), 3.41 (3 H, s), 3.43 (2 H, s), 3.76 (1 H, septet, *J* = 6.9 Hz), 6.53 (1 H, br s), 6.96 (1 H, d, *J* = 7.8 Hz), 6.98 (1 H, t, *J* = 7.8 Hz), 7.10 (1 H, d, 7.8 Hz), 7.23 (1 H, t, *J* = 7.8 Hz).

MS: *m*/*z* (%) = 272 (1.1, [M$^+$]), 229 (100).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found; C, 70.48; H, 7.40; N, 10.25.

(*Z*)-3-(1-Acetylamino-1-cyclohexylmethylene)-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (3d)
Yield: 60%; white solid; mp 183–185 °C (hexane–CH_2Cl_2).

IR (KBr): 3242, 1688, 1643 cm^{-1}.

^{1}H NMR: δ = 1.12–1.19 (2 H, m), 1.36–1.42 (2 H, m), 1.69–1.81 (6 H, m), 2.20 (3 H, s), 3.41–3.47 (6 H, m including 2 s at 3.41, 3.42), 6.55 (1 H, br s), 6.96 (1 H, d, *J* = 7.8 Hz), 6.98 (1 H, t, *J* = 7.8 Hz), 7.09 (1 H, d, *J* = 7.8 Hz), 7.23 (1 H, t, *J* = 7.8 Hz).

MS: *m*/*z* (%) = 312 (6.2, [M$^+$]), 269 (100).

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found; C, 73.12; H, 8.01; N, 8.64.

(*Z*)-3-(1-Acetylamino-1-phenylmethylene)-1,5-dimethyl-3,4-dihydroquinolin-2(1*H*)-one (3e)
Yield: 78%; white solid; mp 144–146 °C (hexane).

IR (KBr): 3240, 1703, 1635, 1614 cm^{-1}.

^{1}H NMR: δ = 2.04 (3 H, s), 2.28 (3 H, s), 3.35 (2 H, s), 3.41 (3 H, s), 6.80 (1 H, br s), 6.87 (1 H, d, *J* = 8.2 Hz), 7.04 (1 H, br d, *J* = 8.2 Hz), 7.24–7.26 (2 H, m), 7.39–7.45 (3 H, m), 11.67 (1 H, br s).

MS: *m*/*z* (%) = 320 (20, [M$^+$]), 277 (100).

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.81; H, 6.26; N, 8.70. Found: C, 74.98; H, 6.29; N, 8.74.

(*Z*)-3-(1-Acetylamino-1-phenylmethylene)-6-chloro-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (3f)
Yield: 79%; pale-yellow solid; mp 161–162 °C (hexane–CH_2Cl_2).

IR (KBr): 3200, 1703, 1637, 1622 cm^{-1}.

^{1}H NMR: δ = 2.05 (3 H, s), 3.36 (2 H, s), 3.41 (3 H, s), 6.89 (1 H, d, 8.7 Hz), 6.97 (1 H, d, 2.3 Hz), 7.20–7.25 (3 H, m), 7.39–7.45 (3 H, m), 11.62 (1 H, br s).

MS: *m*/*z* (%) = 340 (2.4, [M$^+$]), 297 (100).

Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.98; H, 4.99; N, 8.25.

3-(1-Acetylaminoalkyl)quinolin-2(1*H*)-one Derivatives 4; 3-(1-Acetylamino-1-phenylmethyl)-1-methylquinolin-2(1*H*)-one (4a); Typical Procedure
A solution of **3a** (0.15 g, 0.49 mmol) in benzene (5 mL) containing DBU (76 mg, 0.49 mmol) was refluxed for 1 h. After cooling to r.t., the mixture was diluted with $CHCl_3$ (25 mL), washed with 1% HCl, and dried (Na_2SO_4). Evaporation of the solvent gave a residual solid, which was recrystallized from hexane–CH_2Cl_2 to give pure **4a** (0.13 g, 88%); white solid; mp 190–192 °C.

IR (KBr): 3311, 1653 cm^{-1}.

^{1}H NMR: δ = 2.12 (3 H, s), 3.70 (3 H, s), 6.30 (1 H, d, *J* = 8.8 Hz), 7.15 (1 H, t, *J* = 7.3 Hz), 7.28–7.31 (4 H, m), 7.37 (2 H, dd, *J* = 7.3, 2.3 Hz), 7.59 (1 H, ddd, *J* = 8.2, 7.3, 1.4 Hz), 7.63 (1 H, dd, *J* = 7.8, 1.4 Hz), 7.78 (1 H, br d, *J* = 8.8 Hz), 7.87 (1 H, s).

MS: *m*/*z* (%) = 306 (7.6, [M$^+$]), 263 (100).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49, H, 5.92; N, 9.14. Found: C, 74.47; H, 6.23; N, 8.85.

3-[1-Acetylamino-1-(2-fluorophenyl)methyl]-1-methylquinolin-2(1*H*)-one (4b)
Yield: 84%; pale-yellow solid; mp 215–218 °C (hexane–CH_2Cl_2).

IR (KBr): 3306, 1651 cm^{-1}.

^{1}H NMR: δ = 2.09 (3 H, s), 3.69 (3 H, s), 6.54 (1 H, d, *J* = 9.2 Hz), 6.96 (1 H, ddd, *J* = 8.7, 7.8, 1.4 Hz), 7.13 (1 H, td, *J* = 7.3, 1.4 Hz), 7.18–7.23 (1 H, m), 7.28 (1 H, td, *J* = 7.8, 1.0 Hz), 7.34 (1 H, d, *J* = 8.2 Hz), 7.57 (1 H, td, *J* = 8.7, 1.4 Hz), 7.63–7.67 (2 H, m), 7.92 (1 H, br d, *J* = 9.2 Hz), 7.95 (1 H, d, *J* = 2.3 Hz).

MS: *m*/*z* (%) = 324 (17, [M$^+$]), 281 (100).

Anal. Calcd for $C_{19}H_{17}FN_2O_2$: C, 70.36; H, 5.28; N, 8.64. Found; C, 70.19; H, 5.67; N, 8.68.

3-(1-Acetylamino-2-methylpropyl)-1-methylquinolin-2(1*H*)-one (4c)
Purified by preparative TLC on SiO_2 (EtOAc); yield: 78%; white solid; mp 128–129 °C (hexane–CH_2Cl_2).

IR (KBr): 3312, 1645 cm^{-1}.

^{1}H NMR: δ = 0.79 (3 H, d, *J* = 6.4 Hz), 1.04 (3 H, d, *J* = 6.9 Hz), 1.99 (3 H, s), 2.29–2.38 (1 H, s), 3.74 (3 H, s), 4.60 (1 H, t, *J* = 10.1 Hz), 7.26 (1 H, t, *J* = 7.3 Hz), 7.37 (1 H, d, *J* = 8.7 Hz), 7.55–7.59 (3 H, m), 7.63 (1 H, s).

MS: *m*/*z* (%) = 272 (0.16, [M$^+$]), 229 (43), 187 (100).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found; C, 70.38; H, 7.43; N, 10.27.

3-(1-Acetylamino-1-cyclohexylmethyl)-1-methylquinolin-2(1*H*)-one (4d)
Yield: 80%; white solid; mp 210–212 °C (hexane–CH_2Cl_2).

IR (KBr): 3314, 1647 cm^{-1}.

^{1}H NMR: δ = 0.84–0.94 (1 H, m), 0.99–1.08 (1 H, m), 1.11–1.27 (2 H, m), 1.36–1.41 (1 H, m), 1.59–1.65 (4 H, m), 1.74–1.80 (1 H, m), 1.94–2.03 (4 H, m including s at 1.98), 3.74 (3 H, s), 4.67 (1 H, t, *J* = 10.1 Hz), 7.24–7.28 (2 H, m), 7.37 (1 H, d, *J* = 8.7 Hz), 7.54–7.58 (2 H, m), 7.60 (1 H, s).

MS: *m*/*z* (%) = 312 (0.31, [M$^+$]), 229 (54), 187 (100).

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.84; H, 7.84; N, 8.73.

3-(1-Acetylamino-1-phenylmethyl)-1,6-dimethylquinolin-2(1*H*)-one (4e)

Yield: 83%; white solid; mp 156–158 °C (hexane–CH_2Cl_2).

IR (KBr): 3304, 1651 cm^{-1}.

^1H NMR: δ = 2.09 (3 H, s), 2.44 (3 H, s), 3.68 (3 H, s), 6.27 (1 H, d, *J* = 9.2 Hz), 7.21 (1 H, t, *J* = 7.3 Hz), 7.25–7.30 (3 H, m), 7.35–7.42 (4 H, m), 7.80 (1 H, s), 7.84 (1 H, br d, *J* = 9.2 Hz).

MS: *m*/*z* (%) = 277 (56, [(M – Ac)$^+$]), 248 (100).

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.88; H, 6.48; N, 8.84.

3-(1-Acetylamino-1-phenylmethyl)-6-chloro-1-methylquinolin-2(1*H*)-one (4f)

Yield: 82%; pale-yellow solid; mp 226–227 °C (hexane–CH_2Cl_2).

IR (KBr): 3296, 1653, 1628 cm^{-1}.

^1H NMR: δ = 2.09 (3 H, s), 3.67 (3 H, s), 6.28 (1 H, d, *J* = 9.2 Hz), 7.21–7.32 (4 H, m), 7.35 (2 H, d, *J* = 7.8 Hz), 7.52 (1 H, dd, *J* = 8.7, 2.3 Hz), 7.60 (1 H, d, *J* = 2.3 Hz), 7.64 (1 H, br d, *J* = 9.2 Hz), 7.77 (1 H, s).

MS: *m*/*z* (%) = 340 (2.5, [M$^+$]), 297 (100).

Anal. Calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 67.00; H, 5.05; N, 8.13.

3-[1-Acetylamino-1-(pyridin-2-yl)methyl]-6-chloro-1-methylquinolin-2(1*H*)-one (4g)

6-Chloro-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (**1c**; 0.19 g, 0.96 mmol) was allowed to react with pyridine-2-carbonitrile (0.10 g, 0.98 mmol) and worked up in a manner similar to that described for the reaction of 1-methyl-3,4-dihydroquinolin-2(1*H*)-one (**1a**) with benzonitrile. The crude mixture was treated with Ac_2O–pyridine at 60 °C as described for the preparation of **3a**. Purification of the reaction mixture by preparative TLC on SiO_2 (hexane–THF, 2:3) gave directly **4g**; pale-yellow solid; yield: 0.21 g (65%); mp 202–205 °C (hexane–CH_2Cl_2).

IR (KBr): 3352, 1643, 1622 cm^{-1}.

^1H NMR: δ = 2.13 (3 H, s), 3.65 (3 H, s), 6.36 (1 H, d, *J* = 7.8 Hz), 7.16 (1 H, ddd, *J* = 7.3, 4.1, 0.9 Hz), 7.25 (1 H, d, *J* = 8.7 Hz), 7.48 (1 H, dd, *J* = 8.7, 2.3 Hz), 7.58–7.61 (2 H, m), 7.65 (1 H, td, *J* = 7.8, 1.8 Hz), 7.70 (1 H, br d, *J* = 7.8 Hz), 7.82 (1 H, s), 8.49 (1 H, d, *J* = 4.1 Hz).

MS: *m*/*z* (%) = 341 (12, [M$^+$]), 298 (100).

Anal. Calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 62.96; H, 4.70; N, 12.18.

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References

(1) (a) DeVita, R. J.; Walsh, T. F.; Young, J. R.; Jiang, J.; Ujjainwalla, F.; Toupence, R. B.; Parikh, M.; Huang, S. X.; Fair, J. A.; Goulet, M. T.; Wyvratt, M. J.; Lo, J.-L.; Ren, N.; Yudkovitz, J. B.; Yang, Y. T.; Cheng, K.; Cui, J.; Mount, G.; Rohrer, S. P.; Schaeffer, J. M.; Rohdes, L.; Drisko, J. E.; McGowan, E.; Macintyre, D. E.; Vincent, S.; Carlin, J. R.; Cameron, J.; Smith, R. G. *J. Med. Chem.* **2001**, *44*, 917. (b) Hewawasam, P.; Fan, W.; Knipe, J.; Moon, S. L.; Boissard, C. G.; Gribkoff, V. K.; Starrett, J. E. Jr.; Lodge, N. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1779. (c) Angibaud, P.; Bourdrez, X.; Devine, A.; End, D. W.; Freyne, E.; Lingy, Y.; Muller, P.; Mannens, G.; Pilatte, I.; Poncelet, V.; Skrzat, S.; Smets, G.; Dun, J. V.; Remoortere, P. V.; Venet, M.; Wouters, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1543. (d) Hewawasam, P.; Fan, W.; Ding, M.; Cook, D.; Goggins, G. D.; Mters, R. A.; Gribkoff, V. K.; Boissard, C. G.; Dworetzky, S. I.; Starrett, J. E. Jr.; Lodge, N. J. *J. Med. Chem.* **2003**, *46*, 2819. (e) Jiang, J.; DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J.; Lo, J.-L.; Ren, N.; Yudkovitz, J. B.; Cui, J.; Yang, Y. T.; Cheng, K.; Rohrer, S. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1795. (f) Marcaccini, S.; Pepino, R.; Pozo, M. C.; Basurto, S.; García-Valverde, M.; Torroba, T. *Tetrahedron Lett.* **2004**, *45*, 3999. (g) Hewawasam, P.; Fan, W.; Cook, D. A.; Newberry, K. S.; Boissard, C. G.; Gribkoff, V. K.; Starrett, J. E. Jr.; Lodge, N. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4479. (h) DeVita, R. J.; Parikh, M.; Jiang, J.; Fair, J. A.; Young, J. R.; Walsh, T. F.; Goulet, M. T.; Lo, J.-L.; Ren, N.; Yudkovitz, J. B.; Cui, J.; Yang, Y. T.; Cheng, K.; Rohrer, S. P.; Wyvratt, M. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5599; and references cited therein.

(2) See, e.g.: (a) Asherson, J. L.; Young, D. W. *J. Chem. Soc., Chem. Commun.* **1977**, 916. (b) Jha, I. S.; Kanth, A. K.; Singh, L. *Orient. J. Chem.* **1998**, *14*, 489; *Chem. Abstr.* **1999**, *130*, 281972h.

(3) (a) Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* **1982**, *23*, 1597. (b) Kobayashi, K.; Suginome, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2635. (c) Hiyama, T.; Kobayashi, K.; Nishide, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2127. (d) Kobayashi, K.; Kanno, Y.; Seko, S.; Suginome, H. *J. Chem. Soc., Chem. Commun.* **1992**, 780.

(4) Kobayashi, K.; Kitamura, T.; Nakahashi, R.; Shimizu, A.; Morikawa, O.; Konishi, H. *Heterocycles* **2000**, *53*, 1021.

(5) For other recent reports from our laboratory on the heterocycle synthesis utilizing magnesium enolates, see: (a) Kobayashi, K.; Takabatake, H.; Kitamura, T.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1697. (b) Kobayashi, K.; Nakahashi, R.; Shimizu, A.; Kitamura, T.; Morikawa, O.; Konishi, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1747. (c) Kobayashi, K.; Matoba, T.; Irisawa, S.; Takanohashi, A.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2805. (d) Kobayashi, K.; Nakashima, T.; Mano, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2001**, 602. (e) Kobayashi, K.; Nakahashi, R.; Mano, M.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1257. (f) Kobayashi, K.; Honma, K.; Kondo, S.; Morikawa, O.; Konishi, H. *Heterocycles* **2005**, *65*, 619; and references cited therein.

(6) 2,3-Dihydroquinolin-2(1*H*)-one was commercially available and the others were prepared by the procedure reported in the following paper: Guaruna, A.; Machetti, F.; Occhiato, E. G.; Scarpi, D. *J. Med. Chem.* **2000**, *43*, 3718.

(7) Morfat, A.; Carta, M. *Synthesis* **1987**, 515.

(8) Venkov, A. P.; Statkova-Abeghe, S. M. *Tetrahedron* **1996**, *52*, 1451.