Synthesis of 1-Formyl-1,2-dihydroquinoline Derivatives by a Lewis Acid-Catalyzed Cyclization of *o*-(1-Hydroxy-2-alkenyl)phenyl Isocyanides

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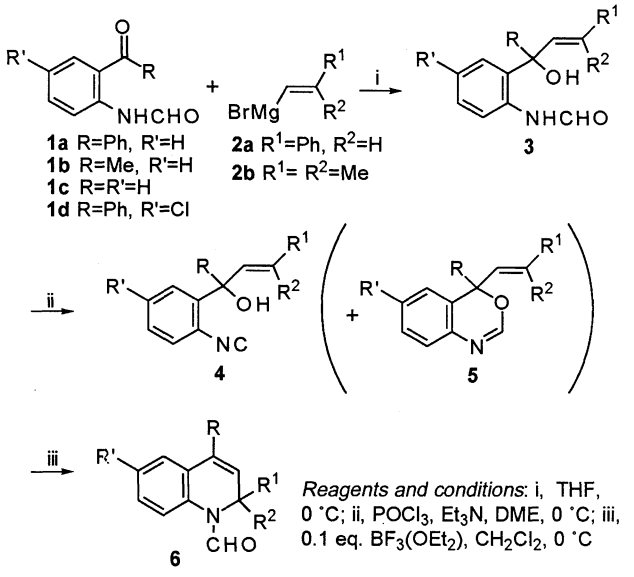
An efficient route to 1-formyl-1,2-dihydroquinolines **6** is described based on the BF_3-catalyzed cyclization of *o*-(1-hydroxy-2-alkenyl)phenyl isocyanides **4**, which can be prepared feasibly by the reaction of *N*-(*o*-acylphenyl)formamides **1** with alkenylmagnesium bromides **2** followed by treatment of the resulting hydroxy formamides **3** with phosphorous oxychloride.

1,2-Dihydroquinoline derivatives are valuable synthetic precursors for the preparation of some biologically active compounds.[1] Furthermore, a number of patent applications[2] concerning the industrial uses of these derivatives have revealed their usefulness, substantially enhancing their importance. The traditional methods employed in the preparation of these derivatives mainly rely upon the addition of nucleophiles to *N*-alkylquinolinium salts.[3] However, these methods are suffering from the simultaneous production of 1,4-dihydro derivatives.[3,4]



Scheme 1.

We herein report that 1-formyl-1,2-dihydroquinolines **6** are readily accessed in a reasonably efficient manner starting from *N*-(*o*-acylphenyl)formamides **1** as shown in Scheme 1. The results of this study are summarized in the Table. Thus, reaction of **1** with alkenylmagnesium bromides **2** in tetrahydrofuran at 0 °C gave *N*-[(*o*-hydroxyalkenyl)phenyl]formamides **3** in 51-84% yields, which were subsequently transformed into the isocyano alcohols **4** by treating with phosphorous oxychloride in the presence of triethylamine in DME at 0 °C. The compounds **4** were found to be unstable during isolation by preparative TLC,

Table. The preparation of 1,2-dihydroquinolines **6** from *o*-(formylamino)phenyl ketones **1**

Entry	1	2	3 (Yield/%)[a]	6 (Yield from 3/%)[a]
1	**1a**[b]	**2a**[f]	**3a** (84)	**6a** (75)
2	**1a**	**2b**[f]	**3b** (56)	**6b** (52)
3	**1b**[c]	**2a**	**3c** (79)	**6c** (77)
4	**1b**	**2b**	**3d** (51)	**6d** (50)
5	**1c**[d]	**2a**	**3e** (74)	**6e** (34)
6	**1d**[e]	**2a**	**3f** (57)	**6f** (66)

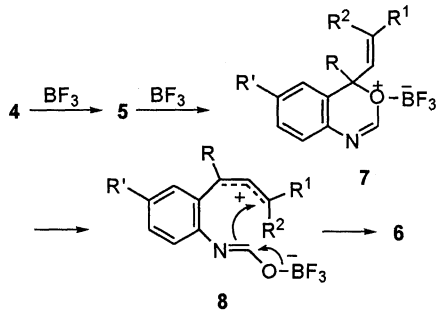
[a]Isolated yields. [b]Ref. 5. [c]Ref. 6. [d]Prepared by the PCC oxidation of *N*-[2-(hydroxymethyl)phenyl]formamide (ref. 7). [e]Ref. 8. [f]Prepared in situ from the corresponding bromides obtained commercially and magnesium activated by 1,2-dibromoethane.

and the crude products, contaminated by the corresponding benzoxazine derivatives **5**, were directly treated with a catalytic amount of boron trifluoride diethyl etherate (0.1 equivalent) in dichloromethane at 0 °C to give **6** in 34-77% yields in two steps from **3**. No detectable formation of the corresponding 1,4-dihydro derivatives could be observed in the reactions of **3a**, **3c**, **3e**, and **3f** (Entries 1, 3, 5, and 6). Entry 6 shows that the chloro substituent has negligible effect on the efficiency of the reaction. Compound **3e**, which carries no substituent at C_1 of the alkenyl side chain, gave **6e** in lower yield (Entry 5).

A typical experimental procedure for conversion of **3** to **6** is illustrated as follows. To a stirred solution of **3a** (0.69 g, 2.1 mmol) and Et_3N (3.8 g, 26 mmol) in DME (35 ml) at 0 °C under argon was added dropwise $POCl_3$ (0.75 g, 8.1 mmol). After stirring for 1 h, aqueous $NaHCO_3$ was added to the resulting mixture, and it was extracted with Et_2O. The extract was washed with brine, dried over anhydrous K_2CO_3. Evaporation of the solvent gave a residue (0.58 g). The production of **4a** was confirmed by IR, which also indicated the presence of **5a** [(neat) 3398, 2121, and 1619 cm^{-1}]. The residue was used in the next step without purification: it was dissolved in CH_2Cl_2 (20 ml), and treated with $BF_3(OEt_2)$ (24 mg, 0.17 mmol) at 0 °C. After the mixture had been stirred for 1 h at the same temperature, it was washed successively with aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue, which was purified by preparative TLC to afford **6a** (0.49 g, 75% from **3a**).[9]

The probable pathway leading to the formation of **6** is outlined in Scheme 2. Thus, the intramolecular insertion of the

isocyano carbon into the O-H linkage of **4** leads to **5**, a cationic 3,3-rearrangement[10] of which gives rise to **6** via the intermediates **7** and **8**. A cationic character of the rearrangement is consistent with the production of **6e** in lower yield.



Scheme 2.

In conclusion, the present study has led to the development of a convenient and efficient method for the preparation of substituted 1,2-dihydroquinolines. The present method has advantages over the previous methods of 1,2-dihydroquinoline synthesis: simple manipulations as well as the ready availability of starting materials. Effects of Lewis acids on the cyclization reaction, together with applications of the present procedure to the preparation of more complex systems containing this structural array, are presently under investigation and will be reported at a later date.

References and Notes

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9 Physical, spectral, and analytical data for the isoquinolines listed in the table are as follows. **6a**: R_f 0.33 (1:5 AcOEt-hexane); mp 115.5-117 °C (hexane); IR (KBr disk) 1679 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.13 (1H, d, *J*=6.2 Hz), 6.37 (1H, d, *J*=6.2 Hz), 7.0-7.45 (14H, m), and 8.61 (1H, s); MS, *m/z* (%) 311 (M, 42), 310 (76), and 206 (100). Anal. Found: C, 84.67; H, 5.64; N, 4.51%. Calcd for $C_{22}H_{17}NO$: C, 84.85; H, 5.51; N, 4.50%. **6b**: R_f 0.42 (1:2 AcOEt-hexane); mp 107-108 °C (hexane); IR (KBr disk) 1672 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.62 (6H, s), 5.63 (1H, s), 6.95-7.4 (9H, m), and 8.61 (1H, s); MS, *m/z* (%) 263 (M, 6.5), 248 (60), and 220 (100). Anal. Found: C, 81.86; H, 6.61; N, 5.11%. Calcd for $C_{18}H_{17}NO$: C, 82.09; H, 6.52; N, 5.32%. **6c**: R_f 0.60 (1:2 AcOEt-hexane); IR (neat) 1674 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.19 (3H, s), 6.01 (1H, d, *J*=5.8 Hz), 6.29 (1H, d, *J*=5.8 Hz), 7.0-7.4 (9H, m), and 8.68 (1H, s); MS, *m/z* (%) 249 (M, 42), 248 (66), 172 (67), and 144 (100). Anal. Found: C, 82.01; H, 6.09; N, 5.59%. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62%. **6d**: R_f 0.52 (1:2 AcOEt-hexane); IR (neat) 1672 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.51 (6H, s), 2.03 (3H, s), 5.58 (1H, br. s), 7.15-7.3 (4H, m), and 8.61 (1H, s); MS, *m/z* (%) 201 (M, 9.0), 186 (49), and 158 (100). Anal. Found: C, 77.33; H, 7.46; N, 7.00%. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96%. **6e**: R_f 0.38 (1:2 AcOEt-hexane); IR (neat) 1683 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.27 (1H, dd, *J*=7.3 and 6.2 Hz), 6.51 (1H, d, *J*=6.2 Hz), 7.0-7.3 (10H, m), and 8.59 (1H, s); MS, *m/z* (%) 235 (M, 63), 206 (70), and 130 (100). Anal. Found: C, 81.73; H, 5.70; N, 5.99%. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95%. **6f**: R_f 0.53 (1:3 AcOEt-hexane); mp 75-76 °C (hexane); IR (KBr disk) 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.23 (1H, d, *J*=6.2 Hz), 6.48 (1H, d, *J*=6.2 Hz), 7.03 (1H, d, *J*=8.7 Hz), 7.14 (1H, d, *J*=2.5 Hz), 7.20 (1H, dd, *J*=8.7 and 2.5 Hz), 7.25-7.5 (10H, m), and 8.72 (1H, s); MS, *m/z* (%) 347 [M(^{37}Cl), 12], 346 (35), 345 [M(^{35}Cl), 50], 344 (82), and 240 (100). Anal. Found: C, 80.35; H, 4.98; N, 4.57%. Calcd for $C_{22}H_{16}ClNO$: C, 80.12; H, 4.89; N, 4.25%.

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