ORGANIC LETTERS

2002
Vol. 4, No. 19
3271−3274

Novel Intramolecular Cyclopropanation Reaction of Unsaturated β-Keto Esters

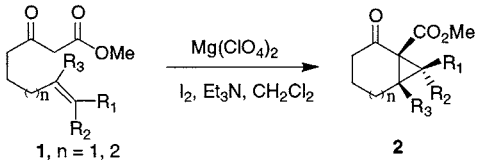
Dan Yang,* Qiang Gao, Chi-Sing Lee, and Kung-Kai Cheung

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

yangdan@hku.hk

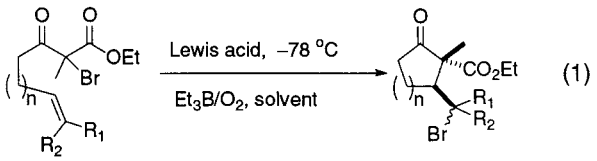
Received July 14, 2002

ABSTRACT



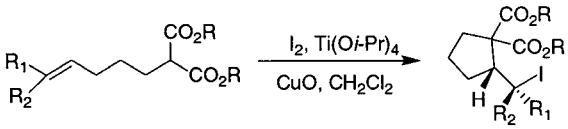
Fused cyclopropane β-keto esters are versatile intermediates for the synthesis of many biologically active natural products. Here we report a new intramolecular cyclopropanation reaction of unsaturated β-keto esters. In the presence of I_2, Et_3N, and Lewis acids such as $Mg(ClO_4)_2$ and $Yb(OTf)_3$, β-keto esters 1 bearing various olefin substituents were transformed to fused cyclopropanes 2 in a highly stereospecific manner with moderate to good yields. The mechanism of the reaction was also investigated.

We recently reported a Lewis acid-catalyzed atom-transfer radical cyclization reaction of unsaturated α-bromo β-keto esters (eq 1).[1] This reaction proceeded under mild conditions and gave excellent diastereo- and enantioselectivities. Furthermore, the transferred bromine atom remained in the product, allowing for further chemical transformations. However, this approach requires the prior introduction of the bromine atom at the α-position before the radical cyclization reaction.



(1)

The halocyclization reaction,[2] which utilizes an electrophilic halogenating reagent to *directly* form the halogenated cyclic products through an ionic pathway, serves as an alternative to the atom-transfer radical cyclization reaction. Taguchi has reported a titanium-salt-promoted iodine-mediated carbocyclization reaction of unsaturated malonic esters and developed a catalytic asymmetric version of this reaction (eq 2).[3]



(2)

This prompted us to apply Taguchi's conditions[3h] to unsaturated β-keto esters such as **1a**. Interestingly, a cyclopropane product **3** was obtained in 30% yield (eq 3). We reasoned that the cyclopropane ring of **3** might come from the enolate

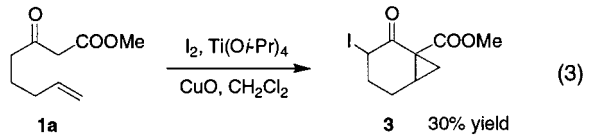
(1) (a) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* **2001**, *123*, 8612−8613. (b) For a recent review on atom-transfer radical cyclization reactions, see: Byers, J. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, Chapter 1.5. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157.

(2) For reviews of halocyclization, see: Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 363.

(3) (a) Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191−1199. (b) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1992**, *33*, 2167−2170. (c) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106−3112. (d) Kitagawa, O.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 1059−1062. (e) Inoue, T.; Kitagawa, O.; Ochiai, O.; Taguchi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 691−692. (f) Inoue, T.; Kitagawa. O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 1479−1482. (g) Inoue, T.; Kitagawa. O.; Ochiai, O.; Shiro, M.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 9333−9336. (h) Inoue, T.; Kitagawa, O.; Oda, Y.; Taguchi, T. *J. Org. Chem.* **1996**, *61*, 8256−8263. (i) Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384−7389.

10.1021/ol0265158 CCC: $22.00
Published on Web 08/20/2002

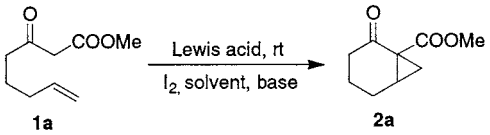
displacement of the primary iodide that was initially formed from an iodocarbocyclization reaction. By further optimizing the reaction conditions, we have found a new Lewis acid-promoted iodine-mediated intramolecular cyclopropanation reaction of unsaturated β-keto esters. The details of this reaction are disclosed herein.



1a **3** 30% yield (3)

The intramolecular cyclopropanation reaction of **1a** was investigated using different Lewis acids, solvents, and bases. The results are summarized in Table 1. When 1 equiv of Lewis acid was used, $Mg(ClO_4)_2$ and $Yb(OTf)_3$ gave notably higher yields of **2a** (45 and 40%, respectively) than $Sc(OTf)_3$ and $Sm(OTf)_3$ in CH_2Cl_2 (entries 1−4). No **2a** was formed when the Lewis acid was absent or changed to $Zn(ClO_4)_2 \cdot 6H_2O$ or CuOTf (entries 5−7). Clearly, some Lewis acids promoted this cyclopropanation reaction. It was important to employ an excess amount of I_2 (4 equiv) for a faster reaction and higher yield (entry 8 vs 1). The highest yield (92%) was obtained when 2 equiv of $Mg(ClO_4)_2$ and 4 equiv of I_2 were used in a 12 h reaction time (entry 9). Toluene was a poor solvent for this reaction: the yield was only 5% even after 24 h (entry 10). When the solvent was changed to a mixture of CH_2Cl_2 and THF (ratio 2:1), the cyclopropanation was completely suppressed (entry 11). Several basic additives such as $NaHCO_3$, 2,6-DMP, and *t*-BuOK were also tested as scavengers of HI, but none were found suitable for the reaction (entries 12−14). No reaction took place for the combination of $Ti(Oi\text{-}Pr)_4$ and Et_3N (entry 15). Therefore, the I_2 (4 equiv)/$Mg(ClO_4)_2$ (2 equiv)/Et_3N (2.5 equiv)/CH_2Cl_2 system was found to be the best reaction conditions.

Table 1. Lewis Acids-promoted Intramoleular Cyclopropanation Reactions[a]



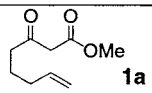
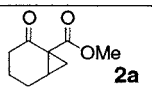
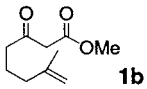
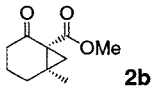
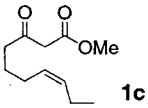
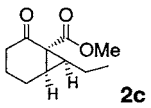
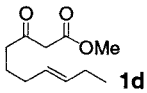
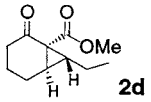
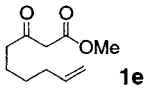
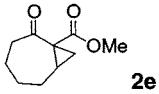
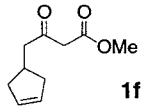
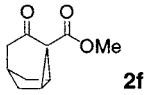
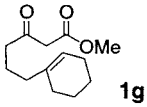
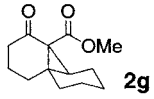
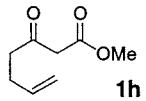
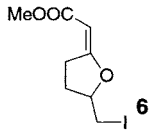
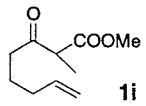
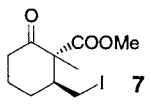
1a **2a**

entry	Lewis acid (equiv)	I_2 (equiv)	base	time (h)	yield (%)[b]
1	$Mg(ClO_4)_2$ (1)	1.5	Et_3N	60	45
2	$Yb(OTf)_3$ (1)	1.5	Et_3N	60	40
3	$Sc(OTf)_3$ (1)	1.5	Et_3N	60	35
4	$Sm(OTf)_3$ (1)	1.5	Et_3N	60	22
5	$Zn(ClO_4)_2 \cdot 6H_2O$ (1)	1.5	Et_3N	60	0
6	CuOTf (1)	1.5	Et_3N	60	0
7	−	4	Et_3N	19	0
8	$Mg(ClO_4)_2$ (1)	4	Et_3N	19	62
9	$Mg(ClO_4)_2$ (2)	4	Et_3N	12	92
10[c]	$Mg(ClO_4)_2$ (2)	1	Et_3N	24	5
11[d]	$Mg(ClO_4)_2$ (1)	1.5	Et_3N	45	0
12	$Mg(ClO_4)_2$ (1)	4	$NaHCO_3$	23	0
13	$Mg(ClO_4)_2$ (1)	1.1	2,6-DMP[e]	20	0
14	$Mg(ClO_4)_2$ (1)	1.1	*t*-BuOK	20	0
15	$Ti(Oi\text{-}Pr)_4$ (1)	1.1	Et_3N	18	0

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.35 mmol), base (0.77−0.87 mmol), Lewis acid, and I_2 in CH_2Cl_2 (8 mL) at rt. [b] Isolated yield. [c] Toluene as the solvent. [d] CH_2Cl_2/THF (2:1) as the solvent. [e] 2,6-Dimethylpyridine.

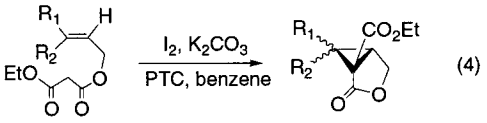
Unsaturated β-keto esters **1a**−**i** bearing different olefin groups were then tested under the above optimized cyclopropanation conditions (Table 2). While monosubstituted olefin **1a** gave cyclopropane product **2a** in 92% yield (entry 1), **2b** was formed smoothly from disubstituted olefin **1b** in good yield (63%; entry 2). Both (*Z*)-olefinic β-keto ester **1c** and (*E*)-isomer **1d** gave their corresponding products **2c** and **2d** in 87 and 67% yields, respectively (entries 3 and 4). The stereochemistries of **2c** and **2d** were confirmed by X-ray

Table 2. Lewis Acid-Promoted I_2-Mediated Cyclopropanation Reactions[a]

entry	substrate	time	product	yield[b]
1	 **1a**	12 h	 **2a**	92%
2	 **1b**	8.5 h	 **2b**	63%
3	 **1c**	19 h	 **2c**	87%
4	 **1d**	14 h	 **2d**	67%
5	 **1e**	18.5 h	 **2e**	43%[c]
6	 **1f**	2.5 d	 **2f**	47%[c]
7	 **1g**	3 d	 **2g**	34%[c]
8	 **1h**	15 h	 **6**	67%
9	 **1i**	10 h	 **7**	47%

[a] Unless otherwise indicated, all reactions were carried out with substrate (0.35 mmol), Lewis acid (0.70 mmol), I_2 (1.4 mmol), and Et_3N (0.875 mmol) in CH_2Cl_2 (8 mL) at rt. [b] Isolated yield. [c] About 30−35% of substrate was recovered.

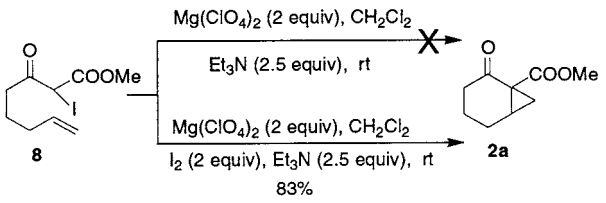
analysis of their corresponding 2,4-DNP derivatives **4** and **5**.[4] Since the stereochemistry of the alkene moiety was retained in the products, the cyclopropanation reaction took place in a highly stereospecific manner. Substrate **1e** was cyclized to form **2e**, in which the cyclopropane ring was fused with a seven-membered ring, in 43% yield (entry 5). When cyclic olefins such as **1f** and **1g** were used, interesting bridged compounds **2f** and **2g**, respectively, were obtained in moderate yields (entries 6 and 7). However, the attempt to get a five/three fused-ring system from **1h** failed, and the major product was the furan-type compound **6** (67%, entry 8).[5] This is because the kinetically favored 5-exo O-alkylation to form the furan ring is much faster than the C-alkylation to form the cyclopentanone.[6] Interestingly, iodo-substituted cyclohexanone **7** was obtained in 47% yield from cyclization of α-methyl *β*-keto ester **1i** (entry 9). Apparently the α-Me group blocked the further nucleophilic substitution of **7**.



(4)

Toke et al. reported a similar I_2-mediated intramolecular cyclopropanation reaction of unsaturated malonic esters under phase transfer catalysis conditions (eq 4).[7] As the stereochemical integrity of the starting olefin was lost, a single electron-transfer cyclopropanation pathway was proposed by Toke.[7b] In our case, however, the observed high stereospecificity suggested that the reaction mechanism is different from that of Toke. The formation of **6** (Table 2, entry 8) ruled out the possibility of carbene intermediates formed by α-elimination of α-iodo *β*-keto esters.[8] To further probe the mechanism, a ^{1}H NMR study on the reaction of **1a** in CD_2Cl_2 was carried out. In the presence of $Mg(ClO_4)_2$, I_2, and Et_3N, the substitution of an α-H by iodine proceeded rapidly to afford **8** and the conversion was about 80% in 10 min. We thus suspected **8** to be a reaction intermediate and prepared **8** independently in about 85% purity using $Mg(ClO_4)_2$/NIS in EtOAc.[9] When **8** was subjected to the above cyclopropanation condition without the addition of I_2, surprisingly no **2a** was detected and most of **8** was slowly converted back to **1a** (Scheme 1); but in the presence of I_2, $Mg(ClO_4)_2$, and

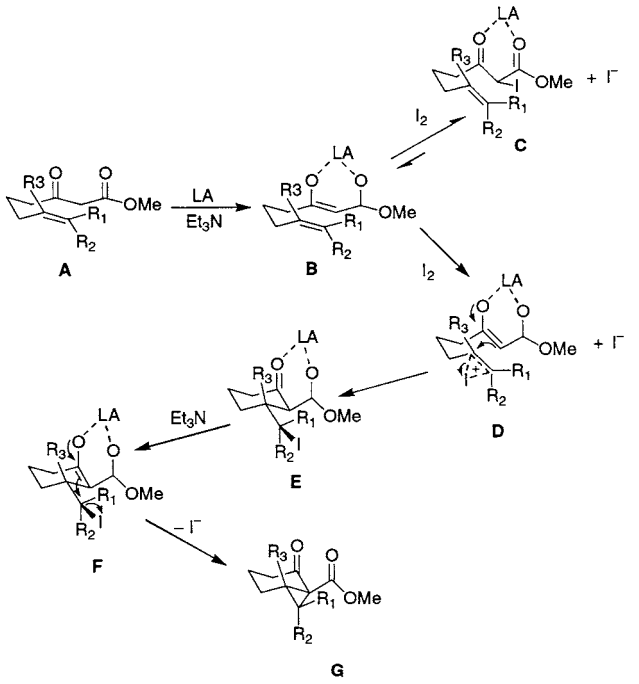
Scheme 1



Et_3N, **8** was converted smoothly to **2a** in 83% yield (Scheme 1). These results indicated the importance of I_2 but not **8** in the intramolecular cyclopropanation reaction.

A plausible mechanism for our intramolecular cyclopropanation reaction is depicted in Scheme 2.[3b] By chelation

Scheme 2



with the two carbonyl groups of *β*-keto esters, Lewis acid (LA) promoted the formation of enolate **B** from substrate **A** in the presence of NEt_3. The iodination of enolate **B** at the α-position to form **C** proceeded quickly due to the higher nucleophilicity of the enolate as compared to that of the olefin, and the equilibrium between **B** and **C** was formed in favor of **C**. Nevertheless, the 6-exo iodocarbocyclization of **B** mediated by I_2 took place via nucleophilic attack of the enolate moiety on the iodoium ion intermediate **D**, yielding cyclic iodo intermediate **E**. The isolation of product **9b** confirmed the intermediacy of **E**. In the presence of Lewis acid and NEt_3, *β*-keto ester **E** was converted to enolate **F**, which underwent intramolecular S_N2 reaction to afford cyclopropane product **G** stereospecifically.

In conclusion, we have developed a mild stereospecific method to prepare fused cyclopropane *β*-keto esters, which

(4) See Supporting Information for details.

(5) Without Lewis acids, some unsaturated *β*-keto esters reacted with I_2/Na_2CO_3 in CH_2Cl_2 to give furan derivatives via O-alkylation. See: (a) Ferraz, H. M.; Sano, M. K.; Scalfo, A. C. *Synlett* **1999**, 567−568. (b) Ferraz, H. M.; Sano, M. K.; Nunes, M. R. S.; Bianco, G. G. *J. Org. Chem.* **2002**, *67*, 4122−4126.

(6) (a) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233−235. (b) House, H. O.; Phillips, W. V.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1978**, *43*, 700−710.

(7) (a) Toke, L.; Szabo, G. T.; Hell, Z.; Toth, G. *Tetrahedron Lett.* **1990**, *31*, 7501−7504. (b) Toke, L.; Hell, Z.; Szabo, G. T.; Toth, G.; Bihari, M.; Rockenbauer, A. *Tetrahedron* **1993**, *49*, 5133−5146. (c) Faigl, F.; Devenyi, T.; Lauko, A.; Toke, L. *Tetrahedron* **1997**, *53*, 13001−13008. (d) Hell, Z.; Finta, Z.; Grunvald, T.; Bocskei, Z.; Balan, D.; Keseru, G. M.; Toke, L. *Tetrahedron* **1999**, *55*, 1367−1376. (e) Finta, Z.; Hell, Z.; Balint, J.; Takacs, A.; Parkanyi, L.; Toke, L. *Tetrahedron: Asymmetry* **2001**, *12*, 1287−1292.

(8) If the reaction proceeded through a carbene intermediate, **1h** should also give a cyclopropane product. See ref 12.

(9) Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.*, in press.

are versatile intermediates for the synthesis of many biologically active natural products.[10,11] Compared to the intramolecular cyclopropanation reactions of unsaturated α-diazo β-keto esters,[12,13] our method is much easier to carry out, as it does not require the prior introduction of the α-diazo group. Future efforts will be directed at developing an enantioselective version of this reaction.

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council. D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry and the Croucher Foundation for a Croucher Senior Research Fellowship Award.

Supporting Information Available: Preparation and characterization of compounds **1**−**8**, and X-ray structural analysis of **4** and **5** containing tables of atomic coordinates, thermal parameters, bond lengths, and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0265158

(10) For recent examples of cyclopropane-containing natural products, see: (a) Clericuzio, M.; Sterner, O. *Phytochemistry* **1997**, *45*, 1567−1572. (b) Arnone, A.; Nasini, G.; Pava, O. V. D. *Phytochemistry* **1997**, *46*, 1099−1101. (c) Guella, G.; Skropeta, D.; Breuils, S.; Mancini, I.; Pietra, F. *Tetrahedron Lett.* **2001**, *42*, 723−725. (d) Bisio, A.; Fontana, N.; Romussi, G.; Ciarallo, G.; Tommasi, N. D.; Pizza, C.; Mugnoli, A. *Phytochemistry* **1999**, *52*, 1535−1540.

(11) For recent examples of using fused cyclopropanes as intermediates for the synthesis of natural products, see: (a) Okamura, W. H.; Zhu, G.-D.; Hill, D. K.; Thomas, R. J.; Ringe, K.; Borchardt, D. B.; Norman, A. W.; Mueller, L. J. *J. Org. Chem.* **2002**, *67*, 1637−1650. (b) Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 12432−12433. (c) Yu, M.; Lynch, V.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 2563−2566. (d) Doyle, M. P.; Hu, W.; Chapman, B.; Marnett, A. B.; Peterson, C. S.; Vitale, J. P.; Stanley, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 5718−5728. (e) Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980−12981. (f) Doyle, M. P.; Peterson, C. S.; Protopopova, M. N.; Marnett, A. B.; Parker, D. L., Jr.; Ene, D. G.; Lynch, V. *J. Am. Chem. Soc.* **1997**, *119*, 8826−8837.

(12) For recent reviews on the synthesis of cyclopropanes through diazo intermediates, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley & Sons: New York, 1998. (b) Ohkita, M.; Nishida, S.; Tsuji, T. In *The Chemistry Of The Cyclopropyl Group*; Rappoport, Z., Eds.; Wiley & Sons: Chichester, UK, 1995; Vol. 2, Chapter 5.

(13) For a recent review on cyclopropanation reactions, see: Pfaltz, A. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998; Vol. 1, pp 100−113.