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New approach to CF_3-containing polysubstituted anilines: reaction of β-trifluoroacetylvinyl ethers with enamines

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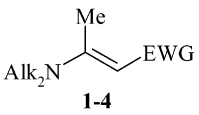
Abstract—The reaction of β-trifluoroacetylvinyl ethers with 'push–pull' enamines having a methyl group at the α-position was investigated. As a result, a set of CF_3-containing dialkyl anilines and their covalent hydrates were obtained. A possible reaction mechanism and the stability of the covalent hydrates obtained are discussed.

1. Introduction

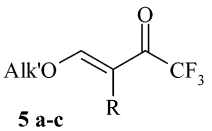
The introduction of a fluorine atom or perfluoroalkyl group into organic molecules often confers significant and useful changes in their chemical and physical properties. Therefore, methods for the synthesis of fluorinated compounds, for example, trifluoromethylated aromatic and heteroaromatic compounds have received considerable interest in recent years.[1] The main methods for the synthesis of trifluoromethyl aromatic compounds are based on the direct introduction of a trifluoromethyl group into the aromatic nucleus, the transformation of other functional groups into a trifluoromethyl group or the reaction of aromatic compounds bearing trifluoromethyl substituents.[2] Meanwhile one of the most satisfactory methods to introduce a trifluoromethyl group into different heterocycles is via the trifluoromethylated building block approach. Some of the recently used trifluoromethylated building blocks are three carbon 1,3-electrophilic agents: 1,3-trifluoromethyl-1,3-diketones,[3] β-alkoxyvinyl trifluoromethyl ketones,[4] β-trifluoromethylsulfones[5] and others. To the best of our knowledge, the synthesis of trifluoromethylbenzenes by this method is unusual.[6] Continuing our research on electrophilic substitution in different systems having an enamine moiety[7] we decided to investigate the possibility of using tertiary 'push–pull' enamines as three-carbon binucleophilic building blocks[8,9] for the synthesis of CF_3-containing benzenes. We chose highly electrophilic β-trifluoroacetylvinyl ethers[10] as the 1,3-electrophilic agents. A set of 'push–pull' enamines **1**–**4** and three β-trifluoroacetylvinyl ethers **5** of different reactivity were chosen as model compounds for investigation of this reaction. These are depicted in Figures 1 and 2. Herein, we report on the result of this investigation.



1-4

Alk_2N = **a:** $N(CH_2)_4$, **b:** $N(CH_2CH_2)_2O$
EWG = **1:** CN; **2:** CO_2Et; **3:** COMe; **4:** COPh

Figure 1. The strucutre of the starting 'push–pull' enamines.



5 a-c

Alk'O = **a:** *i*-BuO; **b,c:** EtO
R = **a:** $COCF_3$; **b:** CO_2Et; **c:** H

Figure 2. The structure of the starting β-trifluoroacetylvinyl ethers.

2. Results and discussion

2.1. Reaction of β-trifluoroacetylvinyl ethers with β-dialkylaminocrotonitriles

Enamines **1**, derivatives of β-aminocrotonitrile, reacted with β-trifluoroacetylvinyl ethers **5** at the enamine β-position giving the corresponding dienamines **6** (Scheme 1). The reaction proved to be very sensitive to the structural features of the enamine and enone. For example, under analogous conditions a more active enone **5a** (compared to **5b**) reacted with enamine **1a**, but did not react with enamine **1b**. Enone **5b** reacted with both enamines. This can be rationalized by steric hindrance.

The behavior of the trifluoroacylated dienamines **6** obtained

Keywords: β-Trifluoroacetylvinyl ethers; 'Push–pull' enamines; Trifluoromethyl; Arene hydrates.
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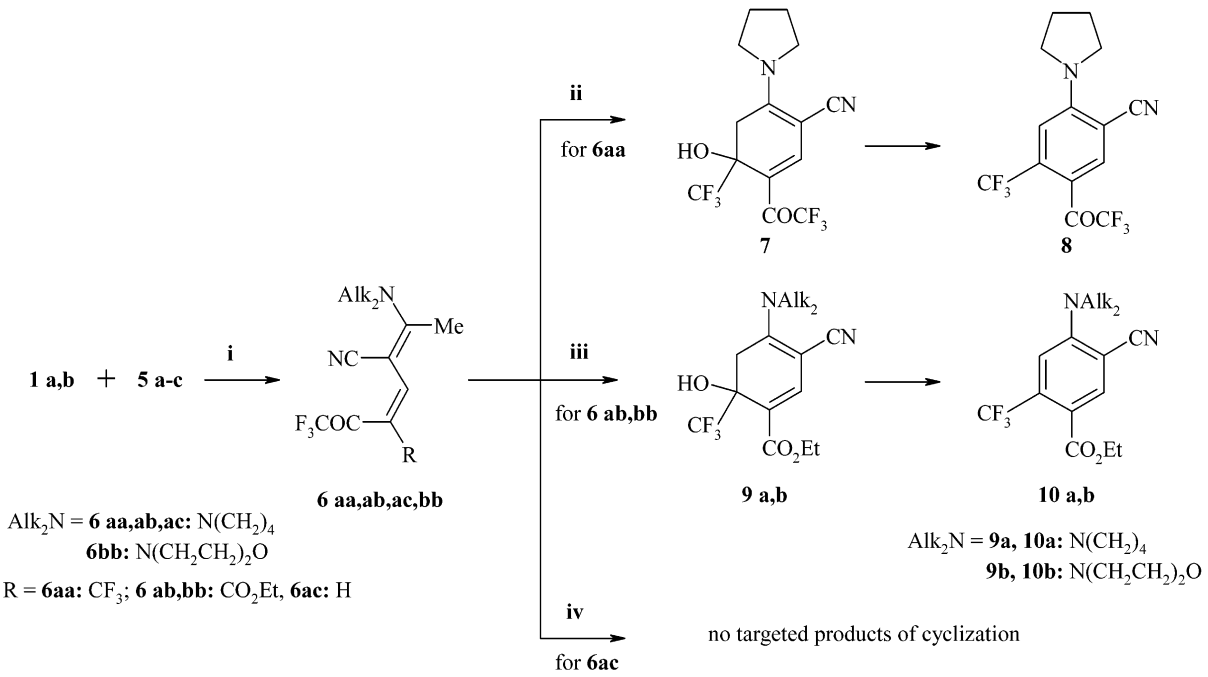
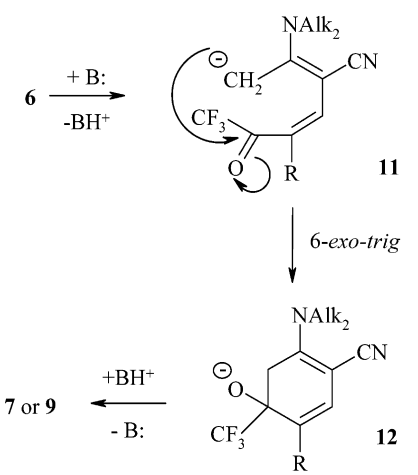


Scheme 1. Reagents and conditions: (i) for **6aa**,**ab**: toluene, rt, 24 h; for **6ac**,**bb**: toluene, rt, 48 h; (ii) toluene, rt, spontaneously; (iii) Et_3N, toluene, 60 °C, 2 h; (iv) NaH, HMPA, Et_2O, reflux, 10 h.

strongly depended on the substituent R at the δ-position. δ,δ-Bistrifluoroacetyldienamine **6aa** (R=$COCF_3$) cyclized spontaneously at rt affording 'arene hydrate' **7** (Scheme 1) thus making purification to an analytically pure state difficult. Unlike **6aa**, dienamines **6ab** and **6bb** (R=CO_2Et) were kinetically stable and could be separated as individual compounds. They cyclized into the corresponding arene hydrate **9** at 60 °C in the presence of catalytic amounts of triethylamine. In the case of dienamine **6ac** (R=H) even the use of a strong base such as NaH in the presence of HMPA did not yield cyclic product.

We suggest the following mechanism. First, abstraction of a proton from the methyl group of dienamines afforded the corresponding resonance-stabilized carbanions **11** which underwent 6-*exo-trig* cyclization to give alkoxides **12**. Finally protonation yielded the corresponding arene hydrate **7** or **9** (Scheme 2). On the one hand, the substituent R influenced CH-acidity of the methyl group. Thus, in the case of dienamine **6aa** due to two trifluoroacetyl groups, CH-acidity was sufficient for abstraction of proton by weak bases, for example, such as the starting enamine **1a** or the dienamine **6aa**, which were present in the reaction mixture. With an ethoxycarbonyl group in dienamine **6ab**, a stronger base such as triethylamine was required for proton abstraction. On the other hand, the substituent R influenced the electrophilicity of the trifluoroacetyl group in carbanion **11**. In resonance-stabilized anions **11** an electron-accepting substituent increases electrophilicity of the neighboring trifluoroacetyl group.



Scheme 2.

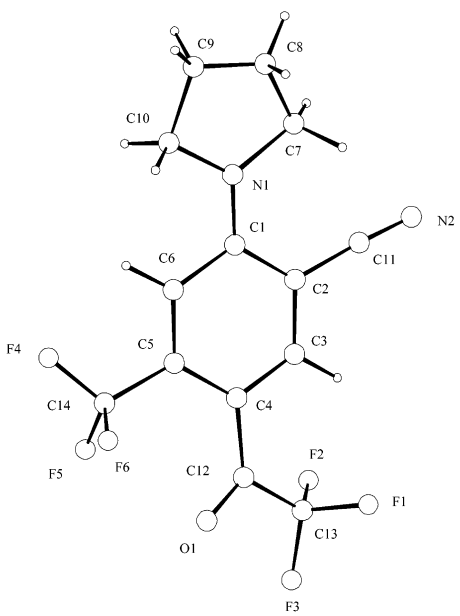
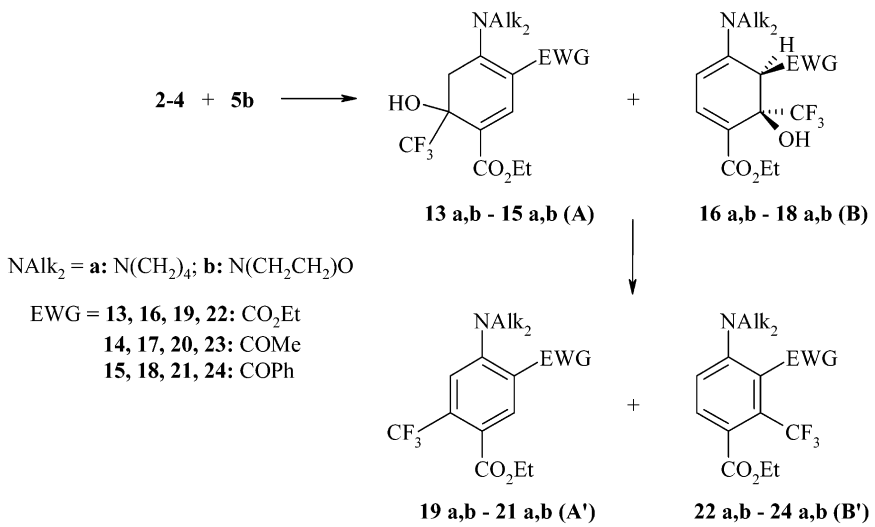


Figure 3. A perspective view and labeling scheme for the independent molecule A of the compound **8**.



Scheme 3.

Table 1. Ratio of regioisomers, summary yields of cyclic products and reaction time of β-trifluoroacetylvinyl ether **5b** with enamines **1**–**4**

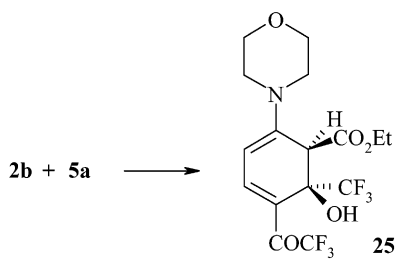
Enamine	Ratio of regioisomers[a]		Yield (%)	Time of reaction (h)[b]
	A	**B**		
1a	100	0	79	—
1b	100	0	42	—
2a	67	33	83	24
2b	84	16	75[c]	72
3a	86	14	68[c]	24
3b	57	43	35[d]	120
4a	59	41	88[c]	48
4b	72	28	34[d]	120

[a] Data of ^{19}F NMR spectra of reaction mixture.
[b] At rt.
[c] Refer to crude mixture of regioisomers.
[d] Data of ^{19}F NMR spectra and GC/MS of reaction mixture.

The structures of trifluoromethyl anilines were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy, mass-spectrometry and elemental analysis. Characteristic features for the aromatic ring in the ^{1}H NMR spectra were two singlets at δ_H~7.0 and 8.0, in ^{19}F NMR spectra presence of chemical shift of CF_3-group at δ_F~−60 and in ^{13}C NMR spectra signal of CF_3–$C(sp^2)$-carbon at δ_C~130 with coupling constant $^{2}J_{CF}$=30 Hz (Tables 2, 5 and 6). Finally, the structure of **8** was confirmed by the X-ray diffraction study (Fig. 3).

2.2. Reaction of β-trifluoroacetylvinyl ethers with β-dialkylaminocrotonoesters and α-methyl-β-enaminones

The transition from the enamine **1** to the enamines **2**–**4** revealed that the latter could react with bielectrophilic β-trifluoroacetylvinyl ethers affording two regioisomers. For in-depth investigation of the reaction use of β-trifluoroacetylvinyl ether **5b** containing only one trifluoromethyl group facilitated monitoring of the reaction by ^{19}F NMR spectroscopy (Scheme 3). The ratio of regioisomers is given in Table 1. Both the ratio of regioisomers and rate of the reaction depended on the structure of the amine residue and the nature of the electron-accepting group of the enamine. Besides, use of morpholine enamines, less active compared to pyrrolidine ones, revealed that many side reactions made separation of the final products more difficult. The reaction was also very sensitive to structural features of the enone. For example, enone **5a** having the electrophilic center shielded by the bulky isobutyl group only yielded a compound of type **B** (Scheme 4). Although compound **25** was separated in a low yield, ^{19}F NMR spectra of the reaction mixture did not show formation of a type **A** regioisomer.



Scheme 4.

The structures of trifluoromethylanilines of types **A′** and **B′** were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy, mass-spectrometry and elemental analysis. Anilines of type **A′** have similar spectral data to those of anilines **8** and **10**. Unlike anilines of **A′** type, anilines of **B′** type have two doublets at δ_H~7.0 and 7.6 with coupling constant

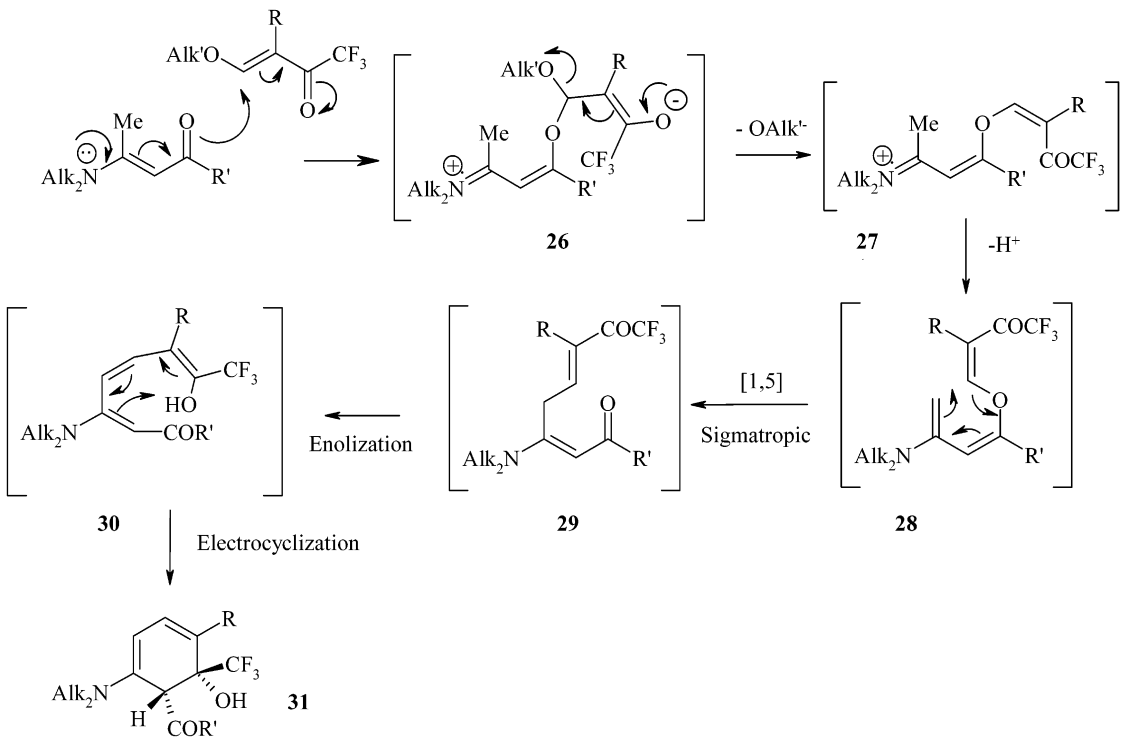
Table 2. Yields, melting points, R_f and ^{19}F NMR data of compounds obtained

Compound	$NAlk_2$	EWG	Yield (%)[a]	Mp (°C)[b]	R_f (eluent)	δ_F (solvent)
6ab[c]	$N(CH_2)_4$	CN	52[d]	108–110	—	−72.3 ($CHCl_3$)
6ac[c]	$N(CH_2)_4$	CN	74[d]	66–69	—	−78.4 ($CHCl_3$)
7	$N(CH_2)_4$	CN	27[d]	113–115	0.28 (EtOAc)	−70.0 (3F), −83.4 (3F) ($CHCl_3$)
8	$N(CH_2)_4$	CN	82[d]	134–135	0.60 (EtOAc)	−62.2 (3F), −71.8 (3F) ($CHCl_3$)
10a	$N(CH_2)_4$	CO_2Et	92[e]	95–97	0.53 (EtOAc)	−59.4 (CH_3CN)
10b	$N(CH_2)_4O$	CO_2Et	42[d]	60–62	0.84 (EtOAc/cyclohexane 1:1)	−59.1 (CH_3CN)
13a	$N(CH_2)_4$	CO_2Et	55[d]	101–102	0.70 (EtOAc/cyclohexane 1:1)	−83.8 ($CHCl_3$)
14a	$N(CH_2)_4$	COMe	21[d]	126	0.26 (EtOAc)	−83.5 ($CHCl_3$)
15a	$N(CH_2)_4$	COPh	38[d]	125–128	0.39 (EtOAc)	−82.3 (benzene)
16a	$N(CH_2)_4$	CO_2Et	27[d]	103	0.88 (EtOAc/cyclohexane 1:1)	−84.6 ($CHCl_3$)
16b	$N(CH_2)_4O$	CO_2Et	12[d]	74	0.40 (EtOAc/cyclohexane 1:1)	−84.4 (toluene)
18a	$N(CH_2)_4$	COPh	22[d]	150–152	0.72 (EtOAc)	−83.1 (benzene)
19a	$N(CH_2)_4$	CO_2Et	91[f]	83	0.65 (EtOAc)	−58.7 (acetone)
19b	$N(CH_2)_4O$	CO_2Et	43[d]	Oil	0.59 (EtOAc/cyclohexane 1:1)	−61.0 ($CHCl_3$)
20a	$N(CH_2)_4$	COMe	90[f]	67	0.65 (EtOAc)	−59.0 ($CHCl_3$)
21a	$N(CH_2)_4$	COPh	78[f]	72	0.68 (EtOAc)	−59.1 (toluene)
22a	$N(CH_2)_4$	CO_2Et	88[f]	Oil	0.67 (EtOAc)	−53.1 (acetone)
22b	$N(CH_2)_4O$	CO_2Et	71[f]	Oil	0.78 (EtOAc/cyclohexane 1:1)	−54.5 (acetone)
24a	$N(CH_2)_4$	COPh	84[f]	Oil	0.71 (EtOAc/cyclohexane=1:1)	−51.0 ($CHCl_3$)
25	$N(CH_2)_4O$	CO_2Et	21[a]	113	0.57 (EtOAc)	−70.0 (3F), −83.4 (3F) ($CHCl_3$)

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] These substances exist as a mixture of *Z*/*E*-isomers, herein and below spectral data refer to major isomer.
[d] Yields refer to the reaction of the corresponding enamines with vinyl ethers.
[e] Yield refers to the reaction of cyclization of dienamine **6ab**.
[f] Yields refer to the reaction of water elimination from the corresponding arene hydrate.

$^3J_{HH}$=8.5 Hz in the aromatic region of their ^1H NMR spectra (Tables 2 and 5).

The formation of compounds of type **A** proceeded analogously to compounds **7** and **9**. The formation of compounds of type **B** testified that electrophilic attack of **5b** at the enamine occurred at the methyl group. Reactions of this type are rare.[11] Although nitrile, carbonyl and alkoxycarbonyl groups are acceptors of the same order, when the EWG was CN, the attack at the methyl group does not occur at all, but when EWG=COR the attack at the methyl group competes with classical attack at the β-position. One can suppose that electrophilic attack at the methyl group proceeds via participation of the carbonyl group. We rationalized the formation of the type **B** compounds by the sequence of reactions shown in (Scheme 5). The reaction proceeded through *O*-nucleophilic attack of enaminone followed by [1,5]-sigmatropic rearrangement



Scheme 5.

(**26**–**28**), analogously to trichloroacylation,[12] phosphorylation[7d] and silylation of previously lithiated enaminones.[13] The intermediate **29** underwent enolization giving **30**, which was converted into the final product **31** via electrocyclic cyclisation.[14] The synchronous nature of the last stage was responsible for the formation of the sole stereoisomer, whose structure was determined by the single crystal X-ray diffraction study of **25** (Fig. 4). Additional proof of the proposed mechanism was obtained by ^{19}F NMR spectroscopy. When the reaction of the enamine **1a** with enone **5a** was run, the signals of the starting enone in the ^{19}F NMR spectra gradually transformed into two equally intense signals at δ −75 and −72 assigned to the dienamine **6aa**, which, in their turn, were converted into two equally intensive signals δ −69 and −84 assigned to arene hydrate **7** and after 48 h were the dominant signals in the spectrum. In the case of enamines **2**–**4** after few hours the ^{19}F NMR spectra of a reaction mixture showed a set of approximately 20 signals of different intensity at the region from δ −67 through δ −80, which gradually transformed into two main signals at δ−82 and ~δ−84 assigned to arene hydrate of type **A** and **B** correspondingly.

2.3. Stability of arene hydrate obtained

Arene hydrate **7**, **13**–**18** and **25** isolated as pure compounds appeared to have interesting and unexpected properties. Spectral methods and elemental analysis confirmed their constituency. For both structural types the CF_3-group appeared at δ −82 to −84 in ^{19}F NMR spectra, and this is typical for a CF_3-group attached to an sp^3 carbon. Also the signals in the ^{13}C NMR spectrum at δ 73 and 75 with coupling constant $^2J_{CF}$=30 Hz for CF_3–$C(sp^3)$ carbons in the type **A** and **B** structures, respectively, were characteristic. Finally, the ^{1}H NMR spectrum of type **A** compounds displayed the CH_2-protons as an AB-system (doublets at δ_A~2.9 and δ_B~3.2 with a geminal coupling constant $^2J_{HH}$~16 Hz) and the ^{1}H NMR spectrum of type **B** compounds showed two doublets at δ~7.5 and 5.0 with the coupling constant $^3J_{HH}$~7 Hz, which corresponded with observation for 'push–pull' dienamines (Tables 3 and 4).

Arene hydrates **7**, **13**–**18** and **25** are crystalline compounds melting without decomposition. They are stable enough to survive chromatographic separation on silica gel. They lost a molecule of water irreversibly upon boiling in toluene in the presence of acids such as *p*-Me–C_6H_4–SO_3H or bases such as Et_3N, with hydrates **B** being far more kinetically stable compared with hydrates **A**.

Our data do not match with data known for the simplest representative of this type of compounds, which are stable at −15 °C in the absence of acids for a few weeks, while in the presence of acids they violently loose water giving the corresponding aromatic compounds.[15] Relatively stable covalent hydrates are described for electron-deficient azine heterocycles, with their stability being rationalized by formation of energy favorable conjugated groups.[16] For example, the hydrated form of the quinazolinium cation is efficiently stabilized by amidinium type resonance. Besides, stable hydrates for 5-$CHal_3$ pyrazoles and isoxazoles are also described,[4,17] but their stability is determined not by thermodynamic, but kinetic factors. The electron-withdrawing $CHal_3$ group destabilizes any carbocation character in the *E1*-like mechanism of elimination of water. In our case, both stabilizing factors could act a part. In both structural types **A** and **B** resonance stabilization of the 'push–pull' dienamine fragment is present. X-ray analysis and ^{19}F NMR spectroscopy data evidence resonance conjugation in the fragment. The chemical shift of the CF_3CO group for compounds **7** and **25** appears at δ−69, which is a typical value for CF_3CO group conjugated with a strong π-donor substituent. At the same time, hydrates prepared by us had prerequisites for kinetic stability as well. Acid catalyzed *E1cb*-elimination of water should form a carbocation, that would be destabilized by CF_3 group, as in the case of 5-CF_3 pyrazoles. Apart from this, the hydrate obtained can eliminate water by an *E1cb*-like mechanism at the expense of electron-accepting substituents that explains the basic catalysis of water elimination. That is the reason why we failed to separate the hydrate **9**.

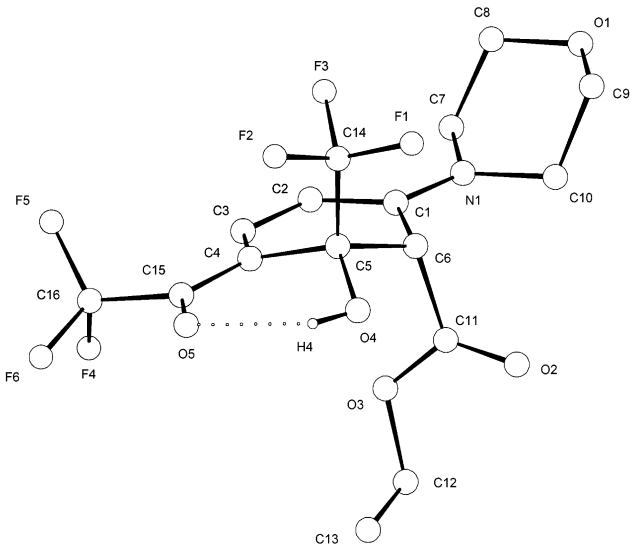


Figure 4. A perspective view and labeling scheme for the molecule **25**.

3. Conclusions

The reaction of β-trifluoroacetylvinyl ethers with 'push–pull' enamines having α-methyl group was investigated. It was shown that the reaction was very sensitive both to the structure of the enamine and the β-trifluoroacetylvinyl ether. The method for synthesis of trifluoromethylated polysubstituted dialkylanilines, which are not accessible by classical methods, was elaborated. A set of stable covalent hydrates was obtained.

4. Experimental

4.1. General

All procedures with hydrolytically sensitive β-trifluoroacetylvinyl ethers were carried out under an atmosphere of dry argon. All solvents were purified and dried by standard methods. NMR spectra were recorded on a Varian VXR-300 spectrometer: ^{1}H and ^{13}C (300 and 75.4 MHz, respectively) with TMS as an internal standard; ^{19}F (282.2 MHz) with $CFCl_3$ as internal standard. IR spectra were recorded on a

Nexus-470 spectrometer for samples in KBr discs. Mass spectra were obtained on a 'Hewlett–Packard' HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on a MX-1321 instrument (EI, 70 eV) by direct inlet for the thermally labile dienamines and arene hydrates. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck $60F_{254}$ plates were used for TLC. Starting enamines[18] and β-trifluoroacetylvinyl ethers[19] were prepared according to the literature.

4.2. X-ray crystallography

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-206106 (**8**) and CCDC-206107 (**25**) and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

4.3. Synthesis of dienamines

4.3.1. Ethyl 4-cyano-5-pyrrolidin-1-yl-2-(trifluoroacetyl)-hexa-2,4-dienoate (6ab). Enamine **1a** (567 mg, 4.17 mmol) was dissolved in toluene (20 mL) and to the solution formed β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) was added. The reaction mixture was maintained at rt overnight, cooled to 4 °C and the precipitate formed was filtered affording **6ab** (715 mg, 52%) as a yellow solid. Mp 108–110 °C. ^{1}H NMR ($CDCl_3$): δ=1.35 (3H, t, $^3J_{HH}$=6.9 Hz, CH_3), 2.07 (4H, br m, CH_2), 2.42 (3H, s, CH_3), 3.75 (2H, br m, NCH_2), 3.97 (2H, br m, NCH_2), 4.53 (2H, q, $^3J_{HH}$=6.9 Hz, OCH_2), 7.82 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ=13.8 (CH_3CH_2O), 21.4 (C(6)H_3), 23.8 (CH_2), 25.7 (CH_2), 53.7 (NCH_2), 54.8 (NCH_2), 60.2 (OCH_2), 80.2 (C(4)), 110.7 (C(2)), 117.2 (CN), 117.6 ($^1J_{CF}$=290.1 Hz, $COCF_3$), 147.7 (C(3)), 165.5 (C(5)), 170.3 ($C(1)O_2Et$), 177.3 ($^2J_{CF}$=33.5 Hz, $COCF_3$). IR, ν_{max} (cm^{-1}): 2989, 2868, 2197, 1716, 1642, 1551, 1522, 1306, 1235, 1193, 1141. MS, *m/z* (%): 330 (M^+, 10), 312 (21), 284 (13), 267 (16), 261 (18), 215 (100), 147 (20), 69 (17), 55 (37), 43 (30). Anal. calcd for $C_{15}H_{17}F_3N_2O_3$: C 54.54; H 5.19; N 8.48. Found C 54.32; H 4.86; N 8.40.

Note. The mother liquor remaining was evaporated to dryness. The solid obtained was treated as described for compound **10a** given below to yield 210 mg (16%) of **10a**.

4.3.2. 6,6,6-Trifluoro-5-oxo-2-(1-pyrrolidin-1-ylethylidene)hex-3-enenitrile (6ac). A solution of enamine **1a** (405 mg, 2.9 mmol) and β-trifluoroacetylvinyl ether **5c** (500 mg, 2.9 mmol) in benzene (20 mL) was maintained at rt for 4 days. Benzene was evaporated in vacuo. The residue was dissolved in boiling cyclohexane (20 mL), after cooling to rt the brown oil formed was maintained under cyclohexane 24 h affording **6ac** (570 mg, 74%) as a red-brown solid. Mp 66–69 °C. ^{1}H HMR ($CDCl_3$): δ=2.05 (4H, br m, CH_2), 2.36 (3H, s, CH_3), 3.70 (2H, br m, NCH_2), 4.00 (2H, br m, NCH_2), 6.39 (1H, d, $^3J_{HH}$=14.1 Hz, CH), 8.09 (1H, $^3J_{HH}$=14.1 Hz, CH). ^{13}C NMR (DMSO-d_6): δ=20.3 (CH_3),

Table 3. ^{1}H NMR data of arene hydrate of type **A**[a]

	^{1}H NMR, δ (ppm), *J* (Hz)					
	$NAlk_2$	EWG	EWG′	C(3)H	$C(6)H_2$	OH
7[b]	2.00–2.28 (4H, m, CH_2), 3.74 (2H, t, $^3J_{HH}$=6.3, NCH_2), 4.15 (2H, t, $^3J_{HH}$=6.3, NCH_2)	—	—	7.68 (1H, s)	2.95 and 3.21 (2H, AB-syst, $^2J_{HH}$=18.6)	6.68 (1H, bs)
13a[b]	1.82 (2H, bm, CH_2), 2.08 (2H, m, CH_2), 3.15 (1H, bm, NCH_2), 3.67 (3H, bm, NCH_2)	1.31 (6H, m, CH_3), 4.20 (4H, m, CH_2)		8.05 (1H, s)	2.96 and 3.21 (2H, AB-syst, $^2J_{HH}$=15.6)	7.11 (1H, s)
14a[b]	1.93 (2H, bm, CH_2), 2.13 (2H, bm, CH_2), 3.70 (4H, bm, NCH_2)	2.30 (3H, s, CH_3)	1.35 (3H, t, $^3J_{HH}$=6.9, CH_3), 4.26 (2H, m, OCH_2)	8.02 (1H, s)	3.01 and 3.19 (2H, AB-syst, $^2J_{HH}$=15.0)	7.08 (1H, s)
15a[c]	0.80–1.20 (4H, m, CH_2), 2.46 (2H, m, NCH_2), 2.82 (1H, bm, NCH_2), 3.29 (1H, bm, NCH_2)	7.12 (3H, m, CH), 7.92 (2H, m, CH)	0.78 (3H, t, $^3J_{HH}$=6.9, CH_3), 3.87 (2H, m, OCH_2)	8.18 (1H, s)	2.85 and 3.05 (2H, AB-syst, $^2J_{HH}$=15.9)	7.15 (1H, s)

[a] Numbering of cycle is started from the carbon atom attached to dialkylamino group.
[b] $CDCl_3$.
[c] C_6D_6.

Table 4. ^{1}H NMR data of arene hydrate of type **B**[a]

	^{1}H NMR, δ (ppm), J (Hz)						
	$NAlk_2$	EWG	EWG′	C(2)H	C(5)H	C(6)H	OH
16a[b]	1.99 (4H, m, CH_2), 3.40 (4H, bm, NCH_2)	1.26 (6H, m, CH_3), 4.15–4.27 (4H, m, CH_2)		3.90 (1H, s)	7.52 (1H, d, $^3J_{HH}$=6.6)	4.76 (1H, d, $^3J_{HH}$=6.6)	7.62 (1H, s)
16b[b]	3.20–3.40 (4H, m, NCH_2), 3.71–3.75 (4H, m, OCH_2)	1.20–1.30 (6H, m, CH_3), 4.20–4.30 (4H, m, CH_2)		3.84 (1H, s)	7.49 (1H, d, $^3J_{HH}$=7.2)	5.05 (1H, d, $^3J_{HH}$=7.2)	7.45 (1H, s)
18a[c]	0.87 (4H, m, CH_2), 2.57–2.76 (4H, m, NCH_2)	7.14 (3H, m, CH), 8.31 (2H, m, CH)	0.87 (3H, t, $^3J_{HH}$=6.9, CH_3), 3.80–4.00 (2H, m, OCH_2)	5.33 (1H, s)	7.92 (1H, d, $^3J_{HH}$=6.6)	4.82 (1H, d, $^3J_{HH}$=6.6)	8.53 (1H, s)
25[b]	3.60–3.76 (8H, m, CH_2)	1.24 (3H, t, $^3J_{HH}$=6.9, CH_3), 4.10–4.30 (2H, m, CH_2)	—	3.95 (1H, s)	7.70 (1H, d, $^3J_{HH}$=7.2)	5.28 (1H, d, $^3J_{HH}$=7.2)	7.47 (1H, s)

[a] Numbering of cycle is started from the carbon atom attached to dialkylamino group.
[b] $CDCl_3$.
[c] C_6D_6.

23.8 (CH_2), 25.5 (CH_2), 53.1 (NCH_2), 53.2 (NCH_2), 80.5 (C(2)), 102.0 (C(4)), 116.8 ($^1J_{CF}$=290.1 Hz, $COCF_3$), 118.3 (*C*N), 150.5 (C(3)), 166.6 (N–*C*=), 176.0 ($^2J_{CF}$=33.5 Hz, *C*OCF_3). IR, ν_{max} (cm^{-1}): 2982, 2197, 1654, 1578, 1509, 1412, 1185, 1133. MS, *m/z* (%): 258 (M^+, 31), 189 (68), 161 (60), 147 (48), 119 (38), 69 (24), 65 (26), 55 (100), 42 (65). Anal. calcd for $C_{12}H_{13}F_3N_2O$: C 55.81; H 5.07; N 10.85. Found C 55.73; H 4.86; N 10.78.

4.4. Synthesis of arene hydrate and dialkylamino-anilines

4.4.1. 4-Hydroxy-2-pyrrolidin-1-yl-5-(trifluoroacetyl)-4-(trifluoromethyl) cyclohexa-1,5-diene-1-carbonitrile (7). A solution of enamine **1a** (234 mg, 1.72 mmol) and β-trifluoroacetylvinyl ether **5a** (500 mg, 1.72 mmol) in toluene (20 mL) was maintained at rt for 40 h. Toluene was evaporated in vacuo. The residue was triturated with *n*-hexane and crystallized from mixture 2-propanol-cyclohexane affording **7** (167 mg, 27%) as a yellow solid. Mp 113–115 °C. IR, ν_{max} (cm^{-1}): 3530–3320 (br), 2953, 2875, 2223, 1708, 1617, 1544, 1477, 1197, 1144, 1021. MS, *m/z* (%): 354 (M^+, 7), 336 (M^+-H_2O, 27), 285 (48), 267 (100), 69 (24), 43 (49). Anal. calcd for $C_{14}H_{12}F_6N_2O_2$: C 47.47; H 3.41; N 7.91. Found C 47.53; H 3.39; N 7.83.

4.4.2. 2-Pyrrolidin-1-yl-5-(trifluoroacetyl)-4-(trifluoromethyl)benzonitrile (8). A solution of **1a** (468 mg, 3.47 mmol) and β-trifluoroacetylvinyl ether **5a** (1 g, 3.47 mmol) in benzene (15 mL) was maintained at rt 3 days. To the reaction mixture few crystals of *p*-toluenesulfonic acid were added and it was refluxed for 1.5 h. Benzene was evaporated in vacuo. The residue was crystallized from cyclohexane affording **8** (946 mg, 82%) as a white solid. Mp 134–135 °C. IR, ν_{max} (cm^{-1}): 3144, 3078, 2950, 2982, 2223, 1708, 1545, 1477, 1363, 1288, 1193, 1144, 1021, 864, 734. MS, *m/z* (%): 336 (M^+, 24), 267 (M^+-CF_3, 100), 225 (19). Anal. calcd for $C_{14}H_{10}F_6N_2O$: C 50.01; H 3.00; N 8.33. Found C 50.00; H 3.01; N 8.30.

4.4.3. Ethyl 5-cyano-4-pyrrolidin-1-yl-2-(trifluoromethyl)benzoate (10a). Dienamine **6ab** (500 mg, 1.5 mmol) was dissolved in hot toluene (15 mL) and to the solution formed Et_3N (0.25 mL) was added. The reaction mixture was maintained at 60 °C for 4 h. Toluene was evaporated in vacuo. The residue was crystallized from cyclohexane affording **10a** (435 mg, 92%) as a white solid. Mp 95–97 °C. IR, ν_{max} (cm^{-1}): 2976, 2868, 2220, 1724, 1613, 1542, 1456, 1363, 1283, 1253, 1148, 1105, 1002. MS, *m/z* (%): 312 (M^+, 100), 311 (M^+-1, 77), 284 ($M^+-C_2H_4$, 67), 267 ($M^+-C_2H_4-OH$, 77), 256 (31), 239 (15), 225 (23). Anal. calcd for $C_{15}H_{15}F_3N_2O_2$: C 57.69; H 4.84; N 8.97. Found C 57.81; H 4.93; N 8.91.

4.4.4. Ethyl 5-cyano-4-morpholin-4-yl-2-(trifluoromethyl)benzoate (10b). A solution of enamine **1b** (633 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (20 mL) was maintained at rt for 4 days. Then to the reaction mixture was added Et_3N (0.25 mL) and it was heated at 60 °C for 2 h. Toluene was evaporated in vacuo. The residue was subjected to a column chromatography over silica gel using EtOAc/cyclohexane 1:1 as eluent affording **10b** (574 mg, 42%) as a white solid.

Table 5. ^{1}H NMR data of trifluoromethyl benzenes[a]

	^{1}H NMR, δ (ppm), J (Hz)				
	$NAlk_2$	EWG	EWG′	C(3 or 5)H	C(6)H
8[b]	2.12 (4H, m, CH_2), 3.82 (4H, NCH_2)	—	—	8.06 (1H, s)	7.09 (1H, s)
10a[c]	1.95 (4H, m, CH_2), 3.62 (4H, m, NCH_2)	—	1.26 (3H, t, $^3J_{HH}$=7.2), 4.21 (2H, q, $^3J_{HH}$=7.2)	8.00 (1H, s)	6.96 (1H, s)
10b[c]	3.35 (4H, t, $^3J_{HH}$=4.8), 3.76 (4H, t, $^3J_{HH}$=4.8)	—	1.27 (3H, t, $^3J_{HH}$=7.2), 4.26 (2H, q, $^3J_{HH}$=7.2)	8.06 (1H, s)	7.32 (1H, s)
19a[b]	2.00 (4H, m, CH_2), 3.33 (4H, NCH_2)	1.34–1.42 (6H, m, CH_3), 4.31–4.41 (4H, m, CH_2)		8.19 (1H, s)	7.07 (1H, s)
19b[b]	3.19 (4H, t, $^3J_{HH}$=4.8), 3.87 (4H, t, $^3J_{HH}$=4.8)	1.35–1.43 (6H, m), 4.33–4.43 (4H, m)		8.25 (1H, s)	7.28 (1H, s)
20a[b]	2.00 (4H, m, CH_2), 3.20 (4H, m, NCH_2)	2.62 (3H, s)	1.37 (3H, t, $^3J_{HH}$=6.9), 4.34 (2H, q, $^3J_{HH}$=6.9)	8.16 (1H, s)	7.10 (1H, s)
21a[b]	1.95 (4H, m, CH_2), 3.21 (4H, m, NCH_2)	7.50 (2H, t, $^3J_{HH}$=7.8), 7.62 (1H, t, $^3J_{HH}$=7.8), 7.92 (2H, d, $^3J_{HH}$=7.8)	1.31 (3H, t, $^3J_{HH}$=7.2), 4.28 (2H, q, $^3J_{HH}$=7.2)	7.89 (1H, s)	7.13 (1H, s)
22a[b]	1.96 (4H, m, CH_2), 3.32 (4H, m, NCH_2)	1.32–1.41 (6H, m), 4.27–4.38 (4H, m)		7.69 (1H, d, $^3J_{HH}$=8.1)	7.39 (1H, d, $^3J_{HH}$=8.1)
22b[b]	3.00 (4H, t, $^3J_{HH}$=4.2), 3.78 (4H, t, $^3J_{HH}$=4.2)	1.32–1.41 (6H, m), 4.33–4.42 (4H, m)		7.57 (1H, d, $^3J_{HH}$=8.7)	6.84 (1H, d, $^3J_{HH}$=8.7)
24a[b]	1.60–1.80 (4H, m), 3.04 (2H, m), 3.21 (2H, m)	7.44 (2H, t, $^3J_{HH}$=7.8), 7.57 (1H, t, $^3J_{HH}$=7.8), 7.82 (2H, d, $^3J_{HH}$=7.8)	1.32 (3H, t, $^3J_{HH}$=7.2), 4.28 (2H, q, $^3J_{HH}$=7.2)	7.65 (1H, d, $^3J_{HH}$=9.0)	6.94 (1H, d, $^3J_{HH}$=9.0)

[a] Numbering of cycle is started from the carbon atom attached to dialkylamino group.
[b] $CDCl_3$.
[c] CD_3CN.

Table 6. ^{13}C NMR data of arene hydrate and benzenes[a]

	^{13}C NMR, δ (ppm), (J_{CF} (Hz))									
	$NAlk_2$	EWG	EWG′	CF_3	C1	C2	C3	C4	C5	C6
7[b]	24.3, 25.4, 52.3, 52.4	118.6	116.6 (290.3), 177.5 (33.5)	125.6 (289.1)	161.4	77.0	152.6	108.3	73.0 (29.6)	36.7
8[b]	25.5, 50.6	118.7	116.4 (289.4), 176.7 (34.7)	122.3 (273.4)	151.0	94.8	140.9	118.6	134.6 (33.0)	115.2 (6.2)
10a[c]	25.2, 50.0	119.1	13.9, 61.3, 163.6	122.8 (273.6)	150.0	94.4	140.0	114.9	132.1 (29.0)	113.6 (5.7)
10b[d]	51.6, 67.2	118.7	14.2, 63.0, 166.1	122.8 (273.6)	146.5	94.8	138.7	118.0	131.8 (29.3)	117.8
13a[b]	25.3 (b), 51.5 (b), 55.0 (b)	14.4, 14.5, 59.9, 60.4, 164.8, 168.2		126.4 (289.2)	161.2	95.1	146.3	103.2	73.4 (29.0)	36.4
14a[c]	25.6 (b), 52.6 (b), 56.5 (b)	27.8, 189.4	14.8, 60.4, 167.7	127.0 (281.9)	162.8	106.1	146.7	101.1	73.3 (27.2)	37.5
15a[c]	24.9, 25.8, 52.4, 55.9	129.0, 129.6, 132.1, 139.4, 189.5	14.7, 60.3, 167.5	126.5 (288.5)	162.5	104.8	147.2	101.2	73.2 (28.7)	37.1
16a[b]	24.9, 48.3	14.0, 14.2, 60.0, 61.6, 166.5, 168.6		126.1 (290.0)	150.4	49.2	74.9 (29.5)	101.1	145.3	91.1
16b[b]	46.9, 66.1	14.1, 14.2, 60.6, 61.7, 166.8, 168.1		125.8 (289.2)	151.6	48.0	74.9 (29.8)	105.8	143.9	94.3
18a[c]	24.2 (b), 48.6 (b)	129.1, 129.4, 134.1, 138.4, 192.2	14.8, 60.3, 168.8	126.4 (289.9)	154.0	46.9	76.1 (30.3)	96.6	146.7	92.4
19a[b]	25.7, 50.9	13.9, 14.1, 61.2, 61.4, 165.5, 167.4		123.0 (272.1)	148.5	115.5	135.5	117.7	132.2 (31.3)	112.5 (5.9)
19b[b]	51.7, 66.5	13.9, 14.1, 61.6, 61.7, 165.4, 166.2		122.8 (272.0)	153.4	124.4	135.1	121.9	132.4 (32.5)	116.4 (6.9)
20a[b]	25.7, 51.8	29.2, 199.1	14.0, 61.2, 165.5	123.1 (272.3)	148.1	126.0	133.9	115.1	131.9 (31.3)	112.9 (8.0)
21a[c]	25.8, 51.3	128.6, 130.5, 133.4, 137.3, 195.1	14.0, 61.2, 165.7	123.0 (272.1)	148.7	124.4	135.1	115.1	131.9 (31.9)	112.6 (4.9)
22a[b]	25.9, 50.0	13.8, 14.0, 61.7, 62.4, 168.0, 168.4		123.6 (274.2)	148.3	117.8	128.2 (30.6)	119.8	131.4	116.1
22b[b]	53.4, 66.5	13.9, 14.0, 62.4, 62.5, 166.2, 166.8		123.4 (274.2)	150.8	123.6	128.5 (30.3)	126.8	131.5	125.0
24a[b]	25.6, 60.0	128.5, 129.3, 131.2, 137.9, 196.8	13.9, 61.6, 168.0	123.4 (277.7)	149.2	124.4	128.4 (31.0)	120.9	133.4	116.4
25[b]	48.7, 65.9	13.6, 61.7, 164.2	117.6 (289.6), 172.9 (32.5)	125.7 (290.6)	158.4	47.5	75.3 (30.0)	102.4	151.9 (3.4)	96.8

[a] Numbering of cycle is started from the carbon atom attached to dialkylamino group.
[b] $CDCl_3$.
[c] DMSO-d_6.
[d] CD_3CN.

R_f(EtOAc/cyclohexane 1:1)=0.84. Mp 60–62 °C (MeOH). IR, ν_{max} (cm^{-1}): 3144, 3078, 2968, 2932, 2864, 2225, 1732, 1609, 1550, 1419, 1285, 1237, 1164, 1120, 1052, 983, 917, 885, 786. MS, *m/z* (%): 328 (M^+, 85), 283 ($M^+-C_2H_4-OH$, 36), 270 ($M^+-C_2H_4-CH_2O$, 61), 242 ($M^+-N(CH_2CH_2)_2O$, 54), 225 ($M^+-N(CH_2CH_2)_2O-OH$, 100), 215 (15). Anal. calcd for $C_{15}H_{15}F_3N_2O_3$: C 54.88; H 4.61; N 8.53. Found C 54.80; H 4.52; N 8.51.

4.4.5. Diethyl 6-hydroxy-4-pyrrolidin-1-yl-6-(trifluoromethyl)cyclohexa-1,3-diene-1,3-dicarboxylate (13a) and diethyl 2-hydroxy-6-pyrrolidin-1-yl-2-(trifluoromethyl)-cyclohexa-3,5-diene-1,3-dicarboxylate (16a). A solution of enamine **2a** (763 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (20 mL) was maintained at rt for 30 h. Toluene was evaporated in vacuo. The residue was triturated with *n*-hexane and was subjected to a column chromatography over silica gel using EtOAc/cyclohexane 1:1 as eluent affording **13a** (860 mg, 55%) and **16a** (340 mg, 27%).

Compound **13a**. Yellow solid. R_f(EtOAc/cyclohexane 1:1)=0.70. Mp 101–102 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3302, 2986, 2868, 1679, 1642, 1588, 1535, 1333, 1210, 1160, 1119, 1053, 760. MS, *m/z* (%): 377 (M^+, 12), 332 (16), 330 (13), 308 (10), 262 (100), 234 (10). Anal. calcd for $C_{17}H_{22}F_3NO_5$: C 54.11; H 5.88; N 3.71. Found C 54.03; H 6.00; N 3.70.

Compound **16a**. Orange solid. R_f(EtOAc/cyclohexane 1:1)=0.88. Mp 103 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3185, 2986, 2860, 1740, 1637, 1535, 1280, 1176, 1109, 1024, 761, 680. MS, *m/z* (%): 377 (M^+, 11), 330 (13), 308 (11), 262 (100), 190 (29). Anal. calcd for $C_{17}H_{22}F_3NO_5$: C 54.11; H 5.88; N 3.71. Found C 54.06; H 6.02; N 3.71.

4.4.6. Diethyl 2-hydroxy-6-morpholin-4-yl-2-(trifluoromethyl)cyclohexa-3,5-diene-1,3-dicarboxylate (16b) and diethyl 4-morpholin-4-yl-6-(trifluoromethyl)isophthalate (19b). A solution of enamine **2b** (829 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (20 mL) was maintained at rt for 30 h and then heated at 40 °C for 4 h. Toluene was evaporated in vacuo. The residue was passed through a short silica gel column using EtOAc as eluent to afford a crude mixture of **16b** and **19b**, which was subjected to a column chromatography over silica gel using EtOAc/cyclohexane 1:1 as eluent affording **16b** (670 mg, 43%) and **19b** (196 mg, 12%).

Compound **16b**. Yellow solid. R_f(EtOAc/cyclohexane 1:1)=0.40. Mp 74 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3500–3250 (br), 2984, 2912, 2854, 1735, 1654, 1535, 1458, 1292, 1233, 1180, 1114. MS, *m/z* (%): 393 (M^+, 16), 324 (21), 278 (100), 206 (27). Anal. calcd for $C_{17}H_{22}F_3NO_6$: C 51.91; H 5.64; N 3.56. Found C 52.13; H 5.81; N 3.63.

Compound **19b**. Colorless oil. R_f(EtOAc/cyclohexane 1:1)=0.59. IR, ν_{max} (cm^{-1}): 2983, 2852, 1727, 1609, 1510, 1370, 1302, 1233, 1148, 1052, 976, 919, 878, 780. MS, *m/z* (%): 375 (M^+, 22), 346 (36), 344 (27), 332 (46), 330 ($M^+-C_2H_4-OH$, 54), 328 (22), 302 ($M^+-C_2H_4-OH-CO$, 100), 288 (46), 272 (28), 260 (13), 244 (20), 217 (14). Anal. calcd for $C_{17}H_{20}F_3NO_5$: C 54.40; H 5.37; N 3.73. Found C 54.39; H 5.35; N 3.70.

4.4.7. Ethyl 3-acetyl-6-hydroxy-4-pyrrolidin-1-yl-6-(trifluoromethyl)cyclohexa-1,3-diene-1-carboxylate (14a). A solution of enamine **3a** (637 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (20 mL) was maintained at rt for 48 h and then heated at 40 °C for 0.5 h. Toluene was evaporated in vacuo. The residue was triturated with *n*-hexane and crystallized from ethanol affording **14a** (295 mg, 21%) as a yellow solid. Mp 126 °C. R_f(EtOAc)=0.26. IR, ν_{max} (cm^{-1}): 3450–3350 (br), 2982, 2860, 1719, 1676, 1606, 1445, 1293, 1270, 1157, 1135. MS, *m/z* (%): 347 (M^+, 13), 329 (10), 278 (9), 232 (100), 70 (20), 43 (21). Anal. calcd for $C_{16}H_{20}F_3NO_4$: C 55.33; H 5.80; N 4.03. Found C 55.62; H 5.61; N 4.00.

Note. The procedure given below allowed the separation of 438 mg (32%) of **20a**. The mother liquor remaining from crystallization of **14a** and hexane washings were combined and solvents were evaporated. The residue was taken up in toluene (5 mL), a few crystals of *p*-toluenesulfonic acid were added and the reaction mixture was refluxed for 15 min. Toluene was evaporated in vacuo, and the residue was subjected to a column chromatography over silica gel using EtOAc as eluent affording **20a**.

4.4.8. Ethyl 3-benzoyl-6-hydroxy-4-pyrrolidin-1-yl-6-(trifluoromethyl)cyclohexa-1,3-diene-1-carboxylate (15a) and ethyl 5-benzoyl-6-hydroxy-4-pyrrolidin-1-yl-6-(trifluoromethyl)cyclohexa-1,3-diene-1-carboxylate (18a). A solution of enamine **4a** (896 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (30 mL) was maintained at rt for 48 h and then heated at 50 °C for 2 h. Toluene was evaporated in vacuo, and the residue was subjected to a column chromatography over silica gel using EtOAc as eluent affording **15a** (650 mg, 38%) and **18a** (380 mg, 22%).

Compound **15a**. Orange solid. R_f(EtOAc)=0.26. Mp 125–158 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3500–3400 (br), 2969, 2922, 2860, 1704, 1655, 1603, 1540, 1448, 1271, 1231, 1146, 1106, 1003. MS, *m/z* (%): 409 (M^+, 18), 391 (23), 340 (9), 294 (100), 105 (30), 91 (9), 77 (19), 70 (22). Anal. calcd for $C_{21}H_{22}F_3NO_4$: C 61.61; H 5.4; N 3.42. Found C 61.66; H 5.38; 3.38.

Compound **18a**. Orange solid. R_f(EtOAc)=0.72. Mp 150–152 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3230–3180 (br), 2983, 2852, 1691, 1640, 1529, 1450, 1399, 1280, 1179, 1107, 759. MS, *m/z* (%): 409 (M^+, 8), 294 (30), 287 (10), 105 (100), 77 (23). Anal. calcd for $C_{21}H_{22}F_3NO_4$: C 61.61; H 5.4; N 3.42. Found C 61.68; H 5.34; 3.38.

4.4.9. Ethyl 6-hydroxy-2-morpholin-4-yl-5-(trifluoroacetyl)-6-(trifluoromethyl)cyclohexa-2,4-diene-1-carboxylate (25). A solution of enamine **2b** (684 mg, 3.47 mmol) and β-trifluoroacetylvinyl ether **5a** (1 g, 3.47 mmol) in cyclohexane (30 mL) was maintained at rt for 24 h and then refluxed for 2 h. Cyclohexane was evaporated in vacuo, and the residue was crystallized from 2-propanol affording **25** (293 mg, 21%) as an orange solid. Mp 103 °C. IR, ν_{max} (cm^{-1}): 3300–3100 (br), 3121, 2990,

2927, 2849, 1736, 1598, 1513, 1412, 1332, 1176, 1026, 958, 925, 703, 642. MS, *m/z* (%): 417 (M^+, 13), 348 (M^+-CF_3, 32), 276 (100), 206 (66), 148 (46), 69 (CF_3^+, 15). Anal. calcd for $C_{16}H_{17}F_6NO_5$: C 46.05; H 4.11; N 3.36. Found C 46.17; H 4.00; N 3.38.

4.5. General procedures for elimination of water from arene hydrate

Procedure A. To a solution of arene hydrate (100 mg) in toluene (2 mL) a few crystals of *p*-toluenesulfonic acid were added and the reaction mixture was refluxed for 2–4 h (reaction was monitored by TLC using EtOAc or mixture EtOAc/cyclohexane 1:1 as eluent). Toluene was evaporated in vacuo. The residue was extracted with boiling *n*-hexane (2 mL) and *n*-hexane was evaporated in vacuo affording the corresponding benzene.

Procedure B. To a solution of arene hydrate (100 mg) in toluene (5 mL) Et_3N (0.25 mL) was added and the reaction mixture was refluxed for 2–4 h (Reaction was monitored by TLC using EtOAc or mixture EtOAc/cyclohexane 1:1 as eluent). Solvent was evaporated in vacuo. The residue was extracted with boiling *n*-hexane (2 mL) and *n*-hexane was evaporated in vacuo affording the corresponding benzene.

Procedure C. To a solution of arene hydrate (50 mg) in chloroform, (2 mL) a few drops of $SOCl_2$ were added. The reaction mixture was heated to boiling, allowed to cool and maintained at rt overnight. Chloroform was evaporated in vacuo. The residue was extracted with boiling *n*-hexane (2 mL) and *n*-hexane was evaporated in vacuo affording the corresponding benzene.

4.5.1. Diethyl 4-pyrrolidin-1-yl-6-(trifluoromethyl)isophthalate (19a). Procedure A was applied. White solid. Mp 83 °C. IR, ν_{max} (cm^{-1}): 2980, 2875, 1706, 1606, 1540, 1451, 1368, 1271, 1251, 1222, 1151, 1088, 996, 858, 780. MS, *m/z* (%): 359 (M^+, 16), 331 ($M^+-C_2H_4$, 25), 330 ($M^+-C_2H_5$, 100), 314 ($M^+-C_2H_4-OH$, 28), 302 (12), 275 (11). Anal. calcd for $C_{17}H_{20}F_3NO_4$: C 56.82; H 5.61; N 3.90. Found C 56.63; H 5.60; N 3.90.

4.5.2. Ethyl 5-acetyl-4-pyrrolidin-1-yl-2-(trifluoromethyl)benzoate (20a). Procedure A was applied. White solid. Mp 67 °C. IR, ν_{max} (cm^{-1}): 2977, 2860, 1725, 1072, 1605, 1533, 1445, 1365, 1292, 1267, 1246, 1148, 1071, 997, 955, 855, 779. MS, *m/z* (%): 329 (M^+, 100), 315 (M^+-CH_3, 13), 312 (13), 301 ($M^+-C_2H_4$, 21), 286 (53), 284 ($M^+-C_2H_4-OH$, 58), 273 (53), 258 (20), 256 (21), 241 (17), 144 (16), 70 ($N(CH_2)_4^+$, 56), 43 (CH_3CO^+, 46). Anal. calcd for $C_{16}H_{18}F_3NO_3$: C 58.35; H 5.51; N 4.25. Found C 58.28; H 5.45; N 4.20.

4.5.3. Ethyl 5-benzoyl-4-pyrrolidin-1-yl-2-(trifluoromethyl)benzoate (21a). Procedure B was applied. White solid. Mp 72 °C. IR, ν_{max} (cm^{-1}): 2975, 2922, 2860, 1734, 1655, 1603, 1540, 1447, 1272, 1231, 1146, 1106, 1003, 955, 879, 724, 688. MS, *m/z* (%): 391 (M^+, 100), 374 (11), 363 ($M^+-C_2H_4$, 23), 362 ($M^+-C_2H_5$, 33), 346 ($M^+-C_2H_4-OH$, 32), 334 (22), 105 ($PhCO^+$, 32), 91 (13), 77 (Ph^+, 33), 70 ($N(CH_2)_4^+$, 26). Anal. calcd for $C_{21}H_{20}F_3NO_3$: C 64.44; H 5.15; N 3.58. Found C 64.41; H 5.01; N 3.51.

4.5.4. Diethyl 4-pyrrolidin-1-yl-2-(trifluoromethyl)isophthalate (22a). Procedure A was applied. Colorless oil. IR, ν_{max} (cm^{-1}): 2982, 2868, 1728, 1596, 1485, 1382, 1321, 1313, 1233, 1183, 1143, 1024, 991, 789. MS, *m/z* (%): 359 (M^+, 47), 331 ($M^+-C_2H_4$, 24), 330 ($M^+-C_2H_5$, 100), 314 ($M^+-C_2H_4-OH$, 42), 285 (16), 266 (19), 244 (18). Anal. calcd for $C_{17}H_{20}F_3NO_4$: C 56.82; H 5.61; N 3.90. Found C 56.62; H 5.60; N 3.90.

4.5.5. Diethyl 4-morpholin-4-yl-2-(trifluoromethyl)isophthalate (22b). Procedure C was applied. Pale yellow oil. 2983, 2914, 2844, 1735, 1594, 1450, 1368, 1298, 1232, 1185, 1149, 1022, 964. MS, *m/z* (%): 375 (M^+, 45), 344 (19), 332 (27), 330 ($M^+-C_2H_4-OH$, 88), 302 ($M^+-C_2H_4-OH-CO$, 100), 262 (62), 240 (41), 224 (33), 204 (28), 176 (16), 144 (18), 59 (43). Anal. calcd for $C_{17}H_{20}F_3NO_5$: C 54.40; H 5.37; N 3.73. Found C 54.25; H 5.25; N 3.70.

4.5.6. Ethyl 3-benzoyl-4-pyrrolidin-1-yl-2-(trifluoromethyl)benzoate (24a). Procedure A was applied. Pale yellow oil. IR, ν_{max} (cm^{-1}): 3054, 2977, 2868, 1723, 1675, 1593, 1449, 1369, 1300, 1143, 1027, 990, 881, 787, 710. MS, *m/z* (%): 391 (M^+, 100), 346 ($M^+-C_2H_4-OH$, 26), 322 (16), 314 (16), 246 (21), 211 (11), 105 ($PhCO^+$, 25), 91 (10), 77 (Ph^+, 32). Anal. calcd for $C_{21}H_{20}F_3NO_3$: C 64.44; H 5.15; N 3.58. Found C 64.38; H 5.00; N 3.49.

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