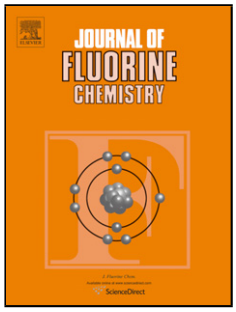

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Efficient and Scalable Synthesis of 3-(Polyfluoroacyl)pyruvaldehydes Dimethyl Acetals: A Novel Functionalized Fluorinated Building-Block.

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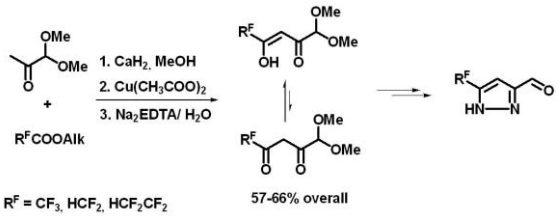
Graphical abstract



Highlights

- The synthesis of 3-(polyfluoroacyl)pyruvaldehydes dimethyl acetals is described
- Disodium EDTA is a mild regent to isolate fluorinated diketones with an acid sensitive moiety from their copper complexes
- A simple synthesis of N-unsubstituted 5(3)-(polyfluoroalkyl)-1*H*-pyrazole-3(5)-carbaldehydes and their acetals is presented

Abstract– An efficient approach for the synthesis of 3-(polyfluoroacyl)pyruvaldehydes dimethyl acetals (1,1-dimethoxy-4-polyfluoroalkyl-butan-2,4-dions) from 1,1-dimethoxyacetone and polyfluorinated carboxylic acid esters has been developed. The procedure includes the Claisen type condensation of the starting materials by means of calcium hydride in methanol, followed by isolation of copper complexes of the corresponding diketones and their destroying with disodium EDTA. A simple synthesis of 5(3)-(polyfluoroalkyl)-1*H*-pyrazole-3(5)-carbaldehydes and their acetals is also presented.

Keywords: Fluorinated 1,3-diketones; Acetals; Claisen condensation; Calcium hydride; 3-(Polyfluoracyl)pyruvaldehydes; Pyrazole-1*H*-3- carbaldehydes

1. Introduction

In the past decades importance of fluorine compounds has substantially increased due to their widespread application in many fields such as medicinal, materials, and synthetic chemistry [1]. Therefore, development of efficient methods for introduction of fluorinated groups into target molecules is a challenging goal for synthetic chemists. Despite the progress in fluoroalkylation reactions [2], as well as direct transformations of some functional groups to the fluorinated ones [3], these approaches still have limitations on structures and regioselectivity. Hence, strategies that allow scalable preparation of fluorinated products with a variety of structures from readily available fluorinated building blocks are essential to fluorine chemistry [4].

Polyfluoroalkyl-containing 1,3-dicarbonyl compounds represent very important building-blocks among various fluorinated ones owing to their ability to be C3 and C2-synthons for construction of numerous fluorinated five-, six, seven-membered and fused heterocyclic systems [4l, 5]. In addition they have a significant role in preparation of metal complexes with challenging magnetic and luminescence properties [1f, 6].

One of the advantages of 1,3-diketones as versatile reagents is a possibility to associate 1,3-dicarbonyl core with some functional groups (e.g., carbonyl) at terminal substituents. This substantially extends a synthetic capability of those building blocks and their derivatives. Meanwhile, a number of such fluorinated carbonyl-functionalized diketones is small so far. Thus, synthesis and reactivity of fluorinated 1,3,5-triketones [7] and 3,5-diketoesters **1** [8], 2,4-diketoester (polyfluoroacyl pyruvate) **2** [9], ketals of 4-trifluoromethyl-1,2,4-triketone **3** [10], and 4-aryl-1-trifluoromethyl-1,2,4-triketones **4**, existing in a cyclic form [11] have been studied in the last two decades (Fig. 1).

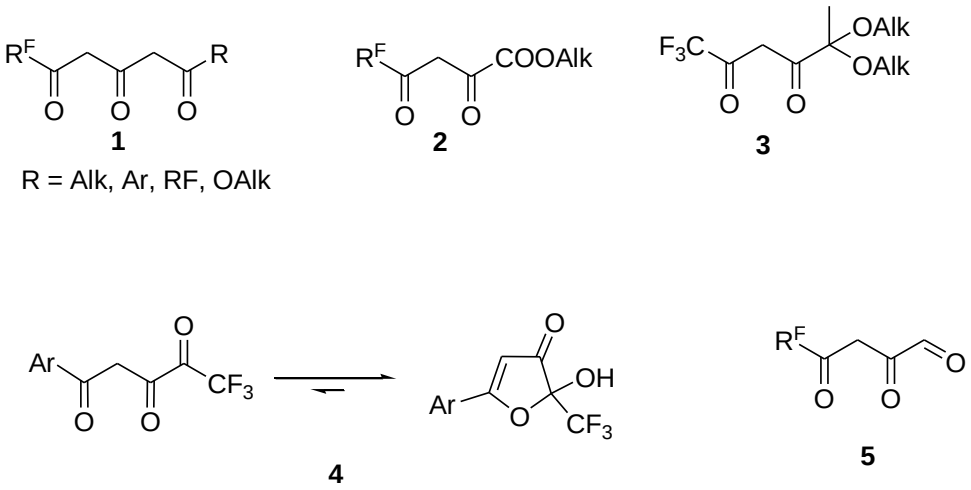


Figure 1. Fluorinated building blocks with 1,3-dicarbonyl fragment.

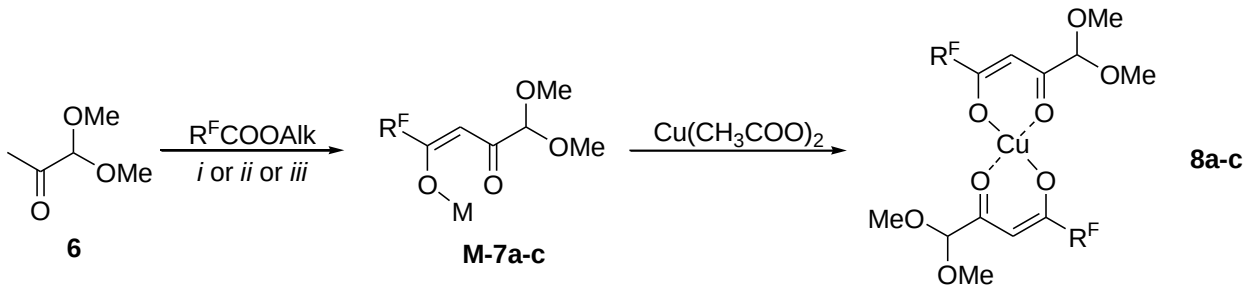
However, to the best of our knowledge, no reports on the synthesis of 4-polyfluoroalkyl-2,4-diketoaldehydes **5** (3-(polyfluoroacyl)pyruvaldehyde) or their acetal derivatives have appeared to date. The latter can be considered as useful building block for a construction of a wide variety of fluoroalkylated heterocycles, bearing a synthetically versatile aldehyde group, by analogy with non-fluorinated acetals of 3-(acyl)pyruvaldehyde [12].

In continuation of our work on synthesis and reactivity investigation of fluorinated polycarbonyl compounds [7, 10a, 13], we herein report the efficient and scalable synthesis of 3-(polyfluoroacyl)pyruvaldehydes dimethyl acetals through the Claisen condensation of readily available 1,1-dimethoxyacetone with the corresponding polyfluorinated esters.

2. Results and discussion

The Claisen condensation of pyruvaldehyde dimethyl acetal (methylglyoxal 1,1-dimethyl acetal, 1,1-dimethoxyacetone) **6** with methyl di- and trifluoroacetates and methyl tetrafluoropropionates has been found to readily occur in the presence of MeONa in diethyl ether at 0-4°C (Scheme 1). However we were not able to isolate pure sodium diketonates **Na-7a-c**. Therefore, the dimethyl acetals of 3-(polyfluoroacyl)pyruvaldehydes were isolated as their copper complexes **8a-c** in 67-74 % yield (Table 1, entries 1-3)**.** It should be noted that isolated yields of complexes decreased up to 40-48 %, when reaction was carried out at the temperature more then 5-10°C (Table 1, entries 4 and 5).

Additionally, we have studied other condensing agents. One of them is LiH that have proved to be very effective for synthesis of various polyfluoroalkyl-containing di- and tricarbonyl compounds [7a, 10, 13]. The compound **6** has been found to react with ethyl trifluoroacetate and methyl trifluoroacetate in the presence of LiH in methyl tert-butyl ether (MTBE), thus affording the corresponding lithium diketonate **Li-7a**. However, the best isolated yield of 52 % has been reached (Table1, entries 6 and 7). Reaction of **6** with methyl difluoroacetate under the same reaction conditions has given the corresponding diketonate **Li-7b** in low 34 % yield (Table1, entry 8).



R^F = CF_3 (a), HCF_2 (b), HCF_2CF_2 (c)
M = Li, Na, Ca

i: NaOMe, Et_2O, 0-4°C, 6h; *ii*: LiH, MTBE, r.t., 12h; *iii*: CaH_2, MeOH, r.t., 24h.

Scheme 1. Synthesis of copper complexes **8a-c**

The novel modification of the Claisen condensation has been used as the third reaction conditions to obtain diketonates based on dimethyl acetals of 3-(polyfluoroacyl)pyruvaldehydes **7a-c**. We found that acetal **6** reacted with fluorinated esters in the presence of 0.75 equiv. of CaH_2 in MeOH resulting in calcium complexes **Ca-7a-c**. However their compositions were variable (according to the ^1H and ^{19}F spectra), so they were converted into copper complexes **8a-c** in 73-92 % isolated yields (Table 1, entries 9-11, Sect. 4.3). When stoichiometric amount (0.5 equiv.) of CaH_2 was used, the yield of **8a** decreased (Table 1, entry 12.)

Table 1. Reaction of 1,1-dimethoxyacetone with polyfluorinated esters and yields of diketonates **Li-7** and **8**.

entry	Compound	R^F	Condensing agent/ Solvent, Temperature	Time, h	Yield [%][a]
1	**8a**	CF_3	1.2 MeONa/ Et_2O, 0-4 °C	6	67
2	**8b**	HCF_2	1.2 MeONa/ Et_2O, 0-4 °C	8	74
3	**8c**	HCF_2CF_2	1.2 MeONa/ Et_2O, 0-4 °C	8	76
4	**8a**	CF_3	1.2 MeONa/ Et_2O, r.t.	4	48
5	**8b**	HCF_2	1.2 MeONa/ Et_2O, r.t.	4	40
6	**Li-7a**	CF_3	1.1 LiH/MTBE, r.t.	20	45
7	**Li-7a**	CF_3	1.1 LiH/MTBE, r.t.	20	52[b]
8	**Li-7b**	HCF_2	1.1 LiH/MTBE, r.t.	20	34
9	**8a**	CF_3	0.75 CaH_2/ MeOH, r.t.	24	92
10	**8b**	HCF_2	0.75 CaH_2/ MeOH, r.t.	24	73
11	**8c**	HCF_2CF_2	0.75 CaH_2/ MeOH, r.t.	24	82
12	**8a**	CF_3	0.5 CaH_2/ MeOH, r.t.	24	69

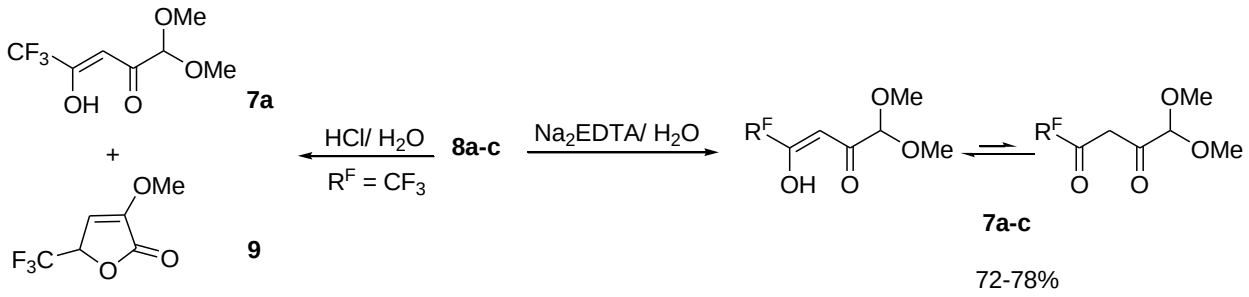
[a]isolated yield;

[b]ethyl trifluoroacetate was used

Isolation of pure compounds **7a-c** by treatment of lithium diketonates **Li-7** or copper complexes **8** with diluted hydrochloric acid was difficult due to the presence of the acid sensitive dimethyl acetal group in their structure. Thus, additional sets of signals was observed in the ^{1}H and ^{19}F spectra of diketone **7a** that was isolated in 48 % yield after destroying of its copper complex **8a** in acidic conditions (Scheme 2). The quartet of doublets at δ 5.23 ppm (J_{HF} = 5.2, J_{HH} = 2.2 Hz), doublet at δ 6.07 ppm (J_{HH} = 2.2 Hz) and singlet at δ 3.89 ppm in the ^{1}H spectrum and doublet at δ 84.21 ppm (J_{FH} = 5.2 Hz) in the ^{19}F spectrum let us suggest the structure of 3-methoxy-5-(trifluoromethyl)furan-2(5*H*)-one **9** for the main impurity compound (Scheme 2, SI). It was probably formed from **7a** in the presence of an acid. Similar acid-catalyzed transformation of non-fluorinated dialkyl acetals of acylpyruvaldehydes has been reported early [14].

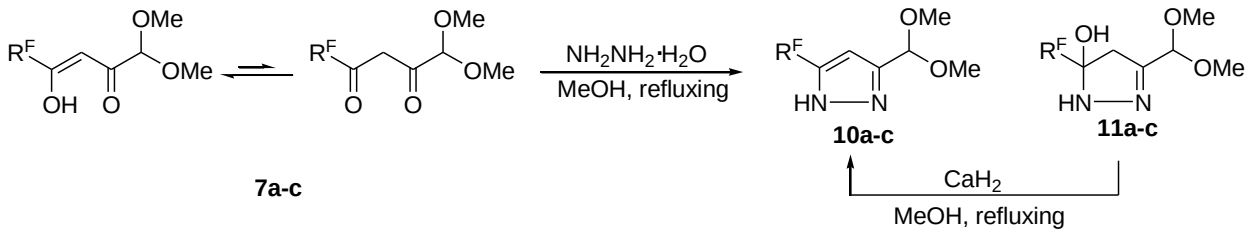
Therefore, we have tried to destroy copper complexes **7** without use of an acid. It have been found that treatment of **8a-c** with water solution of disodium EDTA led to liberation of diketones **7**, which were isolated in 72-78 % yields after extraction and distillation (Scheme 2, Sect. 4.4). It is worth noting that complexes **Ca-7a-c** do not destroy in this non-acidic conditions.

The structure of isolated diketones **7a-c** was proved by ^{1}H, ^{19}F, ^{13}C NMR and IR spectroscopy and elemental analysis. The NMR spectra of obtained dicarbonyl compounds shows that they are enolized almost completely (≥ 95%) in $CDCl_3$ solution (Sect. 4.4.1-4.4.3).



Scheme 2. Preparation of diketones **7a-c** from the corresponding copper complexes

The wide range of synthetic possibilities of fluorinated 1,3-diketones have been demonstrated in heterocyclization reactions [5, 10, 11, 15]. Since novel compounds **7a-c** represent valuable precursors for a synthesis of various heterocyclic carbaldehydes, bearing polyfluoroalkyl groups, we studied a reaction of diketones **7a-c** with hydrazine to highlight their synthetic potential.



Scheme 3. Reaction of diketones **77a-c** with $NH_2NH_2 \cdot H_2O$ and preparation of pyrazoles **10a-c**

It has been found that reaction of **7a-c** with hydrazine hydrate easily occurred in refluxing methanol furnishing mixtures of pyrazoles **10** and 5-hydroxy-5-fluoroalkyl-pyrazoline **11** (Scheme 3). As shown in table 2 trifluoromethyl and tetrafluoroethyl groups of pyrazoline **11a** and **11c** complicate their dehydration into pyrazole **10a** and **10c** (Table 2, entries 1, 2 and 6), whereas pyrazole **10b** with less electron-withdrawing difluoromethyl group can be obtained as a sole product (Table 2, entry 5).

Table 2. Yields and ratios of pyrazoles **10** and pyrazolines **11**.

entry	Diketone	Time (h)	Pyrazole **10** and pyrazoline **11** ratio		Yield (%)
			10	**11**	
1	**7a**	6	5	95	95[a]
2	**7a**	10	7	93	93[a]
3	**7a**	10	100	0	86[b]
4	**7b**	4	90	10	93[a]
5	**7b**	10	100	0	91
6	**7c**	10	8	92	~100[a]
7	**7c**	10	100	0	89[b]

[a]mixture of **10** and **11**; [b]after treatment of reaction mixture with CaH_2 (Sect. 4.6)

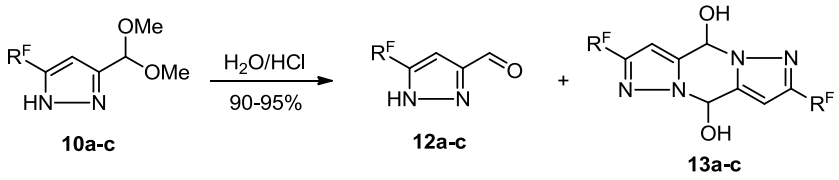
We have failed to isolate pyrazolines **11a**,**c** in pure form neither by chromatography, nor by crystallization of the dried reaction mixtures. Thus, when they were crystallized, their solutions turned yellow and mixtures of crystals with yellow powder (in case **11a**) or oil (in case **11c**) were formed and appearance of at least three new products was observed by TLC. Nevertheless, the structure of pyrazolines **11** was clearly confirmed owing to characteristic signals in the ^{1}H NMR spectra of dried reaction mixtures: two proton AB-system at $\delta \sim 2.9$ and 3.2 ppm ($^2J_{HH}$ = 18-19

Hz) and two three-protons singlets at δ ~ 3.40 and 3.43 ppm. These signals were attributed to CH_2 group attached to stereogenic carbon atom and two magnetically non-equivalent methoxy groups correspondingly. The signals of fluorinated substituents are shifted upfield in the ^{19}F NMR spectra and manifest themselves as AB-systems of multiplets for **11b** and **11c**.

Attempts to obtain pyrazoles **10a** and **10c** under acidic catalysis failed because of the acid-sensitive acetal group in the structure of pyrazolines **11a** and **11c**. Dehydration of these pyrazolines in refluxing toluene was unsuccessful as well. Reaction mixtures were tarred, and a complicated mixture of products was observed by TLC in both cases. Nevertheless, we have found that pyrazoles **10a** and **10c** can be obtained in good yields, when pyrazole and pyrazoline mixtures (obtained from the reaction of the corresponding diketones **7a** and **7c**) were refluxed in methanol with excesses of CaH_2 (3 equiv.) for 10-12 h (Scheme 3, Table 2, entries 3 and 7, Sect. 4.6).

Described synthesis of pyrazoles **10a** from diketone **7a** is a simple and scalable approach that can be a method of choice to heterocyclization of 1,1,1-trifluoro-4-methoxy-5,5-dibromopent-3-en-2-one with hydrazine [16].

Next, we have found that the dimethyl acetal group of pyrazoles **10a-c** can be easily hydrolyzed by water in the presence of a catalytic amount of hydrochloric acid with formation of the corresponding 5(3)-(polyfluoroalkyl)-1*H*-pyrazole-3(5)-carbaldehydes **12a-c** in high 90-95% yields (Scheme 4).



10a-c **12a-c** **13a-c**

Scheme 4. Preparation of 5(3)-(polyfluoroalkyl)-1*H*-pyrazole-3(5)-carbaldehydes **12a-c**

The structures of the pyrazole carbaldehydes **12** were confirmed by elemental analysis, ^1H, ^{19}F NMR, and IR spectroscopy. Characteristic features of the ^1H NMR spectra in Me_2SO-d^6 are the appearance of a singlet at δ 7.23–7.49 ppm for the proton H-4 of the pyrazole ring, a singlet at δ ~ 7.89 ppm for the proton of the aldehyde group and a broadened singlet at δ 14.55–14.93 ppm for the NH group. It should be pointed out that additional double sets of signals were observed in the ^1H and ^{19}F NMR spectra. Taking into account a well known tendency of N-unsubstituted 1*H*-pyrazole-3(5)-carbaldehydes to form dimers [17], we have attributed those signals to two diastereomers of the corresponding 2,7-bis(polyfluoroalkyl)-4*H*,9*H*-dipyrazolo[1,5-*a*:1,5-*d*]pyrazine-4,9-diols **13a-c** (Sect. 4.7). Interestingly, the content of **13** in Me_2SO-d^6 solution increases from 5 mole % for **13b** to 9 mole % for **13c**, and to 16 mole % for **13a**. This fact can be

probably explained by the increase in electron-withdrawing properties of polyfluoroalkyl substituents. On the other hand, carbaldehydes **12** seem to exist predominantly as dimers **13** in the solid state, since their IR spectra showed the presence of intensive absorption bands of hydroxyl groups in the ranges 3140–3160 cm^{-1} and small bands in the range 1700-1720 cm^{-1}, attributed to aldehyde groups.

3. Conclusion

In summary, we have developed efficient and scalable procedure for preparation of 3-(polyfluoroacyl)pyruvaldehydes dimethyl acetals from readily available 1,1-dimethoxyacetone. These compounds can be considered as novel valuable fluorinated building blocks that has been clearly demonstrated by synthesis of N-unsubstituted 5(3)-(polyfluoroalkyl)-1*H*-pyrazole-3(5)-carbaldehydes and their acetals. Further studies on the reactivity of the described 3-(polyfluoroacyl)pyruvaldehydes dimethyl acetals are now in progress.

4. Experimental part

All reagents and solvents are commercially available and were dried and distilled per standard procedures. ^{1}H (400, 500 MHz), ^{19}F (376, 470 MHz) and ^{13}C (100, 125 MHz) NMR spectra were recorded on Bruker DRX-400 and Bruker AVANCE-500 spectrometers with TMS and C_6F_6 as the internal standards. IR spectra were recorded on a Spectrum One FTIR spectrometer (Perkin Elmer) equipped with a diffuse reflectance attachment (DR) and a Nicolet 6700 FTIR spectrometer (Intertech. Corporation) equipped with a horizontal ATR module (ATR). Melting points were determined on a Boetius combined heating stages and were not corrected. Elemental analysis was carried on a Eurovector EA 3000 automated analyzer. Reactions were monitored by thin layer chromatography (TLC) with 0.20 mm Polygram Sil G/ UV_{254} pre-coated silica gel sheets.

*4.1. Reaction of 1,1-dimethoxyacetone **6** with esters of polyfluorocarboxylic acid in the presence of NaOMe.*

To a vigorously stirred suspension of MeONa (generated from NaH (3.6 g, 0.15 mol) and MeOH (4.8 g, 0.15 mol) in anhydrous diethyl ether (150 ml) was added dropwise a mixture of 1,1-dimethoxyacetone (**6**, 11.81 g, 0.1 mol) and an ester of polyfluorocarboxylic acid (0.14 mol) in diethyl ether (100 mL) at 0-4 °C. When addition was completed (2 h), the reaction mixture was stirred for 6 h at the same temperature. Then the solvent was removed under vacuum; a residue was dissolved in a mixture of 100 ml of water with acetic acid (4 g, 0.067 mol). The obtained

solution was slowly added to solution of $Cu(CH_3COO)_2 \cdot H_2O$ (15 g, 0.075 mol) in water (200 mL), and stirred for 2 h. The formed copper complex **7** was filtered off, washed with water, dried on air, and crystallized from an appropriate solvent. Extraction of water solution with ethyl acetate gave an additional amount (1-2 g) of the complex.

*Copper(II) bis(1,1,1-trifluoro-5,5-dimethoxy-2,4-pentanedionate) (**8a**)*. Yield was 16.55 g (67 %). Blue crystalline powder (benzene): mp 176°C (decomp.) IR (DR): 3159, 3013, 2972, 2943, 2840, 1624, 1589, 1534, 1470, 1437, 1346, 1300, 1210, 1197, 1150, 1134, 1114, 1074 cm^{-1}. Anal. Calcd for $C_{14}H_{16}CuF_6O_8 \cdot 0.25H_2O$: C, 34.02; H, 3.36; F, 23.06. Found, %: C, 33.83; H, 3.52; F, 22.98.

*Copper(II) bis(1,1-difluoro-5,5-dimethoxy-2,4-pentanedionate) (**8b**)*. Yield was 17.1 g (74 %). Blue powder (MeOH (aq.): mp 115-120°C (decomp.) IR (DR): 3471, 3139, 2945, 2840, 1608, 1530, 1461, 1360, 1341, 1257, 1189, 1107, 1069 cm^{-1}. Anal. Calcd for $C_{14}H_{18}CuF_4O_8 \cdot 0.5H_2O$: C, 36.33; H, 4.14; F, 16.42. Found, %: C, 36.51; H, 4.28; F, 16.28.

*Copper(II) bis(5,5,6,6-tetrafluoro-1,1-dimethoxy-2,4-hexanedionate) (**8b**)*. Yield was 21.36 g (76 %). Blue-green powder (MeOH (aq.): mp 130-140°C (decomp.) IR (DR): 3463, 3137, 3020, 2969, 2943, 2841, 1611, 1532, 1464, 1352, 1310, 1248, 1193, 1154, 1110, 1070 cm^{-1}. Anal. Calcd for $C_{16}H_{18}CuF_8O_8 \cdot 0.5H_2O$: C, 34.14; H, 3.40; F, 27.00. Found, %: C, 36.34; H, 3.52; F, 26.79.

*4.2. Reaction of 1,1-dimethoxyacetone **6** with esters of polyfluorocarboxylic acid in the presence of LiH.*

To a vigorously stirred suspension of fine powdered LiH (0.42 g, 50.5 mmol) in anhydrous methyl tert-butyl ether (MTBE) (50 mL) was added dropwise a mixture of 1,1-dimethoxyacetone (**6**, 5.9 g, 0.05 mol) and ester of polyfluorocarboxylic acid (0.07 mol) in MTBE (20 mL) at room temperature. Reaction mixture was stirred for 20 h; the solvent was removed, and a residue was maintained on air for 3 days. Then obtained powder was dissolved in THF and filtered off to remove inorganic salts. THF was removed under vacuum and a residue was crystallized from diethyl ether and hexane mixture in freezer. The precipitate was filtered off and dried on air to yield an off white powder.

*Lithium 1,1,1-Trifluoro-5,5-dimethoxy-2,4-pentanedionate (**Li-7a**)*. Yield was 5.72 g (52 %). ^1H NMR (500 MHz, Me_2SO-d^6): δ = 3.27 (s, 6H, $2OCH_3$), 4.41 (s. 1H, CH), 5.68 (s, 1H, =CH-) ppm. ^{19}F NMR (470 MHz, Me_2SO-d^6): δ (C_6F_6) = 87.58 (s, CF_3) ppm. Anal. Calcd for $C_7H_8F_3LiO_4$: C, 38.20; H, 3.66; F, 25.90. Found, %: C, 38.54; H, 3.81; F, 25.63.

*Lithium 1,1-Difluoro-5,5-dimethoxy-2,4-pentanedionate (***Li-7b***)*. Yield was 3.43 g (34 %). ^{1}H NMR (500 MHz, Me_2SO-d^6): δ = 3.25 (s, 6H, $2OCH_3$), 4.36 (s. 1H, CH), 5.59 (s, 1H, =CH-), 5.87 (t, 1H, *J* = 56 Hz, CF_2H) ppm. ^{19}F NMR (470 MHz, Me_2SO-d^6): δ (C_6F_6) = 39.08 (d, *J* = 56 Hz) ppm. Anal. Calcd for $C_7H_9F_2LiO_4$: C, 41.60; H, 4.49; F, 18.80. Found, %: C, 41.47; H, 4.65; F, 18.98.

4.3. Reaction of 1,1-dimethoxyacetone ***6*** *with esters of polyfluorocarboxylic acid in the presence of* CaH_2.

A mixture of 1,1-dimethoxyacetone (**6**, 11.81 g, 0.1 mol) and ester of polyfluorocarboxylic acid (0.12 mol) in MeOH (50 mL) was added dropwise (2h) to a vigorously stirred suspension of CaH_2 (3.15 g, 0.075 mol) in MeOH (100 mL) at r.t. The reaction mixture was stirred for 24 h and acetic acid (6.00 g, 0.1 mol) was added. Then anhydrous $CaCl_2$ (2.22 g, (0.02 mol) and fine powdered $Cu(CH_3COO)_2{\cdot}H_2O$ (15.00 g, 0.075 mol) were added stepwise and obtained mixture was stirred for 3 h. The solvent (~ half in volume) was evaporated, the residue was diluted with water (~ 200 mL), and solid complex **8** was filtered off, washed with water, and dried on air. The complex was dissolved in acetone and filtered to remove a possible copper or calcium carbonates. The solvent was removed and a residue was crystallized as indicated above (Sect. 4.1). The yields are presented in the Table 1.

4.4. Preparation of diketones ***7*** *from their copper complexes (general procedure)*

A suspension of the complex **7** (0.03 mol) in diethyl ether (50 mL) was stirred with disodium EDTA (150 mL of 10 % water solution) until disappearance of green color of the ether layer. Then water layer was separated and washed with diethyl ether (3x20 mL). Combined organic layers were washed with disodium EDTA (3x10 mL of 10 % water solution), brine and dried with Na_2SO_4. The solvent was evaporated at normal pressure and a residue was distilled in vacuum.

*1,1,1-Trifluoro-5,5-dimethoxy-2,4-pentanedione (***7a***)*. Yield was 72 %. Colorless liquid: bp 58-62°C (14 Torr). IR (ATR): 3132, 3004, 2943, 2840, 1665, 1606, 1444, 1280, 1194, 1156, 1098, 1073 cm^{-1}. Enolic form (~ 96 %) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (s, 6H, $2OCH_3$), 4.81 (s. 1H, CH), 6.33 (s, 1H, =CH-), 13.43 (br.s, 1H, OH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ (C_6F_6) = 85.24 (s, CF_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.09 (s, OCH_3), 94.63 (q, *J* = 2 Hz, =CH), 100.46 (s, *C*H$(OMe)_2$), 116.85 (q, *J* = 282 Hz, CF_3), 175.17 (q, *J* = 37 Hz, CF_3*C*(OH)=), 190.24 (s, C=O) ppm. Diketonic form (~ 4 %) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 2H, CH_2), 4.50 (s, 1H, CH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ (C_6F_6) = 82.58 (s, CF_3) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$): δ = 39.45 (s, CH_2), 54.87 (s, OCH_3), 103.72 (s, *C*H(OMe)$_2$), 204.57 (s, C=O) ppm, other signals were not found or overlapped. Anal. Calcd for $C_7H_9F_3O_4$: C, 39.26; H, 4.24; F, 26.62. Found, %: C, 39.48; H, 4.03; F, 26.42.

*1,1-Difluoro-5,5-dimethoxy-2,4-pentanedione (***7b***)*. Yield was 78 %. Colorless liquid: bp 65-66°C (3 Torr). IR (ATR): 3128, 2998, 2941, 2835, 1651, 1602, 1456, 1379, 1223, 1184, 1137 cm^{-1}. Enolic form (~ 95 %) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.43 (s, 6H, 2OCH_3), 4.78 (s. 1H, CH), 5.96 (t, 1H, *J* = 54 Hz), 6.29 (s, 1H, =CH-), 13.98 (br.s, 1H, OH) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ (C_6F_6) = 34.82 (d, *J* = 54 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.13 (s, OCH_3), 94.83 (t, *J* = 3 Hz, =CH), 101.00 (s, *C*H(OMe)$_2$), 109.28 (t, *J* = 247 Hz, CHF_2), 180.02 (t, *J* = 26 Hz, HCF_2*C*(OH)=), 191.32 (s, C=O) ppm. Diketonic form (~ 5 %) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (t, 2H, *J* = 1 Hz), 4.50 (s, 1H, CH), 5.73 (t, 1H, *J* = 54 Hz) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ (C_6F_6) = 33.70 (dt, *J* = 54, 1 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 46.17 (s, CH_2), 55.17 (s, OCH_3), 101.00 (s, *C*H(OMe)$_2$), 109.40 (t, *J* = 252 Hz, CHF_2), 197.68 (s, C=O) ppm, other signals were not found or overlapped. Anal. Calcd for $C_7H_{10}F_2O_4$: 42.86; H, 5.14; F, 19.37. Found, %: C, 43.06; H, 5.22; F, 19.14.

*5,5,6,6-Tetrafluoro-1,1-dimethoxy-2,4-hexanedione (***7c***)*. Yield was 75 %. Colorless liquid: bp 73-75°C (3 Torr). IR (ATR): 3130, 3007, 2966, 2944, 2840, 1657, 1605, 1446, 1256, 1109, 1075 cm^{-1}. Enolic form (~ 100 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 6H, 2OCH_3), 5.61 (s. 1H, CH), 6.13 (tt, 1H, *J* = 53, 4 Hz), 6.58 (s, 1H, =CH-), 11.12 (br.s, 1H, OH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ (C_6F_6) = 25.57 (dt, 2F, *J* = 54, 6 Hz, CF_2H), 48.76 (m, 2F, CF_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.10 (s, OCH_3), 95.85 (t, *J* = 3 Hz, CH=), 100.63 (s, *C*H(OMe)$_2$), 108.88 (tt, *J* = 252 Hz, HCF_2), 109.56 (tt, *J* = 257, 28 Hz, CF_2), 179.08 (t, *J* = 28 Hz, CF_2*C*(OH)=), 190.18 (s, C=O) ppm. Anal. Calcd for $C_8H_{10}F_4O_4$: C, 39.03; H, 4.09; F, 30.87. Found, %: C, C 38.92, H 4.15, F 31.04.

4.5. Reaction of dimethyl acetals of 3-(polyfluoroacyl)-pyruvaldehydes ***7*** *with hydrazine hydrate (general procedure)*

A mixture of **7** (10 mmol) and $NH_2NH_2 \cdot H_2O$ (0.50 g, 10 mmol) was refluxed in MeOH (20 ml) for appropriate time (Table 2), the solvent was removed, and a residue was maintained under vacuum for 1 h.

*3-(Dimethoxymethyl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol (***11a***)*

(*as a 95:5 mixture with 3(5)-(dimethoxymethyl)-5(3)-(trifluoromethyl)-1H-pyrazole (****10a****)* was obtained from compound **7a** in 95 % yield as a viscous-crystalline mass. IR (DR): 3442, 3335, 3286, 2987, 2940, 2893, 2837, 1618, 1443, 1311, 1253, 1154, 1052 cm^{-1}. ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 2.92 (d, 1H, *J* = 18 Hz, C*H*H), 3.17 (d, 1H, *J* = 18 Hz, CH*H*), 3.40 (s, 3H, OMe), 3.43 (s, 3H, OMe), 4.33 (br.s, 1H, NH), 4.96 (s, 1H, C*H*$(OMe)_2$), 6.23 (s, 1H, OH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ (C_6F_6) = 80.66 (s, CF_3) ppm.

*5(3)-(Difluoromethyl)-3(5)-(dimethoxymethyl)-1H-pyrazole (***10b***)* was obtained from compound **6b** in 91 % yield as an yellowish viscous oil. IR (ATR): 3210, 3149, 3005, 2974, 2943, 2837, 1561, 1488, 1468, 1350, 1193, 1150, 1108, 1060, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.36 (s, 6H, 2OMe), 5.60 (s, 1H, C*H*$(OMe)_2$), 6.53 (s, 1H, CHpz), 6.74 (t, 1H, *J* = 55 Hz, HCF_2),11.25 (br.s, 1H, NH) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ (C_6F_6) = 50.04 (d, *J* = 55 Hz, HCF_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.63 (s, OCH_3), 96.85 (s, C*H*$(OMe)_2$), 101.58 (br.s., C-4pz), 111.02 (t, *J* = 234 Hz, HCF_2), 141.88 (s, C-5pz), 147.52 (broad m, C-3pz) ppm. Anal. Calcd for $C_7H_{10}N_2F_2O_4$: C, 43.75; H, 5.25; N, 14.58; F, 19.77. Found, %: C, 43.63; H, 5.24; N, 14.72; F, 19.59.

*3-(Dimethoxymethyl)-5-(1,1,2,2-tetrafluoroethyl)-4,5-dihydro-1H-pyrazol-5-ol (***11c***)*
(as a 92:8 mixture with 3(5)-(dimethoxymethyl)-5(3)-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole (**10c***)* was obtained from compound **7c** in nearly 100 % yield as a viscous-crystalline mass. IR (DR): 3451, 3330, 2984, 2840, 2875, 2837, 1611, 1443, 1425, 1206, 1119, 1060, 1005 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.86 (d, 1H, *J* = 18.8 Hz, C*H*H), 3.19 (d, 1H, *J* = 18.8 Hz, CH*H*), 3.39 (s, 3H, OMe), 3.43 (s, 3H, OMe), 5.32 (br.s, 1H, NH), 4.94 (s, 1H, C*H*$(OMe)_2$), 6.13 (tdd, 1H, *J* = 53, 8, 4 Hz), 6.41 (s, 1H, OH) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ (C_6F_6) = 21.77 (dddd, 1F, *J* = 304, 53, 12, 5 Hz, CF_2CF*F*H), 24.59 (ddd, 1F, *J* = 304, 53, 13 Hz, CF_2C*F*FH), 31.26 (ddd, 1F, *J* = 268, 13, 4 Hz, CF*F*CF_2H), 34.30 (dm, 1F, *J* = 268 Hz, C*F*FCF_2H) ppm.

4.6. Preparation of pyrazoles ***10a*** *and* ***10c***

Pyrazoline and pyrazole mixture obtained from diketones **7a** or **7c** as described above (Sect. 4.5) was refluxed with CaH_2 (1.20 g, 30 mol) in MeOH (20 ml) for 10-12 h. Then a solid was filtered off and washed with MeOH. The solvent was evaporated; a residue was dissolved in Et_2O and passed through a silica pad (2 cm). The solvent was removed and the residue was maintained under vacuum for 1 h.

*3(5)-(Dimethoxymethyl)-5(3)-(trifluoromethyl)-1H-pyrazole (***10a***)*. Yield was 86 % yield (starting from diketone **7a**). Yellowish viscous oil: bp 120-130°C (1.5 Torr). IR (ATR): 3205, 3149, 3002, 2945, 2906, 2839, 1572, 1497, 1468, 1335, 1243, 1186, 1135, 1081, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.36 (s, 6H, 2OMe), 5.60 (s, 1H, C*H*$(OMe)_2$), 6.56 (s, 1H, CHpz), 10.88 (br.s, 1H, NH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ (C_6F_6) = 99.50 (s, CF3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.64 (s, OCH_3), 96.55 (s, C*H*$(OMe)_2$), 102.46 (q, *J* = 2 Hz, C-

4pz), 121.09 (q, *J* = 269 Hz, CF_3), 141.95 (s, C-5pz), 143.42 (q, *J* = 38 Hz, C-3pz) ppm. Anal. Calcd for $C_7H_9F_3N_2O_2$: C, 40.01; H, 4.32; N, 13.33; F, 27.12. Found: C, 39.82; H, 4.51; N, 13.29; F, 27.11.

*3(5)-(Dimethoxymethyl)-5(3)-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole (***10c***)* was obtained as yellowish viscous oil in 89 % yield (starting from diketone **7c**). IR (ATR): 3222, 3153, 3000, 2946, 2913, 2839, 1568, 1467, 1335, 1234, 1195, 1113, 1062 cm-1. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.36 (s, 6H, 2OMe), 5.60 (s, 1H, C*H*$(OMe)_2$), 6.13 (tt, 1H, *J* = 53, 4 Hz, HCF_2CF_2), 6.58 (s, 1H, CHpz), 11.11 (br.s, 1H, NH) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ (C_6F_6) = 48.73 (br. s, CF_2), 25.53 (d, *J* = 54 Hz, HCF_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.68 (s, OCH_3), 96.69 (s, C*H*$(OMe)_2$), 103.34 (br. s., C-4pz), 109.86 (tt, *J* = 251, 38 Hz, CF_2*CF_2H*), 112.42 (tt, *J* = 245, 28 Hz, *CF_2*CF_2H), 141.76 (s, C-5pz), 144.04 (broad m, C-3pz) ppm. Anal. Calcd for $C_8H_{10}F_4N_2O_2$: C, 39.68; H, 4.16; N, 11.57; F, 31.38. Found: C, 39.41; H, 3.94; N, 11.73; F, 31.14.

4.7. Preparation of pyrazolaldehydes ***12***

A mixture of pyrazole **10** (5 mmol) and water (20-30 ml) was heated up to 70-80 °C; one drop of hydrochloric acid was added and reaction mixture was stirred until cooling. A precipitate was filtered off, washed with water and dried on air.

*5-(Trifluoromethyl)-1H-pyrazole-3-carbaldehyde (***12a***)*. Yield was 95 %. White powder: mp 160-170°C (incompletely). IR (DR): 3155, 2874, 2744, 1607, 1552, 1496, 1306, 1258, 1189, 1134, 1102, 1070 cm^{-1}. ^{1}H NMR (500 MHz, Me_2SO-d^6): δ = 7.49 (s, 1H, C-4), 9.89 (s, 1H, C*H*O), 14.93 (broad s, 1H, NH) ppm. ^{19}F NMR (470 MHz, Me_2SO-d^6): δ (C_6F_6) = 102 (broad s.) ppm. Mixture of diastereomeric *2,7-bis(trifluoromethyl)-4H,9H-dipyrazolo[1,5-a:1,5-d]pyrazine-4,9-diols (***13a***)* (Ratio 70:30). Major diastereomer: ^{1}H NMR (500 MHz, Me_2SO-d^6): δ = 6.73 (d, 1H, *J* = 7 Hz, CH), 7.04 (s, 1H, =CH-), 8.40 (d, 1H, *J* = 7 Hz, OH) ppm. ^{19}F NMR (470 MHz, DMSO-d^6): δ (C_6F_6) = 101.81 (s, CF_3) ppm. Minor diastereomer: ^{1}H NMR (500 MHz, Me_2SO-d^6): δ = 6.90 (d, 1H, *J* = 8 Hz, CH), 7.04 (s, 1H, =CH-), 8.33 (d, 1H, *J* = 8 Hz, OH) ppm.

*5-(Difluoromethyl)-1H-pyrazole-3-carbaldehyde (***12b***)*. Yield was 90 %. White powder: mp 155-170°C (incompletely). IR (DR): 3140, 2863, 2752, 1567, 1491, 1314, 1231, 1173, 1115, 1075 cm^{-1}. ^{1}H NMR (400 MHz, Me_2SO-d^6): δ = 7.14 (t, 1H, *J* = 54 Hz, HCF_2), 7.23 (s, 1H, C-4), 9.88 (s, 1H, C*H*O), 14.55 (broad s, 1H, NH) ppm. ^{19}F NMR (376 MHz, Me_2SO-d^6): δ (C_6F_6) = 51.00 (br. dm, *J* = 54 Hz, HCF_2) ppm. Mixture of diastereomeric *2,7-bis(difluoromethyl)-4H,9H-*

*dipyrazolo[1,5-a:1,5-d]pyrazine-4,9-diols (***13b***)* (Ratio 50:50). The first diastereomer: ^{1}H NMR (500 MHz, Me_2SO-d^6): δ = 6.78 (br. s, 1H, CH), 7.09 (t, 1H, *J* = 54 Hz, HCF_2), 7.77 (s, 1H, =CH-), 8.07 (br.s, 1H, OH). The second diastereomer: ^{1}H NMR (500 MHz, Me_2SO-d^6): δ = 6.80 (br.s, 1H, CH), 7.01 (t, 1H, *J* = 55 Hz, HCF_2), 7.77 (s, 1H, =CH-), 8.09 (d, 1H, J = 6Hz, OH) ppm. Signals in ^{19}F NMR spectra are overlapped.

*5-(1,1,2,2-tetrafluoroethyl)-1H-pyrazole-3-carbaldehyde (***12c***)*. Yield was 93 %. White powder: mp 175-180°C (incompletely). IR (DR): 3160, 2871, 2743, 1548, 1498, 1306, 1222, 1169, 1109, 1063 cm^{-1}. ^{1}H NMR (500 MHz, Me_2SO-d^6) δ = 6.86 (tt, 1H, *J* = 52, 5 Hz, CF_2CF_2H), 7.38 (s, 1H, CH-4), 9.88 (s, 1H, C*H*=O), 14.84 (broad s, 1H, NH) ppm. ^{19}F NMR (376 MHz, Me_2SO-d^6) δ (C_6F_6) = 25.49 (br. d, 2F, *J* = ~51 Hz, HCF_2), 50.51-50.79 (m, 2F, CF_2) ppm. Mixture of diastereomeric *2,7-bis(1,1,2,2-tetrafluoroethyl)-4H,9H-dipyrazolo[1,5-a:1,5-d]pyrazine-4,9-diols (***13c***)* (Ratio 63:37). Major diastereomer: ^{1}H NMR (500 MHz, Me_2SO-d^6): δ = 6.90 (br. s, 1H, =CH-), 8.26 (d, 1H, *J* = 7 Hz, OH) ppm, other signals are overlapped. ^{19}F NMR (470 MHz, Me_2SO-d^6): δ (C_6F_6) = 25.78 (dt, 2F, *J* = 52, 8 Hz, HCF_2), 49.50-51.39 (AB-syst m, 2F, *J* = 280 Hz, CF_2) ppm. Minor diastereomer ^{1}H NMR (500 MHz, Me_2SO-d^6): δ = 6.90 (br. s, 1H, =CH-), 8.24 (d, 1H, *J* = 9 Hz, OH) ppm, other signals are overlapped. ^{19}F NMR (470 MHz, Me_2SO-d^6): δ (C_6F_6) = 25.73 (ddd, *J* = 52, 7, 8 Hz, HCF_2) ppm, other signals are overlapped.

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