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Graphical abstract

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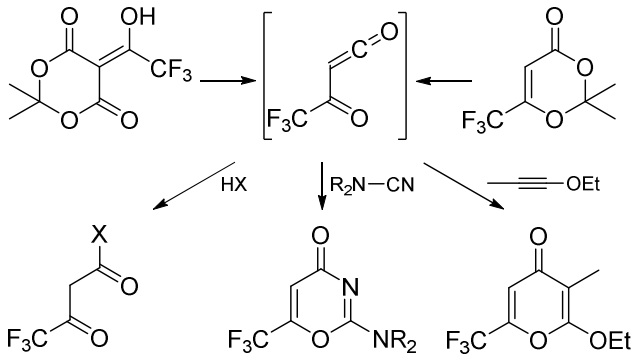

Preparative synthesis of 2,2-dimethyl-5-(trifluoroacetyl)-1,3-dioxane-4,6-dione (2-trifluoroacetyl Meldrum's acid) and 2,2-dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-one and their synthetic usefulness as (trifluoroacetyl)ketene precursors

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A B S T R A C T

A simple and reliable method for the preparation of 2,2-dimethyl-5-(trifluoroacetyl)-1,3-dioxane-4,6-dione and 2,2-dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-one on a multigram scale was developed. These (trifluoroacetyl)ketene precursors were used in the hetero-Diels-Alder reaction with dialkylcyanamides and 1-ethoxyprop-1-yne, as well as in some reactions with nucleophiles.

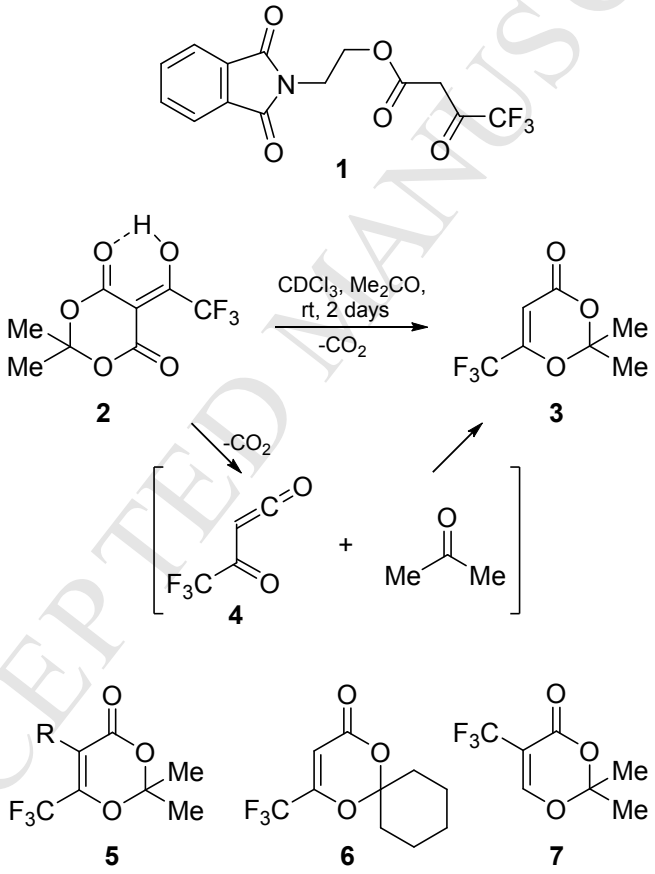
Keywords: Fluorinated compounds, (Trifluoroacetyl)ketene, Meldrum's acid, Hetero-Diels-Alder reaction, Trifluoroacetoacetylation, Preparative method

1. Introduction

For other project, ongoing in our laboratory, we required a sample of trifluoroacetoacetylated *N*-(2-hydroxyethyl)phthalimide **1**. A literature survey showed that this compound can be prepared by alcoholysis of 2,2-dimethyl-5-(trifluoroacetyl)-1,3-dioxane-4,6-dione (2-trifluoroacetylated Meldrum's acid **2**) described by Yamamoto and coworkers in 1997,[1] which reacted with *tert*-butyl alcohol in chloroform at room temperature, yielding 80% of *tert*-butyl trifluoroacetoacetate. It was also shown in the same work that maintaining the acid **2** in chloroform solution in the presence of acetone for 2 days gave a moderate yield of 2,2-dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-one

3, which properties have not been studied. It was proposed by the authors that the transformation **2** → **3** proceeds via the formation of (trifluoroacetyl)ketene **4**, followed by [4+2] cycloaddition at the carbonyl group of acetone[1] (Scheme 1).

The dioxin **3** was first obtained in 1995 by trifluoroacetylation of *in situ* generated ketene with trifluoroacetic anhydride in the presence of acetone, but the yield was merely 8%.[2] Among its closest analogs, syntheses of 5-substituted 2,2-dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-ones **5** have been reported, using the respective ketenes, trifluoroacetic anhydride, and acetone;[2,3] 6-(trifluoromethyl)-4-oxo-1,3-dioxin-2-spirocyclohexane **6** was obtained from 4,4,4-trifluoro-3-oxobutanoic acid, cyclohexanone, and acetic anhydride in the presence of sulfuric acid,[4] and 2,2-dimethyl-5-(trifluoromethyl)-4*H*-1,3-dioxin-4-one **7** was also obtained from 2,2-dimethyl-5-iodo-4*H*-1,3-dioxin-4-one, trifluoromethyliodide, and copper powder in HMPA as a solvent[5] (Scheme 1).

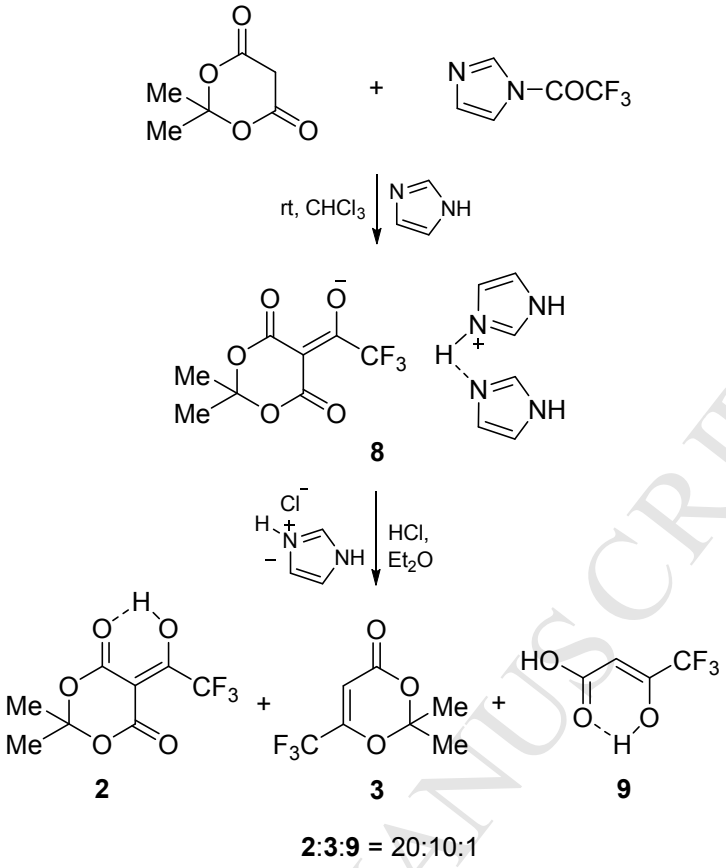


Scheme 1. Target 1,3-ketoester **1** and known fluorinated-4*H*-1,3-dioxin-4-ones.

2. Results and discusion

Despite the obvious synthetic importance of compounds **2** and **3**, which can be considered as a source of the highly reactive (trifluoroacetyl)ketene **4**, the methods suitable for their preparation

have been described only in one brief report,[1] without information about yields, spectral and analytical data. In the work[1] the authors propose a method for the synthesis of 2-trifluoroacetylated Meldrum's acid **2** by treatment of Meldrum's acid with *N*-(trifluoroacetyl)imidazole in the presence of imidazole in chloroform at room temperature, followed by washing the reaction mixture with 10% aqueous HCl. Even though an analogous approach was also used for the trifluoroacetylation of 1,3-cyclohexanediones,[6] we failed to reproduce the synthesis of acid **2** under those conditions despite numerous attempts. The presence of imidazolium salt **8** of the desired tricarbonyl compound in reaction mixture was detected in all cases by ^{1}H and ^{19}F NMR spectroscopy, but it decomposed to 4,4,4-trifluoro-3-oxobutanoic acid **9**, trifluoroacetic acid, and the starting Meldrum's acid when 3–10% aqueous HCl or 5% aqueous citric acid was added for the removal of imidazole, while only trace amounts of the target compound **2** were observed. Only the use of HCl in diethyl ether (saturated solution was diluted with equal amount of diethyl ether) allowed to obtain the trifluoroacetylated acid **2** in mixture with dioxin **3** and trifluoroacetoacetic acid **9** (**2**:**3**:**9** = 20:10:1). Pure compound **2** could be isolated in 24% yield by washing solid imidazolium chloride with chloroform, followed by removal of solvent under vacuum without heating (the conversion of acid **2** to dioxin **3** was accelerated by heating). It should be noted that the use of saturated HCl solution in diethyl ether immediately converted the salt **8** to dioxin **3**. The attempt to synthesize compound **2** by reaction of Meldrum's acid with trifluoroacetic anhydride in the presence of Et_3N and DMAP was not successful (Scheme 2). Tautomeric features of compounds **2** and **9** are discussed in Supporting Information.



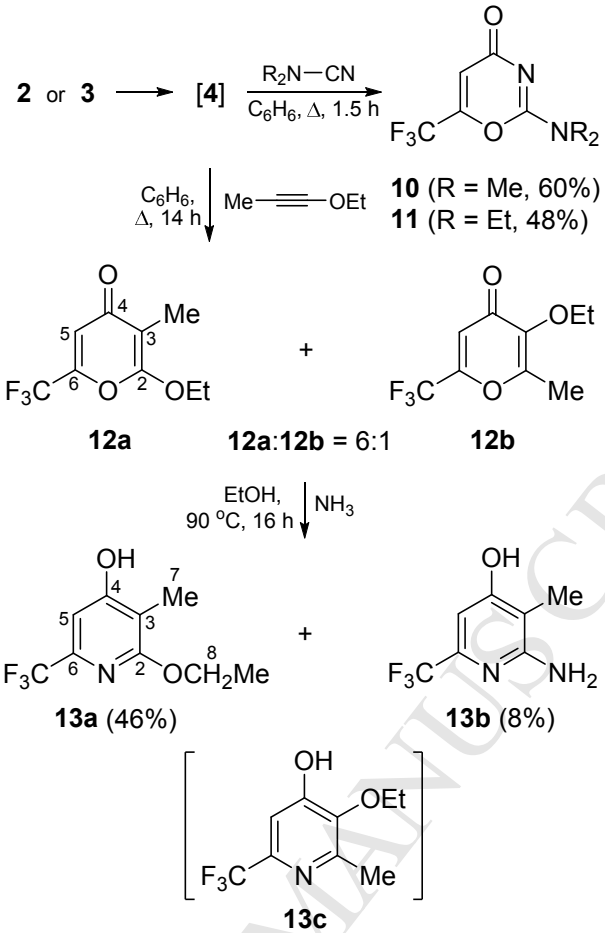
Scheme 2. Synthesis of 2-trifluoroacetylated Meldrum's acid **2**.

As mentioned above, an important reactivity feature of dioxane **2** was its spontaneous decarboxylation to dioxin **3**. Indeed, we found that this transformation occurred not only in $CDCl_3$ solution at room temperature (**2**:**3**:**9** = 91:7:2 after 2 h, 52:44:4 after 22 h, 6:63:31 after 100 h), but also in solid state at –30 °C (**2**:**3**:**9** = 90:6:4 after 10 days and 56:33:11 after 4 months). The transformation **2** → **3** in $CHCl_3$ solution in the presence of acetone was complete in 16 h and provided dioxin **3** in quantitative yield according to NMR. The dioxin **3** has been characterized in the literature[2] as colorless oil, unstable at room temperature and decomposing completely in 24 h. According to our data, the decomposition rate for this compound in closed vessel at ~20 °C to the acid **9** and 1,1,1-trifluoroacetone was fairly slow (**3**:**9**:trifluoroacetone = 85:7:8 after 24 h both in $CDCl_3$ and in solid state), and it could be stored for a few months at –30 °C. When a drop of water was added to an NMR sample of compound **3** in $CDCl_3$, we observed its complete conversion to the acid **9** within 7 days, accompanied by partial decarboxylation to 1,1,1-trifluoroacetone.

Taking into account the fact that compound **2** represents a masked form of (trifluoroacetyl)ketene **4**,[1] it is logical to propose that dioxin **3** can also serve as its precursor. We compared the reactivity of precursors **2** and **3** in hetero-Diels-Alder reactions with

dialkylcyanamides and 1-ethoxyprop-1-yne, and established that both compounds **2** and **3** gave the same products **10**–**12**, but the reactions with dioxin **3** always occurred faster and gave higher yields of products. For example, refluxing the compound **3** with dimethyl- and diethylcyanamides in benzene for 1.5 h gave 2-dialkylamino-6-trifluoromethyl-1,3-oxazin-4-ones **10** and **11** in 60% and 48% yields, respectively, while the yield of product **10** from dioxane **2** was merely 19% after refluxing for 20 h. Based on these data, we can propose that the reaction of dioxane **2** with dienophiles involves the formation of compound **3** as intermediate, according to the route **2** → **3** → **4** (Scheme 3).

The reaction of compounds **2** and **3** with 1-ethoxyprop-1-yne was observed to produce a mixture of regioisomeric 4-pyrones **12a** and **12b** in 6:1 ratio (again, these products were obtained in better yields and purity from the dioxin **3**, than from dioxane **2**). The regioisomers **12a**,**b** could be separated chromatographically, and pure samples were prepared for analysis by using preparative TLC. For the purpose of structure determination, the obtained mixture was heated with ammonia in ethanol for 16 h, leading to the pyridines **13a** and **13b** as products of 4-pyrone **12a** transformation[7] in 46% and 8% yields, respectively, after isolation by column chromatography. The regiochemistry of pyridine **13a** was established by an ^{1}H–^{13}C HMBC 2D NMR experiment, with the most informative cross peaks of H-5/C-3, H-5/C-7, H-7/C-3, H-7/C-2, H-7/C-4 and H-8/C-2, allowing to exclude the isomeric structure **13c** from consideration. It should be noted that pyridine **13c** was not detected even in trace amounts, because the minor 4-pyrone **12b** did not react with ammonia and was recovered in unchanged form. This fact indicates that the initial attack by ammonia molecule on pyrone **12a** occurred at position 2, which was deactivated by the presence of methyl group in pyrone **12b**. In order to elucidate the mechanism for the formation of pyridine **13b**, we treated compound **13a** with excess of 25% aqueous ammonia and found that the reaction did not proceed upon refluxing in 1,4-dioxane and even with heating in autoclave (1,4-dioxane, 140°C, 16 h), and pyridine **13a** was completely recovered. Obviously, the substitution of ethoxy group with amino group occurred prior to the formation of pyridine ring.

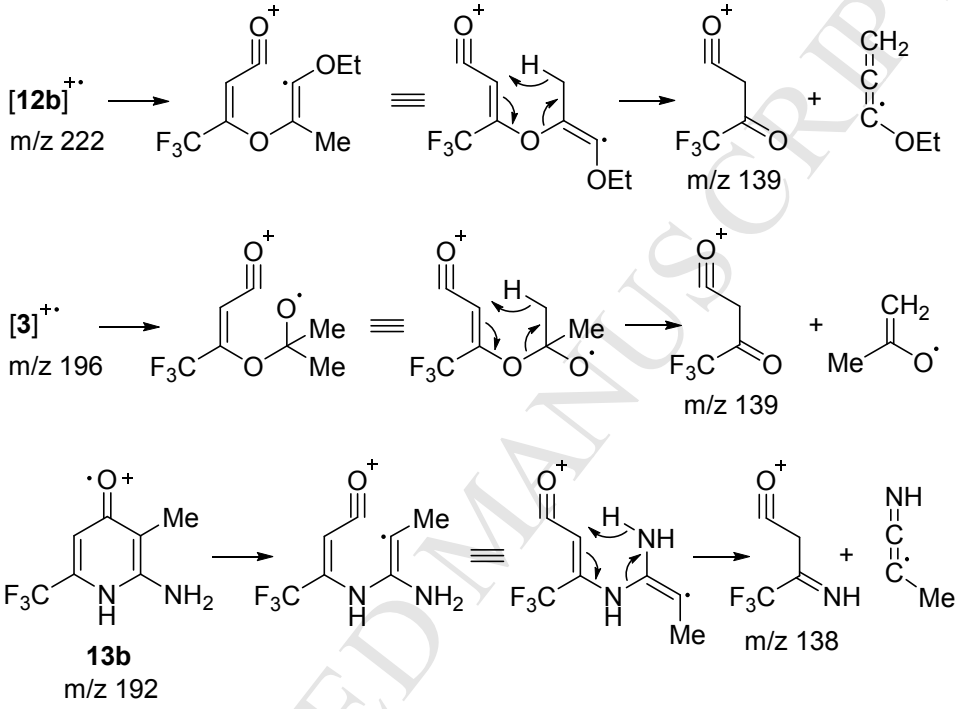


Scheme 3. Hetero-Diels-Alder reactions of **2** and **3**.

In the ^{1}H NMR spectrum of pyridine **13a** taken in $CDCl_3$ the signal of H-5 proton at δ 6.75 ppm was found, instead of the expected δ 7.10–7.28 ppm range for a regioisomer of type **13c**.[8] Besides that, ^{13}C NMR spectrum of this compound showed three downfield signals belonging to carbon nuclei bonded to heteroatoms, while 4 such signals should be expected for its isomer **13c**.[8] The most downfield ^{13}C NMR signals of pyridines **13a** and **13b** were singlets at δ 163.6 and 161.7 ppm, respectively, in agreement with the structure of 4-pyridinol (the 4-pyridone carbonyl signal is usually above 170 ppm[8a]). Thus, the main product of (trifluoroacetyl)ketene **4** reaction with 1-ethoxyprop-1-yne had the structure of 2-ethoxy-4-pyrone **12a**, also in agreement with literature data[9] describing the transformation of related non-fluorinated 4-pyrones to 4-hydroxypyridines.

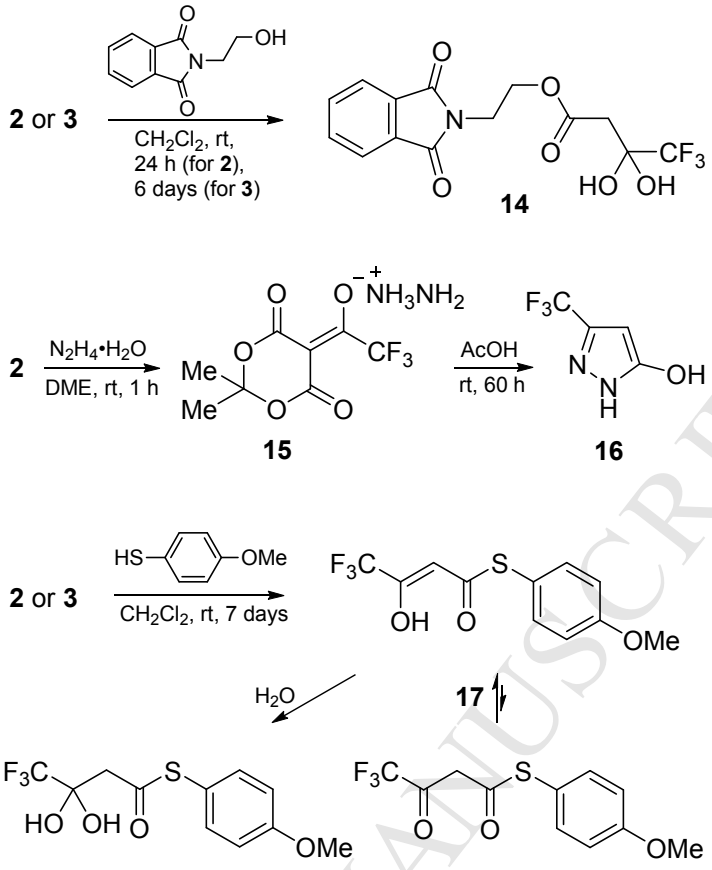
Mass spectra (EI) of compounds **2** and **3** displayed the expected ion with *m/z* 138, due to (trifluoroacetyl)ketene radical cation generated by fragmentation through the retro-Diels-Alder mechanism (its molecular formula $C_4HF_3O_2$ was confirmed by HRMS). However, this signal was totally absent in the mass spectrum of compound **12b**, while another fragment with *m/z* 139 was observed instead (the same peak, although much weaker, was also present in the mass spectrum of dioxin **3**). The presence of this ion can be explained by ring opening via α-cleavage at the carbonyl

group and hydrogen atom transfer through a 6-membered transition state after the appropriate conformational change (Scheme 4). Remarkably, the mass spectra of pyridines **13a**,**b** also did not show the ion with *m/z* 137 from decomposition by retro-Diels-Alder mechanism. Instead, another strong peak with *m/z* 138 was observed, with the molecular formula ($C_4H_3F_3NO$) confirmed by HRMS. The formation of this ion can be explained analogously. Thus, the fragmentation pathways proposed in Scheme 4 appear to be preferred when compared to the expected retro-Diels-Alder reaction, and significant amounts of 4-pyridone tautomer of **13** is present in the gas phase.



Scheme 4. Fragmentation pathways in mass spectra (EI) of compounds **3**, **12b** and **13b**.

With a reliable method for the synthesis of dioxane **2** in hand, we studied its reaction with *N*-(2-hydroxyethyl)phthalimide. As expected, the target compound **1** was obtained in 35% yield as a stable covalent hydrate **14**, when reacted in dichloromethane at room temperature. The use of dioxin **3** in this reaction allowed to increase the yield of product **14** to 43%. In contrast to the thoroughly studied acetoacetylation reaction using 2,6,6-trimethyl-1,3-dioxin-4-one,[10] this is the first known example when alcohols were trifluoroacetoacetylated by the action of 2,2-dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-one **3**. The reaction of hydrazine hydrate with compound **2** in dimethoxyethane at room temperature began with the formation of salt **15**, which was transformed in acetic acid to the previously known[11] pyrazole **16** in 21% yield. This transformation can also be interpreted as trifluoroacetoacetylation of hydrazine followed by intramolecular cyclization at the trifluoroacetyl group (Scheme 5).



Scheme 5. Synthesis of compounds **14**, **16** and **17**.

We further studied the thiophenol trifluoroacetoacetylation, aiming the preparation of a little-known trifluoromethylated β-ketothioesters. Treatment of compounds **2** or **3** with 4-methoxythiophenol in dichloromethane provided the thioester **17** in 20% and 49% yields, respectively (Scheme 5). In the ^{1}H and ^{19}F NMR spectra of this product taken in $CDCl_3$ three sets of signals in 86:13:1 ratio were found, corresponding to hydrate (CH_2 singlet at 3.09 ppm, broadened singlet of two OH groups at 4.8 ppm, CF_3 at –87.2 ppm), enol form (OH at 12.2 ppm, =CH at 6.02 ppm, CF_3 at –74.8 ppm), and keto form (CH_2 singlet at 4.01 ppm, CF_3 at –79.2 ppm), respectively. It should be noted that (trifluoromethyl)ketones are well known to exist as *gem*-diols[12] due to the electron-withdrawing effect of the CF_3 group.

3. Conclusion

We have developed reliable procedures for the preparation of trifluoroacetylated Meldrum's acid and 2,2-dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-one on a multigram scale, enabling their complete characterization. These valuable CF_3-containing building blocks were demonstrated to serve a source of the highly reactive (trifluoroacetyl)ketene. As trifluoroacetoacetylating agent and

diene component in hetero-Diels-Alder reaction, 2,2-dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-one is considerably superior to its precursor **2**. The reported compounds are of particular synthetic interest, demonstrated in reactions with a range of nucleophiles and dienophiles.

4. Experimental section

4.1. General

NMR spectra were recorded on Bruker WB-360 (^{1}H – 360.2 MHz), Bruker DRX-400 (^{13}C – 100.6 MHz), Bruker DPX-200 (^{1}H – 200.1 MHz, ^{13}C – 50.3 MHz and ^{19}F – 188.3 MHz) and Bruker AC-200 (^{1}H – 200.1 MHz and ^{19}F – 188.1 MHz) spectrometers at room temperature. Chemicals shifts are reported relative Me_4Si (^{1}H and ^{13}C: δ = 0.00 ppm) and $CFCl_3$ (^{19}F: δ = 0.00 ppm). As internal standards the residual solvent proton signals (2.50 ppm for DMSO-d_6, 7.25 ppm for $CDCl_3$, 1.94 ppm for CD_3CN and 7.15 ppm for C_6D_6 solutions), $CDCl_3$ and DMSO-d_6 signals (^{13}C: 77.0 and 39.4 ppm, respectively) and C_6F_6 signal (^{19}F: –162.2 ppm) were used. Assignment of signals in ^{13}C NMR spectra based on carbon-fluorine couplings, the results of DEPT 135 (for compounds **3**, **13**, **14** and **17**) and 2D ^{1}H–^{13}C HMBC experiments (**13a**) measured on Bruker DPX-200 spectrometer. The mass spectra were recorded on a Finnigan MAT 95 double-focusing mass-spectrometer (EI, 70 eV, direct inlet). High-resolution measurements (HRMS) were performed on the same instrument using the peak matching method at a resolution of 10000 (10% valley). Reagents were purchased and were used as received without further purification. The reactions were carried out in oven-dried glassware under static N_2 atmosphere. The solvents were dried using standard procedures: CH_2Cl_2 and $CHCl_3$ from P_2O_5, benzene, THF, DME and diethyl ether from sodium/benzophenone ketyl). Silica gel 0.060–0.200 mm, 60 Å (Acros Organics) was used for column chromatography.

4.2. 1-Ethoxy-1-propyne

This compound was prepared using procedure published earlier.[13] ^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H, Me, *J* = 7.1 Hz), 1.72 (s, Me), 4.00 (q, 2H, CH_2, *J* = 7.1 Hz). The product contained ca. 3 mol% of 1-ethoxyallene [^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H, Me, *J* = 6.7 Hz), 3.61 (q, 2H, CH_2, *J* = 6.7 Hz), 5.41 (d, 2H, H-1, *J* = 5.3 Hz), 6.70 (dd, 1H, H-1, *J* = 5.3, 5.1 Hz)] as admixture.

4.3. *N*-(Trifluoroacetyl)imidazole

This compound was prepared by modified procedure published earlier.[14] To a pre-cooled (5 °C) and well-stirred absolute THF (100 mL) trifluoroacetic anhydride (80 g, 380 mmol) was added carefully. The solution formed was added to a pre-cooled (5 °C) and well-stirred solution of imidazole (51.6 g, 759 mmol) in absolute THF (240 mL) carefully. The mixture was stirred for 1 h at ambient temperature, and left at 0 °C overnight. The solid precipitate was filtered off and washed with diethyl ether (25 mL). The filtrate was concentrated *in vacuo* without heating and the residue was distilled to provide the desired product. Yield 49 g (79%), hydrolytically sensitive colorless liquid, very moisture sensitive, bp 73–75 °C (100 Torr) (lit.[14] 45–46 °C (14 Torr)). ^{1}H NMR ($CDCl_3$) δ: 7.21 (dd, 1H, H-4, J = 1.8, 0.8 Hz), 7.55 (m, 1H, H-5), 8.24 (s, 1H, H-2). ^{19}F NMR ($CDCl_3$) δ: –71.3 (s, CF_3). The parameters in agreement with published data.[15]

4.4. 2,2-Dimethyl-5-(trifluoroacetyl)-1,3-dioxan-4,6-dione (2-trifluoroacetyl Meldrum's acid) (2)

4.4.1. To a solution of imidazole (7.15 g, 105 mmol) in anhydrous $CHCl_3$ (180 mL) 2,2-dimethyl-1,3-dioxan-4,6-dione (15.1 g, 105 mmol) was added at room temperature. To the mixture a solution of *N*-(trifluoroacetyl)imidazole (18.1 g, 105 mmol) in $CHCl_3$ (180 mL) was added carefully under stirring within 30 min. The solvent from the yellowish solution formed (contains salt **8** as the only fluorinated compound as revealed by ^{19}F NMR) was removed *in vacuo* without heating. The yellow oily residue [bis-imidazolium 2,2-dimethyl-5-(trifluoroacetyl)-1,3-dioxan-4,6-dionate **8**: yield 100%, yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.71 (s, 6H, 2 Me), 7.23 (s, 4H, imidazolium), 8.11 (s, 2H, imidazolium), 14.08 (s, 3H, 3 NH); ^{19}F NMR ($CDCl_3$) δ: –73.0 (s, CF_3)] was dissolved in $CHCl_3$ (50 mL), cooled down to –30 °C and half-saturated HCl solution in diethyl ether (150 mL, prepared by dilution of saturated solution with diethyl ether 1:1) was added under vigorous stirring. The mixture was stirred for 15 min at ambient temperature, and the precipitate of imidazolium chloride was filtered off under N_2 atmosphere. The volatiles from the filtrate were removed *in vacuo* without heating to provide the mixture of dioxane **2**, dioxine **3**, and ketoacid **9** (20:10:1 as estimated by ^{1}H and ^{19}F NMR spectra) as a yellow waxy solid (10 g). The precipitate of imidazolium chloride above was washed with $CHCl_3$ (2 x 100 mL), the solvent was removed *in vacuo* without heating to provide pure **2** in yield 6.0 g (24%), white solid, mp 87–88 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ: 1.79 (s, 6H, 2 Me), 16.1 (br. s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ: –70.9 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 26.8, 91.9, 107.5, 117.1 (q, J = 280.6 Hz, CF_3), 155.6, 172.3, 175.2 (q, J = 39.9 Hz, $\underline{C}OCF_3$). MS (27 °C), m/z (I_{rel} (%)): 240 $[M]^+$ (3), 225 (18), 138 (3), 69 (32), 58 (31), 43 (100). HRMS: m/z $[M]^+$ found: 240.0242. Calc. for $C_8H_7F_3O_5$: 240.0240; 0.59 ppm. HRMS: m/z 138 found: 137.9926. Calc. for $C_4HF_3O_2$: 137.9923; 1.77 ppm.

*4.4.2. 4,4,4-Trifluoro-3-oxobutanoic acid (**9**).* The precipitate of imidazolium chloride above was washed with anhydrous diethyl ether (2 x 50 mL), the solvent was removed *in vacuo* without heating to leave crude ketoacid **9**. Yield 0.5 g (3%), yellowish solid, mp 54–55 °C. Enol (**C**+**D**), keto (**E**) and hydrate (**F**) forms in 76:12:12 ratio were detected using ^{1}H and ^{19}F NMR for this sample of acid **9** dissolved in $CDCl_3$. The analytical sample was obtained by sublimation of the crude product *in vacuo* at ambient temperature. Colorless prisms, mp 79–81 °C, (**C**+**D**):**E**:**F** = 63:10:27 ratio were detected at room temperature in the freshly prepared $CDCl_3$ solution. MS (56 °C), *m*/*z* (I_{rel} (%)): 156 $[M]^+$ (35), 139 (20), 119 (10), 112 (53), 97 (3), 87 (85), 69 (100).

*4.4.2.1. Enol (**C**+**D**)*: ^{1}H NMR ($CDCl_3$) δ: 5.69 (s, 1H, =CH), 8.0 (br. s, 1H, CO_2H), 11.3 (br. s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ: –75.1 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 91.6 (q, C-2, *J* = 3.5 Hz), 118.2 (q, *J* = 275.0 Hz, CF_3), 161.7 (q, *J* = 36.8 Hz, C-3), 175.7 (C-1).

*4.4.2.2. Keto-form **E***: ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 2H, CH_2), 8.0 (br. s, 1H, CO_2H). ^{19}F NMR ($CDCl_3$) δ: –79.3 (s, CF_3).

*4.4.2.3. Hydrate **F***: ^{1}H NMR ($CDCl_3$) δ: 2.91 (s, 2H, CH_2), 6.5 (br. s, 2H, 2 OH), 8.0 (br. s, 1H, CO_2H). ^{19}F NMR ($CDCl_3$) δ: –87.4 (s, CF_3).

4.5. 2,2-Dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-one (3)

4.5.1. Method A. To a solution of 2 (2.4 g, 10 mmol) in anhydrous $CHCl_3$ (40 mL) acetone (10 mL) was added. The mixture was stirred for 1 h at ambient temperature and then heated (bath temperature 50 °C) for 16 h (CO_2 evolution observed). The volatiles were removed *in vacuo* to provide pure compound **3**. Yield 1.55 g (79%), yellowish liquid. ^{1}H NMR ($CDCl_3$) δ: 1.77 (s, 6H, 2 Me), 5.90 (s, 1H, H-5). ^{1}H NMR (C_6D_6) δ: 1.00 (s, 6H, 2 Me), 5.41 (s, 1H, H-5). ^{19}F NMR ($CDCl_3$) δ: –74.9 (s, CF_3). ^{19}F NMR (C_6D_6) δ: –74.4 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 24.6 (Me), 96.8 (q, *J* = 2.9 Hz, C-5), 109.3, 117.9 (q, *J* = 273.2 Hz, CF_3), 154.7 (q, *J* = 39.8 Hz, C-6), 158.9. MS (26 °C), *m*/*z* (I_{rel} (%)): 196 $[M]^+$ (11), 181 (5), 139 (2), 138 (1), 69 (18), 58 (41), 43 (100). Found (%): C, 42.60; H, 3.55. Calc. for $C_7H_7F_3O_3$ (%): C, 42.87; H, 3.60.

4.5.2. Method B. To a solution of imidazole (17.7 g, 260 mmol) in anhydrous $CHCl_3$ (350 mL) 2,2-dimethyl-1,3-dioxan-4,6-dione (37.4 g, 260 mmol) was added at room temperature. To this mixture a solution of *N*-(trifluoroacetyl)imidazole (45.0 g, 274 mmol) in $CHCl_3$ (260 mL) was added

carefully under stirring within 30 min; 2/3 of the solvent from the yellowish solution of salt **8** was removed *in vacuo* without heating. The residue was cooled down to –30 °C and half-saturated HCl solution in diethyl ether (300 mL) was added under vigorous stirring. The mixture was stirred for 15 min at ambient temperature, the precipitate of imidazolium chloride was filtered off and washed with $CHCl_3$ (2 x 100 mL). The volatiles from the filtrate were removed *in vacuo* to provide the yellow waxy solid which consists of compounds **2** and **3** in 1:2.9 ratio with traces of acid **9** (^{1}H and ^{19}F NMR data). The solid was dissolved in $CHCl_3$ (300 mL) and acetone (150 mL) was added. The mixture was stirred for 20 min at ambient temperature and then heated (bath temperature 50 °C) for 20 h (CO_2 evolution observed). The volatiles were removed *in vacuo* to provide crude compound **3** which is pure enough (ca. 90% assay by NMR) to be used without further purification for the most applications. Yield 34 g (ca. 60%). If necessary, the product can be purified by distillation, however, the considerable tar formation takes place and the losses of the substance are significant: 2.0 g of the crude product being distilled gave 1.0 g of the pure compound **3** as a colorless liquid, bp 62–65 °C (12 Torr).

4.5.3. Method C. To a solution of imidazole (0.72 g, 10.5 mmol) in anhydrous $CHCl_3$ (18 mL) 2,2-dimethyl-1,3-dioxan-4,6-dione (1.51 g, 10.5 mmol) was added at room temperature. To the mixture a solution of *N*-(trifluoroacetyl)imidazole (1.81 g, 110 mmol) in $CHCl_3$ (18 mL) was added carefully under stirring within 30 min. The solvent from the yellowish solution of salt **8** was removed *in vacuo* without heating. The yellow oily salt **8** was dissolved in $CHCl_3$ (5 mL), cooled down to –30 °C and saturated HCl solution in diethyl ether (15 mL) was added under vigorous stirring. The mixture was stirred for 15 min at ambient temperature, and the precipitate of imidazolium chloride was filtered off under N_2 atmosphere. The volatiles from the filtrate were removed *in vacuo* to provide compound **2** with admixture of acid **9** (8%). Yield 1.1 g (ca. 49%).

4.6. 2-Dimethylamino-6-(trifluoromethyl)-1,3-oxazin-1*H*-4-one (10)

4.6.1. Method A. To a solution of compound **3** (400 mg, 2 mmol) in dry benzene (10 mL) dimethylcyanamide (150 mg, 2.1 mmol) was added and the mixture was heated at reflux for 1.5 h. The volatiles were removed *in vacuo* and crude product was recrystallized from heptane/toluene (5:1). Yield 250 mg (60%), yellow crystals, mp 100–101 °C. ^{1}H NMR ($CDCl_3$) δ: 3.14, 3.19 (both s, each one 3H, Me_2N), 6.36 (s, 1H, H-5). ^{19}F NMR ($CDCl_3$) δ: –73.3 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 36.1, 37.9, 107.1 (q, C-5, J = 2.8 Hz), 117.7 (q, CF_3, J = 272.9 Hz), 149.6 (q, C-6, J = 40.4 Hz), 156.9, 165.7. Found (%): C, 40.20; H, 3.25; N, 13.33. Calc. for $C_7H_7F_3N_2O_2$ (%): C, 40.39; H, 3.39; N, 13.46.

4.6.2. Method B. To a solution of compound **2** (120 mg, 0.50 mmol) in dry benzene (2 mL) dimethylcyanamide (40 mg, 0.57 mmol) was added and the mixture was heated on reflux for 20 h. The volatiles were removed *in vacuo*, and compound **10** was isolated by column chromatography (EtOAc/hexane, 1:2 to 2:1) of the crude product. Yield 20 mg (19%).

4.7. 2-Diethylamino-6-(trifluoromethyl)-1,3-oxazin-1*H*-4-one (11)

This compound was synthesized according to *method A* for compound **10** from dioxin **3** (13.2 g, 67 mmol) and diethylcyanamide (6.9 g, 70 mmol) in dry benzene (150 mL). Compound **11** was isolated by column chromatography (EtOAc/hexane, 1:1) of the crude product (fraction with R_f = 0.4 was collected). Yield 7.6 g (48%), orange crystals, mp 44–46 °C. ^{1}H NMR ($CDCl_3$) δ: 1.13–1.35 (m, 6H, 2 Me), 3.44, 3.60 (both q, each one 2H, 2 CH_2, J = 6.8 Hz), 6.36 (s, 1H, H-5). ^{19}F NMR ($CDCl_3$) δ: –73.6 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 12.4, 13.5, 42.4, 43.7, 107.3 (q, C-5, J = 2.8 Hz), 117.8 (q, CF_3, J = 272.8 Hz), 149.6 (q, C-6, J = 40.4 Hz), 156.2, 165.9. Found (%): C, 45.70; H, 4.61; N, 11.64. Calc. for $C_9H_{11}F_3N_2O_2$ (%): C, 45.77; H, 4.69; N, 11.86.

4.8. Reaction of 3 with 1-ethoxy-1-propyne

To a solution of compound **3** (3.9 g, 20 mmol) in dry benzene (60 mL) 1-ethoxy-1-propyne (2.5 g, 30 mmol) was added. The mixture was heated at reflux ($CaCl_2$-drying tube) for 14 h. The yellow solution formed (containing **12a** and **12b** in 6:1 ratio, ^{19}F NMR yield 79%) was evaporated *in vacuo* and the residue was distilled. The fraction boiling in the range 60–70 °C (1 Torr) solidified to yellow waxy solid (1.6 g), which consists of **12a** and **12b** in 5.6:1 ratio; their analytical samples were obtained by preparative TLC (EtOAc/hexane, 1:5).

4.9. Reaction of 2 with 1-ethoxy-1-propyne

To a solution of compound **2** (60 mg, 0.25 mmol) in dry benzene (5 mL) 1-ethoxy-1-propyne (85 mg, 1 mmol) was added. The mixture was heated at reflux for 16 h. The ^{19}F NMR monitoring of the reaction mixture (a yellow solution) revealed the complete conversion of compound **2** with the complex mixture of several products, where **12a** and **12b** in 6:1 ratio could be identified (^{19}F NMR virtual yield ca. 20%).

*4.9.1. 2-Ethoxy-3-methyl-6-(trifluoromethyl)-4H-pyran-4-one (**12a**).* Colorless waxy solid, mp 49–51 °C, R_f = 0.3. ^{1}H NMR ($CDCl_3$) δ: 1.44 (t, 3H, Me, *J* = 7.0 Hz), 1.87 (s, 3H, Me), 4.40 (q, 2H, CH_2, *J* = 7.0 Hz), 6.64 (s, 1H, H-5). ^{19}F NMR ($CDCl_3$) δ: –71.7 (s, CF_3).

*4.9.2. 3-Ethoxy-2-methyl-6-(trifluoromethyl)-4H-pyran-4-one (**12b**).* Colorless crystals, mp 114–115 °C, R_f = 0.4. ^{1}H NMR ($CDCl_3$) δ: 1.44 (t, 3H, Me, *J* = 7.0 Hz), 1.98 (s, 3H, Me), 4.17 (q, 2H, CH_2, *J* = 7.0 Hz), 6.62 (s, 1H, H-5). ^{19}F NMR ($CDCl_3$) δ: –71.5 (s, CF_3). MS (22 °C), *m*/*z* (I_{rel} (%)): 222 $[M]^+$ (100), 207 (2), 194 (62), 117 (4), 166 (100), 153 (14), 139 (15), 125 (40), 97 (30), 83 (14), 69 (34), 43 (4).

4.10. Reaction of 12 with ammonia

To a solution of the mixture **12a** and **12b** from the previous experiment (0.86 g, 5.6:1 ratio) in ethanol (50 mL) 25% aq. NH_3 (2 mL) was added and the stirred mixture was heated at 90 °C for 16 h. The red solution formed was poured onto water (500 mL) and after extraction with diethyl ether (4 × 30 mL) the combined organic layers were washed with water (2 x 10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated. The pyridines **13** have been isolated by column chromatography ($CHCl_3$ as an eluent); pyridine **13b** was purified additionally by preparative TLC (EtOAc/hexane, 1:5).

*4.10.1. 2-Ethoxy-4-hydroxy-3-methyl-6-(trifluoromethyl)pyridine (**13a**).* Yield 330 mg (46%), colorless crystals, mp 59–60 °C, R_f = 0.55 (EtOAc/hexane, 1:5). ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, 3H, H-9, *J* = 7.0 Hz), 2.09 (s, 3H, H-7), 4.40 (q, 2H, CH_2, *J* = 7.0 Hz), 5.6 (br. s, 1H, OH), 6.75 (s, 1H, H-5). ^{1}H NMR (DMSO-d_6) δ: 1.30 (t, 3H, H-9, *J* = 6.9 Hz), 1.98 (s, 3H, H-7), 4.29 (q, 2H, CH_2, *J* = 6.9 Hz), 6.89 (s, 1H, H-5), 11.1 (br. s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ: –69.3 (s, CF_3). ^{19}F NMR (DMSO-d_6) δ: –67.5 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 7.7 (C-7), 14.5 (C-9) , 62.6 (C-8), 103.3 (q, C-5, *J* = 3.0 Hz), 108.6 (C-3), 121.5 (q, CF_3, *J* = 273.7 Hz), 142.9 (q, C-6, *J* = 35.4 Hz), 161.8 (C-4), 163.6 (C-2). MS (24 °C), *m*/*z* (I_{rel} (%)): 221 $[M]^+$ (52), 206 (100), 193 (90), 192 (51), 176 (7), 164 (21), 138 (75), 69 (7). Found (%): C, 48.95; H, 4.70; N, 6.31. Calc. for $C_9H_{10}F_3NO_2$ (%): C, 48.87; H, 4.56; N, 6.33.

*4.10.2. 2-Amino-4-hydroxy-3-methyl-6-(trifluoromethyl)pyridine (**13b**).* Yield 50 mg (8%), white powder, mp 135 °C (subl., from toluene/EtOH, 5:1), R_f = 0.13 (EtOAc/hexane, 1:5). ^{1}H NMR ($CDCl_3$) δ: 2.04 (s, 3H, Me), 4.6 (br. s, 2H, NH_2), 5.9 (br. s, 1H, OH), 6.57 (s, 1H, H-5). ^{1}H NMR (DMSO-d_6) δ: 1.89 (s, 3H, Me), 6.0 (br. s, 2H, NH_2), 6.51 (s, 1H, H-5), 10.4 (br. s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ: –69.1 (s, CF_3). ^{19}F NMR (DMSO-d_6) δ: –67.5 (s, CF_3). ^{13}C NMR (DMSO-d_6) δ:

8.9 (Me), 98.6 (q, C-5, J = 3.0 Hz), 103.5, 122.0 (q, CF_3, J = 274.2 Hz), 142.7 (q, C-6, J = 32.5 Hz), 160.1, 161.7. MS (120 °C), m/z (I_{rel} (%)): 192 $[M]^+$ (100), 173 (10), 172 (25), 163 (15), 144 (12), 138 (25), 69 (2). HRMS: m/z $[M]^+$ found: 192.0505. Calc. for $C_7H_7F_3N_2O$: 192.0505; 0.16 ppm. HRMS: m/z 138 found: 138.0156. Calc. for $C_4H_3F_3NO$: 138.0161; –3.5 ppm.

4.11. 2-(*N*-Phthalimido)ethyl 4,4,4-trifluoro-3,3-dihydroxybutanoate (14)

4.11.1. Method A. To a solution of compound **2** (240 mg, 1 mmol) in anhydrous CH_2Cl_2 (3 mL) *N*-(2-hydroxyethyl)phthalimide (200 mg, 1 mmol) was added. The mixture was maintained in the sealed flask for 24 h at ambient temperature and the volatiles were removed *in vacuo*. The residue was subjected to column chromatography (EtOAc/hexane, 1:1) to provide the compound **14** (R_f = 0.4). Yield 120 mg (35%), white powder, mp 108 °C (subl.). ^{1}H NMR (CD_3CN) δ: 2.73 (s, 2H, CH_2), 3.92, 4.38 (both t, each one 2H, 2 CH_2, J = 5.3 Hz), 5.31 (s, 2H, 2 OH), 7.78–7.88 (m, 4H, Ar). ^{19}F NMR (CD_3CN) δ: –87.3 (s, CF_3). ^{1}H NMR (CD_3CN+$CDCl_3$) δ: 2.71 (s, 2H, CH_2), 3.93, 4.37 (both t, each one 2H, 2 CH_2, J = 5.4 Hz), 7.69–7.88 (m, 4H, Ar). ^{19}F NMR (CD_3CN+$CDCl_3$) δ: –86.2 (s, CF_3). ^{13}C NMR (CD_3CN+$CDCl_3$) δ: 37.1, 38.5, 63.2 (C-4), 92.7 (q, C-3, J = 33.2 Hz), 123.0 (q, CF_3, J = 284.5 Hz), 123.7, 134.8 (both s, Ar), 132.4 (C_i), 168.6, 170.6. Found (%): C, 48.57; H, 3.65; N, 4.00. Calc. for $C_{14}H_{12}F_3NO_6$ (%): C, 48.42; H, 3.48; N, 4.03.

4.11.2. Method B. To a solution of compound **3** (20 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (0.5 mL) *N*-(2-hydroxyethyl)phthalimide (20 mg, 1 mmol) was added. The mixture was maintained in the sealed flask for 6 days at ambient temperature (^{19}F NMR monitoring), and the volatiles were removed *in vacuo*. The residue was subjected to preparative TLC (EtOAc/hexane, 1:1) to provide the compound **14**. Yield 15 mg (43%).

4.12. 5-Hydroxy-3-(trifluoromethyl)-1*H*-pyrazole (16)

To a well stirred solution of compound **2** (220 mg, 0.92 mmol) in absolute DME (3 mL) 100% hydrazine hydrate (50 mg, 1 mmol) was added at ambient temperature and the mixture was stirred for 1 h. In the solution formed the salt, hydrazinium 2,2-dimethyl-5-(trifluoroacetyl)-1,3-dioxan-4,6-dionate, is the only fluorinated species present, as revealed by ^{19}F NMR. The volatiles were removed *in vacuo* to provide crude salt **15** as a beige powder [^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 1.37 (s, 6H, 2 Me), 6.8 (br. s, 5H, $^+NH_3NH_2$); ^{19}F NMR ($CDCl_3$+DMSO-d_6) δ: –72.5 (s, CF_3)]. This powder was dissolved in acetic acid (10 mL) and the solution was maintained for 60 h at ambient temperature. After evaporation of the solvent the yellow oily residue was subjected to column

chromatography ($CHCl_3$/MeOH, 10:1) to provide pyrazole **16**. Yield 30 mg (21%), colorless solid, mp 139–141 °C (lit.[11c] mp 135–137 °C). ^{1}H NMR ($CDCl_3$+acetone-d_6) δ: 5.51 (s, 1H, H-4), 9.1 (br. s, 2H, NH, OH, exchangeable with CD_3CO_2D). ^{19}F NMR ($CDCl_3$+acetone-d_6) δ: –62.8 (s, CF_3).

4.13. *S*-(4-Methoxyphenyl) 4,4,4-trifluoro-3-oxobutanethioate (17)

4.13.1. Method A. To a solution of compound **3** (0.80 g, 4.1 mmol) in anhydrous CH_2Cl_2 (35 mL) 4-(methoxy)thiophenol (0.57 g, 4.1 mmol) was added. The solution formed was maintained for 7 days in the sealed flask at ambient temperature (^{19}F NMR monitoring). The volatiles were removed *in vacuo*, the oily residue left was subjected to column chromatography (EtOAc/hexane, 1:5) to provide ketothioester **17**. Yield 600 mg (49%), white solid, mp 65–66 °C, R_f = 0.30. Hydrate:enol:keto forms in 86:13:1 ratio were detected using ^{1}H and ^{19}F NMR in the freshly prepared $CDCl_3$ solution at room temperature. MS (32 °C), *m*/*z* (I_{rel} (%)): 296 $[M]^+$ (2), 278 (4), 140 (100), 139 (20), 125 (30), 97 (5), 69 (27). HRMS: *m*/*z* $[M]^+$ found: 296.0317. Calc. for $C_{11}H_{11}F_3O_4S$: 296.0325; –2.62 ppm.

4.13.1.1. Enol: ^{1}H NMR ($CDCl_3$) δ: 3.84 (s, 3H, MeO), 6.03 (s, 1H, =CH), 6.98, 7.37 (AA'BB'-system (dd), each one 2H, Ar, $J_{AB} = J_{A'B'}$ = 9.0 Hz), 12.2 (br. s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ: –74.9 (s, CF_3).

4.13.1.2. Keto-form: ^{1}H NMR ($CDCl_3$) δ: 4.01 (s, 2H, CH_2). ^{19}F NMR ($CDCl_3$) δ: –79.2 (s, CF_3).

4.13.1.3. Hydrate: ^{1}H NMR ($CDCl_3$) δ: 3.09 (s, 2H, CH_2), 3.83 (s, 3H, MeO), 4.8 (br. s, 2H, 2 OH), 6.96, 7.34 (AA'BB'-system (dd), each one 2H, Ar, $J_{AB} = J_{A'B'}$ = 8.6 Hz). ^{19}F NMR ($CDCl_3$) δ: –87.2 (s, CF_3). ^{13}C NMR ($CDCl_3$) δ: 43.6 (C-2), 55.3 (Me), 93.3 (q, *J* = 33.4 Hz, C-3), 115.1, 136.0 (CH^{Ar}), 121.9 (q, *J* = 286.0 Hz, CF_3), 132.6, 161.2, 199.2.

4.13.2. Method B. To a solution of compound **2** (80 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (3 mL) 4-(methoxy)thiophenol (45 mg, 0.33 mmol) was added. The solution formed was maintained for 5 days in the sealed flask at ambient temperature. The volatiles were removed *in vacuo*, the oily residue left was subjected to preparative TLC (EtOAc/hexane, 1:5) to provide ketothioester **17**. Yield 20 mg (20%).

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Graphical abstract

Preparative synthesis of 2,2-dimethyl-5-(trifluoroacetyl)-1,3-dioxane-4,6-dione (2-trifluoroacetyl Meldrum's acid) and 2,2-dimethyl-6-(trifluoromethyl)-4*H*-1,3-dioxin-4-one and their synthetic usefulness as (trifluoroacetyl)ketene precursors

Dmitri V. Sevenard,* Andrey V. Didenko, Denis Lorenz, Michael Vorobiev, Johannes Stelten, Thomas Dülcks and Vyacheslav Ya. Sosnovskikh