

Synthesis of Polysubstituted Quinolines from the Acetates of Baylis-Hillman Adducts: Aza-Claisen Rearrangement as the Key Step

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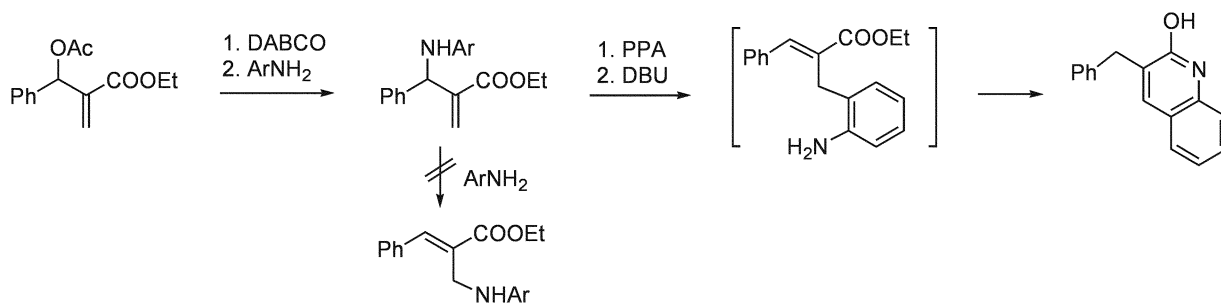
Key Words : Quinolines, Baylis-Hillman adducts, Aza-Claisen rearrangement, PPA

Recently, we have reported a variety of chemical transformations of the Baylis-Hillman adducts into useful heterocyclic compounds.^{1,2} Very recently, we published the synthesis of 3-benzylquinolin-2-ols from the Baylis-Hillman adducts of ethyl acrylate bearing aniline moiety at the secondary position.¹ 3-Benzylquinolin-2-ols could be formed via the sequential aza-Claisen rearrangement of the adduct in PPA, amide bond formation, and the following isomerization with the aid of DBU as shown in Scheme 1.

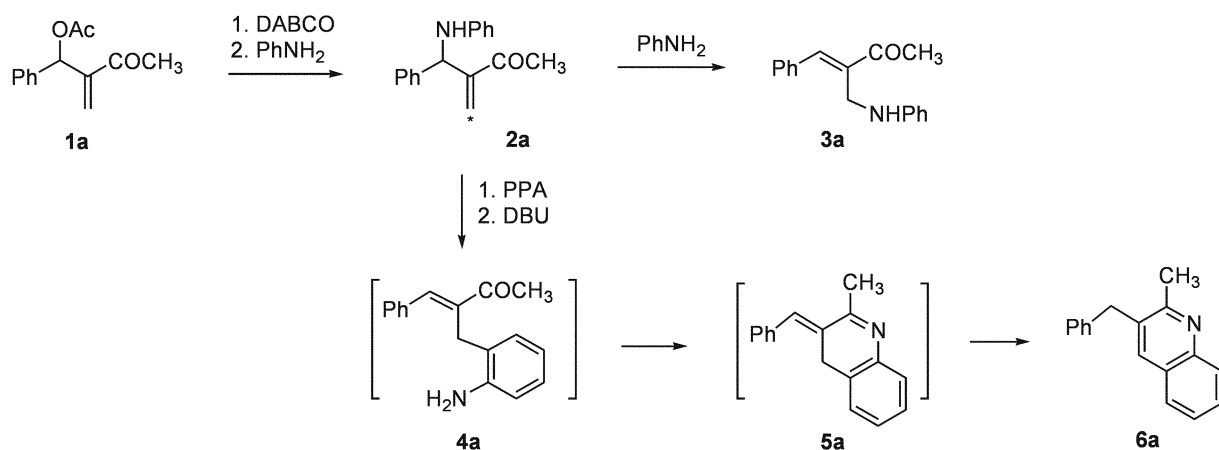
In this paper we would like to report our results on the synthesis of polysubstituted quinolines from the Baylis-Hillman adducts of alkyl vinyl ketones. As exemplified in Scheme 2, the required starting materials **2** were synthesized from the acetates of the Baylis-Hillman adducts of methyl vinyl ketone and ethyl vinyl ketone *via* the corresponding

DABCO salts according to the reported procedure.^{1a,3,4} In the reaction, however, cinnamyl amine derivatives **3** were isolated in variable yields (6-37%) depending upon the nature of anilines (Table 1) as side products.⁵ The formation of primary adducts **3** from **2** under the reaction conditions can be explained by sequential addition and elimination of aniline, presumably due to the higher electrophilicity of the β -carbon (marked with asterisk) of **2** than the cases of ethyl acrylate (Scheme 1).⁵ As can be seen easily in the ratios of **2** and **3** (Table 1), the amounts of primary products **3** were gradually increased according to the increase of the nucleophilicity of anilines.

With the compound **2a** in hand we examined the reaction in PPA at various reaction temperatures. Mixed solvent system of PPA and 1,2-dichloroethane was used in order to



Scheme 1

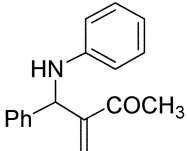
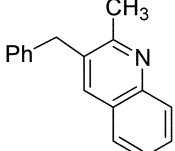
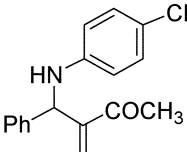
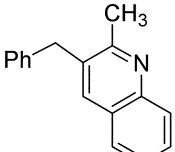
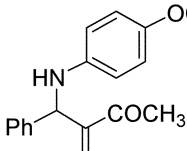
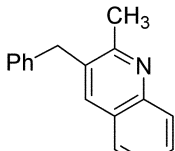
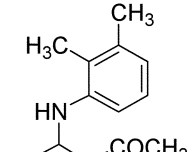
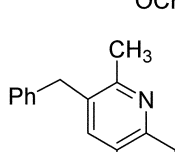
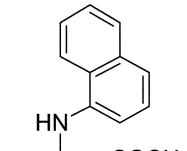
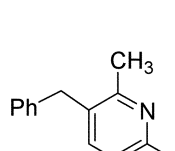
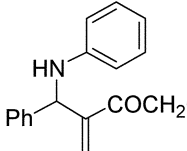
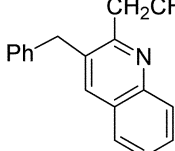
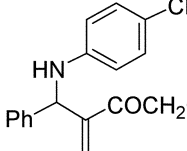
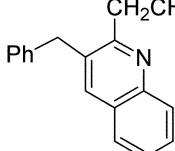


Scheme 2

dissolve the starting materials efficiently (Experimental section). As expected we could obtain the dihydroquinoline compound **5a** (42%), which must be obtained via the sequential aza-Claisen rearrangement^{1,6} and condensation between the

amino and the acetyl group. The optimum temperature was found to be around 70-80 °C. But, the generated dihydroquinoline compound **5a** was very unstable, which decomposed rapidly into intractable mixtures at room temperature.

Table 1. Synthesis of polysubstituted quinolines **6**

Entry	Substrates 2 ^a	Conditions	Products 6 (%)
1	 2a (74), 3a (9)	1. PPA, ClCH ₂ CH ₂ Cl 70-80 °C, 2 h 2. extraction 3. DBU, rt, 20 min	 6a (43)
2	 2b (66), 3b (29)	1. PPA, ClCH ₂ CH ₂ Cl 80-90 °C, 1 h 2. extraction 3. DBU, rt, 10 min	 6b (57)
3	 2c (44), 3c (31)	1. PPA, ClCH ₂ CH ₂ Cl 70-80 °C, 1 h 2. extraction 3. DBU, rt, 10 min	 6c (47)
4	 2d (36), 3d (37)	1. PPA, ClCH ₂ CH ₂ Cl 80-90 °C, 1 h 2. extraction 3. DBU, rt, 10 min	 6d (48)
5	 2e (32), 3e (0) ^b	1. PPA, ClCH ₂ CH ₂ Cl 80-90 °C, 2 h 2. extraction 3. DBU, rt, 20 min	 6e (67)
6	 2f (73), 3f (12)	1. PPA, ClCH ₂ CH ₂ Cl 70-80 °C, 2 h 2. extraction 3. DBU, rt, 20 min	 6f (53)
7	 2g (63), 3g (6)	1. PPA, ClCH ₂ CH ₂ Cl 70-80 °C, 1 h 2. extraction 3. DBU, rt, 10 min	 6g (65)

^aThe yields of primary products **3a-g** were also written. ^bNot separated.

Fortunately, however, treatment of the dihydroquinoline intermediate **5a** with DBU generated 2-methyl-3-benzylquinoline (**6a**) almost quantitatively.⁷ Thus, we carried out the synthesis of **6a** without isolation of the dihydroquinoline intermediate **5a** and we could obtain **6a** in 43% yield. Similarly we prepared polysubstituted quinolines **6b-g** and the results are summarized in Table 1.

As shown, quinolines **6b-g** were obtained in 47-67% yields. In order to increase the yields of quinolines we examined other conditions including *p*-TsOH/CH₃CN/reflux, ZnCl₂/xylene/reflux, LiClO₄/1,2-dichloroethane/reflux. However, rearranged cinnamyl amine derivatives **3** were observed as the major products in all cases. The results showed that the aza-Claisen rearrangement of aniline moiety of **2** was facilitated in PPA in any way. However, we could not explain the reason at this stage.

In summary, we disclosed the synthesis of polysubstituted quinolines starting from Baylis-Hillman adducts of methyl vinyl ketone and ethyl vinyl ketone in moderate yields.

Experimental Section

Typical procedure for the synthesis of starting material

2a: To a stirred solution of the acetate of the Baylis-Hillman adduct **1a** (436 mg, 2 mmol) in aq THF (5 mL, H₂O/THF = 1 : 1) was added DABCO (246 mg, 2.2 mmol) at room temperature. After 30 min, aniline (280 mg, 3 mmol) was added and stirred for 16 h at room temperature. After the usual workup and column chromatographic purification process (hexanes/ether, 10 : 1) we obtained **2a** (372 mg, 74%) and **3a** (45 mg, 9%), respectively. The other starting materials **2b-g** was prepared similarly and the spectroscopic data of **2a-g** are as follows.

Compound **2a**: 74%; white solid, mp 95-97 °C; IR (KBr) 3398, 1674, 1601, 1500 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.33 (s, 3H), 4.11 (br s, 1H), 5.51 (s, 1H), 6.15 (s, 1H), 6.23 (s, 1H), 6.50-6.55 (m, 2H), 6.67-6.74 (m, 1H), 7.10-7.17 (m, 2H), 7.22-7.37 (m, 5H).

Compound **2b**: 66%; white solid, mp 111-112 °C; IR (KBr) 3398, 1674, 1616, 1516 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.21 (s, 3H), 2.32 (s, 3H), 4.00 (br s, 1H), 5.47 (s, 1H), 6.13 (s, 1H), 6.21 (s, 1H), 6.45 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.22-7.36 (m, 5H).

Compound **2c**: 44%; pale yellow solid, mp 78-79 °C; IR (KBr) 3386, 1674, 1512 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.32 (s, 3H), 3.72 (s, 3H), 3.90 (br s, 1H), 5.43 (s, 1H), 6.14 (s, 1H), 6.22 (s, 1H), 6.49 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 7.23-7.37 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 26.67, 55.68, 58.45, 114.59, 114.71, 126.09, 127.39, 127.55, 128.62, 140.93, 141.12, 148.47, 152.25, 199.19.

Compound **2d**: 36%; pale yellow oil; IR (film) 3433, 1674, 1589 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.05 (s, 3H), 2.27 (s, 3H), 2.34 (s, 3H), 3.98 (br s, 1H), 5.54 (s, 1H), 6.13 (s, 1H), 6.22 (s, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 7.22-7.38 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 12.65, 20.71, 26.73, 57.84, 109.14, 119.80, 120.50, 126.02, 126.04, 127.45, 127.62,

128.73, 136.51, 141.23, 144.53, 148.33, 199.21.

Compound **2e**: 32%; pale yellow oil; IR (KBr) 3440, 1670 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.37 (s, 3H), 4.87 (s, 1H), 5.71 (d, *J* = 3.6 Hz, 1H), 6.20 (d, *J* = 1.2 Hz, 1H), 6.24 (s, 1H), 6.43 (dd, *J* = 6.6 and 1.2 Hz, 1H), 7.22-7.47 (m, 8H), 7.77-7.83 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 26.74, 57.95, 105.90, 117.92, 119.88, 123.45, 124.81, 125.72, 126.08, 126.42, 127.55, 127.81, 128.70, 128.82, 134.23, 140.85, 141.58, 147.78, 199.28.

Compound **2f**: 73%; white solid, mp 78-80 °C; IR (KBr) 3398, 1674, 1601, 1504 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.03 (t, *J* = 7.2 Hz, 3H), 2.56-2.84 (m, 2H), 4.13 (br s, 1H), 5.51 (s, 1H), 6.09 (s, 1H), 6.20 (s, 1H), 6.51-6.55 (m, 1H), 6.67-6.73 (m, 1H), 7.10-7.17 (m, 2H), 7.22-7.37 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 8.01, 31.76, 58.10, 113.34, 117.78, 124.57, 127.43, 127.62, 128.69, 129.12, 140.94, 146.71, 147.68, 201.95.

Compound **2g**: 63%; pale yellow oil; IR (KBr) 3398, 1678, 1616, 1520 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.02 (t, *J* = 7.2 Hz, 3H), 2.22 (s, 3H), 2.56-2.84 (m, 2H), 4.02 (br s, 1H), 5.47 (s, 1H), 6.09 (s, 1H), 6.20 (s, 1H), 6.46 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 7.24-7.37 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 8.02, 20.35, 31.77, 58.33, 113.46, 124.54, 126.98, 127.44, 127.56, 128.66, 129.62, 141.11, 144.46, 147.83, 202.02.

Typical procedure for the synthesis of polysubstituted quinoline 6a: A stirred solution of **2a** (251 mg, 1 mmol) in a mixed solvent of PPA (1.0 g) and 1,2-dichloroethane (1 mL) was heated to 70-80 °C for 2 h. The reaction mixture was poured into cold aq NaHCO₃ solution and extracted with ether. The organic layers were washed with water and dried with MgSO₄. To the solution was added a catalytic amounts of DBU (15 mg, 0.1 mmol) and the solvent was removed under reduced pressure by rotary evaporator. During the solvent-removal process complete isomerization toward quinoline occurred. After column chromatographic purification process (hexanes/ether, 10 : 1) we obtained the desired **6a** in 43% yield (101 mg). The corresponding dihydroquinoline derivative **5a** was isolated in a different reaction before treatment with DBU in 42% yield by rapid column purification process. The other quinolines **6b-g** was synthesized in a similar way and the spectroscopic data of **5a** and **6a-g** are as follows. Compound **5a**: 42%; pale yellow solid, mp 87-90 °C; IR (KBr) 1597, 1562, 1493 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.51 (s, 3H), 3.96 (d, *J* = 3.0 Hz, 2H), 7.04-7.15 (m, 3H), 7.19-7.25 (m, 1H), 7.31-7.49 (m, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 23.90, 29.50, 125.92, 126.67, 127.02, 127.35, 127.55, 128.06, 128.39, 129.53, 131.29, 133.24, 135.87, 142.83, 164.78.

Compound **6a**: 43%; pale yellow solid, mp 82-83 °C; IR (KBr) 1601, 1493, 1415 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.64 (s, 3H), 4.13 (s, 2H), 7.12-7.17 (m, 2H), 7.20-7.34 (m, 3H), 7.41-7.47 (m, 1H), 7.60-7.70 (m, 2H), 7.75 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 23.78, 39.37, 125.97, 126.68, 127.28, 127.45, 128.52, 128.86, 129.00, 129.06, 132.93, 136.06, 139.08, 146.87, 159.07.

Compound **6b**: 57%; pale yellow solid, mp 58-60 °C; IR (KBr) 2920, 1604, 1493, 1442 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.48 (s, 3H), 2.61 (s, 3H), 4.11 (s, 2H), 7.12-7.16 (m, 2H), 7.19-7.33 (m, 3H), 7.43-7.47 (m, 2H), 7.66 (s, 1H), 7.90 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 21.45, 23.42, 39.13, 125.95, 126.39, 127.22, 127.96, 128.58, 128.81, 130.98, 132.60, 135.26, 135.44, 138.97, 145.21, 157.78.

Compound **6c**: 47%; white solid, mp 163-165 °C; IR (KBr) 2920, 1604, 1493, 1227 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.61 (s, 3H), 3.87 (s, 3H), 4.11 (s, 2H), 6.96 (d, $J = 2.7$ Hz, 1H), 7.14-7.35 (m, 6H), 7.64 (s, 1H), 7.90 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 23.22, 39.13, 55.44, 104.80, 121.25, 126.42, 128.08, 128.63, 128.91, 129.72, 132.99, 134.83, 138.98, 142.67, 156.09, 157.24.

Compound **6d**: 48%; pale yellow solid, mp 75-77 °C; IR (KBr) 2920, 1616, 1493, 1450, 1427 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.46 (s, 3H), 2.63 (s, 3H), 2.75 (s, 3H), 4.10 (s, 2H), 7.11-7.31 (m, 6H), 7.44 (d, $J = 8.1$ Hz, 1H), 7.67 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.14, 20.67, 23.96, 39.07, 124.03, 125.51, 126.33, 128.54, 128.58, 128.86, 131.14, 133.57, 136.00, 136.31, 139.36, 145.74, 157.48.

Compound **6e**: 67%; pale yellow solid, mp 99-101 °C; IR (KBr) 1601, 1493, 1442 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.74 (s, 3H), 4.18 (s, 2H), 7.15-7.34 (m, 5H), 7.56-7.74 (m, 4H), 7.78 (s, 1H), 7.85-7.88 (m, 1H), 9.30 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 23.66, 39.05, 124.19, 124.91, 125.00, 126.40, 125.75, 126.78, 127.61, 127.69, 128.62, 128.86, 131.21, 133.01, 133.40, 136.05, 139.14, 144.41, 157.23.

Compound **6f**: 53%; pale yellow solid, mp 62-64 °C; IR (KBr) 2970, 1601, 1493 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.31 (t, $J = 7.5$ Hz, 3H), 2.95 (q, $J = 7.5$ Hz, 2H), 4.18 (s, 2H), 7.13-7.18 (m, 2H), 7.23-7.34 (m, 3H), 7.41-7.47 (m, 1H), 7.60-7.70 (m, 2H), 7.76 (s, 1H), 8.04 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.12, 29.10, 38.58, 125.70, 126.42, 127.04, 127.09, 128.52, 128.61, 128.67, 128.85, 132.14, 136.29, 139.39, 146.83, 163.14.

Compound **6g**: 65%; pale yellow oil; IR (film) 2970, 1604, 1493 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.29 (t, $J = 7.5$ Hz, 3H), 2.48 (s, 3H), 2.93 (q, $J = 7.5$ Hz, 2H), 4.15 (s, 2H), 7.12-7.16 (m, 2H), 7.20-7.32 (m, 3H), 7.44-7.48 (m, 2H), 7.66 (s, 1H), 7.93 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.16, 21.46, 28.99, 38.55, 125.92, 126.36, 127.09, 128.18, 128.57, 128.83, 130.90, 132.04, 135.39, 135.73, 139.50, 145.39, 162.12.

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