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Optical methyl 2-chloropropionate synthesis by decomposition of methyl 2-(chlorocarbonyloxy)propionate with hexaalkylguanidinium chloride hydrochloride

Frédéric Violleau,[a] Sophie Thiébaud-Roux,[a,*] Elisabeth Borredon[a] and Pierre Le Gars[b]

[a]*Laboratoire de Chimie Agro-industrielle, UMR 31010 INRA/INP-ENCIACET, 118 route de Narbonne, 31077 Toulouse Cedex 4, France*
[b]*SNPE-Toulouse, Chemin de la loge, 31078 Toulouse Cedex, France*

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Abstract—The decomposition of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate in the presence of hexaalkylguanidinium chloride hydrochloride was confirmed to correspond to a nucleophilic substitution of the second order. However, racemization occured by the contact between the catalyst and methyl *R*-(+)-2-chloropropionate (**I**). This phenomenon is caused by the exchange between the chloride ion from catalyst and the chlorine atom of (**I**) according to a SN_2 mechanism as well.

1. Introduction

The alkyl 2-chloropropionates are the subject of many publications and patents describing their applications. For example, these compounds are generally used in the preparation of biological active molecules such as herbicides,[1,2] fungicides,[3] pesticides[4,5] and drugs.[6,7]

Generally, optically active alkyl 2-chloropropionates are usually synthesized by direct chlorination of the corresponding lactates using chlorinating agents such as hydrogen chloride,[8] sulphuryl chloride,[9] thionyl chloride[10,11] and phosgene.[12] They can also be prepared by decomposition of chlorosulfinates[13–17] and chloroformates.[18] Among the latter, chloroformates seem to be more convenient since their decomposition is accompanied by carbon dioxide release, which is less toxic than sulphur dioxide.

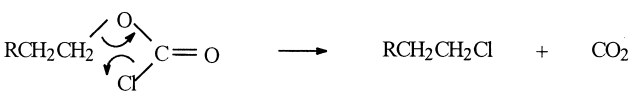
The chloroformate decomposition follows different mechanisms depending on the presence of catalyst.

Without catalyst, according to Hegarty,[19] the chloroformate thermal decomposition corresponds either to a first order nucleophilic substitution (SN_1) or to an intramolecular nucleophilic substitution (SN_i)

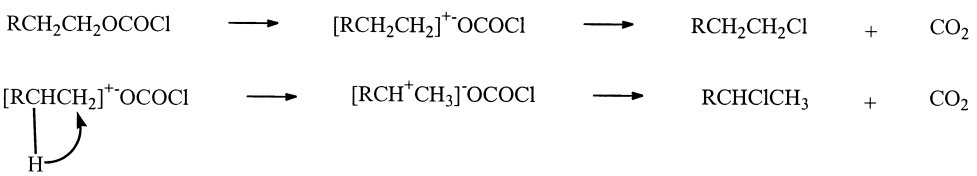
In the SN_1 case (Scheme 1), the intermediate carbocation can be rearranged in a more stable ion by hydrogen transposition and lead to the formation of a chlorinated isomer.

In the SN_i case (Scheme 2), rearrangement occurs inside the molecule. This mechanism was also described in the chlorosulphite decomposition.[20,21]

On the contrary, in the presence of catalyst, the reaction mechanism described in the literature follows a SN_2 reaction. This results in a configuration inversion of the concerned asymmetrical carbons. For example, with



Scheme 2.



Scheme 1.

Keywords: chloroformates; alkyl 2-chloropropionate; hexaalkylguanidinium chloride; optical; racemization; mechanism.
* Corresponding author. Tel.: +33-5-62-88-57-19; fax: +33-5-62-88-57-30; e-mail: sthiebaud@ensct.fr

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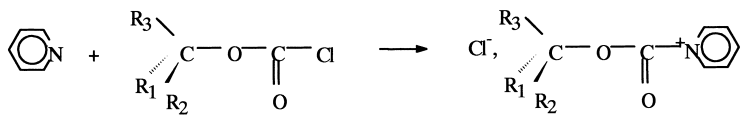
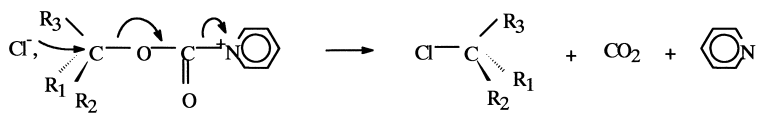


Scheme 3.

pyridine,[18,19] chloroformate is transformed into pyridinium chloride (Scheme 3).

The chloride ion attacks the asymmetrical carbon and causes the decarboxylation of the salt. Then the alkyl chloride is obtained with inversion of configuration (Scheme 4).

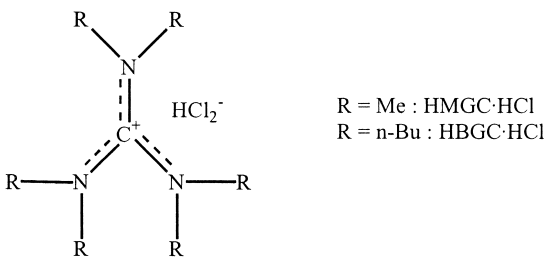


Scheme 4.

The same mechanism is followed when Q^+Cl^- compounds such as pyridine hydrochloride,[22,23] ammonium[24,25] or guanidinium chlorides[26–28] are used as catalysts. The chloride ion of catalyst is thus fixed (Scheme 5).

Scheme 5.

We tried to synthesize methyl *R*-(+)-2-chloropropionate by decomposition of methyl *S*-(−)-2-(chlorocarbonyloxy)-propionate by using a Q^+Cl^- catalyst, i.e., hexaalkyl-guanidinium chloride hydrochloride (Scheme 6).



Scheme 6.

Preliminary experiments using the experimental conditions described in litterature[27] were realized. Instead of obtaining an optical pure compound, we found partially racemised methyl 2-chloropropionate. The purpose of this work was to verify the SN_2 reaction mechanism. The conversion rate of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate and the enantiomeric composition of the product were studied. We proposed an explanation to the racemization phenomenon.

2. Results and discussion

We employed similar experimental conditions than these described by Foulon's et al.[27] for the decomposition of (*S*)-2-octyl chloroformate. According to these authors, chloroformate is totally decomposed into (*R*)-2-chloro-octane with a 96% of enantiomeric excess within 10 h at 80°C without solvent, in the presence of 0.5 mol% of hexabutylguanidinium chloride (HBGC). This catalyst is considered more efficient than pyridine, tetrabutylphos-phonium and tetrabutylammonium chlorides.[26,27]

The decomposition of methyl *S*-(−)-2-(chlorocarbonyl-oxy)propionate in the presence of 0.5 mol% of hexabutyl-guanidinium chloride hydrochloride (HBGC·HCl) with

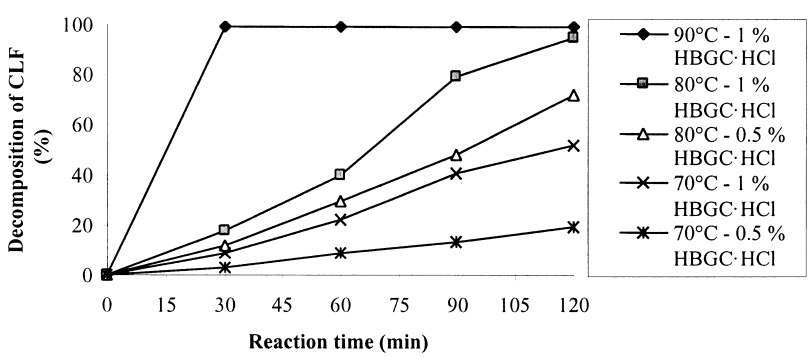


Figure 1. Influence of the temperature on the decomposition of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate in the presence of 0.5 or 1% of HBGC·HCl.

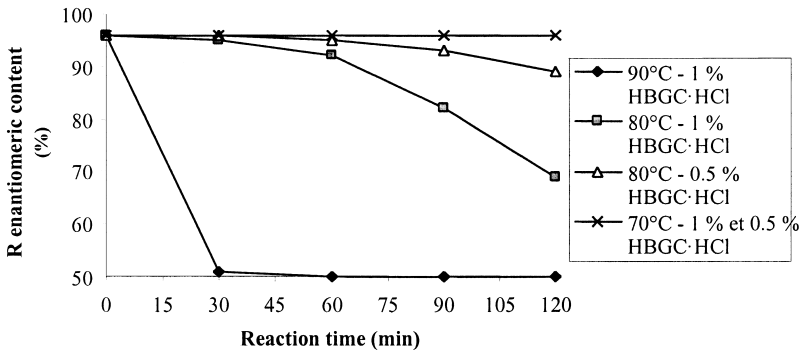


Figure 2. Influence of the reaction temperature on the *R* enantiomeric content of methyl 2-chloropropionate in the presence of 0.5 or 1% of HBGC·HCl.

Foulon's conditions led to the total conversion into methyl 2-chloropropionate with a 76% of *R* enantiomer content after 5 h and 54% after 10 h of reaction.

The racemization phenomenon can be probably due to the nature of the substrate or catalyst which both were different from Foulon's experiment. We can however expect the substrate to be the responsible. Indeed, Bochard[26] used the same catalyst (HBGC) for the decomposition of ethyl *S*-(−)-2-(chlorocarbonyloxy)propionate and also observed the racemization phenomenon.

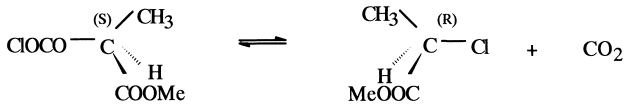
In order to explain the mechanism of racemization, we have studied the influence of temperature and catalyst concentration on the conversion rate of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate (Fig. 1) and on its enantiomeric composition (Fig. 2).

According to Fig. 1, the decomposition rate of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate decreases with temperature. Similarly, the racemization phenomenon is less important at low temperature (Fig. 2). The racemization of methyl *R*-(+)-2-chloropropionate was decreased by limiting the quantity of catalyst, especially at 80°C, but racemization was not eliminated. At 70°C, on the other hand, decomposition yield is only 50% but the product obtained was not racemized. The optical purity did not vary when changing the quantity of catalyst.

Such tests did not permit to obtain, at the same time, methyl *R*-(+)-2-chloropropionate with high yield and optical high purity. We tried to explain this phenomenon by studying the concerned reaction mechanisms.

If the decomposition of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate had followed a SN_i mechanism, we mainly should have obtained methyl *S*-(−)-2-chloropropionate. Moreover, the high percentage of *R* isomer at the beginning of the decomposition confirms, for that reason, the SN_2 mechanism.

This assessment is confirmed by the fact that the thermal degradation of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate starts at 135°C as showed by thermogravimetric analysis. Consequently, in our conditions (70–90°C), only the catalytic degradation of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate by nucleophilic substitution of SN_2 type can take place. The presence of the two enantiomers *R* and *S* at the end of the synthesis does not seem to be related to the competition between the mechanisms SN_2 (catalytic decomposition) and SN_1 or SN_i (thermal decomposition) as described by Foulon[27] in her work on *S*-(+)-2-octyl chloroformate at 80°C in the presence of 0.5% of hexabutylguanidinium chloride attributed to the presence of *S*-(+)-2-chlorooctane.



Scheme 7.

The phenomenon of racemization (Scheme 8) would rather occur after the formation of the *R* isomer and not during the decomposition of the chloroformate (Scheme 7):

first, there would be the catalytic decomposition of methyl *S*-(−)-(2-chlorocarbonyloxy)propionate (Scheme 7) and

Scheme 8.

then the racemization of methyl *R*-(+)-2-chloropropionate (Scheme 8)

In order to determine the exact role played by catalyst during this racemization and to check more precisely whether the chlorine atom of the latter plays a role in the

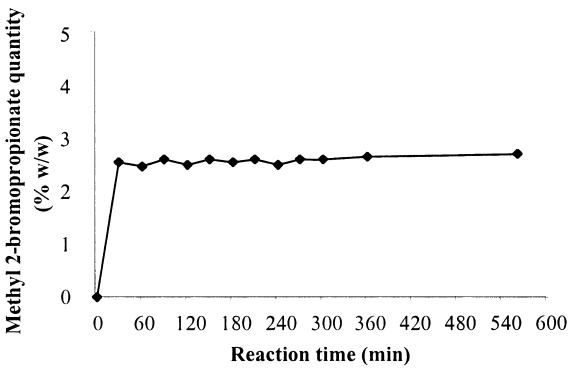


Figure 3. Evolution of the methyl 2-bromopropionate formation from methyl *R*-(+)-2-chloropropionate in the presence of 5% of $Br^-N^+BzEt_3$ at 90°C.

Scheme 9.

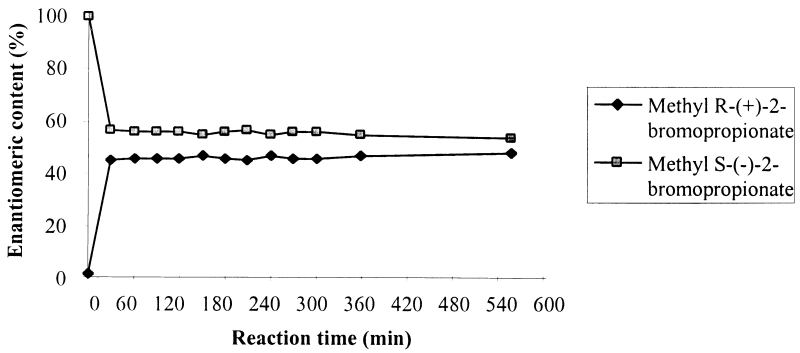


Figure 4. Evolution of the *R*-(+)- and *S*-(−)-methyl 2-bromopropionate enantiomers content during the contact with 5% of $Br^-N^+BzEt_3$ and methyl *R*-(+)-2-chloropropionate at 90°C.

inversion of configuration, the reaction between methyl *R*-(+)-2-chloropropionate (%*R*=94%) with a bromide onium instead of the chloride onium was made. The selected catalyst was benzyltriethylammonium bromide ($Br^-N^+BzEt_3$). We intentionally added 5 mol% in the solution of methyl *R*-(+)-2-chloropropionate to favor racemization. After a 30 min contact at 90°C, we detected by GC the presence of 2.5% w/w of methyl bromopropionate.

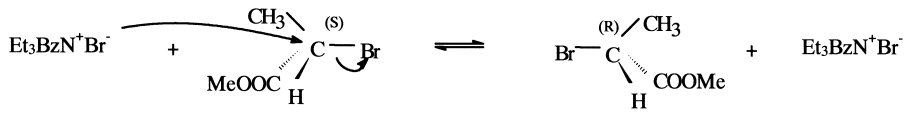
This quantity remained stable along the reaction time (Fig. 3). The presence of this brominated compound confirmed that the catalyst halide ion was the responsible for the configuration inversion through a SN_2 mechanism. The brominated compound is then transformed into benzyltriethylammonium chloride (Scheme 9). At the end of reaction, it was obtained not only methyl *S*-(−)-2-bromopropionate, but also its *R* isomer (Fig. 4). This means that the brominated catalyst reacts with the chlorinated initial derivative but also with the *S* isomer of the brominated derivative as well (Scheme 10).

The benzyltriethylammonium chloride is formed by reaction of benzyltriethylammonium bromide and methyl *R*-(+)-2-chloropropionate (reaction 3). It is also the responsible for the methyl *S*-(−)-2-chloropropionate presence in the reaction medium (Fig. 5) by reaction of chloride ion with methyl *R*-(+)-2-chloropropionate according to a SN_2 mechanism (reaction 5).

In the same way, the significant reduction in the *R* enantiomer content of the methyl 2-chloropropionate (Fig. 5) can be allotted to a reaction between methyl *R*-(+)-2-chloropropionate and benzyltriethylammonium chloride to give methyl *S*-(−)-2-chloropropionate according to a mechanism SN_2 (Scheme 11).

We have thus highlighted that the racemization of the chlorinated derivative occurred after the formation of the latter and was related to the attack of catalyst halide ion according to a mechanism SN_2.

In order to increase the enantiomeric excess of methyl



Scheme 10.

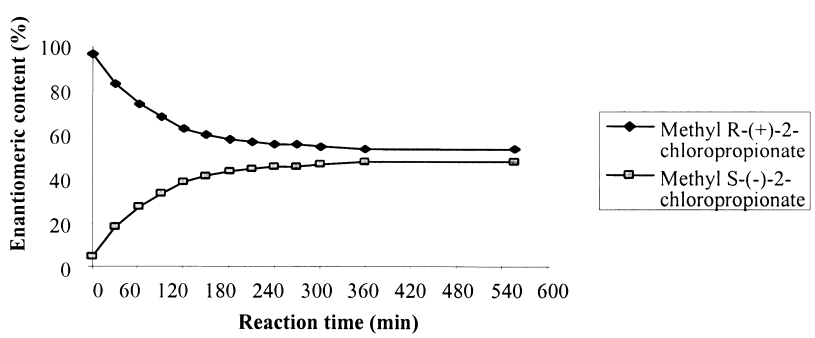


Figure 5. Evolution of the *R*-(+)- and *S*-(−)-methyl 2-chloropropionate enantiomers content during the contact with 5% of $Br^-N^+BzEt_3$ and methyl *R*-(+)-2-chloropropionate at 90°C.

Scheme 11.

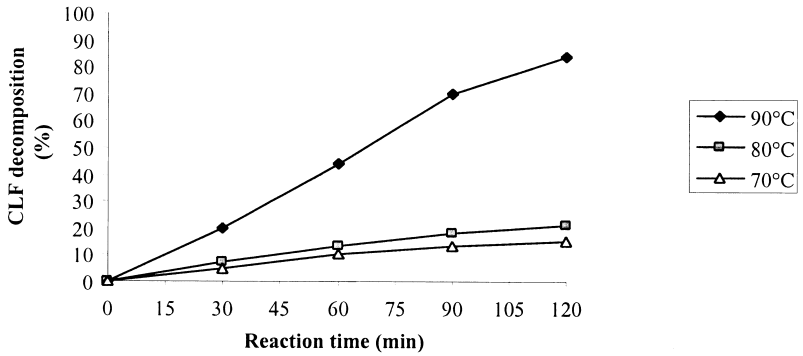


Figure 6. Temperature influence on the decomposition of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate in the presence of 1% of HMGC·HCl.

R-(+)-2-chloropropionate during the decomposition of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate, the hexamethylguanidinium chloride hydrochloride (HMGC·HCl) as catalyst (Figs. 6 and 7) was used. The nucleophilicity of this chloride ion is less important than that of the HBGC·HCl. Indeed, the steric hindrance generated by the methyl substituents over the nitrogen atoms is less important than that generated by the butyl one. So the distance between chlorine atom and the cationic center is smaller in HMGC·HCl than in HBGC·HCl which increases the interaction between the two ions. The results obtained are in conformity with our expectations. The racemization phenomenon is diminished. The decomposition rate of the chloroformate was decreased as well.

3. Conclusion

To obtain a quantity of methyl *R*-(+)-2-chloropropionate with a rate higher or equal to 98%, it is preferable to use the HMGC·HCl as catalyst and to limit the quantity of the latter and the temperature of reaction. However, these tendencies also result in a very slow speed of decomposition of the choroformate. The study of the reaction of decomposition of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate in the presence of hexaalkylguanidinium chloride hydrochloride showed that its mechanism follows a nucleophilic substitution of the second order. The racemization phenomenon observed is due to contact between the catalyst and the methyl *R*-(+)-chloropropionate during the synthesis by the exchange between chloride ion of the catalyst and chlorine atom of final molecule according to a SN_2 mechanism. In order to limit this racemization with preservation at the same time of a high yield of chloroformate decomposition, it will be necessary to isolate the chlorinated product progressively during its formation.

4. Experimental

4.1. Decomposition of the methyl (2-chlorocarbonyloxy)-propionate

In a 250 mL reactor equipped with a mechanical stirrer and a condenser connected to a bubble flask, 40 g of methyl (2-chlorocarbonyloxy)propionate, prepared by the method described by Kimura and Iwakura,[29] are introduced and heated at the desired temperature (70–90°C) with a heating bath. The desired quantity of catalyst (HBGC·HCl or HMGC·HCl) solubilized in 10 g of methyl (2-chlorocarbonyloxy)propionate are introduced in the reactor. The decomposition rate of methyl *S*-(−)-2-(chlorocarbonyloxy)propionate and the enantiomer *R* content of the methyl 2-chloropropionate are calculated after analyses of the reactional medium by gas chromatography.

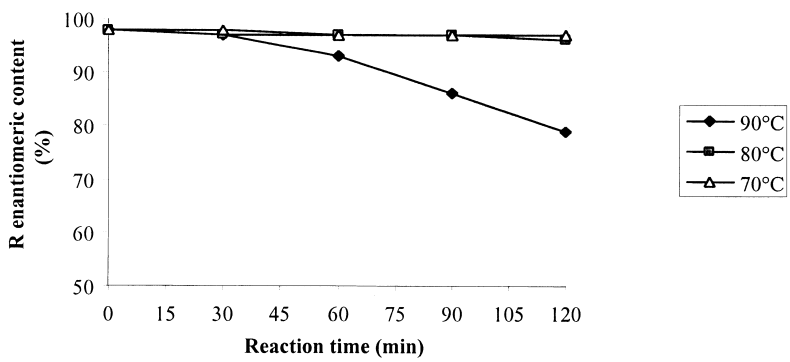


Figure 7. Temperature influence of reaction on the enantiomer *R* rate of methyl *R*-(+)-2-chloropropionate in the presence of 1% of HMGC·HCl.

For the experiment of the mechanism determination of racemization realized with benzyltriethylammonium bromide, 200 g of methyl *S*-(−)-2-chloropropionate and 22.2 g of catalyst (5 mol%) are introduced into a 250 mL reactor equipped with a mechanical stirrer and a condenser connected to a bubble flask. The reactional medium is carried at 90°C during 9.3 h.

4.2. Analysis of the methyl 2-chlorocarbonyloxy, 2-chloro and 2-bromopropionate reactionnal medium

The analysis by gas chromatography was carried out with an HP 5890 GC equipped wtih non-polar column Q1-50-02 (Touzard & Matignon) (50 m×0.25 mm×0.25 μm) with the following temperature program: 50°C during 3 min, then increase to 220°C at 30°C/min. A 8-min final time is carried out at 220°C. The injector temperature is 220°C and the FID detector one was 250°C. The helium pressure was fixed at 20 psi. Observed retention times are: methyl 2-chloropropionate: 5.4 min; methyl 2-bromopropionate: 6.3 min; methyl 2-(chlorocarbonyloxy)propionate: 8.1 min.

A method by internal calibration (internal standard: monochlorobenzene) was used to quantify the methyl 2-chloropropionate and the methyl (2-chlorocarbonyloxy)-propionate. With the methyl 2-bromopropionate, 1,4-dichlorobutane was used as internal standard.

4.3. Quantification of the methyl 2-chlorocarbonyloxy, 2-chloro and 2-bromopropionate enantiomers

The solution to be analyzed was solubilized in dichloromethane at 0.5 mg/mL concentration before injection. The dilution and the compounds vaporization in the injector limit the contact with the catalyst and consequently their racemization.

Quantification was carried out with an HP 5890 CG equipped a chiral column DEX 120 (30 m×0.2 mm× 0.25 μm) with the following temperature program: 60°C during 12 min, then increase to 220°C at 30°C/min. A 5 minute final time is carried out at 220°C. The injector temperature is 220°C and the FID detector one was 250°C. The helium pressure was fixed at 15 psi. Observed retention times are: methyl *S*-(−)-2-chloropropionate: 8.4 min; methyl *R*-(+)-2-chloropropionate: 9.0 min; methyl *S*-(−)-2-bromopropionate: 12.4 min; methyl *R*-(+)-2-bromopropionate: 14.7 min.

For the analysis of the methyl 2-(chlorocarbonyloxy)propionate enantiomers, the programming of temperature is the following one: 160°C during 12 min. Observed retention times are: methyl *S*-(−)-2-(chlorocarbonyloxy)propionate: 8.2 min; methyl *R*-(+)-2-(chlorocarbonyloxy)propionate: 9.4 min.

Acknowledgments

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References

1. (a) Tai, J. J. American Patent US 4 760 172, 1986; *Chem. Abstr. 109*, 190 031. (b) Tai, J. J. American Patent US 4 757 155, 1986; *Chem. Abstr. 109*, 170 039.
2. Andree, R.; Haug, M.; Luerssen, K.; Santel, H. J.; Schmidt, R. R. German Patent DE 4 202 053, 1992; *Chem. Abstr. 119*, 271 016.
3. Grieder, A.; Coers, K. J.; Labahn, P. American Patent US 4 267 356, 1980; *Chem. Abstr. 95*, 81 542.
4. Grieder, A.; Coers, K. J. American Patent US 4 260 782, 1980; *Chem. Abstr. 95*, 62 713.
5. Lukenheimer, W.; Brandes, W.; Paul, V. German Patent DE 2 702 102, 1977; *Chem. Abstr. 89*, 180 007.
6. Biedermann, J.; Leon-Lomeli, A.; Borbe, H. O.; Prop, G. *J. Med. Chem.* **1986**, *29*(7), 1183–1188.
7. (a) Biedermann, J.; Prop, G.; Doppelfeld, I. S. German Patent DE 3 149 009, 1981; *Chem. Abstr. 99*, 122 456. (b) Biedermann, J.; Prop, G.; Doppelfeld, I. S. German Patent DE 3 149 010, 1981; *Chem. Abstr. 99*, 212 523.
8. Visvanathan, T. P. *Curr. Sci.* **1973**, *42*(11), 390.
9. Shibahara, S.; Okonogi, T.; Marai, Y.; Kudo, T.; Yoshida, T.; Nishihata, K.; Kondo, S. European Patent EP 271 916, 1988; *Chem. Abstr. 109*, 170 126.
10. Darzens, M. G. *C. R. Acad. Sci.* **1911**, *152*, 1601–1603.
11. Frankland, P. F.; Garner, W. E. *Chem. Soc. Trans.* **1914**, *105*, 1101–1115.
12. Desmurs, J. R.; Metivier, P.; Padilla, G.; Rajoharisson, H. European Patent EP 380 393, 1990; *Chem. Abstr. 114*, 142 677.
13. Buathier, B.; Bernard, A. French Patent FR 2 459 221, 1979; *Chem. Abstr. 95*, 168 563.
14. Kaminakai, H. Japanese Patent JP 90 104 560, 1990; *Chem. Abstr. 113*, 114 663.
15. Kaminakai, H. Japanese Patent JP 86 57 534, 1986; *Chem. Abstr. 105*, 97 014.
16. Koch, M. German Patent DE 3 102 516, 1981; *Chem. Abstr. 97*, 162 397.
17. Kaminakai, H. Japanese Patent JP 86 68 445, 1986; *Chem. Abstr. 105*, 97 017.
18. Crosby, J. European patent EP 163 435, 1985; *Chem. Abstr. 105*, 114 607.
19. Hegarty, A. F. *Comprehensive Org. Chem.* **1972**, *2*, 1067–1083.
20. Lee, C. C.; Finlayson, A. J. *Can. J. Chem.* **1961**, *39*, 260–261.
21. Lee, C. C.; Clayton, J. W.; Lee, D. G.; Finlayson, A. J. *Tetrahedron* **1962**, *18*, 1395–1402.
22. Clinch, P. W.; Hudson, H. R. *J. Chem. Soc., Chem. Commun.* **1968**, *70*, 925–926.
23. Clinch, P. W.; Hudson, H. R. *J. Chem. Soc.* **1971**, 747–751.
24. Kevill, D.; Johnson, G. H.; Neubert, W. A. *Tetrahedron Lett.* **1966**, *31*, 3727–3729.
25. Pasquato, L.; Modena, G.; Cotarca, L.; Delogu, P.; Mantovani, S. *J. Org. Chem.* **2000**, *65*, 8224–8228.
26. Bochard, F. Ph.D. Thesis, University of Lyon 1, 1996, no. 232-96.
27. Foulon, F.; Fixari, B.; Picq, D.; Le Perchec, P. *Tetrahedron Lett.* **1997**, *38*(19), 3387–3390.
28. Senet, J. P. *Rec. Adv. Phosgene Chem.* **1997**, *1*, 22.
29. Kimura, K.; Iwakura, Y. *Org. Synth.* **1979**, *59*, 195.