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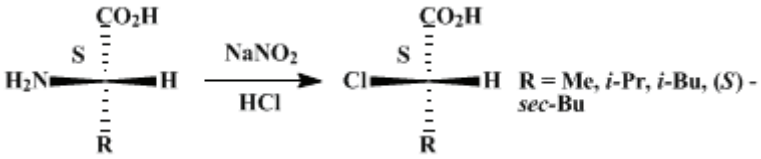
(*S*)-2-CHLOROALKANOIC ACIDS OF HIGH ENANTIOMERIC PURITY FROM (*S*)-2-AMINO ACIDS: (*S*)-2-CHLOROPROPANOIC ACID

[Propanoic acid, 2-chloro-, (*S*)-]



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Checked by G. Nagabhushana Reddy and James D. White.

1. Procedure

(S)-2-Chloropropanoic acid. In a 4-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a 500-mL dropping funnel, and a two-necked adapter fitted with a thermometer and a reflux condenser (Note 1), 89.1 g (1 mol) of (*S*)-alanine (Note 2) is dissolved in 1300 mL of 5 *N* hydrochloric acid (Note 3). The mixture is cooled to 0°C in an ice/sodium chloride bath (Note 4) and a precooled solution of 110 g (1.6 mol) of sodium nitrite in 400 mL of water is added dropwise at a rate of about 2 mL/min under vigorous stirring and efficient cooling so that the temperature of the reaction mixture is kept below 5°C. After 5 hr, the bath is removed and the reaction is allowed to stand overnight at room temperature (Note 5). The reflux condenser is connected with a water aspirator and the flask is carefully evacuated with stirring for 3 hr to remove nitrogen oxides, whereupon the color changes from yellowish brown to pale yellow. While the mixture is stirred vigorously, 100 g of solid sodium carbonate is added carefully in small portions so as to prevent excessive foaming. The reaction mixture is extracted with four portions of 400 mL of diethyl ether. The combined ether layers are concentrated to ca. 300 mL using a rotary evaporator at atmospheric pressure. The solution is washed with 50 mL of saturated brine, which thereafter is reextracted with three portions of 100 mL of diethyl ether. The combined ethereal solutions are dried for 10 hr over calcium chloride. The ether is distilled off with a rotary evaporator at atmospheric pressure (bath temperature 40–50°C). The oily residue is transferred into a distillation flask (rinsing the remainder with small portions of ether) and then fractionally distilled at reduced pressure, the main fraction boiling within a range of 2–3°C (i.e., bp 75–77°C at 10 mm) (Note 6) to give 63–71 g (58–65%) of an oil. The colorless oil is sufficiently pure for most purposes (Note 7) and (Note 8). On prolonged standing in a refrigerator, the oil tends to solidify partially or totally, but the white crystals formed have no sharp melting point. This procedure can be employed for other α-amino acids (see Table I and the Discussion).

2. Notes

1. If the procedure is carried out under an atmosphere of nitrogen, oxidation of nitrogen monoxide to nitrogen dioxide is prevented and the reaction mixture remains colorless, but the yield is not improved.
2. The checkers used (*S*)-alanine of 97% optical purity, purchased from Aldrich Chemical Company, Inc. The enantiomeric purities of the (*S*)-amino acids were checked by preparing the corresponding *N*-trifluoroacetylamino acid methyl esters, which are resolved into enantiomers by gas–liquid chromatography on glass capillary columns coated with the chiral stationary phase "Chirasil-Val"[2] (see Table I). For this purpose, an aliquot of the aqueous solution, containing about 0.1–1 mg of the amino acid, is transferred to a 1-mL vial. Water is removed by a stream of nitrogen and the residue is transformed to the methyl ester hydrochloride (15% hydrochloric acid in methanol, 110°C, 30 min) and finally (after drying in a stream of nitrogen) to the *N*-trifluoroacetyl derivative (trifluoroacetic anhydride, 110°C, 10 min). This material is dried and dissolved in dichloromethane for GLPC analysis. The commercially available (*S*)-amino acids alanine, valine, leucine, and isoleucine usually contained

only negligible amounts (a few parts/thousand) of the (*R*)-antipode, but occasionally up to 2.5% of the (*R*)-enantiomer has been detected in (*S*)-alanine and (*S*)-valine. The (*R*)-enantiomer is almost completely removed by one recrystallization from water.
3. Concentrated hydrochloric acid is diluted by its own volume with water. Hydrochloric acid (2.4 L, 5 *N*) is employed for the less soluble (*S*)-amino acids valine, leucine, and isoleucine.
4. A precipitate of the amino acid hydrochloride that formed on cooling is dissolved during the reaction.
5. The less soluble chloroalkanoic acids (*R* larger than methyl) separate from the solution as an oil.
6. Sometimes a brownish forerun is observed (bp ≤ 70°C/10 mm for 2-chloropropanoic acid), turning green in a refrigerator and occasionally undergoing vigorous decomposition. It is therefore recommended that distillation be interrupted and the flask containing the forerun removed.
7. Redistillation is recommended; overall yields are given in Table I. Enantiomeric purities were determined after conversion to *tert*-butyl amides (catalyzed by dicyclohexylcarbodiimide, 30 min at 0°C in dichloromethane) by gas–liquid chromatography on Chirasil-Val.[3] The specific rotation is adulterated by traces of water (determined by GLC on Porapak using a thermal conductivity detector) and unidentified brownish impurities. The chiroptical data (see Table I) are taken from double-distilled (*S*)-2-chloroalkanoic acids. Azeotropic removal of water from (*S*)-2-chloro-3-methylbutanoic acid by refluxing for 24 hr with dichloromethane in a water separator, followed by repeated spinning band distillation, yielded specific rotation values of up to −1.79°C.
8. The spectral properties of (*S*)-2-chloropropanoic acid were as follows: ^{1}H NMR ($CDCl_3$) δ: 1.66 (d, 3 H, J = 6.7), 4.40 (q, 1 H, J = 6.7), 12.0 (s, 1 H; this signal may be broadened and shifted upfield due to minimal amounts of water); ^{13}C NMR ($CDCl_3$) δ: 20.9, 52.0, 176.0.

3. Discussion

The present procedure is based on the method published by Fu et al.[4] The yields are increased by the very slow addition of an aqueous solution of sodium nitrite to the reaction mixture as well as by a modified workup procedure, specifically, careful removal of nitrogen oxides and the final decomposition of their adducts with carboxylic acids by buffering with sodium carbonate.

By using high-efficiency capillary gas chromatography with chiral stationary phases [i.e., Chirasil-Val[2] and (*R*)-*N*-lauroyl-1-(1-naphthyl)ethylamine;[5] see also recent publications on permethylated β-cyclodextrin[6]], it has been possible for the first time to determine the degree of racemization during the substitution reaction that proceeds with overall retention of configuration because of double inversion via an unstable α-lactone.[7] Thus, the maximum degree of inversion amounts to approximately 2.2%, resulting in a 2-chloroalkanoic acid of ee 95.6% (see Table I) if racemization occurs in the diazotization reaction, and not in the conversion of the free chloroalkanoic acid to the *tert*-butylamide employed for analysis of the enantiomeric composition.[3,5,6] The enantiomeric yields given in Table I represent the lowest values found in various experiments. The degree of racemization at carbon atom 2 is strongly affected by the alkyl group R (see Table I). Racemization is more pronounced in the case of less hindered primary and secondary carbon atoms adjacent to the stereocenter. It is interesting to note that the degree of racemization observed in the diazotization reaction runs parallel to the degree of racemization observed in aqueous solutions of the amino acids at pH 7.6 at elevated temperature.[8]

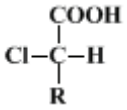
The diazotization in 5 *N* hydrochloric acid is superior to that in aqua regia,[9] where up to 10% inversion has been observed.[10]

The method described may also be used for the preparation of the corresponding (*R*)-2-chloroalkanoic acids when starting from unnatural (*R*)-2-amino acids. For instance, (*R*)-2-aminodecanoic acid has been obtained in high enantiomeric yield by enzymatic cleavage of the racemic *N*-chloroacetyl derivative.[11] For amino acids containing large alkyl side chains, diazotization at higher dilution is recommended. For the synthesis of racemic 2-chloroalkanoic acids, the diazotization method described here appears more convenient than the direct chlorination of alkanoic acids.[12]

2-Chloroalkanoic acids bearing chiral side groups are useful starting materials for the synthesis of chiral alcohols of high enantiomeric purity. Thus, (3*S*)-3-methylpentanol-1 has been obtained from (2*S*,3*S*)-isoleucine via exhaustive lithium aluminum hydride reduction of the chloro acid.[13,14] Similarly, (3*S*)-1,3-butanediol has been obtained from (2*S*,3*S*)-allothreonine.[15] The time-controlled lithium aluminum hydride reduction of 2-chloroalkanoic acids leads to 2-chloro-1-alkanols (chlorohydrins),

which can be cyclized to alkyloxiranes of high enantiomeric purity.[16]

TABLE I
(2*S*)-2-CHLOROALKANOIC ACIDS



Reactant	Substituent R	Yield (%)	bp (° C/mm)	ee (%) of Chloro Acid[a]	d_4^{20} (g/cm³)	$[\alpha]_D^{20}$ (°)[e]
(*S*)-Alanine	-CH_3	64 ± 6	75–77/10	95.6[b]	1.265	−13.98
(*S*)-Valine	-$CH(CH_3)_2$	62 ± 5	103–105/10	97.7[b]	1.140	−1.44
(*S*)-Leucine	-$CH_2CH(CH_3)_2$	58 ± 4	113–115/10	95.8[c]	1.082	−31.73
(2*S*)-Isoleucine	(3*S*)-$CH(CH_3)CH_2CH_3$	59 ± 6	111–112/10	98.3[c,d]	1.115	−4.78

[a]In each case the starting amino acid was ≥99.8% optically pure, as shown by gas chromatography of the trifluoroacetyl methyl esters on Chirasil-Val (Note 2).
[b]By gas chromatography on the *tert*-butyl amides on Chirasil-Val (Note 7).
[c]By gas chromatography of the *tert*-butyl amides on (*R*)-*N*-lauroyl-1-(1-naphthyl) ethylamine ([5,6]).
[d]Diastereomeric excess, referring to (2*R*,3*S*)-2-chloro-3-methylpentanoic acid. Total composition: 99.0% 2*S*,3*S*; 0.8% 2*R*,3*S*; 0.2% 2*S*,3*R*; approximately 0% 2*R*,3*R*. The starting amino acid was contaminated with 0.2% of the 2*S*,3*R*.
[e]Rotations were measured on the neat liquids; specific rotations are given for material of the indicated enantiomeric excess.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 434

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1. Institut für Organische Chemie der Universität, Auf der Morgenstelle 18, D-7400 Tübingen, Federal Republic of Germany. We thank Mr. E. Koch and Professor E. Bayer, University of Tübingen, FRG, and Dr. K. Watabe and Professor E. Gil-Av, Weizmann Institute of Science, Rehovot, Israel, for the determination of the enantiomeric purity of the 2-chloroalkanoic acids. We thank Deutsche Forschungsgemeinschaft and Fonds der chemischen Industrie for support of this work.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

nitrogen oxides

brine

permethylated β-cyclodextrin

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

alanine,
(S)-alanine (56-41-7)

2-chloropropanoic acid (598-78-7)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

nitrogen monoxide

nitrogen dioxide (10102-44-0)

dichloromethane (75-09-2)

lithium aluminum hydride (16853-85-3)

isoleucine,
(2S)-Isoleucine,

(2S,3S)-isoleucine (73-32-5)

leucine,
(S)-Leucine (61-90-5)

valine,
(S)-valine (72-18-4)

dicyclohexylcarbodiimide (538-75-0)

trifluoroacetic anhydride (407-25-0)

(2S,3S)-allothreonine (28954-12-3)

(S)-2-Chloropropanoic acid,
Propanoic acid, 2-chloro-, (S)- (29617-66-1)

(S)-2-chloro-3-methylbutanoic acid

(R)-2-aminodecanoic acid

(3S)-3-methylpentanol-1

(3S)-1,3-butanediol

(2R,3S)-2-chloro-3-methylpentanoic acid

(R)-N-lauroyl-1-(1-naphthyl)ethylamine