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Reaction of enamines with trifluoromethyl containing carbonyl reagents

Dmitriy A. Sibgatulin [a], Tatyana E. Shubina [b,c], Aleksandr N. Kostyuk [a,*], Dmitriy M. Volochnyuk [a], Reinhard Schmutzler [d], Peter G. Jones [d], Aleksandr M. Pinchuk [a]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska 5, Kyiv-94, 02094, Ukraine
[b] Computer-Chemistry-Center and Interdisciplinary Center for Molecular Materials, Universitaet Erlangen/Nuernberg, Naegelsbachstr. 25, D-91052 Erlangen, Germany
[c] Department of Organic Chemistry, National Technical University of Ukraine "KPI", Pr. Pobedy 37, 03056 Kyiv, Ukraine
[d] Institute of Inorganic and Analytical Chemistry, Technical University of Braunschweig, Hagenring 30, 38106 Braunschweig, Germany

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ABSTRACT

The reaction of linear push–pull enamines bearing a methyl group at the α-position with a set of trifluoromethylated carbonyl compounds was investigated. It has been found that the reaction proceeds at the methyl group of the enamines. The first computational study of the reaction between push–pull enamines and strong electrophilic reagents was reported. Out of three pathways considered DFT and MP2 calculations support ene-mechanism previously suggested based on experimental results only.

1. Introduction

The chemistry of enamines including push–pull enamines bearing an electron-acceptor group at the β-position has been extensively developed mainly due to electrophilic reactions that predominantly proceed at the β-position. Electrophilic modification followed by a set of transformations made enamines an indispensable part of the synthetic portfolio. An electron-acceptor group at the β-position of enamines stabilizes them due to conjugation with a dialkyl amino group. Electrophilic reactions at the β-position of enamines have been studied well and widely used particularly in the synthesis of heterocyclic compounds [1]. Although the number of reactions proceeding at the β′-position is markedly smaller as compared to the reactions at the β-position, they have found a practical application in the synthesis of natural compounds [2]. The general approach to β′-functionalized enamines is the interaction of a preformed lithium derivative of the enamines with carbonyl compounds [3], electrophilic olefins [4] or trimethylchlorosilane [5]. However, in the literature there are examples of uncatalyzed electrophilic reactions proceeding at the methyl group of tertiary push–pull linear enamines, despite the absence of convincing proof of the enamine equilibrium that could rationalize these reactions. In these cases the starting electrophilic reagent contain activated C=O [6] or C=N [7] bond. From our point of view one of the most interesting such reactions is the reaction of enamines with MeTFP recently discovered [6e]. In this work we report our study directed on the determination of the scope and limitations of the reaction of tertiary push–pull linear enamines with trifluoromethyl containing carbonyl compounds proceeding at the methyl group.

2. Results and discussion

2.1. Interaction of "push–pull" enamines with trifluoromethyl ketones

A set of push–pull enamines **1**–**4** and trifluoromethyl carbonyl compounds **5**–**11** of different reactivities were chosen as model compounds for investigation of the reaction. These are depicted in Figs. 1 and 2. Among fluorinated ketones we used commercially available ketones **7**, **10**–**12** and in-house prepared azoles **5**, **6** and **9** [8].

It was shown that the reaction of compounds **5**–**12** with enamines **1**–**4** (**a**,**b**) proceeds mainly with participation of the methyl group of the enamines in dry benzene in a few hours. However, the structure of the substituent in the starting trifluoromethyl-containing electrophiles influences the reaction. Enamines **1**–**4** (**a**,**b**) react with trifluoromethyl ketones **5** and **6** in benzene in 1–3 h affording β′-functionalized enamines **13a**,**b** and

* Corresponding author. Fax: +380 445373253.
E-mail address: a.kostyuk@enamine.net (A.N. Kostyuk).

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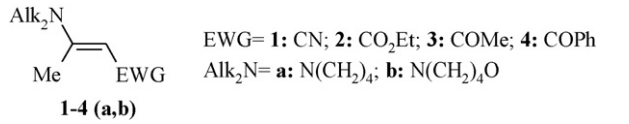
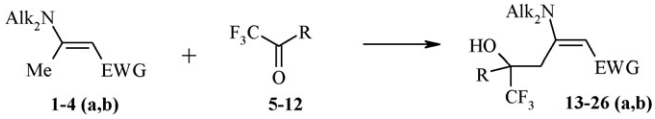


Fig. 1. The structure of the starting enamines.



Scheme 1.

14a,**b** in good preparative yields (Scheme 1, Table 1). It should be noted that unlike methyl MeTFP **8** [6d,e], the reaction of these ketones with enamine **3a**,**b**, is not complicated by side processes with participation of EWG-function of the enamines. The reaction of ketones **9**–**12** with enamines **1**–**4** (**a**,**b**) requires harsher conditions. The reaction comes to completion in 4–6 h in benzene under reflux giving the corresponding β′-functionalized enamines **21**–**25** (**a**,**b**). Moreover, these ketones do not react with enamines **1a**,**b** (EWG=CN). Besides, the reaction of compounds **5**–**12** with enamines **1**–**4b** having less basic morpholine (NAlk$_2$=N(CH$_2$)$_4$O) proceed usually in lower yields compared to enamines **1**–**4a** bearing a pyrrolidine residue (NAlk$_2$=N(CH$_2$)$_4$). The significant experiments are summarized in Table 2.

The adduct's constitution was proved by NMR spectroscopy, mass spectrometry and elemental analysis. Disappearance of the singlet of the methyl group, retention of the β-enamine proton, and presence of characteristic AB-system of a methylene group in ^{1}H NMR spectra of the adducts confirm that the reaction proceeded at the methyl group of the enamines. The observed in ^{13}C NMR signals for the methylene carbon ($\delta \sim 35$ ppm) and the CF_3 carbon ($\delta \sim 77$ ppm, $^2J_{CF} \sim 30$ Hz) serve as additional evidences. At the same time ^{1}H NMR spectrum of the compound **16a** exhibits two proton singlets instead of the expected AB-system of the methylene group. The assignment of signals both in ^{1}H and ^{13}C NMR spectra were based on analysis of 2D NMR (COSY, HMQC and HMBS) data. Also based on NOESY experiments exclusively *E*-configuration of enamine double bond in products **13**–**26** was found (Fig. 3). Also the structures of compounds **16a** and **17b** were unambiguously determined by a single X-ray diffraction studies (Figs. 4 and 5). In both compounds, the bicyclic ring system is

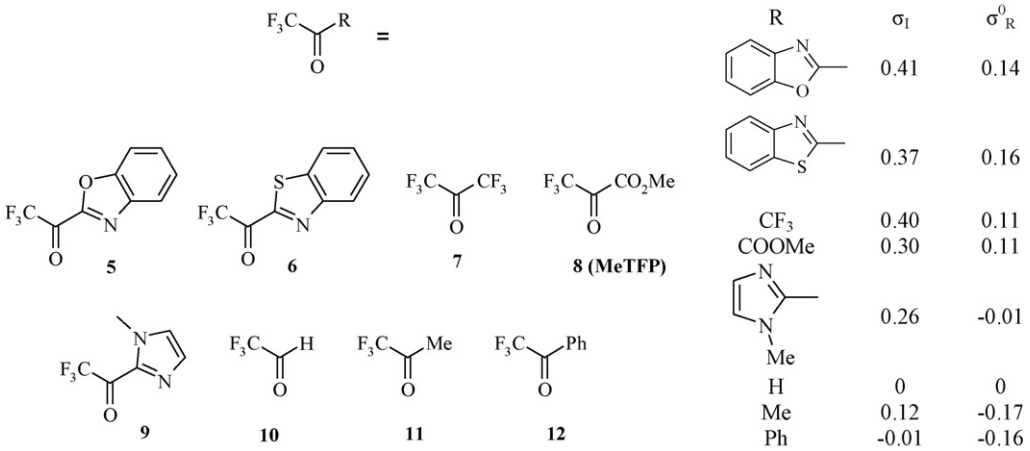


Fig. 2. The structure of the starting CF_3-ketones with constants of electronic effects of the substituent R [9].

Table 1
Compounds **13**–**26** prepared[a].

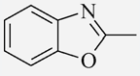
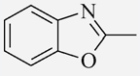
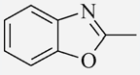
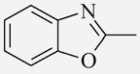
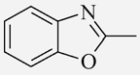
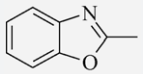
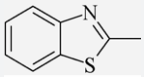
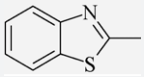
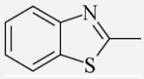
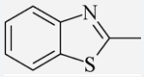
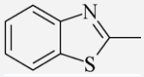
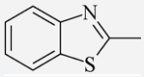
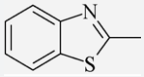
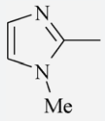
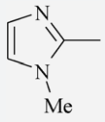
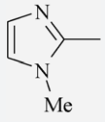
Product	NAlk$_2$	EWG	R	Yield[b] (%)	Mp[c] (°C)	^{19}F NMR[d], δ
13a	N(CH$_2$)$_4$	CN		70	127	−80.7
13b	N(CH$_2$CH$_2$)$_2$O	CN		71	146–149	−80.5
14a	N(CH$_2$)$_4$	CO$_2$Et		83	131	−80.4
14b	N(CH$_2$CH$_2$)$_2$O	CO$_2$Et		78	103	−80.7
15a	N(CH$_2$)$_4$	COMe		91	107	−80.4

Table 1 (*Continued*)

Product	$NAlk_2$	EWG	R	Yield[b] (%)	Mp[c] (°C)	^{19}F NMR[d], δ
15b	$N(CH_2CH_2)_2O$	COMe		88	113	−80.6
16a	$N(CH_2)_4$	CN		86	126	−80.7
16b	$N(CH_2CH_2)_2O$	CN		66	133–135	−80.3
17a	$N(CH_2)_4$	CO_2Et		82	133–135	−80.4
17b	$N(CH_2CH_2)_2O$	CO_2Et		76	131	−80.3
18a	$N(CH_2)_4$	COMe		66	125	−80.4
19a	$N(CH_2)_4$	COPh		80	134	−80.2
19b	$N(CH_2CH_2)_2O$	COPh		86	146–148	−80.5
20b	$N(CH_2CH_2)_2O$	CO_2Et	CF_3	45	Oil	−77.3
21a	$N(CH_2)_4$	CO_2Et		46	104	−80.6
21b	$N(CH_2CH_2)_2O$	CO_2Et		41	139	−80.8
22a	$N(CH_2)_4$	COMe		60	127–131	−80.5
23a	$N(CH_2)_4$	CO_2Et	H	54	Oil	−81.4
24a	$N(CH_2)_4$	CO_2Et	Me	35	Oil	−84.9
24b	$N(CH_2CH_2)_2O$	CO_2Et	Me	31	56	−84.1
25a	$N(CH_2)_4$	CO_2Et	Ph	28	Oil	−78.4
26[e]	$N(CH_2)_4$	CO_2Et	CO_2Et	98	49–51	−78.3

[a] Satisfactory microanalysis obtained C ±0.33; H ±0.45; N ±0.25.
[b] Melting points are uncorrected.
[c] Isolated yields.
[d] $CDCl_3$.
[e] Experimental details described in Ref. [6e].

Table 2
Significant results towards interaction of enamines and ketones.

Entry	Enamine	Ketone	Conditions	Results
1	**1–4** (**a**,**b**)	**5**,**6**	C_6H_6, rt, 2–4 h	In all cases according to ^{19}F NMR of the reaction mixture almost quantitative
2	**2b**	**7**	C_6H_6, rt, 8 h	conversion of the ketone to the final product observed
3[a]	**1**,**2**,**4** (**a**,**b**)	**8**	C_6H_6, rt, overnight	
4[a]	**3a**,**b**	**8**	C_6H_6, rt, overnight	^1H and ^{19}F NMR spectroscopies of the reaction mixture have shown presence of the targeted product, but many by-products made separation impossible.
5	**1–4** (**a**,**b**)	**9–12**	C_6H_6, rt, overnight	No reaction
6	**1a**,**b**	**9–12**	C_6H_6, reflux, 6 h	No reaction
7	**2a**	**9–12**	C_6H_6, reflux, 6 h	According to ^{19}F NMR of the reaction mixture a good conversion (from 60 to 80%) of ketone to final product observed.

[a] Experimental details described in Ref. [6e].

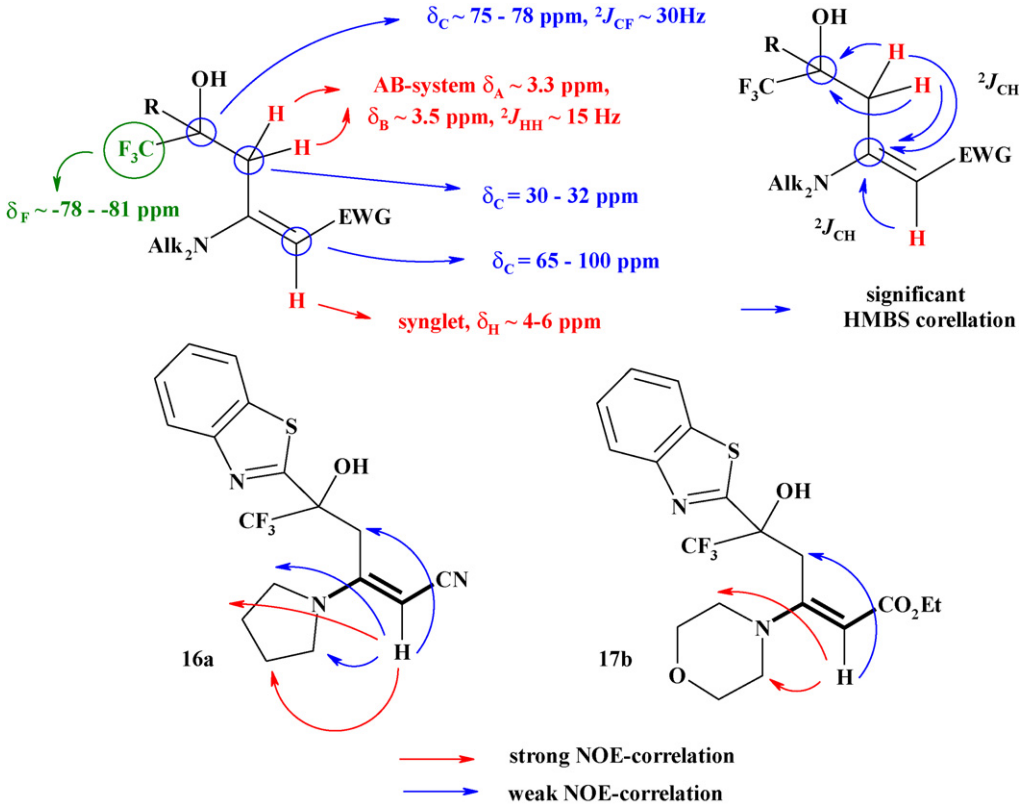


Fig. 3. Significant NMR data of compounds prepared.

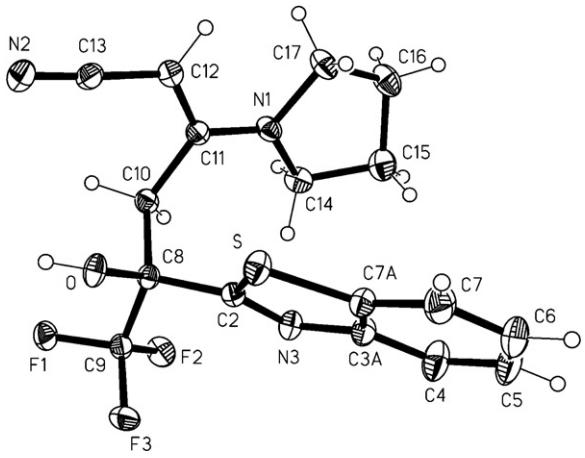


Fig. 4. Ellipsoid representation (50% level) of compound **16a** in the crystal.

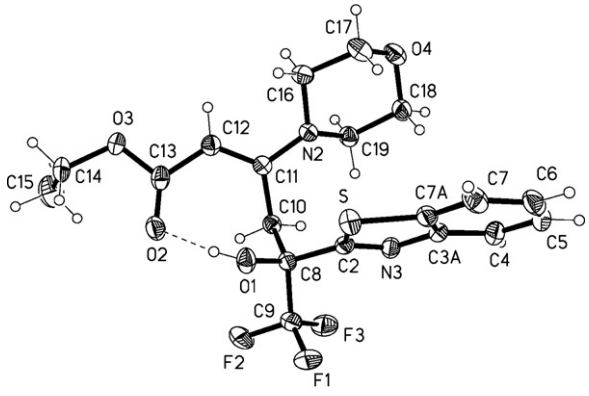


Fig. 5. The molecule of compound **17b** in the crystal. Ellipsoids represent 50% probability levels. Only one position of the disordered ethoxy group is shown.

planar (mean deviations 0.01, 0.02 Å). The five-membered ring of **16a** displays an envelope conformation, with C15 lying 0.60 Å out of the plane of the other four atoms. In compound **16a**, a hydrogen bond O–H···N_2 connects the molecules in centrosymmetric pairs. In compound **17b**, the hydrogen bond O1–H···O_2 is intramolecular.

In terms of reactivity the starting carbonyl compounds **5**–**11** could be divided into three types. The first type of ketones (**5**–**8**) react with enamines **1**–**4** (**a**,**b**) under mild reaction conditions in 1–2 h. The second group, compounds **9** and **10**, react with enamines **2**–**4** (**a**,**b**) at reflux in benzene during 3–6 h. These carbonyl compounds do not react with enamine **1a**,**b** (EWG=CN). The third group of ketones **11** and **12** react only with pyrrolidine derivatives of enamines **2**–**4a** in moderate yields. The reactivity of compounds **5**–**12** of common formula R-$COCF_3$ towards enamines **1**–**4** depends markedly on the nature of the substituent R and correlates quite well with electronic constants of these substituents (Fig. 2) [9]. In our previous works we have investigated the reactions of the enamines with ethyl 4,4,4-trifluoroacetoacetate, and 1,1,1-trifluoroacetylacetone [10]. According to the proposed classification, ethyl 4,4,4-trifluoroacetoacetate and 1,1,1-trifluoroacetylacetone should be placed in the second group (they do not react with enamines **1** (EWG=CN)). These data are in agreement with values of constants of electronic effects: ethyl 4,4,4-trifluoroacetoacetate (R=CH_2CO_2Et, $\sigma_I = 0.12$, $\sigma_R^0 = -0.12$), 1,1,1-trifluoroacetylacetone (R=CH_2COMe, $\sigma_I = 0.11$, $\sigma_R^0 = -0.12$). In our opinion, this correlation between the reactivity and values of constants of electronic effects allows the behavior of electrophilic reagents in respect to the enamines to be predicted.

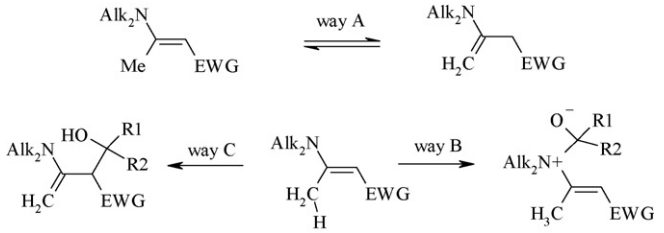
2.2. Computational study

Recently [6e], we have proposed a plausible mechanism for formation of β′-functionalized enamines. To confirm it the theoretical investigation of electrophilic reactions with participation of the methyl group of tertiary "push–pull" linear enamines was carried out. The main goal of our calculations was to gain insight into the mechanism of this reaction. We have studied a model reaction between enamine **2a** and MeTFP **8** computationally considering all three possible pathways (Scheme 2).

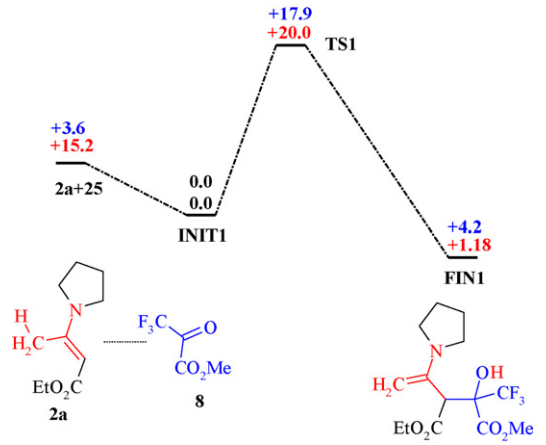
According to our calculations of pathway **A** in the case of structure **2a** equilibrium is shifted towards the structure with the methyl group, which formation is more favourable than the corresponding structure with a methylene group by 12.8 and 12.9 kcal mol^{-1}, B3PW91/6-31G(d) and MP2/6-31G(d) levels of theory, respectively. Moreover, the equilibrium for these enamines was not proved by either spectroscopic or chemical methods [1a]. It was suggested that such equilibrium can be shifted towards the structure with the methylene group in case of some cyclic sterically hindered enamines [11a].

In case of pathway **B**, involving the initial attack at the nitrogen atom, despite many attempts we were unable to locate any transition states or complexes that belong to such a pathway.

After that an alternative ene-mechanism **C** was explored. The reaction starts with exothermic formation (−15.1 and



Scheme 2.



Scheme 3. Relative energies (to **Init1**) are in kcal mol^{-1}, B3PW91/6-31G(d) (top entry) and MP2/6-31G(d) (bottom entry).

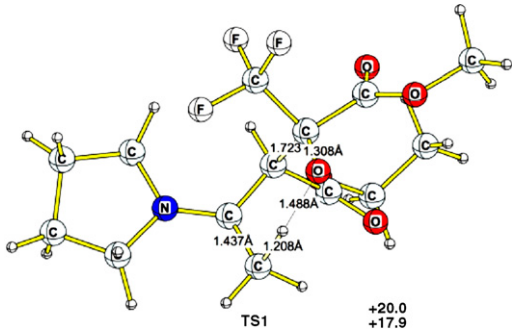


Fig. 6. Optimized geometry of transition state **TS1**. Relative energies (to **Init1**) are in kcal mol^{-1}, MP2/6-31G(d) (top entry) and B3PW91/6-31G(d) (bottom entry). Bond lengths are in Å.

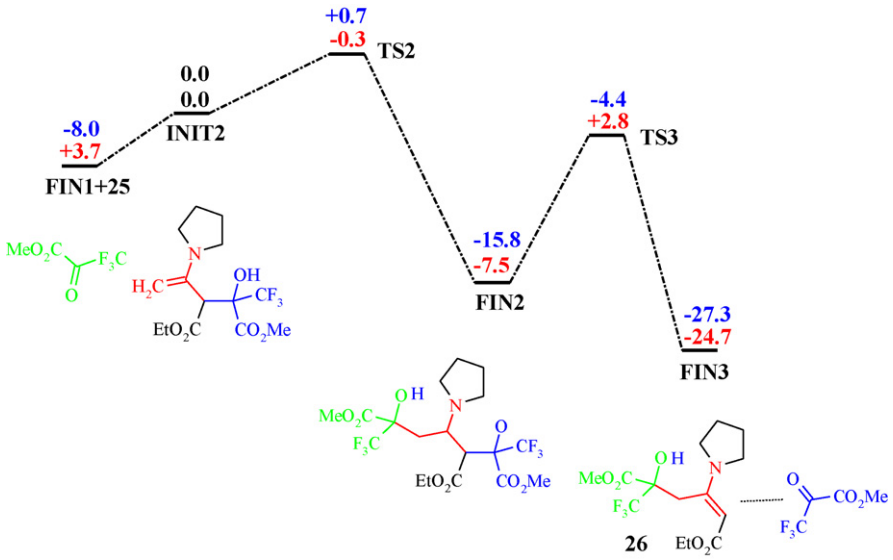
−3.7 kcal mol^{-1} at MP2/6-31G(d) and B3PW91/6-31G(d) levels of theory, respectively) of the initial complex **INIT1** between **2a** and **8**. From **INIT1** reaction proceeds via transition state **TS1**, which describes simultaneous C–C bond formation and H-migration from the methyl group to oxygen atom (Fig. 6). After that final complex **FIN1** is formed (ΔE = +1.9 and +4.3 kcal mol^{-1} relative to **INIT1**, MP2/6-31G(d) and B3PW91/6-31G(d), respectively). The overall energetic of the first step of the reaction is presented in Scheme 3 and Table 3.

Thus, compared to the pathway **A**, pathway **C** is more feasible. While formation of methylene-containing enamine requires ca 13 kcal mol^{-1}, formation of the initial complex **INIT1** is exothermic (Scheme 3). Moreover, in the literature there are examples of ene-reaction of enamines with azine of hexafluoroacetone affording similar structure [11b].

The second step of the reaction is nucleophilic addition of the second molecule of **8** (Scheme 4). Formation of the initial complex **INIT2** from separate **FIN1** and **8** was found to be moderately exothermic (ΔE = +8.0 kcal mol^{-1}) at the B3PW91/6-31G(d) level

Table 3
Relative energies ($E_{rel.}$, kcal mol^{-1}) for the reaction pathway depicted in Scheme 3.

Species	B3PW91/6-31G(d)	B3PW91/6-311+G(d,p)//B3PW91/6-31G(d)	MP2/6-31(G)	MP2/6-311+G(d,p)//MP2/6-31G(d)
2a+8	3.6	1.2	15.2	17.2
INIT1	0.0	0.0	0.0	0.0
TS1	17.9	16.4	20.0	18.3
FIN1	4.2	1.0	1.8	−2.7



Scheme 4. Relative energies (to **Init2**) are in kcal mol^{-1}, B3PW91/6-31G(d) (top entry) and MP2/6-31G(d) (bottom entry).

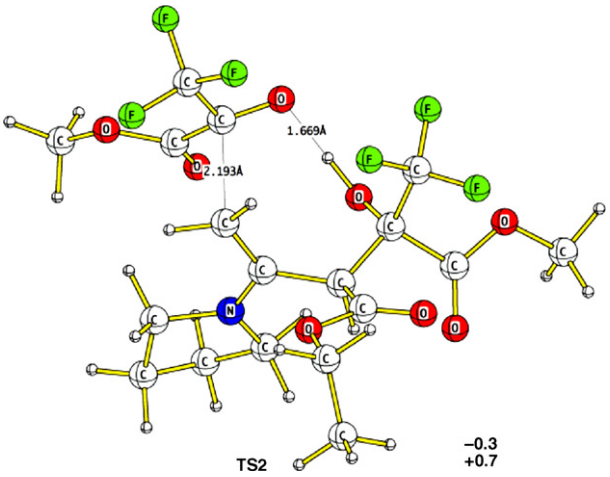


Fig. 7. Optimized geometry of transition state **TS2**. Relative energies (to **Init2**) are in kcal mol^{-1}, MP2/6-31G(d) (top entry) and B3PW91/6-31G(d) (bottom entry). Bond lengths are in Å.

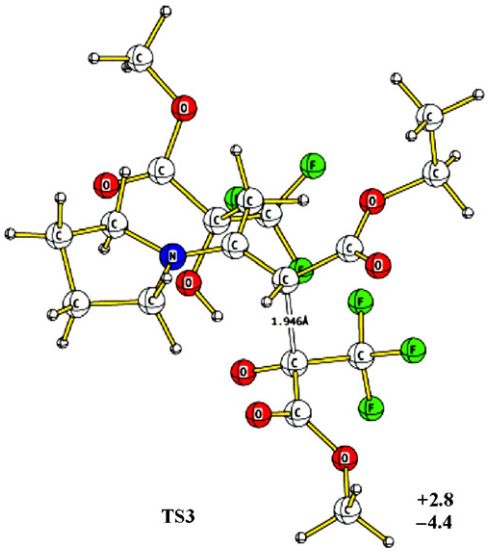


Fig. 8. Optimized geometry of transition state **TS3**. Relative energies (to **Init2**) are in kcal mol^{-1}, MP2/6-31G(d) (top entry) and B3PW91/6-31G(d) (bottom entry). Bond lengths are in Å.

and slightly endothermic at the MP2/6-31G(d) level (ΔE = −3.7 kcal mol^{-1}). Energy corrections with 6-311+G(d,p) basis set shifts these energies to 11.8 and −4.5 kcal mol^{-1}, respectively. Once the initial complex **INIT2** is formed the reaction proceeds via virtually barrierless ($\Delta E^{\neq}$ = +0.7 and −0.3 kcal mol^{-1}, B3PW91/6-31G(d) and MP2/6-31G(d), respectively) transition state **TS2** to form a cyclic structure **FIN2**. Transition state **TS2** describes synchronous addition of **8** and hydrogen atom migration from OH group to carbonyl oxygen of **8** (Fig. 7). From **FIN2** via transition state **TS3** (Fig. 8) complex **FIN3** between final product and **8** is formed (Scheme 4 and Table 4). The activation barrier for this step of the reaction was found to be 11.4 and 10.3 kcal mol^{-1}, at B3PW91/6-31G(d) and MP2/6-31G(d) levels, respectively.

Table 4
Relative energies ($E_{rel.}$, kcal mol^{-1}) for the reaction pathway depicted in Scheme 4.

Species	B3PW91/ 6-31G(d)	B3PW91/ 6-311+G(d,p)// B3PW91/6-31G(d)	MP2/ 6-31(G)	MP2/6-311+ G(d,p)//MP2/ 6-31G(d)
FIN1+8	8.0	11.8	−3.7	−4.5
INIT2	0.0	0.0	0.0	0.0
TS2	0.7	0.9	−0.3	−0.4
FIN2	−15.8	−13.8	−7.5	−6.4
TS3	−4.4	−4.6	2.8	−2.9
FIN3	−27.3	−29.1	−24.8	−24.4

3. Conclusion

Finally the reaction of "push–pull" enamines having a methyl group at the α-position with trifluoromethyl ketones was investigated. As a result, unexpected addition of the ketones to the methyl group was found. Structural sensitivity and the scope and limitations of the reaction are discussed. Computational study of the reaction was performed. As a result, previously suggested ene-mechanism of the transformation was confirmed.

4. Experimental

4.1. General

All procedures were carried out in an atmosphere of dry argon. All solvents were purified and dried by standard methods. ^{1}H and ^{19}F NMR spectra were recorded on a Varian VXR-300 spectrometer and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer. ^{1}H and ^{13}C (300 and 100 MHz, respectively) with TMS as an internal standard; ^{19}F (282.2 MHz) with $CFCl_3$ as an internal standard. Mass spectra were obtained on a MX-1321 instrument (EI, 70 eV) by direct inlet. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine.

4.2. Computation methods

Geometries of all structures were fully optimized at the B3PW91 [12] and MP2 [13] levels of theory using the 6-31G(d) basis set within the Gaussian 03 program package [14]. Stationary points were confirmed to be minima or transition states by calculating the normal vibrations within the harmonic approximation. Due to the large size of the **INIT2**–**FIN3** compounds the normal vibrations at the MP2/6-31G(d) level were not computed, instead the nature of the stationary points was determined by analysis of the Hessian matrix. The reaction pathways along both directions from the transition structures were followed by the IRC method [15]. All DFT and MP2 (for structures **2a**, **8**, **INIT1**–**FIN1**) computed energies are corrected for zero-point vibrational energies (ZPVE). Single-point B3PW91 and MP2 energies with TZ basis sets were computed at the corresponding optimized geometries (denoted as MP2/6-311+G(d,p)//MP2/6-31G(d) and B3PW91/6-311+G(d,p)//B3PW91/6-31G(d), respectively).

4.3. X-ray crystallography

Numerical details are presented in Table 5. *Data collection*: Crystals were mounted in inert oil on glass fibres and transferred to the cold gas stream of the diffractometer (Bruker SMART 1000 CCDC). Measurements were performed with monochromated Mo-Kα radiation. *Structure refinement*: The structures were refined anisotropically against F^2 (program SHELXL-97, G.M. Sheldrick, University of Göttingen). H atoms of OH groups were refined freely, methyls as rigid groups, other H with a riding model. For compound **2**, the ethoxy group is disordered over two positions; appropriate similarity restraints were applied.

Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the numbers CCDC 709642 (**1**), 709643 (**2**). Copies may be requested free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, England (E-mail: deposit@ccdc.cam.ac.uk).

4.4. Synthesis of enamines 12–24

4.4.1. 5-(1,3-Benzoxazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(1-pyrrolidinyl)-2-hexenenitrile (13a)

To a solution of enamine **1a** (0.636 g, 4.65 mmol) in 30 ml of dry benzene ketone **5** (1 g, 4.65 mmol) was added. The reaction mixture was maintained at rt for 2 h (monitoring by ^{19}F NMR spectroscopy). The solvent was evaporated and the residue was crystallized from hexane affording **13a** as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (4H, CH_2), 3.19 (4H, NCH_2), 3.35 and 3.57 (AB-system, $^2J_{H-H}$ = 14.4 Hz, 2 H), 3.72 (1H, OH), 4.89 (1H, CH), 7.25 (2H, CH), 7.67 (1H, CH), 7.77 (1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 28.9, 49.5, 59.6, 77.3 ($^2J_{C-F}$ = 29.5 Hz, CCF_3), 109.8, 112.3, 119.6, 125.4, 126.3, 126.4 ($^1J_{C-F}$ = 286.9 Hz, CF_3), 141.2, 148.9, 151.6, 161.3. MS (EI, 70 eV): *m*/*z* (%) = 351 (44) [M^+], 282 (15), 252 (23), 227 (28), 151 (26), 146 (76), 136 (27), 135 (100), 134 (30), 108 (26). Anal. Calcd. for $C_{17}H_{16}F_3N_3O_2$: C 58.12; H 4.59; N 11.96. Found: C 58.19; H 4.51; N 11.90.

4.4.2. 5-(1,3-Benzoxazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(4-morpholinyl)-2-hexenenitrile (13b)

The procedure for compound **13a** was applied. Pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99–3.07 (4H, CH_2), 3.47 (5H), 3.67 (one part of AB-system, $^2J_{H-H}$ = 15.3 Hz, 1 H), 4.13 (1H, CH), 5.32 (1H, OH), 7.45 (2H, CH), 7.66 (1H, CH), 7.75 (1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.4, 48.3, 65.9, 74.2, 75.4 ($^2J_{C-F}$ = 28.7 Hz, CCF_3), 111.8, 119.5, 120.4, 124.6 ($^1J_{C-F}$ = 284.5 Hz, CF_3), 125.6, 126.8, 139.5, 152.0, 158.9, 161.1. MS (EI, 70 eV): *m*/*z* (%) = 367 (74) [M^+], 327 (11), 298 (26), 268 (20), 243 (24), 216 (27), 215 (26), 167 (32), 151 (100), 146 (99), 121 (33). Anal. Calcd. for $C_{17}H_{16}F_3N_3O_3$: C 55.59; H 4.39; N 11.44. Found: C 55.58; H 4.40; N 11.46.

4.4.3. Ethyl 5-(1,3-benzoxazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(1-pyrrolidinyl)-2-hexenoate (14a)

The procedure for compound **13a** was applied. Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.52 (4H, CH_2), 2.98 (4H, CH_2), 3.31 (one part of AB-system, $^2J_{H-H}$ = 14.1 Hz, 1 H), 4.13 (3H), 4.78 (1H, CH), 7.39 (2H, CH), 7.56 (1H, CH), 7.76 (1H, CH), 8.54 (1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 24.5, 34.4, 48.7, 59.9, 77.1($^2J_{C-F}$ = 29.5 Hz, CCF_3), 88.9, 110.8, 120.5, 123.9 ($^1J_{C-F}$ = 286.5 Hz, CF_3), 124.8, 125.9, 140.3, 150.4, 154.9, 161.2, 172.6. ^{19}F NMR ($CDCl_3$): δ = −80.4. MS (EI, 70 eV): *m*/*z* (%) = 398 (6) [M^+], 215 (49), 183 (20), 154 (42), 146 (100), 138 (63), 111 (37), 110 (77), 102 (38). Anal. Calcd. for $C_{19}H_{21}F_3N_2O_4$: C 57.28; H 5.31; N 7.03. Found: C 57.21; H 5.25; N 7.13.

Table 5
Details of X-ray structure analyses of **16a** and **17b**.

Compound	**16a**	**17b**
Formula	$C_{17}H_{16}F_3N_3OS$	$C_{19}H_{24}F_3NO_4S$
M_r	367.39	419.45
Habit	Colorless tablet	Colorless, irregular
Crystal size (mm)	0.3 × 0.22 × 0.12	0.4 × 0.33 × 0.3
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	$P2_1/n$
Cell constants		
a (Å)	12.8086(6)	14.7826(8)
b (Å)	8.8010(4)	94.368(4)
c (Å)	29.5863(13)	15.9107(11)
α (°)	90	90
β (°)	90	94.368(4)
γ (°)	90	90
V (Å^3)	3335.2	2002.0
Z	8	4
D_x (Mg m^{-3})	1.463	1.392
μ (mm^{-1})	0.24	0.21
F(000)	1520	880
T (°C)	−140	−140
$2\theta_{max}$	60	60
No. of reflections:		
Measured	36346	40745
Independent	4878	5833
R_{int}	0.047	0.038
Parameters	230	279
$wR(F^2$, all refl.)	0.100	0.100
$R(F, > 4\sigma(F))$	0.036	0.035
S	1.05	1.04
max. $\Delta\rho/e$ (Å^{-3})	0.50	0.38

*4.4.4. Ethyl 5-(1,3-benzoxazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(4-morpholinyl)-2-hexenoate (**14b**)*

The procedure for compound **13a** was applied. Crystallized from heptane. Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.76 (2H, CH_2), 2.99–3.07 (6H, CH_2), 3.46 and 3.96 (AB-system, $^2J_{H-H}$ = 14.7 Hz, 2 H), 4.20 (2H, CH_2), 5.11 (1H, CH), 7.42 (2H, CH), 7.61 (1H, CH), 7.72 (1H, OH), 7.79 (1CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 31.8, 50.1, 57.6, 65.8, 78.2 ($^2J_{C-F}$ = 28.3 Hz, *C*CF_3), 110.5, 119.6, 125.4, 126.1, 126.3 ($^1J_{C-F}$ = 285.3 Hz, *C*F_3), 141.3, 149.3, 152.0, 160.3, 168.7. MS (EI, 70 eV): *m*/*z* (%) = 414 (6) [M^+], 215 (58), 199 (23), 170 (12), 154 (32), 146 (100), 126 (92). Anal. Calcd. for $C_{19}H_{21}F_3N_2O_5$: C 55.07; H 5.11; N 6.76. Found: C 55.01; H 5.10; N 6.71.

*4.4.5. 6-(1,3-Benzoxazol-2-yl)-7,7,7-trifluoro-6-hydroxy-4-(1-pyrrolidinyl)-3-hepten-2-one (**15a**)*

The procedure for compound **13a** was applied. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (2H, CH_2), 1.69 (2H, CH_2), 2.17 (3H, CH_3), 2.98–3.31 (4H, CH_2), 3.35 and 4.16 (AB-system, $^2J_{H-H}$ = 14.1 Hz, 2 H), 5.26 (1H, CH), 7.37 (2H, CH), 7.57 (1H, CH), 7.77 (1H, CH), 9.71 (1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 29.3, 31.6, 78.2 ($^2J_{C-F}$ = 28.6 Hz, *C*CF_3), 92.1, 111.3, 119.6, 125.5, 126.1, 126.8 ($^1J_{C-F}$ = 285.5 Hz, *C*F_3), 140.1, 149.7, 151.1, 158.5, 196.4. MS (EI, 70 eV): *m*/*z* (%) = 368 (6) [M^+], 152 (12), 146 (30), 138 (13), 119 (12). Anal. Calcd. for $C_{18}H_{19}F_3N_2O_3$: C 58.69; H 5.20; N 7.61. Found: C 58.61; H 5.15; N 7.55.

*4.4.6. 6-(1,3-Benzoxazol-2-yl)-7,7,7-trifluoro-6-hydroxy-4-(4-morpholinyl)-3-hepten-2-one (**15b**)*

The procedure for compound **13a** was applied. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (3H, CH_3), 2.75–3.31 (7H, CH_2), 3.42 and 3.96 (AB-system, $^2J_{H-H}$ = 14.5 Hz, 2 H), 3.66 (1H, CH_2), 5.52 (1H, CH), 7.41 (2H, CH), 7.61 (1H, CH), 7.78 (1H, CH), 8.75 (1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 32.8, 49.6, 68.3, 78.2 ($^2J_{C-F}$ = 29.3 Hz, *C*CF_3), 98.8, 110.6, 119.6, 125.7, 126.8, 128.1 ($^1J_{C-F}$ = 277 Hz, *C*F_3), 141.6, 149.6, 159.3, 196.3. MS (EI, 70 eV): *m*/*z* (%) = 384 (5) [M^+], 341 (23), 299 (29), 215 (28), 146 (75), 126 (57), 102 (27), 98 (32), 90 (30), 85 (98), 83 (100). Anal. Calcd. for $C_{18}H_{19}F_3N_2O_4$: C 56.25; H 4.98; N 7.29. Found: C 56.23; H 5.01; N 7.28.

*4.4.7. 5-(1,3-Benzothiazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(1-pyrrolidinyl)-2-hexenenitrile (**16a**)*

The procedure for compound **13a** was applied. Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67 (4H, CH_2), 3.11 (4H, CH_2), 3.53 (2H, CH_2), 3.73 (1H, CH), 4.83 (1H, OH), 7.47–7.53 (2H, CH_2), 7.94 (1H, CH), 8.05 (1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 38.1, 65.1, 78.6 ($^2J_{C-F}$ = 28.9 Hz, *C*CF_3), 122.2, 123.8, 124.1 ($^1J_{C-F}$ = 288.3 Hz, *C*F_3), 126.3, 126.8, 136.4, 152.2, 155.5, 167.4. MS (EI, 70 eV): *m*/*z* (%) = 367 (12) [M^+], 327 (11), 298 (14), 232 (18), 162 (21), 136 (58), 135 (100), 134 (67). Anal. Calcd. for $C_{17}H_{16}F_3N_3OS$: C 55.58; H 4.39; N 11.44. Found: C 55.51; H 4.43; N 11.38.

*4.4.8. 5-(1,3-Benzothiazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(4-morpholinyl)-2-hexenenitrile (**16b**)*

The procedure for compound **13a** was applied. Crystallized from isopropanol. Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99 (4H, CH_2), 3.37–3.36 (4H, CH_2), 3.53 and 3.65 (AB-system, $^2J_{H-H}$ = 14.3 Hz, 2 H), 4.22 (1H, CH), 4.83 (1H, OH), 7.47–7.55 (2H, CH), 7.97 (1H, CH), 8.04 (1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.8, 48.2, 65.7, 75.0, 78.7, 120.3, 121.9, 123.4, 124.2 ($^1J_{C-F}$ = 285.5 Hz, *C*F_3), 126.2, 126.7, 151.8, 159.7, 166.5. 122.2, 123.8, 124.1 ($^1J_{C-F}$ = 288.3 Hz, *C*F_3), 126.3, 126.8, 136.4, 152.2, 155.5, 167.4. MS (EI, 70 eV): *m*/*z* (%) = 383 (32) [M^+], 343 (16), 298 (26), 232 (47), 162 (44), 152 (31), 151 (100), 150 (28). Anal. Calcd. for $C_{17}H_{16}F_3N_3O_2S$: C 53.36; H 4.21; N 10.96. Found: C 53.26; H 4.18; N 10.89.

*4.4.9. Ethyl 5-(1,3-benzothiazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(1-pyrrolidinyl)-2-hexenoate (**17a**)*

The procedure for compound **13a** was applied. Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.16–1.62 (4H, CH_2), 2.77–3.10 (4H, NCH_2), 3.38 (one part of AB-system, $^2J_{H-H}$ = 14.1 Hz, 1 H), 4.13 (3H), 4.68 (1H, CH), 7.26–7.48 (2H, CH), 7.88 (1H, CH), 8.03 (1H, CH), 8.83 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): 14.4, 24.5, 34.7, 48.7, 59.9, 78.5 ($^2J_{C-F}$ = 28.3 Hz, *C*CF_3), 88.3, 121.6, 123.3, 124.6 ($^1J_{C-F}$ = 287.6 Hz, *C*F_3), 125.2, 125.9, 135.4, 153.4, 155.5, 167.6, 172.8. MS (EI, 70 eV): *m*/*z* (%) = 414 (11) [M^+], 341 (12), 231 (76), 183 (47), 182 (71), 162 (100), 154 (46), 138 (68), 134 (81), 110 (85). Anal. Calcd. for $C_{19}H_{21}F_3N_2O_3S$: C 55.06; H 5.11; N 6.76. Found: C 54.98; H 5.03; N 6.74.

*4.4.10. Ethyl 5-(1,3-benzothiazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(4-morpholinyl)-2-hexenoate (**17b**)*

The procedure for compound **13a** was applied. Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.77–3.15 (8H, CH_2), 3.53 and 3.94 (AB-system, $^2J_{H-H}$ = 14.2 Hz, 2 H), 4.2 (2H, CH_2), 5.03 (1H, CH), 7.36–7.52 (2H, CH), 7.92 (1H, OH), 8.01 (1H, CH), 8.05 (1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 31.2, 47.5, 60.7, 65.5, 78.3 ($^2J_{C-F}$ = 27.5 Hz, *C*CF_3), 96.4, 121.6, 123.3, 125.4, 126.2, 135.2, 153.6, 158.5, 170.4, 172.4. MS (EI, 70 eV): *m*/*z* (%) = 430 (24) [M^+], 357 (23), 231 (28), 210 (100), 198 (94), 162 (81), 134 (51), 126 (89). Anal. Calcd. for $C_{19}H_{21}F_3N_2O_4S$: C 53.02; H 4.92; N 6.51. Found: C 52.96; H 4.89; N 6.46.

*4.4.11. 6-(1,3-Benzothiazol-2-yl)-7,7,7-trifluoro-6-hydroxy-4-(1-pyrrolidinyl)-3-hepten-2-one (**18a**)*

The procedure for compound **13a** was applied. Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (2H, CH_2), 1.68 (2H, CH_2), 2.14 (3H, CH_3), 2.83 (1H, CH_2), 3.11–3.32 (2H, CH_2), 3.53 (1H, CH_2), 3.41 and 4.09 (AB-system, $^2J_{H-H}$ = 14.1 Hz, 2 H), 5.14 (1H, CH), 7.40–7.47 (2H, CH), 7.89 (1H, CH), 8.03 (1H, CH), 10.03 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 24.8, 30.3, 35.4, 48.9, 49.5, 79.2 ($^2J_{C-F}$ = 28.3 Hz, *C*CF_3), 99.9, 121.7, 123.3, 125.4, 126.1, 135.4, 153.5, 156.5, 171.6, 196.2. MS (EI, 70 eV): *m*/*z* (%) = 384 (16) [M^+], 341 (18), 231 (20), 162 (34), 153 (29), 152 (100), 138 (17), 136 (14), 134 (17). Anal. Calcd. for $C_{18}H_{19}F_3N_2O_2S$: C 56.24; H 4.98; N 7.29. Found: C 56.21; H 4.89; N 7.21.

*4.4.12. 5-(1,3-Benzothiazol-2-yl)-6,6,6-trifluoro-5-hydroxy-1-phenyl-3-(1-pyrrolidinyl)-2-hexen-1-one (**19a**)*

The procedure for compound **13a** was applied. Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (2H, CH_2), 1.74 (2H, CH_2), 2.99–3.3 (3H), 3.55 (2H, CH_2), 4.26 (one part of AB-system, $^2J_{H-H}$ = 14.1 Hz, 1 H), 5.79 (1H, CH), 7.31–7.41 (5H, CH), 7.88 (2H, CH), 8.06 (2H, CH), 10.5 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 33.6, 48.6, 77.3 ($^2J_{C-F}$ = 28.9 Hz, *C*CF_3), 90.1, 123.7, 126.0, 126.7, 127.1, 132.6, 138.8, 139.7, 148.4, 155.6, 176.1, 186.3. MS (EI, 70 eV): *m*/*z* (%) = 446 (14) [M^+], 341 (10), 231 (48), 215 (49), 214 (67), 198 (76), 162 (72), 134 (54), 110 (31), 105 (45), 77 (44), 70 (100). Anal. Calcd. for $C_{23}H_{21}F_3N_2O_2S$: C 61.87; H 4.74; N 6.27. Found: C 61.81; H 4.79; N 6.19.

*4.4.13. 5-(1,3-Benzothiazol-2-yl)-6,6,6-trifluoro-5-hydroxy-3-(4-morpholinyl)-1-phenyl-2-hexen-1-one (**19b**)*

The procedure for compound **13a** was applied. Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.01–3.39 (8H, CH_2), 3.65 and 4.03 (AB-system, $^2J_{H-H}$ = 14.5 Hz, 2 H), 6.07 (1H, CH), 7.41–7.55 (5H, CH), 7.92–8.05 (4H, CH), 9.26 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.0, 47.9, 65.7, 79.1 ($^2J_{C-F}$ = 28.9 Hz, *C*CF_3), 102.6, 121.9, 123.4, 125.7, 126.5, 128.5, 1332.5, 135.4, 139.6, 153.8, 160.6, 171.2, 191.9.

Anal. Calcd. for $C_{23}H_{21}F_3N_2O_3S$: C 59.73; H 4.58; N 6.06. Found: C 59.67; H 4.51; N 6.01.

4.4.14. Ethyl 6,6,6-trifluoro-5-hydroxy-3-(4-morpholinyl)-5-(trifluoromethyl)-2-hexenoate (20b)

Enamine **2b** (1 g, 5 mmol) was dissolved in 50 ml of dry benzene and hexafluoroacetone **7** was passed through resulting solution during 1 h. The reaction mixture was maintained at rt for 6 h. The solvent was evaporated and residue was crystallized from hexane. Yellow oil ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.31 (4H, CH_2), 3.37 (2H, CH_2), 3.73 (4H, CH_2), 4.14 (2H q, $^3J_{HH}$ = 7.2 Hz, CH_2), 5.11 (1H, CH), 8.37 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 26.5, 48.1, 60.8, 65.8, 77.4 ($^2J_{C-F}$ = 29 Hz, CCF_3), 96.2, 123.6 ($^1J_{C-F}$ = 286 Hz, CF_3), 157.2, 172. MS (EI, 70 eV): m/z (%) = 365 (13) [M^+], 320 (42), 292 (46), 199 (14), 198 (100). Anal. Calcd. for $C_{13}H_{17}F_6NO$: C 42.75; H 4.69; N 3.83. Found: C 42.76; H 4.70; N 3.81.

4.4.15. Ethyl 6,6,6-trifluoro-5-hydroxy-5-(1-methyl-1H-imidazol-2-yl)-3-(1-pyrrolidinyl)-2-hexenoate (21a)

To a solution of enamine **2a** (1.03 g, 5.61 mmol) in 30 ml of dry benzene the ketone **9** (1 g, 5.61 mmol) was added. The reaction mixture was refluxed for 5 h (monitoring by ^{19}F NMR spectroscopy). The solvent was evaporated and the residue was crystallized from heptane affording **21a** as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.74–1.81 (4H, CH_2), 3.09–3.33 (5H, CH_2), 3.77 (3H, CH_3), 4.08–4.21 (3H), 4.71 (1H, CH), 6.76 (1H, CH), 6.98 (1H, CH), 7.98 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 25.0, 36.7, 37.7, 47.8, 59.8, 78.3, 83.0, 123.5, 125.6, 126.9, 142.2, 156.2, 172.4. MS (EI, 70 eV): m/z (%) = 362 (81) [M^++1], 361 (38) [M^+], 360 (100) [M^+-1], 184 (59), 182 (52), 179 (48). Anal. Calcd. for $C_{16}H_{22}F_3N_3O_3$: C 53.18; H 6.14; N 11.63. Found: C 53.30; H 6.13; N 11.62.

4.4.16. Ethyl 6,6,6-trifluoro-5-hydroxy-5-(1-methyl-1H-imidazol-2-yl)-3-(4-morpholinyl)-2-hexenoate (21b)

The procedure for compound **21a** was applied. Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.94 (2H, CH_2), 3.35–3.46 (7H, CH_2), 3.51 (one part of AB-system, $^2J_{H-H}$ = 14.4 Hz, 1 H), 3.82 (4H), 4.20 (2H, q, $^3J_{HH}$ = 7.2 Hz, CH_2), 5.02 (1H, CH), 6.80 (1H, CH), 7.00 (1H, CH), 7.44 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 31.6, 34.7, 51.6, 57.4, 67.3, 75.3 ($^2J_{C-F}$ = 29.1 Hz, CCF_3), 90.3, 118.6, 122.3 ($^1J_{C-F}$ = 287.1 Hz, CF_3), 125.1, 143.1, 153.1, 172.3. MS (EI, 70 eV): m/z (%) = 378 (100) [M^++1], 377 (55) [M^+], 376 (97) [M^+-1], 304 (33), 200 (65), 198 (15), 180 (21), 179 (62). Anal. Calcd. for $C_{16}H_{22}F_3N_3O_4$: C 50.93; H 5.88; N 11.14. Found: C 50.87; H 5.87; N 11.12.

4.4.17. 7,7,7-Trifluoro-6-hydroxy-6-(1-methyl-1H-imidazol-2-yl)-4-(1-pyrrolidinyl)-3-hepten-2-one (22a)

The procedure for compound **21a** was applied. Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66–1.81 (4H, CH_2), 2.14 (3H, CH_3), 2.93–3.33 (5H), 3.81 (3H, CH_3), 4.81 (one part of AB-system, $^2J_{H-H}$ = 14.8 Hz, 1 H), 5.21 (1H, CH), 6.78 (1H, CH), 6.99 (1H, CH), 9.31 (1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 29.8, 35.3, 36.1, 49.2, 76.9 ($^2J_{C-F}$ = 28.6 Hz, CCF_3), 95.3, 118.2, 124.3 ($^1J_{C-F}$ = 285 Hz, CF_3), 126.1, 144.5, 152.3, 196.5. MS (EI, 70 eV): m/z (%) = 331 (5) [M^+], 288 (12), 270 (11), 178 (38), 153 (49), 138 (60), 136 (42), 110 (49), 109 (100). Anal. Calcd. for $C_{15}H_{20}F_3N_3O_2$: C 54.38; H 6.08; N 12.68. Found: C 54.29; H 6.01; N 12.72.

4.4.18. Ethyl 6,6,6-trifluoro-5-hydroxy-3-(1-pyrrolidinyl)-2-hexenoate (23a)

The procedure for compound **20b** was applied. The residue was subjected to column chromatography on silica gel using ethyl acetate as an eluent (Rf = 0.88). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 2.75 (1H, d, $^2J_{HH}$ = 14.7 Hz, CH_2), 3.25 (4H, m, CH_2), 3.63–3.78 (6H, m), 4.13 (2H, m), 5.01 (1H, s, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 36.1, 50.1, 58.3, 68.1, 73.1 ($^2J_{C-F}$ = 28.1 Hz, CCF_3), 95.1, 123.4 ($^1J_{C-F}$ = 283 Hz, CF_3), 158.1, 172.6. Anal. Calcd. for $C_{12}H_{18}F_3NO_3$: C 51.24, H 6.45, N 4.98. Found: C 51.29, H 6.39, N 5.01.

4.4.19. Ethyl 6,6,6-trifluoro-5-hydroxy-5-methyl-3-(1-pyrrolidinyl)-2-hexenoate (24a)

The mixture of enamine **2a** (1 g, 5.46 mmol) and 1,1,1-trifluoroacetone **11** (0.62 g, 5.46 mmol) in 50 ml of dry benzene was placed into an ace pressure tube and heated at 80 °C for 6 h. After cooling the solvent was evaporated and the residue was subjected to column chromatography on silica gel using a mixture of ethyl acetate:hexane (1:1) as an eluent (Rf = 0.95). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1,25 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.32 (3H, CH_3), 1.98 (4H, CH_2), 2.65 and 3.83 (AB-system, $^2J_{H-H}$ = 14.4 Hz, 2 H), 3.36–3.47 (4H, CH_2), 4.1 (2H, CH_2), 4.75 (1H, CH), 6.95 (1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 19.5, 25.3, 33.8, 49.1, 59.5, 74.3 ($^2J_{C-F}$ = 27.5 Hz, CCF_3), 87.8, 127.3 ($^1J_{C-F}$ = 285 Hz, CF_3), 157.1, 172.0. MS (EI, 70 eV): m/z (%) = 295 (27) [M^+], 266 (36), 250 (72), 182 (81), 154 (25), 111 (45), 110 (100), 70 (98). Anal. Calcd. for $C_{13}H_{20}F_3NO_3$: C 52.88; H 6.83; N 4.74. Found: C 52.80; H 6.78; N 4.68.

4.4.20. Ethyl 6,6,6-trifluoro-5-hydroxy-5-methyl-3-(4-morpholinyl)-2-hexenoate (24b)

The procedure for compound **24a** was applied. The residue was subjected to column chromatography on silica gel using a mixture of ethyl acetate:hexane (2:1) as an eluent (Rf = 0.91). Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.38 (3H, CH_3), 2.73 and 3.64 (AB-system, $^2J_{H-H}$ = 14.1 Hz, 2 H), 3.3–3.3 (4H, CH_2), 3.75 (4H, CH_2), 4.13 (2H, CH_2), 5.06 (1H, CH), 6.17 (1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 19.7, 30.2, 47.8, 60.1, 68.2, 74.1 ($^2J_{C-F}$ = 27.5 Hz, CCF_3), 94.7, 126.1 ($^1J_{C-F}$ = 285 Hz, CF_3), 158.9, 171.3 Anal. Calcd. for $C_{13}H_{20}F_3NO_4$: C 50.16; H 6.48; N 4.50. Found: C 50.11; H 6.39; N 4.42.

4.4.21. Ethyl 6,6,6-trifluoro-5-hydroxy-5-phenyl-3-(1-pyrrolidinyl)-2-hexenoate (25a)

The procedure for compound **21a** was applied. Yellow oil. ^{1}H NMR (300 MHz, C_6D_6): δ = 1.28 (3H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.48 (2H, CH_2), 2.92 (2H, CH_2), 4.13 (2H), 4.69 (1H, CH), 7.31 (2H, CH), 7.65 (2H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 24.7, 36.4, 48.1, 59.7, 78,0 ($^2J_{C-F}$ = 27.6 Hz, CCF_3), 87,7 127.9 ($^1J_{C-F}$ = 288 Hz, CF_3), 126,3, 127.9, 128,4, 156.2, 172.5. MC (EI, 70 eV): m/z (%) = 357 (54) [M^+], 284 (33), 183 (33), 154 (48), 138 (56), 110 (67), 105 (100), 70 (90). Anal. Calcd. for $C_{18}H_{22}F_3NO_3$ C 60.5; H 6.21; N 3.92; Found C 60.53; H 6.25; N 3.95.

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