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A practical synthesis of chloromethyl esters from acid chlorides and trioxane or paraformaldehyde promoted by zirconium tetrachloride

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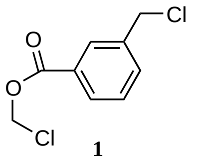
Abstract—A practical synthesis of chloromethyl esters from acid chlorides and trioxane or paraformaldehyde using zirconium tetrachloride as the Lewis acid has been demonstrated. The new procedure is highly chemoselective and applies to a variety of acid chlorides. © 2002 Elsevier Science Ltd. All rights reserved.

Chloromethyl esters represent an important class of intermediates in the synthesis of prodrugs[1] in which the methylene bridge links the lipophilic and hydrophilic parts of a molecule. The need for a practical and scalable synthesis of the linker **1** arose during the process development of an antifungal drug candidate.



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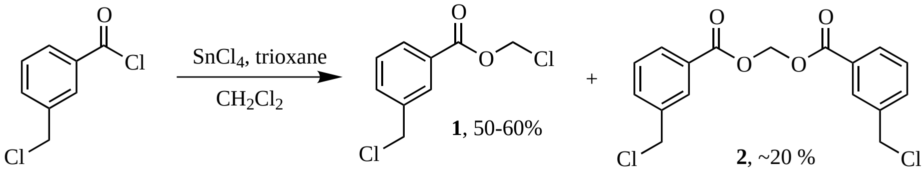
Examination of the literature on the preparation of chloromethyl esters identified two main protocols: (1) alkylation of carboxylates with chlorobromomethane[2] or chloromethyl chlorosulfonate[3] and, (2) condensation of aldehydes with acid chlorides in the presence of a Lewis acid.[4] The latter procedure was selected for evaluation as it did not involve the use of potentially carcinogenic alkylating agents. Our initial attempts (Scheme 1) to improve the reported procedure[4] involved replacing paraformaldehyde with the easier to handle trioxane and the use of tin tetrachloride instead of zinc chloride as the Lewis acid.[5] Although those changes resulted in higher yields of **1** and improved the reaction scale-up feasibility, the formation of the methylene-bridged 'dimer' **2** in ~20% yield was observed on a larger scale as a secondary reaction pathway, resulting in laborious work-up and tedious purification of the product. In addition, the presence of tin salts in the waste streams raised safety concerns.

After screening a series of Lewis acids, we were delighted to find that the use of zirconium tetrachloride instead of tin tetrachloride virtually completely suppressed the formation of dimer **2**. The only by-product under these reaction conditions was the corresponding carboxylic acid, which could be removed easily by an aqueous sodium carbonate wash during work up. The



Scheme 1.

Keywords: chloromethyl ester; acid chloride; trioxane; paraformaldehyde; zirconium tetrachloride.

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Table 1. [a]

Lewis acid	$ArCO_2CH_2Cl$, **1**	$(ArCO_2)_2CH_2$, **2**	$ArCO_2H$
$SnCl_4$	43	18	26
$TiCl_4$	62	2	34
$ZrCl_4$	87	0.1	13

[a] Ar = 3-$ClCH_2C_6H_4$-.

Table 2.

Entry	R	Isolated yield of RCO_2CH_2Cl (%)
1	3-$ClCH_2$-C_6H_4-	72
2	Ph-	75
3	2-NO_2-C_6H_4-	64
4	4-NO_2-C_6H_4-	90
5	4-F-C_6H_4-	98
6	4-Cl-C_6H_4-	94
7	4-Br-C_6H_4-	79
8	3-CH_3-C_6H_4-	66
9	4-CH_3-C_6H_4-	64
10	3-CH_3O-C_6H_4-	64
11	2-CH_3O-C_6H_4-	Mixture
12	4-CH_3O-C_6H_4-	Mixture
13	2-Furyl-	Mixture
14	2-Thienyl-	88
15	1-$C_{10}H_7$-	Mixture
16	$PhCH_2$-	66

absence of the dimer **2** dramatically simplified the processing and product isolation. In addition, substituting tin tetrachloride with the easier to handle zirconium tetrachloride improved the process safety.[6]

Table 1 shows the relative ratios (HPLC area%) of the chloromethyl ester **1**, the methylene bridged dimer **2**, and the carboxylic acid in reaction mixtures when tin, titanium and zirconium tetrachlorides (1 equiv. each) were employed.

Using optimized stoichiometric ratios (0.9 equiv. of $ZrCl_4$, 0.37 equiv. of trioxane or 1.2 equiv. paraformaldehyde) and reaction conditions (dichloromethane, 0–25°C, 1 h) we next examined the scope and generality of this chloromethylation method. Most aromatic and heteroaromatic acid chlorides (Table 2) subjected to the $ZrCl_4$/trioxane (or paraformaldehyde for entries 4–7) system produced the corresponding chloromethyl esters in good yield with only trace amounts of dimeric by-product. The procedure proved to be particularly effective for benzoyl chlorides bearing electron withdrawing substituents in the *para* position (entries 4–6) and 2-thiophenecarbonyl chloride (entry 14). On the other hand, acid chlorides attached to electron-rich aromatic and heteroaromatic rings gave products in moderate yields (entries 8–10) or produced complex mixtures (entries 11–13, 15), presumably as a result of competing Friedel–Crafts processes.

In summary, a convenient and practical procedure for preparation of chloromethyl esters from acid chlorides and trioxane or paraformaldehyde, promoted by the easy to handle zirconium tetrachloride, has been developed. The advantages over alternative methods include high chemoselectivity, shorter reaction time, straightforward processing and simple product isolation.

References

1. For a recent review see: Krise, J. P.; Stella, V. J. *Adv. Drug Delivery Rev.* **1996**, *19*, 287.
2. Ozawa, N.; Yazawa, N. Patent WO 9308152, 1993.
3. (a) Baltzer, B.; Godtfredsen, W. O. *J. Antibiot.* **1980**, *33*, 1183; (b) Binderup, E.; Hansen, E. T. *Synth. Commun.* **1984**, *14*, 857; (c) Harada, N.; Hongu, N.; Tanaka, M.; Kawaguchi, T.; Takayuki, H.; Hashiyama, T.; Tsujihara, K. *Synth. Commun.* **1994**, *24*, 767.
4. Iyer, R. P.; Yu, D.; Ho, N.; Agrawal, S. *Synth. Commun.* **1995**, *25*, 2739.
5. Yang, W.; Wang, X.; Bhattacharya, A.; Chau, M. US Patent 6326509, 2001.
6. A typical procedure is as follows for 3-$ClCH_2C_6H_4$-$COCH_2Cl$ (Table 2, entry 1): The acid chloride (50 g, 1.0 equiv.) was added to a stirred suspension of zirconium tetrachloride (55.4 g, 0.9 equiv.) in dichloromethane (500 mL, 10 mL per 1 g acid chloride) at room temperature. After 15 min, the reaction mixture was cooled to 0°C and trioxane (8.8 g, 0.37 equiv.) was added as a solution in dichloromethane (20 mL). The slurry was stirred at 0–25°C for 1 h (HPLC indicated 92:8 ratio of the product to the acid by-product) and cooled again to 0°C. Water (250 mL) was added slowly while maintaining the temperature below 25°C and the biphasic mixture was agitated for 15 min. The organic phase was separated, washed with 1 N sodium bicarbonate solution (250 mL) to remove the carboxylic acid, and then washed with water (100 mL). Dichloromethane was exchanged for heptane (500 mL) by distillation to a final volume of 300 mL. Ethyl acetate (15 mL) was added to the heptane at 70°C and the product crystallized upon cooling to room temperature. The product was filtered, washed with heptane and dried to give 41.4 g (72%) of **1** as a white solid (mp 42°C), HPLC purity: 99.8 area%. ^1H NMR (300 MHz, $CDCl_3$): δ 4.63 (s, 2H), 5.97 (s, 2H), 7.48 (t, $J=7.7$ Hz, 1H), 7.66 (d, $J=7.5$ Hz, 1H), 8.05 (d, $J=7.9$ Hz, 1H), 8.11 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.29, 69.31, 129.17, 130.10, 134.03, 138.20, 164.11. IR (KBr, cm^{-1}): 1740, 1281, 1175. MS: 220 $[M+H]^+$, 183 $[M-Cl]^+$, 153 $[M-OCH_2Cl]^+$. Anal. calcd for $C_9H_8O_2Cl_2$: C, 49.34; H, 3.68; Cl, 32.36. Found: C, 49.41; H, 3.72; Cl, 32.30.