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Synthesis of functionalized *m*-bistrifluoromethylbenzenes via cyclocondensation of 1,1,1,5,5,5-hexafluoroacetylacetone with enamines

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Abstract—The reaction of 1,1,1,5,5,5-hexafluoroacetylacetone with push–pull enamines having a methyl group at the α-position was investigated. It was found that the reaction is sensitive both to the structure of enamines and to reaction conditions. As a result, a set of bistrifluoromethyldialkylanilines and ethyl bistrifluoromethylsalicylate was prepared. Plausible mechanisms and factors influencing the course of the reaction are discussed.

1. Introduction

Introduction of the trifluoromethyl group, an important functional group in organic chemistry allows chemists to considerably change physico-chemical properties of organic molecules.[1] Thus, derivatives of *m*-bistrifluoromethylbenzene are actively used in the design and synthesis of various ligands[2] and pharmaceutical substances.[3,4] Further development of methods for synthesis of functionalized *m*-bistrifluoromethylbenzenes is investigated. Although this fragment is actively used in many pharmaceutical research projects, in almost all of them 3,5-trifluoromethylaniline is used due to a known synthetic procedure described years ago.[5]

A few works such as the palladium catalyzed arylation of amines with 1-bromo-3,5-bis(trifluoromethyl)benzene[6] and the use of 2-methoxy-4,6-bis(trifluoromethyl) phenyllithium[7] give alternative approaches to the synthesis of bistrifluoromethylbenzene derivatives.

At the same time the commercially available symmetrical 1,3-biselectrophilic building block—1,1,1,5,5,5-hexafluoroacetylacetone has been used for synthesis of bistrifluoromethylated heterocyclic compounds. This approach has proved to be one of the most convenient methods for the synthesis of bistrifluoromethylated pyrazoles, isoxazoles,[8] pyridines,[9] pyrimidines,[10] pyrroles,[11] and diazepines.[12] To the best of our knowledge, the approach has not been applied to the synthesis of bistrifluoromethylated benzenes yet. In our previous work we have demonstrated the possibility of using tertiary push–pull enamines as 1,3-*CCC*-bisnucleophiles in the reactions with β-trifluoroacetylvinyl ethers for synthesis of monotrifluoromethylated functionalized dialkylanilines.[13] In this work we report our results on the reaction of tertiary push–pull enamines having a methyl group at the α-position with 1,1,1,5,5,5-hexafluoroacetylacetone **1**.

2. Results and discussion

2.1. Interaction of 1,1,1,5,5,5-hexafluoroacetylacetone with β-dialkylaminocrotonitriles

Enamines **2** derivatives of β-aminocrotonitrile react with 1,1,1,5,5,5-hexafluoroacetylacetone **1** in benzene at room temperature for 2–3 days affording a mixture of arene hydrate **3** and diol **4** in combined yield 35–40%, precipitated from the reaction mixture. Analysis of the reaction mixture by ^{19}F NMR reveals presence of the starting β-diketone **1** and traces of benzenes **5**. Numerous attempts to optimize the reaction conditions failed. Increasing the reaction temperature or time lead to formation of benzenes **5** and pyridone **6** products of the self-condensation of enamines **2**. Carrying

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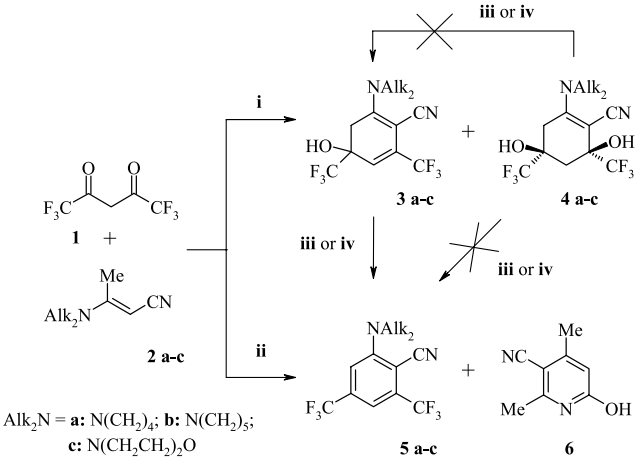
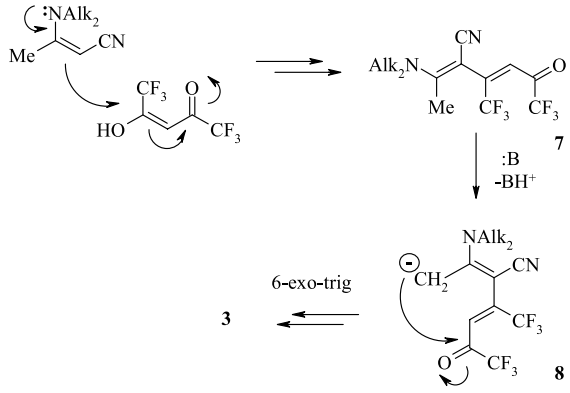
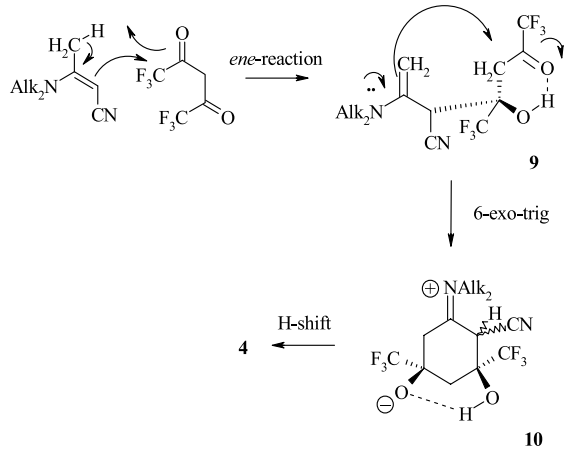


Scheme 1. Reagents and conditions: (i) benzene, rt, 2–3 days; (ii) benzene, reflux, 2 h; (iii) acetone, rt, 7–10 days; (iv) toluene, PTSA, reflux, 30 min.

out the reaction in boiling benzene or methanol results in conversion of 60–70% of the starting enamine, but the ratio of cyclization product **4** to pyridone **6** is ca. ~7:1 for enamine **2a**, and ~4:6 for enamine **2c** (Scheme 1). The ratio of reaction products **3** and **4** depends on the structure of the dialkylamino residue and reaction conditions (Table 1). Thus, for pyrrolidine enamine **2a**, the diol was registered in trace amount, while in the case of morpholine enamine **2c**, the ratio of diol/'hydrate' was 1:1. At the same time for enamine **2c**, diol **4c** was not registered at all when the reaction was run at 40–50 °C. It is worth noting that under the conditions in which hydrates **3** are transformed into benzenes **5**, diol **4** remains intact. Thus, we can draw the conclusion that diols **4** are not intermediate products in the chain of transformations **2**→**3**→**5**. We suppose that formation of **3** and **4** proceeds by different mechanisms. In the case of **3**, hexafluoroacetylacetone **1** reacts as an enol affording dienamine **7**, followed by 6-*exo-trig* cyclization to give 'hydrate' **3** (Scheme 2). At the same time the key step in the formation of diol **4** is the *ene*-reaction of enamines **2** with hexafluoroacetylacetone **1** which react in the ketone form like MeTFP,[14] affording terminal enamines **9** followed by spontaneous cyclization into diol **4**. Formation of only one possible diastereomer of **4** whose stereochemistry was solved by the single X-ray diffraction study could be rationalized by intramolecular hydrogen bonding (Scheme 3). Indirect proof for the proposed mechanisms is the growth of the 'hydrate' **3** produced upon increase of *C*-nucleophilicity of the enamines. Higher nucleophilicity would facilitate the reaction presented on Scheme 2,[13] and would not influence the reaction given on Scheme 3.[14]



Scheme 2.



Scheme 3.

The structures of compounds synthesized were confirmed by a set of physico-chemical methods, and for compounds **3a** and **4c** single X-ray diffraction studies were accomplished. (Figs. 1 and 2). It is worth noting that compounds of type **3** are allied to so-called arene hydrates whose simple representatives are highly unstable compounds under normal conditions.[15] In our previous work[13] two types of arene hydrates (type **A** and **B**, Fig. 3) which are stable under normal conditions have been described. In our viewpoint their stability is stipulated both by kinetic and thermodynamic factors. Substances **3** like arene hydrates of type **A** and **B** are stable compounds in the solid state, melting without decomposition. On heating in solution in the presence of catalytic amounts of acids such as PTSA 'arene hydrates' **3** eliminate water irreversibly turning into the corresponding benzenes **4**. It should be noted that arene

Table 1. Yields of products of the reaction of enamines **2** with hexafluoroacetylacetone **1**

Enamine	Conditions	Yield (%)			
		3	**4**	**5**	**6**
2a[a]	C_6H_6, rt, 3 days	31	Traces	6	—
2b[a]	C_6H_6, rt, 3 days	26	9	3	—
2c[a]	C_6H_6, rt, 3 days	21	23	5	—
2c[a]	C_6H_6, 40 °C, 3 h	14	Traces	15	—
2a[b]	C_6H_6, reflux, 4 h	—	—	43	6
2c[b]	C_6H_6, reflux, 4 h	—	—	28	24

[a] Refer according to ^{19}F NMR spectra of reaction mixture.
[b] Yields of **5** refer according to ^{19}F NMR spectra of reaction mixture and yield of **6** is for isolated product.

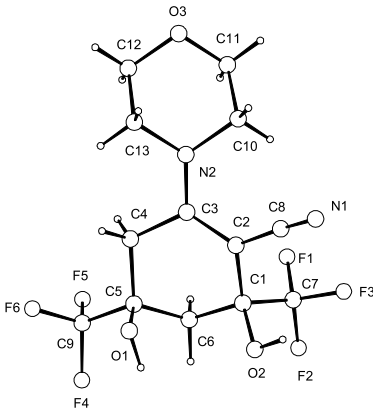


Figure 1. A perspective view and labeling scheme for the molecule **4a**.

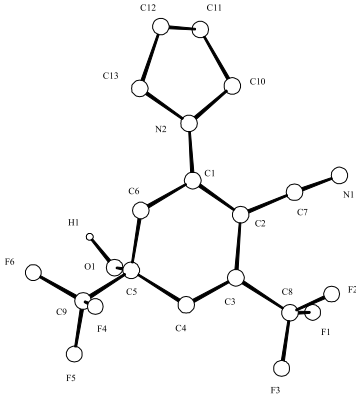


Figure 2. A perspective view and labeling scheme for the molecule **3a**.

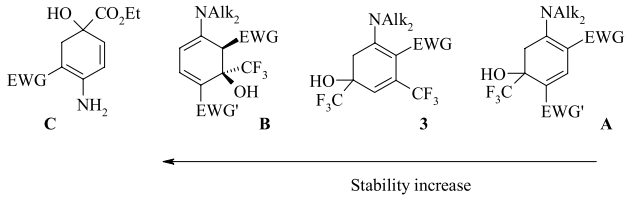


Figure 3.

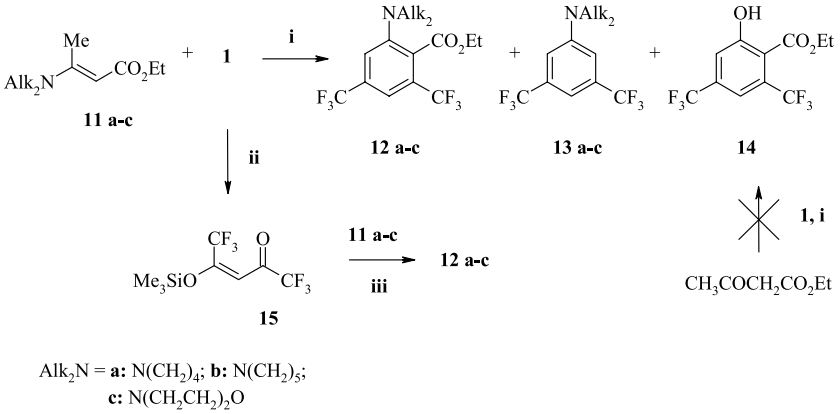
hydrates **3** hold an intermediate position in a stability series with respect to acidic catalysed elimination of water between previously described arene hydrates of types **A** and **B**. We suppose that unlike arene hydrates of types **A** and **B** the stability of **3** is stipulated only by kinetic factors, namely by strong destabilization of the forming carbcation on *E1*-elemination of water with two concurrently influencing trifluoromethyl groups. Besides, there are some similar stable arene hydrates of type **C** described in the literature where the ester group acts as an acceptor instead of the triflurometyl group.[16]

2.2. Interaction of 1,1,1,5,5,5-hexafluoroacetylacetone with β-dialkylaminocrotonoesters and α-methyl-β-enaminones

In going from enaminonitriles **2** to esters of β-dialkylaminocrotonic acids **11**, the reaction of the latter with hexafluoroacetylacetone **1** is complicated with side reactions. Besides the targeted dialkylaminoanthranilic acid esters **12**, symmetrical dialkylanilines **13**, and salicylic acid ester **14** formed in the reaction (Scheme 4). Increase of the basicity of dialkylamino residue leads to higher content of by-products (Table 2). We supposed that the cause of the side reactions which were not observed in the reactions with enones was the water forming in the reaction. To check the assumption the reaction was carried out in the presence of TMSCl as water scavenger affording the targeted esters of dialkylaminoanthranilic acids **12** as the sole products (Scheme 4).

It should be noted that salicylic acids **14** are not derived from hydrolysis of the starting enamine **11** so that under analogous conditions acetoacetic acid esters do not form salicylates **14**. In addition, under the reaction conditions the transformation of **12** into **13** does not occur.

Enaminones **16** derivatives of acetylacetone also react with hexafluoroacetylacetone **1** affording the product without EWG (Scheme 5). Thus, at room temperature in benzene both the expected acetophenones **17** and symmetrical anilines **13** are formed in the reaction. The higher basicity of dialkylamino group and the easier cleavage of the acetyl group mean that in the case of pyrrolidine enaminone, the

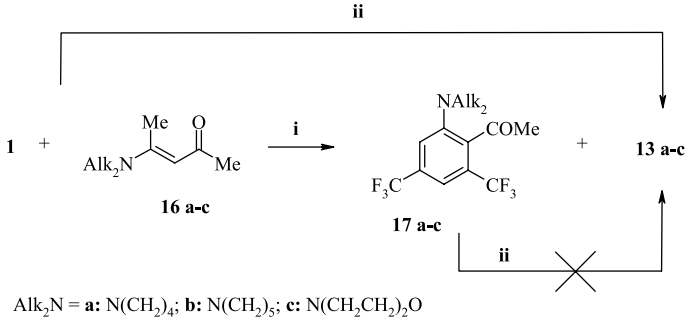


Scheme 4. Reagents and conditions: (i) benzene, rt, 3 days; (ii) 1 equiv Me_3SiCl, 1 equiv Et_3N, benzene, rt, 5 min; (iii) 1 equiv Me_3SiCl, 1 equiv Et_3N, benzene, rt, 1 day, 60 °C, 4 h.

Table 2. Yields of products of the reaction of enamines **11** and **16** with hexafluoroacetylacetone **1**[a]

Enamine	Conditions	Yield (%)		
		12 or **17**	**13**	**14**
11a	C_6H_6, rt, 3 days	15	5	32
11b	C_6H_6, rt, 3 days	17	Traces	29
11c	C_6H_6, rt, 3 days	39	Traces	14
11a	C_6H_6, TMSCl, Et_3N	93	—	—
11b	C_6H_6, TMSCl, Et_3N	71	—	—
11c	C_6H_6, TMSCl, Et_3N	69	—	—
16a	C_6H_6, rt, 3 days	Traces	45	—
16b	C_6H_6, rt, 3 days	26	10	—
16c	C_6H_6, rt, 3 days	27	6	—
16a	AcOH, 60 °C, 4 h	—	48	—
16b	AcOH, 60 °C, 4 h	—	45	—
16c	AcOH, 60 °C, 4 h	—	47	—

[a] Refer according to ^{19}F NMR spectra of reaction mixture.

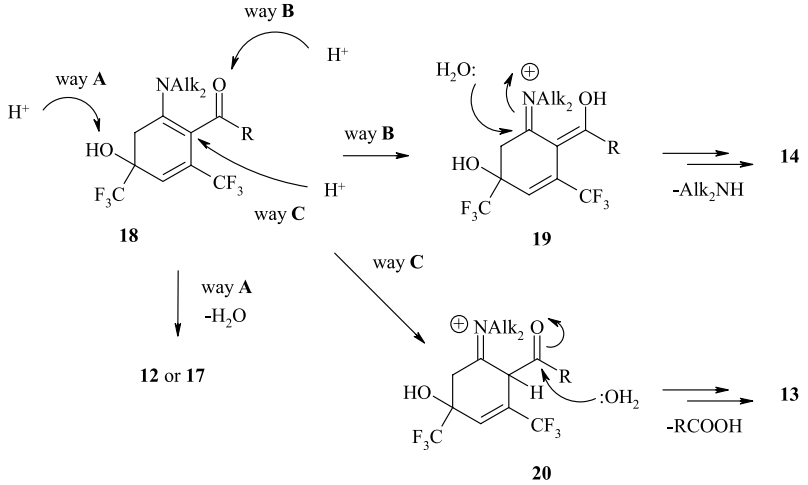


Scheme 5. Reagents and conditions: (i) benzene, rt, 3 days; (ii) AcOH, 60 °C, 4 h.

expected acetophenone **17a** is produced only in trace amounts. Under acidic conditions, influence of the dialkylamino residue basicity is reduced, so that the sole reaction products are anilines **13**.

Use of TMSCl in the reaction increases the conversion of hexafluoroacetylacetone **1** and decreases the yield of symmetrical anilines **13**. At the same time the reaction is accompanied by many side reactions thus complicating separation of the targeted products.

We suppose that enaminoesters **11** and enaminoketones **16** like enaminonitriles **2** react with hexafluoroacetylacetone **1** forming the corresponding arene hydrates **18** which have few protonation sites; three of them are noted on Scheme 6. Hexafluoroacetylacetone **1** as a strong CH-acid itself could act as a proton source in the reaction mixture. Protonation by pathway A followed by elimination of water affords targeted products **12** or **17**. Protonation at the oxygen atom of the enaminone fragment (pathway B) affords iminium salt **19** which upon hydrolysis gives the corresponding phenol **14**. In addition, protonation at the carbon atom of enamine fragment forming iminium salt **20** which could either hydrolize into the corresponding phenol **14** or enter into ketone cleavage giving symmetrical anilines **13**. Increase of the basicity of the dialkylamino residue



Scheme 6.

facilitates protonation by pathways B and C, so that the number of by-products increases. Actually, the increase of by-products was observed in series of enaminoesters **11** and enaminoketones **16**.

3. Conclusions

The reaction of 1,1,1,5,5,5-hexafluoroacetylacetone with push–pull enamines having a methyl group at the α-position was investigated. It has been found that the reaction is very sensitive both to structure of the starting enamines and to reaction conditions. As a result, a series of bistrifluoromethylated dialkylanilines bearing functional groups at the benzene ring, symmetrical bistrifluoromethylated dialkylanilines and ethyl ester of bistrifluoromethylated salicylic acid were obtained. Readily available starting materials and simple synthetic procedures make this method very attractive and convenient for the synthesis of various *m*-bistrifluoromethyl benzenes derivatives, useful building blocks for organic and medicinal chemistry.

4. Experimental

4.1. General

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 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 were prepared according to the literature.[17]

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-235905 (**3a**) and CCDC-235904 (**4c**) and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223/336 033; E-mail: deposit@ccdc.cam.ac.uk).

4.3. Interaction of 1 with β-dialkylaminocrotonitriles

4.3.1. 4-Hydroxy-2-(1-pyrrolidinyl)-4,6-bis(trifluoromethyl)-1,5-cyclohexadiene-1-carbonitrile (3a). Enamine **2a** (5 g, 36.8 mmol) was dissolved in benzene (25 mL) and to the solution formed **1** was added (7.65 g, 36.8 mmol). The reaction mixture was maintained at rt overnight. The precipitate formed was filtered and washed with cyclohexane affording **3a** (3.2 g, 27%) as a colourless solid. Mp 162 °C. ^{1}H NMR (acetone-d_6): $\delta=1.99$ (4H, br, m, CH_2), 2.99 and 3.07 (2H, AB-syst, $^{2}J_{HH}=16.8$ Hz), 3.85 (4H, br, s, NCH_2), 5.73 (1H, s, OH), 5.86 (1H, s, CH). ^{13}C NMR (DMSO-d_6): $\delta=24.7$, 34.5, 51.0, 65.1, 69.4 ($^{2}J_{CF}=28.5$ Hz), 110.3, 118.9, 123.6 ($^{1}J_{CF}=306.5$ Hz), 124.1 ($^{1}J_{CF}=272.1$ Hz), 131.6 ($^{2}J_{CF}=28.6$ Hz), 157.6. ^{19}F NMR (acetone): $\delta=-65.1$ (3F), −81.3 (3F). IR, ν_{max} (cm^{-1}): 3500–3200 (br), 2989, 2868, 2191, 1663, 1545, 1271. MS, *m/z* (%): 326 (M^+, 11), 308 (M^+-H_2O, 14), 307 (22), 280 (37), 257 (M^+-CF_3, 96), 148 (32), 119 (53), 69 (CF_3^+, 39), 55 (45), 42 (86), 41 (100). Anal. calcd for $C_{13}H_{12}F_6N_2O$: C 47.86; H 3.71; N 8.59. Found C 47.92; H 3.65; N 8.60.

4.3.2. 4-Hydroxy-2-(4-morpholinyl)-4,6-bis(trifluoromethyl)-1,5-cyclohexadiene-1-carbonitrile (3c). Enamine **2c** (1 g, 6.6 mmol) was dissolved in benzene (10 mL) and to the solution formed **1** was added (1.37 g, 6.6 mmol). The reaction mixture was maintained at 40 °C for 2 h and then it was left at rt overnight. The precipitate formed was filtered and washed with cyclohexane affording **3c** (316 mg, 14%) as a colourless solid. Mp 144–145 °C. ^{1}H NMR (acetone-d_6): $\delta=2.98$ and 3.05 (2H, AB-syst, $^{2}J_{HH}=16.8$ Hz), 3.67–3.92 (8H, m, CH_2), 5.85 (1H, s, OH), 5.96 (1H, s, CH). ^{13}C NMR (DMSO-d_6): $\delta=33.9$, 50.3, 63.8, 66.1, 69.7 ($^{2}J_{CF}=28.5$ Hz), 112.3, 116.4, 123.6 ($^{1}J_{CF}=306.5$ Hz), 124.1 ($^{1}J_{CF}=272.2$ Hz), 134.3 ($^{2}J_{CF}=33.0$ Hz), 161.7. ^{19}F NMR (acetone): $\delta=-67.0$ (3F), −82.9 (3F). IR, ν_{max} (cm^{-1}): 3510–3180 (br), 3078, 2919, 2868, 2193 1649, 1547, 1285. Mp 144–145 °C. MS, *m/z* (%): 342 (M^+, 78), 324 (M^+-H_2O, 56), 273 (M^+-CF_3, 48), 266 (60), 239 (100), 228 (32), 219 (29), 215 (35), 42 (34). Anal. calcd for $C_{13}H_{12}F_6N_2O_2$: C 45.62; H 3.53; N 8.19. Found C 45.65; H 3.56; N 8.22.

4.3.3. *cis*-4,6-Dihydroxy-2-(4-morpholinyl)-4,6-bis(trifluoromethyl)-1-cyclohexene-1-carbonitrile (4c) and 2-(4-morpholinyl)-4,6-bis(trifluoromethyl)-benzonitrile (5c). To a solution of enamine **2c** (5 g, 32.9 mmol) in benzene (25 mL) was added **1** (6.84 g, 32.9 mmol). The reaction mixture was maintained at rt for 3 days. The precipitate formed was filtered affording a mixture of **4c** and **3c** ~ 1:1. The mixture obtained was dissolved in acetone (25 mL) and maintained at rt for 7 days (the reaction mixture was monitored by ^{19}F NMR spectroscopy). After complete conversion of **3c** to **5c**, acetone was evaporated in vacuo and the residue was triturated with $CHCl_3$ (10 mL) affording **4c** (2.7 g, 23%). The $CHCl_3$ was evaporated in vacuo. The residue was extracted with boiling *n*-hexane (10 mL) and the *n*-hexane was evaporated in vacuo affording **5c** (2.66 g, 25%).

Compound **4c**. Colourless solid. Mp 175 °C (EtOAc). ^{1}H NMR (acetone-d_6): $\delta=2.10$ (1H, d, $^{2}J_{HH}=14.1$ Hz), 2.22 (1H, dd, $^{2}J_{HH}=14.1$ Hz, $^{4}J_{HH}=1.5$ Hz), 2.78 (1H, d, $^{2}J_{HH}=18.0$ Hz), 3.14 (1H, dd, $^{2}J_{HH}=18.0$ Hz, $^{4}J_{HH}=1.5$ Hz), 3.48–3.57 (2H, m, CH_2), 3.62–3.79 (6H, m, CH_2), 5.20 (1H, br. s, OH), 5.87 (1H, br. s, OH). ^{13}C NMR (acetone-d_6): $\delta=34.2$, 34.3, 51.1, 67.4, 72.4 ($^{2}J_{CF}=30.2$ Hz), 74.8 ($^{2}J_{CF}=30.4$ Hz), 79.2, 119.1, 126.0 ($^{1}J_{CF}=285.4$ Hz), 126.2 ($^{1}J_{CF}=284.4$ Hz), 161.3. ^{19}F NMR (acetone): $\delta=-78.9$ (3F), −82.6 (3F). IR, ν_{max} (cm^{-1}): 3384 (br), 3317 (br), 2983, 2933, 2868, 2184, 1555, 1453,

1261. MS, *m/z* (%): 360 (M^+, 16), 291 ($M^+ - CF_3$, 100). Anal. calcd for $C_{13}H_{14}F_6N_2O_3$: C 43.34; H 3.92; N 7.78. Found C 43.37; H 3.95; N 7.82.

Compound **5c**. Colourless solid. Mp 127–130 °C (cyclohexane) with sublimation. R_f (EtOAc)=0.68 ^{1}H NMR ($CDCl_3$): δ=3.33 (4H, t, $^3J_{HH}$=4.2 Hz, NCH_2), 3.93 (4H, t, $^3J_{HH}$=4.2 Hz, NCH_2), 7.42 (1H, s, CH), 7.56 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=51.0, 65.8, 104.1, 113.5, 114.8, 120.4, 121.6 ($^1J_{CF}$=275.2 Hz), 122.3 ($^1J_{CF}$=274.0 Hz), 134.0 ($^2J_{CF}$=34.2 Hz), 134.1 ($^2J_{CF}$=32.8 Hz), 157.5. ^{19}F NMR ($CHCl_3$): δ=−63.5 (3F), −64.9 (3F). IR, ν_{max} (cm^{-1}): 3083, 3052, 2868, 2843, 2228, 1619, 1445, 1395, 1281, 1142, 979. MS, *m/z* (%): 324 (M^+, 34), 266 (57), 239 (100), 219 (32). Anal. calcd for $C_{13}H_{10}F_6N_2O$: C 48.16; H 3.11; N 8.64. Found C 48.25; H 3.22; N 8.61

4.3.4. 2-(1-Pyrrolidinyl)-4,6-bis(trifluoromethyl)-benzonitrile (5a). To a solution of **3a** (100 mg) in toluene (25 mL) a few crystals of *p*-toluenesulfonic acid were added and the reaction mixture was refluxed for 0.5–1 h (The reaction was monitored by TLC using EtOAc 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 **5a** (88 mg, 93%) as a colourless solid. Mp 96 °C. R_f (EtOAc)=0.81. ^{1}H NMR ($CDCl_3$): δ=2.06 (4H, t, $^3J_{HH}$=6.6 Hz, CH_2), 3.71 (4H, t, $^3J_{HH}$=6.6 Hz, NCH_2), 7.09 (1H, s, CH), 7.18 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=25.7, 50.9, 93.2, 109.9, 114.9, 116.0, 120.8 ($^1J_{CF}$=272.8 Hz), 124.1 ($^1J_{CF}$=271.0 Hz), 134.2 ($^2J_{CF}$=33.3 Hz), 136.6 ($^2J_{CF}$=31.0 Hz), 151.8. ^{19}F NMR ($CHCl_3$): δ=−62.2 (3F), −64.1 (3F). IR, ν_{max} (cm^{-1}): 2957, 2875, 2214, 1632, 1481, 1276, 1116, 1085, 1014, 869. MS, *m/z* (%): 308 (M+, 50), 307 (58), 289 (20), 280 (100), 245 (44), 219 (20), 188 (14), 69 (13), 42 (12), 41 (12). Anal. calcd for $C_{13}H_{10}F_6N_2$: C 50.66; H 3.27; N 9.09. Found C 50.61; H 3.22; N 9.07.

4.3.5. 2-(1-Piperidinyl)-4,6-bis(trifluoromethyl)-benzonitrile (5b). To a solution of enamine **2b** (1 g, 6.63 mmol) in benzene (25 mL) was added **1** (1.38 g, 6.63 mmol). The reaction mixture was maintained at rt for 3 days (the reaction mixture was monitored by ^{19}F NMR spectroscopy). The solvent was evaporated in vacuo. The residue was dissolved in acetone (10 mL) and maintained at rt for 5 days (the reaction mixture was monitored by ^{19}F NMR spectroscopy). Acetone was evaporated in vacuo, residue was extracted with boiling cyclohexane (15 mL) and maintained overnight. The precipitate formed was filtered affording **5b** (1.03 g, 48%) as a yellow solid. Mp 42 °C. R_f (EtOAc)=0.62. ^{1}H NMR ($CDCl_3$): δ=1.69 (2H, m, CH_2), 1.83 (4H, m, CH_2), 3.30 (4H, t, $^3J_{HH}$=5.7 Hz, NCH_2), 7.4 (1H, s, CH), 7.46 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=23.8, 25.9, 53.2, 105.3, 114.0, 114.5, 119.3, 121.6 ($^1J_{CF}$=272.8 Hz), 123.7 ($^1J_{CF}$=271.3 Hz), 135.2 ($^2J_{CF}$=34.2 Hz), 135.9 ($^2J_{CF}$=33.5 Hz), 159.1. ^{19}F NMR ($CHCl_3$): δ=−63.5 (3F), −64.9 (3F). IR, ν_{max} (cm^{-1}): 2950, 2858, 2802, 2227, 1620, 1445, 1395, 1280, 1141, 980. MS, *m/z* (%): 322 (M^+, 87), 321 (100), 293 (57), 281 (29), 245 (18), 239 (28), 84 (28), 69 (37), 55 (16), 43 (30), 42 (24), 41 (36). Anal. calcd for $C_{14}H_{12}F_6N_2$: C 52.18; H 3.75; N 8.69. Found C 52.25; H 3.72; N 8.65.

4.3.6. 2,4-Dimethyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (6). To a solution of enamine **2c** (1 g, 6.6 mmol) in benzene (10 mL) was added **1** (1.37 g, 6.6 mmol). The reaction mixture was refluxed for 4 h. After cooling to rt the precipitate formed was filtered affording **6** (230 mg, 24%). The mother liquor was evaporated in vacuo. The residue was subjected to a column chromatography over silica gel using EtOAc as eluent affording **5c** (598 mg, 28%, R_f (EtOAc)=0.68).

Compound **6**. Colourless solid. Mp 293 °C (lit. 294–296 °C).[18] ^{1}H NMR (DMSO-d_6): δ=2.22 (3H, s, CH_3), 2.39 (3H, s, CH_3), 6.10 (1H, s, CH), 12.25 (1H, br. s. OH). MS, *m/z* (%): 148 (M^+, 67), 119 (100), 105 (21), 78 (11), 52 (11), 42 (13).

4.4. Interaction of 1 with β-dialkylaminocrotonoesters

4.4.1. General procedure for synthesis of compounds 12a–c in the presence of TMSCl and Et_3N. *Procedure A*. To a solution of **1** (1 g, 4.81 mmol) in dry benzene (10 mL) was added Me_3SiCl (4.81 mmol) and Et_3N (4.81 mmol). The reaction mixture was maintained at rt for 5 min. Enamine **11a–c** (4.81 mmol), Me_3SiCl (4.81 mmol) and Et_3N (4.81 mmol) was added consecutively. Reaction mixture was maintained at rt for 1 day and heated at 60 °C for 4 h. The precipitate formed was filtered off and the mother liquor was evaporated in vacuo. The residue was dried and recrystallised from *n*-hexane affording the corresponding ethyl ester of benzoic acid (**12a–c**).

4.4.2. Ethyl ester 2-(1-pyrrolidinyl)-4,6-bis(trifluoromethyl)-benzoic acid (12a). Pale yellow solid (1.59 g, 93%). Mp 48 °C. R_f (EtOAc)=0.68. ^{1}H NMR ($CDCl_3$): δ=1.39 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.99 (4H, t, $^3J_{HH}$=6.6 Hz, CH_2), 3.35 (4H, t, $^3J_{HH}$=6.6 Hz, NCH_2), 4.37 (2H, q, $^3J_{HH}$=7.2 Hz, CH_2), 7.08 (1H, s, CH), 7.2 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=13.8, 25.9, 53.0, 62.6, 109.8, 114.2, 119.1, 121.9 ($^1J_{CF}$=272.2 Hz), 122.1 ($^1J_{CF}$=271 Hz), 130.2 ($^2J_{CF}$=31.2 Hz), 132.3 ($^2J_{CF}$=32.4 Hz), 146.9, 167.9. ^{19}F NMR ($CHCl_3$): δ=−60.8 (3F), −64.2 (3F). IR, ν_{max} (cm^{-1}): 2984, 2916, 2858, 1725, 1442, 1383, 1279, 1125, 978. MS, *m/z* (%): 355 (M^+, 25), 326 (100), 310 (31), 290 (38), 280 (18), 240 (14), 234 (15), 213 (18), 41 (11). Anal. calcd for $C_{15}H_{15}F_6NO_2$: C 50.71; H 4.26; N 3.94. Found C 50.75; H 4.31; N 4.01.

4.4.3. Ethyl ester 2-(1-piperidinyl)-4,6-bis(trifluoromethyl)-benzoic acid (12b). Yellow oil (1.26 g, 71%). R_f (EtOAc)=0.62. ^{1}H NMR ($CDCl_3$): δ=1.39 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.56 (2H, m, CH_2), 1.66 (4H, m, CH_2), 2.97 (4H, t, $^3J_{HH}$=5.4 Hz, NCH_2), 4.42 (2H, q, $^3J_{HH}$=7.2 Hz, CH_2), 7.55 (1H, s, CH), 7.59 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=14.1, 24.0, 26.4, 54.4, 62.3, 117.7, 120.1, 121.8, 121.7 ($^1J_{CF}$=275.2 Hz), 122.3 ($^1J_{CF}$=274.0 Hz), 132.2 ($^2J_{CF}$=32.4 Hz), 132.3 ($^2J_{CF}$=32.4 Hz), 153.8, 166.4. ^{19}F NMR ($CHCl_3$): δ=−60.9 (3F), −64.1 (3F). IR, ν_{max} (cm^{-1}): 2938, 2883, 2853, 1730, 1440, 1390, 1282, 1130, 978. MS, *m/z* (%): 369 (M^+, 18), 340 (100), 324 (24), 294 (15), 97 (10), 69 (14), 57 (24), 55 (39), 43 (20), 41 (28). Anal. calcd for $C_{16}H_{17}F_6NO_2$: C 52.04; H 4.64; N 3.79. Found C 51.87; H 4.24; N 3.82.

4.4.4. Ethyl ester 2-(4-morpholinyl)-4,6-bis(trifluoromethyl)-benzoic acid (12c). Colourless solid (1.23 g, 69%). Mp 44 °C. R_f (EtOAc)=0.55. ^{1}H NMR ($CDCl_3$): δ=1.4 (3H, t, $^3J_{HH}$=7.2 Hz, CH_2), 3.04 (4H, t, $^3J_{HH}$=4.5 Hz, NCH_2), 3.8 (4H, t, $^3J_{HH}$=4.5 Hz, OCH_2), 4.44 (2H, q, $^3J_{HH}$=7.2 Hz, CH_2), 7.6 (1H, s, CH), 7.68 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=14.1, 53.2, 53.3, 67.1, 118.8, 121.6 ($^1J_{CF}$=275.2 Hz), 121.8, 122.3 ($^1J_{CF}$=274.0 Hz), 124.2, 132.9 ($^2J_{CF}$=32.8 Hz), 133.3 ($^2J_{CF}$=34.7 Hz), 151.9, 165.9. ^{19}F NMR ($CHCl_3$): δ=−61.0 (3F), −64.1 (3F). IR, ν_{max} (cm^{-1}): 3058, 2996, 2925, 2863, 1732, 1442, 1387, 1282, 1129, 978. MS, *m/z* (%): 371 (M^+, 27), 352 (17), 340 (18), 328 (52), 298 (100), 284 (73), 268 (70), 240 (55), 213 (44), 194 (23), 163 (24), 143 (20), 59 (37), 45 (25). Anal. calcd for $C_{15}H_{15}F_6NO_3$: C 48.53; H 4.07; N 3.77. Found C 48.47; H 4.02; N 3.82.

4.4.5. Ethyl ester 2-hydroxy-4,6-bis(trifluoromethyl)-benzoic acid (14). To a solution of enamine **11a** (5 g, 27.4 mmol) in benzene (75 mL) was added **1** (5.68 g, 27.4 mmol). The reaction mixture was maintained at rt for 3 days (the reaction mixture was monitored by ^{19}F NMR spectroscopy). The solvent was evaporated in vacuo. The residue obtained was placed in short silica gel column and washed with EtOAc (4×25 mL). EtOAc was evaporated in vacuo and the residue obtained was subjected to fractional distillation affording **14** (2.23 g, 27%) and **12a** (0.68 g, 7%). Colourless solid. Mp 24 °C. R_f (EtOAc)=0.56. ^{1}H NMR ($CDCl_3$): δ=1.44 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 4.49 (2H, q, $^3J_{HH}$=7.2 Hz, CH_2), 7.48 (1H, s, CH), 7.53 (1H, s, CH), 10.8 (1H, br s, OH). ^{13}C NMR ($CDCl_3$): δ=13.5, 63.3, 114.6, 115.3, 119.4, 124.3 ($^1J_{CF}$=270.5 Hz), 124.5 ($^1J_{CF}$=273.2 Hz), 131.9 ($^2J_{CF}$=31.7 Hz), 135.6 ($^2J_{CF}$=32.9 Hz), 161.7, 168.1. ^{19}F NMR ($CHCl_3$): δ=59.6 (3F), −65.2 (3F). IR, ν_{max} (cm^{-1}): 3400–2800 (br), 2991, 2944, 1737 (sh), 1683, 1445, 1380, 1324, 1276, 1139, 1012, 962, 885, 730. MS, *m/z* (%): 302 (M^+, 23), 256 (100), 228 (40), 209 (27), 200 (17), 181 (14). Anal. calcd for $C_{11}H_8F_6O_3$: C 43.72; H 2.67; Found C 43.58; H 2.69.

4.4.6. General procedure for interaction of 1 with β-dialkylaminocrotonoesters. To a solution of enamines **11a–c** (9.71 mmol) in benzene (30 mL) was added **1** (2 g, 9.71 mmol). The reaction mixture was maintained at rt for 3 days (the reaction mixture was monitored by ^{19}F NMR spectroscopy). The solvent was evaporated in vacuo. The residue obtained was placed in a short silica gel column and washed with EtOAc (2×25 mL). EtOAc was evaporated in vacuo and the residue obtained was carefully dried in vacuo dissolved in anhyd *n*-hexane (30 mL). To the stirred solution obtained NaH (240 mg, 10 mmol) was carefully added and the solution was maintained until hydrogen evolution had stopped. The precipitate formed was filtered off under argon. The mother liquior was evaporated in vacuo and the residue obtained was subjected to a column chromatography over silica gel using EtOAc as eluent affording **12a–c**. The precipitate obtained was suspended in anhydrous CH_2Cl_2 (25 mL) and to the stirred suspension water (5 mL) was added dropwise and then aq HCl (30%, 1 mL) was added dropwise. The organic layer was separated and dried over Na_2SO_4. CH_2Cl_2 was evaporated in vacuo affording **14** (purity >95%).

4.5. Interaction of 1 with β-enaminones

4.5.1. 1-[3,5-Bis(trifluoromethyl)phenyl]-pyrrolidine (13a). To a solution of enamine **16a** (1 g, 6.54 mmol) in acetic acid (20 mL) was added **1** (1.36 g, 6.54 mmol). The reaction mixture was heated at 60 °C for 4 h. Solvent was evaporated in vacuo and residue was crystallized from mixture methanol/water −1:1 affording **13a** (370 mg, 20%) as a colourless solid. Mp 63 °C. R_f (EtOAc)=0.58. ^{1}H NMR ($CDCl_3$): δ=2.64 (4H, t, $^3J_{HH}$=6.3 Hz, CH_2), 3.34 (4H, t, $^3J_{HH}$=6.3 Hz, NCH_2), 6.85 (2H, s, CH), 7.08 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=25.4, 47.7, 107.9, 110.7, 125.2 ($^1J_{CF}$=270.3 Hz), 131.9 ($^2J_{CF}$=32.2 Hz), 147.9. ^{19}F NMR ($CHCl_3$): δ=−64.7. IR, ν_{max} (cm^{-1}): 2984, 2916, 2858, 1623, 1499, 1481, 1425, 1275, 1162, 1123, 1012, 853, 701, 682. MS, *m/z* (%): 283 (M^+, 61), 282 (100), 264 (21), 240 (32), 227 (71), 213 (40), 163 (13), 41 (10). Anal. calcd for $C_{12}H_{11}F_6N$: C 50.89; H 3.91; N 4.95. Found C 50.92; H 4.02; N 4.91.

4.5.2. 1-[3,5-Bis(trifluoromethyl)phenyl]-piperidine (13b). Enaminone **16b** (1 g, 5.98 mmol) was dissolved in acetic acid (20 mL) and to the solution formed **1** was added (1.24 g, 5.98 mmol). The reaction mixture was maintained at rt overnight and then heated at 60 °C for 4 h. The solvent was evaporated in vacuo. The residue was extracted with boiling *n*-hexane (15 mL). The hexane was evaporated in vacuo and the residue was crystallized from methanol affording **13b** (370 mg, 21%) as a colourless solid. Mp 60–62 °C. R_f (EtOAc)=0.64. ^{1}H NMR ($CDCl_3$): δ=3.25 (4H, t, $^3J_{HH}$=4.8 Hz), 3.87 (4H, t, $^3J_{HH}$=4.8 Hz), 7.24 (2H, s, CH), 7.32 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=24.0, 25.4, 49.5, 111.1, 114.8, 125.6 ($^1J_{CF}$=271.5 Hz), 132.4 ($^2J_{CF}$=31.8 Hz), 152.2. ^{19}F NMR ($CHCl_3$): δ=−64.2. IR, ν_{max} (cm^{-1}): 3077, 3062, 3011, 2938, 2883, 2853, 1619, 1480, 1413, 1283, 1141, 1132, 1024, 953, 859, 699, 682. MS, *m/z* (%): 297 (M^+, 61), 296 (100), 278 (19), 256 (28), 240 (49), 213 (32), 163 (11). Anal. calcd for $C_{13}H_{13}F_6N$: C 52.53; H 4.41; N 4.71. Found C 52.25; H 4.36; N 4.52.

4.5.3. 4-[3,5-Bis(trifluoromethyl)phenyl]-morpholine (13c). To a solution of enaminone **16c** (0.81 g, 4.81 mmol) in acetic acid (20 mL) was added **1** (1 g, 4.81 mmol). The reaction mixture was heated at 60 °C for 4 h. The solvent was evaporated in vacuo and residue was crystallized from methanol affording **13c** (0.268 g, 38%) as colourless solid. Mp 123 °C. R_f (*i*-PrOH)=0.39. ^{1}H NMR ($CDCl_3$): δ=1.63–1.72 (6H, m, $3CH_2$), 3.27 (4H, t, $^3J_{HH}$=4.8 Hz), 7.23 (3H, s, CH). ^{13}C NMR ($CDCl_3$): δ=48.3, 66.5, 112.4, 114.4, 125.3 ($^1J_{CF}$=270.9 Hz), 132.2 ($^2J_{CF}$=32.1 Hz), 151.7.^{19}F NMR ($CHCl_3$): δ=−64.2. IR, ν_{max} (cm^{-1}): 3082, 3060, 2983, 2918, 2847, 1617, 1487, 1405, 1286, 1170, 1114, 970, 857, 691, 683. MS, *m/z* (%): 299 (M^+, 41), 280 (14) 241 (100), 213 (27). Anal. calcd for $C_{12}H_{11}F_6NO$: C 48.17; H 3.71; N 4.68. Found C 48.21; H 3.73; N 4.56.

4.5.4. 1-[2-(1-Piperidinyl)-4,6-bis(trifluoromethyl)-phenyl]-ethanone (17b). Enaminone **16b** (1 g, 5.99 mmol) was dissolved in anhyd benzene (10 mL) and to the solution formed **1** (1.24 g, 5.99 mmol) was added. The reaction mixture was maintained at rt overnight. Benzene

was evaporated in vacuo. The residue was dissolved in methanol. To the solution formed a few drops of water was added (~0.1 mL). The precipitate formed was filtered affording **17b** (406 mg, 20%) as a colourless solid mp 88 °C. R_f (EtOAc)=0.73. ^{1}H NMR ($CDCl_3$): δ=1.54–1.6 (2H, m, CH_2), 1.66–1.71 (4H, m, CH_2) 2.56 (3H, s, CH_3), 2,92 (4H, t, $^3J_{HH}$=5.4 Hz, NCH_2), 7.57 (1H, s, CH), 7.63 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=23.7, 26.2, 31.1, 54.6, 118.1, 121.1, 124.1 ($^1J_{CF}$=271.9 Hz), 124.4 ($^1J_{CF}$=270.8 Hz), 128.3 ($^2J_{CF}$=32.1 Hz), 131.2 ($^2J_{CF}$=33.0 Hz), 140.8, 152.7, 202.6. ^{19}F NMR ($CHCl_3$): δ=−60.1 (3F), −64.1 (3F). IR, ν_{max} (cm^{-1}): 2950, 2858, 2802, 1710, 1386, 1273, 1131, 963, 897. MS, *m/z* (%): 339 (M^+, 47), 324 (100), 306 (39), 268 (25), 248 (17), 238 (27), 213 (16), 43 (26). Anal. calcd for $C_{15}H_{15}F_6NO$: C 53.1; H 4.46; N 4.13. Found C 53.06; H 4.41; N 4.06.

Note. When the residue after evaporating off benzene from the reaction mixture was subjected to a column chromatography over silica gel using EtOAc as eluent we would obtain **13b** (110 mg, 6%) and **17b** (400 mg, 20%).

4.5.5. 1-[2-(4-Morpholinyl)-4,6-bis(trifluoromethyl)-phenyl]-ethanone (17c). Enaminone **16c** (1 g, 5.99 mmol) was dissolved in anhydrous benzene (25 mL) and to a solution formed **1** (1.24 g, 5.99 mmol) was added. The reaction mixture was maintained at rt overnight. The benzene was evaporated in vacuo. The residue was dissolved in methanol. To a solution formed a few drops of water was added (~0.1 mL). The precipitate formed was filtered affording **17c** (430 mg, 21%) as a colourless solid Mp 56 °C. R_f (*i*-PrOH)=0.74. ^{1}H NMR ($CDCl_3$): δ=2.58 (3H, s, CH_3), 2.99 (4H, t, $^3J_{HH}$=4.5 Hz, NCH_2), 3.81 (4H, t, $^3J_{HH}$=4.5 Hz OCH_2), 7.60 (1H, s, CH), 7.69 (1H, s, CH). ^{13}C NMR ($CDCl_3$): δ=31.3, 53.4, 66.9, 119.1, 121.5, 124.4 ($^1J_{CF}$=275.0 Hz), 124.7 ($^1J_{CF}$=271.3 Hz), 128.1 ($^2J_{CF}$=28.9 Hz), 131.7 ($^2J_{CF}$=33.5 Hz), 141.2, 151.0, 202.2. ^{19}F NMR ($CHCl_3$): δ=−59.4 (3F), −62.0 (3F). IR, ν_{max} (cm^{-1}): 3077, 2984, 2847, 1707, 1439, 1380, 1274, 1142, 971. MS, *m/z* (%): 341 (M^+, 48), 326 (39), 296 (19), 280 (24), 268 (100), 255 (27), 240 (19), 213 (17), 43 (44). Anal. calcd for $C_{14}H_{13}F_6NO_2$: C 49.27; H 3.84; N 4.10. Found C 49.19; H 3.91; N 4.12.

Note. When the residue after evaporating off benzene from the reaction mixture was subjected to a column chromatography over silica gel using *i*-PrOH as eluent we would obtain **17c** (490 mg, 24%) and then after washing of column with EtOAc we would obtain **13c** (72 mg, 4%).

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