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Regioselective synthesis of polysubstituted phenol derivatives from Baylis–Hillman adducts via [3+3] annulation strategy

Da Yeon Park,[a] Seong Jin Kim,[a] Taek Hyeon Kim[b] and Jae Nyoung Kim[a,*]

[a]*Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea*
[b]*Department of Applied Chemistry, Chonnam National University, Gwangju 500-757, Republic of Korea*

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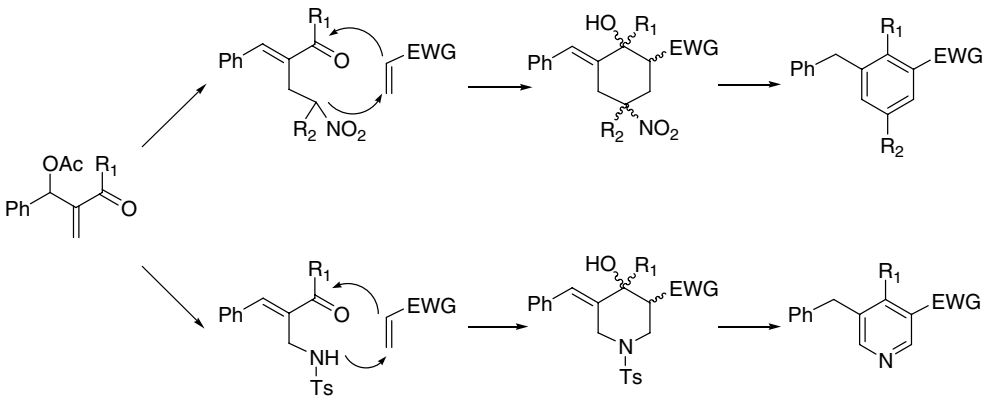
Abstract—Polysubstituted phenol derivatives were synthesized from the acetates of Baylis–Hillman adducts and dimethyl 1,3-acetonedicarboxylate (DMAD) in a one-pot reaction via the sequential S_N2' reaction, aldol condensation, and 1,3-H shift process.

Due to the importance of phenol derivatives in pharmacologically important molecules and their usefulness as synthetic intermediates, much attention has been focused on their synthesis.[1–3] A variety of methods have been examined including palladium-catalyzed enyne–diyne cross-benzannulation,[1b] cycloaddition of Fischer carbenes with alkynes,[1c] and stepwise construction method of benzene ring of phenol by condensation as the key reaction.[1a,d,2]

Recently, we reported the synthesis of polysubstituted benzenes and pyridines starting from the Baylis–Hillman adducts.[4a–c] These valuable compounds were prepared from the Baylis–Hillman acetate by the sequential S_N2' reaction with tosylamide or primary nitroalkane, Michael addition, aldol condensation, elimination of TsH or HNO_2, and the final aromatization process (Scheme 1).[4a–c] In the reactions, the Baylis–Hillman adducts served as 1,3-dielectrophilic components. In order to make a six-membered ring compound, a 1,3-dinucleophilic component is needed. In the previous two cases, the combinations of tosylamide/Michael acceptor or primary nitroalkane/Michael acceptor served the roles of 1,3-dinucleophilic components (Scheme 1).

Thus, when we used certain 1,3-dinucleophilic reagents we could make the six-membered ring directly via the



Scheme 1.

Keywords: Phenols; Baylis–Hillman adducts; Dimethyl 1,3-acetonedicarboxylate; 1,3-Dinucleophile.
* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389; e-mail: kimjn@chonnam.ac.kr

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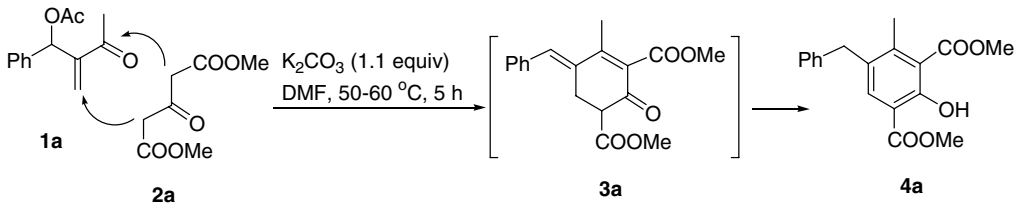
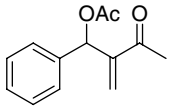
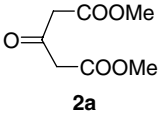
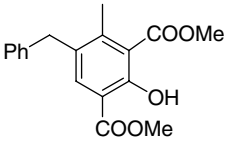
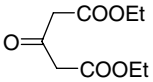
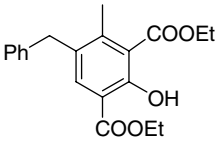
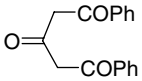
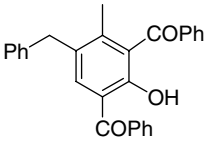
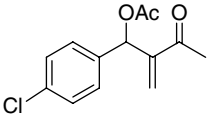
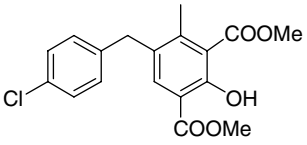
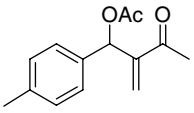
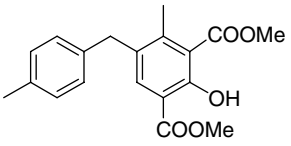
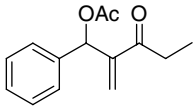
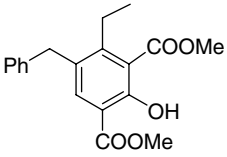
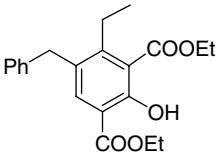
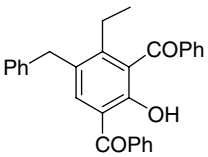


Scheme 2.

[3+3] annulation strategy. As a suitable 1,3-dinucleophilic component, we chose dimethyl 1,3-acetonedicarboxylate (**2a**)[5] and tried the reaction with the Baylis–Hillman acetate **1a** as shown in Scheme 2. To our delight, the reaction of **1a** and **2a** in the presence of K_2CO_3 (1.1 equiv) in DMF at 50–60 °C afforded the

Table 1. Synthesis of phenol derivatives **4a**–**h**

Entry	B–H acetate	1,3-Dinucleophile	Product[a] (%)	
1	 **1a**	 **2a**		**4a** (49)
2	**1a**	 **2b**		**4b** (48)
3	**1a**	 **2c**		**4c** (54)
4	 **1b**	**2a**		**4d** (59)
5	 **1c**	**2a**		**4e** (45)
6	 **1d**	**2a**		**4f** (49)
7	**1d**	**2b**		**4g** (46)
8	**1d**	**2c**		**4h** (40)

[a] Conditions: **1a**–**d** (1.0 equiv), **2a**–**c** (1.1 equiv), K_2CO_3 (1.1 equiv), DMF, 50–60 °C, 5 h.

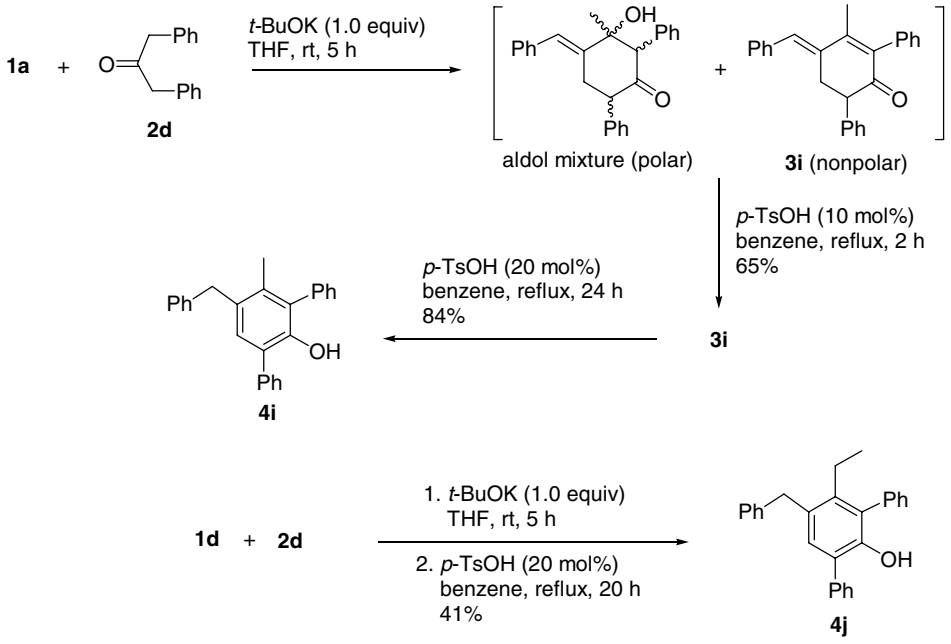
expected polysubstituted phenol derivative **4a** directly in 49% yield.[6] This compound **4a** was definitively formed via the sequential S_N2', aldol-type cyclization, dehydration, keto-enol tautomerization, and 1,3-H shift process.[4a–c] The use of other bases did not show better yields (45% of **4a** with Cs_2CO_3/DMF/50–60 °C, 29% of **4a** with TBAF/THF/reflux). We felt that this method for the synthesis of polysubstituted phenols was interesting and valuable although the yield was moderate when we consider the simplicity of the reaction conditions including one-pot reaction, easily available starting materials, and mild conditions.

Encouraged by the successful results, we examined the reactions with a variety of combinations, and the results are summarized in Table 1. As shown in entries 2 and 3, the reaction of **1a** and diethyl 1,3-acetonedicarboxylate (**2b**) and 1,5-diphenyl-1,3,5-triketone (**2c**) gave the corresponding phenol derivatives **4b** and **4c** in 48% and 54% yields, respectively. The modifications of the structure of the Baylis–Hillman adducts (**1a**–**d**) did not change the reaction progress and all the trials afforded similar results as in entries 4–8.

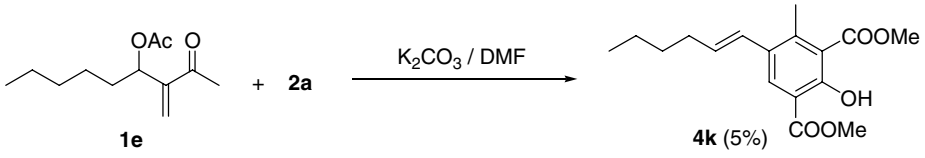
As a next step, we tried the reaction of **1a** and 1,3-diphenylacetone (**2d**). The use of the same conditions (K_2CO_3, DMF) showed almost no reaction. When we replaced the conditions to *t*-BuOK/THF we observed the formation of many components on TLC. A mixture of diastereomeric aldol products were positioned at the polar region, while the single component (**3i**, vide infra) at the non-polar region (Scheme 3). When we subjected the mixtures (after workup) under typical dehydration conditions (*p*-TsOH, benzene, reflux), we found the conversion of polar components (aldol mixtures) to the non-polar component, which was found as the dehydration product **3i**. We also found that the dehydration compound **3i** could be changed to the final phenol compound **4i** slowly by heating under the same conditions. Similarly, we synthesized phenol **4j** from the reaction of **1d** and **2d** according to the same procedures. It is interesting to note that 2,6-diarylphenol derivatives **4i** and **4j** could be prepared by a two-step reaction in moderate yields without the assistance of metal chemistry.[7]

Trials for the synthesis of phenol derivatives having an alkyl group at the 4-position instead of the benzyl group failed. When we examined the reaction of **2a** and the Baylis–Hillman acetate **1e**, derived from hexanal and MVK, we could not obtain the corresponding 4-hexylphenol derivative at all (Scheme 4). The reaction showed a very complex nature on TLC and we could isolate only **4k** in small amounts (5%).[8]

In summary, we suggest the synthesis of polysubstituted phenol derivatives from the reaction between the acetates of the Baylis–Hillman adduct and some 1,3-dinucleophilic components including dimethyl 1,3-



Scheme 3.



Scheme 4.

acetonedicarboxylate (DMAD) in a one-pot reaction via the sequential S_N2' reaction, aldol condensation, and 1,3-H shift process.

Acknowledgments

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5. Acetone dicarboxylate has been used as a three-carbon unit in many reactions, see: (a) Chung, J. Y. L.; Cai, C.; McWilliams, J. C.; Reamer, R. A.; Dormer, P. G.; Cvetovich, R. J. *J. Org. Chem.* **2005**, *70*, 10342; (b) Covarrubias-Zuniga, A.; Rios-Barrios, E. *J. Org. Chem.* **1997**, *62*, 5688; (c) Funk, R. L.; Fitzgerald, J. F.; Olmstead, T. A.; Para, K. S.; Wos, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8849.
6. Typical experimental procedure of **4a**: To a stirred solution of the Baylis–Hillman acetate **1a** (218 mg, 1.0 mmol) and dimethyl 1,3-acetonedicarboxylate (192 mg, 1.1 mmol) in DMF (3 mL) was added K_2CO_3 (152 mg, 1.1 mmol) and heated to 50–60 °C for 5 h. After usual aqueous extractive workup and column chromatographic purification process (hexanes/ether, 15:1), we obtained **4a** as a white solid, 154 mg (49%). The other compounds were synthesized analogously and the spectroscopic data of prepared compounds **4a–k** and **3i** are as follows.
Compound **4a**: 49%; white solid, mp 93–94 °C; IR (film) 3148, 2954, 1736, 1678, 1620, 1442, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.16 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 3.95 (s, 2H), 7.05–7.30 (m, 5H), 7.67 (s, 1H), 10.95 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.20, 38.83, 52.35, 52.41, 110.29, 124.44, 126.22, 128.35, 128.52, 130.22, 131.93, 139.52, 142.63, 157.05, 168.08, 170.05; LC–MS m/z 314 (M^+).
Compound **4b**: 48%; colorless oil; IR (film) 3147, 2981, 1732, 1670, 1458, 1246, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (t, $J = 7.2$ Hz, 6H), 2.16 (s, 3H), 3.95 (s, 2H), 4.37 (q, $J = 7.2$ Hz, 2H), 4.41 (q, $J = 7.2$ Hz, 2H), 7.05–7.29 (m, 5H), 7.68 (s, 1H), 11.03 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.01, 14.11, 16.96, 38.76, 61.37, 61.46, 110.43, 124.67, 126.08, 128.22, 128.39, 129.89, 131.75, 139.52, 142.23, 157.00, 167.55, 169.60; LC–MS m/z 342 (M^+).
Compound **4c**: 54%; colorless oil; IR (film) 3059, 2924, 1674, 1620, 1450, 1342, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 3H), 3.95 (s, 2H), 7.07–7.93 (m, 16H), 12.09 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.03, 38.53, 116.79, 126.20, 128.22, 128.35, 128.49, 128.69, 129.05, 129.32, 130.02, 130.17, 131.93, 133.74, 134.91, 136.89, 137.38, 139.34, 143.46, 158.62, 197.08, 200.73.
Compound **4d**: 59%; colorless oil; IR (film) 3143, 2954, 1736, 1678, 1439, 1246, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.14 (s, 3H), 3.90 (s, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 7.00 (d, $J = 8.7$ Hz, 2H), 7.22 (d, $J = 8.7$ Hz, 2H), 7.64 (s, 1H), 10.99 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.07, 38.05, 52.32, 52.33, 110.24, 124.46, 128.50, 129.58 (2C), 131.71, 131.87, 137.94, 142.37, 157.05, 167.83, 169.85.
Compound **4e**: 45%; white solid, mp 147–148 °C; IR (film) 3147, 2954, 1736, 1678, 1439, 1246,1203 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.16 (s, 3H), 2.31 (s, 3H), 3.90 (s, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 6.95 (d, $J = 8.1$ Hz, 2H), 7.07 (d, $J = 8.1$ Hz, 2H), 7.67 (s, 1H), 10.94 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.20, 20.95, 38.42, 52.34, 52.41, 110.27, 124.40, 128.22, 129.19, 130.48, 131.87, 135.73, 136.45, 142.63, 156.99, 168.12, 170.08.
Compound **4f**: 49%; colorless oil; IR (film) 3147, 2954, 1736, 1678, 1442, 1242, 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.08 (t, $J = 7.5$ Hz, 3H) 2.57 (q, $J = 7.5$ Hz, 2H), 3.88 (s, 3H), 3.93 (s, 3H), 3.97 (s, 2H), 7.06–7.29 (m, 5H), 7.66 (s, 1H), 10.95 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.62, 24.39, 37.79, 52.29 (2C), 110.42, 124.00, 126.17, 128.34, 128.44, 129.48, 132.56, 140.12, 148.20, 156.99, 168.06, 169.94; LC–MS m/z 328 (M^+).
Compound **4g**: 46%; colorless oil; IR (film) 3086, 2981, 1732, 1670, 1454, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.08 (t, $J = 7.5$ Hz, 3H), 1.36 (t, $J = 7.0$ Hz, 3H), 1.38 (t, $J = 7.0$ Hz, 3H), 2.57 (q, $J = 7.5$ Hz, 2H), 3.98 (s, 2H), 4.35 (q, $J = 7.0$ Hz, 2H), 4.42 (q, $J = 7.0$ Hz, 2H), 7.07–7.29 (m, 5H), 7.66 (s, 1H), 11.00 (s, 1H, OH); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 14.03, 14.12, 14.63, 24.26, 37.84, 61.34, 61.45, 110.68, 124.36, 126.12, 128.30, 128.39, 129.23, 132.48, 140.22, 147.92, 157.07, 167.58, 169.56; LC–MS *m*/*z* 356 (M^+).

Compound **4h**: 40%; colorless oil; IR (film) 3059, 2974, 1670, 1601, 1450, 1342, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.03 (t, $J = 7.5$ Hz, 3H), 2.52 (q, $J = 7.5$ Hz, 2H), 3.98 (s, 2H), 7.09–7.94 (m, 16H), 12.05 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.71, 24.08, 37.61, 116.98, 126.29, 128.26, 128.57 (2C), 128.68, 129.14, 129.45, 129.63, 129.68, 131.98, 133.71, 135.81, 137.20, 137.45, 140.08, 149.34, 158.65, 196.93, 200.71.

Compound **4i**: yellow solid, mp 125–127 °C; IR (film) 3537, 3028, 1604, 1493, 1458, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.96 (s, 3H), 4.02 (s, 2H), 4.87 (s, 1H, OH) 7.14-7.58 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.14, 39.50, 125.32, 125.88, 127.03, 127.95, 128.39 (2C), 128.62, 129.21, 129.27, 129.35, 130.40, 131.18, 131.32, 135.20, 136.31, 138.01,140.70, 148.13.

Compound **4j**: white solid, mp 67–68 °C; IR (film) 3537, 2970, 1601, 1493, 1454, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, $J = 7.2$ Hz, 3H), 2.41 (q, $J = 7.2$ Hz, 2H), 4.05 (s, 2H), 4.77 (s, 1H, OH), 7.11–7.57 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.87, 23.38, 38.47, 125.43, 125.89, 126.97, 128.02, 128.32, 128.35, 128.66, 129.00, 129.09, 129.24, 130.41, 130.55, 131.98, 135.96, 138.00, 141.12, 141.33, 148.25.

Compound **4k**: 5%; colorless oil; IR (film) 3169, 2955, 1737, 1678, 1441, 1244, 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.26–1.52 (m, 4H), 2.18–2.23 (m, 2H), 2.27 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 5.99 (dt, $J = 15.6$ and 7.2 Hz, 1H), 6.43 (d, $J = 15.6$ Hz, 1H), 7.87 (s, 1H), 10.94 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.93, 17.34, 22.25, 31.49, 32.86, 52.39, 52.44, 110.55, 123.83, 126.04, 128.00, 129.79, 133.38, 140.56, 157.00, 168.10, 170.14.

Compound **3i**: white solid, mp 117–120 °C; IR (film) 3028, 1666, 1493, 1442, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.08 (s, 3H), 3.29–3.45 (m, 2H), 3.87 (dd, $J = 9.0$ and 6.0 Hz, 1H), 7.10–7.40 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.37, 33.63, 52.35, 126.89, 127.26, 127.59, 127.91, 128.08, 128.34, 128.45, 129.07, 129.95, 131.94, 135.91, 136.59, 136.70, 138.26, 138.89, 150.34, 97.28.

7. For the synthesis of 2,6-diarylphenol derivatives, see: (a) Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 5365; (b) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943.
8. Compound **4k** might be generated via the air oxidation during the corresponding intermediate stage. As we and others reported the major pathway might be the formation of cyclohexene derivatives, which could be formed by the elimination of acetic acid from **1e** and concomitant Diels–Alder reaction.[4g,h]