Hard Acid and Soft Nucleophile Systems. 3.[1] Dealkylation of Esters with Aluminum Halide-Thiol and Aluminum Halide-Sulfide Systems

Manabu Node, Kiyoharu Nishide, Midori Sai, Kaoru Fuji, and Eiichi Fujita*

Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan

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Benzyl and methyl esters of aliphatic and aromatic carboxylic acids have been easily cleaved on treatment with aluminum halide and ethanethiol to give parent carboxylic acids in quantitative yields. A new combination of aluminum halide with dialkyl sulfide has been found to make up a powerful deesterification reagent system useful for general esters.

The nonsaponicative dealkylation of esters is very useful for organic synthesis. Recently, various reagents, for instance, Me_3SiI,[2] Me_3SiCl plus NaI,[3] $PhSiMe_3$ plus I_2,[4] RS^-,[5] $PhSe^-$,[6] and BCl_3,[7] have been reported for this purpose.

We now report aluminum halide–ethanethiol and aluminum halide–dialkyl sulfide as very effective reagent systems for dealkylation of esters.

Results and Discussion

We have proved the aluminum halide–ethanethiol system to be effective for cleavage of methyl esters to alcohols and demethylenation of methylenedioxy groups.[1b,8] The same reagent system is now proved to be useful for deesterification of methyl and benzyl esters.[9] Several examples of the reaction are summarized in Table I (see Chart I for the structures).

This reaction can be explained by the principle of hard and soft acids and bases[10] as shown in Scheme I.

The reactions with the benzyl esters **1** and **7** proceeded rapidly and gave high yields of the carboxylic acids **6** and **10**, respectively. The reactions with the methyl esters **2**, **8**, **15**, **17**, **27**, **29**, and **33** took place smoothly to give very high yields of the corresponding carboxylic acids **6**, **10**, **16**, **19**, **28**, **30**, and **34**, respectively. Methyl *O*-methylpodocarpate (**18**) on treatment with aluminum bromide in ethanethiol gave podocarpic acid (**19**) in almost quantitative yield. Deesterifications for sterically hindered methyl esters, i.e., methyl 1-adamantanecarboxylate (**15**), methyl prodocarpate (**17**), and methyl *O*-methylpodocarpate (**18**), which give very high yields of the products are noteworthy.

In the cases of such higher esters as ethyl esters **3** and **12**, *n*-propyl ester **4**, and isopropyl esters **5** and **13**, the yields decreased in spite of prolonged reaction times because of the steric hindrance of alkyl moieties. Ethyl dodecanoate (**9**) required 33 days to give a 73.5% yield of dodecanoic acid (**10**). Deethylation of ethyl 4-bromobenzoate (**35**) gave an 82% yield of 4-bromobenzoic acid (**36**), but it took 80 h.

In the cases of the compounds **18**, **20**,[11] and **24**,[11] possessing both methyl ether and methyl ester (or ethyl ester) functionalities, results suggesting the different dealkylation rate for the methyl ethers, methyl esters, and ethyl esters were obtained. In the reactions with compounds **27**[1b] and **29**, the acetoxyl groups remained intact. The carbon atoms attached to the acetoxyl group are secondary and sterically hindered for the S_N2 attack of thiol; hence, the reaction at these centers must be much slower than that at the methyl moiety in esters. In compounds **31** and **33** which possess two different esters in the molecule, the selective

Table I. Dealkylation of Esters by AlX_3 (X = Cl or Br)-EtSH System

compd (amt, mmol)	Lewis acid (amt, molar equiv)	amt EtSH, mL	time, h[a]	product	yield, %
1 (1.0)	$AlCl_3$ (2.7)	2.5	1.7	6	91.1
2 (1.4)	$AlBr_3$ (2.8)	3.0	6.5	6	93.9
3 (1.7)	$AlBr_3$ (2.7)	2.5	36	6	16.1
4 (1.1)	$AlBr_3$ (2.3)	2.5	77	6	8.0
5 (1.1)	$AlBr_3$ (2.7)	2.5	77	6	6.1
7 (1.0)	$AlBr_3$ (2.5)	2.0	0.5	10	99.2
8 (1.0)	$AlBr_3$ (2.5)	2.0	48	10	98.7
9 (1.0)	$AlBr_3$ (2.5)	2.0	792	10	73.5
12 (0.8)	$AlBr_3$ (4.1)	2.5	77	14	2.9
13 (0.8)	$AlBr_3$ (4.8)	2.5	77	14	2.9
15 (1.0)	$AlBr_3$ (1.6)	2.0	24[b]	16	95.2
17[1b] (0.3)	$AlCl_3$ (3.0)	2.0	20	19	98.0
17 (0.3)	$AlBr_3$ (3.0)	2.0	5.5	19	98.0
18 (0.5)	$AlBr_3$ (2.5)	3.0	7.5	19	95.7
20[11] (0.2)	$AlBr_3$ (5.3)	1.0[c]	24	21[1b]	17.7
				22	43.8
				23	33.7
24[11] (0.1)	$AlBr_3$ (6.0)	2.0	50	25[1b]	29.6
				26	53.5
				23	7.0
27 (0.14)	$AlBr_3$ (5.3)	2.0	48	28	97.6[d]
29 (0.1)	$AlBr_3$ (4.9)	2.0	9	30	88.9
31 (0.5)	$AlCl_3$ (4.0)	1.5	3	32	75.0
33 (0.5)	$AlBr_3$ (4.4)	1.4	48	34	80.5
35 (0.6)	$AlCl_3$ (3.4)	2.0	80	36	82.0

[a] Reactions run at room temperature except as noted. [b] Reaction run at 0 °C to room temperature. [c] Dichloromethane (2.0 mL) was added as the cosolvent. [d] An isomer (R^1 = Ac, R^2 = H, and R^3 = Me) when treated in the same manner gave a mixture of several unknown products.

Scheme I

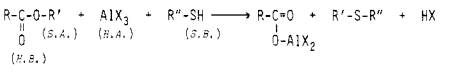

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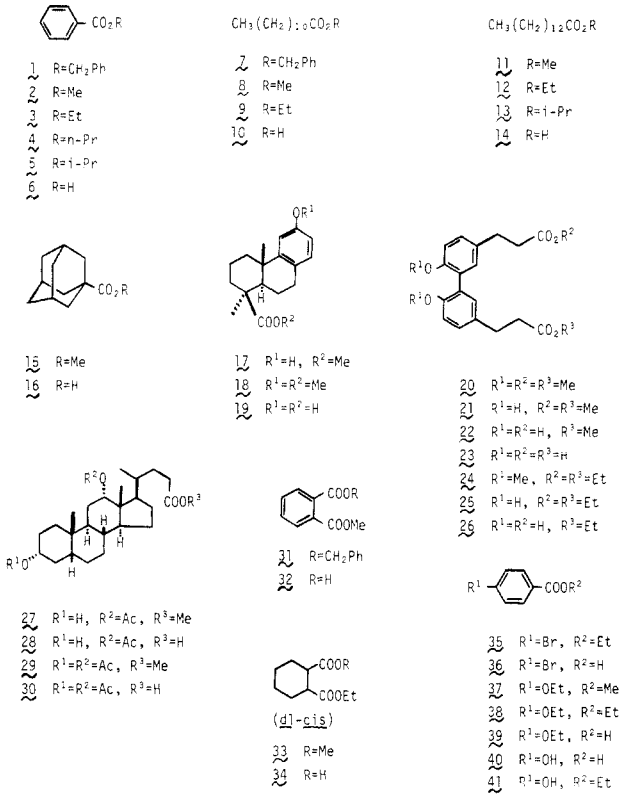
Table II. Dealkylation of Esters by AlX_3 (X = Cl or Br)–Sulfide System

compd (amt, mmol)	Lewis acid (amt, molar equiv)	sulfide (amt, mL)	time, h[a]	product	yield, %
2 (1.0)	$AlBr_3$ (2.5)	Me_2S[b] (2.0)	0.5[c]	6	93.9
3 (1.0)	$AlBr_3$ (3.0)	Me_2S (3.0)	4	6	85.6
4 (1.2)	$AlBr_3$ (2.3)	Me_2S (2.5)	19.5	6	75.4
5 (1.1)	$AlBr_3$ (2.7)	Me_2S (3.0)	22	6	70.0
11 (0.7)	$AlBr_3$ (3.7)	THT[d] (2.0)	1	14	97.5
12 (0.8)	$AlBr_3$ (4.1)	THT (3.0)	13	14	95.5
13 (0.7)	$AlBr_3$ (4.8)	THT (2.5)	84	14	87.5
18 (0.6)	$AlBr_3$ (3.9)	THT (3.8)	6	19	94.9
35 (0.7)	$AlCl_3$ (3.3)	Me_2S (3.0)	16	36	92.5
37 (1.1)	$AlBr_3$ (2.1)	THT[b] (1.0)	4[e]	39	95.1
38 (0.5)	$AlBr_3$ (3.8)	THT (2.5)	5[f]	39	63.0
				40	16.4

[a] Reactions run at room temperature except as noted. [b] Dichlormethane (1.0 mL) was used as the cosolvent. [c] Reaction run at 0 °C. [d] Tetrahydrothiophene. [e] Reaction run at 0 °C to room temperature. [f] Reaction run at 30 °C.

Chart I



dealkylation was achieved under the conditions shown in Table I.

Another development of a new dealkylation reagent system involves a combination of aluminum halide and dialkyl sulfide. This is more powerful than the aluminum halide–ethanethiol system. The data for deesterification by this reagent system are summarized in Table II.

Demethylations of methyl benzoate (2) and methyl myristate (11) proceeded much more rapidly with this new system than with the aluminum halide–ethanethiol system. Even dealkylation of the higher esters, which took place hardly with the aluminum halide–ethanethiol system, proceeded smoothly to give good yields of the products; examples are dealkylations of ethyl benzoate (3), *n*-propyl benzoate (4), isopropyl benzoate (5), ethyl myristate (12), isopropyl myristate (13), and ethyl 4-bromobenzoate (35) (see Table II; cf. Table I).

Methyl *O*-methylpodocarpate (18) on treatment with aluminum bromide and tetrahydrothiophene (THT) gave podocarpic acid (19) in quantitative yield, as in the case of treatment with aluminum bromide and ethanethiol (vide ante). In a previous communication,[8] we reported a selective cleavage of the methyl ether in 18 by the aluminum chloride–ethanethiol system with dichloromethane as the cosolvent. In dealkylations reported so far with compound 18, such reagents as RS^-,[5] RSe^-,[6] and BCl_3[7] have been used for the priority of deesterification, giving *O*-methyl podocarpic acid. It is thus possible to cleave only the ether or the ester selectively or both of them at the same time by choosing one of our and other reagents.

Table III. Conversion of 3 to 6 with $AlBr_3$–R_2S[a]

sulfide	THT	Me_2S	Et_2S	$(n\text{-Pr})_2S$
yield, %	94.4	82.7	53.7	64.1

[a] A solution of ethyl benzoate (3, 1 mmol) and $AlBr_3$ (3.0 molar equiv) in sulfide (2.5 mL) was stirred for 1.5 h at 30 °C.

Methyl 4-ethoxybenzoate (37) was converted into 4-ethoxybenzoic acid (39) by aluminum bromide–THT under mild conditions (at 0 °C to room temperature with dichloromethane as the cosolvent), the methyl ester being cleaved selectively. Ethyl 4-ethoxybenzoate (38) on treatment with the same reagent system at 30 °C gave 4-ethoxybenzoic acid (39, 63.0%) and 4-hydroxybenzoic acid (40, 16.4%), which sharply contrasted with the fact that 38 on treatment with aluminum chloride–ethanethiol gave ethyl 4-hydroxybenzoate (41).[1b] Thus the aluminum halide–dialkyl sulfide system was proved to be suitable for dealkylation of esters rather than ethers, in contrast with the fact that the aluminum halide–thiol system was efficient for demethylation of the methyl ethers rather than the methyl esters.[8]

Finally, we tested several different dialkyl sulfides. The results are shown in Table III. The order of the activity of sulfides for deesterification of ethyl benzoate was found to be THT > Me_2S > Et_2S ≃ n-Pr_2S; the sterically less hindered sulfide proved to be more effective for this reaction. These results are consistent with the S_N2 attack of the sulfide on the ester carbon atom.

In conclusion, the aluminum halide–ethanethiol system was shown to be suitable for cleavage of benzyl and methyl esters, and the aluminum halide–dialkyl sulfide system was found to be generally useful for dealkylation of esters. These reagent systems are characterized by their high reactivity under mild conditions, milder than that in the methods reported so far, and the fact that they give a high yield of the product.

Experimental Section

IR spectra were recorded with a JASCO A-202 diffraction grating infrared spectrophotometer, and ^1H NMR spectra were obtained with a JEOL JNM-FX100 spectrometer. Mass spectra

were determined on a JEOL JMS-O1SG double-focusing mass spectrometer.

Materials. Esters 1–5, 7–9, 11–13, 15, 18, and 35 were commercially available.

Benzyl Methyl Phthalate (31). Pyridine (3 mL) was added to a solution of phthalic anhydride (3.0 g, 20.2 mmol) in benzyl alcohol (2.2 g, 20.3 mmol) and the mixture stirred at room temperature. After 2 days, the reaction mixture was condensed in vacuo, dissolved in ether, and washed with aqueous HCl solution to remove pyridine. The organic layer was shaken with brine, dried (Na_2SO_4), filtered, and then evaporated to leave a crystalline residue. Recrystallization from benzene gave monobenzyl phthalate (2.54 g, 49.0%). Methylation (CH_2N_2) gave benzyl methyl phthalate (31): colorless oil; bp 168–170 °C (1.8 mm); IR ($CHCl_3$) 1720, 1280, 1125, 1070 cm^{-1}; NMR ($CDCl_3$) δ 3.73 (s, 3 H), 5.34 (s, 2 H), 7.24–7.80 (9 H, aromatic).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.50; H, 5.30.

***dl-cis*-Ethyl Methyl Cyclohexane-1,2-dicarboxylate (33).** To a solution of *cis*-1,2-cyclohexanedicarboxylic anhydride (3.09 g, 20 mmol) in ethanol (10 mL) was added pyridine (3 mL), and the mixture was stirred at room temperature. After 3 h, the reaction was treated in the same way described above to give *cis*-2-(ethoxycarbonyl)cyclohexanecarboxylic acid (34): 2.992 g (78.6%); colorless oil; bp 128 °C (0.5 mm); IR ($CHCl_3$) 1720, 1710, 1240, 1080 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 8 Hz, 3 H), 1.36–2.28 (m, 8 H), 2.76–2.96 (m, 2 H), 4.14 (q, J = 8 Hz, 2 H).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.19; H, 7.77.

Methylation (CH_2N_2) gave *dl-cis*-ethyl methyl cyclohexane-1,2-dicarboxylate (33): colorless oil; bp 92 °C (1.5 mm); IR ($CHCl_3$) 1725, 1240, 1230, 1180 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 8 Hz, 3 H), 1.30–2.20 (m, 8 H), 2.64–2.96 (m, 2 H), 3.67 (s, 3 H), 4.14 (q, J = 8 Hz, 2 H).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.61; H, 8.25.

Methyl 4-Ethoxybenzoate (37) and Ethyl 4-Ethoxybenzoate (38). They were prepared from 4-ethoxybenzoic acid according to the standard method.[12] Methyl 4-ethoxybenzoate (37) was purified by recrystallization from petroleum ether: prisms; mp 35.0–36.0 °C; IR (KBr) 1710, 1605, 1280, 1255, 1165, 1110 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3 H), 3.87 (s, 3 H), 4.05 (q, J = 7.5 Hz, 2 H), 6.88 (AB d, J = 9.0 Hz, 2 H), 7.97 (AB d, J = 9.0 Hz, 2 H); mass spectrum, m/e 180 (M). Ethyl 4-ethoxybenzoate (38) was purified with Kugelrohr distillation [120–130 °C (3 mm)]: colorless oil; IR ($CHCl_3$) 1705, 1605, 1280 1250, 1170, 1150 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 3 H), 1.40 (t, J = 7.1 Hz, 3 H), 4.04 (q, J = 7.1 Hz, 2 H), 4.33 (q, J = 7.1 Hz, 2 H), 6.87 (AB d, J = 9.0 Hz, 2 H), 7.97 (AB d, J = 9.0 Hz, 2 H).

General Procedure for Dealkylation of Esters. To a stirred solution of aluminum halide in ethanethiol or dialkyl sulfide was added the substrate under the conditions described in Table I or II. The reaction was monitored by TLC (aluminum halide was quenched by methanol in the capillary). The reaction mixture was poured into water to which dilute HCl was added, and the mixture was extracted with dichloromethane. The organic layer was shaken with brine, dried (Na_2SO_4), filtered, and then evaporated to leave a crude material, which was purified by chromatography over a silica gel column. All products except 19, 22, 23, 26, 28, and 30 were identified by comparison with the known carboxylic acids and phenols (21 and 25). The yields are given in Tables I and II.

Podocarpic acid (19) was converted to methyl podocarpate (17), which was identified with the authentic sample of 17.

Hydrogen methyl 2,2′-dihydroxybiphenyl-5,5′-dipropionate (22): amorphous; IR ($CHCl_3$) 3550, 1735, 1715, 1500, 1230 cm^{-1}; NMR ($CDCl_3$) δ 2.50–2.96 (A_2B_2, 8 H), 3.64 (s, 3 H), 6.76–7.04 (6 H, aromatic), 6.00–7.40 (br s, 3 H, OH); high-resolution mass spectrum, calcd for M^+ $C_{19}H_{20}O_6$ m/e 344.126, found m/e 344.125.

2,2′-Dihydroxybiphenyl-5,5′-dipropionic acid (23): amorphous; IR ($CHCl_3$) 1705 cm^{-1}; NMR (pyridine-d_5) δ 2.80–3.24 (A_2B_2, 8 H), 7.12–7.32 (6 H, aromatic); high-resolution mass spectrum, calcd for M^+ $C_{18}H_{18}O_6$ m/e 330.110, found m/e 330.109.

Ethyl hydrogen 2,2′-dihydroxybiphenyl-5,5′-dipropionate (26): amorphous; IR ($CHCl_3$) 3650, 3550, 1730 1710, 1500, 1230, 1180 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, J = 8 Hz, 3 H), 2.52–2.96 (A_2B_2, 8 H), 4.10 (q, J = 8 Hz, 2 H), 6.80–7.04 (6 H, aromatic), 6.40–7.40 (br s, 3 H, OH); high-resolution mass spectrum, calcd for M^+ $C_{20}H_{22}O_6$ m/e 358.142, found m/e 358.144.

12α-Acetoxy-3α-hydroxy-5β-cholan-24-oic acid (28): amorphous; IR ($CHCl_3$) 1720, 1710, 1250 cm^{-1}; NMR ($CDCl_3$) δ 0.74 (s, 3 H), 0.82 (d, J = 6 Hz, 3 H), 0.92 (s, 3 H), 2.10 (s, 3 H, $OCOCH_3$), 3.40–3.80 (m, 1 H, CHOH), 5.00–5.10 (m, 1 H, CHOAc); high-resolution mass spectrum, calcd for M^+ $C_{26}H_{42}O_5$ m/e 434.303, found m/e 434.300.

3α,12α-Diacetoxy-5β-cholan-24-oic acid (30): amorphous; IR ($CHCl_3$) 1720, 1250 cm^{-1}; NMR ($CDCl_3$) δ 0.72 (s, 3 H), 0.80 (d, J = 6 H, 3 H), 0.89 (s, 3 H), 2.00 (s, 3 H), 2.08 (s, 3 H), 4.40–4.80 (m, 1 H), 4.90–5.10 (m, 1 H); high-resolution mass spectrum, calcd for $M^+ - 60$ $C_{26}H_{40}O_4$ m/e 416.292, found m/e 416.289.

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Registry No. 1, 120-51-4; 2, 93-58-3; 3, 93-89-0; 4, 2315-68-6; 5, 939-48-0; 6, 65-85-0; 7, 140-25-0; 8, 111-82-0; 9, 106-33-2; 10, 143-07-7; 11, 124-10-7; 12, 124-06-1; 13, 110-27-0; 14, 544-63-8; 15, 711-01-3; 16, 828-51-3; 17, 4614-56-6; 18, 1231-74-9; 19, 5947-49-9; 20, 21411-25-6; 21, 70094-76-7; 22, 71057-12-0; 23, 71057-13-1; 24, 70094-74-5; 25, 70094-77-8; 26, 71057-14-2; 27, 55547-48-3; 28, 76756-34-8; 29, 1181-44-8; 30, 33628-48-7; 31, 1225-85-0; 32, 4376-18-5; 33, 76772-95-7; 34, 76756-35-9; 35, 5798-75-4; 36, 586-76-5; 37, 23676-08-6; 38, 23676-09-7; 39, 619-86-3; 40, 99-96-7; $AlCl_3$, 7446-70-0; $AlBr_3$, 7727-15-3; EtSH, 75-08-1; Me_2S, 75-18-3; Et_2S, 352-93-2; $(n\text{-}Pr)_2S$, 111-47-7; THT, 110-01-0; phthalic anhydride, 85-44-9; monobenzyl phthalate, 2528-16-7; *cis*-1,2-cyclohexanedicarboxylic anhydride, 13149-00-3; benzyl alcohol, 100-51-6.