

Facile Synthesis of Quinolines from the Baylis-Hillman Acetates

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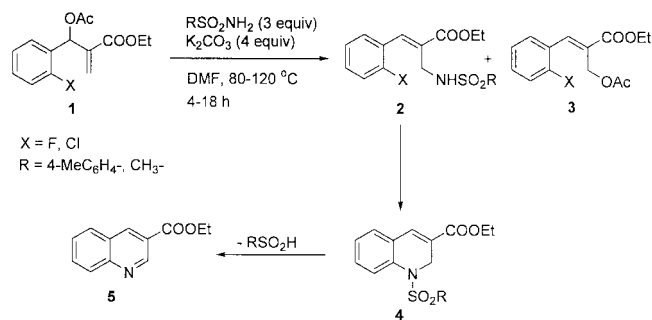
The Baylis-Hillman reaction is well known as a coupling reaction of aldehydes and activated alkenes catalyzed by tertiary amines or tertiary phosphines.¹ The reaction with ethyl acrylate serves α -methylene- β -hydroxy esters, which have been transformed to various useful compounds.²

Some papers were reported on the formation of heterocyclic compounds including quinoline from the Baylis-Hillman adducts.³ Quinolines and their derivatives occur in numerous natural products.⁴ Many quinolines display interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals as well as being general synthetic building blocks.^{4b} Many synthetic methods have been developed for the preparation of quinolines,⁵ but due to their great importance, the development of novel synthetic methods remains an active research area.⁶

Recently, we have reported on the synthesis of 4-hydroxy-3-ethoxycarbonylquinoline *N*-oxide derivatives from the Baylis-Hillman adducts of 2-nitrobenzaldehydes.^{3a} As a continuous work we intended to examine the feasibility of transforming the Baylis-Hillman adducts of 2-halobenzaldehydes into the corresponding quinolines by using the intramolecular nucleophilic aromatic substitution strategy.

Our synthetic rationale is depicted in Scheme 1: (1) synthesis of rearranged tosylamide derivative **2** from the Baylis-Hillman acetate **1**, (2) nucleophilic aromatic substitution reaction of **2** to the dihydroquinoline derivative **4**, and (3) elimination of *p*-toluenesulfonic acid from **4** to give the quinoline **5** directly in a one-pot reaction.

The reaction of the Baylis-Hillman acetate **1a** in *N,N*-dimethylformamide in the presence of potassium carbonate (4.0 equiv) and tosylamide (3.0 equiv) at 110–120 °C afforded the desired quinoline **5a** in 55% yield. The reaction conditions and yields of products for the representative examples are shown in Table 1. The reaction of **1** and tosyl-



Scheme 1

Table 1. Synthesis of 3-alkoxycarbonylquinolines **5**

entry	B-H acetates (1)	conditions	quinolines (5) ^a	dihydroquinolines (4) ^a
1		TsNH ₂ (3 equiv) K ₂ CO ₃ (4 equiv) DMF, 110–120 °C 6 h		
2		TsNH ₂ (3 equiv) K ₂ CO ₃ (4 equiv) DMF, 80–90 °C 18 h		
3		TsNH ₂ (3 equiv) K ₂ CO ₃ (4 equiv) DMF, 110–120 °C 4 h		— ^b
4		TsNH ₂ (3 equiv) K ₂ CO ₃ (4 equiv) DMF, 110–120 °C 4 h		
5		TsNH ₂ (3 equiv) K ₂ CO ₃ (4 equiv) DMF, 110–120 °C 4 h		— ^b
6		CH ₃ SO ₂ NH ₂ (3 equiv) K ₂ CO ₃ (4 equiv) DMF, 110–120 °C 6 h		— ^b

^aIsolated yield in parenthesis. ^bNot isolated.

amide gave the rearranged tosylamide derivatives **2** and trace amounts of rearranged acetates **3**. Nucleophilic aromatic substitution reaction of **2** and the following elimination of *p*-toluenesulfonic acid from **4** gave the desired quinolines **5** in moderate yields. In the reaction mixtures, rearranged acetates **3** were observed in all cases in variable amounts as mentioned before. Such a rearrangement of **1** to **3** can occur via the concerted mechanism as proposed in our previous paper.^{2e}

Elimination of *p*-toluenesulfonic acid from **4** was not efficient in some cases. Thus, variable amounts (2–10%) of dihydroquinoline derivatives **4** were isolated after the reaction in some cases (entries 1, 2, and 4). Methanesulfonamide can be used as effectively as *p*-toluenesulfonamide in the reaction (entry 6). Methyl ester did not affect the reaction (entry 5), however, the reaction of nitrile substituted Baylis-Hillman acetate produced trace amounts of quinoline. Instead, low yields of rearranged acetate and rearranged tosylamide derivatives were isolated as *E-Z* mixtures.

The reaction mechanism was shown in Scheme 1 (*vide supra*): (1) successive S_N2' type reaction of **1a–e** to the primary rearranged allylic tosylamides **2a–e** (selective formation of *E*-isomer),^{2e–g} (2) S_NAr reaction with the aid of

potassium carbonate to produce the dihydroquinolines **4a-e**, and finally (3) elimination of *p*-toluenesulfinic acid gave quinolines **5a-e**.

Typical procedure for the synthesis of 5a: A stirred solution of **1a** (266 mg, 1 mmol), tosylamide (513 mg, 3 mmol), and K_2CO_3 (552 mg, 4 mmol) in *N,N*-dimethylformamide (5 mL) was heated at 110–120 °C during 6 h. After cooling to room temperature, the reaction mixture was poured into cold HCl solution and extracted with ether. After the usual workup process, column chromatographic purification (hexane/ether, 8 : 2) gave **5a** as a white solid, 110 mg (55%); mp 64–65 °C; IR (KBr) 1713 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.47 (t, $J = 7.2$ Hz, 3H), 4.49 (q, $J = 7.2$ Hz, 2H), 7.60–8.18 (m, 4H), 8.85 (s, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.91, 61.07, 122.93, 126.45, 126.95, 128.64, 129.08, 131.31, 138.20, 149.42, 149.65, 164.94; MS (70 eV) m/z (rel intensity) 75 (28), 101 (44), 128 (82), 156 (100), 173 (45), 201 (M^+ , 60). Dihydroquinoline derivative **4a** was also isolated, 25 mg (7%); mp 113–114 °C; 1H NMR ($CDCl_3$) δ 1.32 (t, $J = 7.2$ Hz, 3H), 2.33 (s, 3H), 4.22 (q, $J = 7.2$ Hz, 2H), 4.67 (s, 2H), 6.96 (s, 1H), 7.03–7.75 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 14.27, 21.44, 44.24, 60.75, 125.25, 126.89 (2C by 1H - ^{13}C COSY), 127.15, 127.98, 128.46, 129.06, 130.35, 133.27, 135.73, 136.08, 143.72, 164.16; MS (70 eV) m/z (rel intensity) 28 (100), 91 (46), 128 (55), 130 (61), 156 (41), 174 (92), 202 (88), 357 (M^+ , 28).

Spectroscopic data of 4b, 4d, and 5b-e. **4b:** 1H NMR ($CDCl_3$) δ 1.32 (t, $J = 7.2$ Hz, 3H), 2.34 (s, 3H), 4.22 (q, $J = 7.2$ Hz, 2H), 4.67 (s, 2H), 6.92–7.55 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 14.34, 21.54, 44.12, 60.91, 114.01, 114.31, 114.41, 114.75, 124.25, 124.30, 124.33, 124.37, 126.96, 129.28, 129.80, 129.92, 132.57, 135.72, 137.93, 138.08, 144.07, 161.55, 164.16, 164.88; MS (70 eV) m/z (rel intensity) 91 (54), 146 (40), 148 (44), 174 (38), 192 (82), 220 (73), 375 (M^+ , 15).

4d: 1H NMR ($CDCl_3$) δ 1.32 (t, $J = 7.2$ Hz, 3H), 2.34 (s, 3H), 4.22 (q, $J = 7.2$ Hz, 2H), 4.65 (s, 2H), 6.93 (s, 1H), 7.03–7.32 (m, 6H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.29, 21.49, 44.26, 60.95, 125.61, 126.43, 127.02, 127.09, 127.14, 129.22, 129.27, 132.37, 135.82, 135.94, 137.31, 144.06, 164.00.

5b: mp 88–89 °C; 1H NMR ($CDCl_3$) δ 1.47 (t, $J = 7.2$ Hz, 3H), 4.49 (q, $J = 7.2$ Hz, 2H), 7.38–7.97 (m, 3H), 8.83 (s, 1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.31, 61.55, 113.21, 113.48, 117.94, 118.28, 122.79, 123.85, 131.18, 131.31, 138.40, 150.86, 151.06, 162.70, 165.13, 166.06; MS (70 eV) m/z (rel intensity) 99 (23), 119 (27), 126 (18), 146 (75), 174 (100), 191 (42), 219 (M^+ , 48).

5c: mp 97–98 °C; IR (KBr) 3299, 2987, 1724, 1279 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.48 (t, $J = 7.2$ Hz, 3H), 4.51 (q, $J = 7.2$ Hz, 2H), 7.66–7.78 (m, 2H), 8.09 (dt, $J = 8.1$ and 1.2 Hz, 1H), 9.22 (dd, $J = 2.1$ and 0.9 Hz, 1H), 9.48 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.33, 61.75, 124.10, 125.26, 127.45, 128.63, 131.38, 132.68, 135.44, 150.41, 150.70, 164.99; MS (70 eV) m/z (rel intensity) 99 (38), 162 (66), 190 (100), 192 (35), 207 (54), 235 (M^+ , 60), 237 ($M^+ + 2$, 20).

5d: mp 91–92 °C; 1H NMR ($CDCl_3$) δ 1.47 (t, $J = 7.2$ Hz, 3H), 4.48 (q, $J = 7.2$ Hz, 2H), 7.57 (dd, $J = 8.7$ and 2.1 Hz, 1H), 7.88 (d, $J = 8.7$ Hz, 1H), 8.16 (d, $J = 2.1$ Hz, 1H), 8.81

(d, $J = 2.1$ Hz, 1H), 9.45 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.32, 61.63, 123.58, 125.27, 128.59, 128.66, 130.18, 137.89, 138.31, 150.15, 151.12, 165.04; MS (70 eV) m/z (rel intensity) 99 (30), 127 (21), 162 (62), 190 (100), 207 (54), 235 (M^+ , 55), 237 ($M^+ + 2$, 19).

5e: mp 150–151 °C; 1H NMR ($CDCl_3$) δ 4.03 (s, 3H), 7.58 (dd, $J = 9.0$ and 2.1 Hz, 1H), 7.88 (d, $J = 9.0$ Hz, 1H), 8.17 (d, $J = 2.1$ Hz, 1H), 8.83 (d, $J = 2.1$ Hz, 1H), 9.45 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.60, 123.16, 125.18, 128.58, 128.63, 130.23, 137.95, 138.45, 150.07, 151.02, 165.49.

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