Radical cyclization of allyl α-bromocarboxylates into γ-butyrolactones. Effect of the ester structure on the cyclization

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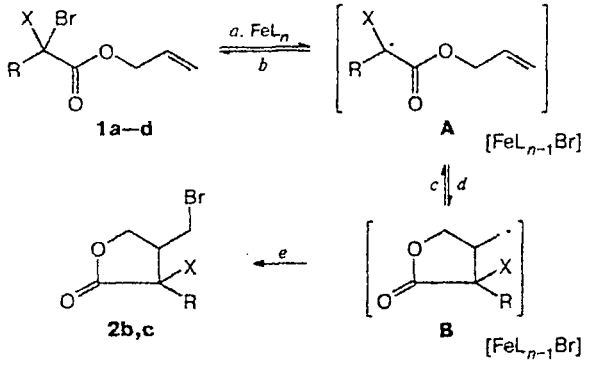
Allyl dibromoacetate, allyl α-bromopropionate, and allyl phenylbromoacetate undergo cyclization in benzene in the presence of increased concentration of $Fe(CO)_5$—DMF as the initiating system to give the corresponding bromo-substituted butyrolactones.

Key words: cyclization, allyl esters, bromocarboxylic acids, iron pentacarbonyl, radicals.

Allyl trichloroacetate and allyl dichloropropionate cyclize into γ-lactones in benzene in the presence of $Fe(CO)_5$—amide systems, whereas allyl bromoacetate (**1a**) and allyl 2-bromopropionate (**1b**) do not react under similar conditions.[1,2] Benzoyl peroxide is ineffective in these reactions.

Taking into consideration that esters of the above-mentioned bromo-substituted acids readily undergo radical addition to α-olefins under conditions of metal-complex initiation with the cleavage of the C—Br bond, we assumed that the absence of the products of intramolecular addition (cyclization) (see Scheme 1, pathways *a—d*) in the case of allyl bromocarboxylates is due to the insufficient efficiency of chain transfer at the step of stabilization of a primary radical **B**, which results in its reversible opening into a linear radical **A** to give the starting ester. The principal possibility of the reversible opening of similar cycles follows from kinetic data.[3]

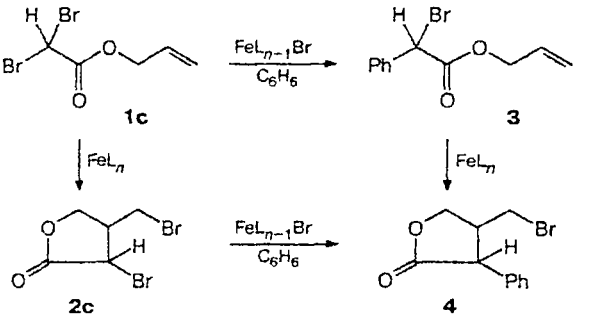
Scheme 1



a: X = R = H; **b**: X = H, R = Me, **c**: X = Br, R = H; **d**: X = CO_2Me, R = H; L = DMF, CO

In a continuation of our research, we extended the set of allyl bromocarboxylates and studied the behavior of esters **1a,b** and allyl dibromoacetate (**1c**), allyl methyl bromomalonate (**1d**) (see Scheme 1), and allyl bromophenylacetate (**3**) (Scheme 2) under modified reaction conditions.

Scheme 2



To increase the efficiency of the step of chain transfer by a cyclic radical **B** with elimination of the bromine atom from the bromo-containing iron carbonyl complex (see Scheme 1, pathway *e*) we increased twofold the concentration of the initiating system ($Fe(CO)_5$—DMF) (in comparison with the reaction conditions used previously[1]) and slightly increased the reaction temperature (by 5—10 °C).

Under these conditions, allyl 2-bromopropionate (**1b**) cyclizes to give 3-bromomethyl-2-methyl-γ-butyrolactone (**2b**) as a mixture of two diastereomers in the ratio 4 : 1. According to chromato-mass spectrometric data, the reaction mixture also contains small amounts of the products of replacement of the bromine atom for phenyl both in the original ester **1b** and in lactone **2b**.

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One of the reasons for this effect of increased concentration of the initiating system on the efficiency of cyclization is the formation of complexes of radicals **A** and **B** with derivatives of iron that appear in the reaction mixture due to the reaction between $Fe(CO)_5$, DMF, and compounds **1b,c**. The complexation can stabilize the cyclic radical **B** (see Scheme 1). Since tha cyclization is carried out in benzene and the reaction mixture contains iron salts, the appearance of phenyl derivatives in this and other examples can be rationalized by the reaction of the ester and the lactone with benzene catalyzed by iron salts.

It is interesting to note that almost complete racemization of the starting ester occurs when allyl (*S*)-2-bromopropionate (*S*-**1b**) is used in this reaction (*cf.* Ref. 4). As a result, both the lactone formed and the unconsumed original ester were present in the reaction mixture as racemates as follows from enantiomeric GLC analysis. Allyl bromoacetate (**1a**) remains unchanged under these conditions as well,[1] which indicates the considerable role of the presence and the nature of the second substituent at the α-C atom. This is also confirmed by the rather high efficiency of the cyclization of allyl dibromoacetate (**1c**) under similar conditions to give 2-bromo-3-bromomethyl-γ-butyrolactone (**2c**), also in the form of two diastereomers. Chromato-mass spectrometric data for the reaction mixture showed that, along with the starting ester **1c** and the corresponding lactone **2c**, it also contains products of the replacement of one bromine atoms in ester **1c** and in lactone **2c** for a phenyl group (see Scheme 2, compounds **3** and **4**, respectively).

Lactone **4** can also result from the cyclization of ester **3**, which in this case should occur quite efficiently, judging by the ratio of compounds **3** and **4** in the reaction mixture. It is difficult to solve this problem unambiguously, because chromato-mass spectrometric analysis of the reaction mixture resulting from the cyclization of ester **1b** also revealed, but in minor quantities, products of the replacement of bromine atoms for a phenyl group, both in the starting ester and in the lactone, although the cyclization of allyl 2-phenylpropionate (**5**) into the corresponding lactone (**6**) in analogy to Scheme 2 is impossible under these conditions.

In view of this, we have synthesized authentic allyl (*R*)-bromo(phenyl)acetate (*R*-**3**) and studied its behavior under the cyclization conditions. GLC analysis using the previously isolated lactone **4** as the standard indicates that the latter is present in the reaction mixture.

The fact that a five-membered ring is formed upon cyclization is confirmed by literature data (see Refs. 1 and 2 and references cited therein), by the presence of ions with *m/z* corresponding to the fragmentation of a molecular ion with the elimination of a CH_2Br group in the mass spectra of lactones, and by good agreement between the experimental and calculated[5] chemical shifts of the carbon atom of the CH_2Br group in the ^{13}C NMR spectra of lactones **2b,c**.

A somewhat unexpected result was obtained in an attempt at the cyclization of a mixed ester, *viz.*, allyl methyl bromomalonate (**1d**). GLC analysis showed that the reaction mixture contained five main compounds, which are, according to chromato-mass spectrometric data, the products of symmetrization of the mixed ester followed by their partial reduction, *i.e.*, dimethyl bromomalonate, diallyl bromomalonate, dimethyl malonate, allyl methyl malonate, and diallyl malonate are formed under the reaction conditions.

Thus, the presence and the nature of substituents at the carbon atom carrying the bromine atom affect considerably the cyclization and the character of the side processes.

Experimental

Mass spectra were obtained on a VG-7070E chromato-mass spectrometer using a DB-5 column (50 m), with temperature programming from 30 to 220 °C (2.5 deg min^{-1}); *m/z* values for ions are given for the ^{79}Br isotope. GLC analysis was carried out on a LKhM-80 chromatograph using a steel column (1300×3 mm) with 15% SKTFT-50X on Chromaton N-AW, helium as the carrier gas (60 cm^3 min^{-1}), and a katharometer as a detector; the temperature was programmed from 50 to 250 °C (6 deg min^{-1}). Preparative GLC was performed on a steel column (1300×9 mm) with 20% SKTFT-50X on the same carrier and helium as the carrier gas (120 cm^3 min^{-1}), 180 °C. The $[\alpha]_D$ values were measured on a Perkin—Elmer 241 polarimeter.

Enantiomeric GLC analysis was performed on a Khromatograph 3700-00 instrument with a flame ionization detector, on a quartz capillary column (32 m×0.23 mm) with DP-TFA-γ-CD; thickness of the liquid phase 0.12 μm, temperature programming from 85 to 170 °C, with helium (1.5 bar) as the carrier gas.

^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200 instrument (200 MHz) in C_6D_6 as the solvent. Chemical shifts δ are given relative to $SiMe_4$. All spectroscopic data are presented for one of the diastereomers.

The procedure for the preparation of esters **1a,b** and their properties were reported previously.[1]

Allyl dibromoacetate (1c) (see Ref. 1, procedure *A*) was obtained by transesterification of methyl dibromoacetate (0.05 mol) with allyl alcohol (0.25 mol) in the presence of H_2SO_4; b.p. 84—85 °C (5 Torr), n_D^{20} 1.5151, d_4^{20} 1.8519, yield 85%. ^1H NMR, δ: 5.85 (s, 1 H, $CHBr_2$); 5.82 (m, 1 H, CH=); 5.38 (m, 2 H, CH_2O); 4.70 (m, 2 H, CH_2=). MS, *m/z* (I_{rel} (%)), number of bromine atoms: 201 $[CHBr_2CO]^+$ (4.3), 2 Br; 177 $[M-Br]^+$ (23.9), 1 Br; 171 $[CHBr_2]^+$ (15.2), 2 Br; 85 $[M-CHBr_2]^+$ (19.6); 41 $[CH_2=CHCH_2]^+$ (100).

Allyl (*S*)-2-bromopropionate (*S*-1b). $SOCl_2$ (2.5 g, 0.022 mol) was added dropwise with stirring and cooling (−25 °C) over a period of 1 h to a solution of (*S*)-2-bromopropionic acid ($[\alpha]_D^{25}$ −28.04° (*c* = 1, $CHCl_3$), 3.1 g, 0.02 mol) obtained as reported previously[2] in allyl alcohol (11.6 g, 0.2 mol) maintaining the temperature not higher than −20 °C. The mixture was stirred for another 2 h under the same conditions and then kept for 2 h at ~20 °C. The reaction mixture was then cooled to −10 °C, and ether (10 mL) was added. Cold water was then added dropwise until self-heating ceased; the mixture was washed with a cold solution of Na_2CO_3 until neutral pH and dried with Na_2SO_4. The ether was

distilled off, and the residue was distilled *in vacuo*. Yield 1.8 g (46%), b.p. 74 °C (15 Torr), n_D^{20} 1.4660, d_4^{20} 1.3688, $[\alpha]_D^{25}$ −24.39° (*c* = 1, $CHCl_3$). Optical purity is 98.8%.

Allyl methyl bromomalonate (1d). A mixture of dimethyl bromomalonate (21.1 g, 0.1 mol), allyl alcohol (29.04 g, 0.5 mol), and H_2SO_4 (0.2 g) was boiled with distillation of MeOH, and the composition of the reaction mixture was monitored by GLC so as to avoid complete transesterification. After 2 h, when the reaction mixture contained ~35% of compound **1d**, the excess of allyl alcohol was distilled off. The residue was dissolved in $CHCl_3$ and washed with water, aqueous Na_2CO_3, and again with water, and dried with $MgSO_4$. The solvent was distilled off, and the residue was fractionated. Distillation gave a fraction with b.p. 117 °C (7 Torr), yield 3.8 g (16%), n_D^{20} 1.4750, d_4^{20} 1.4515. ^{1}H NMR, δ: 6.07 (m, 1 H, CH=); 5.32 (m, 2 H, CH_2=); 5.02 (s, 1 H, CHBr); 4.81 (d, 2 H, CH_2O); 3.93 (s, 3 H, Me). MS, *m/z* (I_{rel} (%)), number of bromine atoms: 205 $[M-MeO]^+$ (1.19), 1 Br; 179 $[M-CH_2=CHCH_2O]^+$ (7.65), 1 Br; 151 $[M-COOCH_2CH=CH_2]^+$ (4.93), 1 Br; 120 $[CHBr=CO]^{+\cdot}$ (4.18), 1 Br; 101 $[CHOCHCOOMe]^+$ (100); 59 $[MeCOO]^+$ (14.5); 41 $[CH_2=CHCH_2]^+$ (81.15).

Allyl (*R*)-bromo(phenyl)acetate (*R*-3) was obtained similarly to compound *S*-**1b**, yield 28.5%. ^{1}H NMR, δ: 5.21 (s, 1 H, CHBr); 6.8–7.3 (m, 5 H, Ph); 5.57 (m, 1 H, CH=); 4.91 (m, 2 H, CH_2=); 4.31 (d, 2 H, CH_2O). Allyl chloro(phenyl)acetate is formed as a side product. ^{1}H NMR, δ: 5.12 (s, 1 H, CHCl); 7.1–7.5 (m, 5 H, Ph); 5.25 (m, 1 H, CH=); 4.83 (m, 2 H, CH_2=); 4.26 (d, 2 H, CH_2O).

Cyclization of esters 1b,c and 3 in the presence of the system $Fe(CO)_5$—DMF. The reaction was carried out at 145–150 °C for 3 h, as described previously,[1] using the following amounts of the reagents: 1 mmol of ester **1** or **3**, 0.2 mmol of $Fe(CO)_5$, and 0.6 mmol of DMF in benzene (10 mL). Preparative syntheses using esters **1b,c** gave the corresponding lactones **2b,c**. In the case of ester **3**, the fraction containing 45% ester **3** and 55% chloro-substituted analog, which was shown not to react and to remain unchanged under these conditions, was used as the starting compound. The degree of conversion of ester **3** was 70% (GLC). The corresponding lactone **4** was identified in the reaction mixture by GLC by comparison with an authentic sample.

3-Bromomethyl-2-methylbutyrolactone (2b): yield 30% (GLC), isolated from the reaction mixture by preparative GLC; n_D^{20} 1.5010, d_4^{20} 1.5273. ^{1}H NMR, δ: 1.01 (d, 3 H, Me); 2.20 (m, 2 H, CH_2Br); 3.23 (m, 2 H, CH_2O); 3.71 (t, 1 H, C<u>H</u>—CH_2Br); 4.15 (m, 1 H, C<u>H</u>—Me). ^{13}C NMR, δ: 178.2 (CO); 69.5 (CH_2O); 44.5 (<u>C</u>HCO); 38.8 (CH); 32.0 (CH_2Br); 13.4 (Me); calculation by the additive scheme[5] for the CH_2Br group gave: δ 31.0. MS, *m/z* (I_{rel} (%)), number of bromine atoms: 192 $[M]^+$ (1.24), 1 Br; 69 $[M-CH_2Br-CH_2O]^+$ (100); 55 $[69-CH_2]^+$ (50.3); 41 $[CH_2CH=CH_2]^+$ (64.6).

Allyl 2-phenylpropionate (5). MS, *m/z* (I_{rel}(%)): 190 $[M]^+$ (12.5); 106 $[MeCH_2Ph]^+$ (9.32); 105 $[MeCHPh]^+$ (100); 77 $[Ph]^+$ (9.14); 41 $[CH_2=CHCH_2]^+$ (21.22).

3-Benzyl-2-methylbutyrolactone (6). MS, *m/z* (I_{rel} (%)): 190 $[M]^+$ (11.48); 99 $[M-CH_2Ph]^+$ (29.5); 91 $[C(O)CH(Me)CHCH_2O]^+$ (100); 77 $[Ph]^+$ (2.9); 28 $[CO]^{+\cdot}$ (12.37).

2-Bromo-3-bromomethylbutyrolactone (2c): yield 29% (GLC), isolated by preparative GLC. ^{13}C NMR, δ: 171.4 (CO); 69.7 (CH_2O); 46.9 (<u>C</u>HCO); 40.7 (CH); 30.2 (CH_2Br); calculation by the additive scheme[5] for the CH_2Br group gave: δ 29.6. MS, *m/z* (I_{rel} (%)), number of bromine atoms: 256 $[M]^+$ (2.2), 2 Br; 147 $[M-Br-CH_2O]^+$ (4.3), 1 Br; 133 $[M-Br-CO_2]^+$ (100), 1 Br; 119 $[M-CO_2-CH_2Br]^+$ (28.3), 1 Br.

Allyl bromo(phenyl)acetate (3). MS, *m/z* (I_{rel} (%)), number of bromine atoms: 254 $[M]^{+\cdot}$ (8.7), 1 Br; 175 $[M-Br]^+$ (39.1); 169 $[Ph-CHBr]^+$ (93.5), 1 Br; 41 $[CH_2=CH-CH_2]^+$ (100).

3-Bromomethyl-2-phenylbutyrolactone (4): yield 12% (GLC), isolated by preparative GLC. ^{1}H NMR, δ: 2.96 (m, 1 H, C<u>H</u>—CH_2Br); 3.46 (m, 2 H, CH_2Br); 3.67 (d, 1 H, C<u>H</u>—Ph); 4.30 (m, 2 H, CH_2O). ^{13}C NMR, δ: 175.8 (CO); 128.1–129.1 (Ph); 69.6 (CH_2O); 50.5 (<u>C</u>HCO); 46.2 (CH); 31.7 (CH_2Br). MS, *m/z* (I_{rel} (%)), number of bromine atoms: 254 $[M]^+$ (15.2), 1 Br; 131 $[M-Br-CO_2]^+$ (100); 117 $[M-CO_2-CH_2Br]^+$ (30.4).

Products of transformation of allyl methyl bromomalonate (1d) under cyclization conditions. Dimethyl malonate. MS, *m/z* (I_{rel} (%)): 132 $[M]^+$ (2.46); 101 $[M-MeO]^+$ (74.53); 74 $[MeCOOMe]^{+\cdot}$ (40.46); 59 $[COOMe]^+$ (100); 42 $[CH_2=CO]^{+\cdot}$ (26.39); 15 $[Me]^+$ (63.02).

Allyl methyl malonate. MS, *m/z* (I_{rel} (%)): 127 $[M-OMe]^+$ (6.52); 101 $[M-OCH_2CH=CH_2]^+$ (70.23); 74 $[MeCOOMe]^{+\cdot}$ (55.34); 59 $[MeCOO]^+$ (73.29); 57 $[CH_2=CHCH_2O]^+$ (39.77); 42 $[CH_2=CO]^{+\cdot}$ (37.08); 41 $[CH_2=CHCH_2]^+$ (100); 15 $[Me]^+$ (35.22).

Diallyl malonate. MS, *m/z* (I_{rel} (%)): 143 $[M-CH_2=CHCH_2]^+$ (1.79); 127 $[M-CH_2=CHCH_2O]^+$ (6.76); 87 $[M-CH_2=CHCH_2-CH_2=CHCHO]^+$ (31.98); 57 $[CH_2=CHCH_2O]^+$ (37.04); 42 $[CH_2=CO]^{+\cdot}$ (9.04); 41 $[CH_2=CHCH_2]^+$ (100).

Dimethyl bromomalonate. MS, *m/z* (I_{rel} (%)), number of bromine atoms: 210 $[M]^{+\cdot}$ (2.34), 1 Br; 179 $[M-MeO]^+$ (8.15), 1 Br; 151 $[M-COOMe]^+$ (8.65), 1 Br; 120 $[CHBr=CO]^{+\cdot}$ (8.05), 1 Br; 69 $[COCHCO]^+$ (33.46); 59 $[MeCOO]^+$ (100).

Diallyl bromomalonate. MS, *m/z* (I_{rel} (%)), number of bromine atoms: 165 $[M-CH_2=CHCH_2O-C_3H_4]^+$ (2.70), 1 Br; 120 $[CHBr=CO]^{+\cdot}$ (1.05), 1 Br; 57 $[CH_2=CHCH_2O]^+$ (17.27); 41 $[CH_2=CHCH_2]^+$ (100).

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