On the mechanism of the $Fe(CO)_5$-catalyzed Kharasch reaction
2.* Reinvestigation of stereochemistry of $BrCCl_3$ addition to methyl *N*-acryloyl-(*S*)-prolinate

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Addition of $BrCCl_3$ to methyl *N*-acryloyl-(*S*)-prolinate (**1**) catalyzed by $Fe(CO)_5$ or $Fe(CO)_5$—PPh_3 at 75—80 °C in benzene solution affords in good total yield methyl *N*-((*S*)-2-bromo-3,3,3-trichlorobutyryl)-(*S*)-prolinate (**2**) and methyl *N*-((*R*)-2-bromo-3,3,3-trichlorobutyryl)-(*S*)-prolinate (**3**) in an ~1.5 : 1 ratio, which does not depend on the catalytic system employed or its concentration. Catalysis by the $Fe(CO)_5$—PPh_3 system substantially increases the adducts yield.

Key words: Kharash reaction, diastereoselectivity, catalysis, iron pentacarbonyl, triphenylphosphine, bromotrichloromethane, addition, olefins, mechanism, redox catalysis, second order asymmetric transformation.

In communication 1[1] we found that the addition of $BrCCl_3$ to (*R*)-3-acryloyl-4-phenyloxazolidin-2-one catalyzed by $Fe(CO)_5$ with or without an addition of DMF occured with a low diastereoselectivity independent of the catalyst concentration.

These results, however, did not agree with the data on the stereochemistry of addition of polyhaloalkanes to methyl *N*-acryloyl-(*S*)-prolinate (**1**) obtained earlier in our laboratory.[2,3]

Taking into account the fundamental importance of stereochemical results for understanding the Kharash reaction mechanism we repeated the investigation of the reaction between **1** and $BrCCl_3$.

Results and Discussion

The stereochemistry of $BrCCl_3$ addition to **1** was studied under the conditions summarized in Table 1. The reactions were carried out either in sealed tubes (A) or in an open system under an inert atmosphere (B).

The reaction was controlled with the help of TLC on SiO_2 with the mixture n-C_6H_{14}—C_6H_6—Et_2O employed as an eluent. Effective separation of diastereomers **2** and **3** arising in the course of the reaction (Scheme 1) is achieved in this system. Analytical samples were isolated chromatographically on SiO_2. Diastereomer **2** is a crystal substance with the specific rotation value practically identical to that of the earlier described[2,3] sample. In the course of column chromatography **2** crystallizes as it leaves the column and in eluates. Diastereomer **3** presents a non-crystallizing viscous oil. It was isolated as an individual substance and characterized for the first time in the present work. Both products have the same easily identifiable set of signals in NMR spectra.

The ratio of compounds **2** and **3** was estimated using their NMR spectra region (3.2 ppm) where each of isomers has four well-resolved signals corresponding to one of hydrogen atoms of CH_2CCl_3 fragment (doublet of doublets). For the mixture of **2** and **3** this spectral region demonstrates two relatively well resolved "triplets" resulting from the superposition of the parts of two closely situated doublets of doublets. Diastereoisomers ratio, **2** : **3**, can be approximately estimated using the heights of terminal peaks of these triplets. The rest of NMR spectra has less information content.

Total yields and ratios of adducts **2** and **3** are summarized in Table 1. The addition of $BrCCl_3$ to **1** catalyzed by $Fe(CO)_5$ resulted in 55% yield of these adducts (1 run). With the addition of PPh_3 the yield of **2** and **3** achieves 80—86 % (runs 2 and 3).

On this work data, as well as on the earlier received data,[3] diastereoselectivity of $BrCCl_3$ addition catalyzed by $Fe(CO)_5$ is not high (1 run). However, on the contrary, the use of $Fe(CO)_5$—PPh_3 system does not bring about the change in diastereoselectivity (run 2). The increase in concentration of constituents of the reaction mixture also does not influence diastereoselectivity (*cf.* runs 1, 2, 4, and 3).

Special experiment with pure diastereomer **2** showed that not more than 10% epimerization of **2** giving rise to

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* For Part 1 see Ref. 1.

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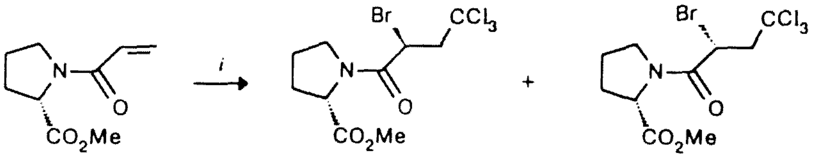
Table 1. Addition of $BrCCl_3$ to compound **1** in benzene (75—80 °C, 2 h)

Run	c_1 mol L^{-1}	Catalyst	**1** : Ct^a : BrCCl	Mode	Yield **2**+**3**^{b} (%)	Ratio **2**:**3**^{c}
1	0.3	$Fe(CO)_5$	10 : 1 : 17	A	55	1.7 : 1
2	0.3	$Fe(CO)_5—PPh_3{}^d$	10 : 1 : 17	A	86	1.6 : 1
3	1.0	$Fe(CO)_5—PPh_3{}^d$	10 : 1 : 12	Б	80	1.5 : 1
4	0.26	$Fe(CO)_5—PPh_3{}^d$	10 : 1 : 14	Б	69^e	1.5 : 1^f

^{a} Catalyst (Ct). ^{b} Total yield of products isolated by PTLC. ^{c} Estimated by NMR technique. ^{d} Ratio $Fe(CO)_5$:PPh_3 1:1. ^{e} Yield of compounds **2** and **3** isolated by of column chromatography. ^{f} Mass ratio.

Scheme 1



1 **2** **3**

i. $BrCCl_3$, catalyst

3 occurs under the conditions of the addition reaction. Thus, the results obtained in the present work reflect (within the limits of experimental error) kinetical diastereoselectivity of the addition.

Nevertheless, products **2** and **3** are able to interconvert. $CDCl_3$ solutions of pure **2** and **3** staying for a month under ambient temperature gave as a result of solvent evaporation and slow epimerization excellently formed single crystals of **2** in both cases. We find it interesting to use an asymmetric conversion of the second order for preparative synthesis of **2**.

Therefore, the causes for "isolation of only one diastereomer **2**" in the works[2,3] may be both the difference in physical and chemical properties of diastereomers **2** and **3** and the possibility of accidental asymmetric conversion of the second order. However in any case the isolation of only one diastereomer **2** has nothing in common with the true stereochemistry of addition.

We failed to obtain satisfactory yields[3] of appropriate adducts on the reaction of CCl_4 with **1** (80 °C, 8 h, sealed tubes) under the conditions of catalysis by $Fe(CO)_5$ (c_1 = 0.4 mol L^{-1}, the ratio **1** : Fe = 50:1, the solvent: CCl_4) and $Fe(CO)_5—PPh_3$ (c_1 = 0.9 mol L^{-1}, the ratio **1** : Fe : CCl_4 = 10 : 1 : 17, the solvent: benzene). The TLC analysis of reaction mixtures revealed the formation of traces of at least two products in approximately equal amounts.

Thus the results of reinvestigation of stereochemistry of $BrCCl_3$ addition to **1** and the data from paper 1[1] indicate that the fundamental character of the Kharash reaction mechanism does not change with $Fe(CO)_5$ concentration and is independent of the presence or absence of nucleophilic additives.

Experimental

All reagents were of a quality not lower than chemically pure grade. Benzene was distilled over P_2O_5 in an argon atmosphere. $Fe(CO)_5$ was used without additional purification. Freshly distilled $BrCCl_3$ was used in all cases. TLC was performed on SiO_2 plates (Merck 60 F254). Silicagel 60 (Merck) was used for column chromatography. Melting and boiling points are uncorrected. ^1H NMR spectra were taken with a Bruker WP-200 instrument; chemical shifts (δ, ppm) were measured relative to the internal standard (HMDS); spin-spin coupling constants are given (*J*/Hz). Rotation angles were measured with a Perkin Elmer M241 polarimeter.

Methyl *N*-acryloyl-(*S*)-prolinate (1). Triethylamine (7.4 mL, 54 mmol) were added dropwise to a mixture of methyl (*S*)-prolinate hydrochloride[4] (4 g, 24.2 mmol) and CH_2=CHCOCl (1.1 mL, 1.2 g, 26.6 mmol) in 20 mL of dry CH_2Cl_2 on cooling (0 °C) and stirring. After that the cooling was stopped, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was washed successively with 0.1 *N* HCl, H_2O, saturated $NaHCO_3$, and H_2O and dried over $MgSO_4$. The remaining mobile fluid was distilled *in vacuo* to give 3.8 g (85 %), b.p. 135 °C (1 Torr). $[\alpha]_D^{25}$ −133 (*c* 2, MeOH). Found (%): C, 59.09; H, 7.28; N, 7.61. $C_9H_{13}NO_3$. Calculated (%): C, 59.00; H, 7.15; N, 7.65. NMR spectra, δ: 1.8—2.4 (m, 4 H, β-H and γ-H Pro); 3.5—3.9 (m, 2 H, δ-H Pro); 3.73 (s, 3 H, CH_3O); 4.45—4.6 (m, 1 H, α-H Pro); 5.71 (dd, 1 H, $=CHH_{trans}$, *J* = 2.9 and 9.4); 6.36 (dd, 1 H, $=CHH_{cis}$, *J* = 2.9 and 16.6); 6.50 (dd, 1 H, =CHCO, *J* = 9.4 and 16.6).

Addition of $BrCCl_3$ to 1 was carried out in sealed tubes, from which air traces were preliminary removed by double repetition of the following cycle: freeze—pump—thaw under Ar (mode A), or else in an open system under low Ar flow (mode B). The conditions are summarized in Table 1. Reaction mixtures were diluted with $CHCl_3$, washed with water, dried over $MgSO_4$, and concentrated by evaporation. Mixtures were fractionated by PTLC on SiO_2 (n-C_6H_{12}—Et_2O—C_6H_6, 4 : 1 : 1) using known standards. Fractions containing **2** and **3** were combined and analyzed by NMR technique (Table 1).

Preparative experiment (Table 1, run 4). Methyl *N*-((*S*)-2-bromo-3,3,3-trichlorobutyryl)-(*S*)-prolinate (2) and methyl *N*-((*R*)-2-bromo-3,3,3-trichlorobutyryl)-(*S*)-prolinate (3). A mixture of **1** (0.5 g, 2.7 mmol), $BrCCl_3$ (0.38 mL, 3.8 mmol), $Fe(CO)_5$ (0.038 mL, 0.28 mmol), and PPh_3 (0.08 g, 0.3 mmol) in 10 mL of benzene was heated at 75—77 °C with stirring in a slow Ar flow. Reaction mixture was diluted with $CHCl_3$ and washed with water. Organic layer was separated, dried over $MgSO_4$ and concentrated by evaporation. The semicrystalline residue obtained was chromatographed on a SiO_2 (25×1.7 cm) column with elution with a n-C_6H_{14}—Et_2O—C_6H_6 (4 : 1 : 1) mixture affording 0.27 g of **2** and 0.17 g of **3** in a total yeild of 69%. Product **2** was additionally purified by crystallization from n-C_6H_{14}—C_6H_6 mixture, and diastereomer **3** — chromatographically on SiO_2 plates.

Ester 2. B.p. 115—117 °C. $[\alpha]_D^{25}$ −32.3 (*c* 1, $CHCl_3$) [Ref. 2: $[\alpha]_D^{25}$ −33.5 (*c* 1, $CHCl_3$)]. Found (%): C, 31.50; H, 3.50; N, 3.57. $C_{10}H_{13}BrCl_3NO_3$. Calculated (%): C, 31.48; H, 3.43; N, 3.67. NMR spectra, δ: 1.8—2.3 (m, 4 H, β-H and γ-H Pro); 3.21 (dd, 1 H, CH_aCCl_3, J = 2 and 15.1); 3.6—3.8 (m, 2 H, δ-H Pro); 3.63 (s, 3 H, CH_3O); 4.09 (dd, 1 H, CH_bCCl_3, J = 8.6 and 15.1); 4.49 (dd, 1 H, α-H Pro, J = 4 and 4); 4.61 (dd, 1 H, CHBr, J = 2 and 8.6).

Ester 3. $[\alpha]_D^{25}$ −40.7 (*c* 1, $CHCl_3$). Found (%): C, 31.82; H, 3.37; N, 3.74. $C_{10}H_{13}BrCl_3NO_3$. Calculated (%): C, 31.48; H, 3.43; N, 3.67. NMR spectra, δ: 1.8—2.3 (m, 4 H, β-H and γ-H Pro); 3.22 (dd, 1 H, CH_aCCl_3, J = 2.4 and 15.2); 3.5—3.7 (m, 1 H, δ-H_a Pro); 3.7 (s, 3 H, CH_3O); 3.7—3.9 (m, 1 H, δ-H_b Pro); 4.06 (dd, 1 H, CH_bCCl_3, J = 8.6 and 15.3); 4.44 (dd, 1 H, α-H Pro, J = 2.8 and 6.5); 4.60 (dd, 1 H, CHBr, J = 2.4 and 8.6).

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