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Stereoselective Dehydrobromination of Alkyl α-Br-α-Cl-Carboxylates

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Abstract: (Z)-Alkyl α-Cl-α,β-unsaturated esters are prepared in excellent yields by stereoselective dehydrobromination of alkyl α-Br-α-Cl-carboxylates with LiCl-Li_2CO_3 in dimethylformamide.

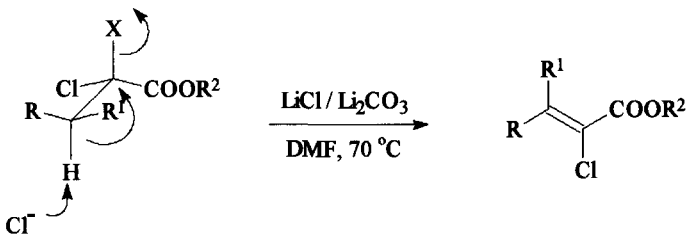
α-Cl-α,β-Unsaturated esters, which are used for α-aminoacid preparations[1] and for vinylogous Darzen reactions,[2] have been till now obtained by dehydrohalogenation of α,β-dichloroesters,[1a,3] by rearrangement of polyhalogenated allylic alcohols,[4] or mainly by connective procedures[5] based on Wittig type reactions. These methods, however, generally suffer from poor stereoselectivities and lengthy procedures. Following the achievement of an efficient route for the preparation of methyl α,α-dihalocarboxylates,[6] their dehydrohalogenation to α-Cl-α,β-unsaturated esters appeared as an immediate and attractive preparative route.

Now we report that alkyl α-Br-α-Cl-carboxylates can be stereoselectively dehydrobrominated by using LiCl-Li_2CO_3 (Scheme 1). As far as we know, the dehydrohalogenation of α,α-dihalocarboxylic acid derivatives has been applied only to the preparation of α-chloro-butenolides from α,α-dichloro-γ-lactones by DBU in boiling benzene.[7]

At first we tried potassium t-butoxide or a number of amine bases (DBU, triethylamine, collidine, DABCO) in many solvents, but with poor results. Next we used lithium salts in dimethylformamide (DMF), a reagent which was used successfully for the dehydrohalogenation of cyclic α- or α,α-dihaloketones.[8]

Excellent yields were obtained from alkyl α-Cl-α-Br esters by LiCl-Li_2CO_3 in DMF[9] at 70 °C (see Table), whereas the corresponding α,α-dichloro esters were poorly reactive. At higher temperatures reactions were faster but yields lower, owing to by-products (such as amides), likely originating from the partial decomposition of DMF. LiBr was less effective than LiCl, comparable yields being obtained on longer reaction times (see Table). The dehydrohalogenation is characterized by a high (Z) stereoselectivity, very little affected by the size of the alcoholic moiety of the ester. Owing to the predominant nucleophilic displacement of the α-Br with the Cl anion, methyl α-Br-α-Cl-propanoate gave poor yields; on using LiBr yields were comparable, but the conversion was much cleaner.

On testing the lithium salts individually, it was observed that with LiCl the conversion was lower (about



Scheme

TABLE . Dehydrobromination of alkyl α,α-dihalogeno-carboxylates with LiCl-Li_2CO_3 in DMF at 70 °C

entry	R	R^1	R^2	X	LiX	yield[a] (%)	(Z)/(E)[b]	Time (h)
1	$CH_3CH_2CH_2$-	H-	CH_3-	Br	LiCl	96(93)	24	3
2	$CH_3CH_2CH_2$-	H-	CH_3-	Br	LiBr	95[c]	19	17
3	$CH_3CH_2CH_2$-	H-	CH_3CH_2-	Br	LiCl	94	24	3
4	$CH_3CH_2CH_2$-	H-	$(CH_3)_2CH$-	Br	LiCl	97	27	3
5	$CH_3CH_2CH_2$-	H-	CH_3-	Cl	LiCl	2[d]	/	17
6	$CH_3(CH_2)_3CH_2$-	H-	CH_3-	Br	LiCl	97(97)	23	3
7	CH_3CH_2-	H-	CH_3-	Br	LiCl	97(97)	27	4
8	CH_3-	CH_3-	CH_3-	Br	LiCl	94(93)	/	17
9	CH_3-	CH_3-	CH_3-	Cl	LiCl	2[e]	/	17
10	C_6H_5-	H-	CH_3-	Br	LiCl	97	[f]	3
11	H-	H-	CH_3-	Br	LiCl	25[g]	/	19
12	H-	H-	CH_3-	Br	LiBr	29[h,i]	/	24

a) in parenthesis are reported the yields for the larger scale preparations; b) determined by GC; c) 57% conversion after 3h; d) 79% conversion; e) 89% conversion; f) only the (Z) isomer was obtained; g) 88% conversion, 61% methyl α,α-dichloropropanoate; h) 35% conversion; i) doubling LiBr amounts, compared to the standard procedure, gave 33% yield and a 35% conversion after 24h.

90%), whereas with Li_2CO_3 no reaction occurred. Reasonably, LiCl is the real reagent and Li_2CO_3 is useful for quenching the acidity developed during the elimination. More specifically, since LiCl dissociates in DMF,[10] and

anions in dipolar solvents are not solvated and are therefore hard bases,[11] dehydrohalogenation is likely promoted by the chloride ion (Scheme).[11] When, indeed, the reaction was carried out in a dissociating and strongly solvating solvent, such as methanol, no conversion was observed; moreover, on replacing LiCl by LiBr reaction rates were somewhat lower, likely because bromide ion is a less hard base.

EXPERIMENTAL PART

Mass spectra were obtained on a combined HP 5890 GC - HP 5989A MS Engine. ^{1}H NMR spectra were recorded on a Bruker WP80 spectrometer. Anhydrous LiCl and Li_2CO_3 were purchased from Aldrich. DMF was dried over three batches of 3Å sieves (5% w/v, 12h). Methyl α,α-dihalocarboxylates were prepared starting from 2-bromo aldehyde dimethyl acetal, as reported below, according to known procedures,[6] now improved.

Preparation of 2-(1-bromoalkyl)-4-methyl-1,3-dioxolane. p-Toluenesulphonic acid monohydrate (0.5 mol) was added to a vigorously stirred solution of 2-bromo aldehyde dimethyl acetal (1 mol) and 1,2-propanediol (1.25 mol) in acetonitrile (600 ml). The mixture was thermostatted at 40 °C, and after 24-36 h diluted with H_2O (1 l). The organic phase was separated, and the aqueous layer extracted with CH_2Cl_2 (2 x 100 ml). The combined organic phases were dried and neutralized over solid Na_2CO_3, then evaporated at 20-40 mmHg. Yields were 92-98%. Crude products were purified by distillation.

Preparation of Methyl α-Br-α-Cl-Carboxylates. The reaction must be carried out under a hood and behind a safety shield. In a four-necked round bottom flask (1 l) fitted with a mechanical stirrer, a drying tube, a dropping funnel and a thermometer, trichloroisocyanuric acid (420 mmol) was dissolved in dried DMF (240 ml). The stirred solution was thermostatted at -3 °C and 2-(1-bromoalkyl)-4-methyl-1,3-dioxolane (600 mmol) was slowly dripped in 6-8 h, taking care that the temperature did not exceed 5 °C. When substrate addition ended, the temperature of the bath was gradually increased to 5 °C (about 2 h). Owing to the precipitation of cyanuric acid, the mixture became somewhat viscous. After 18-24 h acetone (50 ml) was added to reduce the residual oxidant, and when the mixture turned from light yellow to white, it was diluted with 1:1 diethyl ether/petroleum ether (30-50 °C) (250 ml). The solid was filtered off and washed with 1:1 diethyl ether/petroleum ether (4 x 50 ml). The combined organic phases were washed with H_2O (800 ml), dried and neutralized over Na_2CO_3, and then concentrated under vacuum. The crude products were transesterified to methyl esters with $LiOCH_3/CH_3OH$ following a previously reported procedure.[6] Yields of isolated products were 60-80%. Ethyl and isopropyl α-Br-α-Cl-hexanoates were obtained by transesterification of the corresponding methyl ester.

General procedure for dehydrobromination. To LiCl (2.4 mmol) and Li_2CO_3 (.5 mmol) in a Schlenk tube, DMF (2 ml) and the alkyl α-Br-α-Cl-carboxylate (2 mmol) were added under N_2 . The mixture was stirred at 70 °C, and, after the time reported in Table 2, diluted with H_2O (3 ml) and then extracted with 1:4 diethyl ether/petroleum ether (30-50 °C) (2 x 3 ml). The organic phases were collected, dried over Na_2CO_3 and the solvent evaporated. Methyl α-Cl-α,β-unsaturated esters were purified by distillation except (Z) methyl 2-chloro-cinnamate, which was crystallized from petroleum ether (30-50 °C). The assigned stereochemistry was based upon the δ value of the vinylic proton.[4b,5a,5g]

(Z) Methyl 2-chloro-2-butenoate. ^{1}H NMR ($CDCl_3$) δ: 1.93 (3H, d, CH_3-CH=); 3.82 (3H, s, -$COOCH_3$); 7.15 (1H, q, CH_3-CH=). MS (EI, 70 eV) *m/z*: 134 (100%) [M^+]; 103 (95%) [M^+ - OCH_3]; 75 (74%) [M^+ -$COOCH_3$]. Found: C, 44.8; H, 5.3%. $C_5H_7ClO_2$ requires C, 44.63; H, 5.24%. B. p. 69-71 °C (30 mmHg).

(Z) Methyl 2-chloro-2-hexenoate. ^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t, -$CH_2C\underline{H}_3$); 1.52 (2H, m, -$CH_2C\underline{H}_2CH_3$); 2.33 (2H, m, -$CH_2C\underline{H}_2$-CH=); 3.82 (3H, s, -$COOCH_3$); 7.06 (1H, t, -CH_2-C$\underline{H}$=). MS (EI, 70 eV) *m/z*: 162 (22%) [M^+]; 131 (16%) [M^+ - OCH_3]; 121 (100%) [M^+ - C_3H_7]. Found: C, 51.8; H, 6.8%. $C_7H_{11}ClO_2$ requires C, 51.70; H, 6.82%. B. p. 99-101 °C (30 mmHg).

(Z) Ethyl 2-chloro-2-hexenoate. ^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, t, -$CH_2C\underline{H}_3$); 1.32 (3H, t, J = 7.2 Hz, -$OCH_2C\underline{H}_3$); 1.45 (2H, m, -$CH_2C\underline{H}_2CH_3$); 2.33 (2H, m, -$CH_2C\underline{H}_2$-CH=); 4.26 (2H, q, J = 7.2 Hz, -$OC\underline{H}_2CH_3$); 7.08 (1H, t, -CH_2-C$\underline{H}$=). MS (EI, 70 eV) *m/z*: 176 (22%) [M^+]; 148 (23%) [M^+ - OC_2H_5]; 107 (100%). Found: C, 54.3; H, 7.4%. $C_8H_{13}ClO_2$ requires C, 54.40; H, 7.42%. B. p.108-110 °C (30 mmHg).

(Z) Isopropyl 2-chloro-2-hexenoate. ^{1}H NMR ($CDCl_3$) δ: 0.96 (3H, t, -$CH_2C\underline{H}_3$); 1.33 (6H, d, J = 6.4 Hz, -$OCH(C\underline{H}_3)_2$); 1.53 (2H, m, -$CH_2C\underline{H}_2CH_3$); 2.33 (2H, m, -$CH_2C\underline{H}_2$-CH=); 5.09 (1H, m, J = 6.4 Hz, -$OC\underline{H}(CH_3)_2$); 7.07 (1H, t, -CH_2-C<u>H</u>=). MS (EI, 70 eV) *m/z*: 190 (8%) [M^+]; 148 (71%) [M^+ - C_3H_6]; 107 (100%). Found: C, 56.5; H, 7.8%. $C_9H_{15}ClO_2$ requires C, 56.69; H, 7.93. B. p. 114-117 °C (30 mmHg).

(Z) Methyl 2-chloro-2-octenoate. ^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, t, -$CH_2C\underline{H}_3$); 1.10-1.73 (6H, m, -$CH_2(C\underline{H}_2)_3CH_3$); 2.32 (2H, m, -$CH_2C\underline{H}_2$-CH=); 3. (3H, s, -$COOCH_3$); 7.05 (1H, t, -$CH_2$-CH=). MS (EI, 70 eV) *m/z*: 190 (2%) [M^+]; 155 (12%) [M^+ - Cl]; 147 (18%) [M^+ - C_3H_7]; 121 (100%). Found: C, 56.7; H, 8.0%. $C_9H_{15}ClO_2$ requires C, 56.69; H, 7.93. B. p. 81-83 °C (4 mmHg).

(Z) Methyl 2-chloro-cinnamate. ^{1}H NMR ($CDCl_3$) δ: 3.88 (3H, s, -$COOCH_3$); 7.25-8.05 (5H, m, -C_6H_5); 7.93 (1H, s, C_6H_5-C<u>H</u>=). MS (EI, 70 eV) *m/z*: 196 (100%) [M^+]; 161 (96%) [M^+ - Cl]; 102 (93%) [M^+ - $COOCH_3$ - Cl]. Found: C, 61.0; H, 4.7%. $C_{10}H_9Cl_2O_4$ requires C, 61.08; H, 4.61%. M. p. 32 °C

Methyl 2-chloro-3-methyl-2-butenoate. ^{1}H NMR ($CDCl_3$) δ: 2.05 (3H, s, =C-CH_3); 2.20 (3H, s, =C-CH_3); 3.80 (3H, s, -$COOCH_3$). MS (EI, 70 eV) *m/z*: 148 (38%) [M^+]; 117 (64%) [M^+ - OCH_3]; 53 (100%) [M^+ - $COOCH_3$ - HCl]. Found: C, 48.6; H, 6.0%. $C_6H_9ClO_2$ requires C, 48.50; H, 6.11%. B. p. 81-83 °C (30 mmHg).

Large scale preparation. Methyl α-Br-α-Cl-hexanoate (40 mmol, 9.14 g) was treated with LiCl (24 mmol, 2.23 g), Li_2CO_3 (5 mmol) in DMF (40 ml), following the above described procedure; the dehydrobrominated product was obtained in 93% yield.

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