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Addition of α-Halocarboxylic Acid Esters to *para*-Substituted Benzaldehydes in the Presence of Pentacarbonyliron

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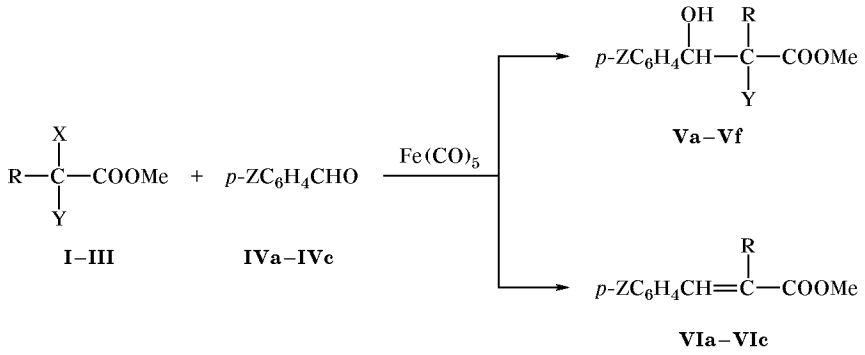
Abstract—Pentacarbonyliron promotes addition of α-halocarboxylic acid esters at the carbonyl group of benzaldehyde and its *para*-substituted analogs. The substituent in the benzene ring strongly affects the process.

We previously showed [1, 2] that $Fe(CO)_5$ is an efficient promotor of Reformatsky type reactions. In some cases the yield of the adducts attained 80–95%. In the present work we studied the effect of *para*-substituent in benzaldehyde on its reactions with methyl bromoacetate (**I**), methyl α-bromopropionate (**II**), and methyl trichloroacetate (**III**) in the presence of pentacarbonyliron. Benzaldehyde (**IVa**), *p*-chlorobenzaldehde (**IVb**), and *p*-methoxybenzaldehyde (**IVc**) were involved in the reaction. The molecule of ester **II** contains a chiral center. For that reason we also tried to find conditions allowing the reaction of **II** with aldehydes to be performed in an inert solvent with a minimal amount of HMPA at room temperature (with a view to accomplish stereoselective syntheses). The reactions of esters **I**–**III** with benzaldehyde were studied in [2, 3].

Esters **I**–**III** readily reacted with aldehydes **IVa**–**IVc** to give the corresponding hydroxy esters **Va**–**Vf** in good yields. However, in some cases the reactions with *p*-methoxybenzaldehyde resulted in formation of acrylic acid derivatives **VI** instead of the expected hydroxy esters **V**, presumably due to elimination of water (or HOCl) during the process (Scheme 1).

The reactions of methyl bromoacetate (**I**) with aldehydes **IVa** and **IVb** at 130°C (in chlorobenzene) afforded hydroxy esters **V**, while in the reaction with aldehyde **IVc** unsaturated ester **VIa** was isolated. Similar results were obtained in the reactions of methyl α-bromopropionate (**II**) and methyl trichloroacetate (**III**) with aldehydes **IVa**–**IVc** at 80°C (in boiling benzene) and at room temperature in the presence of HMPA. Presumably, the effect of *para*-methoxy group (compound **IVc**) in the reactions

Scheme 1.



I–III **IVa–IVc** **Va–Vf** **VIa–VIc**

I, R = Y = H, X = Br; **II**, R = Me, X = Br, Y = H; **III**, R = X = Y = Cl; **IV**, Z = H (**a**), Cl (**b**), MeO (**c**); **V**, R = Y = H, Z = H (**a**); R = Y = H, Z = Cl (**b**); R = Me, Y = H, Z = H (**c**); R = Me, Y = H, Z = Cl (**d**); R = Y = Cl, Z = H (**e**); R = Y = Cl, Z = Cl (**f**); **VI**, R = H, Z = MeO (**a**); R = Me, Z = MeO (**b**); R = Cl, Z = MeO (**c**).

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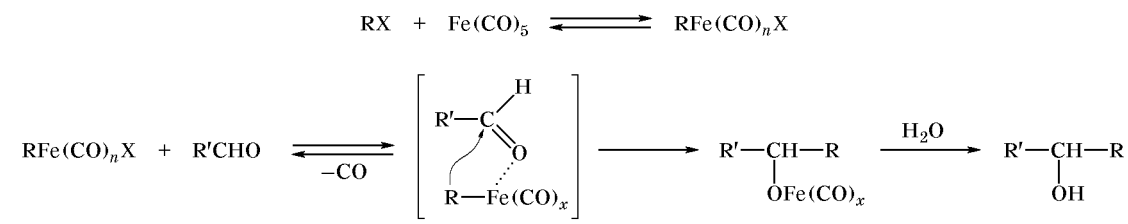
Scheme 2.



with α-haloesters originates from the ability of the methoxy group to stabilize the carbocationic center formed via elimination of OH and H or OH and Cl species.

It should be emphasized that just the use of HMPA as co-catalyst in combination with $Fe(CO)_5$ allowed us to carry out the reaction of prochiral methyl bromopropionate **II** with aldehydes **IVa**–**IVc** under as mild conditions as possible (as applied to the given type of the process), i.e., in benzene at room temperature.

With the goal of finding conditions for stereoselective synthesis of hydroxy esters and their derivatives we examined the reaction with aldehydes of (4*R*)-3-(2-bromopropionyl)-4-phenyltetrahydrooxazol-2-one (**VII**) as initial bromide. Compound (**VII**) was synthesized by acylation of (*R*)-4-phenyltetrahydrooxazol-2-one with 2-bromopropionyl bromide [4]. However, unlike the corresponding ester **II**, amide **VII** turned out to react quite differently under the same conditions. No adducts like **V** or **VI** were formed when the reaction was performed in boiling benzene or in the presence of HMPA at room temperature. Moreover, the reaction of α-bromo ester **II** with benzaldehyde in the presence of 10% of amide **VII** gave neither adduct **Vb** nor **VIb**; this result suggests that amide **VII** inhibits the main process. On the other hand, heating of amide **VII** in benzene–THF (10 : 1) under reflux in the presence of an equimolar amount of $Fe(CO)_5$ (no aldehyde added) resulted in reduction (with elimination of bromine) and/or stereoselective reductive dimerization of the amide [4].

It should be noted that the substituent nature does not affect Reformatsky type reactions [5] *a priori* involving intermediate formation of organometallic compounds which then react with substituted benzaldehydes. By special experiments we showed [2] that the reaction of ester **II** with $Fe(CO)_5$ gives no organoiron compound or at least it does not accumulate in the reaction mixture. Nevertheless, the mechanism of the process under study undoubtedly includes oxidative addition of the organic substrate to pentacarbonyliron. At this stage the equilibrium is likely to be displaced toward initial compounds. The intermediate adduct reacts with aldehyde, yielding iron alkoxide; hydrolysis of the latter (on treatment with dilute hydrochloric acid) leads to formation of the final product (Scheme 2). Electon-donor substituent in the aldehyde creates most unfavorable conditions for intramolecular attack on the CHO group by the anionic center formed by reduction of the initial radical species.

Thus, we revealed an unusual effect of the *para*-methoxy group in the reaction of substituted benzaldehydes with α-halocarboxylic acid esters in the presence of $Fe(CO)_5$: The reactions with benzaldehyde and *p*-chlorobenzaldehyde yield the corresponding hydroxy esters, whereas from *p*-methoxybenzaldehyde acrylic acid derivatives are formed.

EXPERIMENTAL

The mass spectra were obtained on a Finnigan MAT Magnum GC–MS system using a 25-m Ultra-2 column; the oven temperature was programmed from 30 to 220°C at a rate of 2.5 deg/min. GLC analysis was performed on an LKhM-80 chromatograph using a 1300 × 3-mm steel column packed with 15% of SKTFT-50Kh on Chromaton-N-AW; carrier gas helium, flow rate 60 ml/min; thermal conductivity detector; oven temperature programming from 50 to 250°C at a rate of 6 deg/min. The ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200 instrument (200 MHz) using $CDCl_3$ as solvent; the chemical shifts were measured relative to tetramethylsilane. All organic reagents were purified by distillation; $Fe(CO)_5$ (Fluka; purity 97%) was used without additional purification.

Reactions of methyl bromoacetate with benzaldehydes in the presence of $Fe(CO)_5$. A solution of 1 mmol of methyl bromoacetate (**I**), 1 mmol of aldehyde **IVa**–**IVc**, 2 mmol of $Fe(CO)_5$, and 0.01 g (0.05 mmol) of $CBrCl_3$ in 1 ml of chlorobenzene was refluxed (130°C) for 4 h. The mixture was treated with dilute hydrochloric acid and extracted with benzene, the extract was dried over Na_2SO_4, and the solvent and unreacted initial compounds were distilled off.

Methyl 3-hydroxy-3-phenylpropionate (Va). Yield 41% [3].

Methyl 3-hydroxy-3-(*p*-chlorophenyl)propionate (Vb). Yield 26%. Mass spectrum, *m/z* (I_{rel}, %): 214 (19) $[M]^{+\cdot}$, 196 (42) $[M-OH]^+$, 165 (90) $[M-H_2O-OMe]^+$, 141 (100) $[M-CH_2COOMe]^+$. ^{1}H NMR spectrum, δ, ppm: 2.64 m (2H, CH_2), 3.63 s (3H, OMe), 3.92 br.s (1H, OH), 5.04 m (1H, CH).

Methyl *p*-chlorocinnamate. Yield 3%. Mass spectrum, *m/z* (I_{rel}, %): 196 (60) $[M]^+$, 165 (100) $[M-OMe]^+$, 137 (30) $[M-COOMe]^+$, 85 (1).

Methyl *p*-methoxycinnamate (VIa). Yield 31%. Mass spectrum, *m/z* (I_{rel}, %): 192 (80) $[M]^{+\cdot}$, 161 (100) $[M-OMe]^+$, 133 (30) $[M-COOMe]^+$, 118 (8), 102 (5). ^{1}H NMR spectrum, δ, ppm: 3.77 s, 3.81 s (6H, OCH_3); 6.26 d, 6.34 d, 7.60 d, 7.69 d (1H, CH, J = 4 Hz; J_{trans} = 53 Hz); 6.85 d, 6.89 d (1H, CH, J = 2 Hz, J_{cis} = 24 Hz).

Reactions of methyl 2-bromopropionate with benzaldehydes in the presence of $Fe(CO)_5$. A solution of 1 mmol of methyl 2-bromopropionate (**II**), 1 mmol of aldehyde **IVa**–**IVc**, 2 mmol of $Fe(CO)_5$, and 2 mmol of HMPA in 1 ml of benzene was kept for 5 days at room temperature. The mixture was then treated as described above. The ratio of diastereoisomers was determined from the ^{1}H NMR spectra.

Methyl 3-hydroxy-2-methyl-3-phenylpropionate (Vc). Yield 54% [3]. Diastereoisomer ratio 1.5:1. ^{1}H NMR spectrum, δ, ppm: 0.95 d, 0.98 d; 1.09 d, 1.12 d (3H, C**H**$_3$CH, J = 8.7 Hz); 2.75 br.s (1H, OH); 3.61 s, 3.67 s (3H, CH_3O); 4.75 m; 5.07 m (1H, CH); 7.3 m (H_{arom}).

Methyl 3-(*p*-chlorophenyl)-3-hydroxy-2-methylpropionate (Vd). Yield 69%. Diastereoisomer ratio 1.5:1. Mass spectrum, *m/z* (I_{rel}, %): 228 (5) $[M]^{+\cdot}$, 210 (3) $[M-H_2O]^{+\cdot}$, 197 (1) $[M-OMe]^+$, 141, 143 (42) $[ClC_6H_4CHOH]^+$, 88 (100) $[CH_3CH_2COOMe]^{+\cdot}$. ^{1}H NMR spectrum, δ, ppm: 0.95 d, 0.98 d; 1.09 d, 1.12 d (3H, CH_3CH, J = 7.9 Hz); 2.75 br.s (1H, OH); 3.61 s, 3.67 s (3H, CH_3O); 4.75 m, 5.07 m (1H, CH), 7.3 m (H_{arom}).

Methyl 3-*p*-methoxyphenyl-2-methylpropenoate (VIb). Yield 25%. Mass spectrum, *m/z* (I_{rel}, %): 206 (100) $[M]^{+\cdot}$, 175 (38) $[M-H_2O-OMe]^+$, 147 (43) $[M-H_2O-COOMe]^+$, 146 (75) $[MeOC_6H_4-CH=C=CH_2]^{+\cdot}$.

Reactions of methyl trichloroacetate with benzaldehydes in the presence of $Fe(CO)_5$. A solution of 1 mmol of methyl trichloroacetate (**III**), 1 mmol of aldehyde **IVa**–**IVc**, and 2 mmol of $Fe(CO)_5$ in 1 ml of benzene was refluxed (80°C) for 2 h (method *a*) or was kept for 3 days at room temperature in DMF (method *b*). The mixture was then treated as described above.

Methyl 2-chloro-3-phenylacrylate (method *a*) [2]. Yield 41%; *cis*–*trans* ratio 1:5.

Methyl 2,2-dichloro-3-hydroxy-3-phenylpropionate (Ve) (method *b*) [3]. Yield 30%.

Methyl 2-chloro-3-*p*-chlorophenylacrylate (method *a*). Yield 50%; *cis*–*trans* ratio 1:5. ^{1}H NMR spectrum, δ, ppm: 3.71 s, 3.85 s (3H, OCH_3); 7.77 s, 7.81 s (1H, CH); 7.29–7.32 m (5H, H_{arom}). Mass spectrum, *m/z* (I_{rel}, %): 230 (95) $[M]^{+\cdot}$, 199 (40) $[M-OMe]^+$, 195 (100) $[M-Cl]^+$, 171 (20) $[M-COOMe]^+$.

Methyl 2,2-dichloro-3-(*p*-chlorophenyl)-3-hydroxypropionate (Vf) (method *b*). Mass spectrum, *m/z* (I_{rel}, %): 282 (0) $[M]^{+\cdot}$, 265 (1) $[M-OH]^+$, 237 (25) $[M-OH-CO]^+$, 141 (100) $[CCl_2COOMe, ClC_6H_4CHOH]^+$, 113 (30) $[CCl_2OMe]^+$, 77 (85) $[C_6H_5]^+$.

Methyl 2-chloro-3-*p*-methoxyphenylacrylate (VIc) (method *a*). Yield 50%; *cis*–*trans* ratio 1:4.5. ^{1}H NMR spectrum, δ, ppm: 3.80 s, 3.84 s (6H, OCH_3); 6.88 s, 6.92 s (1H; CH); 8.27–8.30 m (5H, H_{arom}). Mass spectrum, *m/z* (I_{rel}, %): 226 (100) $[M]^{+\cdot}$, 195 (30) $[M-OMe]^+$, 191 (35) $[M-Cl]^+$, 167 (15) $[M-COOMe]^+$.

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