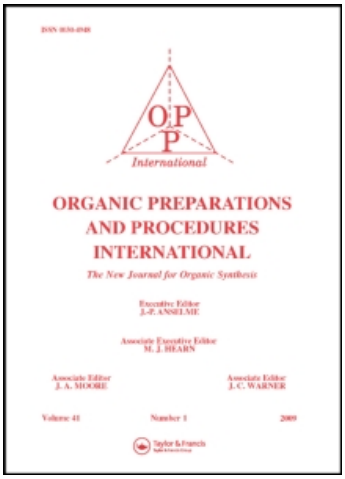


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT AND STEREOSELECTIVE SYNTHESIS OF (Z)-ALLYL CHLORIDES FROM BAYLIS-HILLMAN ADDUCTS USING VILSMEIER-HAACK REAGENT

Y. Liu[a]; H. Zheng[a]; D. Xu[a]; Z. Xu[a]; Y. Zhang[b]
[a] State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou, P. R. CHINA [b] Department of Chemistry, Zhejiang University, Hangzhou, P. R. CHINA

To cite this Article Liu, Y. , Zheng, H. , Xu, D. , Xu, Z. and Zhang, Y.(2007) 'AN EFFICIENT AND STEREOSELECTIVE SYNTHESIS OF (Z)-ALLYL CHLORIDES FROM BAYLIS-HILLMAN ADDUCTS USING VILSMEIER-HAACK REAGENT', Organic Preparations and Procedures International, 39: 2, 190 — 195
To link to this Article: DOI: 10.1080/00304940709356011
URL: http://dx.doi.org/10.1080/00304940709356011

AN EFFICIENT AND STEREOSELECTIVE SYNTHESIS OF (Z)-ALLYL CHLORIDES FROM BAYLIS-HILLMAN ADDUCTS USING VILSMEIER-HAACK REAGENT

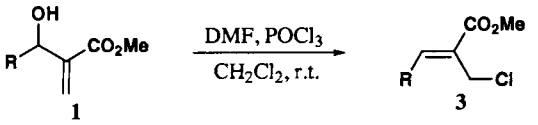
Submitted by Y. Liu,[†] H. Zheng,[†] D. Xu,[†] Z. Xu,*[†] and Y. Zhang[††]
(08/22/06)

[†] *State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology Hangzhou, 310014, P. R. CHINA*

[††] *Department of Chemistry, Zhejiang University Hangzhou, 310028, P. R. CHINA*

E-mail: greensyn@zjut.edu.cn

The Vilsmeier-Haack reagent (halomethyleneiminium salt) formed from treatment of dialkylformamides such as DMF with $POCl_3$ has been an old but useful reagent since its discovery in 1927.[1] It is usually used as reagent for the introduction of an aldehydic (CHO) group into aromatic or heteroaromatic compounds;[2,3] other new applications including halogenation, alkylation and haloalkylation have been recently reported.[4-6] The Baylis-Hillman reaction has received much attention as a useful carbon-carbon bonding-formation reaction in the last decades because it possesses several basic properties of efficient synthetic reactions: atom economy, selective transformations and catalytic process.[7-9] The adducts, 3-hydroxy-2-methyl enealkanoates (derived from acrylate esters), have been utilized as important precursors for stereoselective synthesis of different multifunctional molecules.[7-9] Among these transformations, the preparation of 2-(halomethyl)-2-alkenoates from Baylis-Hillman adducts has drawn much attention as these compounds are useful in the synthesis of various naturally occurring biologically active compounds and their analogs such as α-methylene-γ-butyrolactone, α-alkylidene-β-lactams and flavanoids.[10-12] To date, several methods for the conversion of Baylis-Hillman adducts into 2-(halomethyl)-2-alkenoates have been achieved. For example, the use of hydrogen halides in combination with strong acids (HBr-H_2SO_4, HI-H_3PO_4),[13,14] the reagent Ph_3P-I_2,[15] organic acid halides (oxalyl chloride, MsCl),[16,17] and other reagents including NCS/NBS-Me_2S,[18-20] $AlCl_3$,[21] $FeCl_3$,[22] or $InCl_3$,[23] *etc.* have been reported. However, some limitations are still found in the reported methods including the use of concentrated acids, lack of general applicability, the need to use of O-acetyl derivatives of Baylis-Hillman adducts, long reaction times, and poor yields, *etc.* As part of our continued interest in the conversion of Baylis-Hillman adducts into trisubstituted alkenes,[24-27] herein we report an efficient transformation of Baylis-Hillman adducts into corresponding (*Z*)-allyl chlorides by treatment with Vilsmeier-Haack reagent (halomethyleneiminium salt) in CH_2Cl_2 at room temperature.



a) R = C_6H_5, b) R = 4-$CH_3C_6H_4$, c) R = 2-$CH_3OC_6H_4$, d) R = 3,4-$OCH_2OC_6H_3$, e) R = 4-ClC_6H_4, f) R = 2-ClC_6H_4, g) R = 2-$NO_2C_6H_4$, h) R = 3-$NO_2C_6H_4$, i) R = $C_6H_5CH_2CH_2$, j) R = *n*-C_7H_{15}

The procedure is based on the reaction of $POCl_3$ with DMF to generate the Vilsmeier-Haack reagent chloromethyleneiminium salt **2** *in situ*, followed by the addition of a CH_2Cl_2 solution of the Baylis-Hillman alcohols **1**. At room temperature, the process proceeds efficiently and provides very high yields of allyl chlorides from the corresponding Baylis-Hillman alcohols (*Table*). A variety of substrates were used in this reaction to establish its generality and efficiency, and most reactions proceeded smoothly under the similar conditions. The experimental results showed that the present method was effective for substrates possessing either aryl groups or alkyl substituents, although, the reaction required longer time for alkyl substituted **1** and gave slightly lower yields of products. Among substrates bearing aryl groups, there is not much difference between those containing electron-donating and electron-withdrawing functionalities with respect to reaction times and yields of products. The present reaction conditions tolerate several functionalities such as halogen, nitro, methoxy and ether groups. Besides good yields, the present process also exhibited high stereoselectivity. In all cases, the reaction gave products with Z configuration which was confirmed by NOESY experiments and by comparison with the reported values of products **3**.[22-23] It was shown in NOESY experiments that there is no NOE correlation between the signals of the internal olefinic proton and the allylic methylene protons. According to the reported literature,[28] a possible mechanism for the reaction is depicted in *Fig. 1*.

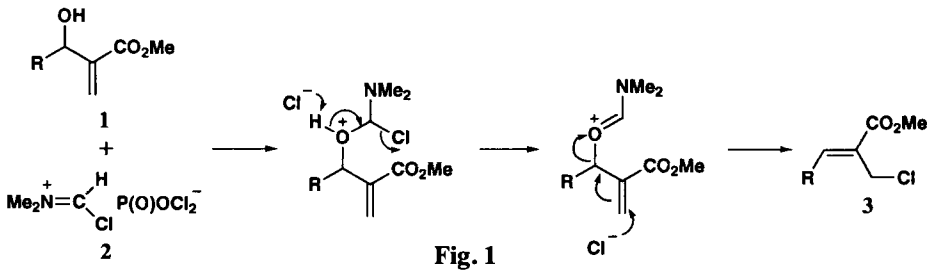


Fig. 1

In summary, we have described a new protocol for the synthesis of (Z)-allyl chlorides from Baylis-Hillman adducts by using Vilsmeier-Haack reagent. The advantages of the method are good yields, excellent stereoselectivity, mild reaction conditions, simple operational procedures as well as readily available reagents and starting materials.

Table. Yields, Elemental Analysis and Spectral Data of Compounds **3**

Cmpd	Yield (%)	IR (cm^{-1})	^1H NMR (δ)	^{13}N NMR (δ)	MS m/z (M^+)	Elemental Analysis (Found) C	H	N
3a[23]	96	1715 1630	7.87 (s, 1H), 7.55-7.52 (m, 2H), 7.46-7.38 (m, 3H), 4.46 (s, 2H), 3.86 (s, 3H)		210	----	----	----
3b[23]	95	1718 1630	7.87 (s, 1H), 7.48 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 4.51 (s, 2H), 3.88 (s, 3H), 2.41 (s, 3H)		224	----	----	----
3c[a]	90	1718 1629	8.08 (s, 1H), 7.64 (d, 1H, J = 8.0 Hz), 7.41 (t, 1H, J = 8.0 Hz), 7.05 (t, 1H, J = 8.0 Hz), 6.94 (d, 1H, J = 8.0 Hz), 4.46 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H)		240	59.88 (59.62)	5.44 (5.51)	---- ----
3d[b]	90	1713 1621	7.76 (s, 1H), 7.10-7.06 (m, 2H), 6.87 (d, 1H, J = 8.0 Hz), 6.02 (s, 2H), 4.49 (s, 2H), 3.86 (s, 3H)		254	56.59 (56.86)	4.35 (4.40)	----
3e[23]	95	1722 1632	7.81 (s, 1H), 7.49 (d, 2H, J = 8.0 Hz), 7.42 (d, 2H, J = 8.0 Hz), 4.43 (s, 2H), 3.88 (s, 3H)	166.37, 142.29, 135.82, 132.44, 130.86, 129.11, 128.78, 52.45, 38.74	244	----	----	----
3f[23]	94	1726 1636	7.97 (s, 1H), 7.67-7.64 (m, 1H), 7.46-7.43 (m, 1H), 7.37-7.34 (m, 2H), 4.36 (s, 2H), 3.90 (s, 3H)	166.38, 140.59, 134.69, 132.98, 130.96, 130.42, 130.30, 130.04, 127.32, 52.8, 39.16	244			
3g[23]	93	1718 1642	8.19 (d, 1H, J = 8.0 Hz), 8.08 (s, 1H), 8.08 (s, 1H), 7.78-7.74 (m, 1H), 7.66-7.59 (m, 2H), 4.22 (s, 2H), 3.87 (s, 3H)		255	----	----	----
3h[c]	92	1721 1637	8.34 (s, 1H), 8.21 (d, 1H, J = 8.0 Hz), 7.87-7.83 (m, 2H), 7.64 (t, 1H, J = 8.0 Hz), 4.38 (s, 2H), 3.86 (s, 3H)		255	51.68 (51.47)	3.94 (3.90)	5.48 (5.53)
3i[23]	90	1721 1646	7.21-7.35 (m, 5H), 7.07 (t, 1H, J = 7.6 Hz), 4.27 (s, 2H), 3.82 (s, 3H), 2.84 (t, 2H, J = 7.6 Hz), 2.66 (q, 2H, J= 7.6 Hz)	166.02, 147.22, 140.34, 129.51, 128.49, 128.26, 126.28, 52.08, 34.35, 30.60	238	----	----	----

Table. Continued...

Cmpd	Yield (%)	IR (cm^{-1})	^1H NMR (δ)	^{13}N NMR (δ)	MS m/z (M^+)	Elemental Analysis (Found) C	H	N
3j[d]	88	1723 1647	6.95 (t, 1H, J= 7.6 Hz), 4.27 (s, 2H), 3.73 (s, 3H), 2.26 (q, *J* = 7.6 Hz, 2H), 1.46-1.22 (m, 10H), 0.82 (t, 3H, J= 6.8 Hz)		232	61.92 (61.70)	9.09 (9.04)	----

a.) Colorless solid, mp. 83-84°C. b) Colorless solid, mp. 79-80°C. c) Light yellow solid, mp. 75-76°C. d) Colorless liquid, bp. 259°C.

EXPERIMENTAL SECTION

Melting and boiling points are uncorrected. Baylis-Hillman adducts **1** are easily prepared according to a reported procedure.[29] ^1H NMR spectra were obtained on a Bruker AC 400 (400 MHz) instrument in $CDCl_3$ using TMS as internal standard. ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on a Bruker AC-100 spectrometer with TMS as internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants J are given in Hz. IR spectra were taken on a Bruker Victor 22 spectrometer. Mass spectra were obtained on a HP 5989B mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

General Procedure.- Phosphorus oxychloride (0.3 g, 2.0 mmol) was added to DMF (0.3 mL) and the mixture was stirred at room temperature for 10 min., then CH_2Cl_2 (15 mL) was added, followed by the Baylis-Hillman alcohol (1.0 mmol) in one portion. After the addition, the mixture was stirred at room temperature and monitored (TLC) until completion. Water (20 mL) was added, and then the organic phase was washed with 15 mL of brine. The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product, which was purified by preparative TLC using ethyl acetate and cyclohexane (1:6) as eluent. All the products are isolated as colorless or light yellow liquids or solids.

Acknowledgement.- We are grateful to the Opening Foundation of Zhejiang Provincial Top Key Discipline for financial support.

REFERENCES

1. A. Vilsmeier and A. Haack, *Ber.*, **60B**, 119 (1927).

2. G. Jones and S. P. Stanforth, *Org. React.*, **49**, 1 (1997).

3. Tasneem, *Synlett.*, 138 (**2003**).

4. S. Paul, M. Gupta and R. Gupta, *ibid.*, 1115 (**2000**).

5. K. Dinakaran and P. T. Perumal, *Indian. J. Chem., Sect. B.*, **39B**, 135 (2000).

6. G. D. Krapivin, N. D. Kozhina, L. A. Chernousenko and V. E. Zavodinik, *Chem. Heterocyclic. Cmpd.*, **35**, 23 (1999).

7. E. Ciganek, *Org. React.*, **51**, 201 (1997).

8. D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, **52**, 8001 (1996).

9. D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, **103**, 811 (2003).

10. H. M. R. Hoffman and J. Rabe, *Angew. Chem. Int. Ed.*, **24**, 94 (1985).

11. R. Buchholz and H. M. R. Hoffmann, *Helv. Chim. Acta*, **74**, 1213 (1991).

12. D. Basavaiah, M. Bakthadoss and S. Pandiaraju, *J. Chem. Soc., Chem. Commun.*, 1639 (**1998**).

13. F. Ameer, S. E. Drewes, N. D. Emsile, P. T. Kaye and R. L. Mann, *J. Chem. Soc., Perkin Trans. 1*, 2293 (**1983**).

14. F. Ameer, S. E. Drewes, M. S. Houston-McMillan and P. T. Kaye, *ibid.*, 1143 (**1985**).

15. B. Das, A. Majhi, J. Banerjee, N. Chowdhury and K. Venkateswarlu, *Tetrahedron Lett.*, **46**, 7913 (2005).

16. H. G. MacFadden, R. L. N. Harris and C. L. D. Jenkins, *Australian J. Chem.*, **42**, 301 (1989).

17. S. P. Chavan, K. S. Ethiraj and S. K. Kamat, *Tetrahedron Lett.*, **38**, 7415 (1997).

18. O. Goldberg and A. S. Dreiding, *Helv. Chim. Acta*, **59**, 1904 (1976).

19. J. Rabe and H. M. R. Hoffmann, *Angew. Chem. Int. Ed.*, **22**, 795 (1983).

20. H. M. R. Hoffman and J. Rabe, *J. Org. Chem.*, **50**, 3849 (1985).

21. D. Basavaiah, S. Pandiarajulu and K. Padmaja, *Synlett.*, 393 (**1996**).

22. P. R. Krishna, V. Kannan and G. V. Sharma, *Synth. Commun.*, **34**, 55 (2004).

23. B. Das, J. Banerjee, N. Ravindranath and B. Venkataiah, *Tetrahedron Lett.*, **45**, 2425 (2004).

24. Y. K. Liu, J. Li, H. Zheng, D. Q. Xu, Z. Y. Xu and Y. M. Zhang, *Synlett.*, 2999 (**2005**).

25. Y. K. Liu, X. S. Xu, H. Zheng, D. Q. Xu, Z. Y. Xu and Y. M. Zhang, *ibid.*, 571 (**2006**).

26. Y. K. Liu, H. Zheng, D. Q. Xu, Z. Y. Xu and Y. M. Zhang, *ibid.*, 2492 (**2006**).

27. J. Li, X. X. Wang and Y. M. Zhang, *ibid.*, 1039 (**2005**).

28. L. D. Luca, G. Giacomelli and A. Porcheddu, *Org. Lett.*, **4**, 553 (2002).

29. H. M. R. Hoffman and J. Rabe, *Angew. Chem., Int. Ed. Engl.*, **22**, 795 (1983).

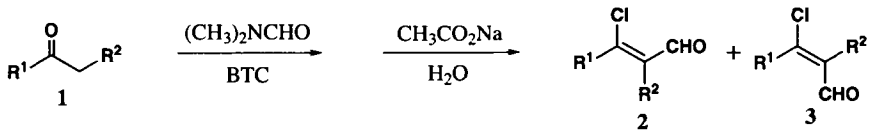
****

A CONVENIENT SYNTHESIS OF β-CHLOROVINYLALDEHYDES WITH *bis*-(TRICHLOROMETHYL) CARBONATE

Submitted by W. K. Su,* Y. G. Zhuang, D. Z. Wu and W. H. Zhong
(06/02/06)

College of Pharmaceutical Sciences, Zhejiang University of Technology
Zhejiang Key Laboratory of Pharmaceutical Engineering
Hangzhou, 310014, P. R. CHINA
E-mail: suweike@zjut.edu.cn

β-Chlorovinylaldehydes are used widely in the synthesis of many natural products,[1] pharmaceutical[3] and pesticide[4] compounds such as triacylbenzene,[1] acridine,[2] pyrimidine,[3] pyrethroid,[4] thiophene,[5] quinoline[6] and thiazepine.[7] In view of the considerable importance of these compounds, various methods have been developed for their preparation. The traditional methods involve the reaction of acetylenic compounds,[8] α-methylene ketones,[9] or silyl keteneacetals[10] under Vilsmeier-Haack conditions. Among these methods, the formylation reaction of α-methylene ketones is one of the most efficient methods for this purpose. However, the traditional Vilsmeier-Haack reaction employs toxic reagents such as phosgene gas and phosphorus oxychloride which form phosphorus salts, which are hazardous to human health and to the human environment.[8] The use of *bis*-(trichloromethyl) carbonate (BTC, triphosgene) in place of $POCl_3$ and $COCl_2$ has been examined in a variety of organic reactions.[11] Recently, we have reported the synthesis of aryl aldehydes using BTC and DMF as a novel Vilsmeier equivalent.[12] Herein, we provide an improved method for the preparation of β-chlorovinylaldehydes from ketones **1** using BTC and DMF under mild conditions (*Scheme 1*).



a) $R^1 = C_6H_5$, R^2 = H; b) $R^1 = p$-$(CH_3)C_6H_4$, R^2 = H; c) $R^1 = p$-$(CH_3O)C_6H_4$, R^2 = H; d) $R^1 = p$-ClC_6H_4, R^2 = H; e) $R^1 = p$-BrC_6H_4, R^2 = H; f) R^1 = 4-(CH_3)-3-$(NO_2)C_6H_3$, R^2 = H; g) $R^1 = C_6H_5$, $R^2 = CH_3$; h) $R^1 = p$-$(CH_3)C_6H_4$, $R^2 = C_6H_5$; i) R^1-R^2 = 1, 2-$C_6H_4(CH_2)_2$; j) R^1-$R^2 = (CH_2)_3$; k) R^1-$R^2 = (CH_2)_4$

Scheme 1