

Regioselective construction of polysubstituted benzene ring from Baylis–Hillman adduct via [4+2] annulation strategy

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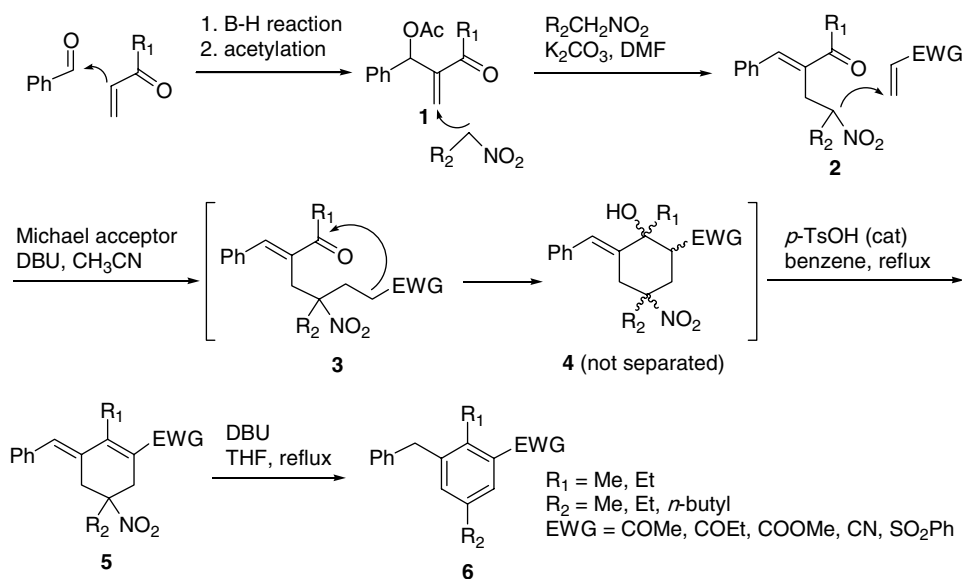
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Abstract—A new and regioselective [4+2] benzannulation protocol toward polysubstituted benzenes was developed. Nitroalkane derivative, which was prepared from Baylis–Hillman adduct, served as the four-carbon unit and Michael acceptor as a two-carbon unit.

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Polysubstituted benzenes are highly useful entities, which are widely used in industry as well as in the laboratory. The regioselective preparation of polysubstituted aromatic compounds is one of the challenging problems in organic synthesis.¹ Classical approaches are based on aromatic substitution, which introduces a substituent to

the given arene. A variety of synthetic methodologies based on this route have been developed including the electrophilic or nucleophilic substitutions, catalyzed coupling reactions, and metalation–functionalization reactions. However, these methods suffer from a long multi-step reaction sequence, low yields of products,



Scheme 1.

Keywords: Polysubstituted benzenes; Baylis–Hillman adducts; Michael acceptor.

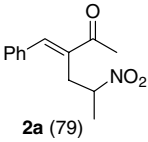
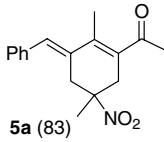
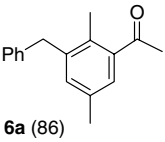
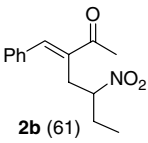
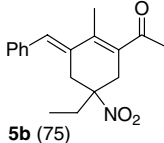
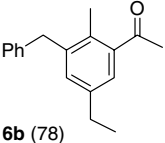
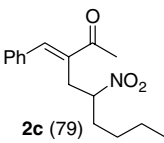
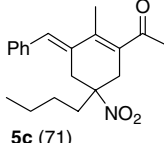
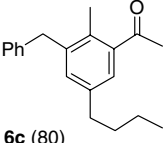
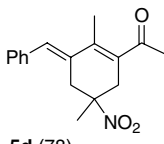
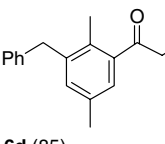
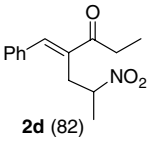
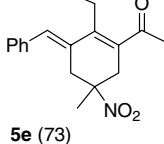
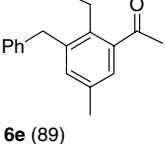
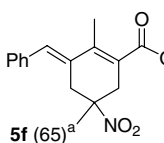
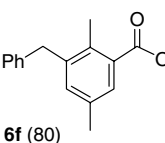
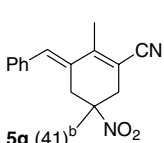
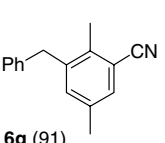
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and production of regiochemical ambiguities originating from the activating or deactivating and orienting effects of the substituents.

Conceptually different approaches that construct the aromatic backbone from acyclic precursors have received growing interest due to their short synthetic steps and the avoidance of regioisomeric problems. These general features are common in the most useful benzannulation reactions such as [3+2+1] Dotz reaction of Fisher carbene complexes,² Danheiser alkyne-cyclo-

butenone [4+2] cyclization,³ [4+2] cycloaddition of metalcyclopentadienes and alkynes,⁴ transition-metal-catalyzed [2+2+2] and [4+2] cycloadditions,⁵ [4+2] Yamamoto benzannulation of *o*-alkynyl benzaldehyde and alkyne,⁶ [3+3] cyclocondensation between bielelectrophiles and binucleophiles,⁷ and 1,6-electrocyclization reaction.⁸ Recently, an efficient approach was developed for the synthesis of highly substituted phenols using a [5+1] benzannulation strategy by the reaction of α -alkenyl ketene-(*S,S*)-acetals and nitroalkane.⁹ Ballini and co-workers also reported an interesting synthetic

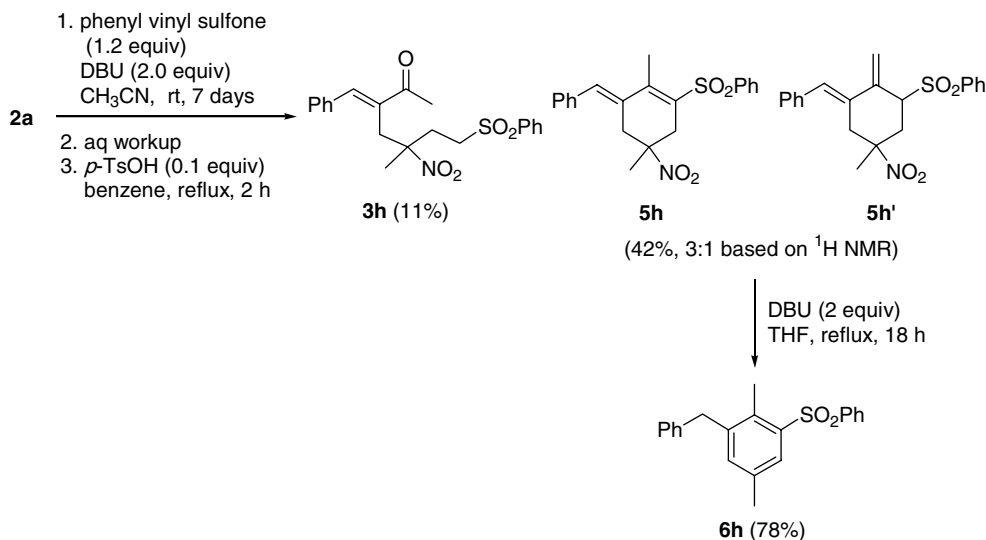
Table 1. Synthesis of regioselectively substituted benzenes

Entry	Substrate (%)	Conditions	Cyclohexene (%)	Product (%) ^c
1	 2a (79)	1. DBU (1.0 equiv), MVK (1.5 equiv), CH ₃ CN, rt, 30 min 2. aq workup 3. <i>p</i> -TsOH (0.1 equiv), PhH, reflux, 1 h	 5a (83)	 6a (86)
2	 2b (61)	1. DBU (1.0 equiv), MVK (1.5 equiv), CH ₃ CN, rt, 30 min 2. aq workup 3. <i>p</i> -TsOH (0.1 equiv), PhH, reflux, 1 h	 5b (75)	 6b (78)
3	 2c (79)	1. DBU (1.0 equiv), MVK (1.8 equiv), CH ₃ CN, rt, 5 h 2. aq workup 3. <i>p</i> -TsOH (0.1 equiv), PhH, reflux, 1 h	 5c (71)	 6c (80)
4	2a	1. DBU (1.0 equiv), EVK (1.5 equiv), CH ₃ CN, rt, 1 h 2. aq workup 3. <i>p</i> -TsOH (0.1 equiv), PhH, reflux, 3 h	 5d (78)	 6d (85)
5	 2d (82)	1. DBU (1.0 equiv), MVK (1.5 equiv), CH ₃ CN, rt, 12 h 2. aq workup 3. <i>p</i> -TsOH (0.1 equiv), PhH, reflux, 3 h	 5e (73)	 6e (89)
6	2a	1. DBU (2.0 equiv), methyl acrylate (1.8 equiv), CH ₃ CN, rt, 40 h 2. aq workup 3. <i>p</i> -TsOH (0.1 equiv), PhH, reflux, 4 h	 5f (65)^a	 6f (80)
7	2a	1. DBU (2.0 equiv), acrylonitrile (2.0 equiv), CH ₃ CN, rt, 4 days 2. aq workup 3. <i>p</i> -TsOH (0.1 equiv), PhH, reflux, 15 h	 5g (41)^b	 6g (91)

^aMichael addition product **3f** was isolated in 7%.

^bMichael addition product **3g** was isolated in 41% yield.

^cDBU (2 equiv), THF, reflux, 5–96 h.



Scheme 2.

approach for acetophenones and methyl benzoates via an anionic domino process from the reaction of primary 1,3-dinitroalkanes with 2-ene-1,4-dione or 2-ene-4-oxo ester derivatives.¹⁰

Recently, Baylis–Hillman reaction and the chemical transformation of the Baylis–Hillman adducts have been investigated deeply.^{11,12} During the studies on the chemical transformations of Baylis–Hillman adducts,¹² we envisioned that the Baylis–Hillman adducts might be used as a four-carbon unit for the construction of highly substituted benzene ring in a regio-controlled manner. Appropriate Michael acceptor can serve as the remaining two-carbon unit for the purpose as depicted in Scheme 1.

The synthesis of starting material **2** (four-carbon unit) was carried out by the addition–elimination protocol from the acetate of the Baylis–Hillman adduct of methyl (or ethyl) vinyl ketone **1** and primary nitroalkane in the presence of K₂CO₃.¹³ The benzyldene moiety, which will be isomerized at the final stage, is essential for the construction of benzene ring at the final aromatization stage (vide infra). The next step was the construction of six-membered ring intermediate **4** via the consecutive Michael addition of **2** to Michael acceptor and aldol-type cyclization, which occurred with the aid of DBU in CH₃CN in good yield. The intermediate **4** was not separated due to the complex nature of **4** by the formation of diastereoisomeric mixtures. Thus, we subjected the crude mixtures, after usual workup, in the dehydration conditions (*p*-TsOH, benzene, reflux) and obtained the dehydration product **5** in good overall yield.¹⁴ The final step was the elimination of HNO₂ and isomerization of the *exo*-double bond to the desired benzene ring. We expected that elimination of HNO₂ can occur with DBU and the isomerization will also occur simultaneously due to the favorable aromatization effect. As expected, the final step occurred in good yield with DBU in THF under refluxing conditions to our delight.¹⁴

As shown in Table 1, variation of the substituents of the Baylis–Hillman adducts or of nitroalkanes did not alter the reactivity (entries 1–3 and 5). However, the reactivity was affected by the nature of Michael acceptor. The reaction rates of the Michael addition of **2** to methyl vinyl ketone, ethyl vinyl ketone, phenyl vinyl sulfone, methyl acrylate, and acrylonitrile were similar (TLC monitoring). But, the reactivities of the next aldol cyclization reaction were found to be different much depending on the nature of the electron-withdrawing group of the Michael acceptors presumably due to the different acidities of the α -protons nearby the EWG groups of the Michael acceptors. Fortunately, the following dehydration, elimination, and aromatization reactions from **4** to the final product **6** were all straightforward in these cases also (entries 4, 6, and 7). The use of acrylonitrile (entry 7) as the Michael acceptor required long reaction time for the cyclization and gave low yield of **5g** (41%). Actually, we could isolate the Michael addition product **3g** in 41% after the whole reaction. This type of Michael addition product was also found in the cases of methyl acrylate (entry 6) and phenyl vinyl sulfone (Scheme 2). Especially, when we used phenyl vinyl sulfone as the Michael acceptor we found the formation of *exo*-methylene compound **5h'**, which showed the same reactivity to give **6h**.

In summary, we disclosed a new route for the synthesis of polysubstituted benzene derivatives starting from Baylis–Hillman adducts via a regioselective [4+2] benzannulation protocol. Nitroalkane derivative, which was prepared from Baylis–Hillman adduct, served as the four-carbon unit and Michael acceptor as a two-carbon unit.

Acknowledgments

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13. The starting materials **2a–d** were prepared according to the reported methods.^{15–17}
14. Typical procedure for the synthesis of **5a** and **6a**: To a stirred solution of **2a** (233 mg, 1.0 mmol) and methyl vinyl ketone (105 mg, 1.5 mmol) in CH₃CN (5 mL) was added DBU (153 mg, 1.0 mmol) and stirred at room temperature for 30 min. TLC observation showed complete disappearance of starting material **2a** and the formation of diastereomeric mixtures of **4a**. After aq workup the crude diastereomeric mixtures were dissolved in benzene (5 mL), added *p*-TsOH (20 mg, 0.1 mmol), and heated to reflux for 1 h. After the usual workup and column chromatographic purification process (hexanes/ether, 5:1) we obtained the desired **5a** as a white solid, 237 mg (83%). To a stirred solution of **5a** (143 mg, 0.5 mmol) in THF (3 mL) was added DBU (152 mg, 1.0 mmol) and heated to reflux for 6 h. After the usual workup and column chromatographic purification process (hexanes/ether, 10:1) we obtained the desired **6a** as a white solid, 103 mg (86%). The spectroscopic data of **5a** and **6a** are as follows:
Compound **5a**: white solid, mp 81–83 °C; IR (KBr) 1685, 1539, 1350, 1234 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.58 (s, 3H), 2.03 (t, *J* = 1.8 Hz, 3H), 2.37 (s, 3H), 2.66 (dd, *J* = 17.7 and 1.8 Hz, 1H), 2.82 (dd, *J* = 15.3 and 1.8 Hz, 1H), 3.28 (d, *J* = 17.7 Hz, 1H), 3.43 (d, *J* = 15.3 Hz, 1H), 6.92 (s, 1H), 7.25–7.42 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 15.78, 25.74, 29.82, 36.34, 36.62, 86.01, 127.36, 128.34, 128.98, 131.18, 133.09, 133.66, 133.83, 136.60, 204.25.
Compound **6a**: white solid, mp 40–41 °C; IR (KBr) 2924, 1685 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.26 (s, 3H), 2.32 (s, 3H), 2.54 (s, 3H), 3.99 (s, 2H), 7.05–7.29 (m, 7H); ¹³C NMR (CDCl₃, 75 MHz) δ 15.97, 20.86, 30.45, 39.57, 126.01, 126.80, 128.41, 128.55, 132.06, 133.65, 134.84, 139.96, 140.34, 140.53, 204.00.
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