An Expedient Synthesis of β-Phenyl Substituted Baylis-Hillman and *Aza*-Baylis-Hillman Adducts

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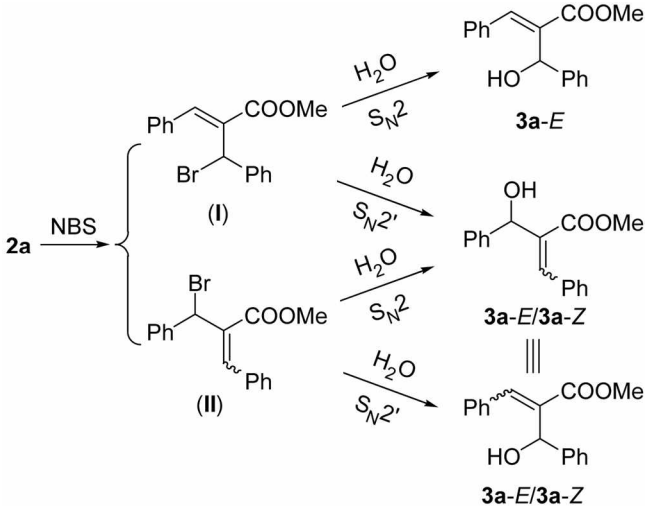
During the last two decades notable improvements in the Baylis-Hillman chemistry have been achieved in view of its reaction rate and synthetic applications of Baylis-Hillman adducts.[1] However, synthesis of β-branched Baylis-Hillman adducts has still remained as a difficult task.[2,3] Synthesis of these compounds has been carried out either *via* the vinylalumination of activated carbonyl compounds[2a-c] or SmI_2-mediated reaction of α-halo-α,β-unsaturated esters with carbonyls.[2d] However, these methods suffer from the use of expensive/moisture-sensitive reagents and α,β-acetylenic esters as starting materials which are not easily accessible.

For the synthesis of poly-substituted benzenes[4a-c] and pyridines[4d] we required β-phenyl Baylis-Hillman adducts such as **3a**. Thus, we examined the synthesis of β-phenyl Baylis-Hillman adduct by following the successive Friedel-Crafts reaction of Baylis-Hillman adduct **1a** to **2a**,[5] bromination at the benzylic position of **2a** with NBS (*N*-bromosuccinimide),[6] and the final substitution reaction with water as a nucleophile,[7] as depicted in Scheme 1.

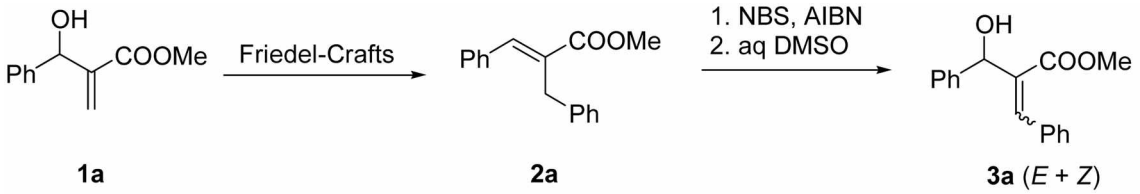
The starting material **2a** (*E*) was prepared according to the reported method by the Friedel-Crafts reaction of **1a** and benzene in the presence of H_2SO_4 in moderate yield (68%).[5] Trace amounts of the corresponding *Z*-isomer was removed during the column separation stage. Bromination of **2a** with NBS in CCl_4 in the presence of AIBN produced the corresponding allylic bromides (**I**) and (**II**) which turned out too unstable to be isolated. The bromide (**II**) was generated via the bromination after allylic rearrangement of the initially generated allylic radical (vide infra, Scheme 2).

During the bromination reaction we observed the formation of trace amounts of **3a**, which might be produced by the substitution reaction of the intermediate bromides with trace amounts of water in the reaction mixture. Thus, we decided to prepare **3a** without isolation of the bromide intermediates. The actual experiment was carried out as follows: bromination of **2a** (NBS, CCl_4, AIBN, reflux, 1 h), filtration, concentration, and followed by the reaction in aqueous DMSO (80 °C, 1 h). By following the procedure we obtained **3a**-*Z* (61%) and **3a**-*E* (21%). The stereochemistry of **3a** could be assigned based on the chemical shift of vinyl proton by comparison with the reported data.[2a-c,3e] The vinyl proton of **3a**-*Z* appeared at $\delta = 6.93$ ppm, while that of the *E*-form at $\delta = 7.97$ ppm. As depicted in Scheme 2, both isomers **3a**-*Z* and **3a**-*E* can be formed by following different pathways due to allylic rearrangement in the bromination stage and the competition between S_N2 and S_N2' pathways in the substitution reaction.[8]

Encouraged by the results we carried out the synthesis of some analogous derivatives **3b-f** and the results are summarized in Table 1. Irrespective of the electron-withdrawing groups (-COOEt, -COMe, -CN) we obtained desired products **3b-d** in moderate yields (53-68%, entries 2-4). However, we could not isolate the minor components (**3c**-*E*

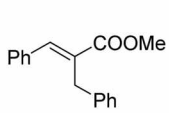
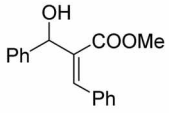
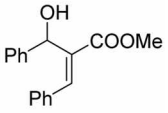
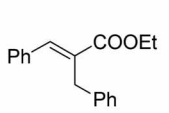
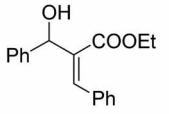
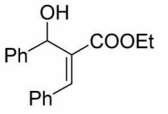
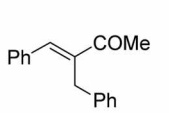
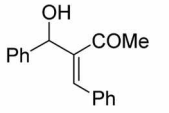
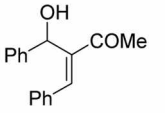
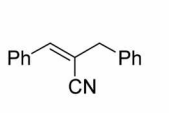
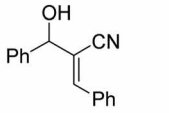
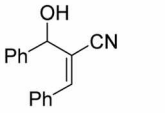
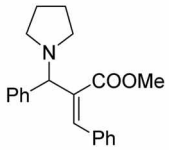
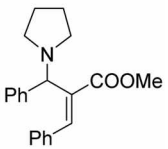
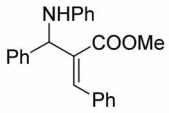
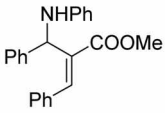


Scheme 2



Scheme 1

Table 1. Synthesis of β-phenyl Baylis-Hillman and *aza*-Baylis-Hillman adducts

Entry	Substrate[a]	Nucleophile	Products (%)	
1	 **2a** (68)	H_2O[b]	 **3a**-*Z* (61)	 **3a**-*E* (21)
2	 **2b** (76)	H_2O[b]	 **3b**-*Z* (60)	 **3b**-*E* (8)
3	 **2c** (52)	H_2O[b]	 **3c**-*Z* (53)	 **3c**-*E* (-)[c]
4	 **2d** (80)	H_2O[b]	 **3d**-*E* (61)	 **3d**-*Z* (-)[c]
5	**2a**	pyrrolidine[d]	 **3e**-*Z* (61)	 **3e**-*E* (11)
6	**2a**	aniline[e]	 **3f**-*Z* (54)	 **3f**-*E* (30)

[a]Prepared by Friedel-Crafts reaction according to the reported method[5] and stereochemically pure compounds were used (*E* for **2a-c** and *Z* for **2d**) and the yield is shown in parenthesis. [b]Conditions: (i) NBS (1.2 equiv), CCl_4, cat AIBN, reflux, 1 h; (ii) filter; (iii) aq DMSO, 80 °C, 1 h. [c]Not isolated. [d]Conditions: (i) NBS (1.2 equiv), CCl_4, cat AIBN, reflux, 1 h; (ii) pyrrolidine (3.0 equiv), rt, 18 h. [e]Conditions: (i) NBS (1.2 equiv), CCl_4, cat AIBN, reflux, 1 h; (ii) aniline (3.0 equiv), rt, 18 h.

and **3d**-*Z*) in the reactions of **2c** and **2d** (entries 3 and 4). When we used amine nucleophiles such as pyrrolidine (entry 5) or aniline (entry 6) instead of water we obtained the corresponding β-phenyl *aza*-Baylis-Hillman adducts **3e** and **3f**,[2e] respectively, in good yields (72-84%).

The reaction was investigated with structurally similar compounds, **2e** and **2f** (Scheme 3). Cinnamyl alcohol **3g** was obtained in 58% from the reaction of α-methyl compound **2e** presumably via the bromination at the benzylic position and the following S_N2' type substitution with water. It is interesting that β-methyl derivative **2f** produced butenolide **4** (57%),[9] which might be formed by the in situ lactonization of the corresponding intermediate γ-hydroxy ester **3h**.

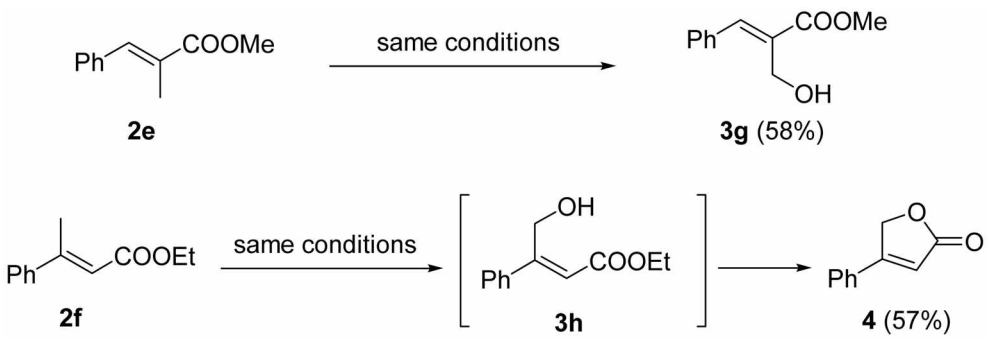
In summary, we disclosed an efficient synthesis of β-phenyl-substituted Baylis-Hillman and *aza*-Baylis-Hillman adducts starting from Baylis-Hillman adducts *via* the reaction sequence comprised of the Friedel-Crafts reaction, allylic bromination and nucleophilic substitution reaction. Further studies on the synthetic applications of β-phenyl Baylis-Hillman adducts are currently underway.

Experimental Section

Typical procedure for the synthesis of 3a: A stirred mixture of **2a** (252 mg, 1.0 mmol), NBS (214 mg, 1.2 mmol), AIBN (17 mg) in carbon tetrachloride (4 mL) was heated to reflux for 1 h. After filtering off some solid materials and removal of solvent the residue was dissolved in aqueous DMSO (3 mL) and maintained 80 °C for 1 h with stirring. After usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 6:1) we obtained **3a**-*Z* (164 mg, 61%) and **3a**-*E* (57 mg, 21%) as colorless oils. Other compounds were prepared similarly and the spectroscopic data of prepared compounds **3a-f** and **4** are as follows.

Compound **3a**-*Z*:[3e] 61%; colorless oil; IR (film) 3479, 1718, 1435, 1227, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.05 (br s, 1H), 3.53 (s, 3H), 5.60 (s, 1H), 6.93 (s, 1H), 7.23-7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.68, 75.62, 126.56, 127.99, 128.17, 128.34, 128.39, 128.51, 135.20, 135.25, 135.40, 140.92, 169.09.

Compound **3a**-*E*: 21%; colorless oil; IR (film) 3510, 1697, 1250, 1103 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s,



Scheme 3

3H), 4.06 (d, J = 11.4 Hz, 1H), 5.88 (d, J = 11.4 Hz, 1H), 7.23-7.43 (m, 10H), 7.97 (s, 1H); ^{1}H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 3.75 (s, 3H), 5.87 (s, 1H), 7.24-7.43 (m, 10H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.07, 69.73, 125.44, 127.26, 128.42, 128.69, 129.10, 129.23, 132.37, 134.20, 141.85, 142.67, 168.02; ESIMS m/z 269 (M^++1). Anal Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.34; H, 6.29.

Compound **3b-*Z***:[2a-c] 60%; colorless oil; IR (film) 3450, 1711, 1225, 1097, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.2 Hz, 3H), 3.07 (d, J = 5.7 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 5.59 (d, J = 5.7 Hz, 1H), 6.94 (s, 1H), 7.25-7.46 (m, 10H).

Compound **3b-*E***: 8%; colorless oil; IR (film) 3510, 1691, 1628, 1246, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 4.05 (d, J = 11.7 Hz, 1H), 4.13-4.26 (m, 2H), 5.87 (d, J = 11.7 Hz, 1H), 7.24-7.43 (m, 10H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.05, 61.11, 69.72, 125.41, 127.20, 128.38, 128.68, 129.11, 129.16, 132.72, 134.31, 141.60, 142.84, 167.60; ESIMS m/z 283 (M^++1).

Compound **3c-*Z***: 53%; colorless oil; IR (film) 3429, 1684, 1493, 1188, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80 (s, 3H), 3.20 (d, J = 5.1 Hz, 1H), 5.57 (d, J = 5.1 Hz, 1H), 6.93 (s, 1H), 7.20-7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.49, 76.26, 126.41, 127.94, 128.57, 128.59, 128.65 (2C), 132.37, 135.46, 140.99, 144.88, 207.91; ESIMS m/z 253 (M^++1). Anal Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.78; H, 6.26.

Compound **3d-*E***:[3a-d] 61%; colorless oil; IR (film) 3442, 2216, 1495, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66 (br s, 1H), 5.46 (s, 1H), 7.33-7.48 (m, 9H), 7.74-7.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 75.57, 114.29, 117.19, 126.46, 128.81, 128.85, 128.91, 129.07 130.57, 132.94, 139.86, 142.68; ESIMS m/z 236 (M^++1).

Compound **3e-*Z***: 61%; colorless oil; IR (film) 2951, 1726, 1493, 1238, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.76-1.80 (m, 4H), 2.42-2.45 (m, 2H), 2.64-2.67 (m, 2H), 3.51 (s, 3H), 4.14 (s, 1H), 7.16 (s, 1H), 7.21-7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.51, 51.52, 53.20, 73.65, 127.89, 128.05, 128.15, 128.21, 128.24, 128.26, 133.19, 135.99, 139.98, 140.79, 169.44; ESIMS m/z 322 (M^++1).

Compound **3e-*E***: 11%; colorless oil; IR (film) 2951, 1716, 1493, 1238, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.72-1.76 (m, 4H), 2.46-2.55 (m, 4H), 3.73 (s, 3H), 4.68 (s, 1H), 7.13-7.25 (m, 3H), 7.33-7.42 (m, 5H), 7.50-7.53 (m, 2H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.50, 51.83, 52.86, 66.86, 126.75, 127.73, 128.19, 128.21 (2C), 129.48, 135.20, 135.48, 140.61, 141.53, 167.95; ESIMS m/z 322 (M^++1).

Compound **3f-*Z***: 54%; pale yellow oil; IR (film) 3446, 1699, 1680, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.53 (s, 3H), 4.27 (br s, 1H), 5.41 (s, 1H), 6.66-6.74 (m, 3H), 6.92 (s, 1H), 7.07-7.45 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.72, 61.66, 113.52, 118.03, 127.70, 127.99, 128.12, 128.15, 128.28, 128.82, 129.19, 133.85, 134.29, 135.48, 139.89, 146.62, 169.32; ESIMS m/z 344 (M^++1). Anal Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.67; H, 6.05; N, 3.93.

Compound **3f-*E***: 30%; pale yellow oil; IR (film) 3423, 1682, 1493, 1188 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H), 5.17 (br s, 1H), 5.91 (s, 1H), 6.37-6.41 (m, 2H), 6.62-6.68 (m, 1H), 7.02-7.09 (m, 2H), 7.22-7.43 (m, 10H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.88, 53.99, 113.42, 117.59, 126.44, 127.05, 128.44, 128.74, 128.91, 129.08, 129.21, 132.17, 134.82, 141.20, 141.72, 146.82, 167.26; ESIMS m/z 344 (M^++1).

Compound **4**:[9c] 57%; white solid, mp 90-91 °C; IR (film) 1732, 1450, 1167, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.23 (d, J = 1.8 Hz, 2H), 6.38 (t, J = 1.8 Hz, 1H), 7.44-7.55 (m, 5H).

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