Montmorillonite K10 Clay Catalyzed Mild, Clean, Solvent Free One-pot Protection-Isomerisation of the Baylis–Hillman Adducts with Alcohols

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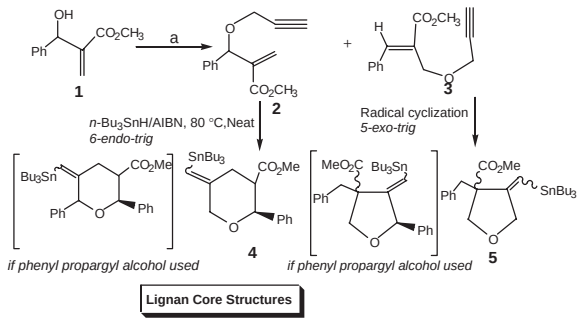
The montmorillonite K10 clay catalyzed mild, clean, and solvent free one-pot reactions of the Baylis–Hillman adducts with a number of alcohols undergo secondary alcohol protection followed by a facile 1,3-sigmatropic shift isomerised products in excellent yield. The isomerised products with propargyl alcohol are highly functionalized and useful for lignan natural product synthesis.

The usefulness of montmorillonite K10 clay in organic synthesis and its application as a catalyst for a number of organic reactions are well documented.[1] Montmorillonite K10 and its structurally modified clays are known to act as both Brønsted and Lewis acid catalysts for a variety of industrially important organic reactions.[1] The clay catalysts are known as eco-friendly acid catalysts which have potential for replacing the conventional mineral acids and are nonpollutant. The advantages of the clay-catalyzed reactions are that they are generally mild and solvent free and work-up is easy. The Baylis–Hillman reaction is one of the important carbon–carbon bond forming reactions and has been used in organic synthesis for the synthesis of a variety of compounds having diverse functional groups and has been used as the starting point for a variety of synthetic organic transformations.[2] Stereoselective isomerisation of acetates of Baylis–Hillman adducts catalyzed by TMSOTf,[2d,e] trifluoroacetic acid,[2f] and benzyltrimethylammonium fluoride[2g] has appeared in the literature. In continuation of our research work on clay catalysis,[3] we have recently reported the mont-K10-microwave assisted stereoselective isomerisation of acetates of Baylis–Hillman adducts into its (*E*)-trisubstituted alkenes and a one-pot protection-isomerisation of Baylis–Hillman adduct with trimethyl orthoformate under similar isomerisation conditions.[3d]

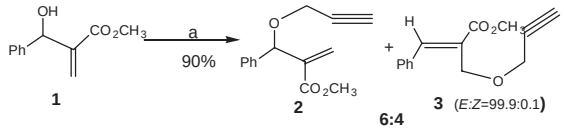


Reagents and Conditions: a. Cat. H_2SO_4, CH_2Cl_2, propargyl alcohol, RT, 1 h, 70% **; 2:3** ratio varies

Scheme 1.

Our attempt to the conventional acid catalyzed (concd H_2SO_4) reaction of Baylis–Hillman adduct with propargyl alcohol furnished the protected secondary alcohol **2** and its isomerised product **3**. We have observed that the ratio of the formation of the products (**2** and **3**) varies (as estimated by ^{1}H NMR) when the reaction was repeated under similar condition although in low yield. Hence, we have developed a high yield and clean green chemistry methodology to effect the transformation. In this letter, we report the reaction of alcohols with Baylis–Hillman adducts under solvent free and mild conditions. The propargyl derivatives **2** and **3** obtained by this methodology are extremely useful for the synthesis of core structures of natural lignans[4] **4** and **5** through an *n*-Bu_3SnH/AIBN mediated vinyl radical cyclization[5] protocol. Suitably substituted propargyl derivatives would furnish the natural lignans[4] such as lariciresinol, olivil and hydroxysugiresinol (Scheme 1).

The isomerisation study with clay catalyst is represented in Scheme 2. The Baylis–Hillman adduct **1** was prepared according to the literature procedure.[2d] The isomerisation study was initiated by heating a slurry (75 °C, 1.5 h) made with the adduct **1**, 2.5 equiv. of propargyl alcohol and 60% w/w montmorillonite K10 without any solvent in an oil bath furnished the ether **2** and its isomerised product **3**[6] (99.9; *E*-selectivity)[7] in 90% combined yield in 6 : 4 product ratio.[8] The reaction proceeded smoothly and furnished clean products. The compounds were separated by a silica gel column chromatography and characterized by spectral and analytical data.[9]

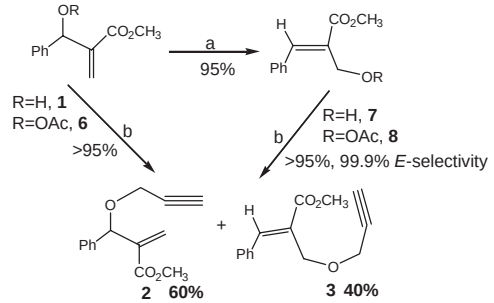


Reagents and Conditions: a. 60% w/w Mont. K10, 2.5 equvi. propargyl alcohol, Neat, 75 °C, 1.5 h.

Scheme 2.

The reactivity of the Baylis–Hillman adduct **1**, its OAc protected adduct **6** and their isomerised compounds **7** and **8** with propargyl alcohol under optimized condition described above was compared and all of them furnished compounds **2** and **3** almost in the same yield and product ratio. Interestingly, the simple Baylis–Hillman adduct **1**, without any protection, underwent protection-isomerisation with propargyl alcohol and provided an excellent yield (95%) of compounds **2** and **3** under clay catalytic condition. Reaction of compounds **1** and **6** without propargyl alcohol furnished the compounds **7** and **8** under clay catalytic condition in high yield respectively. Reaction of compounds **7** and **8** with propargyl alcohol under the optimized clay catalytic condition furnished compounds **2** and **3** in the ratio of 6 : 4 in excellent yield (>95%). Therefore, the nucleophilic nature of the propargyl alcohol on the isomerised **7** and **8** and unisomerized **1** and **6** Baylis–Hillman adducts are the same, since they afforded same products **2** and **3** in the same product ratio (6 : 4). Hence, the experiment reveals that the reaction of alcohol with simple unisomerized adduct **1** itself provides the required products in excellent yield and no protection/isomerised starting materials (**6**, **7** and **8**) are necessary to effect this transformation. The detail of the study is represented in scheme 3.

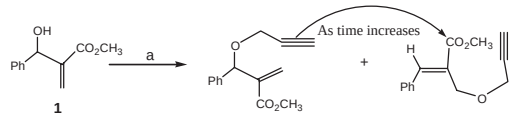
The formation of the only isomerised product **3** over **2** under the



Reagents and Conditions: a. 60% w/w Mont. K10, Neat, 2 h, 75 °C. b. 60% w/w Mont. K10, propargyl alcohol, Neat, 6 h, 75 °C.

Scheme 3.

optimized condition described above can be achieved by increasing the reaction time (Scheme 4). Complete conversion of **2** into isomerised product **3** was observed at the reaction time 24 h and was purified by passing through a silica gel column chromatography. The distribution of products with respect to reaction time is summarized in Table 1.



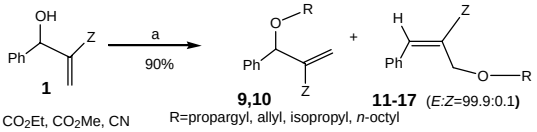
Reagents and Conditions: a. 60% w/w Mont. K10, 2.5 equvi. propargyl alcohol, Neat, 75 °C, 2 h.

Scheme 4.

Table 1.

Time(h)	**2**(%)	**3**(%)
6	42	58
15	25	75
22	<5	>95
24	trace	>99

In order to exemplify the general nature of this reaction, we have chosen a number of alcohols and found that the reactions are clean and high yielding (**11–17**) under the optimized conditions described above (Scheme 5). However, the reaction with phenols and high boiling alcohols furnished a mixture of inseparable compounds in poor yield. The results are summarized in Table 2.



Reagents and Conditions: a. 60% w/w Mont. K10, 2.5 equiv. R-OH, 75 °C, 24 h, Neat

Scheme 5.

Table 2. Isomerisation of Baylis–Hillman adducts with alcohols[a,b,c]

Alcohol	Z	Product	Yield/%[d]
Propargyl	CO_2Me	11	95
〃	CO_2Et	12	96
〃	CN	13	96
Allyl	CO_2Me	14	95
Isopropyl	CO_2Me	15	95
n-Octyl	CN	16	98
〃	CO_2Me	17	97

[a]60% w/w mont. K10 clay was used. [b]The clay was dried at 100 °C for 1 h. [c]60% mont-K10, 75 °C, 24 h. [d]Isolated yield after column purification.

The clay catalyst recovered from this reaction can be recycled three times after activating the clay by heating at 100 °C for 3 h. In conclusion, we have demonstrated that mont. K10 clay is a useful, speedy and efficient catalyst for the protection/isomerisation of the Baylis–Hillman adducts with a variety of alcohols which provide highly functionalized stereoselective (*E*)-alkenyl ethers. These ethers are good candidates for the synthesis of lignan natural products and useful substrates for RCM reactions. Further studies involving the above catalyst system are underway.

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7 The ^{1}H NMR spectra of the isomerised product **3** showed a peak at δ 7.92 for the presence of *E*-vinylic proton.

8 The product ratio was estimated by ^{1}H NMR.

9 A Typical Procedure: A slurry of the adduct **1** (150 mg, 1.3 mmol), propargyl alcohol (182 mg, 2.5 equiv., 3.25 mmole) and montmorillonite K10 clay (60% w/w) was taken in a 50 mL RB flask which was tightly closed and kept in an oil bath (75 °C) for 24 h. Then the flask was cooled to room temperature and 20 mL of CH_2Cl_2 was added and filtered through a celite pad. The solvent was removed under vacuum. The crude mixture was purified through a column of silica gel using 98 : 2 mixture of hexane: ethyl acetate afforded 95% isomerised compound **3** with 99.9% *E*-selectivity. By adjusting the reaction time (1.5 h), propargyl ether derivative **2** can be isolated in 60% yield along with the isomerised product **3**. *3-aryl-2-methylene-3(prop-2-en-1-yloxy) propeonitrile* **9**: IR (neat) ν_{max}: 1728, 1600, 1630, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.93 (d, 2H, J = 5.67 Hz), 4.87 (s, 1H), 5.23 (s, 2H), 5.84 (m, 1H), 5.97 (s, 2H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 69.75, 80.09, 107.23, 117.77, 127.03, 128.80, 128.83, 129.70, 130.01, 133.72, 137.65; MS *m/z*: 199 (M^+); Anal. Calcd for $C_{13}H_{13}NO$: Cacld. C, 78.36, H, 6.58, N, 7.03% Found: C, 78.30, H, 6.55, N, 7.00%; *Methyl (2E)3-aryl-2(prop-2-yn-1-yloxymethyl) prop-2-enoate* **11**: IR (neat) ν_{max}: 3285, 2112, 1714, 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.42(t, 1H, J = 2.34 Hz), 3.84 (s, 3H), 4.26 (d, 2H, J = 2.34 Hz), 4.39 (s, 2H), 7.32 (m, 3H), 7.53 (m, 2H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.26, 58.08, 64.25,74.70, 79.63, 128.51, 128.54, 129.55, 129.99, 134.51, 145.27, 167.98; MS *m/z*: 230 (M^+); Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03, H, 6.13% Found: C, 73.00, H, 6.08%.