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TRICHLOROMETHYL CARBONATE AS A PRACTICAL PHOSGENE SOURCE: APPLICATION TO THE SYNTHESIS OF *α–CHLORO CHLOROFORMATES*

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Summary: Trichloromethyl carbonate **1** is used as a phosgene source in the preparation of α–chloro chloroformates. This stable, crystalline reagent smoothly delivers products **3** in good yield under mild conditions.

The chemistry of α-chloro chloroformates **3** (ACC's) and their derived carbonates has recently seen several applications. Selective dealkylation of tertiary amines,[1] *t* -butoxycarbonyl (BOC) protection of amino acids,[2] and preparation of primary alkyl chlorides from piperidinyl substrates[3] serve as representative examples of the growing utility of the simple ACC's. Unfortunately, synthesis of more complex analogous materials has been slowed by the lack of a convenient preparation. The reported synthesis of these compounds[4] necessitates the use of phosgene thereby introducing the associated handling hazards. Potential difficulties arising with exact measurement of phosgene for those cases where small amounts of substrate are used are also potential concerns. In this communication, we wish to report that trichloromethyl carbonate **1**, a commercially available, crystalline phosgene source[5,6] reacts readily with a variety of aldehyde substrates under mild conditions thereby affording the product α-chloro chloroformates **3** in good to high yields. The preparation of ACC's from a given aldehyde **2** using this reagent can be summarized by the following equation:

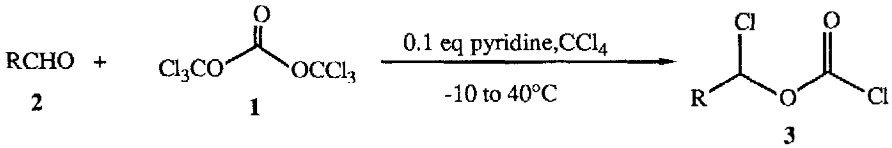
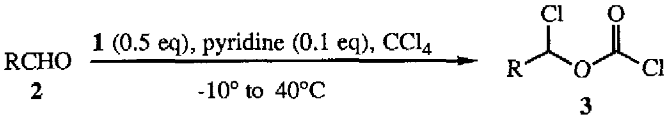


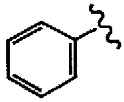
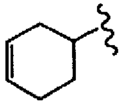
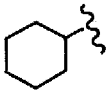
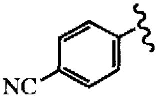
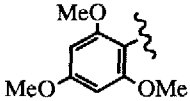
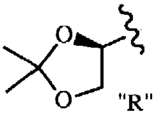
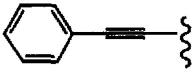
Table I details the examples of ACC's prepared using this reagent which offers a number of advantages as a phosgene source. Reactions proceed smoothly in all examined cases and the product chloroformates **3** are usually isolated as clear, colorless oils. Small quantities of trichloromethyl carbonate can be conveniently weighed using normal safety procedures thus facilitating stoichiometric reactions on small scale. In theory, one third of a mole of carbonate **1** per mole of aldehyde would deliver the desired product. However, optimal yields were observed with a 0.5:1 carbonate / aldehyde ratio. The chloroformate products were usually isolated via vacuum distillation of the filtrate from the reaction mixture[8] and they are most easily identified by a strong, characteristic IR band at 1770-1780 cm^{-1}. This procedure affords yields equal or better than earlier preparations. Yields obtained in this study for acrolein and cyclohexane carboxaldehyde (50% and 89% respectively) are similar to those reported for the phosgene reaction (54% and 87%) yet reaction of **1** with benzaldehyde gives a considerably higher yield than that reported (82% vs 68%).[4] The mechanism of this reaction presumably begins with the generation of phosgene in situ followed by subsequent condensation with an aldehyde to form the ACC product.[4,5] Once isolated, these compounds are conveniently kept neat at -20 °C and show no signs of decomposition after several months storage. The experimental conditions needed for this addition are relatively mild. Slow addition of **1** to a cooled solution of aldehyde in CCl_4[9] followed by brief warming and overnight stirring at room temperature provides the desired product. The following procedure details the reaction of cyclohexane carboxaldehyde (Example D in Table I):

> A mechanically stirred solution of cyclohexane carboxaldehyde (4.05 g, 36.1 mmol) and pyridine (300 mg, 3.79 mmol) in CCl_4 (40 mL) was stirred under a nitrogen atmosphere at -20 °C as solid trichloromethyl carbonate **1** (5.37 g, 18.1 mmol) was added such that the reaction temperature remained between -10 to -20 °C (~ 5 min). The resulting viscous slurry was allowed to warm to room temperature over 90 minutes followed by heating to 40 °C for one hour. The reaction mixture was cooled and allowed to stir overnight at room temperature. Filtration of the pyridinium salts followed by removal of the solvent in vacuo gave ~ 8 g of crude product which was purified via distillation (b.p. 90-91 °C at 10 torr) thereby affording the desired cyclohexyl α–chloro chloroformate **3D** (6.80 g, 89 %).[11]

In conclusion, we have found that trichloromethyl carbonate **1** readily serves as a practical, non-hazardous phosgene source for the synthesis of α–chloro chloroformates. This reagent will enable a broader study of more interesting analogs. Investigations continuing to characterize the chemistry of the ACC's and their derivatives are currently underway.

Table I: Preparation of α- Chloro Chloroformates by Trichloromethyl Carbonate



Entry	R	Distilled yield of **3**, % [a]	bp (lit.) [4]
A		50	50 °C / 16 torr (38 °C /10 torr)
B		82	78-80 °C / 2 torr (70 °C / 0.4 torr)
C		93	93 °C / 8 torr
D		89	90 - 91 °C / 10 torr (90-93 °C / 10 torr)
E		62	b,d
F		64	112 - 116 °C / 0.5 torr [c]
G		66 [c]	76 - 81 °C / 8 torr [c]
H	$CH_3(CH_2)_8$—	94 [d]	90 - 100 °C / 0.5 torr [c]
I		85	d
J	Ferrocene Carboxaldehyde	78	d

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a) All yields reported are for isolated, characterized [10] products. b) The product was isolated as a crystalline solid. c) compound decomposes during distillation. d) The reported yield represents the material remaining after filtration and solvent removal which was shown to be >95 % pure by ^{1}H and ^{13}C NMR. e) see ref. 7.

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3. Olofson,R.A.; Abbott, D.E. *J. Org. Chem.* **1984**, *49*, 2795-9. For a recent review of the chemistry of haloformates see Olofson, R.A. Pure & Appl. Chem. **1988**, *60* , 1715 - 1724.
4. Cagnon,G.; Piteau,M; Senet,J.P.; Martz,J.T.; Olofson,R.A. European Patent # 40,153, **1981**; Chem. Abstr. **1982**, *96*, 142281y. Reactions with quaternary ammonium chlorides as a pyridine substitute generally gave lower yields of the desired ACC.
5. Eckert,H.; Forster,B. *Angew. Chem. Intl. Ed. Eng.* **1987**, *26*, 894-5.
6. Carbonate **1** has been used as a phosgene source in another report where a less hazardous alternative to phosgene was desirable.[5] This material is available from Aldrich Chemical Co. as a new listing under the name "Triphosgene" (catalog # 33,075-2).
7. When (R) - glyceraldehyde acetonide was used, a 1:1 mixture of diastereomeric products was observed by ^{13}C and ^{1}H NMR.
8. After filtration and solvent removal, the product ACC is usually > 95% pure by NMR analysis. Distillation of the more stable products serves to further purify and characterize the products and allows comparison with data reported in previous syntheses of these compounds. Any excess phosgene remaining is dissipated thru an appropriate trap during solvent removal and distillation.
9. A mild (4-5 °C) exotherm occurs as carbonate **1** is added. The addition is monitored such that this exotherm does not cause the reaction temperature to exceed -10 °C.
10. All new compounds were fully characterized by ^{1}H and ^{13}C NMR, infrared, and mass spectroscopy.
11. Spectral data for the cyclohexyl chloroformate **3D**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.08 (d, J= 5.0 Hz, 1H), 1.84 - 1.66 (m, 6H), 1.18 - 1.08 (m, 5H) ppm . ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 149.4, 93.1, 44.3, 27.6, 25.8, 25.0 ppm. IR (film) 2900, 2840, **1775**, 1440, 1290, 1130, 960, 940, 850, 700 cm^{-1}. Mass Spectrum (FAB) m/e = 210 (M^+), 191, 149, 133, 95 amu.

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