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

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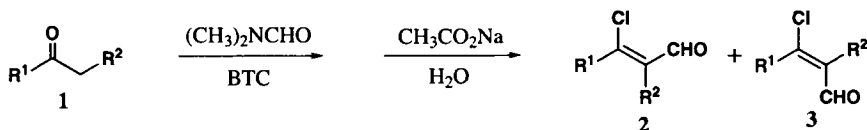
27. J. Li, X. X. Wang and Y. M. Zhang, *ibid.*, 1039 (2005).
 28. L. D. Luca, G. Giacomelli and A. Porcheddu, *Org. Lett.*, **4**, 553 (2002).
 29. H. M. R. Hoffman and J. Rabe, *Angew. Chem., Int. Ed. Engl.*, **22**, 795 (1983).

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

Submitted by W. K. Su,* Y. G. Zhuang, D. Z. Wu and W. H. Zhong
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β -Chlorovinylaldehydes are used widely in the synthesis of many natural products,¹ pharmaceutical³ and pesticide⁴ compounds such as triacylbenzene,¹ acridine,² pyrimidine,³ pyrethroid,⁴ thiophene,⁵ quinoline⁶ 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 keteneacetals¹⁰ 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 POCl₃ and COCl₂ 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) R¹ = C₆H₅, R² = H; b) R¹ = *p*-(CH₃)C₆H₄, R² = H; c) R¹ = *p*-(CH₃O)C₆H₄, R² = H; d) R¹ = *p*-ClC₆H₄, R² = H; e) R¹ = *p*-BrC₆H₄, R² = H; f) R¹ = 4-(CH₃)-3-(NO₂)C₆H₃, R² = H; g) R¹ = C₆H₅, R² = CH₃; h) R¹ = *p*-(CH₃)C₆H₄, R² = C₆H₅; i) R¹-R² = 1, 2-C₆H₄(CH₂)₂; j) R¹-R² = (CH₂)₃; k) R¹-R² = (CH₂)₄

Scheme 1

As shown in *Table 1*, one equiv. of BTC to three equiv. of DMF *in situ* readily formylated acetophenone (**1a**, 2 equiv.) to give **2a** in 55-81% yields (*Table 1, Entries 1-3*). If the ratio was decreased, the yield was reduced dramatically (*Table 1, Entry 5*). Another factor was the temperature and it was found that 60°C was sufficient to carry out the conversion. When other solvents such as CH₂Cl₂, CCl₄ or THF were used in this reaction, the yields did not improve even under refluxing conditions or longer reaction times (*Table 1, Entries 6-8*). Several ketones were reacted with BTC-DMF under similar conditions to determine the scope and limitation of our chlorovinylaldehydes synthesis (*Table 2*). Generally, aromatic ketones gave better yields than alicyclic ones.

Table 2 shows the influence of the substituent group R² on the (*Z/E*) ratio of products. *p*-Substituted and unsubstituted acetophenones gave (*Z*)-isomers (**2a-f, h**) exclusively (*Table 2, Entries 1-6, 8*), but in the case of propiophenone (**1g**), the major product was the (*E*)-isomer (**3g**). The (*Z/E*) ratio of products was established on the basis of ¹H NMR spectra. In addition, the ¹H NMR spectrum of the aldehyde protons in the (*Z*)- and (*E*)-β-aryl-β-chlorovinylaldehydes appeared in the ranges of δ 10.18-10.58 and 9.47 respectively.

In summary, the advantages of present protocol are the use of less hazardous reagents, simple work-up and mild reaction conditions with good yields.

EXPERIMENTAL SECTION

Melting points were obtained on an electrothermal melting-point apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 370 spectrophotometer. ¹H NMR and ¹³C NMR spectra were measured on a Varian Mercury plus-400 spectrometer with tetramethylsilane (TMS) as an internal standard and CDCl₃ as the solvent. Mass spectra were obtained with a Finnigan Trace DSQ spectrometer. Elemental analyses were performed by the Instrumental Analysis Center at Zhejiang University, Flash EA1112. Preparative TLC was performed with silica gel GF-254. All chemicals were from commercial sources.

Typical Procedure.- Dimethylformamide (3 mL) was added to well-stirred BTC (0.3 g, 1 mmol) cooled to 5°C within 10 min, and a solution of acetophenone (**1a**, 0.24 g, 2 mmol) in DMF (5 mL) was added dropwise at room temperature. The reaction mixture was stirred at 25°C for 20 min and then heated to 60°C for 6 h. The reaction was monitored by TLC and quenched with aqueous saturated sodium acetate (10 mL). The mixture was extracted with dichloromethane (20 mL x 2). The combined organic layer was washed with brine, dried (MgSO₄), and the solvent was removed under reduced pressure. The residue obtained was subjected to chromatographic purification on silica gel with cyclohexane/ethyl acetate (90:10) to give (*Z*)-3-chloro-3-phenyl-2-propenal (**2a**).

Table 1. Reaction of Acetophenone with BTC-DMF

Entry	Ratio of BTC:DMF:1a	Solvent	Conditions	Yield (%)
1	1:3:2	DMF	60°C, 6h	81
2	1:3:2	DMF	75°C, 6h	76
3	1:3:2	DMF	r.t., 8h	55
4	1:3:1	DMF	60°C, 6h	80
5	1:3:3	DMF	60°C, 6h	54
6	1:3:2	CH ₂ Cl ₂	reflux, 8h	57
7	1:3:2	CCl ₄	reflux, 6h	75
8	1:3:2	THF	reflux, 7h	78

Table 2. Synthesis of β -Chlorovinylaldehydes using BTC and DMF^a

Entry	Product	Yield (%)	mp (°C) (<i>lit.</i> mp)	IR (cm ⁻¹)	¹ H NMR (δ)
1	2a	81	oil (oil ⁶)	1673	6.66 (1 H, d, J = 6.8 Hz, C = CH), 7.40-7.46 (3 H, m, ArH), 7.70-7.73 (2 H, m, ArH), 10.20 (1 H, d, J = 6.8 Hz, CHO)
2	2b	74	oil (oil ¹³)	1670	2.39 (3 H, s, CH ₃), 6.63 (1 H, d, J = 6.8 Hz, C = CH), 7.23 (2 H, d, J = 8.0 Hz, ArH), 7.63 (2 H, d, J = 7.6 Hz, ArH), 10.18 (1 H, d, J = 6.8 Hz, CHO)
3	2c	72	57-58 (59-60 ¹⁴)	1679	3.87 (3 H, s, OCH ₃), 6.62 (1 H, d, J = 6.8 Hz, C = CH), 6.96 (2 H, d, J = 8.4 Hz, ArH), 7.73 (2 H, d, J = 8.4 Hz, ArH), 10.19 (1 H, d, J = 6.8 Hz, CHO)
4	2d	78	102-103 (103-104 ¹⁴)	1668	6.65 (1 H, d, J = 6.8 Hz, C = CH), 7.44 (2 H, d, J = 8.8 Hz, ArH), 7.70 (2 H, d, J = 8.4 Hz, ArH), 10.21 (1 H, d, J = 6.8 Hz, CHO)
5	2e	80	101-102 (101-102 ¹⁴)	1669	6.66 (1 H, d, J = 6.8 Hz, C = CH), 7.62 (4 H, d, J = 2.0 Hz, ArH), 10.21 (1 H, d, J = 6.8 Hz, CHO)
6	2f ^b	76	109	1673	2.68 (3 H, s, CH ₃), 6.73 (1 H, d, J = 6.8 Hz, C = CH), 7.48 (1 H, d, J = 8.0 Hz, ArH), 7.87 (1 H, dd, J = 8.0 and 2.0 Hz, ArH), 8.38 (1 H, d, J = 2.0 Hz, ArH), 10.23 (1 H, d, J = 6.8 Hz, CHO)
7	2g	75 ^c	oil (oil ¹⁵)	1676	1.83 (1 H, s, CH ₃), 7.38-7.49 (5 H, m, ArH), 10.39 (1 H, s, CHO)
	3g		oil (oil ¹⁵)	1676	2.08 (3 H, s, CH ₃), 7.34-7.45 (5 H, m, ArH), 9.47 (1 H, s, CHO)
8	2h	71	118-119 (118-119 ¹⁶)	1676	2.28 (3 H, s, CH ₃), 6.98-7.00 (4 H, m, ArH), 7.16 (2 H, d, J = 8.4 Hz, ArH), 7.22-7.25 (3 H, m, ArH), 10.58 (1 H, s, CHO)

Table 2. Continued...

Entry	Product	Yield (%)	mp (°C) (lit. mp)	IR (cm ⁻¹)	¹ H NMR (δ)
9	2i	69	37 (37 ¹⁷)	1668	2.59-2.63 (2 H, m, CH ₂), 2.79-2.83 (2 H, m, CH ₂), 7.20 (1 H, d, <i>J</i> = 7.2 Hz, ArH), 7.30-7.38 (2 H, m, ArH), 7.84 (1 H, d, <i>J</i> = 7.6 Hz, ArH), 10.37 (1 H, s, CHO)
10	2j	58	oil (oil ¹⁸)	1671	1.98-2.06 (2 H, m, CH ₂), 2.56-2.61 (2 H, m, CH ₂), 2.80-2.85 (2 H, m, CH ₂), 10.00 (1 H, s, CHO)
11	2k	65	oil (oil ¹⁸)	1678	1.63-1.69 (2 H, m, CH ₂), 1.75-1.81 (2 H, m, CH ₂), 2.26-2.30 (2 H, m, CH ₂), 2.56-2.61 (2 H, m, CH ₂), 10.20 (1 H, s, CHO)

a) Substrate **1** (2 mmol), BTC (1 mmol) and DMF (8 mL) was used. b) MS (EI): *m/z* (%) 227 (14), 225 (35) [M⁺], 115 (100); ¹³C NMR (CDCl₃): δ 20.4, 123.4, 125.3, 130.6, 133.5, 134.8, 137.2, 148.9, 149.5, 190.7; *Anal. Calcd.* for C₁₀H₈ClNO₃: C, 53.23; H, 3.57; N, 6.21; Found: C, 53.27; H, 3.49; N, 6.26. c) Based on the integrals of the aldehyde proton resonances.

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REFERENCES

1. D. Joseph, R. Jankowski, D. Prim, J. Mahuteau and A. Chiaroni, *Tetrahedron Lett.*, **43**, 8051 (2002).
2. D. Pan, G. K. Kar, J. K. Ray, J. M. Lin, S. Amin, S. Chantrapromma and H. K. Fun, *J. Chem. Soc., Perkin Trans. 1*, 2470 (2001).
3. A. S. Tasker, B. K. Sorensen, H. S. Jae, M. Winn, T. W. von Geldern, D. B. Dixon, W. J. Chiou, B. D. Dayton, S. Calzadilla, L. Hernandez, K. C. Marsh, J. R. WuWong and T. J. Opgenorth, *J. Med. Chem.*, **40**, 322 (1997).
4. Y. J. Chen, R. Q. Huang and J. A. Ma, *Gaodeng Xuexiao Huaxue Xuebao*, **16**, 585 (1995); *Chem. Abstr.*, **123**, 199162r (1995).
5. G. Kirsch, D. Prim, F. Leising and G. Mignani, *J. Heterocycl. Chem.*, **31**, 1005 (1994).
6. B. C. Roy, G. K. Kar and J. K. Ray, *Synth. Commun.*, **23**, 1959 (1993).
7. G. Alvernhe, B. Langlois, A. Laurent, I. Le Drean, A. Selmi and M. Weissenfels, *Tetrahedron Lett.*, **32**, 643 (1991).
8. W. Ziegenbein and W. Franke, *Angew. Chem.*, **71**, 573 (1959).

9. J. A. Virgilio and E. Heilweil, *Org. Prep. Proced. Int.*, **14**, 9 (1982).
10. C. P. Reddy and S. Tanimoto, *Synthesis*, 575 (1987).
11. W. K. Su, W. H. Zhong, G. F. Bian, X. J. Shi and J. P. Zhang, *Org. Prep. Proced. Int.*, **36**, 499 (2004).
12. W. G. Shan, X. J. Shi and W. K. Su, *Org. Prep. Proced. Int.*, **36**, 337 (2004).
13. I. A. Rivero, K. A. Espinoza and A. Ochoa, *J. Comb. Chem.*, **6**, 270 (2004).
14. M. Weissenfels, H. Schurig and G. Huehsam, *Z. Chem.*, **6**, 471 (1966); *Chem. Abstr.*, **66**, 55177f (1967).
15. A. Chakraborty and J. K. Ray, *Synth. Commun.*, **25**, 1869 (1995).
16. M. Weissenfels and M. Pulst, *Tetrahedron Lett.*, **9**, 3045 (1968).
17. T. R. Alessi and J. W. Ellingboe, US 4895860 (1990); *Chem. Abstr.*, **113**, 40693m (1990).
18. W. R. Benson and A. E. Pohland, *J. Org. Chem.*, **30**, 1126 (1965).

**A RELIABLE, HIGH-YIELDING PREPARATION OF
2,6-DIMETHYL-4-HYDROXYBENZALDEHYDE**

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(12/01/06)

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2,6-Dimethyl-4-hydroxybenzaldehyde (**4**) is a versatile intermediate in the preparation of compounds which are useful as neuro-protective agents,¹ analgesics,² PPAR α agonists,³ protein kinase C inhibitors,⁴ herbicides⁵ and BODIPY probes for multicolor fluorescence imaging of membrane dynamics.⁶ Several preparations of **4** have been reported and all suffer from either low yield or the use of toxic reagents. Treatment of 3,5-dimethylphenol (**1a**) with dichloromethyl methyl ether in the presence of TiCl₄ produced **4** as a minor product in 15% yield.⁵ A Reimer-Tiemann reaction of **1a** with KOH/CHCl₃ gave **4** in 10% yield⁶ and a modified