Facile Synthesis of Quinolines from the Baylis-Hillman Acetates

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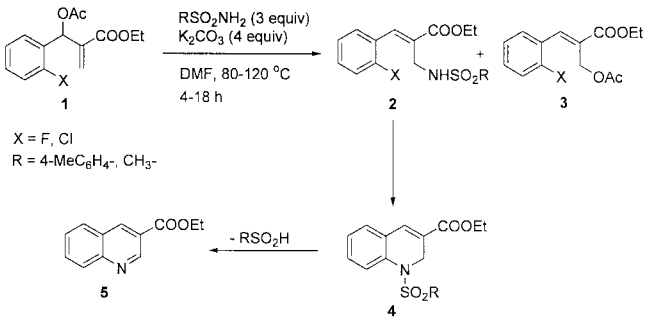
The Baylis-Hillman reaction is well known as a coupling reaction of aldehydes and activated alkenes catalyzed by tertiary amines or tertiary phosphines.[1] The reaction with ethyl acrylate serves α-methylene-β-hydroxy esters, which have been transformed to various useful compounds.[2]

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.

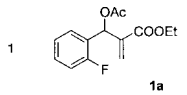
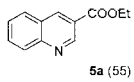
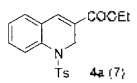
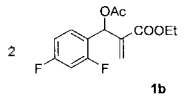
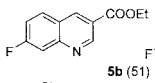
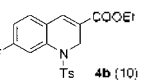
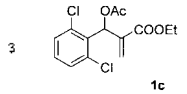
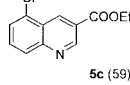
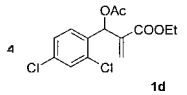
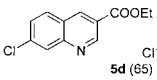
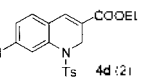
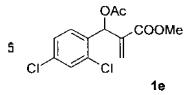
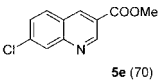
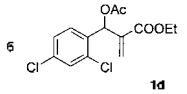
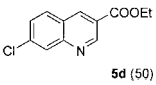
Our synthetic rationale is depicted in Scheme 1: (1) synthesis of rearranged tosylamide derivative **2** from the Baylis-Hillman acetate **1**, (2) nucleophilic aromatic substitution reaction of **2** to the dihydroquinoline derivative **4**, and (3) elimination of *p*-toluenesulfinic acid from **4** 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 tosylamide 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*-toluenesulfinic 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]



Scheme 1

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

entry	B-H acetates (**1**)	conditions	quinolines (**5**)[a]	dihydroquinolines (**4**)[a]
1	 **1a**	$TsNH_2$ (3 equiv) K_2CO_3 (4 equiv) DMF, 110-120 °C 6 h	 **5a** (55)	 **4a** (7)
2	 **1b**	$TsNH_2$ (3 equiv) K_2CO_3 (4 equiv) DMF, 80-90 °C 18 h	 **5b** (51)	 **4b** (10)
3	 **1c**	$TsNH_2$ (3 equiv) K_2CO_3 (4 equiv) DMF, 110-120 °C 4 h	 **5c** (59)	[b]
4	 **1d**	$TsNH_2$ (3 equiv) K_2CO_3 (4 equiv) DMF, 110-120 °C 4 h	 **5d** (65)	 **4d** (21)
5	 **1e**	$TsNH_2$ (3 equiv) K_2CO_3 (4 equiv) DMF, 110-120 °C 4 h	 **5e** (70)	[b]
6	 **1d**	$CH_3SO_2NH_2$ (3 equiv) K_2CO_3 (4 equiv) DMF, 110-120 °C 6 h	 **5d** (50)	[b]

[a]Isolated yield in parenthesis. [b]Not isolated.

Elimination of *p*-toluenesulfinic 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 infra*): (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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