Facile One-Pot Synthesis of Poly-substituted Phenols from Baylis-Hillman Adducts *via* [4+2] Annulation Protocol

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Regioselective synthesis of poly-substituted phenol derivatives is important in organic synthesis due to the abundance of phenol compounds in nature and their biological activity.[1-3] Various synthetic approaches of poly-substituted phenols have been reported including the use of Baylis-Hillman adducts.[3] The synthesis of phenols from Baylis-Hillman adducts was carried out very recently by using either [3+3][3a] or [3+1+2] annulation protocols.[3b]

Our recent studies on the synthesis of α-pyrones[4] have enabled us to prepare poly-substituted phenols when we used the Baylis-Hillman adduct of methyl vinyl ketone and deoxybenzoin derivatives *via* [4+2] annulation protocol as shown in Scheme 1. The Baylis-Hillman acetate **1a** and deoxybenzoin (**2a**) provide 4-carbons and 2-carbons, respectively, for the final phenol product **5a**.

As expected, to our delight, we obtained 4,5-diarylphenol **5a** in 87% yield in a one-pot from the reaction of **1a** and deoxybenzoin (**2a**) in DMF in the presence of K_2CO_3 (3.0 equiv) at 110-120 °C within 1 h (entry 1 in Table 1, vide infra). When we run the reaction of **1a** and **2a** at room temperature (K_2CO_3, DMF, 5 h), we obtained **3a** in 78% yield as *E*-form.[3-5] The reaction of **3a** under elevated temperature (K_2CO_3, DMF, 110-120 °C, 1 h) gave **5a** in 85% yield. From the experimental observations the reaction mechanism can be regarded as in Scheme 1 involving the first S_N2' reaction followed by sequential aldol reaction, dehydration, double bond isomerization and keto-enol tautomerization processes.

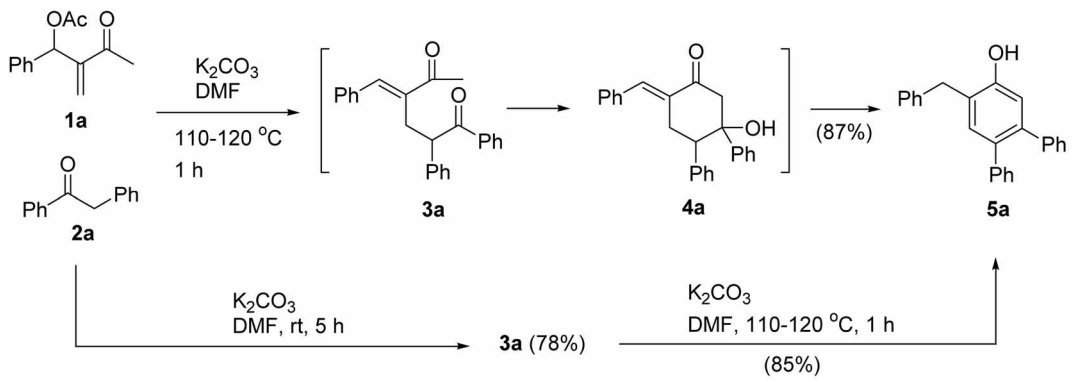
Encouraged by the results we examined the reactions of Baylis-Hillman acetates **1a-c**[3a,3b,5] and diaryl ketones **2b-d**[6] or monoaryl ketone **2e**, **2f**, and the results are summarized in Table 1. The reactions of **1a** and **2b-d** afforded the corresponding diaryl phenols **5b-d** in 52-82% yields (entries 2-4). The reaction of **1a** and propiophenone (**2e**) also produced **5e** in good yield (71%, entry 5). The reaction of **1a** and acetophenone (**2f**) also produced desired compound **5f** (47%, entry 6). The reaction of **1b** and **2a** gave penta-substituted phenol **5g** in 78% (entry 7). The reaction of **1c** and **2a** required longer reaction time (5 h) than for other entries, and we isolated **5h** in 48% yield (entry 8).

However, the reaction of **1a** and **2g**[6b] was failed completely to produce the corresponding phenol compound **5i** (Scheme 2). In the reaction, we obtained **3i** (the S_N2' product) in 79% yield and this compound was not converted to **5i** presumably due to the increased steric hindrance around the benzoyl moiety.

In summary we disclosed an efficient synthetic procedure for poly-substituted phenol derivatives starting from the Baylis-Hillman adducts. The reaction afforded phenol derivatives regioselectively in moderate to good yields in a one-pot from the readily available starting materials.

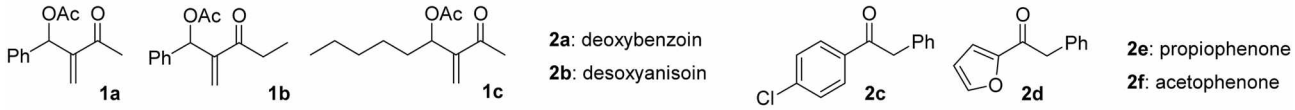
Experimental Section

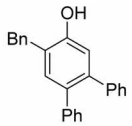
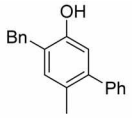
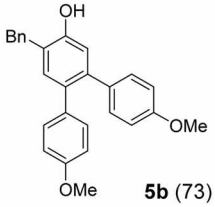
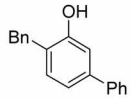
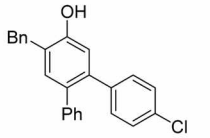
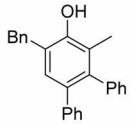
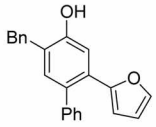
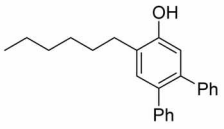
Typical procedure for the synthesis of compound 5a: To a stirred solution of **1a** (218 mg, 1.0 mmol) and deoxybenzoin (**2a**, 196 mg, 1.0 mmol) in DMF (2 mL) was added K_2CO_3 (415 mg, 3.0 mmol) and the reaction mixture was heated to 110-120 °C for 1 h. After the usual aqueous workup and column chromatographic purification process



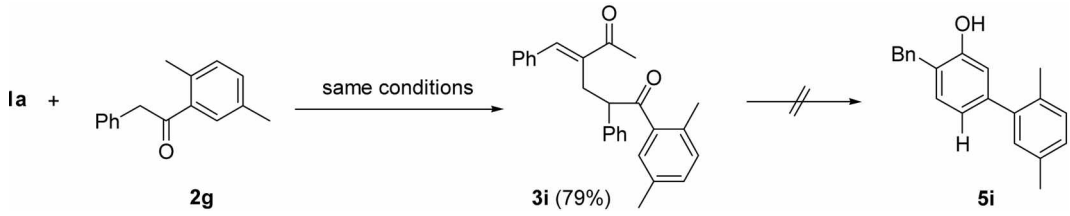
Scheme 1

Table 1. Synthesis of poly-substituted phenols[a]



Entry	Substrate	Product (%)	Entry	Substate	Product (%)
1	**1a** + **2a**	 **5a** (87)	5	**1a** + **2e**	 **5e** (71)
2	**1a** + **2b**	 **5b** (73)	6[b]	**1a** + **2f**	 **5f** (47)[c]
3	**1a** + **2c**	 **5c** (82)	7	**1b** + **2a**	 **5g** (78)
4	**1a** + **2d**	 **5d** (52)[c]	8[d]	**1c** + **2a**	 **5h** (48)[c]

[a]Conditions: Baylis-Hillman acetate **1** (1.0 mmol), ketone **2** (1.0 mmol), DMF, K_2CO_3 (3.0 mmol), 110-120 °C, 1-2 h. [b]Acetophenone (2.0 equiv) was used. [c]Intractable side products formed. [d]Reaction time is 5 h.



Scheme 2

(hexanes/EtOAc, 15:1) we obtained compound **5a** (293 mg, 87%) as a pale yellow solid. The spectroscopic data of prepared compounds **3a**, **3i** and **5a-h** are as follows.

Compound **3a**: 78%; colorless oil; IR (film) 1680, 1664, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 3.15-3.29 (m, 2H), 4.91 (dd, J = 9.0 and 6.0 Hz, 1H), 6.99-7.03 (m, 2H), 7.04-7.07 (m, 2H), 7.09-7.14 (m, 3H), 7.27-7.36 (m, 5H), 7.40-7.44 (m, 1H), 7.46 (s, 1H), 7.85-7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.16, 30.03, 51.50, 126.94, 128.28, 128.34, 128.38, 128.50, 128.58, 128.69, 128.74, 132.72, 135.37, 136.53, 138.42, 139.92, 142.32, 199.49, 200.65; ESIMS m/z 355 (M^++1).

Compound **3i**: 79%; colorless oil; IR (film) 1685, 1666, 1491, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 3H), 2.25 (s, 3H), 2.34 (s, 3H), 3.24-3.27 (m, 2H), 4.71 (dd, J = 8.7 Hz and 6.6 Hz, 1H), 6.92-6.97 (m, 3H), 7.02-7.13 (m, 6H), 7.20-7.21 (m, 1H), 7.31-7.35 (m, 3H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.17, 20.86, 26.10, 29.40, 54.31, 126.89, 128.29, 128.38 (2C), 128.57, 128.63, 128.74, 131.29, 131.44, 134.63, 134.74, 135.45, 137.60, 138.33, 140.08, 141.88, 200.55, 203.71; ESIMS m/z 383 (M^++1).

Compound **5a**: 87%; pale yellow solid, mp 106-108 °C; IR (film) 3531, 1601, 1493, 1481, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.06 (s, 2H), 5.01 (br s, 1H), 6.84 (s, 1H), 7.05-7.33 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.15, 117.68, 126.02, 126.28, 126.37, 126.46, 127.76, 127.82, 128.65, 128.75, 129.74, 129.93, 133.17, 133.32, 139.84, 140.03, 141.02, 141.17, 153.04; ESIMS m/z 337 (M^++1). Anal Calcd for $C_{25}H_{20}O$: C, 89.25; H, 5.99. Found: C, 89.03; H, 6.12.

Compound **5b**: 73%; white solid, mp 42-44 °C; IR (film) 3529, 3410, 3028, 2935, 1608, 1493, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H), 3.77 (s, 3H), 4.04 (s, 2H),

4.79 (s, 1H), 6.72-6.77 (m, 4H), 6.80 (s, 1H), 6.97-7.05 (m, 4H), 7.15 (s, 1H), 7.18-7.25 (m, 1H), 7.30 (d, J = 4.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.19, 55.15 (2C), 113.30, 113.34, 117.58, 125.82, 126.38, 128.66, 128.73, 130.76, 130.89, 132.88, 133.12, 133.56, 133.77, 139.53, 139.87, 152.74, 157.93, 158.23; ESIMS m/z 397 (M^++1). Anal Calcd for $C_{27}H_{24}O_3$: C, 81.79; H, 6.10. Found: C, 81.87; H, 6.22.

Compound **5c**: 82%; pale yellow solid, mp 123-125 °C; IR (film) 3437, 1614, 1481, 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.06 (s, 2H), 4.82 (s, 1H), 6.81 (s, 1H), 7.01-7.08 (m, 4H), 7.14-7.25 (m, 7H), 7.30-7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.23, 117.54, 126.26, 126.51, 126.59, 127.96, 128.08, 128.71, 128.74, 129.90, 131.00, 132.58, 133.34, 133.39, 138.76, 139.46, 139.57, 140.81, 153.10; ESIMS m/z 371 (M^++1).

Compound **5d**: 52%; pale yellow solid, mp 58-60 °C; IR (film) 3533, 3390, 2924, 1485, 1261, 1230, 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.02 (s, 2H), 4.82 (br s, 1H), 5.55 (d, J = 3.3 Hz, 1H), 6.20 (dd, J = 3.6 and 1.8 Hz, 1H), 7.06 (s, 1H), 7.19-7.36 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.14, 108.89, 111.24, 113.82, 126.24, 126.41, 126.89, 128.21, 128.67 (2C), 128.81, 129.37, 132.37, 133.39, 139.67, 141.26, 141.68, 152.39, 153.07; ESIMS m/z 327 (M^++1).

Compound **5e**: 71%; sticky oil; IR (film) 3527, 2924, 1489, 1452, 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 4.00 (s, 2H), 4.66 (br s, 1H), 6.67 (s, 1H), 7.00 (s, 1H), 7.18-7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.45, 36.07, 117.06, 125.89, 126.31, 126.75, 127.48, 128.02, 128.63, 128.72, 129.08, 132.72, 140.06, 141.19, 141.48, 151.45; ESIMS m/z 275 (M^++1).

Compound **5f**: 47%; sticky oil; IR (film) 3533, 3417, 2924, 1570, 1489, 1410, 1228 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.03 (s, 2H), 4.80 (br s, 1H), 7.02 (d, J = 1.5 Hz, 1H), 7.11-7.35 (m, 8H), 7.41 (t, J = 7.2 Hz, 2H), 7.55 (d, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.13, 114.42, 119.73, 126.03, 126.42, 126.94, 127.29, 128.69, 128.71 (2C), 131.28, 139.74, 140.57, 141.14, 153.95; ESIMS m/z 261 (M^-+1).

Compound **5g**: 78%; pale yellow solid, mp 86-88 °C; IR (film) 3570, 3059, 3026, 1601, 1493, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (s, 3H), 4.07 (s, 2H), 4.76 (s, 1H), 6.98-7.03 (m, 4H), 7.05-7.09 (m, 4H), 7.15-7.26 (m, 4H), 7.32-7.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.67, 36.94, 122.35, 125.31, 125.64, 126.30, 126.54, 127.36, 127.63, 128.76 (2C), 129.78, 129.92, 130.65, 134.13, 139.60, 140.14, 140.23, 141.98, 151.53; ESIMS m/z 351 (M^++1).

Compound **5h**: 48%; pale yellow solid, mp 80-82 °C; IR (film) 3417, 2954, 2925, 1481, 1223 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 6.9 Hz, 3H), 1.30-1.46 (m, 6H), 1.63-1.71 (m, 2H), 2.67 (t, J = 7.5 Hz, 2H), 4.80 (br s, 1H), 6.84 (s, 1H), 7.08-7.21 (m, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.10, 22.62, 29.33, 29.73, 29.83, 31.74, 117.14, 125.99, 126.40, 127.76, 127.81, 127.84, 129.77, 129.95, 132.47, 133.22, 139.26, 141.11, 141.37, 152.72; ESIMS m/z 331 (M^++1).

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References and Notes

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6. The starting materials were purchased from the commercial sources (**2a-c**, **2e**, **2f**) or synthesized easily by the Friedel-Crafts acylation of the corresponding acid chlorides and arenes (**2d**[6a] and **2g**[6b]). (a) Inaba, S.-i.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373-1381. (b) Kim, T. Y.; Kim, H. S.; Chung, Y. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2000**, *21*, 673-674.