Synthesis of Poly-Substituted Phenols from Baylis-Hillman Adducts and 1,3-Dinitroalkanes

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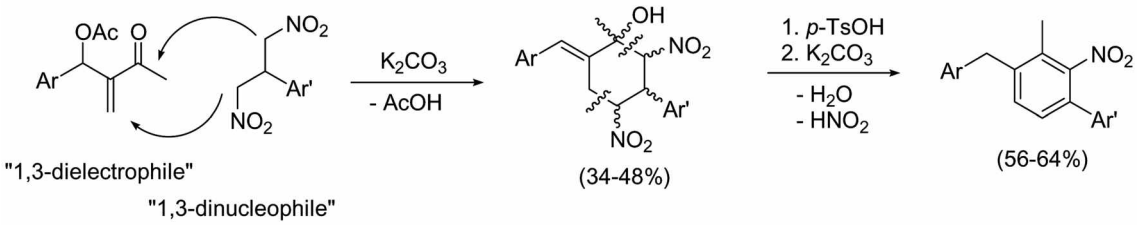
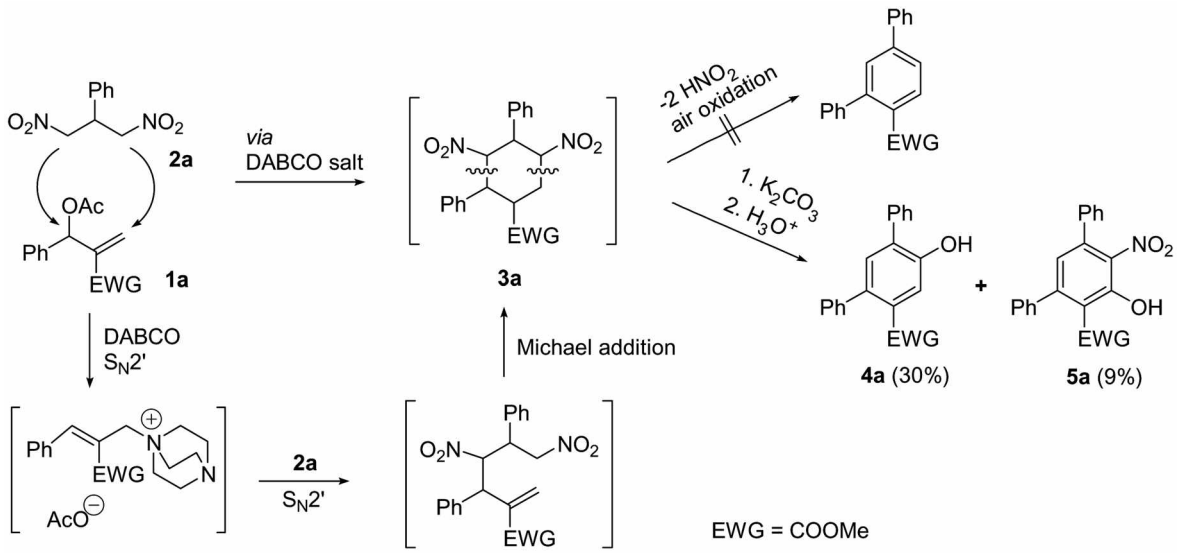
Recently various aromatic and hetero-aromatic compounds have been synthesized starting from the Baylis-Hillman adducts including poly-substituted benzenes,[1a,b] phenols,[1c,d] naphthalenes,[1e] and pyridines.[1f] Very recently we reported the synthesis of poly-substituted nitrobenzenes from the Baylis-Hillman adducts of methyl vinyl ketone (Scheme 1).[2] In the synthesis, the Baylis-Hillman adducts served as 1,3-dielectrophilic three-carbon components and 1,3-dinitroalkanes as 1,3-dinucleophilic components. The reaction between the two components could provide poly-substituted nitrobenzene derivatives as shown in Scheme 1.[2]

During the project we examined the introduction of 1,3-dinitroalkane derivative **2a**[3,4] at the secondary position of the Baylis-Hillman acetate **1a** by using the DABCO salt concept.[5] As we and others have studied and used extensively, selective introduction of nucleophile at the secondary position of Baylis-Hillman adduct could be carried out by the reaction of the nucleophile and the *in situ* generated DABCO salt of the corresponding Baylis-Hillman acetate (Scheme 2).[5]

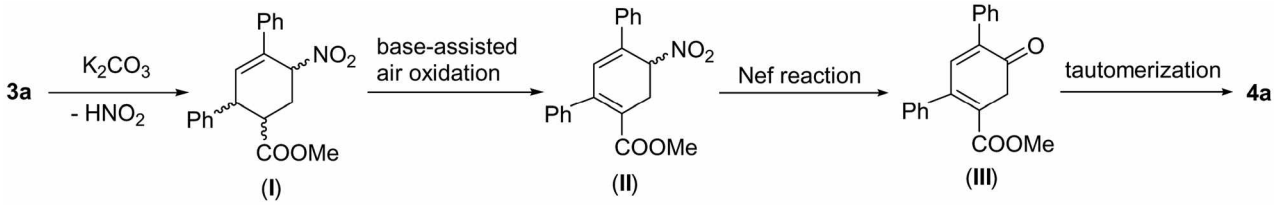
Actually, as expected easily, the reaction of **1a** and **2a** in the presence of DABCO produced many spots on TLC presumably due to the formation of many diastereomeric cyclohexane intermediates **3a**, which might be formed *via* the sequential S_N2'-S_N2'-Michael addition pathway as shown. Thus, we separated the diastereomeric mixture **3a** (aqueous extractive workup followed by passing through a short silica column) and treated them with K_2CO_3 in DMF in order to check the possibility for the formation of 2,4-diphenylbenzoic acid derivative, which could be obtained



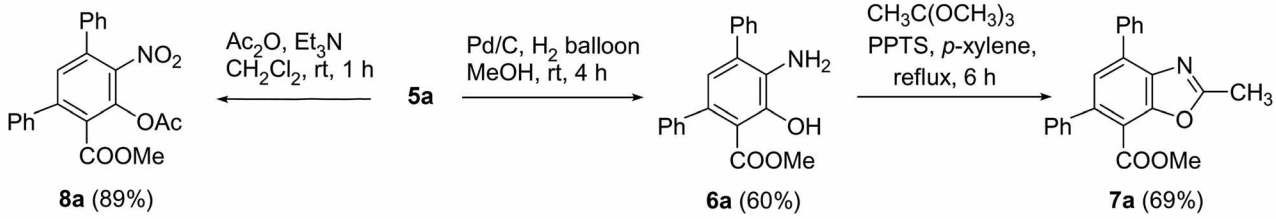
Scheme 1



Scheme 2



Scheme 3



Scheme 4

from the elimination of two molecules of nitrous acid followed by concomitant air-oxidation. The reaction showed the formation of many intractable complex mixtures on TLC, after acidic workup with aqueous HCl. However, we could isolate two major components, fortunately. The two compounds were found as **4a** (30%, R_f = 0.45 in hexanes/EtOAc, 3:2) and **5a** (9%, R_f = 0.60 in hexanes/EtOAc, 3:2) based on their IR, ^{1}H, ^{13}C, Mass and elemental analyses. The reaction produced so many intractable compounds that we could separate only two compounds in pure states in low yields, however, we decided to proceed the study based on the importance of poly-substituted phenols[6] or nitrophenols[7] and the mechanistic peculiarity (*vide infra*).

The formation of **4a** could be explained tentatively as shown in Scheme 3: elimination of HNO_2 from **3a** might produce the cyclohexene intermediate (**I**), base-assisted unusual oxidation[8] and the following Nef reaction[4e] generated the phenol compound **4a**. Although we do not have further evidences for the reaction mechanism at this stage, the structure of **4a** was assigned easily by their spectroscopic data, D_2O treatment experiment (Experimental Section), and comparison with the spectroscopic data of similar compounds.[6b,c]

Based on its IR, ^{1}H, ^{13}C and mass data we assigned the structure of **5a** as 2-hydroxy-4,6-diphenyl-3-nitrobenzoic acid methyl ester. However, assignment of the structure of **5a** and the reaction mechanism for its formation was a difficult task. Thus, in order to confirm the structure of **5a** we carried out some chemical transformations as shown in Scheme 4. Reduction of **5a** under typical hydrogenation conditions (Pd/C, H_2) gave **6a**, which was converted into benzoxazole derivative **7a** by the reaction with trimethylorthoacetate and PPTS (pyridinium *p*-toluenesulfonate) in refluxing *p*-xylene.[9] Acetylation of **5a** (Ac_2O, Et_3N) afforded **8a** in 89% yield. From these chemical transformations the structure of minor product **5a** was confirmed successfully, however, we could not find a plausible reaction mechanism until now.

All the efforts for the improvement of yields of these valuable compounds were failed, unfortunately.[10] The use of aqueous H_2SO_4 instead of aqueous HCl for the final workup stage showed similar results. Replacement of K_2CO_3/DMF with DBU/CH_3CN conditions showed more complex TLC pattern. However, the reaction applied well to other similar substrates **1b-e** to give the corresponding products **4b-e** and **5b-e** in similar yields as demonstrated in Table 1.

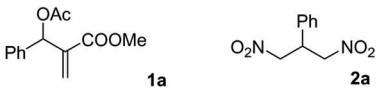
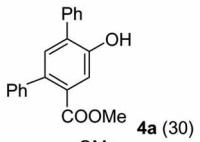
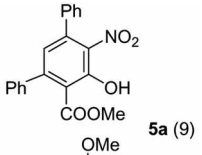
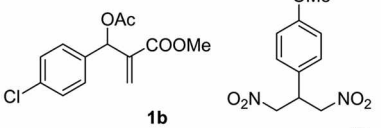
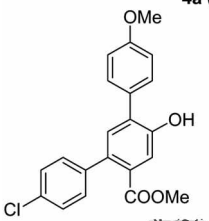
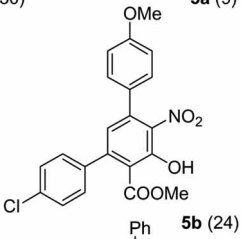
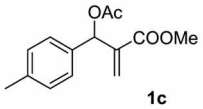
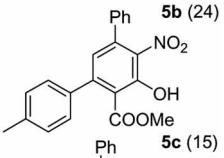
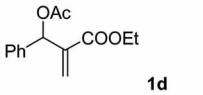
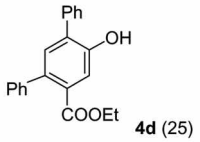
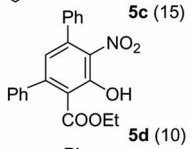
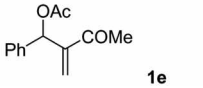
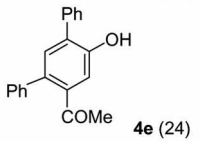
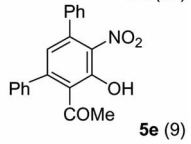
In summary, we prepared poly-substituted phenols from Baylis-Hillman adducts *via* the [3+3] annulation strategy as the key step. In the reaction, 1,3-dinitroalkanes served the 1,3-dinucleophilic component and the Baylis-Hillman acetates as a 1,3-dielectrophilic partner. Although the yields of the phenol derivatives were much low, the reaction was general and could provide many insights for further study on related chemistry. The studies on the scope and reaction mechanism of this novel finding are currently underway.

Experimental Section

Typical procedure for the synthesis of compound 4a and 5a: To a stirred solution of Baylis-Hillman acetate **1a** (234 mg, 1.0 mmol) in aqueous THF (2 mL) was added DABCO (224 mg, 2.0 mmol) and stirred at room temperature for 15 min. 1,3-Dinitroalkane **2a** (252 mg, 1.2 mmol) was added to the reaction mixture and stirred at room temperature for 3 h. After the usual aqueous workup we separated crude diastereomeric mixture of **3a** by passing through a short-path silica column. The crude **3a** was dissolved in DMF (1.5 mL), K_2CO_3 (690 mg, 5.0 mmol) was added, and stirred at room temperature for 16 h. The reaction mixture was poured into water and adjusted the pH around 5-6 with dilute HCl solution and extracted with ether. After the usual workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 2:1:0.1) we obtained **4a** (92 mg, 30%) and **5a** (32 mg, 9%) as colorless oils. Other compounds were synthesized similarly and the spectroscopic data of prepared compounds **4a-e** and **5a-e** are as follows.

Compound **4a**: 30%; colorless oil; IR (film) 3406, 2952, 1714, 1558, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ3.65

Table 1. Synthesis of poly-substituted phenols

Entry	Starting materials	Conditions	Products (%)
1	 **1a** **2a**	1. aq THF, DABCO (2.0 equiv), rt, 15 min 2. **2a** (1.2 equiv), rt, 3 h 3. aq workup 4. K_2CO_3 (5.0 equiv), DMF, rt, 16 h 5. aq HCl	 **4a** (30)  **5a** (9)
2	 **1b** **2b**	1. aq THF, DABCO (2.0 equiv), rt, 15 min 2. **2b** (1.2 equiv), rt, 3 h 3. aq workup 4. K_2CO_3 (3.0 equiv), DMF, rt, 6 h 5. aq HCl	 **4b** (34)  **5b** (24)
3	 **1c** **2a**	1. aq THF, DABCO (2.0 equiv), rt, 15 min 2. **2a** (1.2 equiv), rt, 2 h 3. aq workup 4. K_2CO_3 (5.0 equiv), DMF, rt, 16 h 5. aq HCl	**4c** (trace)[a]  **5c** (15)
4	 **1d** **2a**	1. aq THF, DABCO (2.0 equiv), rt, 15 min 2. **2a** (1.2 equiv), rt, 2 h 3. aq workup 4. K_2CO_3 (5.0 equiv), DMF, rt, 15 h 5. aq HCl	 **4d** (25)  **5d** (10)
5	 **1e** **2a**	1. aq THF, DABCO (2.0 equiv), rt, 15 min 2. **2a** (1.2 equiv), rt, 3 h 3. aq workup 4. K_2CO_3 (3.0 equiv), DMF, rt, 6 h 5. aq HCl	 **4e** (24)  **5e** (9)

[a]We observed the formation of 4c on TLC, but we failed to isolate pure **4c**.

(s, 3H), 5.64 (br s, 1H, D_2O exchangeable), 7.28-7.54 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.02, 117.40, 126.93, 127.96, 128.34, 128.45, 128.95, 129.22, 130.82, 131.20, 132.74, 135.23, 136.09, 140.86, 151.69, 168.65; ESIMS *m/z* 305 (M^++1). Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.79; H, 5.16.

Compound **5a**: 9%; colorless oil; IR (film) 3303, 2924, 1739, 1535, 1402, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.71 (s, 3H), 7.34-7.59 (m, 10H), 7.63 (s, 1H), 11.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.91, 128.26, 128.44, 128.47, 128.58, 128.59, 128.80, 129.31, 131.69, 132.82, 133.89, 134.99, 137.63, 139.24, 151.78, 166.15; HRMS (MALDI-TOF) Calcd for $C_{20}H_{15}NO_5Na$ [M^-+Na]: 372.0848. Found: 372.0860. Anal. Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found: C, 68.83; H, 4.51; N, 3.91.

Compound **4b**: 34%; colorless oil; IR (film) 3406, 2952, 1711, 1518, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3H), 3.86 (s, 3H), 5.63 (br s, 1H), 7.02 (d, J = 8.7 Hz, 2H), 7.19 (s, 1H), 7.23 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.08, 55.37, 114.74, 117.56, 127.94, 128.10, 129.84, 130.05, 130.14, 131.18, 132.61, 132.97, 134.13, 139.50, 151.96, 159.78, 168.22; ESIMS *m/z* 369 (M^++1).

Compound **5b**: 24%; colorless oil; IR (film) 3215, 2924, 1739, 1516, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.73 (s, 3H), 3.86 (s, 3H), 6.99 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 9.0 Hz, 2H), 7.56 (s, 1H), 11.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.04, 55.37, 113.99, 127.08, 128.36, 128.72, 130.03, 130.58, 131.51, 131.79, 133.85, 134.56, 136.19, 138.56, 152.01, 159.99, 166.04.

Compound **5c**: 15%; colorless oil; IR (film) 3219, 2951, 1741, 1537, 1336, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 3.73 (s, 3H), 7.19-7.58 (m, 9H), 7.62 (s, 1H), 11.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.17, 52.89, 128.43, 128.45, 128.54, 128.71, 129.20, 129.32, 131.75, 132.88, 133.83, 134.74, 135.09, 138.14, 139.37, 151.67, 166.25.

Compound **4d**:[5b] 25%; colorless oil; IR (film) 3413, 2981, 1711, 1560, 1315, 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, J = 6.9 Hz, 3H), 4.10 (q, J = 6.9 Hz, 2H), 5.70 (s, 1H), 7.28-7.54 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.59, 61.08, 117.33, 126.85, 127.91, 128.30, 128.54, 128.96, 129.19, 131.05, 131.27, 132.66, 135.17, 136.14, 141.05, 151.71, 168.36.

Compound **5d**: 10%; colorless oil; IR (film) 3219, 2925, 1736, 1535, 1408, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (t, J = 7.5 Hz, 3H), 4.17 (q, J = 7.5 Hz, 2H), 7.38-7.59 (m, 10H), 7.63 (s, 1H), 11.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.58, 62.13, 128.23, 128.37, 128.45, 128.55, 128.80, 129.22, 129.32, 131.68, 132.83, 133.72, 135.08, 137.70, 139.19, 151.75, 165.56.

Compound **4e**: 24%; yellow solid, mp 170-174 °C; IR (film) 3383, 2924, 1658, 1398, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.04 (s, 3H), 5.91 (s, 1H), 7.24 (s, 1H), 7.31 (s,

1H), 7.32-7.56 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ30.41, 115.59, 127.59, 128.26, 128.64, 128.91, 129.00, 129.15, 130.78, 132.45, 133.42, 136.21, 140.33, 140.82, 152.10, 204.57; ESIMS *m/z* 289 (M^++1).

Compound **5e**: 9%; colorless oil; IR (film) 3309, 2924, 1707, 1529, 1398 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ2.17 (s, 3H), 7.27-7.59 (m, 10H), 7.60 (s, 1H), 10.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.11, 128.38, 128.44, 128.52, 128.65, 129.30, 129.33, 130.85, 131.56, 133.03, 135.01, 137.16, 137.37, 139.47, 151.72, 200.51.

Synthesis of compound 6a, 7a and 8a: Compound **5a** (17 mg, 0.05 mmol) and Pd/C (2 mg) were dissolved in MeOH (1.0 mL) and the reaction mixture was stirred under hydrogen atmosphere (H_2 balloon) for 4 h. Filtering the reaction mixture through a pad of Celite, concentration, and column chromatographic purification afforded **6a** (10 mg, 60%) as colorless oil. A mixture of compound **6a** (10 mg, 0.03 mmol), trimethyl orthoacetate (6 mg, 0.05 mmol) and PPTS (2 mg) in *p*-xylene (0.5 mL) was heated to reflux for 6 h. After the usual aqueous workup and column chromatographic purification process we obtained compound **7a** (7.5 mg, 69%) as a pale yellow solid. Compound **8a** was synthesized by usual acetylation process with Ac_2O/Et_3N conditions in 89% yield. The spectroscopic data of **6a**, **7a** and **8a** are as follows.

Compound **6a**: 60%; colorless oil; IR (film) 3494, 3388, 3059, 2924, 1697, 1597, 1433, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ3.45 (s, 3H), 5.34 (br s, 3H, D_2O exchangeable), 6.60 (s, 1H), 7.25-7.52 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.27, 113.46, 119.87, 126.42, 127.86, 127.99, 128.37, 128.78, 128.80, 129.49, 135.59, 136.47, 137.81, 139.22, 142.67, 169.69.

Compound **7a**: 69%; yellow solid, mp 97-99 °C; IR (film) 2925, 1732, 1288, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (s, 3H), 3.73 (s, 3H), 7.35-7.55 (m, 9H), 7.83-7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.83, 52.33, 121.97, 125.60, 126.22, 127.49, 128.33, 128.34, 128.55, 128.69, 128.90, 134.64, 137.98, 140.45, 141.01, 147.72, 165.83, 167.28. Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.77; H, 5.07; N, 4.03.

Compound **8a**: 89%; colorless oil; IR (film) 2952, 1784, 1734, 1543, 1367, 1255, 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ2.09 (s, 3H), 3.66 (s, 3H), 7.34-7.45 (m, 10H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ20.32, 53.10, 127.12, 128.20, 128.55, 128.62, 128.64 (2C), 128.74, 128.87, 134.98, 135.06, 137.88, 139.29, 139.40, 139.85, 164.98, 167.57; ESIMS *m/z* 392 (M^++1).

References and Notes

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9. Nishioka, H.; Ohmori, Y.; Iba, Y.; Tsuda, E.; Harayama, T. *Heterocycles* **2004**, *64*, 193. During the evaluation process of this paper, one of the reviewers raised the possibility for the structure of compound **5a** as the one having the two substituted groups (hydroxyl and nitro) in the reverse direction. However, we do not have further evidence at this stage, unfortunately.
10. During the workup stage, when we adjusted the pH of the water phase too acidic (pH = 1-2) the yield of **4a** was decreased and the yield of **5a** was increased slightly. On the contrary, when we poured the reaction mixture in neutral water, we could obtain **4a** in similar yield but we could not observe the formation of **5a**. Thus, we adjusted the pH of the water phase as 5-6 throughout the whole entries in Table 1. We also examined one-pot reaction of **1a** and **2a** in DMF in the presence of K_2CO_3. Similar amount of **5a** was observed on TLC but the yield of **4a** was decreased much.