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DEALKYLATION OF ESTERS AND CLEAVAGE OF ALCOHOLIC CARBON-OXYGEN BOND OF LACTONES WITH ALUMINIUM HALIDE-THIOL SYSTEM

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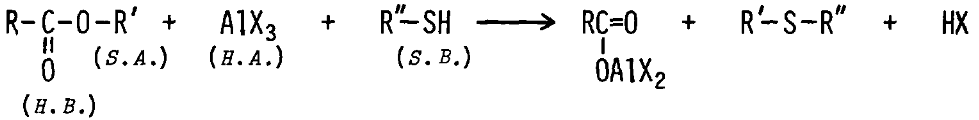
Among the reagents for the nonsaponificative dealkylation of ester,[1] a powerful nucleophile, alkanethiolate anion[1h,2] has effectively been used. In our method, the non-activated thiol itself is used as the nucleophile, while the substrate is activated by the coordination of the Lewis acid to oxygen. Thus, demethylation of the aliphatic methyl ethers by BF_3-etherate in thiol was exploited and published.[3] Then, various Lewis acid were checked for this reaction and aluminium halide was found to be much more active than BF_3-etherate. Thus aluminium halide-thiol system was proved to be very effective demethylation agent for aliphatic as well as aromatic methyl ethers, and its application was extended to demethylenation of methylenedioxy compounds.[4]

Now, this new reagent system was applied to dealkylation of esters. This method is rationalised by the "Hard and Soft Acids and Bases Principle"[5] as shown in Scheme I.



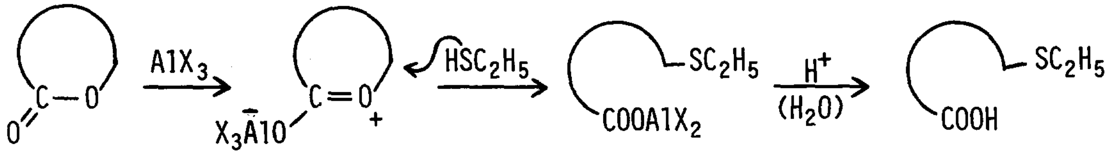
$$R-\underset{\substack{\| \\ O \\ (H.B.)}}{C}-O-R' \;\underset{(S.A.)}{}\; + \underset{(H.A.)}{AlX_3} + \underset{(S.B.)}{R''-SH} \longrightarrow \underset{\substack{| \\ OAlX_2}}{RC{=}O} + R'-S-R'' + HX$$

Scheme I

This method is easy for handling and gives very high yield of carboxylic acid under mild conditions. Data of dealkylation of esters through this method are summarized in Table 1.

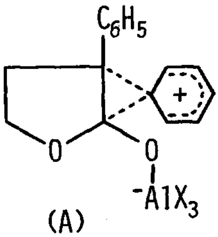
In the reaction with compound 2, the acetoxy groups remained intact. The carbon atoms attached to the acetoxy groups are secondary, hence the S_N2 reaction by thiol at these carbons must be slower than that at the methyl group in ester. Demethylations with methyl podocarpate (3) and methyl O-methylpodocarpate (4) gave almost quantitative yields of podocarpic acid (11), which demonstrated the efficiency of this reagent system also for demethylation of the sterically hindered ester. In the reaction with 4, selective demethylation for methyl ether was also successful when treated for a short time.[4] Dealkylation occurred more rapidly in the methyl ester 5 than in the ethyl ester 6, which is reasonable because of easier attack of nucleophile (thiol) to methyl group. Debenzylation of benzyl esters was also achieved (see the reactions with 7 and 8).

Subsequently, aluminum halide-thiol system was applied to lactones. Although β-lactone ring is subjected to ring opening by the attack of several reagents (*e.g.* CN^-)[6] at β-carbon atom because of its ring strain, powerful nucleophile, *e.g.* RSe^-[7] or RS^-,[1h] is required generally for ring opening of the larger lactones by the cleavage of their ω-carbon-oxygen bond. In our reaction, operation is much more simple and easier than those reported so far. The reaction proceeds as shown in Scheme II and gives a ring opening product, ω-ethylthio-carboxylic acid in good yield.

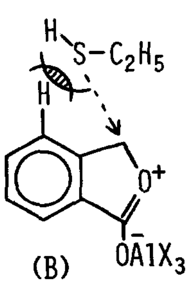


Scheme II

The examples of the reactions with various lactones are shown in Table 2. γ-Butyrolactone (19) on treatment with 1 mol equivalent of $AlBr_3$ in ethanethiol caused ring opening immediately, while α,α-diphenyl-γ-butyrolactone (20) took long time for completion of the ring opening, probably due to inactivation of the oxonium ion by the formation of a phenonium ion (A). The reactions with γ-lactones, 21 and 22, which had γ-substituents, took rather long time because of steric hindrance for nucleophilic attack of thiol. Since the steric hindrance of the γ-carbon atom in compound 22 is larger than that in compound 21, the reaction time with 22 is longer than that with 21. Phthalide (23) was shown to be almost inactive for this reaction, which may be attributed to the steric hindrance of the hydrogen atom at C-4 for the S_N2-type nucleophilic attack of ethanethiol as shown in formula (B). δ-Valerolactone (24) and especially ε-caprolactone (25) are more inactive than γ-lactones. The preferred conformations of the seven-membered ring lactone have been known to be less suitable for S_N2-type displacement than six- and five-membered ring counterpart.[7]



(A)



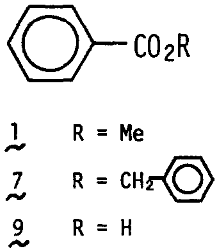
(B)

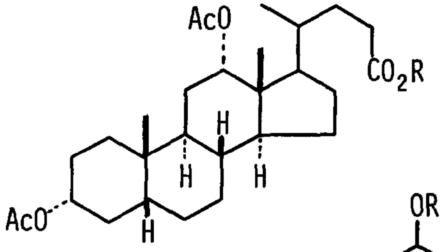
Thus, a new efficient reagent system for conversions of esters into carboxylic acids by dealkylation and of lactones into ω-ethylthio-carboxylic acids, useful synthetic intermediates, by the C-O bond cleavage has been exploited.

Table 1. Ester Cleavage *via* S_N2-Type Dealkylation[a]

Substrate	Lewis acid (mol equiv.)	Reaction time (hr)	Product (yield %)
1	AlBr$_3$ (2.8)	6.5	9 (93.9)
2	AlBr$_3$ (4.9)	9	10 (88.9)[b]
3	AlCl$_3$ (3)	< 20	11 (98.0)
"	AlBr$_3$ (3)	5.5	11 (98.0)
4	AlBr$_3$ (2.5)	7.5	11 (95.7), 3 (2.0)
5	AlBr$_3$ (5)[c]	24[d]	12 (17.7), 13 (43.8), 14 (33.7)
6	AlBr$_3$ (6)	50[d]	15 (29.6), 16 (53.5), 14 (7.0)
7	AlCl$_3$ (2.7)	1.7	9 (91.1), 17 (75.8)
8	AlCl$_3$ (2.6)	1.5	18 (98.1), 17 (71.4)

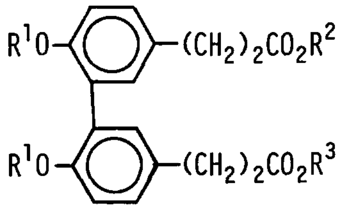
a Reactions were carried out in ethanethiol under stirring at room temperature, unless otherwise stated. *b* Recovery of substrate : 5.8%. *c* In 10% EtSH in CH_2Cl_2. *d* On the way to demethylation, insoluble substance with 2 or 3 O-Al bonds was precipitated, hence the reaction took long time.





2 R = Me

10 R = H



5 $R^1 = R^2 = R^3 = Me$

6 $R^1 = Me, R^2 = R^3 = Et$

12 $R^1 = H, R^2 = R^3 = Me$

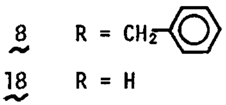
13 $R^1 = R^2 = H, R^3 = Me$

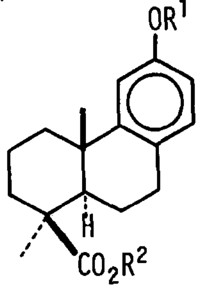
14 $R^1 = R^2 = R^3 = H$

15 $R^1 = H, R^2 = R^3 = Et$

16 $R^1 = R^2 = H, R^3 = Et$

$CH_3(CH_2)_{10}CO_2R$





3 $R^1 = H, R^2 = Me$

4 $R^1 = R^2 = Me$

11 $R^1 = R^2 = H$

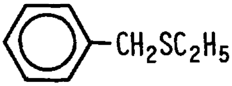


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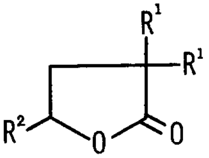
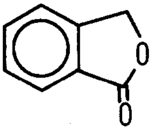
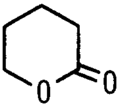
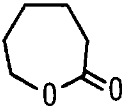
Table 2. Ring opening reaction of lactones to ω-ethylthiocarboxylic acids[a]

Substrate		Lewis acid (mol equiv.)	Reaction time (hr)	Yield of product[b]
	**19** $R^1 = R^2 = H$	$AlBr_3$ (1.1)	< 0.2	87.7
	20 $R^1 = C_6H_5$, $R^2 = H$	$AlBr_3$ (1.3)	43.5	88.0
	21 $R^1 = H$, $R^2 = Me$	$AlCl_3$ (1.1)	23	84.6
	"	$AlBr_3$ (1.1)	2	80.5
	22 $R^1 = H$, $R^2 = C_7H_{15}$	$AlCl_3$ (3)	37	91.3
	"	$AlBr_3$ (3)	< 13	91.2
	**23**	$AlBr_3$ (3)	23	9.5[c]
	**24**	$AlBr_3$ (1.2)	3.5	53.0
	**25**	$AlBr_3$ (1.2)	13	45.3

[a] All reactions were carried out in ethanethiol under stirring at room temperature.
[b] Purity was checked by NMR spectrum. [c] Recovery of substrate was 85.5%.

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