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Alkylaluminum Chloride Catalyzed Ene Reactions of Formaldehyde with Unsaturated Carboxylic Acids, Esters and Alcohols

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Dimethylaluminum chloride and ethylaluminum sesquichloride catalyze the ene reactions of formaldehyde with the C,C-double bond of unsaturated carboxylic acids, for example oleic acid and 10-undecenoic acid, and of the respective alcohols. Ethylaluminum dichloride catalyzes the ene reactions of formaldehyde with the respective carboxylic acid esters.

The ene reaction of formaldehyde with alkenes is a potentially valuable route to primary homoallylic alcohols. Snider reported recently that dimethylaluminum chloride in equivalent or greater amounts is a useful catalyst for the ene reaction and leads to improved yields of ene adducts from formaldehyde.[1] The introduction of functionality into the alkene i.e. COOH, OH, OCOR requires the stronger Lewis acid ethylaluminum dichloride however.[2]
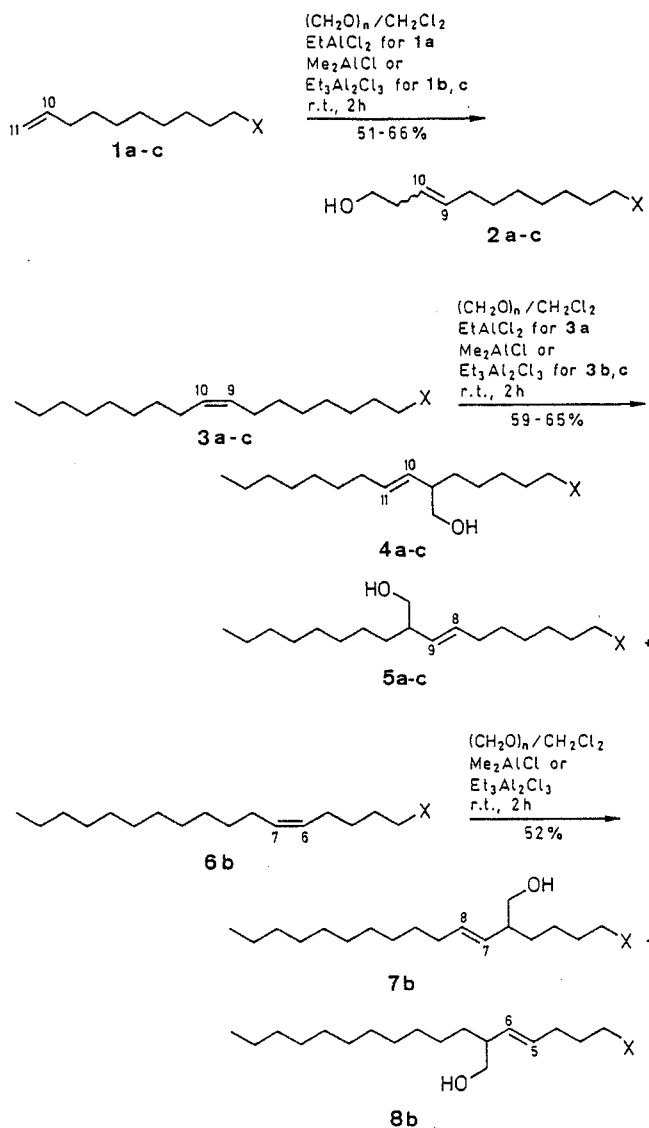
We have been interested in the ene addition of formaldehyde to unsaturated fatty acids, for example oleic acid, petroselinic acid, 10-undecenoic acid and the respective esters and alcohols[3] which are of interest as renewable raw materials.[4]

Ethylaluminum dichloride as catalyst[2] gave good yields in the ene addition of formaldehyde to methyl 10-undecenoate (**1a**) (51 %) and methyl oleate (**3a**) (63 %), whereas poor yields were observed in the reaction with the respective unsaturated carboxylic acids and the unsaturated alcohols. However, we observed that dimethylaluminum chloride as well as ethylaluminum sesquichloride are suitable catalysts for the ene reaction of formaldehyde with these substrates (yield, 52–65 %).

The ene addition of formaldehyde to 10-undecenoic acid (**1b**) and 10-undecenol (**1c**) takes place regioselectively to the terminal carbon atom. The (E)/(Z)-ratios of the products are approximately 4:1. The addition to oleic acid (**3b**) and derivatives gives approximately equal amounts of the 9- and 10-regioisomers as E-adducts. The addition to petroselinic acid (**6b**) gives a mixture of the regioisomeric addition products **7b** and **8b** (ratio, 55:45). Comparable results with respect to regio- and stereoselectivity were reported by Snider.[2]

Oleic acid (new sun flower, 83 %), petroselinic acid (81.6 %), oleyl alcohol (new sun flower, 85.8 %) and methyl oleate (new sun flower, 83 %) were obtained from Henkel KGaA. The amounts of the starting olefines used in the reactions were calculated based on 100 % purity. 10-Undecenoic acid and methyl 10-undecenoate (Atochem), 10-undecenol (Aldrich), Me₂AlCl, Et₃Al₂Cl₃ and EtAlCl₂ (Schering AG), paraformaldehyde and trioxane (Merck) were used without further purification. All reactions were run under N₂.

¹H and ¹³C NMR spectra were recorded on a Bruker AM 300 using TMS as internal standard. Analytical GC was performed on a Carlo Erba Fractovap 2150 with a FID (DB1-column, 13 m). Mass spectra were obtained using a MAT 212-mass spectrometer.

1–8	**a**	**b**	**c**
x	CO_2Me	CO_2H	CH_2OH

Addition of Formaldehyde to Unsaturated Carboxylic Acid Esters; General Procedure:

A mixture of the appropriate unsaturated carboxylic acid ester **1a** or **3a** (5 mmol) and paraformaldehyde (0.3 g, 10 mmol) in CH_2Cl_2 was stirred magnetically in N_2 atmosphere for 5 min at – 15 °C. After dropwise addition of $EtAlCl_2$ (1 M in hexane, 10 mL, 10 mmol) the sample was stirred for additional 2 h at r.t. The reaction was quenched by the addition of Et_2O (10 mL) and H_2O (40 mL). 10 % HCl was added until the precipitated aluminum salts dissolved. The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The ene adduct was purified by Kugelrohr distillation (Tables 1 and 2).

Table 1. Lewis Acid Catalyzed Ene Reactions of Formaldehyde with Unsaturated Fatty Acids and Derivatives

Starting Material	Product (s)	Yield (%)	mp (°C) or bp (°C)/mbar	n_{20}(°C)	Molecular Formula	MS (PCI, i-Butane)
1a	(E)/(Z)-2a (4:1)	51	170/0.01	1.4625 (19)	$C_{13}H_{24}O_3$ (228.1)	–
1b	(E)/(Z)-2b (4:1)	61	32–34	–	$C_{12}H_{22}O_3$ (214.1)	215 (M+H)$^+$, 197 [(M+H)$^+$-H$_2$O]
1c	(E)/(Z)-2c (4:1)	66	35–37	–	$C_{12}H_{24}O_2$ (200.1)	201 (M+H)$^+$, 183 [(M+H)$^+$-H$_2$O]
3a	(E)-4a/5a (1:1)	63	180/0.01	1.4620 (19)	$C_{20}H_{38}O_3$ (326.2)	327 (M+H)$^+$, 309 [(M+H)$^+$-H$_2$O]
3b	(E)-4b/5b (1:1)	65	–^{b}	1.4678 (22)	$C_{19}H_{36}O_3$ (312.2)	313 (M+H)$^+$, 295 [(M+H)$^+$-H$_2$O]
3c	(E)-4c/5c (1:1)	59	–^{b}	1.4727 (22)	$C_{19}H_{38}O_2$ (298.2)	299 (M+H)$^+$, 281 [(M+H)$^+$-H$_2$O]
6b	(E)-7b/8b (55:45)	52	–^{b}	1.4740 (20)	$C_{19}H_{36}O_3$ (312.2)	–

^{a} Satisfactory microanalyses obtained: C ± 0.2, H ± 0.15 (exception **2a**: C, − 0.52).
^{b} Purified by column chromatography (see experimental).

Table 2. NMR Data of the New Compounds Prepared

Product	^{1}H NMR (CDCl$_3$/TMS)	^{13}C NMR (CDCl$_3$/TMS)
(E)/(Z)-2a (4:1)	1.25–1.40 (m, 8H, H-4 to 7), 1.61 (tt, 2H, J = 7.4, 7.1, H-3), 2.02 (dt, 2H, J = 6.8, 6.7, H-8), 2.26 (ddt, 2H, J = 6.6, 6.3, 1.2, H-11), 2.30 (t, 2H, J = 7.4, H-2), 3.62 (t, 2H, J = 6.3, CH$_2$OH), 3.66 (s, 3H, OCH$_3$), 5.37 (dtt, 1H, J = 15.3, 6.8, 1.2, H-9), 5.54 (dtt, 1H, J = 15.3, 6.6, 1.2, H-10)^c	24.8, (27.2),^{a} 28.8–29.5, (30.7),^{a} 32.5, 34.0, 35.9, 51.3, 62.0, (62.2),^{a} (125.1),^{a} 125.8, (131.1),^{a} 133.9, 174.3
(E)/(Z)-2b (4:1)	1.27–1.40 (m, 8H, H-4 to 7), 1.63 (tt, 2H, J = 7.4, 7.1, H-3), 2.01 (dt, 2H, J = 6.9, 6.7, H-8), 2.26 (ddt, 2H, J = 6.6, 6.3, 1.2, H-11), 2.34 (t, 2H, J = 7.4, H-2), 3.63 (t, 2H, J = 6.3, CH$_2$OH), 5.37 (dtt, 1H, J = 15.3, 6.9, 1.2, H-9), 5.55 (dtt, 1H, J = 15.3, 6.9, 1.2, H-10)^c	24.6, (27.2),^{a} 28.8–29.5, (30.7),^{a} 32.6, 34.0, 35.9, 62.0, (62.3),^{a} (125.0),^{a} 125.8, (133.3),^{a} 134.2, 179.4
(E)/(Z)-2c (4:1)	1.26–1.35 (m, 10H, H-3 to 7), 1.57 (tt, 2H, J = 6.6, 6.7, H-2), 2.01 (dt, 2H, J = 6.8, 6.7, H-8), 2.26 (dt, 2H, J = 6.5, 6.3, H-11), 3.62 (t, 2H, J = 6.3, CH$_2$OH), 3.63 (t, 2H, J = 6.6, H-1), 5.38 (dtt, 1H, J = 15.3, 6.7, 1.2, H-9), 5.55 (dt, 1H, J = 15.3, 6.5, H-10)^c	25.6, (27.3),^{a} 29.0–29.5, (30.8),^{a} 32.5, 32.7, 35.9, 62.0, 63.0, 125.7, 134.1
(E)-4a/5a (1:1)	0.88 (t, 3H, J = 6.7, H-18), 1.20–1.40 [m, 20H, (CH$_2$)$_{10}$], 1.61 (tt, 2H, J = 7.4, 7.2, H-3), 2.03 [dt, 2H, J = 6.7, 6.6, H-12 (7)], 2.14 [m, 1H, H-9 (10)],^{a} 2.30 (t, 2H, J = 7.4, H-2), 3.33 (dd, 1H, J = 10.1, 8.6, HCHOH), 3.52 (dd, 1H, J = 10.1, 5.1, HCHOH), 3.67 (s, 3H, OCH$_3$), 5.14 [ddt, 1H, J = 15.3, 8.8, 1.2, H-10 (9)], 5.53 [dt, 1H, J = 15.3, 6.7, H-11 (8)]	14.0, 22.6, 24.8, 27.0, (27.0),^{b} 28.6–29.6, 31.1, 31.8, 32.5, (32.6),^{b} 34.0, 45.9, 51.3, 65.9, 131.2, (131.5),^{b} (133.5),^{b} 133.8, 174.2
(E)-4b/5b (1:1)	0.87 (t, 3H, J = 6.7, H-18), 1.24–1.40 [m, 20H, (CH$_2$)$_{10}$], 1.58–1.66 (m, 2H, H-3), 2.03 [dt, 2H, J = 6.7, 6.6, H-12 (7)], 2.15 [m, 1H, H-9 (10)], 2.33 (t, 2H, J = 7.4, H-2), 3.34 (dd, 1H, J = 10.1, 8.6, HCHOH), 3.52 (dd, 1H, J = 10.1, 5.1, HCHOH), 5.13 [ddt, 1H, J = 15.3, 8.8, 1.2, H-10 (9)], 5.52 [dt, 1H, J = 15.3, 6.7, H-11 (8)]	14.1, 22.6, 24.6, 27.0, (27.1)^b, 28.6–29.7, 31.1, (31.1),^{b} 31.9, 32.5, (32.6),^{b} 34.0, 45.8, 66.0, 131.1, (134.4),^{b} (133.6),^{b} 134.0, 179.3 (179.4)^b
(E)-4c/5c (1:1)	0.88 (t, 3H, J = 6.8, H-18), 1.20–1.40 [m, 22H, (CH$_2$)$_{11}$], 1.56 (tt, 2H, J = 6.8, 6.6, H-2), 2.03 [dt, 2H, J = 6.8, 6.7, H-12 (7)], 2.14 [m, 1H, H-9 (10)], 3.33 (dd, 1H, J = 10.1, 8.5, HCHOH), 3.52 (dd, 1H, J = 10.1, 4.9, HCHOH), 3.62 (t, 2H, J = 6.6, H-1), 5.13 [dd, 1H, J = 15.3, 8.7, H-10 (9)], 5.53 [dt, 1H, J = 15.3, 6.7, H-11 (8)]	14.1, 22.7, 25.7, 27.1, 29.1–29.7, 31.1, 31.9, 32.7, (32.7),^{b} 45.9, 62.9, 66.0, 131.3, (131.4),^{b} (133.8),^{b} 133.9
(E)-7b/8b (55:45)	0.88 (t, 3H, J = 6.8, H-18), 1.24–1.40 [m, 20H, (CH$_2$)$_{10}$], 1.63 (m, 2H, H-3), 2.02 [dt, 2H, J = 6.8, 6.7, H-9 (4)], 2.13 [m, 1H, H-6 (7)], 2.33 (t, 2H, J = 7.4, H-2), 3.37 (dd, 1H, J = 10.5, 8.2, HCHOH), 3.53 (dd, 1H, J = 10.5, 5.4, HCHOH), 5.17 [dd, 1H, J = 15.3, 8.8, H-7 (6)], 5.53 [dt, 1H, J = 15.3, 6.7, H-8 (5)]	14.0, 22.6, (24.1),^{b} 24.6, 26.4, (26.9),^{b} 29.0–29.5, 30.6, (31.0),^{b} 31.5, 31.8, (31.9),^{b} 32.5, 33.3, 33.8, 45.5, (45.7),^{b} 65.8, (65.9),^{b} 130.6, (131.9),^{b} (132.7),^{b} 134.1, (178.8),^{b} 179.1

^{a} The chemical shifts in brackets refer to the (Z)-isomer. The (E)/(Z)-ratio is determined by GC using a carbowax-column (47 m).
^{b} The chemical shifts in brackets refer to the regioisomers **5** and **8** respectively.
^{c} The ^{1}H NMR data refer to the (E)-isomer.

Addition of Formaldehyde to Unsaturated Carboxylic Acids and Alcohols 1b,c and 3b,c; General Procedure:

A mixture of the appropriate unsaturated acid **1b**, **3b** or the alcohol **1c**, **3c** (5 mmol) and paraformaldehyde (0.3 g, 10 mmol) in CH$_2$Cl$_2$ (25 mL) was stirred magnetically in N$_2$ atmosphere for 5 min at − 15°C. Me$_2$AlCl (0.9 g, 10 mmol) or Et$_3$Al$_2$Cl$_3$ (1.24 g, 5 mmol) was added dropwise by a syringe. The mixture was stirred for additional 2 h at r.t. Workup of the mixture was carried out as described above

for the adducts of formaldehyde and unsaturated carboxylic acid esters. The combined organic layers were dried (Na_2SO_4) and evaporated. The products were purified by recrystallization or by column chromatography (28 cm × 2 cm) on silica gel 60 (Merck, 70–230 mesh) with petrolether/EtOAc (7:3 for acids; 6:4 for alcohols) as eluent. Fractions containing the ene product were collected, the solvent evaporated and the residue dried at 20 °C/0.01 mbar.

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(4) Baumann, H.; Bühler, M.; Fochem, H.; Hirsinger, F.; Zoebelein, H.; Falbe, J. Angew. Chem. 1988, 100, 41; Angew. Chem., Intl. Ed. Engl. 1988, 27, 41.

Boron Trifluoride Monohydrate Catalyzed One-Flask Preparation of Sulfides from Carbonyl Compounds with Thiols and Triethylsilane[1]

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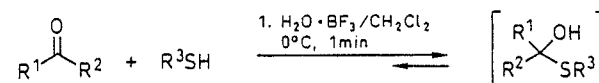
Boron trifluoride monohydrate catalyzed thiolation of aldehydes and ketones with thiols and triethylsilane to the corresponding sulfides was carried out in good to excellent yields.

The most common method for the synthesis of sulfides is by the alkylation of thiolate anions with alkyl halides in a typical nucleophilic substitution.[2] Many other synthetically useful methods are also known and the chemistry has been reviewed.[3] More recent methods include reduction of hemithioacetals with reducing agents such as lithium aluminum hydride/aluminum chloride[4] or triethylsilane.[5] Kikugawa[6] has carried out direct reductive thiolation of aldehydes and ketones with thiols to symmetrical and unsymmetrical sulfides using pyridine–borane complex in trifluoroacetic acid medium.

Recently, we have reported boron trifluoride monohydrate catalyzed thioacetalization of carbonyl compounds.[7] Boron trifluoride monohydrate is an inexpensive, non-oxidizing strong acid catalyst comparable in strength to sulfuric acid. We now report that thiols (thiophenol) react with ketones and aldehydes under boron trifluoride monohydrate catalysis to form in situ hemithioacetals which upon treatment with triethylsilane (ionic hydrogenation) then give sulfides in a highly efficient one-pot procedure.
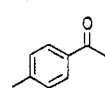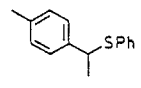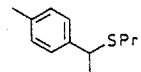
The boron trifluoride monohydrate catalyzed reaction of benzaldehyde with 2-propanethiol and triethylsilane in dichloromethane solution gave benzyl isopropyl sulfide in 97% isolated yield. The reaction was also similarly successful with a wide variety of carbonyl compounds and thiols. Symmetrical and unsymmetrical sulfides were obtained in good to excellent yields (Table 1). The physical data of the sulfides are shown in Table 2.

The mechanism of the reaction is suggested in the Scheme involving the intermediacy of hemithioacetals followed by ionic hydrogenation. An alternative pathway involv-

$$R^1\underset{\displaystyle \|}{\overset{\displaystyle O}{C}}R^2 \; + \; R^3SH \quad \xrightarrow[\substack{0°C,\; 1min}]{1.\; H_2O\cdot BF_3/CH_2Cl_2} \quad \left[R^2\overset{R^1}{\underset{SR^3}{\diagdown\!\diagup}}OH \right]$$

	6	PhSH		6a 90
		i-PrSH		6b 83

a Isolated yields.