

Zinc-Promoted Selective Cleavage of Ethers in Presence of Acyl Chloride

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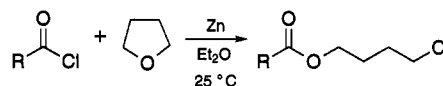
The protection of hydroxyl groups as suitable ether derivatives and their subsequent cleavage constitute an important process in the synthesis of natural products and polyfunctional molecules. A variety of reagents are available for the cleavage of ethers but these are not always satisfactory for complex molecules containing sensitive functionalities and requiring selective deprotection.¹ Thus, there is continued interest in developing new reagents which dealkylate ethers more selectively and under mild conditions.²

During an investigation of reactions of organozinc compounds in THF we have encountered an unusual cleavage of THF with the combination of zinc and acyl chloride leading to the formation of 4-chlorobutyl alkanates. To the best of our knowledge, this type of cleavage of THF or ether with acyl chlorides in the presence of zinc is unprecedented.³ This prompted us to investigate this unusual zinc-promoted cleavage of ethers in more details.

We have discovered that tetrahydrofuran does undergo cleavage with a variety of acid chlorides including acyclic, cyclic, and aromatic ones in the presence of zinc to produce 4-chlorobutyl alkanates in high yields (Table 1). In a general typical procedure, a suspension of a catalytic amount of commercial zinc dust (25 mol %) in ether was stirred with THF (1 mmol) and acid chloride (1 mmol) at room temperature for a certain period of time as required for completion. The product was isolated by a simple workup involving filtration of the zinc dust (approximately 85% of Zn dust was recovered) and evaporation of ether.

This reagent system is also very effective in the cleavage of acyclic ethers. The procedure is the same as for the cleavage of THF except that petroleum ether (40–60 °C) is used as solvent replacing ether. As shown in Table 2 different types of ethers underwent cleavages by this procedure to produce the corresponding alkyl chlorides and the alkanates.⁴ If one of the alkyl groups is benzyl, allyl, or pyranlyl, the C–O bond attached to these moieties is cleaved exclusively (entries 10, 11, 13–16) regardless of the nature of the other alkyl part. Possibly, the cleavage is being facilitated by electronic influence

Table 1. Cleavage of Tetrahydrofuran with Zn/Acyl Chloride



entry	R	time (h)	yield (%) ^a
1	CH ₃	3	87 ^{5a}
2	C ₂ H ₅	6	80 ^{5a}
3	n-C ₃ H ₇	14	88 ^{5a}
4	i-C ₃ H ₇	14	80 ⁷
5	PhCH ₂	6	90 ⁸
6	cyclohexyl	8	82 ⁹
7	Ph	18	70 ^{5a}

^a The yields refer to pure isolated products, fully characterized by IR and ¹H NMR.

of these groups. Thus, the C–O bond cleavage can be directed to the desired way by proper choice of alkyl groups (entries 2, 14). Another interesting feature of this procedure is that aryl alkyl ethers are inert to this reagent system (entry 12). Selective cleavage of dialkyl ethers in presence of an aryl alkyl ether are very efficiently achieved (entry 13). A cyclic ether is also found to be cleaved preferentially over an acyclic one as observed in the cleavage of THF in ether solvent. The reaction condition is mild enough not to induce any rearrangement even during the cleavage of tertiary and secondary ethers (entries 6–8), although one tertiary ether (entry 9) furnishes the corresponding olefin by facile elimination of HCl during the reaction.

To extend the scope of this reagent further, a few epoxides were also subjected to cleavage by this procedure to produce the corresponding chloroethyl alkanates (Table 3). In the reaction of 1,1-diphenyl-2,2-dimethylethylene oxide, the parent olefin is obtained by the elimination reaction of initially formed chloroacetate (entry 3). This indicates that this reagent has also the potential to be used for regeneration of olefins from epoxides.

The exact mechanism and the precise role of zinc in this cleavage reaction is not very clear to us. Presumably, it is an electrophilic cleavage in which the oxonium species undergoes nucleophilic attack by chloride at the site best able to accommodate an incipient carbocation. There are some reports in the literature^{1,5} about the cleavage of THF and ether by acyl chlorides catalyzed with zinc chloride, although no systematic study has been made. So, it was considered whether this cleavage reaction was effected by zinc chloride, arising from the reaction of zinc dust and traces of HCl present in the acid chloride. Taking into consideration the fact that 85% of the zinc dust is recovered and only 15% is consumed during reaction (see Experimental Section), a few cleavage reactions have been carried out in the presence of 15% of usual amount of zinc dust and also with an equivalent amount of zinc chloride. In both the cases, although the reactions have been initiated, the progress of the cleavage was only 10–20%. Thus the presence of zinc dust is necessary for the satisfactory progress of the reaction. So it may be speculated that the cleavage is

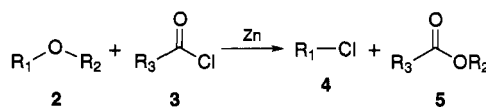
(1) (a) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* 1983, 249. (b) Maercker, A. *Angew. Chem. Int. Ed. Engl.* 1987, 26, 972.

(2) (a) Baldwin, J. W.; Haraldsson, G. G. *Acta. Chem. Scand. B* 1986, 40, 400. (b) Sarma, J. C.; Borbaruah, M.; Sarma, D. N.; Barua, N. C.; Sharma, R. P. *Tetrahedron* 1986, 42, 3999. (c) Narayana, C.; Padmanabhan, S.; Kabalka, G. W. *Tetrahedron Lett.* 1990, 31, 6977. (d) Nishiguchi, T.; Bougauchi, M. *J. Org. Chem.* 1990, 55, 5606. (e) Kadam, S. M.; Nayak, S. K.; Banerjee, A. *Tetrahedron Lett.* 1992, 33, 5129. (f) Nayak, S. K.; Kadam, S. K.; Banerji, A. *Synlett* 1993, 581. (g) Hwang, K.; Park, S. *Synth. Commun.* 1993, 23, 2845. (h) Mereyala, H. B.; Guntha, S. *Tetrahedron Lett.* 1993, 34, 6929.

(3) A DIALOG CA search reports no example.

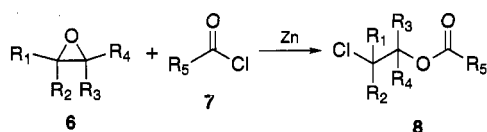
(4) For a number of substrates, the alkanates formed and being volatile have been evaporated during the reaction and workup process and thus could not be isolated under usual reaction conditions. No attempt has also been made to isolate these compounds under low temperature conditions.

(5) (a) Cloke, J. B.; Pilgrim, F. J. *J. Am. Chem. Soc.* 1939, 61, 2667. (b) Wilson, C. L. *J. Chem. Soc.* 1945, 48. (c) Synerholm, M. E. *Organic Synthesis*; Wiley: New York, 1955; Collect. Vol. III, p 187. (d) Mimceco, P.; Saluzzo, C.; Ammouroux, R. *Tetrahedron Lett.* 1994, 35, 1553 and references cited therein.

Table 2. Cleavage of Ether with Zn/Acyl Chloride

entry	ether 2	acyl chloride 3	time (h)	yield of 4 (%) ^a	yield of 5 (%) ^a
1	R ₁ = Et R ₂ = Et	R ₃ = CH ₂ Ph	4	<i>b</i>	80 ¹⁰
2	R ₁ = n-C ₆ H ₁₃ R ₂ = Me	R ₃ = CH ₂ Ph	4	82 ¹⁰	82 ¹⁰
3	R ₁ = cyclohexyl R ₂ = Me	R ₃ = CH ₂ Ph	4	84 ¹⁰	84 ¹⁰
4	R ₁ = Me R ₂ = (CH ₂) ₃ Ph	R ₃ = Me	15	—	85 ¹¹
5	R ₁ = (CH ₂) ₂ PH R ₂ = Me	R ₃ = Me	4	78 ¹⁰	R ₃ COOR ₁ (20) ¹¹
6	R ₁ = CH(Me)(CH ₂) ₂ PH R ₂ = Me	R ₃ = Me	5	78 ¹²	<i>b</i>
7	R ₁ = C(Me) ₂ (CH ₂) ₂ Ph R ₂ = Me	R ₃ = Me	1	80 ¹³	<i>b</i>
8	R ₁ = C(Me) ₂ CH ₂ Ph R ₂ = Me	R ₃ = Me	1	82 ¹⁴	<i>b</i>
9	R ₁ = C(Me) ₂ CHPh ₂ R ₂ = Me	R ₃ = Me	2	—	—
10	R ₁ = CH ₂ Ph R ₂ = Me	R ₃ = Me	1	80 ¹⁰	Ph ₂ C=CMe ₂ (90) ¹⁵ <i>b</i>
11	R ₁ = CH ₂ Ph R ₂ = n-C ₅ H ₁₁	R ₃ = Me	1.5	84 ¹⁰	84 ¹⁰
12	R ₁ = Ph R ₂ = Me	R ₃ = Me	12	—	—
13	R ₁ = CH ₂ Ph-OMe-3 R ₂ = Me	R ₃ = Me	1	90 ¹⁰	<i>b</i>
14	R ₁ = CH ₂ CH=CH ₂ R ₂ = C ₆ H ₁₃	R ₃ = CH ₂ Ph	2	<i>b</i>	85 ¹⁶
15	R ₁ = THP R ₂ = C ₆ H ₁₃	R ₃ = Me	2	<i>c</i>	75 ¹⁰
16	R ₁ = THP R ₂ = cyclohexyl	R ₃ = Me	1	<i>c</i>	82 ¹⁰

^a The yields refer to pure isolated products, fully characterized by IR and ¹H NMR. ^b The product was not isolated, being volatile and evaporated during workup and solvent-removal process. ^c The pyranyl moiety forms some tarry material and gets absorbed on silica gel column during purification of crude product.

Table 3. Cleavage of Epoxide with Zn/Acyl Chloride

entry	epoxide 6	acyl chloride 7	time (h)	yield of 8 (%) ^a
1	R ₁ , R ₂ , R ₃ , R ₄ = H	R ₅ = CH ₂ Ph	1	80 ¹⁷
2	R ₁ = Ph R ₂ , R ₃ , R ₄ = H	R ₅ = Me	2	84 ¹⁸
3	R ₁ , R ₂ = Ph R ₃ , R ₄ = Me	R ₅ = Me	2	Ph ₂ C=CMe ₂ (75) ¹⁵

^a The yields refer to pure isolated products fully characterized by IR and ¹H NMR.

possibly triggered by traces of zinc chloride and then propagated on the zinc dust surface.⁶ On the other hand,

(6) Wu, S. H.; Liu, W. Z.; Jiang, X. K. *J. Org. Chem.* **1994**, *59*, 854.
(7) IR (CHCl₃) 1730 cm⁻¹; ¹H NMR δ 1.13 (6H, d, *J* = 7 Hz), 1.56–2.0 (4H, m), 2.16–2.73 (1H, m), 3.53 (2H, t, *J* = 6 Hz), 4.08 (2H, t, *J* = 6 Hz). Anal. Calcd for C₈H₁₅O₂Cl: C, 53.78; H, 8.40. Found: C, 53.62; H, 8.36.

(8) IR (CHCl₃) 1735 cm⁻¹; ¹H NMR δ 1.43–2.0 (4H, m), 3.46 (2H, t, *J* = 6 Hz), 3.56 (2H, s), 4.1 (2H, t, *J* = 6 Hz), 7.33 (5H, s). Anal. Calcd for C₁₂H₁₅O₂Cl: C, 63.57; H, 6.62. Found: C, 63.42; H, 6.69.

(9) IR (CHCl₃) 1730 cm⁻¹; ¹H NMR δ 1.2–2.66 (15H, m), 3.53 (2H, t, *J* = 6 Hz), 4.06 (2H, t, *J* = 6 Hz). Anal. Calcd for C₁₁H₁₉O₂Cl: C, 60.41; H, 8.69. Found: C, 60.25; H, 8.48.

(10) Pouchert, C. J. *The Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich Chemical Co. Inc.: Milwaukee, 1983; Vols. 1 and 2.

it has been found that the cleavage of THF or ether with ZnCl₂ (25 mol % or more) in the absence of Zn-dust often leads to formation of some tarry material, thus reducing the yield of desired product. Thus, this zinc-promoted reaction being cleaner and high-yielding is more useful for practical purposes.

In conclusion, the present zinc-mediated procedure provides a very simple and efficient cleavage of THF and ethers leading to useful synthetic intermediates. The most significant features of this methodology are the following: (a) excellent selectivity (selective cleavage of nonaromatic ethers in the presence of aromatic ones are very difficult to achieve by conventional reagents¹); (b)

(11) Beilstein **1923**, *6*, 504. IR (CHCl₃) 1730 cm⁻¹; ¹H NMR δ 1.50–2.33 (2H, m), 2.0 (3H, s), 2.53–2.86 (2H, m), 4.0 (2H, t, *J* = 7 Hz), 7.3 (5H, s).

(12) ¹H NMR δ 1.51 (3H, d, *J* = 7 Hz), 1.8–2.13 (2H, m), 2.66–3.03 (2H, m), 3.88 (1H, sextet, *J* = 7 Hz), 7.13 (5H, s). Anal. Calcd for C₁₀H₁₃Cl: C, 71.22; H, 7.72. Found: C, 71.45; H, 7.84.

(13) ¹H NMR δ 1.6 (6H, s), 1.66–2.13 (2H, m), 2.66–2.93 (2H, m), 7.13 (5H, s). Anal. Calcd for C₁₁H₁₅Cl: C, 72.33; H, 8.22. Found: C, 72.46; H, 8.16.

(14) ¹H NMR δ 1.56 (6H, s), 3.05 (2H, s), 7.16 (5H, s). Anal. Calcd for C₁₀H₁₃Cl: C, 71.22; H, 7.72. Found: C, 71.08; H, 7.62.

(15) IR (CHCl₃) 1600 cm⁻¹; ¹H NMR δ 1.76 (6H, s), 7.1 (10H, s).
(16) IR (CHCl₃) 1735 cm⁻¹; ¹H NMR δ 0.66–1.66 (11H, m), 3.53 (2H, s), 4.06 (2H, t, *J* = 6 Hz), 7.26 (5H, s). Anal. Calcd for C₁₄H₂₀O₂: C, 76.36; H, 9.09. Found: C, 76.12; H, 9.24.

(17) IR (CHCl₃) 1735 cm⁻¹; ¹H NMR δ 3.5 (2H, s), 3.56 (2H, t, *J* = 6 Hz), 4.16 (2H, t, *J* = 6 Hz), 7.23 (5H, s). Anal. Calcd for C₁₀H₁₁O₂Cl: C, 60.45; H, 5.54. Found: C, 60.68; H, 5.48.

(18) IR (CHCl₃) 1730 cm⁻¹; ¹H NMR δ 2.0 (3H, s), 4.36 (2H, d, *J* = 8 Hz), 5.0 (1H, t, *J* = 8 Hz), 7.33 (5H, s). Anal. Calcd for C₁₀H₁₁O₂Cl: C, 60.45; H, 5.54. Found: C, 60.32; H, 5.36.

directed cleavage of C₁-O-C₂ with proper choice of alkyl group; (c) easy access to alkyl chlorides, including secondary and tertiary ones; (d) low cost; (e) operational simplicity.

Experimental Section

General. ¹H NMR spectra were recorded at 60 MHz in CCl₄ solutions. Elemental analyses were performed by Mr. S. Sarkar of this laboratory. TLC was done on precoated silica gel plates (E. Merck). Silica gel (60–120 mesh, SRL, India) was used for column chromatography. Ether refers to diethyl ether. Petroleum ether refers to the fraction boiling in the range of 40–60 °C. All solvents were dried and distilled before use.

Commercial zinc-dust (325 mesh, Loba, India) as supplied was used for all the reactions. The ethers were obtained from the corresponding alcohols by reaction with the alkyl halides in the presence of sodium hydride following the standard procedure. Acid chlorides were freshly distilled before the reaction.

General Procedure for Cleavage of THF, Ethers, and Epoxides. Representative Procedure for Benzyl Pentyl Ether. A suspension of Zn-dust (130 mg, 2 mmol, 25 mol %) in

petroleum ether (20 mL) (for cleavage of THF, ether was used as solvent) was stirred with benzyl pentyl ether (1.42 g, 8 mmol) and acetyl chloride (691 mg, 0.625 mL, 8.8 mmol) at room temperature (28 °C) under N₂ for 1.5 h (monitored by TLC). The reaction mixture was then quenched with a drop of water and diluted with ether (40 mL). Zinc dust was filtered off [110 mg (85%) was recovered and 20 mg (15%) was lost or consumed] and was washed successively with ether (5 × 5 mL). The combined washings and the filtrate were washed with aqueous sodium bicarbonate solution and brine and then dried (Na₂SO₄) and evaporated to leave the crude product (1.72 g, 84%) as a 1:1 mixture of benzyl chloride and pentyl acetate (¹H NMR and GC). This mixture was separated by column chromatography over silica gel to produce pure benzyl chloride (790 mg, 79%) and pentyl acetate (780 mg, 75%). These compounds were easily identified by comparison with authentic samples, (IR, ¹H NMR).

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