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Poly(β-malic acid alkyl esters) derived from 4-alkyloxycarbonyl-2-oxetanones obtained via the ketene route

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Summary

The cycloaddition of ketene to methyl, ethyl, isopropyl and n-butyl glyoxylates resulting from the scission of corresponding tartrate diesters has been used to prepare racemic 4-alkyloxycarbonyl 2-oxetanones. The reaction was conducted in dichloromethane at low temperature in the presence of triethylamine as catalyst. The use of a chiral tertiary amine instead of triethylamine yielded an optically active β - lactone as shown in the case of methyl glyoxylate. The maximum enantiomeric excess was about 70 per cent and the sign of the elected enantiomer depended on the chiral base. Racemic n-butyl malolactonate was homopolymerized and copolymerized with benzyl malolactonate. High molecular weight polymers resulting from the homopolymerization of n-butyl malolactonate or from the copolymerization of this monomer with benzyl malolactonate were characterized by SEC and NMR. The ketene route was also used to synthesize racemic 4-trichloroethyloxycarbonyl 2-oxetanone, a β - substituted β - lactone, which had never been synthesized by other routes.

Keywords

4-alkyloxycarbonyl 2-oxetanones - Ketene - Alkyl glyoxylates - Poly (β - malic acid alkyl esters).

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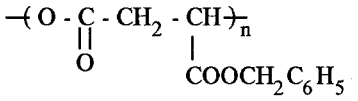
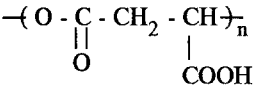
Introduction

Racemic and optically active poly (β - malic acids) (PMLA 100) have been synthesized by ring opening polymerization of benzyl malolactonate derived from bromosuccinic acid (1), aspartic acid enantiomers (2) and malic acid enantiomers (3), the final step being the cleavage of the benzyl protecting group in resulting poly (β - benzyl malates) (PMLA Be). Recently, pure optically active poly (L-malic acid) was detected in extracts of plasmodial PHYSARUM POLYCEPHALUM (4), a finding which suggests that optically active poly (β - malic acid) might be also prepared via a biosynthesis route.



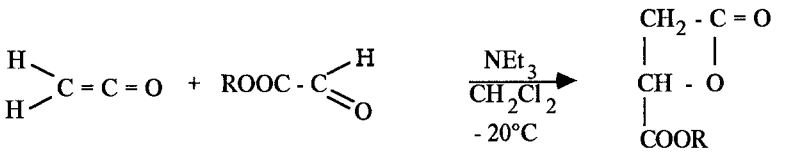
PMLA Be



PMLA 100

PMLA 100 is the parent compound of a large family of functional polymers, copolymers (3) and stereocopolymers (5) which can be prepared by direct copolymerization of suitable β-substituted β-lactones and/or by chemical modification (6).

In this paper, we wish to report a new synthesis route to make such β-substituted β-lactones, namely 4-alkyloxycarbonyl 2-oxetanones, which is based on the cycloaddition of ketene to suitable alkyl glyoxylates.



This type of reaction has been successfully used by H. WYNBERG for the asymmetric synthesis of malic acid or citramalic acid from ketene and chloral or 1,1,1-trichloroacetone and a chiral catalyst (9). It had also been investigated with different chlorinated aldehydes and ketones.

The interest of the method is twofold. First, higher molecular weights and higher yields are obtained than by the aspartic acid route. Secondly, new malolactonates which have not yet been synthesized through other ways have been obtained as exemplified by racemic 4-trichloroethyloxycarbonyl 2-oxetanone.

Experimental

Chemicals

All solvents were dried and purified by distillation as previously described (5). Ketene was produced using a ketene lamp as described by WILLIAMS and HURD (8). All ketene reactions were performed in a dried N_2 atmosphere. Benzyl malolactonate was prepared from aspartic acid as described before (2).

Dialkyl L-tartrates : Dimethyl, Diethyl, Diisopropyl, Di n-butyl L-tartrates were purchased from Janssen Chimica and used without further purification.

Dichloroethyl L-tartrate was prepared by refluxing a mixture of L-tartaric acid (0.5 mol ; 75 g) and trichloroethanol (1.6 mol ; 153 cm^3) in benzene (350 cm^3) for 18 hrs in the presence of Amberlyst ® 15 ion-exchange resin (15 g). After filtration, the organic solution was washed twice with 150 cm^3 of a sodium bicarbonate saturated solution and then with water. The aqueous phase was further washed with dichloromethane and all the organic fractions were mixed and dried on Na_2SO_4. After evaporation of the solvents, the residual solid was recrystallized from a warm mixture of cyclohexane and hexane (1/3, v/v). 8.3 g of dichloroethyl L-tartrate were recovered by filtration. CCl_3OCOCH_2OH $CH_2OHCOOCCl_3$: yield = 30 % (8.3 g) ; mp = 101 °C ; ^1H NMR ($CDCl_3$; δ ppm) : 4.80 (s, 4H) ; 4.70 (s, 2H) ; 3.15 (s, 2H) ; IR (ν ; cm^{-1}) : 1750 (C = O) ; 1250 (C-O ester) ; 700 (C - Cl).

Alkyl glyoxylates : The general procedure was based on the oxidative cleavage of tartaric acid diesters by ethereal periodic acid according to KELLY and al. (12).

The typical procedure described for dimethylglyoxylate was used for all glyoxylates according to specified amounts of reagents. Typically, dimethyl L-tartrate (200 mmol ; 3.5 g) in anhydrous diethyloxide (360 cm^3) and H_5IO_6 (200 mmol ; 58 g) were progressively added over a period of 2.5 hours at 30°C under N_2. The whole mixture was further stirred for 3 hours at 30°C before filtration. The colorless filtrate was dried on molecular sieves (4 Å) and concentrated to yield a viscous liquid which was purified by distillation on P_2O_5 under reduced pressure to yield pure methyl glyoxylate.

Methyl glyoxylate : $CH_3OOCCHO$ (oil) : yield = 43 % (15 g) ; bp (18 mm Hg) = 30-35°C ; ^1H NMR ($CDCl_3$; δ ppm) : 9.30 (s, 1H) ; 3.95 (s, 3H).

Ethyl glyoxylate : diethyl L-tartrate (276 mmol ; 56.9 g) ; H_5IO_6 (276 mmol ; 62.9 g) ; $(C_2H_5)_2O$ (570 cm^3). $C_2H_5OOCCHO$ (oil) : yield = 28 % (15.5 g) ; bp (18 mm Hg) = 30-35°C; ^1H NMr ($CDCl_3$; δ ppm) : 9.30 (s, 1H) ; 4.35 (q, 2H) ; 1.38 (t, 3H).

Isopropyl glyoxylate : diisopropyl L-tartrate (100 mmol ; 23.4 g) ; H_5IO_6 (100mmol ; 22.8 g); $(C_2H_5)_2O$ (230 cm^3). i-$C_3H_7OOCCHO$ (oil) : yield = 43 % (10 g) ; bp (18 mmHg) = 42-44°C; ^1H NMR ($CDCl_3$; δ ppm) : 9.35 (s, 1H) ; 5.17 (m, 1H) ; 1.42 (d, 6H).

n-butyl glyoxylate : dibutyl L-tartrate (58 mmol ; 15.2 g) ; H_5IO_6 (29 mmol ; 6.6 g) ; $(C_2H_5)_2O$ (150 cm^3). n-$C_4H_9OOCCHO$ (oil) : yield = 26 % (4.3 g) ; bp (18 mm Hg) = 55-60°C ; ^1H NMR ($CDCl_3$; δ ppm) : 9.35 (s, 1H) ; 4.30 (t, 2H) ; 2.00-1.00 (m, 4H) ; 1.10-0.70 (m, 3H).

Trichloroethyl glyoxylate : a mixture of trichloroethyl L-tartrate (20 mmol ; 8.25 g), H_5IO_6 (20 mmol; 4.56 g) and anhydrous tetrahydrofuran (200 cm^3) was allowed to stirred for 16 hours at room temperature. After filtration and evaporation of the filtrate, the resulting crude product was purified by crystallization in cyclohexane (white solid ; mp = 90°C). Before any use, the resulting compound was dried by heating at 90°C under reduced pressure (10^{-1} mm Hg / for 4 hours in the presence of P_2O_5) and at 120°C for 2 hours (10^{-1} mm Hg). $CCl_3CH_2OOCCHO$ (oil) : yield = 33 % (3.2 g) ; bp (10^{-1} mm Hg) = 140°C ; ^1H NMR (CD_3COCD_3 ; δ ppm) = 9.40 (s, 1H) ; 5.05 (s, 2H).

Racemic 4-alkyloxycarbonyl 2-oxetanones : All alkyl malolactonates were prepared according to the method used for methyl malolactonate. IR spectra of all resulting alkyl malolactonates presented the two characteristic bands at 1840 and 1740 cm^{-1}.

Methyl malolactonate : typically, 0.22 cm^3 (1.53 mmol) of anhydrous triethylamine NEt_3 and 250 cm^3 of anhydrous CH_2Cl_2 were mixed in a 500 cm^3 three necked flask, equipped with a thermometer and a ketene inlet tube. The mixture thus obtained was cooled at -20°C. A solution of freshly distillated alkyl glyoxylate was then introduced in the flask at a flow rate of 0.12 mol per hour while ketene was bubbled gently through the solution at a rate of 0.12 mol per hour. When the addition (62 mmol) was completed (31 mn), the whole mixture was further stirred at -20°C during 1mn and the temperature increased to 20°C. The organic solution was washed with 100 cm^3 of HCl (2N) and then with water in order to bring the solution to neutrality before drying with anhydrous $MgSO_4$. After filtration and evaporation, the recovered oil (7.2 g) was purified by chromatography over silica gel (diethyl oxide/petroleum ether, 6/4) and then was distillated under vacuum to yield 5 g (38.4 mmol) of colorless methyl malolactonate. Yield = 63 % (5 g) ; bp (0.1 mm Hg) = 62-68°C ; ^1H NMR ($CDCl_3$; δ ppm) : 4.91 (dd, 1H) ; 3.85 (s, 3H) ; 4.02-3.47 (m, 2H).

Ethyl malolactonate : ethyl glyoxylate (152 mmol ; 15.5 g), ketene (186 mmol), CH_2Cl_2 (350 cm^3), NEt_3 (3.8 mmol ; 0.53 cm^3). Reaction at -25°C (84 mn). Yield after distillation = 38 % (8.4 g) ; bp (0.05 mm Hg) = 57-63°C ; colorless liquid. ^1H NMR ($CDCl_3$, δ ppm) : 4.88 (dd, 1H) ; 4.30 (q, 2H) ; 3.99-3.45 (m, 2H) ; 1.33 (t, 3H).

Isopropyl malolactonate : isopropyl glyoxylate (86 mmol ; 10.0 g), ketene (92 mmol), CH_2Cl_2 (350 cm^3), NEt_3 (2.2 mmol ; 0.3 cm^3). Reaction at -25°C (46 mn). Yield after distillation : 54 % (8.4 g) ; bp (0.05 mm Hg) = 58-60°C ; colorless liquid. ^1H NMR ($CDCl_3$, δ ppm) : 5.14 (m, 1H) ; 4.84 (dd, 1H). 3.96-3.42 (m, 2H) ; 1.30 (d, 3H). ^{13}C NMR ($CDCl_3$, δ ppm) : 167.10 (C=0) ; 160.00 (C=0) ; 69.40 (CH) ; 64.90 (CH) ; 42.50 (CH_2) ; 20.70 ($2CH_3$).

n-butyl malolactonate : n-butyl glyoxylate (195 mmol ; 25.4 g), ketene (205 mmol), CH_2Cl_2 (400 cm^3), NEt_3 (9.2 mmol ; 1.29 g). Reaction at -20°C (98 mn). Yield after distillation = 52 % (18.8 g) ; bp (0.1 mm Hg) = 76/80°C ; colorless liquid. ^1H NMR ($CDCl_3$, δ ppm) : 4.88 (dd, 1H) ; 3.98-3.45 (m, 2H) ; 1.76-1.51 (m, 2H) ; 1.46-1.28 (m, 2H) ; 1.02-0.85 (t, 3H). ^{13}C NMR ($CDCl_3$; δ ppm) : 167.80 (C=O) ; 165.80 (C=O) ; 65.35 (CH_2) ; 64.92 (CH) ; 42.76 (CH_2) ; 29.76 (CH_2) ; 18.32 (CH_2) ; 12.91 (CH_3).

Trichloroethyl malolactonate : trichloroethyl glyoxylate (15.5 mmol ; 3.2 g), ketene (17.5 mmol), CH_2Cl_2 (250 cm^3), NEt_3 (1.39 mmol ; 0.2 cm^3). Reaction at -20°C (85 mn). After the standard treatment, the recovered oily product (2.9 g) was purified by column chromatography using a silica gel to separate pure trichloroethyl malolactonate. Yield = 21 %. White solid, mp = 55°C. ^1H NMR ($CDCl_3$, δ ppm) : 5.05 (dd, 1H) ; 4.90 (s, 2H) ; 3.90-3.70 (m, 2H). ^{13}C NMR ($CDCl_3$; δ ppm) : 166.50 (C=O) ; 165.00 (C=O) ; 94.00 (CCl_3) ; 74.20 (CH) ; 64.70 (CH_2) ; 43.70 (CH_2).

Optically active 4-methyloxycarbonyl 2-oxetanones

Quinine as catalyst : methyl glyoxylate (70 mmol ; 15.0 g), ketene (180 mmol), CH_2Cl_2 (350 cm^3), quinine (4.26 mmol ; 1.38 g). Reaction temperature -30°C (94 mn). The standard purification procedure led to 8 g of (S)-(+)-methyl malolactonate. bp (0.05 mm Hg) = 57-62°C ; $[\alpha]^{25}_D$ = + 2.05 (C = 10.25 ; THF) ; e.e. = 35 % ; litt : bp (0.01 mm Hg) : 57°C [3] ; $[\alpha]^{25}_D$ = + 5.9 (C = 10.3 ; THF) ; e.e. = 36 % determined by ^1H NMR in the presence of Eu [hfe]$_3$.

Quinidine as catalyst : methyl glyoxylate (43 mmol ; 3.8 g), ketene (44 mmol), CH_2Cl_2 (350 cm^3), quinidine (1.25 mmol ; 0.4 g). Reaction at -30°C (22 mn). 1.8 g (13.8 mmol) of (R)-(-)-methyl malolactonate after purification. Yield = 32 % ; bp (0.05 mm Hg) : 62°C ; $[\alpha]^{25}_D$ = + 4.25 (C = 10.4 ; THF) ; e.e. = 72 % determined by ^1H NMR in the presence of Eu [hfc]$_3$.

Poly (n-butyl β-malate) : (PMLA n-Bu) : n-butyl malolactonate, obtained from the ketene synthesis route, was polymerized at 37°C (3 days) with $C_6H_5COO^-NEt_4^+$ as the initiator ([initiator]/[monomer] = 10^{-3}). The crude material was purified by dissolution in acetone and precipitation with ethanol to yield PMLA n-Bu. Molecular weights were evaluated in dioxane by SEC using a WATERS apparatus equipped with μ-styragel columns. SEC data were given with regard to polystyrene standards : M_{SEC} = 73 000.

^1H NMR ($CDCl_3$, δ ppm : 5.53-5.48 (m, 1H) ; 4.88-4.13 (t, 2H) ; 3.06-2.91 (m, 2H) ; 1.67-1.58 (m, 2H) ; 1.42-1.30 (m, 2H) ; 0.95-0.90 (t, 3H).

^{13}C NMR ($CDCl_3$; δ ppm) : 168.23 (C=O) ; 168.08 (C=O) ; 68.63-68.54 (CH) ; 65.77 (CH_2) ; 35.49 (CH_2) ; 30.47 (CH_2) ; 18.99 (CH_2) ; 13.63 (CH_3).

Poly (n-butyl β-malate-co-benzyl β-malate) : Racemic benzyl malolactonate and n-butyl malolactonate were mixed in the ratio 0.7/0.3 (mol/mol) and then polymerized at 37°C (3 days) with $C_6H_5COO^-NEt_4^+$ as the initiator ([initiator]/[monomer] = 10^{-3}). The crude copolymer was dissolved in acetone and precipitated in ethanol. M_{SEC} = 85 000 (dioxane, polystyrene standards).

^{13}C NMR and ^1H NMR spectra exhibited the different peaks which are characteristic of the two monomer units in 0,7/0,3 molar ratio as determined on the ^1H NMR spectrum.

NMR spectra

^1H and ^{13}C NMR spectra were recorded by using BRUKER WM250FT analyser at 25°C.

Tris [(3-heptafluoropropylhydroxymethylene)-d-camphorato] Europium(III) (Eu[hfc]$_3$) (JANSSEN CHIMICA) was dried for 48 h. under high vacuum before being used for the preparation of a $CDCl_3$ stock solution (0.17 M). Suitable amounts of the Eu[hfc]$_3$ stock solution were mixed to the substrate solution (0.04 M) in NMR tubes. The enantiomeric composition was determined from the areas of shifted NMR resonance peaks by using a HEWLETT PACKARD computer. ^1H NMR [$CDCl_3$, δ ppm : in the presence of - 0.33 eq Eu[hfc]$_3$: 6.16 (t, 1H) ; 6.11 (t, 1H) ; 4.73 (s, 3H) ; 4.67 (s, 3H) ; 4.80-4.27 (m, 2H) ; 4.79-4.26 (m, 2H). (e.e. = 36 %).

Results and Discussion

The first member of the malolactonic acid esters family (alkyl or aryl malolactonates) was benzyl malolactonate (MLABe) which can be synthesized starting from various compounds such as bromosuccinic acid, malic acid or aspartic acid. In the latter case, the amino acid was transformed to bromosuccinic acid ; MLABe was obtained by lactonization of the α-bromosuccinic acid monobenzyl ester. Before any purification, the yield in benzyl malolactonate was about 70 %, with regard to lactonisable monoester. However, monomer purification was necessary to obtain high molecular weigths and the yield after purification was never more than 10 % based on bromosuccinic acid. This method was applied to prepare alkylmalolactonates. All monoalkyl bromosuccinates were obtained with excellent yield (95 %). However, the yield in alkyl malolactonates depended very much on the alkyl group.

Before any purification, yields were already as low as 40 % in the case of CH_3, 44 % for C_2H_5 compared with 70 % for n-C_4H_9.

To overcome this problem, we have selected a new synthesis route, namely the base-catalyzed 2+2 cycloaddition between ketene and alkyl glyoxylate. All glyoxylates were prepared by using the oxidative cleavage of the corresponding diesters of tartaric acid with yields ranging from 50 to 70 %. However, the critical stage appeared to be the dehydratation of glyoxalic acid esters. These compounds were always obtained more or less hydrated. Their hygroscopy was assigned to the presence of a carbonyl group in β-position to the ester one. Anyhow, only distillation on the presence of P_2O_5 led to dehydrated glyoxylates. Attempts to synthesize benzyl glyoxylate via the same route failed because the compound was completly unstable on heating in the presence of P_2O_5.

Racemic alkyl malolactonates were prepared from corresponding glyoxylates in the presence of NEt_3 as the catalyst. After the recovering of the crude lactones, purification was necessary in order to stabilize these monomers. Yields of pure alkyl malolactonates calculated from alkyl glyoxylates were sufficiently high to produce racemic poly (alkyl β-malates) in rather large quantities : the overall yield being 30 % (Et), 45 % (Me) and 50 % (n-Bu) with respect to starting compounds. An important factor determining the capacity and the rate of reaction of glyoxylates seems to be the polarization of the carbonyl group by the aldehyde function, the alkyloxycarbonyl substituent acting as an efficient electron withdrawing substituent. The major limiting factor was the difficulty to achieve alkyl glyoxylate dehydration.

1,1,1-trichloroethyl malolactonate was synthesized by the same method. The synthesis of this product was previously attempted by the bromosuccinic anhydride route, but trichloroethanol never reacted with this anhydride, even in the presence of a catalyst. In contrast, the cycloaddition of ketene to 1,1,1-trichloroethyl glyoxylate worked very well according to the procedure used for alkylmalolactonates and yielded the expected solid lactone (mp = 56°C).

For testing the capacity of the ketene route to prepare optically active alkylmalolactonates, NEt_3 was replaced by chiral amines to catalyze the reaction between methyl glyoxylate and ketene. Quinine and quinidine were selected from the literature dealing with the asymmetric synthesis of chiral 4-substituted 2-oxetanone (13). In our cases, the two alkaloïds yielded oxetanones with opposite absolute configurations. Quinine conducted to R-(-)-MLAMe and quinidine to S-(+)-MLAMe, based on literature data (13). The enantiomeric excesses were 36 % and 72 %, respectively. It is worth to note that MLABe with enantiomeric excesses close to 100 % (≥ 98 %) were obtained when prepared from optically active aspartic acid or malic acid (3,5).

The n-butyl malolactonate which was prepared by the ketene route was used to make racemic poly (n-butyl malolactonate) and a copolymer of benzyl malolactonate and n-butyl malolactonate (70/30 as determined by ^1H NMR). The resulting PMLA^{50}n-Bu presented an unusual solubility in diethyl ether and lower glass temperature (T_g = - 50°C vs 37°C, PMLA^{50}Be). It is interesting to observe that the ketene route led to molecular weights systematically higher than the classical route suggesting less transfer reactions. In the case of MLABe/MLAn-Bu, evidence for a random distribution of repeat units has been shown by ^{13}C NMR structural analysis and by comparison with previous results (7). The copolymer structure was deduced from the fact that the carbonyl carbon region exhibited more peaks in the PMLA^{50}Be$_{70}$n-Bu$_{30}$ spectrum than a corresponding mixture of homopolymers namely of 30 % PMLA^{50}n-Bu$_{100}$ and 70 % of PMLA Be$_{100}$ as shown on the figure 1.

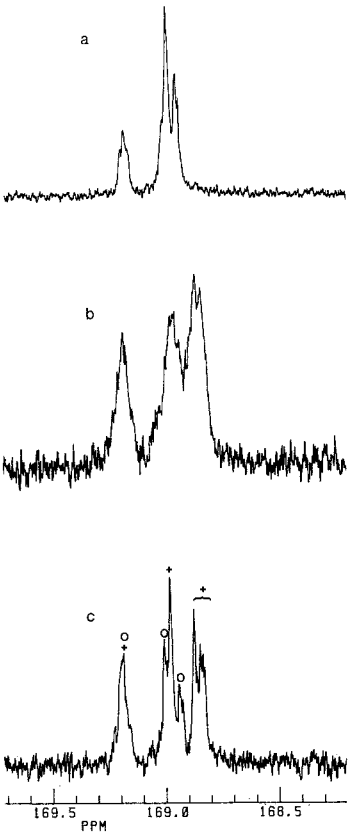


Figure 1. ^{13}C NMR spectra (carbonyl carbon atom region) in deuterated acetone under normal conditions : (a) PMLA^{50}n-Bu ; (b) mixture of PMLA^{50}Be (7) (+) and PMLA^{50}n-Bu (o) (70/30) ; (c) PMLA^{50}Be$_{70}$n-Bu$_{30}$.

Conclusion

The 4-alkyloxy carbonyl 2-oxetanones can be prepared by reacting ketene with alkylglyoxylates. This new route presents two major interests. First, it allows the synthesis of usual alkyl malolactonates and further provide also possibilities to tailor make derivatives of poly(β-malic acid) with different structures and properties by copolymerization. Secondly, it opens the way to a series of malolactone-type monomers which have not been prepared otherwise.

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