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Synthesis of Optically Active Chloro Alkanoic Esters

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Summary: The stereospecific synthesis (optical yield up to 94%) of optically active (R)-alkyl-2-chloropropionate and (S)-alkyl-3-chlorobutanoate by the action of $AlCl_3$ on the corresponding (S)-2-mesyloxy- and (R)-3-mesyloxy-derivatives is described.

In the course of our investigation to prepare optically active arylalkanoic esters by $AlCl_3$ catalyzed stereospecific Friedel-Crafts alkylation of aromatic compounds with optically active esters of (S)-2-(mesiloxy)propanoic acid (**1a, b**) and (R)-3-(mesiloxy)butanoic acid (**1c, d**),[1-3] we have observed, as a competitive reaction, the formation of optically active esters of (R)-2-chloropropionic acid (**2a, b**) and (S)-3-chlorobutanoic acid (**2c, d**). This reaction occurred with inversion of configuration at the chiral carbon atom and, when measured, with a very high stereospecifity (79-93%, based on optical purity of starting materials and maximum specific rotations reported in the literature for compounds **2**). Under the experimental conditions used these chloro esters should be able to alkylate aromatic compounds in low extent,[4] if any.

$$CH_3\text{-}{}^{*}CH(OSO_2CH_3)\text{-}(CH_2)_n\text{-}COOR \xrightarrow{AlCl_3} CH_3\text{-}{}^{*}CH(Cl)\text{-}(CH_2)_n\text{-}COOR$$

1a: $n = 0$, $R = CH_3$	**2a:** $n = 0$, $R = CH_3$
1b: $n = 0$, $R = C_2H_5$	**2b:** $n = 0$, $R = C_2H_5$
1c: $n = 1$, $R = CH_3$	**2c:** $n = 1$, $R = CH_3$
1d: $n = 1$, $R = C_2H_5$	**2d:** $n = 1$, $R = C_2H_5$

Esters of 2-chloropropionic acid are useful intermediates in the synthesis of a variety of products including drugs[5] and herbicides[6] and there is a strong interest in the industrial manufacture of them. An example concerning esters of 3-chlorobutanoic acid as intermediates in the synthesis of herbicides has also been reported.[7]

It has long been known[8] that these compounds can be prepared starting from the corresponding hydroxy-derivatives by reaction with a variety of chlorinating reagents, such as $SOCl_2$, PCl_5, or $COCl_2$ in the presence or absence of a base, <u>e.g.</u> pyridine; furthermore, **2b** has been also prepared by the reaction of the corresponding chlorosulphonate with aniline or pyridine hydrochloride,[8b] by the reaction of tosylate with LiCl[8c], and by thermal decomposition of chlorosulphonate[8d] and chloroformate.[8g] Partial or total racemization of compounds **2** can occur depending on the experimental conditions. To the best of our knowledge, nothing is known on the reaction of such or similar derivatives with Lewis acids to afford compounds **2**. We have therefore investigated on the possibility to achieve a new stereospecific synthesis of these interesting substrates in non aromatic solvents.

Table - Preparation of (R)-2-chloropropionates (2a, b) and (S)-3-chlorobutanoates (2c, d).[a]

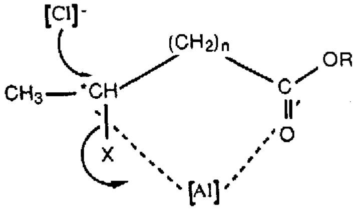
Compound	Solvent	T(°C)	t(h)	Yield, %	$[\alpha]_D$	Optical yield, %	$[\alpha]_D$max	Ref.
2a	CH_2Cl_2	40	24	48	31.6[b]	94.3	33.5[b]	8g
2b	CH_2Cl_2	10	168	44[c]	18.4[d]	92.7	19.8[d]	5a
2b	CH_2Cl_2	40	24	45[c]	17.8[d]	90.0	19.8[d]	5a
2b	$CHCl_3$	61	14	59[c]	14.2[d]	71.8	19.8[d]	5a
2c	CH_2Cl_2	0	2	67	26.9[e]	91.8	29.3[e]	e
2d	CH_2Cl_2	0	2	76[c]	25.8[f]	89.0	29.0[f]	f
2d	cyclo-C_6H_{12}	0	2	42	10.0[f]	34.5	29.0[f]	f
2d	cyclo-C_6H_{12}	10	2	45	6.6[f]	22.8	29.0[f]	f
2c	C_6H_6	10	4	29	23.4[e]	79.9	29.3[e]	e
2d	C_6H_6	10	2	36	26.9[f]	92.8	29.0[f]	f
2d	C_6H_5Cl	0	2	35	22.9[f]	79.0	29.0[f]	f

[a] Absolute configuration-optical rotations of compounds **1** [optical purity (o.p.), confidently evaluated on the basis of the o.p. of the corresponding hydroxyl esters]: (S)-**1a**: $[\alpha]_D^{25}$= -56.4 (c = 1, $CHCl_3$), o.p. 100%; (S)-**1b**: $[\alpha]_D^{25}$= -53.9 (c = 1, $CHCl_3$), o.p. 100%; (R)-**1c**: α_D^{20} = -46.5 (neat), o.p. 99.4%; (R)-**1d**: α_D^{25}= -39.5 (neat), o.p. 100%. [b] Measured in CCl_4, c = 1, at 30°C; the same sample showed $[\alpha]_D^{25}$= 25.6 (neat, d_4^{25}= 1.143), o.y. 92.1%, according to ref. 9. [c] Loss of optical activity not exceeding 3-5% has been observed for recovered **1**. [d] Measured on neat compound at 20°C, d_4^{20}= 1.0720;[8c] the $[\alpha]_D$max value was found in excellent agreement with $[\alpha]_D^{20}$max = 19.7 (neat), calculated in this work by acidic hydrolysis to (R)-2-chloropropionic acid.[10] [e] Measured on neat compound at 25°C, d_4^{25}= 1.077; the $[\alpha]_D$max value has been calculated by us from data reported in ref. 11 and 12; our attempts to confirm this datum, as well as the corresponding datum for **2d**, by acidic hydrolysis to 3-chlorobutanoic acid gave unreliable results; also HPLC and GLC methods with commercially available chiral columns were, in our hands, useless. [f] Measured in $CHCl_3$, c = 5 at 25°C; the $[\alpha]_D$max = 29.0 has been calculated by us from data reported in ref. 4 and 12, and used to calculate the stereoselectivity of the reactions; $[\alpha]_D^{20}$max = 31.2 (neat, d_4^{20}= 1.0517) has been reported in ref. 4; the latter value is unreliable, in our opinion, due to a wrong calculation of the optical purity of the corresponding hydroxy-derivative, used as a starting material; see also the preceding note.

In a typical experiment, 15 mmol of compound **1** were added to a suspension of 30 mmol of $AlCl_3$ in 15 ml of dry solvent chilled to 0°C, and the reaction mixture was stirred at the reported temperature. After the indicated reaction time, the mixture was quenched with 10% aqueous HCl; usual work-up and careful fractional distillation afforded the products.

The results are reported in the Table, where it is shown that compounds **2** can be obtained in fair to good chemical yields with optical yields up to 94%. As a comparison, it can be observed that nucleophilic displacement of the tosylate group of ethyl 2-(tosyloxy)propanoate with LiCl occurred with 21.5% optical yield,[8c] whereas reaction of the corresponding chlorosulphonate with pyridine hydrochloride occurred with 79.3% optical yield;[8b] in the latter case, optical yields up to 95% were obtained using aniline hydrochloride but, as pointed out by the authors, the secondary reaction of aniline with the sulphonate seriously affected the chemical yield.[8b]

To explain the high stereospecificity of this reaction, as well as the different reactivity of compounds **1** (n = 0 vs. n = 1, cfr., for example, entries 2 and 6 of the Table), we suggest, as a necessary requirement, the formation of an intermediate complex between compounds **1** and the Lewis acid (Scheme, fig. **A**, brackets, [], meaning that we are not able to specify the environment of Al and Cl).



Scheme: Fig. **A**, X = OSO_2CH_3
Fig. **B**, X = Cl

A similar hypothesis has been advanced to justify the stereospecificity in the Friedel-Crafts alkylation of aromatic substrates (ArH) with compounds **1**,[1-3] as well as with compound **2d**,[4] where ArH attacks the chiral carbon atom from the backside (the different relative concentration and nucleophilic ability of ArH and $[Cl]^-$ account for the results obtained when both are present in the reaction mixture).

The observed partial loss of optical activity of compounds **2** might be explained admitting that a similar intermediate complex is formed and subsequently attacked by $[Cl]^-$ (Scheme, fig. **B**), this scrambling of chlorine atoms causing racemization without apparent reaction. According to this hypothesis, the optical activity of compounds **1** recovered from the reaction mixtures (entries 2, 3, 4 and 6 of the Table) results almost unchanged. Also the considerable loss of optical activity of compounds **2c** and **2d** under typical reaction conditions,[13] in agreement with a literature report,[4] supports such a mechanistic picture; however, it should be pointed out that, in related experiments, compounds **2a** and **2b** do not racemize to a similar extent.[14] Of course, all the reaction parameters that influence the stability of such complexes, i.e., the solvent, the reaction temperature, the value of n (and perhaps also the nature of the R group, although no clear-cut evidence has been obtained so far), affect chemical and optical yields. Work is in progress to define the importance of such parameters and to throw light on some contradictory data on max. optical rotatory powers of compounds **2** reported in the literature.

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13. Loss of optical activity up to 60% has been observed when compounds **2c** and **2d** were allowed to react with 2 equivalents of $AlCl_3$ in CH_2Cl_2 at 0^oC.
14. Loss of optical activity not exceeding 5-7% has been observed when compounds **2a** and **2b** were allowed to react with 2 equivalents of $AlCl_3$ in boiling $CHCl_3$.

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