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

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Received November 7, 2005

Key Words : Cyclopropane, Baylis-Hillman adducts, Sulfur ylide, Michael acceptor

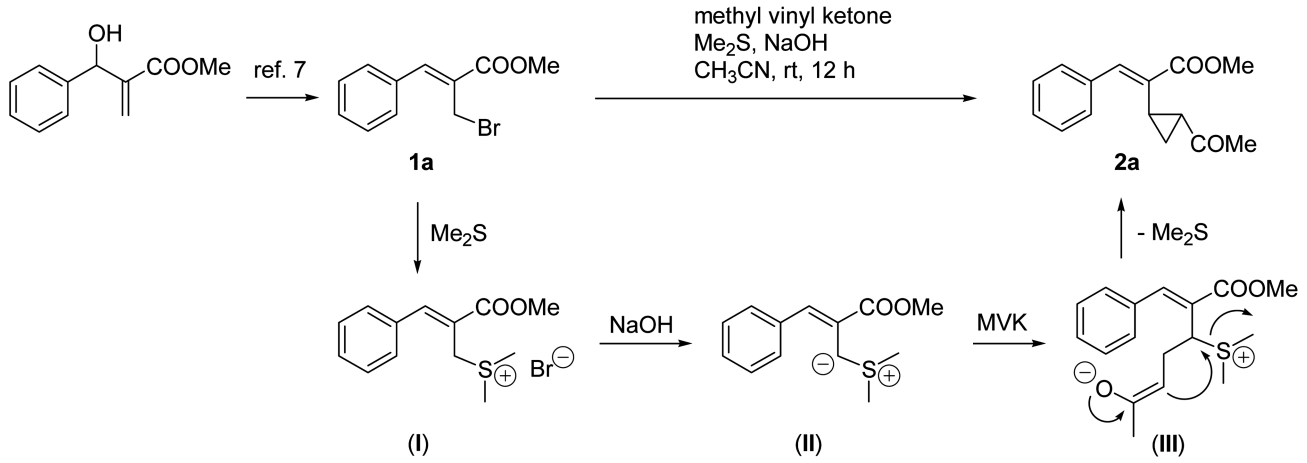
Cyclopropane moiety is a fundamental class of functional group that is the focus of many organic synthesis programs and performs a key structural role in a wide range of biologically active molecules.[1,2] The importance of cyclopropanes is reflected in the enormous effort that has been invested in their 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 insectides,[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 CH_3CN 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 CH_3CN 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]

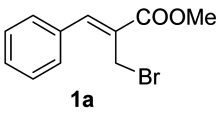
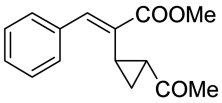
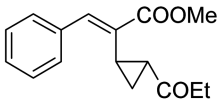
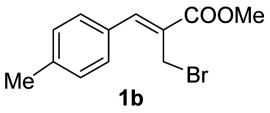
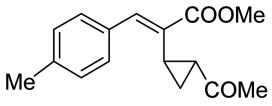
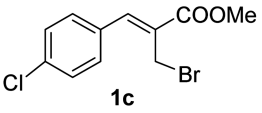
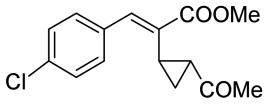
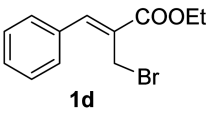
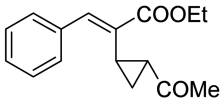
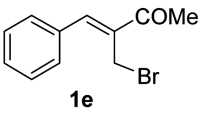
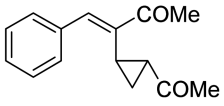
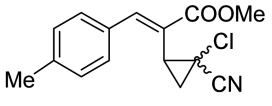
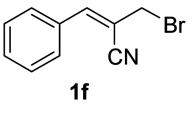
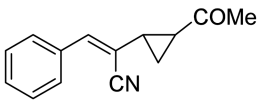
The use of Cs_2CO_3 instead of NaOH showed similar yield of **2a**. However, the use of K_2CO_3 gave **2a** in only trace amounts. When we used nitrogen ylide, which was made from the reaction of **1a** and DABCO in the presence of NaOH, we could not observe the formation of **2a** at all. Variation 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

Table 1. Synthesis of cyclopropane derivatives

Entry	Substrate[a]	Conditions[b]	Products (%)[c]
1	 **1a**	methyl vinyl ketone (1.5 equiv), 12 h	 **2a** (45)[d]
2	**1a**	ethyl vinyl ketone (1.5 equiv), 12 h	 **2b** (42)
3	 **1b**	methyl vinyl ketone (1.5 equiv), 12 h	 **2c** (47)
4	 **1c**	methyl vinyl ketone (1.5 equiv), 13 h	 **2d** (49)
5	 **1d**	methyl vinyl ketone (1.5 equiv), 8 h	 **2e** (54)
6	 **1e**	methyl vinyl ketone (1.5 equiv), 12 h	 **2f** (45)
7	**1b**	2-chloroacrylonitrile (1.5 equiv), 20 h	 **2g** (57)[e]
8	 **1f**	methyl vinyl ketone (1.5 equiv), 12 h	 **2h** (48)

[a]The stereochemistry of double bond of **1a-e** is *Z* and that of **1f** is *E*. [b]Me_2S (1.5 equiv), NaOH (1.5 equiv), CH_3CN, rt, given time. [c]We obtained *trans* isomers in all cases (except for entry 7). [d]The use of Cs_2CO_3 (1.5 equiv) instead of NaOH under the same conditions gave 48% of **2a**. [e]Two stereoisomers were mixed in a ratio of 3 : 2.

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 benzaldenyde and methyl acrylate with aq HBr (rt, 5 h).[7] 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 CH_3CN (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 **2a** as clear oil, 110 mg (45%). Synthesis of **2b-h** was carried out similarly and the spectroscopic data of **2a-h** are as follows.

Compound **2a**: 45%; clear oil; IR (KBr) 1712, 1628, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90-0.97 (m, 1H), 1.47-1.53 (m, 1H), 1.94-2.04 (m, 1H), 2.19 (s, 3H), 2.29-2.36 (m, 1H), 3.82 (s, 3H), 7.34-7.46 (m, 5H), 7.76 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.98, 23.33, 31.01, 31.99, 52.23, 128.46, 129.16, 130.20, 130.34, 134.70,

142.18, 168.16, 207.70; ESIMS *m/z* 245 (M^++H).

Compound **2b**: 42%; clear oil; IR (KBr) 1712, 1628, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89-0.95 (m, 1H), 1.05 (t, J = 7.2 Hz, 3H), 1.45-1.51 (m, 1H), 1.92-1.98 (m, 1H), 2.29-2.36 (m, 1H), 2.47 (qd, J = 7.2 and 2.7 Hz, 2H), 3.81 (s, 3H), 7.33-7.46 (m, 5H), 7.75 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.71, 19.58, 22.67, 30.91, 36.89, 51.98, 128.19, 128.90, 130.01, 130.28, 134.53, 141.90, 167.99, 210.02; ESIMS *m/z* 259 (M^++H).

Compound **2c**: 47%; clear oil; IR (KBr) 1712, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91-0.98 (m, 1H), 1.48-1.54 (m, 1H), 1.96-2.02 (m, 1H), 2.21 (s, 3H), 2.27-2.34 (m, 1H), 2.37 (s, 3H), 3.81 (s, 3H), 7.18 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.02, 21.57, 23.44, 31.00, 32.18, 52.12, 129.14, 129.30, 130.34, 131.77, 139.45, 142.26, 168.27, 207.75; ESIMS *m/z* 259 (M^++H).

Compound **2d**: 49%; clear oil; IR (KBr) 1712, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89-0.95 (m, 1H), 1.47-1.53 (m, 1H), 1.99-2.05 (m, 1H), 2.23 (s, 3H), 2.24-2.32 (m, 1H), 3.82 (s, 3H), 7.35 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.79, 23.11, 31.05, 32.04, 52.29, 128.70, 130.84, 131.50, 133.03, 135.14, 140.68, 167.86, 207.47; ESIMS *m/z* 279 (M^++H).

Compound **2e**: 54%; clear oil; IR (KBr) 1705, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90-0.96 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.47-1.53 (m, 1H), 1.94-2.00 (m, 1H), 2.19 (s, 3H), 2.32-2.36 (m, 1H), 4.27 (qd, J = 7.2 and 1.2 Hz, 2H), 7.35-7.46 (m, 5H), 7.76 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.43, 20.02, 23.25, 30.92, 31.91, 61.01, 128.32, 128.98, 130.09, 130.50, 134.63, 141.80, 167.58, 207.66; ESIMS *m/z* 259 (M^++H).

Compound **2f**: 45%; clear oil; IR (KBr) 1697, 1666, 1612, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83-0.89 (m, 1H), 1.46-1.52 (m, 1H), 1.83-1.89 (m, 1H), 2.17 (s, 3H), 2.27-2.35 (m, 1H), 2.44 (s, 3H), 7.35-7.47 (m, 5H), 7.57 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.87, 22.81, 27.00, 30.85, 31.60, 128.32, 129.11, 130.03, 134.51, 138.86, 141.50, 199.55, 207.63; ESIMS *m/z* 229 (M^++H).

Compound **2g**: 57% (3 : 2 mixture); clear oil; IR (KBr) 2241, 1716, 1261 cm^{-1}; major isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (dd, J = 9.0 and 7.2 Hz, 1H), 2.07 (dd, J = 9.9 and 6.9 Hz, 1H), 2.39 (s, 3H), 2.72 (td, J = 9.6 and 2.1 Hz, 1H), 3.89 (s, 3H), 7.22 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 1.8 Hz, 1H); minor isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47 (dd, J = 8.7 and 7.2 Hz, 1H), 1.86 (dd, J = 9.6 and 7.2 Hz, 1H), 2.39 (s, 3H), 2.64 (td, J = 9.0 and 1.5 Hz, 1H), 3.90 (s, 3H), 7.22 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.40, 21.43, 25.74, 26.35, 26.68, 29.24, 31.16, 31.54, 52.41 (2C), 116.85, 118.73, 123.51, 123.57, 128.83, 129.19, 129.93, 130.21, 130.34, 130.48, 140.19, 140.37, 145.23, 145.38, 166.86, 167.29; ESIMS *m/z* 276 (M^++H).

Compound **2h**: 48%; clear oil; IR (KBr) 2214, 1701, 1184 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.69, 27.98, 28.61, 31.03, 110.84, 116.06, 128.47, 128.78, 130.13, 133.14, 143.52, 205.70; ESIMS *m/z* 212 (M^++H).

Acknowledgments. This work was supported by the grant (R-05-2003-000-10042-0) from the Basic Research Program of the Korea Science and Engineering Foundation (Now controlled under the authority of Korea Research Foundation). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

References and Notes

1. For reviews, see (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (b) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247. (c) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.
2. For the biologically active cyclopropane derivatives, see (a). Kondo, K.; Matsui, K.; Takahatake, Y. *Tetrahedron Lett.* **1976**, *17*, 4359. (b) Midura, W. H.; Mikolajczyk, M. *Tetrahedron Lett.* **2002**, *43*, 3061. (c) Cebula, R. E. J.; Hanna, M. R.; Theberge, C. R.; Verbicky, C. A.; Zercher, C. K. *Tetrahedron Lett.* **1996**, *37*, 8341.
3. For the synthesis of cyclopropane compounds, see (a) Bremeyer, N.; Smith, S. C.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 2681. (b) Oswald, M. F.; Raw, S. A.; Taylor, R. J. K. *Chem. Commun.* **2005**, 2253. (c) Oswald, M. F.; Raw, S. A.; Taylor, R. J. K. *Org. Lett.* **2004**, *6*, 3997. (d) Jain, S. L.; Sain, B. *Tetrahedron Lett.* **2005**, *46*, 37. (e) Jonczyk, A.; Konarska, A. *Synlett* **1999**, 1085. (f) Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 828.
4. For leading references of cyclopropane synthesis involving ylide chemistry, (a) Liao, W.-W.; Li, K.; Tang, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13030. (b) Muller, P.; Ghanem, A. *Org. Lett.* **2004**, *6*, 4347. (c) Avery, T. D.; Fallon, G.; Greatrex, B. W.; Pyke, S. M.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2001**, *66*, 7955. (d) Ye, S.; Huang, Z.-Z.; Xia, C.-A.; Tang, Y.; Dai, L.-X. *J. Am. Chem. Soc.* **2002**, *124*, 2432. (e) Kowalkowska, A.; Sucholbiak, D.; Jonczyk, A. *Eur. J. Org. Chem.* **2005**, 925.
5. For the examples of synthetic applications of cyclopropanes, see (a) Honda, M.; Naitou, T.; Hoshino, H.; Takagi, S.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2005**, *46*, 7345. (b) Leroy, B. *Tetrahedron Lett.* **2005**, *46*, 7563. (c) Hubner, J.; Liebscher, J.; Patzel, M. *Tetrahedron* **2002**, *58*, 10485. (d) Lee, P. H.; Kim, J. S.; Kim, Y. C.; Kim, S. *Tetrahedron Lett.* **1993**, *34*, 7583. (e) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2005**, *7*, 4565.
6. For our recent publications on the chemical transformations of Baylis-Hillman adducts, see (a) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859. (b) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387. (c) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493. (d) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481 and further references cited therein.
7. For the synthesis of cinnamyl bromides from the Baylis-Hillman adducts, see (a) Basavaiah, D.; Hyma, R. S.; Padmaja, K.; Krishnamacharyulu, M. *Tetrahedron* **1999**, *55*, 6971. (b) Crist, R. M.; Reddy, P. V.; Borhan, B. *Tetrahedron Lett.* **2001**, *42*, 619. (c) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213.
8. The yields of **2a-h** were moderate due to the formation of many intractable side products.