

Addition of Halocarboxylic Acids Esters and Halohydrocarbons to Pentafluorobenzaldehyde Promoted by Iron Pentacarbonyl

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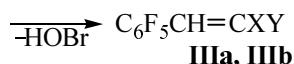
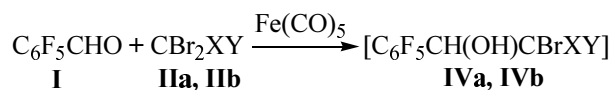
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Abstract—Iron pentacarbonyl is an efficient promoter of addition to the carbonyl group of pentafluorobenzene of alkyl α -halocarboxylates and alkyl halides. The electron-acceptor character of the pentafluorophenyl group essentially affects the course of reaction and the nature of the arising products.

We showed formerly [1–3] that $\text{Fe}(\text{CO})_5$ was an efficient promoter of processes of Reformatsky and Barbier type, and in some cases the yield of adducts attained 80–95%. The reactions proceed under homogeneous conditions, do not require application of anhydrous solvents and inert atmosphere. It was besides established that the polar character of substituents in the substrates (both in the aldehyde and in the organohalogen compound) significantly affected the yield of the final products and the direction of the reactions [3, 4]. The involving into these reactions of pentafluorobenzaldehyde (**I**) with a strong electron-acceptor pentafluorophenyl group provides a possibility, on the one hand, to extend the range of studies of the effect on the process of polar characteristics of substituents in the aldehyde, and on the other hand, taking into account the ready occurrence of the reaction in the presence of $\text{Fe}(\text{CO})_5$ and the good yields of adducts, to develop sufficiently efficient preparative method of introducing the pentafluorophenyl group into various polyfunctional compounds.

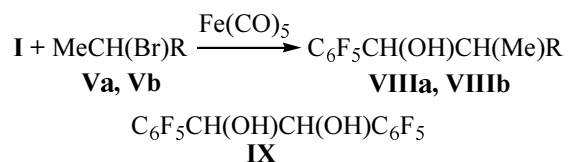
The reactions of pentafluorobenzaldehyde (**I**) with dibromoacetonitrile (**IIa**) or diethyl dibromomalonate (**IIb**) proceeded in benzene at 80°C to give the corresponding unsaturated compounds **IIIa** and **IIIb** whose structure was confirmed by ^1H , ^{19}F , ^{13}C NMR and mass spectra.



X = H, Y = CN (**a**), X = Y = CO_2Et (**b**).

In reaction of nitrile **IIa** with aldehyde **I** at room temperature we succeeded in detecting the formation of bromohydroxynitrile **IVa** confirming the above scheme. Note that both these reactions in the yields and the character of products obtained proved to be similar to the analogous reactions with benzaldehyde [5, 6]. Apparently due to the high efficiency of the functionally substituted dibromo derivatives of esters or nitriles the difference in the reactivity of benzaldehyde and pentafluorobenzaldehyde does not considerably affect the course of the process.

The reaction of aldehyde **I** with methyl 2-bromopropionate (**Va**), with the corresponding nitrile **Vb**, methyl trichloroacetate (**VI**), and bromoform (**VII**) occurred along another pattern yielding hydroxyester **VIIIa** and hydroxynitrile **VIIIb** respectively. From the reaction products obtained from aldehyde **I** and ester **Va** 1,2-di-(pentafluorophenyl)-1,2-ethanediol (**IX**) was isolated alongside hydroxyester **VIIIa**. The formation of product like diol **IX** was not previously observed in this type reactions.



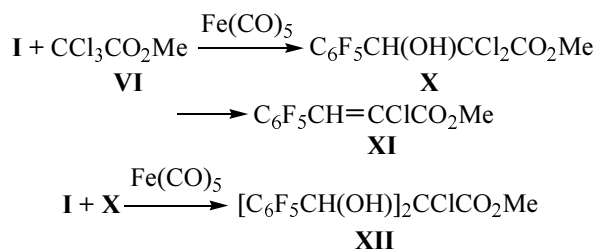
R = CO_2Me (**a**), CN (**b**).

It is presumable that because of the strong electron-withdrawing effect of the pentafluorophenyl group aldehyde **I** is reduced a lot easier than the other aldehydes with an electron transfer from the iron pentacarbonyl to afford diol **IX**.

The considerable competing process of diol **IX** formation reduces naturally the yield of the target hydroxyester **VIIIa**. For instance, at the molar ratio of the reagents (**I**):(**Va**) equal to 1:1 adduct **VIIIa** formed in a ~70% yield, and diol **IX** in a 20% yield. At the same time using the double amount of aldehyde **I** we obtained adduct **VIIIa** in a quantitative yield and ~30% of compound **IX** (calculated on the excess aldehyde).

It should be noted that 2-bromopropionitrile (**Vb**), more reactive than ester **Va**, reacted with aldehyde **I** selectively giving only adduct **VIIIb**.

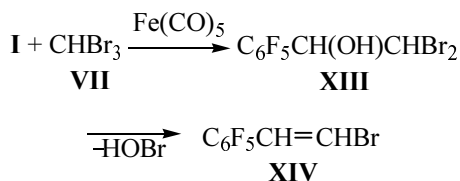
In reaction of ester **VI** with aldehyde **I** alongside the formation of addition product **X** and unsaturated ester **XI** we observed for the first time a second stage reaction of adduct **X** with the second aldehyde **I** molecule to afford «diadduct» **XII**.



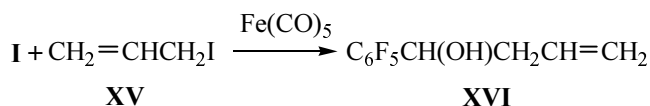
Ester **XII** can be obtained as the main product (yield 80–85%) applying 2 moles of aldehyde **I** per 1 mole of ester **VI**.

Hydroxydichloroester **X** whose formation confirms the above mentioned scheme can be obtained in a low yield only in reaction in DMF at room temperature; at 80°C only compounds **XI** and **XII** form in an overall yield ~80%. The reaction with the benzaldehyde furnished only the corresponding unsaturated ester of **XI** type in a 35% yield [2].

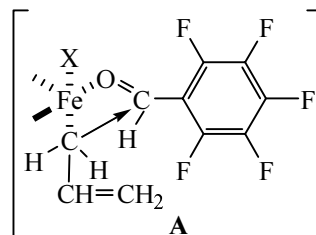
The use of aldehyde **I** in Barbier reactions in the presence of $\text{Fe}(\text{CO})_5$ also resulted in significantly different behavior as compared to analogous processes with the benzaldehyde. The reaction with bromoform (**VII**) gave rise to adducts in keeping with the Barbier type process affording hydroxydibromide **XIII** that partially underwent elimination of a HOBr group giving unsaturated bromide **XIV**.



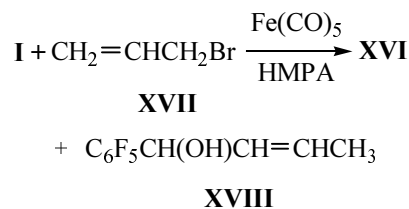
These compounds were detected in the reaction mixture by GC–MS method. The main product of the reaction was diol **IX** in the form of two diastereomers in a ~1:1 ratio. Allyl iodide (**XV**) with aldehyde **I** in the presence of $\text{Fe}(\text{CO})_5$ furnished adduct **XVI** in a quantitative yield; therewith at raising the temperature from 60°C to 80°C common for these processes the yield of the product was reduced from 95 to 60%. It is possible that at the higher temperature iodide **XV** partially decomposed in the presence of $\text{Fe}(\text{CO})_5$.



This reaction does not take place at room temperature. Note that in analogous reactions with the benzaldehyde and *p*-chlorobenzaldehyde the yield of adducts did not exceed 15–20%. We believe that here also the favorable combination of polar factors plays the main role: The pentafluorophenyl group sharply increases the electrophilic character of aldehyde **I** considerably facilitating its reaction with the allyl anion in the transition iron-carbonyl complex **A**.

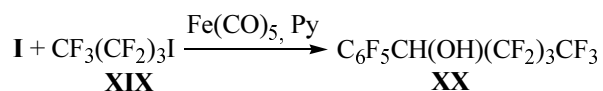


The reactions with allyl bromide (**XVII**) are less efficient and more complicated. At 60°C in benzene adduct **XVI** formed in a 35% yield. However, the reaction carried out in the presence of HMPA gave rise alongside compound **XVI** with a terminal double bond also to its isomer **XVIII** with a double bond in the position 2. This fact is illustrated by comparison of the mass spectra. The characteristic ion of compound **XVI** 197 [$M - \text{C}_3\text{H}_5$]⁺ (100) corresponds to the rupture of the C–allyl bond, whereas in the mass spectrum of isomer **XVIII** ion 233 [$M - \text{Me}$]⁺ (100) arises in the first stage by elimination



of a methyl group neighboring to the C=C bond. In the reaction mixture was also identified diol **IX**.

In reaction of aldehyde **I** with perfluorobutyl iodide (**XIX**) performed in the presence of pyridine the GC-MS method revealed the formation of adduct **XX** in a low yield (10–15%).



The comparison of results obtained with those for the corresponding reactions with the benzaldehyde [1, 2] permits a conclusion that as a rule aldehyde **I** reacts more efficiently than benzaldehyde: With allyl iodide the adduct forms in a quantitative yield, aldehyde **I** reacts with bromoform, the process with methyl trichloroacetate is accompanied by side reactions and 1,3-diol formation; in some cases 1,2-diol is obtained as a product of reductive dimerization of aldehyde **I**.

It should be emphasized that Reformatsky and Barbier reactions with the use of aldehyde **I** in some cases provided preparative yields of products in the presence of an uncommon for these reactions agent like iron entacarbonyl.

EXPERIMENTAL

Mass spectra were measured on a GC-MS instrument Finnigan Mat Magnum, column 25 m long (Ultra-2), temperature programmed from 30 to 220°C at a rate 2.5 deg/min. GLC analysis was carried out on a chromatograph LKhM, steel column (1300 × 3 mm), stationary phase 15% SKTFT-50X on Chromaton-N-AW, carrier gas helium (60 ml/min), detector thermal-conductivity detector, temperature programmed from 50 to 250°C at a rate of 6 deg/min. ¹H and ¹³C NMR spectra were registered on a spectrom-eter Bruker WP-200 (200 MHz), solvent CDCl₃, chemical shifts were presented with respect to TMS.

All organic reagents were subjected to distillation; Fe(CO)₅ purchased from Fluka was used without additional purification.

Reaction of pentafluorobenzaldehyde (I) with halogen derivatives IIa, IIb, Va, Vb, VI, VII, XV, XVII, and XIX. A solution of a mixture of 1 mmol of halocompound, 1 mmol of aldehyde, 2 mmol of Fe(CO)₅, 4 mmol of HMPA, and 1–2 drops of CCl₃Br in 1 ml of benzene was heated for 3–4 h at 80°C or kept for 3–5 days at room temperature. Then the reaction mixture was diluted with 2 ml of benzene, treated with 1 N hydro-

chloric acid, washed with water, and dried on MgSO₄. The reaction products were isolated either by preparative GLC or TLC (eluent petroleum ether–chloroform–ethyl acetate, 8:1:1). Yields were determined by GLC using standards.

3-Pentafluorophenylacrylonitrile (IIIa). Reaction temperature 80°C, yield 75%, mp 96–98°C. ¹H NMR spectrum, δ, ppm (*J*, Hz): *trans*-isomer – 6.21, 6.29 d (1H, =CHCN, *J* 17), 7.29, 7.37 d (1H, C₆F₅CH=, *J* 16); *cis*-isomer – 5.88, 5.94 d (1H, =CHCN, *J* 12), 7.01, 7.07 d (1H, C₆F₅CH=, *J* 12). Mass spectrum, *m/z* (*I*_{rel}, %): 219 [*M*]⁺ (100), 192 [*M* – CN–H]⁺ (10), 168 [C₆F₅H]⁺ (12), 52 [*M* – C₆F₅]⁺ (3). Found, %: C 49.20; H 1.20; F 43.4; N 6.25. C₉H₇F₅N. Calculated, %: C 49.3; H 1.0; F 43.4; N 6.4.

2-Bromo-3-hydroxy-3-pentafluorophenylpropionitrile (IVa). Reaction temperature 20°C, yield 16%. Mass spectrum, *m/z* (*I*_{rel}, %): 315, 317 [*M*]⁺ (0.5), 219 [*M* – BrOH]⁺ (0.2), 197 [C₆F₅CH(OH)]⁺ (100). Nitrile (**IIIa**), yield 6%.

Diethyl (pentafluorobenzylidene)malonate (IIIb). Reaction temperature 80°C, yield 35%. ¹H NMR spectrum, δ, ppm (*J*, Hz): 7.45 s (1H, CH=), 4.10 q (2H, CH₂O, *J* 18), 1.18 t (3H, CH₃CH₂, *J* 16). ¹³C NMR spectrum, δ, ppm: 163.6 (COO), 133.9–146.9 (Ar), 128.3 (C=), 62.7 (CH₂O), 53.6 (CH=), 14.5 (CH₃). Mass spectrum, *m/z* (*I*_{rel}, %): 338 [*M*]⁺ (35), 310 [*M* – C₂H₄]⁺ (30), 293 [*M* – C₂H₅O]⁺ (78), 264 [*M* – HCO₂Et]⁺ (100), 192 [*M* – 2CO₂Et]⁺ (85), 143 [*M* – C₆F₅CH–CH₃]⁺ (30), 45 [C₂H₅O]⁺ (40).

Methyl 2-methyl-3-hydroxy-3-pentafluorophenylpropionate (VIIa). Reaction temperature 80°C, ratio of ester to aldehyde 1:1, yield 71%, *n*_D²⁰ 1.4541, *d*₄²⁰ 1.4761. ¹H NMR spectrum, δ, ppm (*J*, Hz): 5.19 m (1H, CHOH), 3.06 m (1H, CHCOO), 3.72 s, 3.56 s (3H, CH₃O), 3.00 m (1H, OH), 1.31, 1.27; 0.98 d, 0.94 d (3H, CH₃, *J* 16). ¹³C NMR spectrum, δ, ppm: 174.5 (COO), 136.7–147.0 (Ar), 68.1 (CHO), 52.5 (CH₃O), 45.3 (CHCOO), 14.0 (CH₃C). Mass spectrum, *m/z* (*I*_{rel}, %): 197 [C₆F₅CHOH]⁺ (63), 88 [CH₃CH₂CO₂CH₃]⁺ (100). Found, %: C 46.25; H 3.20; F 33.8. C₁₁H₉F₅O₃. Calculated, %: C 46.5; H 3.2; F 33.4.

1,2-Dipentafluorophenyl-1,2-ethanediol (IX). Yield 21%, mp 152°C. ¹H NMR spectrum, δ, ppm (*J*, Hz): 5.45 br.s (2H, CH), 3.15 s (2H, OH). Calculated: 5.32 (+/– 0.29), 3.97(+/– 0.97).

Ester VIIa, reaction temperature 80°C, ratio of ester to aldehyde 1:2, yield 95%; **diol IX**, yield 30% (calculated on excess aldehyde).

3-Hydroxy-2-methyl-3-pentafluorophenyl-propionitrile (VIIIb). Reaction temperature 80°C, yield 75%, n_D^{20} 1.4611, d_4^{20} 1.4774. ^1H NMR spectrum, δ , ppm (J , Hz): 5.01 m (1H, CHOH), 3.20 m (1H, CHCN), 3.55 br.s (1H, OH), 1.47, 1.43; 1.18 d, 1.14 d (3H, CH_3 , J 16). Found, %: C 47.6; H 2.6; F 37.6; N 5.6. $\text{C}_{10}\text{H}_6\text{F}_5\text{NO}$. Calculated, %: C 47.8; H 2.4; F 37.8; N 5.6.

Methyl di[hydroxy(pentafluorophenyl)methyl]-chloroacetate (XII). Reaction temperature 80°C, ratio of ester to aldehyde 1:1, yield 57%, mp 180°C. ^1H NMR spectrum, δ , ppm (J , Hz): 5.47 s (2H, CHOH), 3.68 br.s (2H, OH), 3.36 s (3H, CH_3O). Mass spectrum, m/z (I_{rel} , %): 304 [$M - \text{C}_6\text{F}_5\text{C}(\text{OH})$] $^+$ (10), 286 [$M - \text{C}_6\text{F}_5\text{C}(\text{OH}) - \text{OH}$, 1Cl] $^+$ (100), 251 [$M - \text{C}_6\text{F}_5\text{C}(\text{OH}) - \text{OH} - \text{Cl}$] $^+$ (75), 197 [$\text{C}_6\text{F}_5\text{CH}(\text{OH})$] $^+$ (80), 59 [CO_2CH_3] $^+$ (25). Found, %: C 41.20; H 1.35; Cl 6.90; F 36.60. $\text{C}_{17}\text{H}_7\text{ClF}_{10}\text{O}_4$. Calculated, %: C 40.8; H 1.4; Cl 7.0; F 38.0.

Methyl 3-pentafluorophenyl-2-chloroacrylate (XI), yield 25%. Mass spectrum, m/z (I_{rel} , %): 286 [M] $^+$ (85), 251 [$M - \text{Cl}$] $^+$ (100), 192 [$M - \text{Cl} - \text{CO}_2\text{Me}$] $^+$ (90), 59 [CO_2Me] $^+$ (35).

Ester XII, reaction temperature 80°C, ratio of ester to aldehyde 2:1, yield 82%; **ester XI,** yield 11%.

Methyl 3-hydroxy-3-pentafluorophenyl-2,2-dichloropropionate (X). Reaction temperature 20°C, yield 12%. Mass spectrum, m/z (I_{rel} , %): 338 [M] $^+$ (0), 251 [$M - \text{HOCl} - \text{Cl}$] $^+$ (7), 197 [$\text{C}_6\text{F}_5\text{CH}(\text{OH})$] $^+$ (82), 142 [$\text{CHCl}_2\text{CO}_2\text{Me}$, 2Cl] $^+$ (100); **ester XII,** yield 5%.

1,1-Dibromo-2-pentafluorophenylethanol (XIII). Reaction temperature 80°C. Mass spectrum, m/z (I_{rel} , %): 370 [M] $^+$ (0.9), 274 [$M - \text{BrOH}$] $^+$ (0.7), 197 [$\text{C}_6\text{F}_5\text{CHOH}$] $^+$ (100).

1-Bromo-2-pentafluorophenylethene (XIV). Mass spectrum, m/z (I_{rel} , %): 272 [M] $^+$ (55), 193 [$M - \text{Br}$] $^+$ (100). **Diol IX,** diastereomers mixture at a ratio ~1:1, yield 87%. ^1H NMR spectrum, δ , ppm (J , Hz): 5.45 br.s (CH), 3.02 s (OH).

1-Pentafluorophenyl-3-buten-1-ol (XVI). Reaction temperature 80°C, yield 60%, n_D^{20} 1.4580, d_4^{20} 1.4220.

^1H NMR spectrum, δ , ppm (J , Hz): 5.60–5.81 m (1H, CH=), 5.02–5.16 m (3H, $\text{CH}_2=$, CH), 2.48–2.80 m (2H, CH_2), 2.38, 2.41 d (1H, OH, J 12). Mass spectrum, m/z (I_{rel} , %): 197 [$M - \text{C}_3\text{H}_5$] $^+$ (100). Found, %: C 50.20; H 3.14; F 39.60. $\text{C}_{10}\text{H}_7\text{F}_5\text{O}$. Calculated, %: C 50.43; H 2.96; F 39.88.

Adduct (XVI), reaction temperature 60°C, yield 95%; reaction temperature 60°C, solvent benzene, yield 35%; reaction temperature 60°C, solvent HMPA, yield 12%. Mass spectrum, m/z (I_{rel} , %): 197 [$M - \text{C}_3\text{H}_5$] $^+$ (100); **1-pentafluorophenyl-2-buten-1-ol (XVIII),** yield 7%. Mass spectrum, m/z (I_{rel} , %): 238 [M] $^+$ (95), 223 [$M - \text{CH}_3$] $^+$ (100), 197 [$M - \text{C}_3\text{H}_5$] $^+$ (35), 195 [$M - \text{C}_3\text{H}_7$] $^+$ (75), 43 [C_3H_7] $^+$ (85); **diol IX,** yield 11%.

Adduct (XVI), reaction temperature 60°C, solvent HMPA, reaction time 72 h, yield 10%; **diol IX,** yield 17%; **adduct XVIII** virtually absent.

1-Pentafluorophenyl-2,2,3,3,4,4,5,5,5-nonafluoropentan-1-ol (XX). Reaction temperature 65°C, in the presence of 4 mmol of pyridine, yield ~15%. Mass spectrum, m/z (I_{rel} , %): 416 [M] $^+$ (1.8), 397 [$M - \text{F}$] $^+$ (1.05), 197 [$M - \text{C}_4\text{F}_9$] $^+$ (100), 69 [CF_3] $^+$ (13.2).

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