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Convenient preparation of dichloromethyl alkyl ethers

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ABSTRACT

Dichloromethyl alkyl ethers have been synthesized from alkyl formates (C1–C4) and oxalyl chloride in the presence of catalytic amount of *N*-methylformanilide. *N,N*-Dimethylformamide is not suitable for the reaction. The method has the advantages of simple experimental procedure, which is applicable to large scale synthesis, without use of harmful reagents.

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Formylation of aromatic compounds suggests the Vilsmeier reagent, but it is restricted to use with electron-rich aromatics.^{1,2} Dichloromethyl alkyl ethers (**2**) are known as useful reagents for formylation of electron-poor aromatics, as well as electron-rich ones.³ For example, treatment of fluorobenzene with dichloromethyl methyl ether (**2a**) in the presence of iron(III) chloride was reported to give a mixture of fluorobenzaldehydes in a US patent.⁴ **2a** is also very effective in the conversion of pyruvic acid to pyruvoyl chloride, a transformation which has not been achieved in good yield by the usual chlorinating agents, such as thionyl chloride, oxalyl chloride, and phosphorous trichloride.⁵

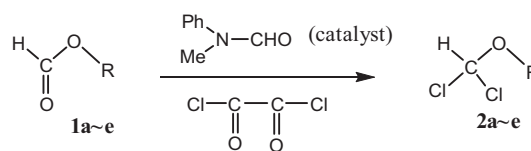
Even though **2** are useful reagents, the only known methods for their preparation have been performed using highly toxic PCl_5 ^{3,6} or triphenylphosphine oxide-phosgene.⁷ Chlorination of chloromethyl ether affords **2a** as a minor product.⁸

We would like to report here a new preparation method for **2**. Thus, oxalyl chloride (COCl_2) (1.0 equiv.) was added dropwise to a mixture of methyl formate (**1a**) (1.5 equiv.) and *N*-methylformanilide (NMF) (0.1 equiv.), followed by the stirring at 25–30 °C until generation of gas had stopped (Scheme 1).

The reaction time was dependent on the reaction scale (8–10 h at 0.1 mol scale, 24 h at 1 mol scale). Direct distillation of the reaction mixture afforded dichloromethyl methyl ether (**2a**) in 71% yield having bp 83–84 °C (lit.^{6a} bp 82–85.5 °C). The ¹H and ¹³C NMR spectra were identified with those in the literature. Other dichloromethyl alkyl ethers (**2b–2e**) were prepared from the corresponding alkyl formates (**1b–1e**) in a similar fashion.

As **1a** (bp 32 °C) and **1b** (bp 54 °C) are volatile, having boiling points lower than that of oxalyl chloride (bp 64 °C), excess amount of **1a** or **1b** were used and the reaction was conducted at a slightly lower temperature than that of boiling point of **1a** or **1b** (25–30 °C or 40 °C, respectively). The yields of **2a** and **2b** were determined based on oxalyl chloride (method A). **1c–1e** having higher boiling points than that of oxalyl chloride were reacted at 60 °C, using excess amount of oxalyl chloride. (Method B) For example, oxalyl chloride (1.3 equiv.) was added dropwise to a mixture of isobutyl formate (**1e**) (1.0 equiv.) and NMF (0.1 equiv.) at 60 °C over 2–3 h, and the whole mixture was stirred at the same temperature until the evolution of gas had stopped. All synthetic examples are summarized in Table 1.

The new preparation method employed NMF as a catalyst, which example gave 97% conversion of **1d** by NMR analysis. When *N,N*-dimethylformamide (DMF) was used as a catalyst, poor results were achieved. Treatment of **1d** with oxalyl chloride in the presence of DMF (0.1 equiv.) did not result in the formation of **2d** under the same reaction conditions by NMR analysis (Scheme 2).



R: a:Me b:Et c:Pr d:Bu e:i-Bu

Scheme 1. Preparation of dichloromethyl alkyl ethers.

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Table 1
Preparation of dichloromethyl alkyl ethers.

1	R	Method ^a	Temp (°C)	Time (h) ^b	Product	Isolated yield (%)	bp °C/torr	lit. bp °C/torr
1a	Me	A ^c	25–30	7 + 24	2a	71	83–84	82–85.5 ^{6a}
1b	Et	A ^c	40	6 + 14	2b	68	54–56/23	107.3 ^{6b}
1c	<i>n</i> -Pr	B ^d	60	2 + 7	2c	76	68–72/101	129 ^{6b}
1d	<i>n</i> -Bu	B ^d	60	2 + 7	2d	83(97) ^f	59/20	48–49/15 ³
1e	<i>i</i> -Bu	B ^d	60	2 + 7	2e	79	42/15	33.5–34.0/8 ^{6b}
1e	<i>i</i> -Bu	B ^e	60	3 + 16	2e	84	59–60/34	

^a Method A; **1**: (COCl)₂: NMF = 1.5:1:0.1 Method B; **1**: (COCl)₂: NMF = 1.0:1.3:0.1.

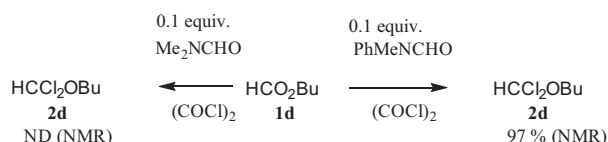
^b Dropwise time of (COCl)₂ + stirring time.

^c 1.5 mol of **1** and 1.0 mol of (COCl)₂ were used.

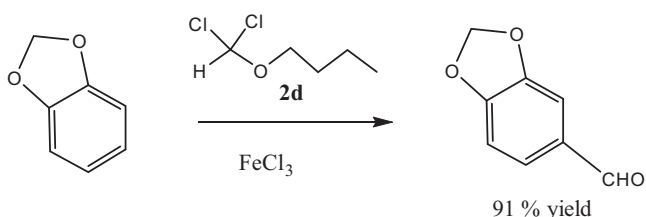
^d 0.10 mol of **1** and 0.13 mol of (COCl)₂ were used.

^e 0.50 mol of **1e** and 0.65 mol of (COCl)₂ were used.

^f Number in parentheses refer to conversion by NMR.



Scheme 2. Comparison of catalysts for preparation of **2d**.



Scheme 3. Direct formylation of 1,3-benzodioxole.

When ca. 10% of the oxalyl chloride had been added, the evolution of gas was stopped whereupon a solid or heavy liquid layer was observed in the bottom of the flask. The precise reason is not clear; however (chloromethylene)-dimethyliminium chloride (DMF Vilsmeier reagent) generated from DMF and (COCl)₂, which is a crystalline solid, does not dissolve in the reaction medium. In contrast, (chloromethylene)methylphenyliminium chloride (NMF Vilsmeier reagent) is reported as a liquid^{9,10} and the appearance of the reaction was homogeneous throughout.

A formylation reaction was demonstrated using **2d** prepared by this method (Scheme 3). Thus, a dichloromethane solution of 1,3-benzodioxole, **2d**, and iron (III) chloride (1:1:1) was stirred at 5 °C for 1 and gave a 91% yield of 1,3-benzodioxole-5-carbaldehyde (piperonal) by an aqueous work up, which was purified by bulb to bulb distillation (180 °C/5 torr) in 67% yield. Mp 36.1 °C (lit.¹¹ 35–36 °C). Piperonal is known as an ingredient of perfume, and many methods have been proposed.¹² However, a direct formylation of 1,3-benzodioxole has never been reported.

This procedure for the preparation of dichloromethyl alkyl ethers, through its use of readily available non-toxic reagents, and its simplicity, might be considered as a convenient method for both laboratory and industrial use.

Representative experiments

Method A

Oxalyl chloride 127 g (1 mol) was slowly added dropwise to a mixture of methyl formate 90 g (1.5 mol) and *N*-methylformanilide

13.5 g (0.1 mol) at 25–30 °C for 7 h. (the condenser was cooled with ice-water) The mixture was stirred for a further 24 h at the same temperature until generation of the gas had stopped. The mixture was distilled through a 300 mm vigreux column to give 81.4 g of **2a** (71% yield) having bp 83–84 °C (lit^{6a} 82–85.5 °C).

GCMS: *m/z* = 79 (M–35, base peak); 81 (M–35+2) = 3:1.

¹H NMR (300 MHz, CDCl₃): δ 3.68 (s, 3H, CH₃), 7.34 (s, 1H, CH).

¹³C NMR (75 MHz, CDCl₃): δ 52.56, 98.82.

Method B

Oxalyl chloride 83.1 g (0.65 mol) was slowly added dropwise to a mixture of isobutyl formate 51 g (0.5 mol) and *N*-methylformanilide 6.75 g (0.05 mol) at 60 °C during 3 h. After the addition, the mixture was stirred for a further 16 h at the same temperature until generation of the gas had stopped. The mixture was distilled through a 300 mm vigreux column to give 66.2 g of **2e** (84% yield) having bp 59–60 °C/34 torr (lit^{6b} 33.5–34.0 °C/8 torr).

GCMS: *m/z* = 85, 83, 78, 57 (base peak), 56, 43, 41.

¹H NMR (300 MHz, CDCl₃): δ 0.96 (d, *J* = 6.6 Hz, 6H, CH₃), 1.88–2.01 (*m*, 1H, CH), 3.75 (d, *J* = 6.6 Hz, 2H, CH₂), 7.34 (s, 1H, CH).

¹³C NMR (75 MHz, CDCl₃): δ 19.04, 27.61, 72.51, 98.13.

(1 torr = 133.32 Pa).

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