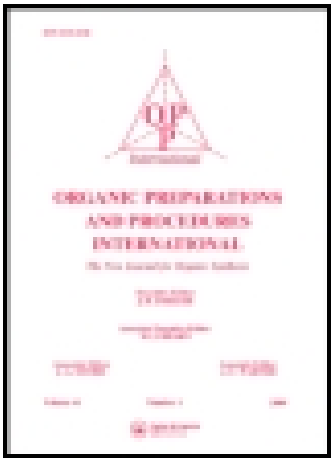

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A CONVENIENT SYNTHESIS OF β-CHLOROVINYLALDEHYDES WITH bis-(TRICHLOROMETHYL) CARBONATE

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

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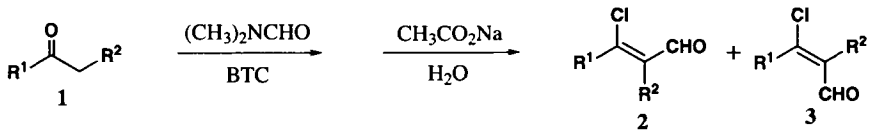
β-Chlorovinylaldehydes are used widely in the synthesis of many natural products,[1] pharmaceutical[3] and pesticide[4] compounds such as triacylbenzene,[1] acridine,[2] pyrimidine,[3] pyrethroid,[4] thiophene,[5] quinoline[6] and thiazepine.[7] In view of the considerable importance of these compounds, 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

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 CH_2Cl_2, CCl_4 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 R^2 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 ^{13}C NMR spectra were measured on a Varian Mercury plus-400 spectrometer with tetramethylsilane (TMS) as an internal standard and $CDCl_3$ 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 ($MgSO_4$), 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_2Cl_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) (*lit.* mp)	IR (cm^{-1})	^1H 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})	^1H 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, J = 7.2 Hz, ArH), 7.30-7.38 (2 H, m, ArH), 7.84 (1 H, d, J = 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); ^{13}C NMR ($CDCl_3$): δ 20.4, 123.4, 125.3, 130.6, 133.5, 134.8, 137.2, 148.9, 149.5, 190.7; *Anal*. Calcd. for $C_{10}H_8ClNO_3$: 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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A RELIABLE, HIGH-YIELDING PREPARATION OF 2,6-DIMETHYL-4-HYDROXYBENZALDEHYDE

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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] PPARα agonists,[3] protein kinase C inhibitors,[4] herbicides[5] 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 $TiCl_4$ produced **4** as a minor product in 15% yield.[5] A Reimer-Tiemann reaction of **1a** with $KOH/CHCl_3$ gave **4** in 10% yield[6] and a modified