A Convenient Synthesis of 4-Trifluoromethyl-(2*H*)-pyridazin-3-ones from Methyl 3,3,3-Trifluoropyruvate

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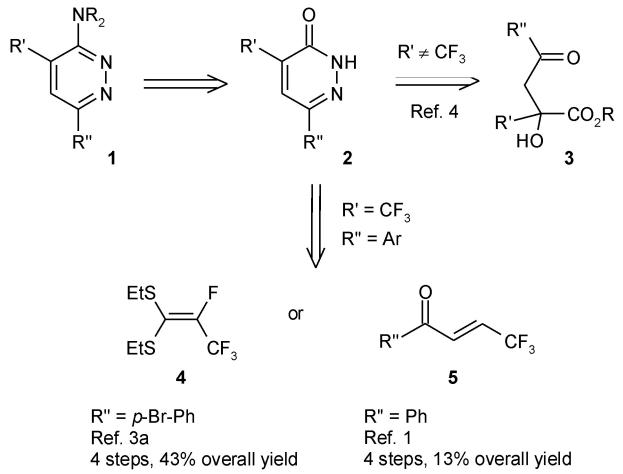
Abstract: A convenient two-step synthesis of 4-CF_3-(2*H*)-pyridazin-3-ones starting from methyl 3,3,3-trifluoropyruvate (MeTFP) and carbonyl compounds has been elaborated. As a result, a set of various 4-CF_3-(2*H*)-pyridazin-3-ones was obtained. The scope and limitations of the methodology is defined.

Key words: methyl 3,3,3-trifluoropyruvate, pyridazinones, trifluoromethyl, aldol condensation, cyclocondensation

The pyridazine nucleus is an interesting heterocyclic ring, which plays the role of a pharmacophore in several classes of derivatives possessing a variety of pharmacological properties.[1] In the past, great attention has been particularly paid to various (2*H*)-pyridazin-3-ones due to their synthetic versatility, well-balanced physico-chemical properties, and the presence of possible binding sites for interaction with various receptors. Some derivatives have become promising drug candidates.[2] Therefore, functionalization and fine-tuning of substituents around the pyridazine nucleus is an activity of continued interest in the overall design and development of drugs.

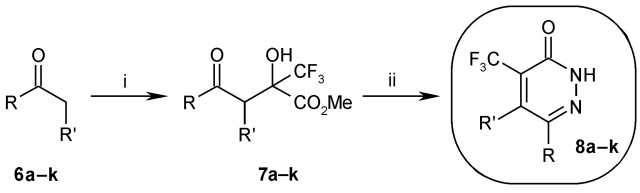
Additionally, (2*H*)-pyridazin-3-ones are very useful starting materials for synthesis of libraries based on the pyridazine scaffold, for example, 3-(alkylamino)pyridazine derivatives of type **1**, potential biologically active compounds.



Scheme 1

Introduction of fluorine-containing substituents is a very useful tool for changing physico-chemical properties of molecules, which are widely used in the search for new drugs. At the same time there are only a few reported studies devoted to synthesis of derivatives of trifluoromethyl-containing pyridazine derivatives.[1,3] It should be noted that the synthesis of 4-trifluoromethyl-(2*H*)-pyridazin-3-ones **2** (R′ = CF_3) was accomplished in four steps starting from commercially unavailable compounds in low overall yields (Scheme 1). The increasing interest in fluorinated heterocyclic compounds[4] prompted us to develop a general method for the synthesis of 4-trifluoromethyl pyridazine derivatives. The general approach to (2*H*)-pyridazin-3-ones bearing various substituents at the 4-position is the reaction of α-hydroxy-γ-ketoacids with hydrazine derivatives (Scheme 1).[5] However, this very convenient approach has never been applied to synthesis of 4-trifluoromethyl pyridazine derivatives, despite the fact that derivatives of α-hydroxy-α-CF_3-γ-ketoacids are known in the literature.[6–8] Synthesis of these compounds can easily be carried out by reaction of methyl 3,3,3-trifluoropyruvate (MeTFP) with carbonyl compounds or enamines.

A wide set of ketones was used by us in the reaction with MeTFP affording derivatives **7a**–**j**. Optimized conditions were found to be heating equivalent amounts of ketone and MeTFP at 100 °C in a pressure tube. Under these conditions in the majority of cases ketones transform into the corresponding aldols in almost quantitative yields so that analytically pure products can be prepared by triturating products with hexane. There are a few exceptions such as pyridylmethylketones **6e**–**g**, in that cases the reaction mixtures underwent extensive resinification and in the case of acetylpyrrole **6j**, which was shown to react at the pyrrole ring as well.[9] In these cases, analytically pure products can be prepared by silica gel column chromatography using EtOAc as eluent (Scheme 2, Table 1).



Scheme 2 *Reagents and conditions*: i: 1 equiv MeTFP, 100 °C, 1–5 h, neat; ii: 3 equiv $NH_2NH_2 \cdot H_2O$, AcOH, reflux, 1 h.

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The aldols **7**[10–13] react readily with hydrazine in acetic acid during one hour affording the targeted 4-trifluoromethyl-(2*H*)-pyridazin-3-ones **8a**–**k**[14–17] in high yields (Table 1).

In our previous work[7] a convenient method for the synthesis of trifluoromethyl containing aldols of type **7** containing additional groups was offered. In the reaction with hydrazines, additional electrophilic centers participate in the reactions affording cyclocondensation products (Scheme 3).

Table 1 Yields, Reaction Time and Melting Points of Compounds **7** and **8**

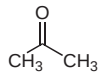
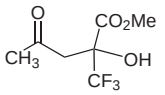
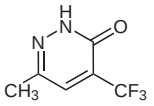
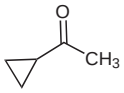
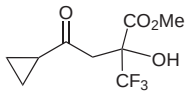
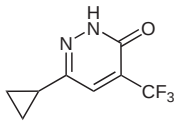
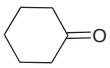
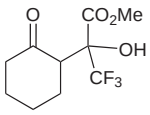
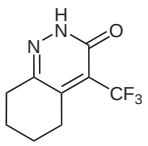
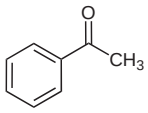
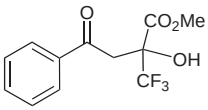
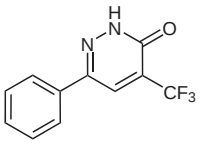
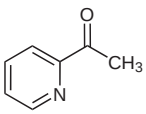
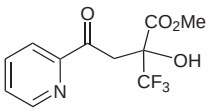
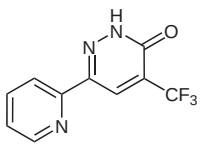
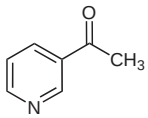
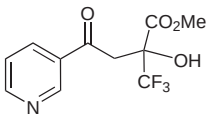
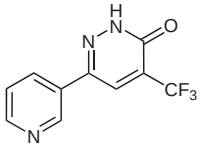
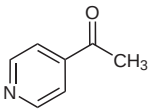
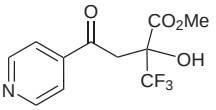
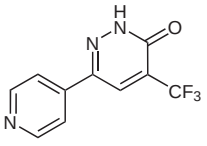
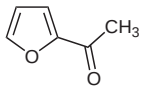
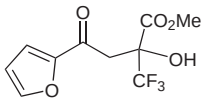
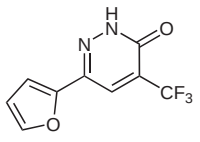
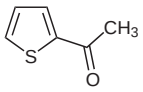
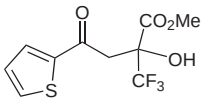
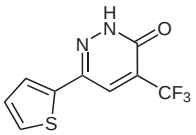
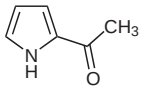
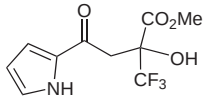
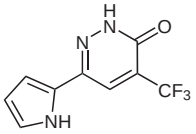
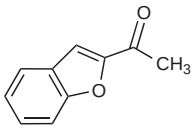
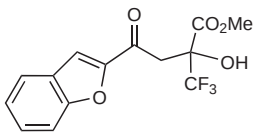
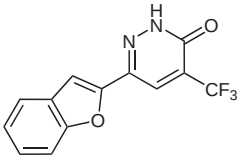
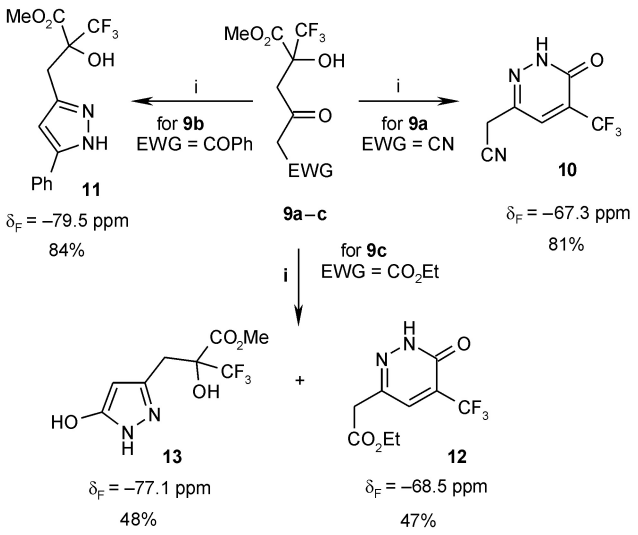
	Substrates **6**	Time (h)[a]	Products **7**	Yield (%)[b]	Mp (°C)[c]	Products **8**	Yield (%)[b]	Mp (°C)[c]
a		1	 δ_F = –86.6 ppm	98	61[e]	 δ_F = –67.8 ppm	95	187–189[f]
b		1	 δ_F = –77.9 ppm	85	51	 δ_F = –66.3 ppm	96	111
c		1	 δ_F = –75.8 ppm	91	58–60[g]	 δ_F = –59.5 ppm	97	150 (dec)
d		2	 δ_F = –80.0 ppm	97	84[h]	 δ_F = –66.7 ppm	89	144[i]
e		3	 δ_F = –80.0 ppm	51	67	 δ_F = –66.6 ppm	82	213
f		4	 δ_F = –66.1 ppm	42	117	 δ_F = –66.1 ppm	78	198–200
g		1	 δ_F = –77.8 ppm	62	137	 δ_F = –66.2 ppm	85	206
h		3	 δ_F = –80.2 ppm	85	52	 δ_F = –66.2 ppm	81	180

Table 1 Yields, Reaction Time and Melting Points of Compounds **7** and **8** (continued)

	Substrates **6**	Time (h)[a]	Products **7**	Yield (%)[b]	Mp (°C)[c]	Products **8**	Yield (%)[b]	Mp (°C)[c]
i		4	 δ_F = –80.1 ppm	82	84	 δ_F = –66.1 ppm	86	204–206
j		3	 δ_F = –80.4 ppm	80[d]	Oil[i]	 δ_F = –65.9 ppm	81	193
k		5	 δ_F = –77.8 ppm	67	134	 δ_F = –66.2 ppm	91	225

[a] According to ^{19}F NMR spectra of the reaction mixture.
[b] Isolated yields.
[c] Melting points are uncorrected.
[d] Data of ^{19}F NMR spectra of the reaction mixture.
[e] Lit. 61–63 °C.[6a]
[f] Lit. 190–191 °C.[3]
[g] Lit. 57–59 °C.[6a]
[h] Lit. 85–87°C.[6a]
[i] Purity >85%, but can be used for following transformation without purification. Analytically pure products can be prepared by silica gel column chromatography using EtOAc as eluent (R_f = 0.8); Mp = 99–101 °C.

The course of the reaction depends on the character of the electron-withdrawing function in the starting compounds **9**.



Scheme 3 *Reagents and conditions*: i: 3 equiv $NH_2NH_2 \cdot H_2O$, AcOH, reflux, 1–3 h.

Thus, for compound **9a** (EWG = CN) reaction with hydrazine leads to the formation of the targeted pyridazin-3-one (**10**).[18] In the case of aldol **9b** (EWG = COPh), the reaction proceeds with participation of the additional carbonyl group affording pyrazole **11**.[19] In a case of compound **9c** (EWG = CO_2Et) the reaction runs non-regioselectively, affording the mixture of targeted pyridazin-3-one (**12**) and pyrazolone **13**.[20]

In conclusion, a convenient synthesis of 4-CF_3-(2*H*)-pyridazin-3-ones starting from methyl 3,3,3-trifluoropyruvate (MeTFP) and carbonyl compounds has been elaborated. As a result, a set of various 4-CF_3-(2*H*)-pyridazin-3-ones was obtained. A wide set of substrates performed well in the reaction. Nevertheless, some limitations were encountered in the development of this methodology. The presence of additional functional groups reactive toward hydrazine in the starting CF_3-containing aldols can lead to other products.

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(10) **Typical Procedure for Preparation of Compounds 7a–k.**
A neat mixture of ketone **6** (1 equiv) and MeTFP (1 equiv) in a pressure tube was heated at 100 °C 1–5 h (reaction mixture was monitored by ^{19}F NMR). After cooling the tube was opened (*Caution! Excessive pressure inside!*) and the residue was triturated with *n*-hexane yielding targeted compound **7**.

(11) Typical ^{1}H NMR data (Varian Mercury-300 spectrometer) of aldols **7**.
Compound **7f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.59 and 3.71 (2 H, AB-syst., $^{2}J_{HH}$ = 18.0 Hz, CH_2), 3.83 (3 H, s, OCH_3), 4.18 (1 H, br s, OH), 7.48 (1 H, dd, $^{3}J_{HH}$ = 7.8 Hz, $^{3}J_{HH}$ = 4.8 Hz, CH), 8.13 (1 H, dt, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 2.5 Hz, CH), 8.72 (1 H, dd, $^{3}J_{HH}$ = 4.8 Hz, $^{4}J_{HH}$ = 2.5 Hz, CH), 9.07 (1 H, d, $^{4}J_{HH}$ = 2.5 Hz, CH).
Compound **7g**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.77 (3 H, s, OCH_3), 3.83 (2 H, s, CH_2), 7.05, (1 H, s, OH), 7.87 (2 H, d, $^{3}J_{HH}$ = 6.0 Hz, CH), 8.20 (2 H, d, $^{3}J_{HH}$ = 6.0 Hz, CH).
Compound **7i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 and 3.70 (2 H, AB-syst., $^{2}J_{HH}$ = 17.1 Hz, CH_2), 3.93 (3 H, s, OCH_3), 4.24 (1 H, br s, OH), 7.17 (1 H, t, $^{3}J_{HH}$ = 4.8 Hz, CH), 7.72 (1 H, d, $^{3}J_{HH}$ = 4.8 Hz, CH), 7.76 (1 H, d, $^{3}J_{HH}$ = 4.8 Hz, CH).

(12) Typical ^{13}C NMR data (Varian Mercury-400 spectrometer) of aldols **7**.
Compound **7f**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.0, 54.2, 74.9 (CCF_3, $^{2}J_{CF}$ = 32.9 Hz), 123.1 (CF_3, $^{1}J_{CF}$ = 285.1 Hz), 123.8, 128.3, 131.2, 135.5, 149.4, 154.1, 169.1, 193.6.
Compound **7g**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.1, 53.2, 73.2 (CCF_3, $^{2}J_{CF}$ = 28.2 Hz), 121.3, 123.7 (CF_3, $^{1}J_{CF}$ = 285.7 Hz), 141.8, 151.0, 168.5, 195.2.
Compound **7i**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.0, 54.2, 75.2 (CCF_3, $^{2}J_{CF}$ = 29.5 Hz), 122.1 (CF_3, $^{1}J_{CF}$ = 285.3 Hz), 128.4, 133.1, 135.1, 142.7, 169.2, 187.4.

(13) Typical MS data (MX-1321 instrument) of aldols **7**.
Compound **7f**: MS (EI, 70 eV): *m/z* (%) = 277 (4) [M^+], 218 (26) [$M^+ - CO_2Me$], 106 (100) [3-pyridyl – CO^+], 78 (40) [3-pyridyl$^+$], 51 (17).
Compound **7g**: MS (EI, 70 eV): *m/z* (%) = 277 (5) [M^+], 218 (27) [$M^+ - CO_2Me$], 106 (100) [4-pyridyl – CO^+], 78 (42) [4-pyridyl$^+$], 51 (21).
Compound **7i**: MS (EI, 70 eV): *m/z* (%) = 282 (4) [M^+], 223 (15) [$M^+ - CO_2Me$], 111 (100) [2-thienyl – CO^+], 39 (16).

(14) **Typical Procedure for Preparation of (2*H*)-Pyridazine-3-ones 8.**
To a solution of aldol **7** (1 equiv) in HOAc (5 mL) $NH_2NH_2 \cdot H_2O$ (3 equiv) was added. The reaction mixture was refluxed for 1 h. After cooling the solvent was evaporated in vacuum and the residue was triturated with H_2O affording **8**.

(15) Typical ^{1}H NMR data (Varian Mercury-300 spectrometer) of 4-trifluoromethyl-(2*H*)-pyridazine-3-ones **8**.
Compound **8f**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.54 (1 H, t, $^{3}J_{HH}$ = 7.2 Hz, CH), 8.31 (1 H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 8.51 (1 H, s, CH), 8.66 (1 H, d, $^{3}J_{HH}$ = 3.6 Hz, CH), 9.12 (1 H, s, CH), 13.97 (1 H, br s, NH).
Compound **8g**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.52 (2 H, d, $^{3}J_{HH}$ = 6.3 Hz, CH), 9.10 (1 H, s, CH), 9.29 (2 H, d, $^{3}J_{HH}$ = 6.3 Hz, CH).
Compound **8i**: ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.18 (1 H, s, CH), 7.69 (1 H, s, CH), 7.91 (1 H, s, CH), 8.47 (1 H, s, CH), 13.73 (1 H, s, NH).

(16) Typical ^{13}C NMR data (Varian Mercury-400 spectrometer) of 4-trifluoromethyl-(2*H*)-pyridazine-3-ones **8**.
Compound **8f**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 121.6 (CF_3, $^{1}J_{CF}$ = 271.8 Hz), 123.8, 127.6 (CCF_3, $^{2}J_{CF}$ = 31.9 Hz), 129.7, 130.4 ($CCCF_3$, $^{3}J_{CF}$ = 5.0 Hz), 133.6, 141.6, 147.1, 150.3, 156.1.
Compound **8g**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 119.9, 121.5 (CF_3, $^{1}J_{CF}$ = 270.9 Hz), 127.6 (CCF_3, $^{2}J_{CF}$ = 31.6 Hz), 129.9 ($CCCF_3$, $^{3}J_{CF}$ = 4.9 Hz), 140.9, 141.2, 150.3, 156.3, 172.0.
Compound **8i**: ^{13}C NMR (100 MHz, DMSO-d_6): δ = 121.3 (CF_3, $^{1}J_{CF}$ = 271.4 Hz), 127.8, 127.9 (CCF_3, $^{2}J_{CF}$ = 31.2 Hz), 128.4, 128.9, 129.5 ($CCCF_3$, $^{3}J_{CF}$ = 4.9 Hz), 138.3, 140.3, 156.0.

(17) Typical MS data (MX-1321 instrument) of 4-trifluoromethyl-(2*H*)-pyridazine-3-ones **8**.
Compound **8f**: MS (EI, 70 eV): *m/z* (%) = 242 (9) [M + 1], 241 (100) [M^+], 184 (37).
Compound **8g**: MS (EI, 70 eV): *m/z* (%) = 242 (10) [M + 1], 241 (100) [M^+], 184 (24).
Compound **8i**: MS (EI, 70 eV): *m/z* (%) = 247 (9) [M + 1], 246 (100) [M^+], 189 (54).

(18) **Procedure for Preparation of 1,6-Dihydro-6-oxo-5-(trifluoromethyl)-3-pyridazineacetonitrile (10).**
To a solution of aldol **9a** (1 g, 4.2 mmol) in HOAc (10 mL) $NH_2NH_2 \cdot H_2O$ (0.63 g, 12.6 mmol) was added. The reaction mixture was refluxed for 3 h (reaction mixture was monitored by ^{19}F NMR). After cooling the solvent was evaporated in vacuum and the residue was triturated with H_2O and extracted with Et_2O (10 mL). The Et_2O was evaporated in vacuum affording **10** (0.68 mg, 81%). Mp 175 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.15 (2 H, s, CH_2), 7.93 (1 H, s, CH), 13.8 (1 H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.1, 117.1, 121.4 (CF_3, $^{1}J_{CF}$ = 270.8 Hz), 127.8 (CCF_3, $^{2}J_{CF}$ = 31.2 Hz), 132.8, 139.1, 156.5. MS (EI, 70 eV): *m/z* (%) = 204 (100) [M^+], 148 (15), 120 (39), 106 (14), 75 (19).

(19) **Procedure for Preparation of Methyl α-Hydroxy-5-phenyl-α-(trifluoromethyl)-1*H*-pyrazole-3-propanoate (11).**
To a solution of aldol **9b** (1 g, 3.1 mmol) in HOAc (10 mL) $NH_2NH_2 \cdot H_2O$ (0.47g, 9.3 mmol) was added. The reaction mixture was refluxed for 1 h (reaction mixture was monitored by ^{19}F NMR). After cooling the solvent was evaporated in vacuum and the residue was triturated with H_2O affording **11** (0.83 mg, 84%). Mp 98 °C. ^1H NMR (300 MHz, DMSO-d_6): δ = 3.11 and 3.33 (2 H, AB-syst., $^2J_{HH}$ = 14.1 Hz, CH_2), 3.76 (3 H, s, OCH_3), 6.46 (1 H, s, CH), 7.04 (1 H, br s, OH), 7.32–7.41 (3 H, m, CH), 7.72 (2 H, d, $^3J_{HH}$ = 6.3 Hz, CH), 12.94 (1 H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.2 (br, $\Delta\nu_{1/2}$ ca. 30 Hz), 53.7, 78.1 (CCF_3, $^2J_{CF}$ = 27.7 Hz), 102.9, 124.6 (CF_3, $^1J_{CF}$ = 288.0 Hz), 125.4, 128.1, 129.3, 132.0 (br, $\Delta\nu_{1/2}$ ca. 65 Hz), 141.2 (br, $\Delta\nu_{1/2}$ ca. 300 Hz), 146.6 (br, $\Delta\nu_{1/2}$ ca. 270 Hz), 168.6. MS (EI, 70 eV): *m/z* (%) = 314 (38) [M^+], 255 (40) [$M^+ - CO_2Me$], 157 (100) [M^+ – MeTFP].

(20) **Procedure for Preparation of Ethyl 1,6-Dihydro-6-oxo-5-(trifluoromethyl)-3-pyridazineacetate (12) and Methyl α,5-Dihydroxy-α-(trifluoromethyl)-1*H*-pyrazole-3-propanoate (13).**
To a solution of aldol **9c** (1 g, 3.5 mmol) in HOAc (10 mL) $NH_2NH_2 \cdot H_2O$ (0.53 g, 10.5 mmol) was added. The reaction mixture was refluxed for 1 h (reaction was monitored by ^{19}F NMR). After cooling the solvent was evaporated in vacuum and the residue was triturated with Et_2O. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (10 mL). The insoluble precipitate was filtered affording **13** (0.43 g, 48%). The mother liquid was evaporated and the residue was triturated with hexane giving **12** (0.41 g, 47%).
Compound **12**: mp 87 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.3 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.75 (2 H, s, CH_2), 7.71 (1 H, s, CH), 10.02 (1 H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 20.9, 39.5, 53.6, 61.3, 120.1 (CF_3, $^1J_{CF}$ = 272.9 Hz), 127.3 (CCF_3, $^2J_{CF}$ = 31.4 Hz), 133.9, 141.8, 156.5, 168.4, 170.0. MS (EI, 70 eV): *m/z* (%) = 250 (35) [M^+], 178 (86) [$M^+ - CO_2Et$], 158 (40), 120 (20), 101 (49), 97 (33), 75 (20), 74 (43), 69 (24) [CF_3], 51 (25), 43 (100).
Compound **13**: mp 196 °C ^1H NMR (300 MHz, DMSO-d_6): δ = 2.94 and 3.16 (2 H, AB-syst., $^2J_{HH}$ = 14.4 Hz, CH_2), 3.73 (3 H, s, OCH_3), 5.24 (1 H, s, CH), 7.0 (1 H, br s, OH), 10.6 (1 H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.8, 53.6, 77.8 (CCF_3, $^2J_{CF}$ = 27.5 Hz), 89.8, 124.4 (CF_3, J_{CF} = 285.6 Hz), 137.3, 160.5, 168.4. MS (EI, 70 eV): *m/z* (%) = 254 (10) [M^+], 195 (10) [$M^+ - CO_2Me$], 98 (100) [M^+ – MeTFP].