Montmorillonite K10 Clay-catalyzed Synthesis of Substituted 1-Aryl Indenes from Baylis–Hillman Adducts

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An eco-friend method for the synthesis of 1-aryl indenes from Baylis–Hillman adducts using Mont. K10 and microwave combination as catalyst system and a procedure for the synthesis of β-phenyl-substituted-protected Baylis–Hillman adducts with highly *Z*-selectivity have been reported.

The Baylis–Hillman reaction[1] is one of the important C–C bond forming reactions and it has been used in organic synthesis for the preparation of a variety of compounds having diverse functional groups. The clay catalysts are known as eco-friendly acid catalysts which have potential for replacing the conventional mineral acids and are non-pollutant.[2] The advantages of the clay-catalyzed reactions are that they are generally mild, solvent free, and easy work-up.[2] In continuation of our research work[3,4] on montmorillonite K10 clay catalyst and Baylis–Hillman adducts in organic synthesis, herein we report the Mont. K10 clay-microwave mediated synthesis of functionalised indenes by the generation of two types of stabilized allylic carbocation intermediates as shown in Figure 1, structures B and C.

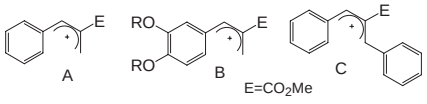
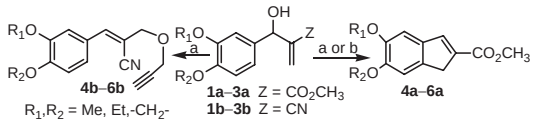


Figure 1. Structure of allylic carbocations. A. Less stabilized B. Stabilized by electron releasing group at phenyl group; C. Stabilized by diaryl group.

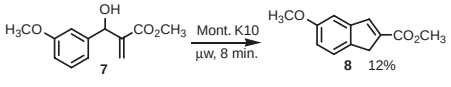
During the course of our studies on the synthesis of oxacycles,[4c–4e] we attempted the preparation of enyne ethers from the Baylis–Hillman adduct **1a** with 2-propynyl alcohol under thermal condition (Mont. K10, heat).[4b] We did not get the desired enenyne ether but indene[5] **4a** was obtained in 52% yield. The result prompted us to explore the present catalyst system would be a good replacement of the earlier P_2O_5 catalyzed synthesis of indenes (Scheme 1).[5] Similarly, under the optimized condition, the other adducts **2a** and **3a** furnished the corresponding indenes **5a** and **6a** in moderate yields. (Table 1)

In order to compare and examine the difference in the reactivity of the Baylis–Hillman adducts bearing the nitrile substitution, the adduct **1b**, in contrary, afforded only the enenyne ether **4b** in 70% yield and not the expected indene derivative (Scheme 1).



(a) 2-Propynyl alcohol, Mont. K10, 80 °C, 12 h. (b) Mont. K10 clay, μw, 8 min.

Scheme 1.



Scheme 2.

The reason could probably be due to the cumulative effect of stereochemical disfavor of the intermediate carbocation with respect to the arene group and destabilization of the carbocation by the nitrile group (Figure 2). Similarly, the other adducts **2b** and **3b** furnished enyne ethers **5b** and **6b** in good yields (Table 1).

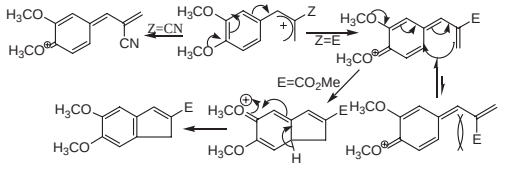


Figure 2.

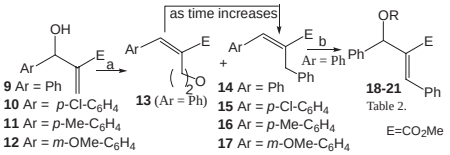
Table 1. Synthesis of indenes (**4a–6a**) and enyne ethers (**4b–6b**)

Entry	Adduct	R_1 & R_2	Product	Yield/%
1	**1a**	Methyl	**4a**	52
2	**2a**	Ethyl	**5a**	50
3	**3a**	$-CH_2-$	**6a**	49
4	**1b**	Methyl	**4b**	70
5	**2b**	Ethyl	**5b**	69
6	**3b**	$-CH_2-$	**6b**	65

According to the reported mechanism,[5] the reaction proceed through electrocyclic ring closure facilitated by an alkoxy group at 3-position of the arene. However, the role of 4-alkoxy substitution is not revealed by the mechanism. Hence, we examined the reactivity of adduct with only 3-alkoxy substitution. Accordingly, to our surprise, the 3-methoxy substituted adduct **7** furnished only 12% yield of the indene derivative **8** (Scheme 2). The low yield of the product formation showed the necessity of an electron releasing group at 4-position and is essential to facilitate the ring closure more effectively for higher yield. Hence, we propose the role of 4-methoxy group in the electrocyclic ring closure based on the mechanism shown in Figure 2.

On the other hand, to achieve the goal for the synthesis of indene derivatives irrespective of whether the aryl ring is substituted or unsubstituted in the Baylis–Hillman adducts, we envisaged by introduction of a phenyl group at the β-position which would stabilizes the allylic cation intermediate by both the aryl groups. (Figure 1, structure C). Thus, the suitable precursor for the construction of indenes would be the β-phenyl substituted Baylis–Hillman adducts **18–21** (Scheme 3).

The literature known Heck coupling[6] for the synthesis of β-phenyl substituted adduct **18** from acetate adduct **9** failed to afford the desired product and furnished only the isomerized product as evidenced by spectral studies.[7] Hence, we developed a procedure for the preparation of the adduct **18–21** by a three-step-reaction sequence viz. 1. An intermolecular Friedel–Crafts reaction catalyzed by Mont. K10 clay, 2. Allylic bromination, and 3. An alkoxide substitution (Scheme 3). The side dimerised product **13** was readily converted to compound **14** upon longer heating under Mont. K10 clay catalyst. Accordingly, compounds **9–12** were converted to compounds **14–17**. It should be noteworthy that the procedure de-



(a) Benzene, Mont. K10, 6 h, (b) i) NBS, CCl_4, AIBN, reflux, 4 h; ii) ROH, reflux, 5 h

Scheme 3.

Table 2. Synthesis of functionalized (*Z*)-β-phenyl-substituted-protected adducts (**18**–**24**)

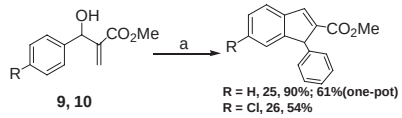
Entry	ROH	Product	Yield/%
1	Methanol	**18**	82
2	Ethanol	**19**	81
3	Propargyl alcohol	**20**	80
4	Homo propargyl	**21**	76
5	Phenol	**22** and **23**	74
6	*p*-Cresol	**24**	65

scribed herein furnished only the (*Z*)-β-phenyl-substituted-protected adduct **18** as a single product as evidenced by NMR.[8] The effect of alkoxide substitution at allylic position with various alcohol were also studied and all of them furnished the functionalized products in good yield (Schemes 3 and Table 2).

The stereochemistry of alkene was fixed at the allylic bromination step based on ^{1}H NMR analysis. Heating the β-phenyl-substituted protected-adduct **18** in the presence of Mont. 10 clay and microwave combination furnished the functionalized indene **25** in 90% yield (Scheme 4). The Mont. K10 clay recovered from the reaction mixture by filtration can be recycled three times without losing its activity by activating the clay at 100 °C for 3 h. In an attempt, we also successfully developed a two-pot synthesis of substituted indenes **25** and **26** from adducts **9** and **10** respectively without isolation and purification of intermediates (see experimental). Some of the related cyclization reactions involving the Baylis–Hillman adducts are known for organic synthesis.[9–11]

In conclusion, we have developed an efficient; eco-friend method for the synthesis of indenes from the Baylis–Hillman adducts having both electron rich and simple aryl groups through the intramolecular Friedel–Crafts reaction. Thereby we have disclosed the importance of β-phenyl substituted adduct as a precursor for the synthesis of highly substituted indenes. It is noteworthy that the methodology could be applied for the total synthesis of indatraline[11] and related natural products by choosing appropriate substrates. Further work in this direction is under progress.

Synthesis of Indene **4a**: A mixture of adduct **1a** (125 mg, 0.5 mmol) and Mont. K10 (75 mg, 30% w/w) was taken in a 25 mL conical flask and irradiated in a microwave oven for 8 min. The mixture was cooled and diluted with 5 mL of CH_2Cl_2. The solvent was removed in vacuo and the crude was purified through silica gel column chromatography using hexane–EtOAc (95:5) to give indene **4a** as crystal in 52% yield. *Synthesis of indene* **25**: The adduct **9** (250 mg, 1.3 mmol) in dry benzene (3 mL) and Mont. K-10 (125 mg, 50% w/w) was refluxed for 6 h. The clay was filtered off and 125 mg of fresh clay was added to the mixture and refluxed further 6 h. The clay was filtered out and solvent was removed in vacuo. *N*-bromosuccinimide (231 mg, 2 equiv.), 5 mL of CCl_4 and 50 mg of AIBN were added to the reaction mixture and refluxed for 4 h. Then 3 equiv. of methanol was added and reflux was continued for 2 h. The solvents were removed under vacuum. The crude mixture was treated with Mont. K10 clay (75 mg, 30% w/w) and irradiated in a microwave oven for 4 min. Finally, the mixture was cooled to rt and diluted with 5 mL of CH_2Cl_2 and filtered. The solvent was removed and the crude was purified through silica gel column using hexane–EtOAc (95:5) to give highly functionalized indene **25** as colourless crystal in 61% overall yield.



a) (i) Benzene, Mont. K10, 12 h; (ii) 2 equiv. NBS, CCl_4, 4 h, reflux; (iii) Methanol, reflux, 2 h; (iv) Mont. K10, microwave, 4 min.

Scheme 4.

Compound 4b: ^{1}H NMR: δ 2.49 (t, 1H, J = 2.25 Hz), 3.92 (s, 6H), 4.25 (d, 2H, J = 2.25 Hz), 4.31 (s, 2H), 6.87 (d, 1H, J = 8.35 Hz), 7.09 (s, 1H), 7.22 (d, 1H, J = 8.35 Hz), 7.60 (s, 1H). ^{13}C NMR: δ 55.86, 55.89, 57.24, 70.58, 75.51, 78.74, 104.12, 110.59, 110.83, 118.11, 124.17, 125.90, 145.51, 151.41. Mass spectra m/z: 257 (M^+); HRMS (m/z): cacld for $C_{15}H_{15}NO_3$, 257.1052; found: 257.1048. **Compound 8**: White solid; mp 86–88 °C; Yield: 12%; IR (neat) $\nu_{max:}$ 1721 cm^{-1}.^{1}H NMR: δ 3.6 (s, 2H), 3.82 (s, 6H), 6.86 (1H, dd, J = 8.26 and 2.35 Hz), 7.0 (d, 1H, J = 2.35 Hz), 7.36 (d, 1H, J = 8.26 Hz), 7.64 (s, 1H). ^{13}C NMR: δ 37.51, 51.35, 55.18, 107.86, 114.24, 124.57, 136.76, 138.07, 140.98, 143.79, 158.99, 164.90. Mass spectra m/z: 204 (M^+); HRMS (m/z): cacld for $C_{12}H_{12}O_3$, 204.0786; found: 204.0794. **Compound 18**: ^{1}H NMR: δ 3.29 (s, 3H), 3.52 (s, 3H), 5.06 (s, 1H), 6.64 (s, 1H), 7.15–7.32 (m, 10H). ^{13}C NMR: δ 51.51, 57.14, 83.73, 127.36, 128.03, 128.14, 128.31, 133.29, 134.96, 135.23, 138.64, 168.76. Mass spectra m/z: 282 (M^+); HRMS (m/z): cacld for $C_{18}H_{18}ClO_3$, 282.1256; found: 282.1259. **Compound 25**: Colorless solid; mp 126–128 °C; Yield: 61%; IR (neat) $\nu_{max:}$ 1702, 1610 cm^{-1}. ^{1}H NMR: δ 3.69 (s, 3H), 4.85 (s, 1H), 7.06–7.33 (m, 8H), 7.50 (d, 1H, J = 7.23 Hz), 7.79 (s, 1H). ^{13}C NMR: δ 51.50, 55.64, 123.42, 124.48, 126.87, 127.29, 127.83, 128.31, 128.52, 128.61, 138.31, 141.13, 141.56, 150.41, 164.72. Mass spectra m/z: 250 (M^+); HRMS (m/z): cacld for $C_{14}H_{16}O_2$, 250.0994; found: 250.0992.

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