ORGANIC LETTERS

2007
Vol. 9, No. 9
1667−1670

Acylation of Alkylidenecyclopropanes for the Facile Synthesis of α,β-Unsaturated Ketone and Benzofulvene Derivatives with High Stereoselectivity

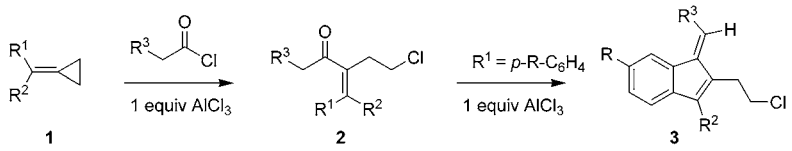
Xian Huang*,†,‡ and Yewei Yang†

Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, PRC, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PRC

huangx@mail.hz.zj.cn

Received February 8, 2007

ABSTRACT



A variety of substituted α,β-unsaturated ketone and benzofulvene derivatives were readily prepared in good to excellent yields via the reaction of alkylidenecyclopropanes with various acyl chlorides in the presence of aluminum chloride. The stereochemistry of the acylation and cyclization is discussed.

Alkylidenecyclopropanes (ACPs) are highly strained but readily available molecules that have served as useful building blocks in organic synthesis.[1] So far, increasing attention has been paid to the transition-metal-catalyzed reactions of unsubstituted methylenecyclopropanes, which have been employed for the construction of complex organic molecules.[2,3] Examples of Lewis acid or Brønsted acid mediated reactions of ACPs have also been disclosed.[4] An attractive but often troublesome feature of methylenecyclopropanes is their multiform reactivities that may lead to formation of a variety of products through various reaction pathways: addition to a C=C double bond or cleavage of proximal and distal bonds of the three-membered ring.[5] Moreover, for the reactions with unsymmetrical ACPs, the

† Zhejiang University (Xixi Campus).
‡ Chinese Academy of Sciences.

(1) (a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (b) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (c) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213.

(2) (a) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6458. (b) Siriwardana, A. I.; Kamada, M.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 5932. (c) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3365. (d) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270. (e) Tsukada, N.; Shibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8123. (f) Nakamura, I.; Siriwardana, A. I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3445. (g) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298. (h) Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203.

(3) (a) Bessmertnykh, A. G.; Blinov, K. A.; Grishin, Y. K.; Donskaya, N. A.; Tveritinova, E. V.; Yur'eva, N. M.; Beletskaya, I. P. *J. Org. Chem.* **1997**, *62*, 6069. (b) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996**, *118*, 10676. (c) Chatani, N.; Takeyasu, T.; Hanafusa, T. *Tetrahedron Lett.* **1988**, *29*, 3979. (d) Ishiyama, T.; Momota, S.; Miyaura, N. *Synlett* **1999**, 1790. (e) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015.

(4) (a) Nakamura, I.; Kamada, M.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2903. (b) Patient, L.; Berry, M. B.; Kiburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1015. (c) Shi, M.; Xu, B. *Org. Lett.* **2002**, *4*, 2145. (d) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175. (e) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043.

(5) (a) Huang, X.; Fu, W.-J. *Synthesis* **2006**, 1016. (b) Zhou, H.; Huang, X.; Chen, W. *J. Org. Chem.* **2004**, *69*, 5471. (c) Huang, X.; Zhou, H.; Chen, W. *J. Org. Chem.* **2004**, *69*, 839. (d) Huang, X.; Zhou, H. *Org. Lett.* **2002**, *4*, 4419.

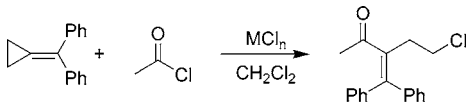
10.1021/ol070331h CCC: $37.00
Published on Web 03/27/2007

regiochemistry generally makes the reaction complicated. Thus, the regio- and stereoselectivity of the insertion and ring-opening methods have been the highlight of methylenecyclopropane chemistry.[6]

The Lewis acid promoted Friedel−Crafts reaction is a powerful carbon−carbon bond-forming process in organic chemistry.[7] Since the 1960s, the chemistry of the acylation of cyclopropanes has been explored with regard to the similarity between the cyclopropane ring and the olefinic double bond.[8] However, the addition of an acyl chloride−aluminum chloride complex to ACPs has not been reported so far. Because of the fact that ACPs are generally more strained than cyclopropanes, they are also expected to react with the acyl cation. Herein, we wish to report the reaction of ACPs with various acyl chlorides in the presence of aluminum chloride. Special emphasis will be placed on the regio- and stereochemical aspects.

We started our investigations by the reaction of diphenylmethylenecyclopropane **1a** and acetyl chloride in the presence of metal halides, in CH_2Cl_2 under an N_2 atmosphere (Table 1). The reaction proceeded smoothly in the presence

Table 1. Effects of Reaction Conditions on the Reaction of ACP **1a** with Acetyl Chloride in the Presence of Metal Chlorides[a]



1a **2a**

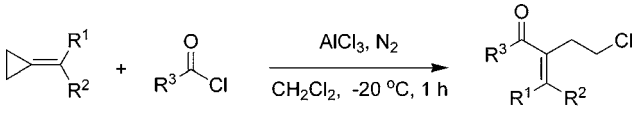
entry	metal chloride (equiv)	temp (°C)	time (h)	yield (%)[b]
1	$TiCl_4$ (1)	−20	0.5	trace
2	$FeCl_3$ (1)	−20	0.5	trace
3	$SnCl_4$ (1)	−20	1	trace
4	$ZnCl_2$ (1)	rt	3	trace
5	$ZrCl_4$ (1)	−20	0.5	46
6	$AlCl_3$ (0.1)	−20	3	trace
7	$AlCl_3$ (1)	rt	0.5	24
8	$AlCl_3$ (1)	−20	1	84
9	$AlCl_3$ (1)	−20	2	81
10	$AlCl_3$ (1)	−20	1	56[c]

[a] Unless otherwise specified, the reaction was carried out using **1a** (1.0 mmol) and acetylchloride (1.0 mmol) in CH_2Cl_2 in the presence of Lewis acids and then quenched by the addition of 10% HCl solution. [b] Isolated yields and the reaction time are determined by TLC on the basis of consuming the starting materials **1a**. [c] Quenched by the addition of Et_3N (0.22 mL, 1.5 mmol) in 4 mL of pentane at −20 °C.

of $ZrCl_4$ to give the α,β-unsaturated ketone derivative **2a**, albeit in moderate yield (Table 1, entry 5). However, when a stoichiometric amount of $AlCl_3$ was used, the yield was improved to 84% (Table 1, entry 8). On the other hand, changing the catalyst to $TiCl_4$, $FeCl_3$, $SnCl_4$, or $ZnCl_2$ only afforded a trace of **2a** (Table 1, entries 1−4). In addition, using a catalytic amount of $AlCl_3$, only a trace of **2a** was formed (Table 1, entry 6).

Next, we carried out the $AlCl_3$-mediated acylation of various ACPs **1** with aliphatic and aromatic acyl chlorides. The results are summarized in Table 2. The symmetrical ACP

Table 2. Reactions of Various Acyl Chlorides with ACPs in the Presence of 1.0 Equiv of $AlCl_3$[a]



1 **2**

entry	ACP **1** (R^1/R^2)	R^3	yield (%)[b]
1	C_6H_5/C_6H_5 (**1a**)	Me	**2a**, 84
2	**1a**	*i*-Pr	**2b**, 67
3	**1a**	Ph	**2c**, 80
4	**1a**	*p*-$MeOC_6H_4$	**2d**, 92
5	**1a**	Bn	**2e**, 89 (**3c**, 5)
6	*p*-MeC_6H_4/*p*-MeC_6H_4 (**1b**)	Me	**2f**, 92
7	*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$ (**1c**)	Me	**2g**, 30
8	**1c**	Bn	**2h**, 55
9	**1c**	*i*-Pr	**2i**, 73
10	**1c**	Ph	**2j**, 76
11	*p*-ClC_6H_4/*p*-ClC_6H_4 (**1d**)	Ph[c]	**2k**, 79
12	*p*-FC_6H_4/*p*-FC_6H_4 (**1e**)	Me	**2l**, 66 (**3i**, 9)
13	C_6H_5/H (**1f**)	Me	(*E*)-**2m**, 68
14	**1f**	Et	(*E*)-**2n**, 71
15	**1f**	Ph	(*E*)-**2o**, 64
16	*p*-BrC_6H_4/H (**1g**)	Me	(*E*)-**2p**, 50
17	**1g**	Et	(*E*)-**2q**, 63
18	2,6-Cl_2-C_6H_3/C_6H_5 (**1h**)	Me	(*E*)-**2r**, 59

[a] Unless otherwise specified, the reaction was carried out using **1** (1.0 mmol) and acyl chloride (1.0 mmol) in CH_2Cl_2 at −20 °C for 1 h. [b] Isolated yields. [c] $(p\text{-}ClC_6H_4)_2C{=}CHCH_2Cl$ was obtained with 8% isolated yield.

1a smoothly reacted with various acyl chlorides, affording the corresponding α,β-unsaturated ketones **2a**−**e** in good yields (Table 2, entries 1−5). For ACP **1b** having an electron-donating methyl group on the benzene ring, the corresponding product **2f** was obtained in higher yield (Table 2, entry 6). However, using ACP **1c** as the substrate, the products **2g**−**j** were formed in moderate yields, along with an unidentified polymeric byproduct (Table 2, entries 7−10). On the other hand, for **1d** and **1e** having electron-withdrawing substituents on the benzene ring, the corresponding adducts **2k** and **2l** were obtained in 79% and 66% yield, respectively (Table 2, entries 11 and 12). All reactions were completed within 1 h.

For the unsymmetric ACPs, only the *E* isomers of the products **2** were obtained (Table 2, entries 13−18). The *E*/*Z*

(6) (a) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 184. (b) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645.

(7) (a) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.8, pp 293−339. (b) Meima, G. R.; Lee, G. S.; Garces, J. M. In *Friedel−Crafts Alkylation*; Sheldon, R. A., Bekkum, H., Eds.; Wiley-VCH: New York, 2001; pp 155−160.

(8) (a) Hart, H.; Curtis, O. E., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 931. (b) Hart, H.; Sandri, J. M. *J. Am. Chem. Soc.* **1959**, *81*, 320. (c) Hart, H.; Levitt, G. *J. Org. Chem.* **1959**, *24*, 1261. (d) Hart, H.; Schlosberg, R. H. *J. Am. Chem. Soc.* **1966**, *88*, 5030. (e) Hart, H.; Schlosberg, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 5189.

selectivity was determined by the ^{1}H NMR spectra of the crude reaction mixture. The structure of the product (*E*)-**2m** was established by spectroscopic analysis and single-crystal X-ray diffraction analysis (Figure 1).

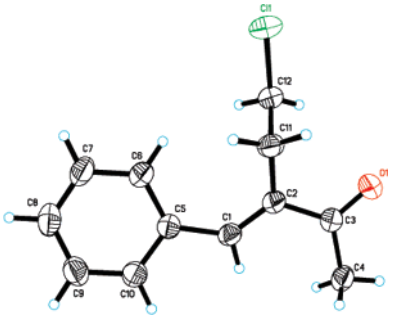
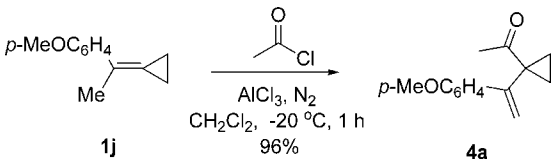


Figure 1. Single-crystal X-ray structure of compound (*E*)-**2m**.

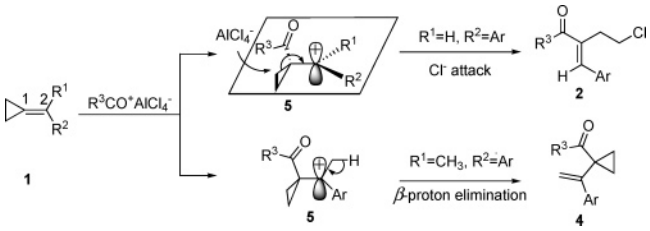
However, for unsymmetric aliphatic ACP **1j**, we observed that the acyl cation easily added to the C=C bond without cleavage of the cyclopropane ring giving the vinylcyclopropane derivative **4a** as a single product under the same conditions (Scheme 1).

Scheme 1. Reaction of ACP **1j** with Acetyl Chloride



A possible pathway for the observed selectivity is based on Yamamoto's model for the HX addition of ACPs (Scheme 2).[9] Attack of an acyl cation on the C-1 position of the C=

Scheme 2. Proposed Mechanistic Pathway for the Reaction in Table 1 and Scheme 1

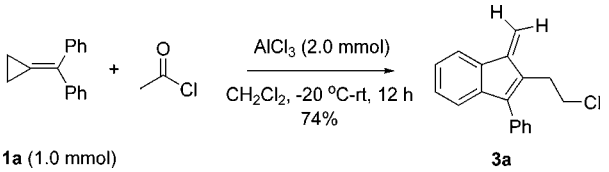


C bond affords cation intermediate **5**. Subsequent nucleophilic attack of the chloride ion (or $AlCl_4^-$) produces the stereospecific ring-opened *E*-isomer **2** (R^1 = H, R^2 = Ar).

If R^1 = CH_3, the intermediate carbonium ion **5** gives **4** via β-proton elimination.[10]

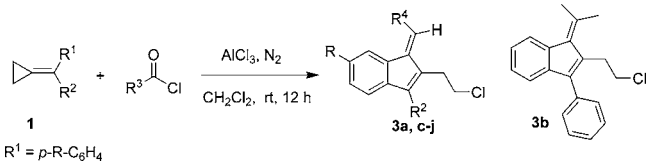
Controlled experiments with varying stoichiometries of aluminum chloride revealed an interesting reactivity pattern, leading to entirely different products. In the presence of 2.0 equiv of $AlCl_3$, **1a** was consumed within 12 h at room temperature to afford **3a** as a major product in 74% yield (Scheme 3).[11]

Scheme 3. Reaction of ACP **1a** with Acetyl Chloride in the Presence of 2.0 Equiv of $AlCl_3$



This reaction also appears to be general, and the results are summarized in Table 3. ACPs **1** having an electron-withdrawing group or an electron-donating group which is para substituted on the aromatic ring did not significantly affect the reaction, and the reaction proceeded readily in satisfactory yields. However, the bulky acyl chloride gives the desired products in low yield (Table 3, entry 2), indicating that the reaction is sensitive to steric hindrance. We also found that arylacetyl chloride reacted with various ACPs very well to give the corresponding adducts in moderate to good

Table 3. Reactions of ACPs with Various Acyl Chlorides in the Presence of 2.0 Equiv of $AlCl_3$[a]



entry	ACP **1**	R^3	R^4	yield of **3** (%)[b]
1	**1a**	Me	H	**3a**, 74
2	**1a**	*i*-Pr	–	**3b**, 19
3	**1a**	Bn	Ph	**3c**, 63
4	**1a**	*p*-MeOC$_6$H$_4$CH$_2$	*p*-MeOC$_6$H$_4$	**3d**, 70
5	**1b**	Me	H	**3e**, 81
6	**1c**	Me	H	**3f**, 54
7	**1d**	Me	H	**3g**, 57
8	**1d**	Bn	Ph	**3h**, 88
9	**1e**	Me	H	**3i**, 49
10	**1e**	Bn	Ph	**3j**, 86

[a] Unless otherwise specified, the reaction was carried out using **1** (1.0 mmol) and acyl chloride (1.0 mmol) in the presence of $AlCl_3$ (2.0 mmol) in 3 mL of CH_2Cl_2 at −20 °C for 30 min and stirred for 12 h at room temperature. [b] Isolated yields.

(9) Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 985.

(10) Liu, L.-P.; Shi, M. *J. Org. Chem.* **2004**, *69*, 2805.

(11) See the Supporting Information for experimental details.

yields (Table 3, entries 3, 4, 8, and 10). The reaction exhibited a surprising degree of stereochemical control, and only *Z*-isomer **3** was isolated. The *E*/*Z* selectivity was determined by the ^{1}H NMR spectra of the crude reaction mixture.

The product **3c** was characterized on the basis of spectroscopic data and the single-crystal X-ray diffraction analysis (Figure 2).

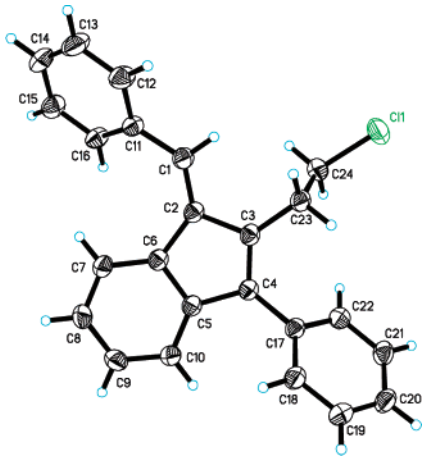
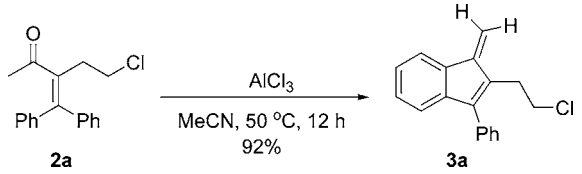


Figure 2. Single-crystal X-ray structure of compound **3c**.

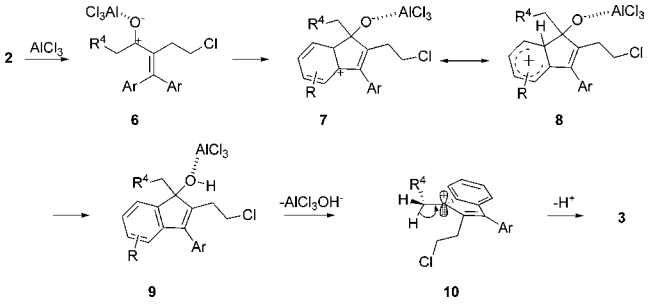
In addition, we investigated the reaction of **2a** with a stoichiometric amount of aluminum chloride in dry MeCN under an N_2 atmosphere at 50 °C for 12 h. The desired product was obtained in 92% yield (Scheme 4).

Scheme 4. Reaction of **2a** in the Presence of 1.0 Equiv of $AlCl_3$



A possible pathway for the formation of **3** is shown in Scheme 5. The carbonyl group of **2** coordinates to aluminum chloride to give the cationic intermediate **6**. The intramolecular Friedel−Crafts reaction of **6** produces the bicyclic intermediate **7**. Proton migration in carbocation **7** or **8** gives intermediate **9**. Tandem elimination of water from the intermediate **9** finally affords product **3** with high stereoselectivity through the E1 process.[12]

Scheme 5. Proposed Mechanism for the Reaction



The fulvene system represents a very attractive unit which is known as a model for theoretical studies.[13] Therefore, our methodology for the easy preparation of functionalized benzofulvene derivatives is unique and important from the viewpoint of both mechanistic and organic synthesis.

In conclusion, we have developed two novel reactions of ACPs with acyl chlorides leading to two different ring-opened products under $AlCl_3$-mediated conditions. In one case, the acylation products **2** can be obtained in good to excellent yields. This bifunctional moiety is one of the most interesting structural units for organic chemists.[14] In the other case, the ACPs are converted to benzofulvene derivatives efficiently with a high *Z*-stereoselectivity. Further studies to expand the scope and synthetic utility of the method are underway.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (Project No. 20472072, 20332060) and CAS Academician Foundation of Zhejiang Province for financial support.

Supporting Information Available: General experimental procedures and spectroscopic data for all compounds and crystallographic data for (*E*)-**2m** and **3c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL070331H

(12) (a) Rodríguez, J. G.; Tejedor, J. L.; Parra, T. L.; Díaz, C. *Tetrahedron* **2006**, *62*, 3355. (b) Cambie, R. C.; Metzler, M. R.; Rutledge, P. S.; Woodgate, P. D. *J. Organomet. Chem.* **1992**, *429*, 41. (c) Neuenschwander, M.; Vögeli, R.; Fahrni, H.-P.; Leahmann, H. *Helv. Chim. Acta* **1977**, *60*, 1073.

(13) (a) Neuenschwander, M. In *The Chemistry of Double-Bonded Functional Groups*; Suppl. A; Patai, S., Eds.; Wiley & Sons, Ltd: Chichester, 1989; Vol. 2, pp 1131−1286. (b) Möllerstedt, H.; Piqueras, M. C.; Crespo, R.; Ottosson, H. *J. Am. Chem. Soc.* **2004**, *126*, 13938. (c) Kovalenko, S. V.; Peabody, S.; Manoharan, M.; Clark, R. J.; Alabugin, I. V. *Org. Lett.* **2004**, *6*, 2457. (d) Alabugin, I. V.; Kovalenko, S. V. *J. Am. Chem. Soc.* **2002**, *124*, 9052.

(14) (a) Perlmutter, P. *Conjugated Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (b) Ebenezer, W. J.; Wight, P. In *Comprehensive Organic Functional Group Transformation*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: Oxford, 1995; Vol. 3, pp 206−276.