Synthesis of Cyclopropane Derivatives Starting from the Baylis-Hillman Adducts Using Sulfur Ylide Chemistry

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Cyclopropane moiety is a fundamental class of functional group that is the focus of many organic synthesis programs and performs a key structural role in a wide range of biologically active molecules.1,2 The importance of cyclopropanes is reflected in the enormous effort that has been invested in their diastereo- and enantioselective synthesis.1,4 In addition, cyclopropane derivatives could be transformed to structurally diverse compounds.5

During the extensive studies on the chemical transformations of Baylis-Hillman adducts,6 we examined the introduction of cyclopropane moiety at the primary position of Baylis-Hillman adducts to form vinyl cyclopropane derivatives 2 (Scheme 1). Such vinyl cyclopropane backbone is an important entity in many naturally occurring and synthetic pyrethroidal insecticides,2a and could be used for further chemical transformations.5

Our synthetic rationale is shown in Scheme 1. The starting cinnamyl bromide 1a was prepared from the Baylis-Hillman adduct and HBr according to the reported method.7 The reaction of 1a and dimethyl sulfide in CH3CN generated the sulfonium salt (I), which was converted into the corresponding sulfur ylide (II) by treatment with NaOH. The in situ-generated sulfur ylide (II) reacted with methyl vinyl ketone to give the desired cyclopropane derivative 2a in 45% yield as shown in Scheme 1 via the intermediate (III). The synthesis of 2a was carried out in CH3CN at room temperature within 12 h. Encouraged by the successful results we prepared other cyclopropane derivatives 2b-h and the results are summarized in Table 1.8

The use of Cs2CO3 instead of NaOH showed similar yield of 2a. However, the use of K2CO3 gave 2a in only trace amounts. When we used nitrogen ylide, which was made from the reaction of 1a and DABCO in the presence of NaOH, we could not observe the formation of 2a at all. Variation of the electron-withdrawing substituents (-COOMe, -COOEt, -COMe, -CN) of the starting materials 1a-f did not alter the reactivity for the formation of cyclopropanes. Ethyl vinyl ketone (entry 2) could also be used successfully as the Michael acceptor in the reaction with 1a. However, we failed to obtain the corresponding products when we replaced methyl vinyl ketone with other Michael acceptors such as methyl acrylate, acrylonitrile, and 2-cyclohexen-1-one. In these cases we could not observe any major component on TLC. The reason for the failure could be explained either by the hydrolysis or low reactivity of these Michael acceptors. Fortunately, 2-chloroacrylonitrile could be used as the Michael acceptor efficiently to give 2g (entry 7) as inseparable cis-trans mixtures in 57% yield.

The relative stereochemistry of the two substituents of cyclopropane was trans in all cases as reported in similar systems.3,4 We could not isolate the other stereoisomer from the reaction mixtures. Further synthetic applications of the cyclopropane products are currently underway.

Scheme 1
Experimental Section

Typical procedure for the synthesis of cinnamyl bromide 1a and cyclopropane derivative 2a. The cinnamyl bromide derivative 1a was prepared in 92% yield by the treatment of the Baylis-Hillman adduct of benzaldene and methyl acrylate with aq HBr (rt, 5 h). Synthesis of 1b-f was also carried out similarly with HBr at room temperature (5-16 h, 85-95%). To a stirred solution of 1a (254 mg, 1.0 mmol) and methyl vinyl ketone (105 mg, 1.5 mmol) in CH₃CN (3 mL) was added successively dimethyl sulfide (93 mg, 1.5 mmol) and NaOH (60 mg, 1.5 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. After the normal aqueous workup and column chromatographic purification process (hexanes/ether = 10 : 1) we obtained trans isomers in all cases (except for entry 7). The use of Cs₂CO₃ (1.5 equiv) instead of NaOH under the same conditions gave 48% of 2a. Two stereoisomers were mixed in a ratio of 3 : 2.

Table 1. Synthesis of cyclopropane derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="" /></td>
<td>methyl vinyl ketone (1.5 equiv), 12 h</td>
<td><img src="image2" alt="" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="" /></td>
<td>ethyl vinyl ketone (1.5 equiv), 12 h</td>
<td><img src="image4" alt="" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="" /></td>
<td>methyl vinyl ketone (1.5 equiv), 12 h</td>
<td><img src="image6" alt="" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="" /></td>
<td>methyl vinyl ketone (1.5 equiv), 13 h</td>
<td><img src="image8" alt="" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="" /></td>
<td>methyl vinyl ketone (1.5 equiv), 8 h</td>
<td><img src="image10" alt="" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="" /></td>
<td>methyl vinyl ketone (1.5 equiv), 12 h</td>
<td><img src="image12" alt="" /></td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="" /></td>
<td>2-chloroacrylonitrile (1.5 equiv), 20 h</td>
<td><img src="image14" alt="" /></td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="" /></td>
<td>methyl vinyl ketone (1.5 equiv), 12 h</td>
<td><img src="image16" alt="" /></td>
</tr>
</tbody>
</table>

*The stereochemistry of double bond of 1a-e is Z and that of 1f is E. Me₂S (1.5 equiv), NaOH (1.5 equiv), CH₃CN, rt, given time. We obtained trans isomers in all cases (except for entry 7). The use of Cs₂CO₃ (1.5 equiv) instead of NaOH under the same conditions gave 48% of 2a. Two stereoisomers were mixed in a ratio of 3 : 2.*
\[ \text{Compound 2h: 48\%; clear oil; IR (KBr) 2214, 1701, 1184 cm}^{-1}; \text{H NMR (CDCl}_3, 300 MHz) \delta 1.41-1.47 (m, 1H), 1.53-1.59 (m, 1H), 2.31-2.42 (m, 2H), 2.34 (s, 3H), 7.10 (s, 1H), 7.38-7.42 (m, 3H), 7.68-7.71 (m, 2H); ^{11}\text{C NMR (CDCl}_3, 75 MHz) \delta 16.69, 27.98, 28.61, 31.03, 110.84, 116.06, 128.47, 128.78, 130.13, 133.14, 143.52, 205.70; \text{ESIMS} m/z 212 (M}^+). \]

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\textbf{References and Notes}


8. The yields of 2a-h were moderate due to the formation of many intractable side products.