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A Convenient Procedure for the Preparation of Oxime Chloroformates

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ABSTRACT

Triphosgene is a convenient reagent for the preparation of *O*-(chloroformyl)oximes from aliphatic and aromatic ketoximes.

O-(Chloroformyl)oximes (**2**) are prepared from oximes (**1**) upon the reaction with excess of phosgene in the yield ranging from 51 to 88%, according to the original procedure of Jumar et al.[1] These ketone derivatives are excellent substrates for the preparation of nitrilium salts[2] under the Beckmann rearrangement conditions, while the reaction is accompanied by the evolution of carbon dioxide. Ketoxime chloroformates react easily with alcohols, amines, thiols, and hydroperoxides to

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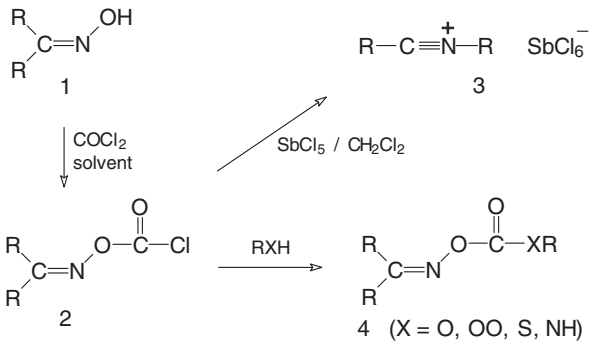
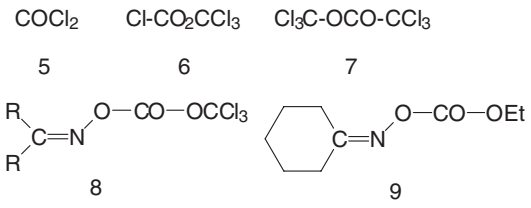
give the respective derivatives.[1,3] The efficient Beckmann rearrangement of ethyl carbonates (**4**, X = O, R = Et) has recently been reported.[4]

In synthesis, the highly toxic gaseous phosgene (**5**) has been successfully replaced by liquid trichloromethyl chloroformate (diphosgene **6**) or



solid *bis*(trichloromethyl)carbonate (triphosgene **7**) as safer and more convenient phosgene substitutes. These reactions include chloroformylation, carbonylation, chlorination, and dehydration.[5] In other examples triphosgene is used for preparation of carbonates,[6] lactams,[7] and



chloro compounds.[8] The application of diphosgene and triphosgene for the preparation of *O*(chloroformyl)oximes has been questioned, however.[2] The reaction of aliphatic and aromatic ketoximes with **2** and **3** was reported to give unseparable mixtures of chloroformyl esters **2** and (trichloromethoxy)formyl esters **8** in variable ratios. These mixtures were reported as not suitable for further transformations to nitrilium salts.[2] Since we required oxime derivatives of formula **2**, the application of triphosgene **7** as the source of phosgene was reconsidered.

We found that addition of **7** to the benzene-pyridine mixture at −15°C results in formation of yellow, solid complex of phosgene-pyridine

$COCl_2 \cdot 2Py$.[9] This in situ formed complex was then used for the preparation of chloroformates **2a–2f**. This was accomplished by addition of the solution of an oxime (0.33 mol equiv.) in benzene followed by reaction carried out at room temperature for one to 2 h. The pure products were isolated by filtration–evaporation–chromatography or extraction–chromatography procedure in the yield exceeding 60%. When 10% excess of **7** was used in the reaction with cyclohexanone oxime **1e**, the yield of **2e** did not improve significantly. The crude chloroformates were obtained in the yield 60–80% and their purity, as estimated by ^{1}H NMR spectra, was sufficient for using them in further reactions. Chromatography of crude chloroformates gave pure samples in the yield generally over 65%. The formation of any traces of *O*-(trichloromethoxy)formyl esters (**8**) was excluded by careful analysis of ^{13}C NMR spectra of the reaction products, which did not show up signals at δ 107.8 characteristic for trichloromethyl carbon atom –O**C**Cl_3. Finally, oxime chloroformates could be transformed to the respective carbonates. For example, compound **2e** when treated with silver nitrite in ethanolic solution gave the ketoxime ethylcarbonate **9**.

EXPERIMENTAL

Melting point values were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared Spectra were determinated with a FT-IR Bruker FS 113 V spectrophotometer for solutions in chloroform. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 300 VT spectrometer operating in the Fourier transform mode using solutions in deuteriochloroform. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane. Electron impact mass spectra were recorded with a AMD 402 spectrometer using ionization energy of 70 eV. The progress of reactions and purity of compounds was monitored by TLC using a precoated aluminium-backed silica plates (E. Merck, no. 5554). Silica gel 60 (Merck 70–230 mesh, no. 7734) was used for flash chromatography.

General Experimental Procedure for the Preparation of Oxime Chloroformates

Triphosgene (**7**) (295 mg, 1 mmol) is added to the solution of pyridine (0.8 mL, 10 mmol) in benzene (5 mL) at −15°C. The solid yellow complex is formed quickly. To this vigorously stirred mixture a solution of the oxime (0.33 mmol) in benzene (2 mL) is added and the reaction mixture is

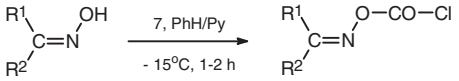
warmed gradually to room temperature. Stirring is continued for 1 to 2 h, while the solid turns white. The precipitate is filtered of, the precipitate is washed with benzene and the filtrate is evaporated to give crude product. This is chromatographed on silica gel column. Alternatively, the crude product is isolated by dilution of the reaction mixture with benzene, washing the benzene solution with water, drying ($MgSO_4$), and evaporation of the solvent under reduced pressure. The yields of chloroformates **2a–2f** are given in the Table 1. The ^1H and ^{13}C NMR spectra of chloroformates **2a–2c** are in accordance with the published data.[2]

2d. Oil, ν_{max}: 1788 (C=O), 1648 (C=N); δ_H 2.44 and 2.38 (two q, $J = 7.4$ Hz, $\underline{CH_2}CH_3$), 2.04 and 2.02 (two s ,CH_3), 1.17 and 1.13 (two t , $J = 7.4$ Hz, CH_3); δ_C: isomer anti: 10.6, 14.8, 28.9, 152.7, 167.9; isomer syn: 10.0, 19.2, 23.7, 159.6, 168.6; *m/z*: 87 (M^+–COCl), 70 (M^+–OCOCl).

2e. Oil, ν_{max}: 1796 (C=O), 1643 (C=N); δ_H 2.58 (2H, t, $J = 6.3$ Hz), 2.40 (2H, t, $J = 6.3$ Hz), 1.70 (6H, m); δ_C 168.7 (C=O), 153.0 (C=N), 31.9, 26.8, 25.8, 25.4 *m/z*: 96 (M^+-OCOCl).

2f. M.p. 168–172°C (from ethyl acetate); ν_{max}: 1783 (C=O), 1641 (C=N); δ_H 3.18 (1H, d, $J = 14.3$ Hz), 2.95 (1H, d, $J = 14.4$ Hz), 2.57 (1H, d, $J = 15.1$ Hz), 2.4−2.0 (5H, m), 0.91 (3H, s, C-19), 0.659 (3H, s, C-18); δ_C 168.8 (C=O), 153.2 (C=N); *m/z*: 401 (M^+–COCl), 385 (M^+–OCOCl), 246, 231.

Table 1. The preparation of the oxime chloroformates.



1a-1f **2a-2f**

	R^1	R^2	The isolation procedure[a]	The yield of **2** after chromatography (crude product)
a	CH_3	CH_3	A	55
b	CH_3	Ph	B	64
c	Ph	Ph	A	57 (79)
			B	45 (78)
d	CH_3	C_2H_5	B	67
e	$(CH_2)_5$		A	62
			B	66 (77)
f	3-cholestane		B	60 (73)

[a]A: filtration-chromatography; B: extraction-chromatography.

The Preparation of Oxime Ethylcarbonate 9

To a solution of the chloroformate **2e** (21.2 mg) in ethanol (0.6 mL) a solution of silver nitrite (26.6 mg) in ethanol (1.6 mL) was added and the mixture was refluxed for 0.5 h until all the substrate reacted (TLC test). The solvent was evaporated and the residue was filtered through a short column of silica gel to give pure **9** as an oil. δ_H: 4.31 (q, 2H, $J = 7.1$, $\underline{CH_2}CH_3$), 2.56 (t, 2H, $J = 6.6$ Hz), 2.37 (t, 2H, $J = 6.6$ Hz), 1.69 (m, 6H), 1.36 (t, 3H, $J = 7.1$ Hz, CH_3). Anal. calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.30; H, 8.50; N, 7.34.

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