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Synthesis of fluoroalkyl-containing 2-oxyimino-1,3-dicarbonyl compounds and their reaction with hydrazine hydrate

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Abstract

Reaction of fluoroalkyl-containing 1,3-keto esters and 1,3-diketones and their copper chelates with sodium nitrite gives the corresponding 2-hydroxyiminosubstituted ligands and chelates. 1,1,1-Trifluoro-3-hydroxyimino-4-phenyl-2,4-butanedione reacts with hydrazine hydrate with the formation of 4-hydroxyiminopyrazole. The 1,3-keto ester with a nonafluorobutyl substituent gives the stable 3-nonafluorobutyl-3-dihydroxy-4-hydroxyiminopyrazolidone-5. The similar reaction of ethyl trifluoroacetoacetate oxime leads to a pyrazolidone-5 (which can be dehydrated to 4-oxyiminopyrazolinone-5) and the hydrazide of 4,4,4-trifluoro-2-hydroxyimino-3-dihydroxybutanoate. © 1997 Elsevier Science S.A.

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1. Introduction

It is well known that 1,3-dicarbonyl compounds (acetoacetyl [1], benzoylacetyl esters [2], acetylacetone [3,4], diphenylpropanedione [5]) react with sodium nitrite to give the corresponding 2-oxyiminoderivatives. It is proved in Ref. [4] that isonitrosoderivatives of trifluoro- and hexafluoroacetylacetone exist in solution but isolation is not possible because of instability in air.

The reaction of non-fluorinated 2-oxyimino-1,3-diketones with hydrazines leads to formation of 4-nitrosopyrazoles [3,6]. However data on the reactions of 2-oxyiminosubstituted 1,3-keto esters with hydrazines are absent (although nitrosoderivatives of 3-pyrazolin-5-ones were obtained by nitrosation of pyrazolones rather than direct cyclisation of 2-oxyimino-1,3-keto esters [6]).

This paper describes the synthesis of novel fluoroalkyl-containing 2-oxyiminoderivatives of 1,3-dicarbonyl compounds, their copper chelates and reactions with hydrazine hydrate.

2. Experimental details

Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were measured on a Specord 75 IR spectrometer. ^{1}H-NMR spectra were recorded on a Tesla BS-567A instrument (^{1}H: 100 MHz) using TMS as an internal standard. ^{19}F-NMR spectra were recorded on a Tesla BS-587A instrument (^{19}F: 75 MHz) using $CFCl_3$ as internal standard. Column chromatography was performed on silica gel L 100/250. Thin-layer chromatography was performed on "Silufol-UV 254" plates in chloroform.

2.1. Synthesis of 2-oxyimino-1.3-dicarbonyl compounds

A solution of $NaNO_2$ (4 g, 0.058 mol) in 15 ml of water was added dropwise to a solution of compounds **1a**, **1b**, **2b** (Scheme 1) in 15 ml of acetic acid with stirring and cooling to 8–10 °C. The mixture was stirred at 20 °C for 1 h. The reaction mixture was extracted with ether (3 × 50 ml). The ether extracts were combined, washed in a saturated solution of sodium hydrogencarbonate to pH ~ 7, then washed by water and dried under reduced pressure for 2 h.

2.1.1. Ethyl 2-hydroxyimino-3-oxo-4,4,4-trifluorobutanoate (3a) (nc)

Yield, 82%.; oil; ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, t, CH_3, $J_{(H-H)} = 7.2$ Hz); 4.4 (2H, q, CH_2, $J_{(H-H)} = 7.2$ Hz); 10.7 (1H, br.s, OH) ppm. IR: 3380, 2880–2400 (OH); 1740 sh, 1720 (C=O); 1620 (C=N) cm^{-1}. Analysis: Found: C, 34.18; H, 3.08; F, 26.70; N, 6.17. Calc. for $C_6H_6F_4NO_3$: C,33.82; H, 2.84; F, 26.74, N, 6.57%.

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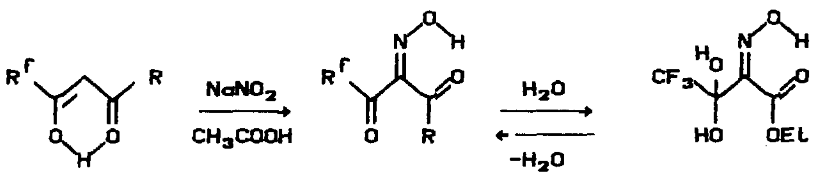


1a,b, 2a,b **3a,b, 4b** **5**

Compound	R^f	R
1a, 3a	CF_3	OEt
1b, 3b	C_4F_9	OEt
2a	CF_3	Me
2b, 4b	CF_3	Ph

Scheme 1.

2.1.2. Ethyl 2-hydroxyimino-3-oxo-4,4,5,5,6,6,7,7,7-nonafluoroheptanoate (3b) (nc)

Yield, 75%; oil; ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, t, CH_3, $J_{(H-H)}=7.0$ Hz); 4.4 (2H, q, CH_2, $J_{(H-H)}=7.0$ Hz); 11.17 (1H, br.ws, OH) ppm. IR: 3300, 2850–2500 (OH); 1750, 1720 (C=O); 1620 (C=N) cm^{-1}. Analysis: Found: C, 29.72; H, 1.50; F, 47,16; N, 3.74. Calc. for $C_9H_6F_9NO_4$: C,29.77; H, 1.67; F, 47.08; N, 3.86%.

2.1.3. 1,1,1-Trifluoro-3-hydroxyimino-4-phenyl-2,4-butanedione (4b) (nc)

Yield, 73%; m.p., 135–137 °C. ^{1}H-NMR ($(CD_3)_2CO$) δ: 7.7 (5H, m, C_6H_5); 13.2 (1H, s, OH) ppm. IR: 3350, 2650 (OH); 1725, 1660 (C=O); 1640, 1600, 1580 (C=N, C=O) cm^{-1}. Analysis: Found: C, 48.71; H, 2.61; F, 23.19; N, 5.68. Calc. for $C_{19}H_6F_3NO_4$: C, 48.99; H, 2.47; F, 23.25; N, 5.71%.

2.1.4. Ethyl 2-hydroxyimino-3-dihydroxy-4,4,4-trifluorobutanoate (5) (nc)

To a solution of oxime **3a** (4.3 g, 0.02 mol) in 20 ml of ether, 10 ml of water was added. The mixture was stirred for 30 min and extracted by ether. The ether layer was separated. The removal of solvent gave 4.5 g (98%) of compounds **5** as an oil. IR: 3650–2500 (OH); 1720 (C=O); 1650 (C=N) cm^{-1}. Analysis: Found: C, 31.31; H, 3.60; F, 24.78; N 6.01. Calc. for $C_6H_8F_3NO_5$: C, 31.18; H, 3.49; F, 24.66; N, 6.06%.

2.2. Synthesis of copper chelate of 2-hydroxyimino-1,3-dicarbonyl compounds

2.2.1. Method A

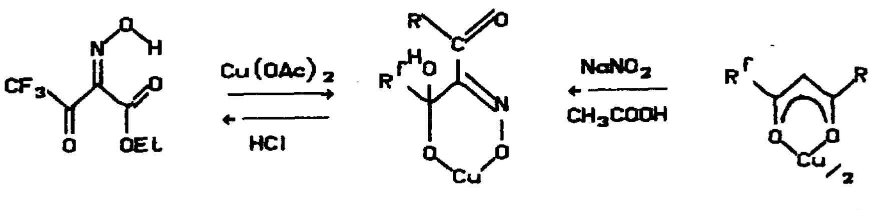
A solution of $NaNO_2$ (4 g, 0.058 mol) in 15 ml of water was added dropwise to a solution of compounds **6a**, **6b**, **7a**, **7b** (Scheme 2) (0.05 mol) in 15 ml of acetic acid with stirring and cooling at 8–10 °C. The reaction mixture was stirred at 20 °C for 1 h. The precipitate was filtered off, washed by water. The reprecipitation from acetone by water gave chelates **8a**, **8b**, **9a**, **9b** as green precipitates.

2.2.1.1. (Ethyl 4,4,4-trifluoro-3-dihydroxy-2-hydroxyimino-butanoato) copper(II) (8a) (nc)

Yield, 62%; m.p. 250–252 °C. IR: 3300, 2650 (OH); 1730, 1720 (C=O); 1590 (C=N) cm^{-1}. Analysis: Found: C, 24.80; H, 2.29; F, 19.05; N, 4.36. Calc. for $C_6H_6F_3NO_5Cu$: C, 24.62; H, 2.06; F, 19.47; N, 4.79%.

2.2.1.2. (Ethyl 4,4,5,5,6,6,7,7,7-nonafluoro-3-dihydroxy-2-hydroxyimino heptanoato)copper(II) (8b) (nc)

Yield, 59%; m.p. 170 °C (decomp.). IR: 3310, 2650 (OH); 1730 sh, 1710 (C=O); 1600 (C=N) cm^{-1}. Analysis: Found: C, 24.30; H, 1.67; F, 38.17; N, 2.88. Calc. for $C_9H_6F_9NO_5Cu$: C, 24.42; H, 1.37; F, 38.62; N, 3.16%.



3a **8a,b, 9a,b** **6a,b, 7a,b**

Compound	R^f	R
6a, 8a	CF_3	OEt
6b, 8b	C_4F_9	OEt
7a, 9a	CF_3	Me
7b, 9b	CF_3	Ph

Scheme 2.

*2.2.1.3. (1,1,1-Trifluoro-2-dihydroxy-4-butane-3-hydroxyimato)copper(II) (**9a**) (nc)*

Yield, 69%; m.p. 240 °C (decomp.). IR: 3280, 2650 (OH); 1720, 1700 (C=O); 1600 (C=N) cm^{-1}. Analysis: Found: C, 23.06; H, 1.55; F, 21.63; N, 5.21. Calc. for $C_5H_4F_3NO_4Cu$: C, 22.87; H, 1.53; F, 21.70; N, 5.33%.

*2.2.1.4. (1,1,1-Trifluoro-2-dihydroxy-4-phenylbutan-3-hydroxyimato)-copper(II) (**9b**) (nc)*

Yield, 68%; m.p. 175–177 °C. IR: 3300, 2650 (OH); 1670 (C=O); 1590, 1540 (C=N, C=C) cm^{-1}. Analysis: Found: C, 36.91; H, 1.97; F, 17.15; N, 4.25. Calc. for $C_{10}H_6F_3NO_4Cu$: C, 36.99; H, 1.86; F, 17.55; N, 4.31%.

2.2.2. Method B

A saturated aqueous solution of copper acetate was added to a solution of compounds **3a** and **5** (0.02 mol) in 10 ml ethanol. The precipitate was filtered off. Crystallization from acetone gave chelate **8a** with yield 85% (from **3a**) and 86% (from **5**). The physical data were identical to those listed above.

*2.2.2.1. Reaction of trifluoroacetylacetone **2a** with $NaNO_2$*

A solution of $NaNO_2$ (1.6 g, 0.023 mol) in 15 ml of water was added dropwise to a solution of compound **2a** (3 g, 0.02 mol) with stirring at 20 °C for 30 min. A saturated aqueous solution of $Cu(OAc)_2$ was added to the reaction mixture. The precipitate was filtered off, reprecipitated from acetone by water to give chelate **9a** (2.5 g, 48%). The physical data were identical to those listed above.

*2.3. Reactions of compounds **3a**, **3b**, **4b** with hydrazine hydrate*

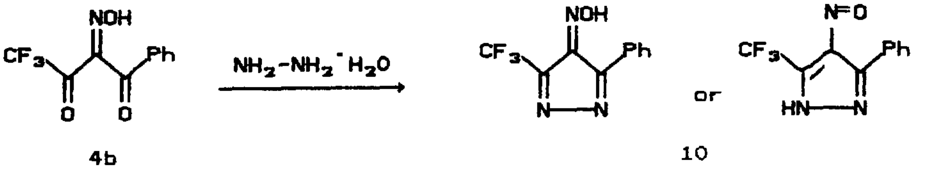
A solution of hydrazine hydrate (0.5 g, 0.01 mol) in 10 ml of ethanol was added dropwise to a solution of compounds **3a**, **3b**, **4b** in 25 ml of ethanol with stirring and cooling to 10 °C over 30 min. The mixture was stirred at 20 °C for 3 h. The solvent was removed. 50 ml of ether was added to the residue. The isolation of products **10**, **11**, **12a**, **12b**, **13** is described below (Schemes 3 and 4).

*2.3.1. 3-Trifluoromethyl-4-hydroxyimino-5-phenylpyrazol (**10**) (nc)*

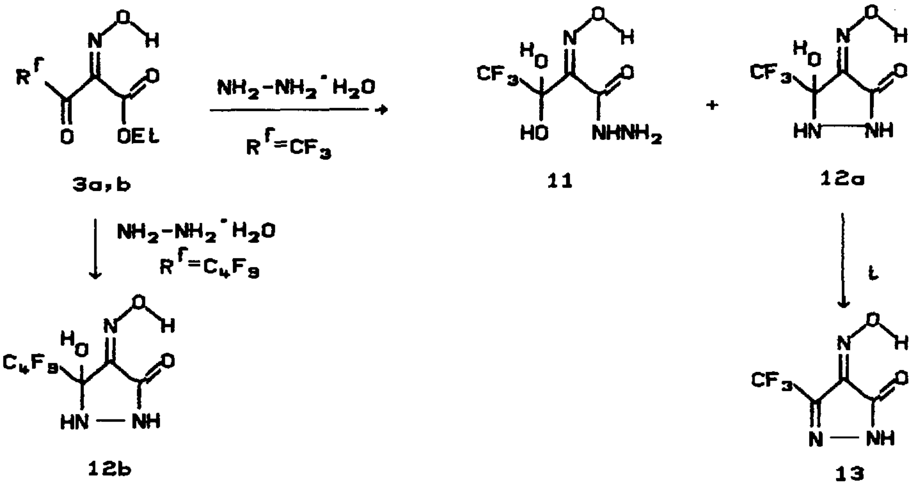
Hexane was added to an ether solution of **10**, and the precipitate was filtered off. Recrystallization from chloroform gave **10** (2 g, 83%) as a green powder (m.p. 124–126 °C). IR: 3600, 3150, 2700–2300 (OH); 1680 (C=NOH); 3050, 1600, 1750 (C=N) cm^{-1}. ^1H-NMR ($(CD_3)_2CO$) δ: 7.67 (5H, m, C_6H_5); 11.49 (1H, ws, OH) ppm. ^{19}F-NMR: 63.76 c (s, CF_3) ppm. Analysis: Found: C, 49.87; H, 2.36; F, 23.89; N, 17.40. Calc. for $C_{10}H_6F_3N_9O$: C, 49.80; H, 2.51; F, 23.63; N, 17.42%.

*2.3.2. Hydrazide of 2-hydroxyimino-3-dihydroxy-4,4,4-trifluorobutanoate (**11**) (nc)*

The precipitate of **11** was filtered off. Reprecipitation from ethanol by ether gave **11** (0.35 g, 16%) as a white powder (m.p. 183–184 °C). IR: 3550, 3450, 3200–3100, 2650–2020 (OH, NH); 1700 (C=O); 1690 (C=N); 1650, 1610, 1500 (NH) cm^{-1}. ^1H-NMR ($(CD_3)_2CO$) δ: 3.56, 5.48, 7.42, 10.53 (6H, ws, OH, NH) ppm. ^{19}F-NMR: 57(s, CF_3) ppm.



Scheme 3.



Scheme 4.

Analysis: Found: C, 22.23; H, 2.75; F, 26.18; N, 19.34. Calc. for $C_4H_6F_3N_3O_4$: C, 22.13; H, 2.79; F, 26.25; N, 19.35%.

*2.3.3. 3-Dihydroxy-4-hydroxyimino-3-trifluoromethyl-pirazolidin-5-one (**12a**) (nc)*

Hexane was added to an ether solution of **12a**. The precipitate was filtered off to give **12a** (1.35 g, 68%) as a yellow powder (m.p. 70 °C (decomp.)). IR: 3670, 3430, 3230, 2670–2350, 2150 (OH, NH); 1750 (C=O); 1690 (C=NOH); 1620, 1570, 1515, 1500 (NH) cm^{-1}. ^{1}H-NMR ($(CD_3)_2CO$) δ: 7.11 (3H, ws, NH, OH); 11.83 (1H, ws, N–OH) ppm. Analysis: Found: C, 24.60; H, 1.76; F, 28.60; N, 21.15. Calc. for $C_4H_4F_3N_3O_3$: C, 24.13; H, 2.02; F, 28.62; N, 21.11%.

*2.3.4. 3-Dihydroxy-4-hydroxyimino-3-nonafluorobutyl-pirazolidin-5-one (**12b**) (nc)*

Hexane was added to an ether solution of **12b**. The precipitate was filtered off to give **12b** (1.45 g, 83%) as a light-yellow powder (m.p. 119–121 °C). IR: 3650, 3480–3100, 2370–2700 (OH, NH); 1730 (C=O); 1690 (C=NOH); 1620, 1600, 1530 (C=N, NH) cm^{-1}. ^{1}H-NMR ($(CD_3)_2CO$) δ: 7.07 (3H, ws, NH, OH); 11.84 (1H, ws, N–OH) ppm. Analysis: Found: C, 24.12; H, 1.12; F, 48.86; N, 12.22. Calc. for $C_7H_4F_9N_3O_3$: C,24.08; H, 1.15; F, 49.98; N, 12.04%.

*2.3.5. 4-Hydroxyimino-3-trifluoromethylpyrazolin-5-one (**13**) (nc)*

The compound **12a** was heated under the reduced pressure for 30 min. Recrystallization from chloroform gave **13** as an orange powder (m.p. 110 °C). IR: 3480–3080, 2650–2350 (OH, NH); 1740 (C=O); 1690 sh (C=NOH); 1600,1580, 1550 (C=N, NH) cm^{-1}. ^{1}H-NMR ($(CD_3)_2CO$) δ: 6.3 (ws, NH); 11.8 (ws, NOH) ppm. ^{19}F-NMR: 64.65 (s, CF_3); 65.75 (s, CF_3) ppm. Analysis: Found: C, 26.72; H, 1.11; F, 31.44; N, 23.25. Calc. for $C_4H_2F_3N_3O_2$: C, 26.53; H, 1.11; F, 31.48; N, 23.21%.

3. Results and discussion

3.1. Synthesis of fluoroalkyl-containing 2-hydroxyimino-1,3-dicarbonyl compounds

It has been found that the fluoro-containing 1,3-keto esters **1a**, **1b** and 1,1,1-trifluoro-4-phenyl-2,4-butanedione **2b** react with $NaNO_2$ in acetic acid with the formation of the corresponding oximes of 1,3-dicarbonyl compounds **3a**, **3b** (Scheme 1). It was proved by IR and ^{1}H-NMR spectroscopies that the compounds obtained (**3a**, **3b**, **4b**) existed as oximes, as is typical for aliphatic nitrosocompounds with hydrogens at the carbon atom [7]. The IR spectra of products **3a**, **3b**, **4b** showed C=O stretching absorption at 1750–1660 cm^{-1} from the keto form of 1,3-dicarbonyl compounds. In the ^{1}H-NMR spectra the resonance signal of a methine proton was absent. The low frequency of the C=N stretching absorption is probably the result of the conjugation of the C=N and C=O bonds and participation of the C=N group in an intramolecular hydrogen bond. The latter is confirmed by observation of a broadened OH stretching absorption at 2670 cm^{-1}.

Compounds **3a**, **3b**, **4b** are hygroscopic and able to form hydrates such as **5**, which is typical for fluoroalkyl-containing 1,3-dicarbonyl compounds and their 2-mono substituted derivatives [8,9]. The IR spectrum of hydrate **5** is different from those of oximes.

Compound **5** was dehydrated by heating on a water bath under reduced pressure to reform oxime **3a** (Scheme 1).

The literature and the present work show the low stability of oximes derived from 1,3-diketones. Thus 1,1,1-trifluoro-3-hydroxyimino-4-phenyl-2,4-butanedione **4b** is the only stable representative of fluorinated oximes of 1,3-diketone derivatives isolated as free compound probably because of the phenyl substituent. Unfortunately, the analogous 1,3-diketone with the more bulky tetrafluoroethyl substituent, 1,1,2,2-tetrafluoro-5-phenyl-3,5- pentanedione, underwent decomposition at the C–C bond to form benzoic acid with 80% yield.

Our attempts to obtain an oxime from trifluoroacetyl-acetone **2a** by the reaction of **2a** with $NaNO_2$ in acetic acid were also unsuccessful because of decomposition.

3.2. Synthesis of the copper chelates of 2-hydroxyimino-1,3-dicarbonyl compounds

The treatment of oxime **3a** by copper acetate leads to a copper chelate of hydroxyderivative 2-oxyiminosubstituted trifluoroaceto-acetic ester **8a** (Scheme 2). This compound and analogous copper chelates **8b**, **9a**, **9b** are obtained by the reaction of fluoroalkyl-containing bis(1,3-keto esterates) **6a**, **6b** and bis(1,3-diketonates) **7a**, **7b** with $NaNO_2$. In the IR spectra of compounds **8a**, **8b** and **9a**, **9b** the frequency of the C=O vibration increases as compared with the starting metal chelates of 1,3-diketones and 1,3-keto esters. The C=N absorption band in compounds **8a**, **8b**, **9a**, **9b** is observed at lower frequencies relative to the values cited in the literature [10], indicating considerable conjugation of this group. A distinctive peculiarity in the IR spectra of the new chelates **8a**, **8b**, **9a**, **9b** is the presence of very strong OH absorption bands, also confirming the suggested structure of the chelates.

Decomposition of chelates **8a** gives ethyl 2-hydroxyimino-3-oxo-4,4,4-trifluorobutanoate **3a** (Scheme 2).

3.3. Reaction of fluoroalkyl-containing 2-hydroxyimino-1,3-dicarbonyl compounds with hydrazine hydrate

It has been found that the oxime of fluorinated 1,3-diketone **4b** reacts with hydrazine hydrate to form the substituted pyrazol **10** (Scheme 3). Compound **10** may exist in nitroso- and oxyiminoforms. The ^{19}F-NMR spectrum of **10** has one CF_3 group signal, indicating the presence of the only tautomer.

Compound **10** is green, as are many nitrosoarenes [7], but the data of the IR and NMR spectroscopies could be assigned to the either nitroso or oxyimino isomers.

Reaction of oxyiminosubstituted fluoroalkyl-containing 1,3-keto esters **3a**, **3b** with hydrazine hydrate, unlike the above reaction of 1,3-diketone oxime, proceed ambigiously and depend on the size of fluoroalkyl substituent. Thus, the substituted trifluoroacetoacetic ester **3a** reacts with hydrazine hydrate to give two products: the hydrazide of 2-hydroxyimino-3-dihydroxy-4,4,4-trifluorobutanoate **11** and 3-dihydroxy-4-hydroxyimino-3-trifluoromethylpyrazolidin-5-one **12a** (Scheme 4). The latter is readily dehydrated on heating to 70 °C with formation of the brightly orange pyrazolynone **13** (Scheme 4).

In the ^{19}F-NMR spectrum of compound **13**, the presence of two singlet signals of CF_3 groups indicated that this compound exists as a 1:1 mixture of two tautomers. Compound **13** could exist in four tautomeric forms but the NMR spectra gave little information on this compound. In the IR spectrum of pyrazolinone **13**, the absorption bands C=NOH and C=O showed the presence of the oxyiminoamide tautomer in solid. The absorption bands at 1600 and 1500 cm^{-1} are typical for C=N bonds. This confirms the presence of the oxyiminoamide tautomer for compound **13**, but does not exclude the presence of other tautomers (the C–N=O absorption bands can be overlapping C=N and NH bands).

The oxyiminosubstituted 1,3-keto ester **3b** with a nonafluorobutyl substituent gives pyrazolidone **12b** as the only product of the reaction (Scheme 4). Compound **12b** differs from hydrate **12a** in the greater stability to dehydration.

The substituted pyrazolidones may exist as a mixture of tautomeric forms (oxyiminoamide, oxyiminoimide, nitrosoform). IR data of these compounds show a preference for the oxyiminoamide form.

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