A Mild and Efficient Method for Chlorination of *Baylis–Hillman* Adducts Using PPh_3/Cl_3CCONH_2[1])

by **Biswanath Das***, **Nikhil Chowdhury**, **Kongara Damodar**, and **Bommena Ravikanth**

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500007, India (phone: +91-40-7193434; fax: +91-40-7160512; e-mail: biswanathdas@yahoo.com)

A new and convenient stereoselective synthesis of (*Z*)-2-(chloromethyl)alk-2-enoates has been achieved from *Baylis–Hillman* adducts by treatment with PPh_3/Cl_3CCONH_2 at room temperature. The synthesis can proceed under mild and acid-free conditions to form the products in high yields.

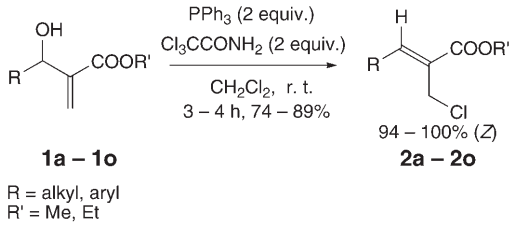
Introduction. – *Baylis–Hillman* adducts [1] have recently been utilized as important building blocks for stereoselective synthesis of different multifunctional molecules [2]. These adducts can be converted into (*Z*)-2-(halomethyl)alk-2-enoates, which are valuable synthons for the synthesis of a variety of important bioactive molecules such as micanecic acid, kizanolide, rennin inhibitor A-72517, β-lactams, α-methylene-γ-butyrolactones, and flavonoids [3]. The conversion of the *Baylis–Hillman* adducts to the corresponding halides has earlier been carried out using hydrogen halides along with strong protic acids ($HBr-H_2SO_4$, $HI-H_3PO_4$) [4], organic acid halides (oxalyl chloride, MsCl) [5], NCS/NBS-Me_2S [6], and Na-halides/KSF clay under microwaves [7]. However, many of the procedures have limitations in terms of yield, selectivity, reaction time, and also the quantity of the catalyst used. Therefore, the developments of new reagents, which are more efficient and lead to convenient procedures with better yields, are highly useful.

Results and Discussion. – In continuation of our of work [8] on the application of *Baylis–Hillman* adducts, we describe herein a simple and efficient process for the one-step conversion of *Baylis–Hillman* adducts, 3-hydroxy-2-methylidenalkanoates **1** into the corresponding (chloromethyl)alkenoates **2** using PPh_3/Cl_3CCONH_2 reagent. The adducts were treated with this reagent in CH_2Cl_2 at room temperature to afford (*Z*)-2-(chloromethyl)alk-2-enoates **2** in high yields (*Scheme 1*). The products were characterized on the basis of their spectral (IR, ^{1}H-NMR, and MS) data. The reaction was found to be equally applicable to both 3-aryl- and 3-alkyl-3-hydroxy-2-methylidenalkanoates. However, with 3-alkyl-3-hydroxy-2-methylidenalkanoates, the yields were lower. *Baylis–Hillman* adducts having electron-withdrawing groups in the aromatic ring also led to the products with somewhat lower yields.

The present reaction conditions tolerated several functionalities such as halogen, NO_2, and ether groups. The method is highly stereoselective. The desired products were

[1]) Part 151 in the series, 'Studies on novel synthetic methodologies'.

Scheme 1



formed with excellent (*Z*)-selectivity (94–100%) as suggested by the ^{1}H-NMR spectra of the crude products. In the ^{1}H-NMR spectrum of a trisubstituted alkene, the β-vinylic H-atom, *cis* and *trans* to the ester group are known to resonate at *ca.* δ 7.5 and δ 6.5 ppm, respectively, when R is aryl, while the signals of the same H-atoms *cis* and *trans* to the ester group appear at *ca.* δ 6.8 and 5.7 ppm, respectively, when R is alkyl [9]. These reported ^{1}H-NMR values were useful to determine the configuration of the products.

PPh_3/Cl_3CCONH_2 has recently been utilized for the conversion of alcohols into the corresponding alkyl chlorides, and the mechanism has been mentioned [10]. We consider that this conversion operates similarly (*Scheme 2*). PPh_3 reacts with Cl_3CCONH_2 to give the intermediate **3**, which then reacts with a *Baylis–Hillman* adduct to give alkoxyphosphonium salt **4**, which subsequently decomposes to form allyl chloride and Ph_3PO.

The stereochemistry of the present conversion can be explained by considering the transition state models **A** and **B** (*Fig.*). Model **A** is more favored than **B**, and (*Z*)-products are formed predominantly.

Scheme 2

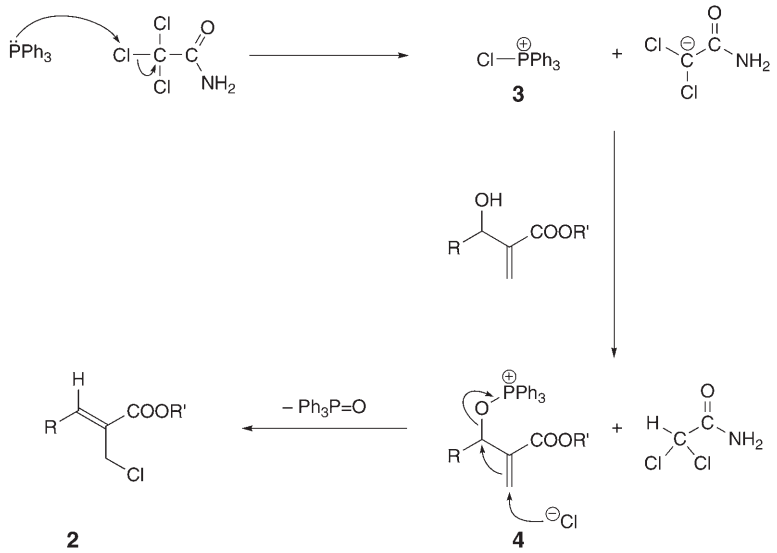
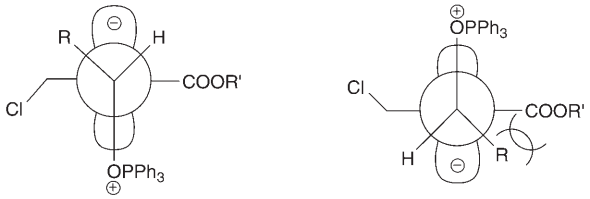


Table. *Synthesis of (Z)-2-(Chloromethyl)alk-2-enoates* **2**[a]) *Using* PPh_3/Cl_3CCONH_2

1	R	R′	Time [h]	Yield [%]
a	Ph	Me	3	89
b	4-Cl−C_6H_4	Me	3.5	85
c	2-NO_2−C_6H_4	Me	3.5	77
d	4-MeO−C_6H_4	Me	3	88
e	4-Me−C_6H_4	Me	3	84
f	4-NO_2−C_6H_4	Me	3.5	77
g	3-NO_2−C_6H_4	Me	3.5	74
h	2-Cl−C_6H_4	Me	3.5	83
i	$Me(CH_2)_5CH_2$	Me	4	76
j	$Me(CH_2)_7CH_2$	Me	4	74
k	$PhCH_2CH_2$	Me	4	75
l	Naphthalen-1-yl	Me	3.5	76
m	4-Cl−C_6H_4	Et	3	77
n	Ph	Et	3	76
o	4-MeO−C_6H_4	Et	3	80

[a]) The structures of all the products were established on the basis of their spectral (IR, ^{1}H-NMR, and MS) and analytical data (see *Exper. Part*). The yields refer to isolated material.



A **B**

In conclusion, we have described a simple and convenient method for the stereoselective synthesis of (*Z*)-2-(chloromethyl)alk-2-enoates using a combination of readily available PPh_3 and Cl_3CCONH_2 as a reagent system at room temperature. The mild and acid-free conditions, application of cheaper reagents, easy experimental procedure, and high yields are the notable advantages of the present protocol.

The authors thank *CSIR*, New Delhi, for financial support.

Experimental Part

General Procedure for the Preparation of Alkenoates **2**. To a stirred soln. of a 3-hydroxy-2-methylidenalkanoate **1** (2 mmol) and PPh_3 (4 mmol) in dry CH_2Cl_2 (10 ml), Cl_3CCONH_2 (4 mmol) was added under N_2. The mixture was stirred at r.t., and the reaction was monitored by TLC. After completion, the reaction was quenched with cold water (10 ml), and the mixture was extracted with CH_2Cl_2 (3×10 ml). The org. layer was dried (anh. Na_2SO_4) and concentrated. The crude product was purified by column chromatography (CC) over silica gel with hexane/AcOEt 9:1 as eluent to yield the corresponding (*Z*)-2-(chloromethyl)alk-2-enoate **2**.

The spectral (IR, ^{1}H-NMR, and MS) and analytical data of some representative products are given below.

Methyl (Z)-2-(Chloromethyl)-3-(4-chlorophenyl)prop-2-enoate (**2b**): IR (KBr): 2926, 1720, 1466, 1290, 770. ^{1}H-NMR: 7.78 (*s*, 1 H); 7.48 (*d*, *J* = 8.0, 2 H); 7.35 (*d*, *J* = 8.0, 2 H); 4.36 (*s*, 2 H); 3.84 (*s*, 3 H). EI-MS: 211, 209 ([*M* – Cl]$^+$), 155, 149, 127, 115. Anal. calc. for $C_{11}H_{10}Cl_2O_2$: C 54.10, H 4.10; found: C 54.03, H 4.07.

Methyl (Z)-2-(Chloromethyl)-3-(3-nitrophenyl)prop-2-enoate (**2g**): IR (KBr): 2962, 1727, 1463, 1295, 778. ^{1}H-NMR: 8.39 (*s*, 1 H); 8.27 (*d*, *J* = 8.0, 1 H); 7.90 (*d*, *J* = 8.0, 1 H); 7.85 (*s*, 1 H); 7.66 (*t*, *J* = 8.0, 1 H); 4.38 (*s*, 2 H); 3.91 (*s*, 3 H). EI-MS: 257, 255, 220 ([*M* – Cl]$^+$). Anal. calc. for $C_{11}H_{10}ClNO_4$: C 51.76, H 3.92; found: C 51.88, H 4.02.

Methyl (Z)-2-(Chloromethyl)dec-2-enoate (**2i**): IR (KBr): 2942, 2853, 1728, 1452, 759. ^{1}H-NMR: 6.95 (*t*, *J* = 7.0, 1 H); 4.28 (*s*, 2 H); 3.79 (*s*, 3 H); 2.31 (*q*, *J* = 7.0, 2 H); 1.56 – 1.46 (*m*, 2 H); 1.39 – 1.24 (*m*, 8 H); 0.89 (*t*, *J* = 7.0, 3 H). EI-MS: 234, 232, 197 ([*M* – Cl]$^+$), 195. Anal. calc. for $C_{12}H_{21}ClO_2$: C 62.09, H 9.05; found: C 62.17, H 9.12.

Methyl (Z)-2-(Chloromethyl)dodec-2-enoate (**2j**): IR (KBr): 2929, 2853, 1720, 1442, 768. ^{1}H-NMR: 6.95 (*t*, *J* = 7.0, 1 H); 4.28 (*s*, 2 H); 3.82 (*s*, 3 H); 2.35 – 2.28 (*m*, 2 H); 1.44 – 1.23 (*m*, 14 H); 0.98 (*t*, *J* = 7.0, 3 H). EI-MS: 227, 225 ([*M* – Cl]$^+$), 193, 165, 149, 135, 109. Anal. calc. for $C_{14}H_{25}ClO_2$: C 64.61, H 9.61; found: C 64.71, H 9.66.

REFERENCES

[1] A. B. Baylis, M. E. D. Hillman, German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.

[2] D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001, and refs. cit. therein; D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811, and refs. cit. therein.

[3] H. M. R. Hoffmann, J. Rabe, *Helv. Chim. Acta.* **1984**, *67*, 413; W. R. Roush, B. B. Brown, *J. Org. Chem.* **1993**, *58*, 2151; H. Mazdiyasani, D. B. Konopacki, D. A. Dickman, T. M. Zydowski, *Tetrahedron Lett*. **1993**, *34*, 435; R. Buchholz, H. M. R. Hoffmann, *Helv. Chim. Acta.* **1991**, *74*, 1213; H. M. R. Hoffmann, J. Rabe, *Angew. Chem., Int. Ed.* **1985**, *24*, 94; D. Basavaiah, M. Bakthadoss, S. Pandiaraju, *Chem. Commun.* **1998**, 1639.

[4] S. E. Drewes, N. D. Emslie, *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079; F. Ameer, S. E. Drewes, N. D. Emsile, P. T. Kaye, R. L. Mann, *J. Chem. Soc., Perkin Trans. 1* **1983**, 2293.

[5] H. G. McFadden, R. L. N. Harris, C. I. D. Jenkins, *Aust. J. Chem.* **1989**, *42*, 301; S. P. Chavan, K. S. Ethiraj, S. K. Kamat, *Tetrahedron Lett*. **1997**, *38*, 7415.

[6] O. Goldberg, A. S. Dreiding, *Helv. Chim. Acta* **1976**, *59*, 1904; J. Rabe, H. M. R. Hoffmann, *Angew. Chem., Int. Ed.* **1983**, *22*, 795.

[7] J. S. Yadav, B. V. S. Reddy, C. Madan, *New J. Chem.* **2001**, *25*, 1114.

[8] B. Das, N. Chowdhury, J. Banerjee, A. Majhi, G. Mahender, *Chem. Lett.* **2006**, *35*, 358; B. Das, N. Chowdhury, J. Banerjee, A. Majhi, *Tetrahedron Lett.* **2006**, *47*, 6615.

[9] G. L. Larson, C. F. de Kaifer, R. Seda, L. E. Torres, J. R. Ramirez, *J. Org. Chem.* **1984**, *49*, 3385; D. Basavaiah, P. K. S. Sarma, A. K. D. Bhavani, *J. Chem. Soc., Chem. Commun.* **1994**, 1091; P. G. Baraldi, M. Guarneri, G. P. Pollini, D. Simoni, A. Barco, S. Benetti, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2501; K. Tanaka, N. Yamagishi, R. Tanikaga, A. Kaji, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3619.

[10] W. Pluempanupat, W. Chavasiri, *Tetrahedron Lett*. **2006**, *47*, 6821.

Received June 21, 2007