Unexpected formation of diethyl 2-ethoxy-6-CF_3-2*H*-pyran-3,5-dicarboxylate from the condensation of ethyl 4,4,4-trifluoroacetoacetate with $CH(OEt)_3$

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Unexpected formation of diethyl 2-ethoxy-6-CF_3-2*H*-pyran-3,5-dicarboxylate from the condensation of ethyl 4,4,4-trifluoroacetoacetate with $CH(OEt)_3$

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Abstract

The one-step preparation of diethyl 2-ethoxy-6-CF_3-2*H*-pyran-3,5-dicarboxylate *via* the condensation of ethyl 4,4,4-trifluoroacetoacetate with $CH(OEt)_3$ has been reported and a plausible mechanism for this transformation is discussed. To demonstrate the synthetic potential of the obtained pyran, the reactions with ammonia and aromatic amines to give trifluoromethylated pyridine derivatives are presented.

Keywords: Pyran, Detrifluoroacetylation, Ethyl trifluoroacetoacetate, Condensation, Pyridines

Introduction

Ethyl 4,4,4-trifluoroacetoacetate (β-keto ester **1**) is an attractive building block in organic synthesis due to its readily availability and ease of handling in various condensation reactions to produce compounds of biological interest.[1,2] Three non-equivalent carbon centers in the structure of β-keto ester **1** open the possibility for highly chemo- and regioselective modification, thereby providing numerous heterocyclic, aromatic and multi-functional frameworks.[2] This diversity can be achieved by varying the reagents in two- or three-component condensations with β-keto ester **1**, for example, a number of trifluoromethylated pyrazoles and pyrimidines have been obtained (Fig. 1). In most cases the target product skeleton is based on the β-dicarbonyl fragment of β-keto ester **1** and only a few reports describe C-C bond cleavage resulting in trifluoroacetyl group elimination.[3]

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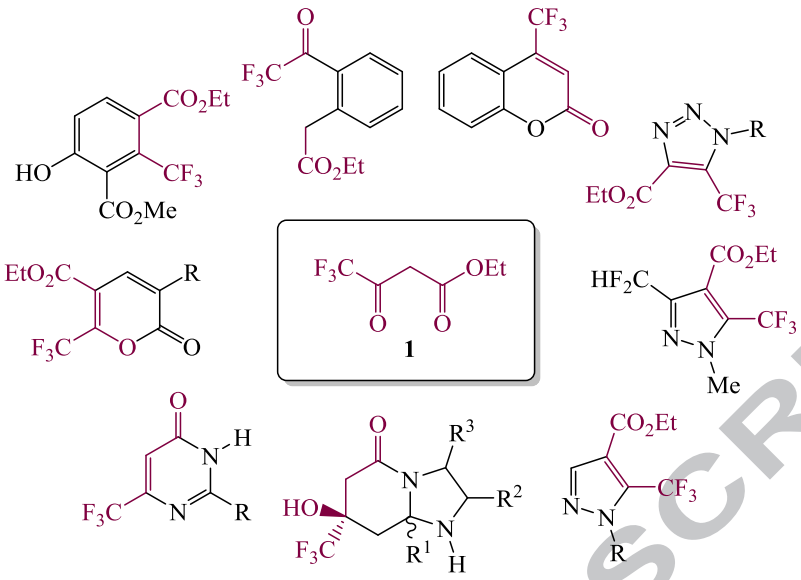
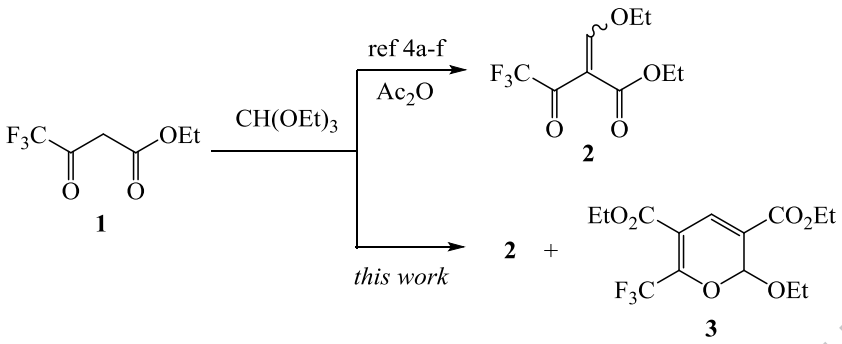


Figure 1. Representative examples of the applications of β-keto ester **1**

The reaction between β-keto ester **1** and $CH(OEt)_3$ was described more than 60 years ago and nowadays the condensation product (**2**) is commercially available (Scheme 1).[2b] In the initial report, Jones and co-workers obtained ethyl 2-ethoxymethylene trifluoroacetoacetate **2** in 67-70% isolated yield after distillation, with recovery of the starting reagents.[4a] Later, it was shown that minor changes in the reagent ratio resulted in increased yields of the target compound **2**[4b-e] (Table 1). Previously, our research group described a more economical method for this condensation without the use of toxic Ac_2O.[4f] The proposed two-component synthesis from β-keto ester **1** and $CH(OEt)_3$ seemed reasonable due to the high α-CH-activity of fluorinated β-ketoesters, however, the drawback was a lower yield of compound **2** compared to Ac_2O-based procedures.[5] In general, the α-functionalization of trifluorinated 1,3-dicarbonyl derivatives leads to enhanced reactivity of the trifluoroacetyl moiety which can be a reason for unpredictable reaction routes.[6] Taking this into account, we focused on investigating the reaction between β-keto ester **1** and $CH(OEt)_3$ in detail.

Herein, we report a novel method for the construction of a trifluoromethylated pyran derivative from the condensation of β-keto ester **1** with $CH(OEt)_3$.



Scheme 1. Two possible pathways for the reaction of β-keto ester **1** with $CH(OEt)_3$

Table 1. Reaction of β-keto ester **1** with $CH(OEt)_3$ under different conditions

Entry	Reactant ratio **1** : $CH(OEt)_3$: Ac_2O, (mol)	Reaction conditions	Yield, **2** (%)	Yield, **3** (%)	Ref
1	0.5 : 0.75 : 1.5	120-140 °C	67-70	-	4a
2	0.25 : 0.5 : 0.75	120-140 °C, 7 h, N_2	98	-	4b
3	0.54 : 0.81 : 1.62	reflux, 5 h	79	-	4c
4	0.548 : 1.106 : 1.118	120-140 °C, 1.5 h	75	-	4d
5	0.54 : 0.81 : 1.62	120-140 °C, 7 h	63	-	4e
6	0.1 : 0.4 : 0	reflux, 1 h	59	-	4f
7	0.1 : 0.4 : 0	reflux, 24 h	56	30	
8	0.1 : 0.4 : 0.1	reflux, 24 h	65	21	
9	0.1 : 0.4 : 0.4	reflux, 10 h	84	-	

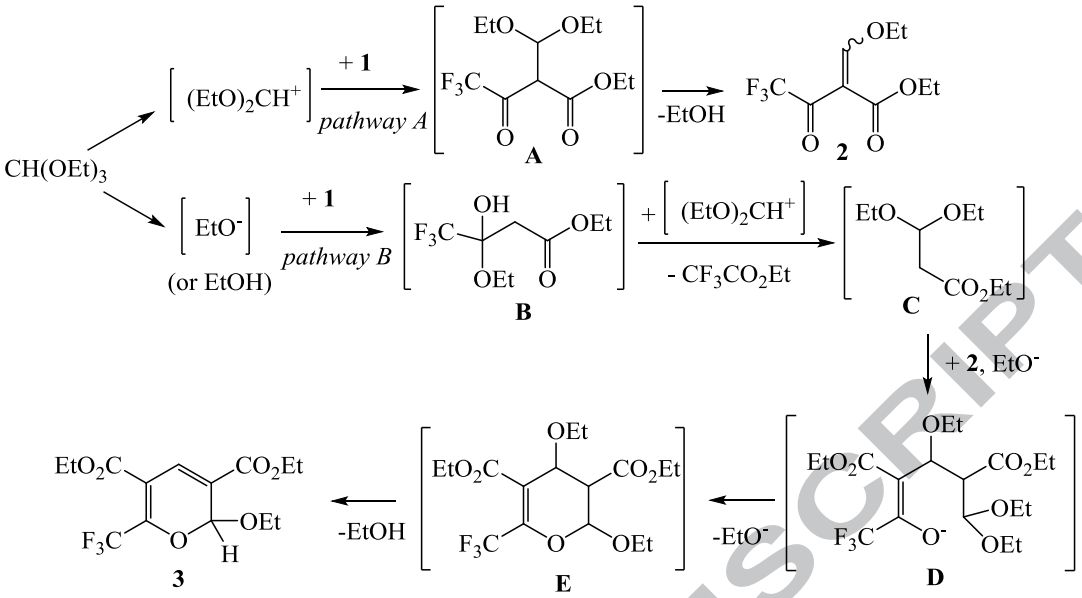
To begin, the condensation reaction between β-keto ester **1** and $CH(OEt)_3$ without Ac_2O was studied. In contrast to the previous report, the reaction time was increased from 1 to 24 hours to increase the conversion of β-keto ester **1** (Table 1, entry 7). Distillation of the reaction mixture gave two main fractions. The first fraction (colorless liquid) was collected under reduced pressure (10 Torr) at 130-132 °C and contained compound **2** while the second fraction (yellow-colored liquid) was collected at 157-159 °C/10 Torr. To our surprise, the second distillation fraction contained diethyl 2-ethoxy-6-CF_3-2*H*-pyran-3,5-dicarboxylate (**3**). The structure of compound **3** was confirmed by NMR, GS-MS and HRMS. In the ^{1}H NMR spectrum, besides the

signals for ethyl groups, singlets for the 2*H*- and 4*H*-pyran protons at δ_H = 6.17 and 7.61 ppm, respectively, were observed. The ^{19}F NMR spectrum also contained a characteristic singlet for the CF_3 group at δ_F = 95.17 ppm (C_6F_6 as an internal standard).

The reaction process could easily be monitored by ^{19}F NMR. According to the ^{19}F NMR in $CDCl_3$, there are two main peaks (δ_F 87.12 and 83.54 ppm) in β-keto ester **1** attributed to the enol and keto forms, respectively. As 2-ethoxymethylene **2** started to form in the reaction mixture, two signals corresponding to the geometric isomers of **2** appeared at δ_F = 89.22 and 86.17 ppm. Additional signals at δ_F = 79.65, 86.54 and 95.17 ppm were also observed, indicating the formation of a new species. According to literature data,[7] the signal at δ_F = 79 ppm corresponded to hemiketal formation as a result of the reaction of β-keto ester **1** with ethanol generated *in situ* from $CH(OEt)_3$. Also the signal at δ_F = 86.54 ppm could be attributed to the appearance of ethyl trifluoroacetate during the condensation reaction.

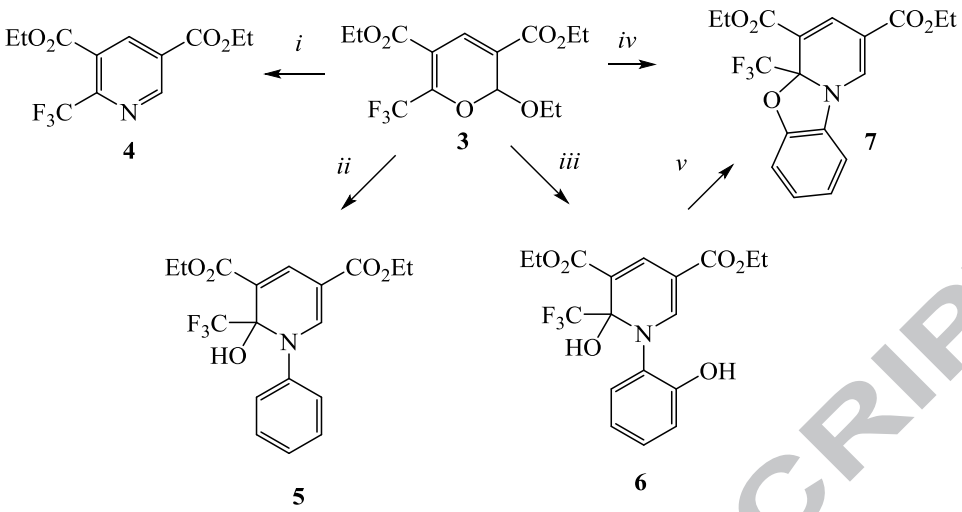
To understand this process, an extensive screening of reaction parameters was carried out. Acidic and basic agents (H_2SO_4, PTSA, DBU), and the Lewis acid BF_3•Et_2O were investigated in the reaction between β-keto ester **1** and $CH(OEt)_3$. In most cases low conversion along with the formation of a mixture of by-products was observed. We also verified the effect of Ac_2O on the outcome of the condensation reaction. The use of equal equivalents of β-keto ester **1** and Ac_2O along with an excess of $CH(OEt)_3$ resulted in the high conversion of 3-oxo ester **1** to give compounds **2** and **3** in 65% and 21% yield, respectively (Table 1, entry 8).

From these experiments, a plausible mechanism for product **3** formation from β-keto ester **1** and $CH(OEt)_3$ was proposed (Scheme 2). It is well known that $CH(OEt)_3$ generates both $(EtO)_2CH^+$ and EtO^-, which in the reaction with β-keto ester **1** can initiate two possible pathways (*A* and *B*). Discussing pathway *A*, the crucial role of Ac_2O can be explained as a scavenger of EtO^- and EtOH, thereby preventing by-product formation. To provide an irreversible reaction between **1** and $CH(OEt)_3$, a major factor is either the removal of EtOH from the reaction media by distillation or its acylation by Ac_2O. In accordance with pathway *B*, the electron-withdrawing properties of the CF_3 group accelerate the nucleophilic addition of ethanol to the trifluoroacetyl moiety of β-keto ester **1**, producing intermediate hemiketal **B**. This suggestion is reasonable in view of the ^{19}F NMR data described above. After the detrifluoroacetylation of **B**, the highly reactive intermediate formed then interacts with excess $CH(OEt)_3$ to give **C**. Intermediate **C** acts as a *C*-nucleophile in the Michael addition on the activated C=C bond of **2**, with subsequent intermolecular cyclization resulting in pyran **3** formation.



Scheme 2. Plausible mechanism for 6-(trifluoromethyl)-2*H*-pyran (**3**) formation

CF_3-containing pyrans are well known scaffolds for the construction of different heterocyclic compounds.[8] To demonstrate the synthetic potential of novel pyran **3**, the reactions with ammonia, aniline and *o*-aminophenol were performed. The reaction of **3** with ammonia in ethanol under ambient conditions afforded diethyl 2-(trifluoromethyl)pyridine-3,5-dicarboxylate (**4**) in 83% yield (Scheme 3). Initially, the reaction of **3** with aromatic amines was carried out at reflux, resulting in the formation of 2-hydroxy-1,2-dihydropyridine (**5**) and benzopyrido-1,3-oxazole (**7**). To the best of our knowledge, compounds similar to **5** and **7** were recently synthesized from the three-component reaction of β-keto ester **1** with 3-formylchromones and aromatic amines.[9] In contrast, we found that the formation of benzopyrido-1,3-oxazole derivative **7** proceeds *via* formation of the corresponding 2-hydroxy-1,2-dihydropyridine **6** at room temperature. The structures of compounds **4**-**7** were confirmed by NMR, LCMS analysis and single crystal X-ray diffraction (Fig. 2, 3).[10] In the ^{19}F NMR spectra of 2-CF_3-2-hydroxy-1,2-dihydropyridines **5**, **6** and benzopyrido-1,3-oxazole **7**, characteristic signals of the CF_3-group appeared in the range of 75-78 ppm.



Scheme 3. Reagents and conditions: (i) **3** (3 mmol), NH_3 (gas, excess), EtOH, rt, 1 h, 83%; (ii) **3** (30 mmol), aniline (3 mmol), EtOH, reflux, 2 h, 72%; (iii) **3** (3 mmol), *o*-aminophenol (30 mmol), EtOH, rt, 4 h, 75%; (iv) **3** (3 mmol), *o*-aminophenol (3 mmol), EtOH, reflux, 4 h, 82%; (v) EtOH, reflux, 2 h, 95%.

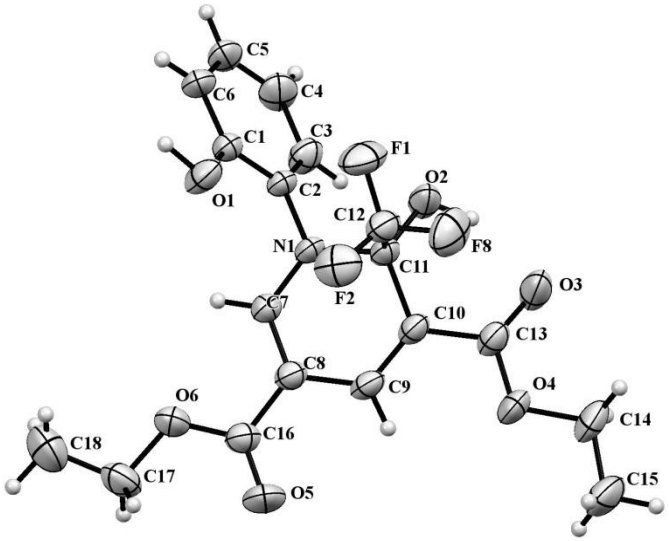


Figure 2. ORTEP view of molecule **6** (thermal ellipsoids at the 50% probability at 150K)

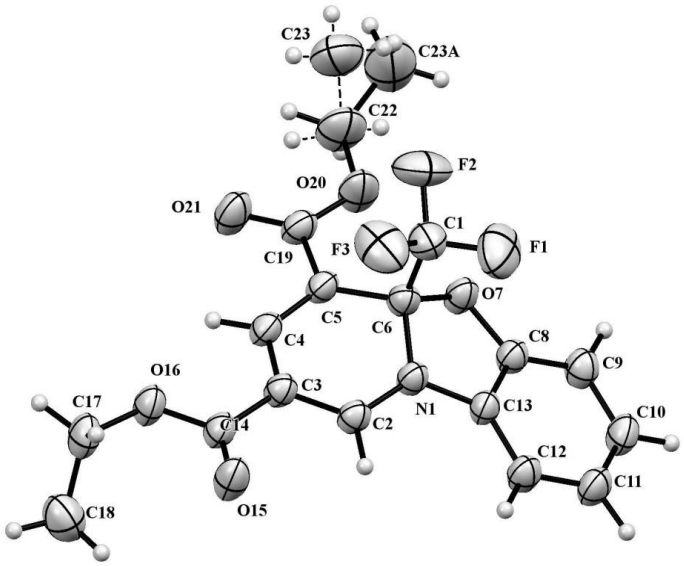


Figure 3. ORTEP view of molecule **7** (thermal ellipsoids at the 50% probability at 150K)

Notably, in contrast to compounds **4-6**, heterocycle **7** gave bright-yellow crystals that were luminescent under visible light (see ESI).

In summary, we describe the unexpected synthesis of a novel (trifluoromethyl)pyran from ethyl trifluoroacetoacetate and $CH(OEt)_3$. The remarkable feature of this condensation is the construction of a pyran core from two molecules of both starting reactants in a one-step reaction. The obtained CF_3-pyran is of interest as a precursor for the synthesis of heterocyclic compounds. Further studies on the improved preparation of fluorinated pyran derivatives and their reactivity are in progress.

Acknowledgments

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Supplementary data

Supplementary data with experimental procedure, spectral data and copies of ^{1}H, ^{19}F, ^{13}C spectra associated with this article can be found, in the online version, at http://dx.doi.org/

References and notes

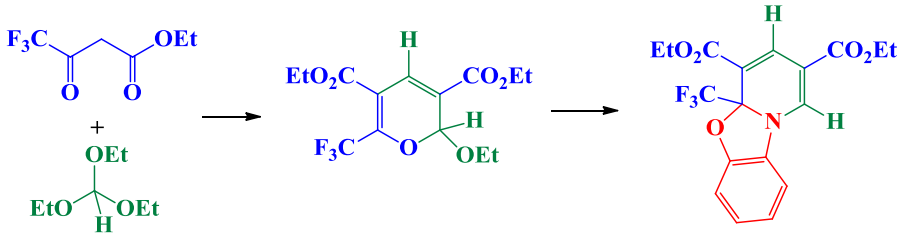
1. (a) Schiffler, M.A.; Antonysamy, S.; Bhattachar, S.N.; Campanale, K.M.; Chandrasekhar, S.; Condon, B.; Desai, P.V.; Fisher, M.J.; Groshong, C.; Harvey, A.; Hickey, M.J.; Hughes, N.E.; Jones, S.A.; Kim, E.J.; Kuklish, S.L.; Luz, J.G.; Norman,

B.H.; Rathmell, R.E.; Rizzo, J.R.; Seng, T.W.; Thibodeaux, S.J.; Woods, T.A.; York, J.S.; Yu, X.-P. *J. Med. Chem.* **2016**, *59*, 194; (b) Wityak, J.; McGee, K.F.; Conlon, M.P.; Song, R.H.; Duffy, B.C.; Clayton, B.; Lynch, M.; Wang, G.; Freeman, E.; Haber, J.; Kitchen, D.B.; Manning, D.D.; Ismail, J.; Khmelnitsky, Y.; Michels, P.; Webster, J.; Irigoyen, M.; Luche, M.; Hultman, M.; Bai, M.; Kuok, I.D.; Newell, R.; Lamers, M.; Leonard, P.; Yates, D.; Matthews, K.; Ongeri, L.; Clifton, S.; Mead, T.; Deupree, S.; Wheelan, P.; Lyons, K.; Wilson, C.; Kiselyov, A.; Toledo-Sherman, L.; Beconi, M.; Muñoz-Sanjuan, I.; Bard, J.; Dominguez, C. *J. Med. Chem.* **2015**, *58*, 2967; (c) Bach, P.; Boström, J.; Brickmann, K.; Giezen, J.J.J.; Hovland, R.; Petersson, A.U.; Ray, A.; Zetterberg, F. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 2877; (d) Ladzik, S.; Lubbe, M.; Kelzhanova, N.K.; Abilov, Z.A.; Feist, H.; Langer, P. *J. Fluorine Chem*. **2012**, *136*, 38.

2. (a) Gerus, I.I.; Tolmachova, N.A.; Vdovenko, S.I.; Fröhlich, R.; Haufe, G. *Synthesis* **2005**, 1269; (b) Kudyakova, Yu.S.; Bazhin, D.N.; Goryaeva, M.V.; Burgart, Ya.V.; Saloutin,V.I. *Russ. Chem. Rev*. **2014**, *83*, 120; (c) Liu, J.; Li, J.; Zhang, L.; Song, L.; Zhang, M.; Cao, W.; Zhu, S.; Deng, H.; Shao, M. *Tetrahedron Lett.* **2012**, 53, 2469; (d) Rozin, Y.A.; Leban, J.; Dehaen, W.; Nenajdenko, V.G.; Muzalevskiy, V.M.; Eltsov, O.S.; Bakulev, V.A. *Tetrahedron* **2012**, *68*, 614; (e) Volochnyuk, D.M.; Kostyuk, A.N.; Sibgatulin, D.A.; Chernega, A.N.; Pinchuk, A.M.; Tolmachev, A.A. *Tetrahedron* **2004**, *60*, 2361; (f) Schmitt, E.; Rugeri, B.; Panossian, A.; Vors, J.-P.; Pazenok, S.; Leroux, F.R. *Org. Lett.* **2015**, 4510; (g) Goryaeva, M.V.; Burgart, Y.V.; Kudyakova, Y.S.; Ezhikova, M.A.; Kodess, M.I.; Slepukhin, P.A.; Saloutin, V.I. *Eur J. Org. Chem*. **2015**, 6306; (h) Chizhov, D.L.; Sosnovskikh, V.Ya.; Pryadeina, M.V.; Burgart, Y.V.; Saloutin, V.I.; Charushin, V.N. *Synlett* **2008**, 281.
3. (a) Bazhin, D.N.; Kudyakova, Y.S.; Nemytova, N.A.; Burgart, Y.V.; Saloutin, V.I. *J. Fluorine Chem.* **2016**, *186*, 28; (b) Raju, B.C.; Suman, P. *Chem. Eur. J.* **2010**, *16*, 11840.
4. (a) Jones, R.G. *J. Am. Chem. Soc*. **1951**, *73*, 3684; (b) Palanki, M.S.S.; Erdman, P.E.; Gayo-Fung, L.M.; Shevlin, G.I.; Sullivan, R.W.; Suto, M.J.; Goldman, M.E.; Ransone, L.J.; Bennet, B.L.; Manning, A.M.. *J. Med. Chem*. **2000**, *43*, 3995; (c) I.I. Gerus, R.X. Mironetz, I.S. Kondratov, A.V. Bezdudny, Y.V. Dmytriv, O.V. Shishkin, V.S. Starova, O.A. Zaporozhets, A.A. Tolmachev, P.K. Mykhailiuk. *J. Org. Chem*. **77**, 47 (2012); d) P.J. Sanfilippo, M.J. Urbanski, K.N. Beers, A. Eckardt, R. Falotico, M.H. Ginsberg, S. Offord, J.B. Press, J. Tighe, K. Tomko, P. Andrade-Gordon. *J. Med. Chem*. **38**, 34 (1995); e) Kim, R.M.; Parmee, E.R.; Sinz, C.J.; Ziouzina, O.A. Patent US 2010/0216764; f) M.V. Pryadeina, Ya.V. Burgart, V.I. Saloutin, P.A. Slepukhin, O.N. Kazheva, G.V. Shilov, O.A. D'yachenko, O.N. Chupakhin. *Russ. J. Org. Chem*. **2007**, *43*, 945.
5. Reactions of various (non)fluorinated 1,3-dicarbonyl compounds with $CH(OEt)_3$ proceeds without by-product formation. See, for example: (a) Kudyakova, Yu.S.; Bazhin, D.N.; Burgart, Ya.V.; Saloutin, V.I. *Mendeleev Commun.* **2016**, *26*, 54; (b) Bazhin, D.N.; Kudyakova, Yu.S.; Gorbunova, T.I.; Kozhevnikova, N.S.; Suntsov, A.Yu.; Burgart, Ya.V.; Rempel', A.A.; Saloutin, V.I.; Chupakhin, O.N. *Russ. J. Org. Chem.* **2013**, *49*, 315; (c) Bazhin, D.N.; Kudyakova, Yu.S.; Gorbunova, T.I.; Burgart, Ya.V.; Zapevalov, A.Ya.; Saloutin, V.I. *Russ. J. Gen. Chem.* **2013**, *87*, 1330.
6. (a) Mei, H.; Xie, C.; Aceña, J.L.; Soloshonok, V.A.; Röschenthaler, G.-V.; Han, J. *Eur. J. Org. Chem.* **2015**, 6401; (b) Barkov, A.Yu.; Korotaev, V.Yu.; Sosnovskikh, V.Ya. *Tetrahedron Lett.* **2013**, *54* 6819; (c) Danheiser, R.L.; Miller, R.F.; Brisbois, R.G.; Park, S.Z. *J. Org. Chem.* **1990**, 55, 1959; (d) Fioravanti, S.; Pellacani, L.; Ramadori, F.; Tardella, P.A. *Tetrahedron Lett.* **2007**, *48*, 7821; (e) Ruddraraju, K.V.; Parsons, Z.D.; Llufrio, E.M.; Frost, N.L.; Gates, K.S. *J. Org. Chem.* **2015**, *80*, 12015; (f) Riofski, M.V.; John, J.P.; Zheng, M.M.; Kirshner, J.; Colby, D.A. *J. Org. Chem.* **2011**, *76* 3676; (g) Shchegolkov, E.V.; Khudina, O.G.; Burgart, Ya.V.; Saloutin, V.I.; Chupakhin, O.N. *Russ. J. Org. Chem.* **2004**, *40*, 813.

7. (a) Camps, F.; Coli, J.; Messenguer, A.; Roca, A. *Tetrahedron*, **1977**, *33*, 1637; (b) Jagodzinska, M.; Huguenot, F.; Zanda, M. *Tetrahedron* **2007**, *63*, 2042; (c) Von Arx, M.; Mallet, T.; Baiker, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2302.
8. Usachev, B.I. *J. Fluorine Chem.* **2015**, *175*, 36; Usachev, B.I. *J. Fluorine Chem.* **2015**, *172*, 80.
9. Rajkumar, K.; Suman, P.; Raju, B.C. *RSC Adv.* **2015**, *5*, 73850.
10. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1515308 (compound **6**), 1515307 (compound **7**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

Graphical Abstract



Highlights

- Novel route for the condensation of β-oxo ester with $CH(OEt)_3$.
- One-step formation of a novel CF_3-pyran was described.
- Synthesis of CF_3-pyridine derivatives was elaborated.