Stereoselective dimerization of chiral α-bromoamides promoted by $Fe(CO)_5$

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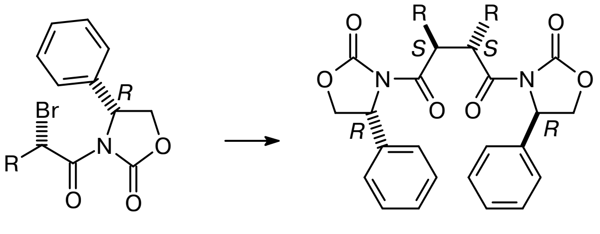
Organic α-bromocarboxylates react with aldehydes and ketones in the presence of $Fe(CO)_5$ (the Reformatsky-type reactions). Unlike them, *N*-oxazolidinone derivatives of the same acids undergo diastereoselective reductive dimerization to give (2*S*,3*S*)-dimers, regardless of the configuration of the α-chiral center in the starting reagent.

Key words: *N*-(α-bromoacyl)oxazolidinones, iron pentacarbonyl, diastereoselective dimerization.

Earlier, it was shown that $Fe(CO)_5$ effectively promotes the Reformatsky-type reactions.[1,2] Thus, methyl α-bromopropionate adds to benzaldehyde in boiling benzene in the presence of $Fe(CO)_5$ to give hydroxyester. Moreover, we have recently found that methyl dibromoacetate and methyl trichloroacetate in an HMPA solution add to benzaldehyde at room temperature.[3] For the purpose of synthesizing the desired stereoisomers of β-hydroxyesters or their derivatives, we tried to involve (4*R*)-*N*-(α-bromoacyl)-4-phenyloxazolidin-2-ones (**1a**—**c**) in this reaction. Starting reagents were prepared by acylating (*R*)-4-phenyloxazolidin-2-one (**2**) with the corresponding α-bromine-containing acid bromides. However, it turned out that amides **1a**—**c** form no adducts with aldehydes either in boiling benzene or in an HMPA solution at room temperature. At the same time, refluxing bromides **1a**—**c** with an equimolar amount of $Fe(CO)_5$ results in diastereoselective reductive dimerization of the amides (Scheme 1).

Scheme 1



1a—c **3a—c**

Compound	R	Yield	*de*
		%	
a	Me	96	>99
b	Et	95	>99
c	$\mathrm{Pr^i}$	30	>99

Reagents and conditions: $Fe(CO)_5$, PhH—THF (10 : 1), refluxing for 4 h.

Although 2,3-dialkylsuccinamides (**3a**—**c**) can form three isomers, the reaction affords only the (2*S*,3*S*)-isomer. The structure of dimers **3a**—**c** and their absolute configuration were determined by X-ray diffraction analysis. The structure of the dimer with R = Et is shown in Fig. 1. Its molecule contains four chiral atoms (C(4), C(7), C(8), and C(14)). The C(4) and C(14) atoms originally possess (*R*)-configuration, while the new chiral centers (C(7) and C(8)) have inverse, (*S*)-configuration. Amides **1a**,**b** containing a linear alkyl R (Me and Et) afford dimers in virtually quantitative yield.

The same dimer is formed from the (4*R*,α-*S*)- and (4*R*,α-*R*)-isomers, *i.e.*, independently of the configuration of the α-chiral center in starting compounds **1a**—**c**. The dimerization conditions suggest that a high

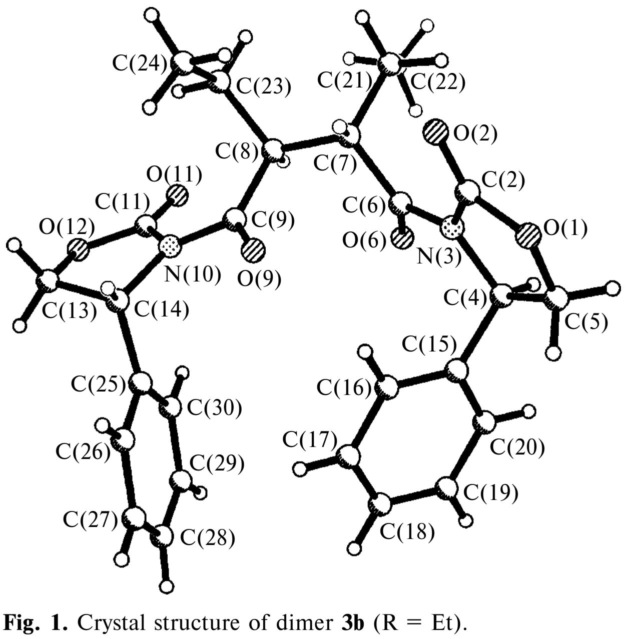


Fig. 1. Crystal structure of dimer **3b** (R = Et).

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diastereoselectivity of radical dimerization is due to the formation of an intermediate chelate with iron ions.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker WP-200-SY and Bruker AMX-400 spectrometers (200.13 and 400.13 MHz, respectively). Chemical shifts ($CDCl_3$) are referred to HMDS or Me_4Si as the internal standards. Optical rotation was measured on a Perkin—Elmer M-241 polarimeter in a thermostatically controlled cell at 25 °C. GLC analysis was carried out on an LKhM-80 chromatograph using a steel column (1300×3 mm) with 15% SKTFT-50Kh and a Carbowax-20000 column with Chromaton-N-AW (helium was used as the carrier gas (40—60 cm^3 min^{-1}), katharometer as a detector). Preparative GLC was performed on a steel column (1300×9 mm) with 20% SKTFT-50Kh using the same stationary phase and helium as the carrier gas (120 cm^3 min^{-1}). Enantiomeric analysis was carried out on a 3700-00 gas chromatograph equipped with a flame ionization detector; columns (32 000 × 0.20 mm) were filled with a DP-TFA-γ-cD chiral phase. In the case of methyl derivatives, an SE-54 capillary quartz column (25 000 × 0.20 mm) was used. Column chromatography used Kieselgel 60 silica gel (Merck). TLC was performed on 60 F_{254} glass or aluminum plates coated with SiO_2 or Al_2O_3 (Merck). Preparative TLC was carried out on glass plates with LSL_{254} 5/40 silica gel (Chemapol).

Preparation of chiral amides of α-bromo acids. (4′*R*,2*R*)- and (4′*R*,2*S*)-2-bromo-1-(2′-oxo-4′-phenyloxazolidin-3′-yl)propan-1-ones (1a). A 60% suspension of NaH (0.52 g, 13 mmol) in oil was added to a solution of (*R*)-4-phenyloxazolidin-2-one (**2**) (1.6 g, 10 mmol) in 25 mL of anhydrous THF (Ar). Stirring was continued until gas evolution ceased. The resulting thick suspension was cooled to −78 °C with an acetone—solid CO_2 mixture, and a solution of α-bromopropanoyl bromide (2.38 g, 1.16 mL, 11 mmol) in 5 mL of THF was added dropwise. The reaction mixture was stirred for 1.5 h until the starting compound **2** disappeared completely (monitoring by TLC in hexane—THF (1.5 : 1)), filtered through a thin layer of silica gel on a glass filter, and additionally washed with THF. The filtrate was concentrated *in vacuo* to give a yellow oil, which solidified upon adding hexane. The solid product was crushed, washed with hexane, filtered off, and dried *in vacuo.* The yield of the mixture of diastereoisomers was 2.56 g (86%). Found (%): C, 47.97; H, 3.82; Br, 25.95. $C_{12}H_{12}BrNO_3$. Calculated (%): C, 48.34; H, 4.06; Br, 26.80. Diastereoisomers **1a** were separated by column chromatography on SiO_2 in THF—hexane (1 : 1.5). Recrystallization of each isomer from a hexane—EtOAc mixture gave the isomers with R_f^{max} (m.p. 134—135 °C) and R_f^{min} (m.p. 149—152 °C) (*cf.* Ref. 4: m.p. 136—137 °C (R_f^{max}); m.p. 151—154 °C (R_f^{min})). Found (%): C, 48.72; H, 4.26; Br, 26.05. $C_{12}H_{12}BrNO_3$. Calculated (%): C, 48.34; H, 4.06; Br, 26.80. ^1H NMR (for the diastereoisomer with R_f^{max}), δ: 7.38—7.33 (m, 5 H); 5.72 (q, 1 H_α, *J* = 6.7 Hz); 5.43 (br.d, 1 H, *J* = 8.3 Hz); 4.77 (t, 1 H, *J* = 8.5 Hz); 4.35 (d, 1 H, *J* = 8.8 Hz); 1.77 (d, 3 H, *J* = 6.7 Hz). ^1H NMR (for the diastereoisomer with R_f^{min}), δ: 7.41—7.38 (m, 5 H); 5.76 (q, 1 H_α, *J* = 6.7 Hz); 5.45 (dd, 1 H, *J* = 8.8 and 5.1 Hz); 4.74 (t, 1 H, *J* = 8.9 Hz); 4.28 (dd, 1 H, *J* = 9.0 and 5.1 Hz); 1.77 (d, 3 H, *J* = 6.7 Hz).

An analogous procedure was used to prepare **(4′*R*,2*R*)- and (4′*R*,2*S*)-2-bromo-1-(2′-oxo-4′-phenyloxazolidin-3′-yl)butan-1-ones (1b).** A mixture of diastereoisomers **1b** (1 : 1) was obtained in 95% yield and separated as described above on a column (2.5×26 cm) in $CHCl_3$—EtOAc—C_6H_{14} (8 : 1 : 5). The isomer with R_f^{max}, m.p. 89—90 °C (hexane—EtOAc), $[\alpha]_D^{25}$ −108.9 (*c* 1, $CHCl_3$). Found (%): C, 50.14; H, 4.60; Br, 25.56; N, 4.45. $C_{13}H_{14}NO_3Br$. Calculated (%): C, 50.02; H, 4.52; Br, 25.60; N, 4.49. The isomer with R_f^{min}, m.p. 81—82 °C (hexane), $[\alpha]_D^{25}$ −52.8 (*c* 1, $CHCl_3$). Found (%): C, 49.98; H, 4.60; Br, 25.64; N, 4.36. $C_{13}H_{14}BrNO_3$. Calculated (%): C, 50.02; H, 4.52; Br, 25.60; N, 4.49.

(4′*R*,2*R*)- and (4′*R*,2*S*)-2-Bromo-3-methyl-1-(2′-oxo-4′-phenyloxazolidin-3′-yl)-butan-1-one (1c). The reaction mixture was concentrated to an oil, which was crystallized by trituration with hexane for a long time. The hexane was decanted, and another portion of hexane was added. The precipitate was left for 12 h, then filtered off, and dried. The yield of **1c** was 78%. Found (%): C, 50.97; H, 4.82; Br, 24.55. $C_{14}H_{16}BrNO_3$. Calculated (%): C, 51.55; H, 4.95; Br, 24.49. ^1H NMR, δ: 7.35—7.32 (m, 5 H); 5.51—5.40 (m, 2 H); 4.70 (m, 1 H); 4.27 (m, 1 H); 2.03 (m, 1 H); 1.06 (d, relates to one of the diastereoisomers, 1.5 H, *J* = 6.4 Hz); 0.97 (inequivalent triplet, 3 H); 0.82 (d, 1.5 H, *J* = 6.6 Hz). The diastereoisomers with R_f^{max} (m.p. 110—111 °C) and R_f^{min} (m.p. 89—90 °C) were separated as described above.

Asymmetric dimerization promoted by $Fe(CO)_5$. 2,3-Dimethyl-1,4-bis(2′-oxo-4′-phenyloxazolidin-3′-yl)butane-1,4-dione (3a). A mixture of diastereoisomers **1a** (3 g, 10 mmol) was dissolved in a mixture of PhH (15 mL) and THF (5 mL). Iron pentacarbonyl (1.4 mL, 10 mmol) was added, and the solution was degassed by three cycles of evacuating—freezing—pumping with argon and refluxed until the evolution of CO ceased (~1.5 h). The yield of dimer **3a** was 90%, m.p. 220—222 °C, $[\alpha]_D^{25}$ −209 (*c* 1, acetone). Found (%): C, 66.10; H, 5.66; N, 6.35. $C_{24}H_{24}NO_6$. Calculated (%): C, 66.04; H, 5.54; N, 6.42. ^1H NMR, δ: 7.04 (m, 5 H); 5.32 (dd, 1 H, *J* = 3.1 and 8.4 Hz); 4.58 (t, 1 H, *J* = 8.6 Hz); 4.11—4.05 (m, 2 H); 1.14 (d, 3 H, *J* = 6.0 Hz). ^{13}C NMR, δ: 175.97 (C(1)=O); 153.67 (C(2)=O); 138.89 (C(1), Ar); 129.29 (C(2) and C(6), Ar); 128.61 (C(4), Ar); 125.31 (C(5) and C(3), Ar); 70.60 (C—N); 57.95 (C—O); 40.50 (C_α); 14.57 (Me).

2,3-Diethyl-1,4-bis(2′-oxo-4′-phenyloxazolidin-3′-yl)-butane-1,4-dione (3b). Dimerization of **1b** was carried out analogously for 1 h. The yield of dimer **3b** was 95%, m.p. 215—216 °C, $[\alpha]_D^{25}$ −128.3 (*c* 0.3, $CHCl_3$). Found (%): C, 67.41; H, 6.36; N, 6.05. $C_{26}H_{28}N_2O_6$. Calculated (%): C, 67.23; H, 6.08; N, 6.03. ^1H NMR, δ: 7.29—7.25 (m, 5 H); 5.42 (dd, 1 H, *J* = 4.3 and 8.5 Hz); 4.65 (t, 1 H, *J* = 8.6 Hz); 4.18 (m, 2 H).

2,3-Diisopropyl-1,4-bis(2′-oxo-4′-phenyloxazolidin-3′-yl)butane-1,4-dione (3c). A mixture of diastereoisomers **1c** (0.49 g, 1.5 mmol) was dissolved in 4 mL of PhH containing a small amount of THF (0.4 mL). Iron pentacarbonyl was added (0.21 mL, 1.5 mmol), and the reaction mixture was refluxed for 2 h until the evolution of CO ceased. The above workup gave a mixture of dimer (2*S*,3*S*)-**3c** (the yield of the recrystallized product was 30%), 4-phenyloxazolidin-2-one (15%, identified by TLC with an authentic sample), and the reduction product of **1c**, namely, (4′*R*)-3-methyl-1-(2′-oxo-4′-phenyloxazolidin-3′-yl)butan-1-one (**4**) (yield 40%, for ^1H NMR data, see below). Dimer (2*S*,3*S*)-**3c** crystallizes from a $CHCl_3$—C_6H_{14} mixture, m.p. 223—225 °C. Found (%): C, 68.10; H, 6.46; N, 5.60. $C_{14}H_{16}NO_3$. Calculated (%): C, 68.27; H, 6.55; N, 5.69. ^1H NMR, δ: 6.99 (m, 5 H); 5.34 (dd, 1 H, *J* = 1.8 and 7.7 Hz); 4.48 (m, 2 H); 4.02 (dd, 1 H, *J* = 1.8 and 8.6 Hz); 2.08 (m, 1 H); 1.03 (d, 6 H, *J* = 6.8 Hz). The mother liquor was separated by preparative TLC on SiO_2. The fraction with R_f^{max} was found to be a derivative of **1c**, in which the Br atom is replaced by the H atom (**4**). ^1H NMR, δ: 7.31 (m, 5 H); 5.39

(dd, 1 H, J = 4.4 and 8.4 Hz); 4.62 (t, 1 H, J = 8.4 Hz); 4.20 (dd, 1 H, J = 4.7 and 8.4 Hz); 2.85 (dd, 1 $C\underline{H}_aH_b$, J = 6.4 and 15.7 Hz); 2.68 (dd, 1 $CH_a\underline{H}_b$, J = 7.0 and 15.7 Hz); 2.08 (m, 1 H); 0.85 (dd, 6 H, J = 6.4 and 3.0 Hz). According to the ^{1}H NMR data, the fraction with R_f^{min} includes dimer (2*S*,3*S*)-**3c**, 4-phenyloxazolidin-2-one (**2**), and an unidentified product. The mixture was separated by preparative TLC on glass plates covered with Al_2O_3 (Merck, 60_{254} Type E) in CCl_4—$CHCl_3$—C_6H_{14} (1 : 2 : 3).

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