

SELECTIVE CLEAVAGE OF ETHERS BY SODIUM IODIDE-ACYL CHLORIDE

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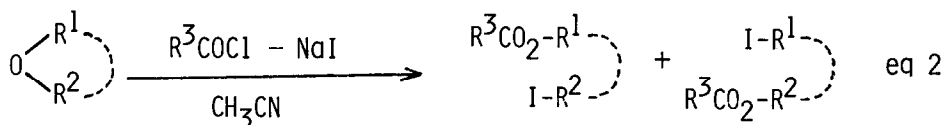
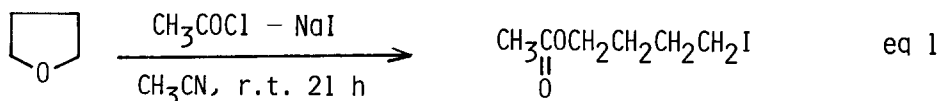
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Abstract: Cyclic and acyclic ethers are regioselectively cleaved at less substituted α -carbon-oxygen bond in the absence of Lewis acid by the reagent system of sodium iodide and acyl chlorides.

The regioselective cleavage of α -substituted cyclic ethers will provide a potential method of stereocontrolled synthesis of acyclic structures. This cleavage, when applied to simple alkyl ethers, will also afford us a convenient tool for the protection-deprotection method of alcoholic hydroxyl groups. In these contexts, the search for an effective and efficient method for the cleavage of ethers seems indispensable. The cleavage of ethers by Lewis acid and acyl chloride (or acid anhydride) has been studied since the early part of this century.¹ Recently several modifications which can be applied under less acidic conditions have been reported.² We wish to report here that cyclic and acyclic ethers can be cleaved effectively and regioselectively without the use of Lewis acid through the employment of the reagent system of sodium iodide and acyl chlorides.

Acyl iodide, though not readily available, has been reported to cleave ethers affording the corresponding esters and iodides without the aid of Lewis acid.^{3,4} Intending to generate acyl iodides in situ in the ether cleavage reactions, we performed the reaction of tetrahydrofuran (THF) with sodium iodide and acetyl chloride (eq 1).⁵ To an acetonitrile (10 mL) solution of THF (0.17 mol) and sodium iodide (0.20 mol) was added acetonitrile (5 mL) solution of acetyl chloride (0.17 mol) at 0 °C. After 21 h of stirring the reaction mixture at an ambient temperature, reaction was quenched by the addition of aqueous NaHSO₃. After the extraction with ether followed by drying over Na₂SO₄, the distillation of the solution gave 3.66 g (91%) of 4-iodobutyl acetate (bp 92-95 °C/1.5 mmHg, Kugelrohr). Under similar conditions, various kinds of ethers (eq 2) were cleaved. Results are summarized in Table 1.

The cleavage reaction proceeds effectively without the use of an excess amount of acyl chlorides. Benzoyl and pivaloyl chloride can also be used in place of acetyl chloride to give the corresponding esters (entries 2 and 3). Tetrahydropyran (THP) has been known to be less reactive than THF in cleavage reactions. Thus, for example, Goldsmith and coworkers reported that THP was

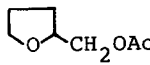
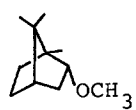
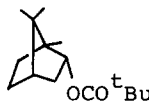


cleaved by $\text{MgBr}_2\text{-Ac}_2\text{O}$ at 85°C to give 5-bromopentyl acetate in 50% yield whereas THF was cleaved by the same reagent at an ambient temperature in a higher yield.^{2c} However, with the use of NaI-AcCl in our experiment, the cleavage of THF proceeds smoothly at an ambient temperature providing 5-iodopentyl acetate in 75% (entry 4).

This reaction shows a high regioselectivity in the cleavage of unsymmetrically substituted ethers particularly when pivaloyl chloride is employed: 2-methyltetrahydrofuran (2-Me-THF) reacted with NaI-pivaloyl chloride to give selectively 5-iodo-2-pentyl pivalate in a high yield (entry 6). Similarly, both 2-acetoxymethyltetrahydrofuran and 2-methyltetrahydropyran were cleaved to give preferentially the corresponding primary iodide (entries 9 and 8). The regioselectivity which is observed in these ether cleavage reactions giving the iodide of the less substituted α -carbon is in a marked contrast to the hitherto reported ether cleavage reactions with Lewis acid-acyl chloride (or acid anhydride⁶) reagents: with $\text{MgBr}_2\text{-Ac}_2\text{O}$, 2-Me-THF was reported to cleave preferentially at the secondary carbon-oxygen bond to give a 8:2 mixture of 4-bromopentyl and 5-bromopentyl acetate.^{2c} However, the present selectivity depends highly on the kinds of acyl chloride employed and, as shown in entries 5 and 7, neither acetyl nor benzoyl chloride exhibits any appreciable selectivity.

While the methylation of hydroxyl group is one of the most effective as well as straightforward methods for the protection of alcoholic hydroxyl groups, its utilization has been limited due to the lack of versatile deprotecting procedures under mild conditions.⁷ Among several recent reports,⁸ trimethylsilyl iodide^{8a,b} and the combination of aluminum halide and thiol^{8c} are reported to be effective demethylation reagents. Analogously, the present regioselective cleavage reaction of ethers, particularly NaI-pivaloyl chloride system, seems to provide us with a simple deprotection procedure of methyl ethers when it is combined with the hydrolysis of pivalates. In fact, methyl ethers are selectively cleaved at $\text{CH}_3\text{-OR}$ bond to give methyl iodide and the pivalate of substrate fraction R in high yields (entries 10, 11, and 12). Noteworthy is the difference between the results of methyl bornyl ether (entry 12) and its stereoisomer, methyl isobornyl ether: in the former case the pivalate was obtained in a high yield (84%) without racemization or skeletal rearrangement whereas

Table I Cleavage of Ethers by NaI-RCOCl^{a)}

Entry	Ether	Acyl Chloride	Time (h)	Product(s) ^{b)}	Yield (%) ^{c)} [ratio] ^{d)}
1	THF	CH ₃ COCl	21	RCO ₂ (CH ₂) ₄ I <u>1</u> (R = CH ₃)	90
2	THF	^t BuCOCl	22	<u>1</u> (R = ^t Bu)	96
3	THF	PhCOCl	46	<u>1</u> (R = Ph)	71
4	THP	CH ₃ COCl	44	CH ₃ CO ₂ (CH ₂) ₅ I	75
5	2-Me-THF	CH ₃ COCl	23	RCO ₂ CH(CH ₃)(CH ₂) ₃ I <u>2</u> (R = CH ₃)	85
				RCO ₂ (CH ₂) ₃ CH(CH ₃)I <u>3</u> (R = CH ₃)	[<u>2/3</u> = 49/51]
6	2-Me-THF	^t BuCOCl	22	<u>2</u> , <u>3</u> (R = ^t Bu)	91
					[<u>2/3</u> = 97/3]
7	2-Me-THF	PhCOCl	23	<u>2</u> , <u>3</u> (R = Ph)	78
					[<u>2/3</u> = 64/36]
8 ^{e)}	2-Me-THP	^t BuCOCl	21	^t BuCO ₂ CH(CH ₃)(CH ₂) ₄ I <u>4</u>	59
				^t BuCO ₂ (CH ₂) ₄ CH(CH ₃)I <u>5</u>	[<u>4/5</u> = 80/20]
9		^t BuCOCl	23	^t BuCO ₂ CH(CH ₂) ₃ I CH ₂ OAc	71
10	Octyl methyl ether	^t BuCOCl	22	^t BuCO ₂ C ₈ H ₁₇	90
11 ^{f)}	β-Cholestanyl methyl ether	^t BuCOCl	14	β-Cholestanyl-OCO ^t Bu	90
12		^t BuCOCl	37		84

a) Unless otherwise stated, reactions were performed employing 1.2 equiv of NaI and 1.0 equiv of RCOCl in acetonitrile at an ambient temperature for the period indicated. b) All products showed satisfactory spectral data (IR, ¹H NMR, and mass spectra). c) Isolated yields. d) Ratios of regioisomers were determined by VPC. e) The reaction was performed at refluxing temperature. f) The reaction was performed employing 1.05 equiv of ^tBuCOCl in acetonitrile-CHCl₃ (1:1).

in the latter case the corresponding pivalate was obtained only in a low yield (33%) together with unidentified by-products.

These results demonstrate the applicability of the present reaction as a convenient demethylation method.

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