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ORIGINAL PAPER

An E-factor minimized solvent-free protocol for the preparation of 4,5-dihydro-5-(trifluoromethyl)-1*H*-pyrazoles

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Abstract The efficient synthesis of 4,5-dihydro-1*H*-pyrazoles from the reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones [$CF_3C(O)CH{=}C(R^1)(OR)$, where R = Me, Et and R^1 = H, Me, Et, Pr, *i*-Bu, Ph, 4-Me-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, fur-2-yl, Naphth-2-yl, biphenyl-4-yl] and ethyl 3-hydrazino-3-oxopropionate [$NH_2NHC(O)CH_2C(O)OEt$] is reported. The products were obtained in good yields (72–87%). Two protocols were developed: (1) conventional thermal heating using EtOH as solvent and under solvent-free conditions, and (2) a microwave-assisted method using EtOH as solvent and under solvent-free conditions. The E-factor was determined for all protocols, and the results showed that the microwave-assisted method under solvent-free conditions results in a greener process.

Keywords Microwave irradiation · Solvent-free · E-factor · Pyrazoles · Cyclocondensation reactions

Introduction

In the last 30 years, the amount of attention devoted worldwide to the concept of chemistry sustainability, both in industry and academia, has undergone an explosive growth. The design of greener, more sustainable products and processes has become a top priority item in annual reports, and many chemical and pharmaceutical companies have appointed global green chemistry managers. In this context, in the late 1980s Sheldon [1] introduced the concept of the E- (environmental) factor for assessing the environmental impact of manufacturing processes. The E-factor is designated as the weight of waste generated per weight of product. Waste is defined as everything produced in the process except the desired product. To calculate the E-factor, the product yield, reagents, solvent losses, all process aids, and even energy consumption (though this is frequently difficult to estimate) are taken into account [2–4].

The combination of the use of microwave irradiation and solvent-free conditions may have an important role in reducing or eliminating waste in chemical processes. The main impact of microwave irradiation in the calculation of the E-factor is due to the increases in the product yield, purity of products, and sometimes different product distribution as compared with the conventional methods [5, 6].

In the last 20 years, we have developed a general synthesis of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones [7–10], important halogen-containing building blocks, and shown their usefulness in heterocyclic preparations [7–10]. In particular, 4,5-dihydro-1*H*-pyrazoles are important five-membered heterocyclic compounds with significant agrochemical [11] and pharmacological activities [12–16]. Our research program is committed to the optimization of synthetic procedures by employing eco-friendly reaction protocols, including the use of solvent-free conditions [17, 18], and substitute classic organic solvents in organic reactions [19–23]. So, as part of our research program in this work we present the synthesis of 4,5-dihydro-1*H*-pyrazoles from the reaction between 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones and ethyl 3-hydrazino-3-oxopropionate for which we (1) developed different protocols: a microwave-assisted

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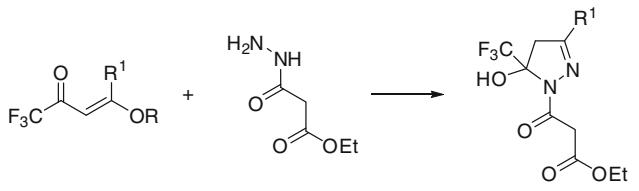
method (MM) in the presence of EtOH as solvent and under solvent-free (SF) conditions and a conventional thermal heating method (CM) using EtOH as solvent and under solvent-free conditions; (2) determined the E-factor for each process to determine which is greener; and (3) applied the greener process to the synthesis of a novel series of fluorine-containing 4,5-dihydro-1*H*-pyrazoles.

Results and discussion

Enones **1a**–**1l** were obtained from the acylation reaction of enol ether or acetal with trifluoroacetic anhydride in accordance with the methodology developed in our laboratory [7–10]. Ethyl 3-hydrazino-3-oxopropionate (**2**) was obtained commercially.

In order to determine the E-factor of the synthesis process of 4,5-dihydro-1*H*-pyrazoles we started with the reaction of enones **1a**, **1b** with hydrazine **2** at a molar ratio of 1:1.2. The reactions were performed using the microwave-assisted method (MM) and the conventional method (CM) to obtain the products **3a**, **3b**. Both methods were performed in the presence of EtOH (5 cm^3) and under solvent-free conditions. Reaction conditions and yields of all process are depicted in Table 1. From the results we concluded that, in general, yields of products were very similar in both methods and solvents, or slightly higher with the MM method.

Table 1 Reactions of enones **1a**, **1b** with hydrazine **2** using different conditions



1a, **1b** **2** **3a**, **3b**

	R	R^1	Prod.	MM method[a]		CM method[b]	
				Solvent	Yield (%)	Solvent	Yield (%)
1a	Et	H	**3a**	EtOH	73	EtOH	71
1a	Et	H	**3a**	SF	78	SF	63
1b	Me	Me	**3b**	EtOH	76	EtOH	77
1b	Me	Me	**3b**	SF	80	SF	61

[a] Reaction time 6 min, reaction temperature 50 °C

[b] Reaction time 1 h, reaction temperature 78 °C

In sequence, we determined the E-factor of all processes to accurately evaluate which method minimizes environmental impacts. The E-factor may be obtained (1) only for the synthesis step (SYS), (2) for the synthesis and product isolation steps (SYS + PIS), (3) for the synthesis and product purification steps (SYS + PPS), or (4) for the synthesis and workup steps (SYS + PIS + PPS) (Fig. 1).

For the case studied, data involved in each synthetic procedure were recorded for the E-factor calculation, such as the amount of reactants and the volume of solvents used in the synthesis step, and in the workup, (SYS + PIS) at one purification step are not necessary. The E-factor was calculated from the equation described in Fig. 2. E-factor values found for all processes are described in Table 2.

As expected, better E-factor values were found for products **3a** and **3b** using solvent-free conditions for both methods, MM and CM. However, the E-factor for formation of **3b** was more favorable than for the formation of **3a**. Although the yield of **3b** was slightly superior to **3a**, it was probably caused by differences in E-factor values.

Recently, we published a review about solvent-free heterocyclic synthesis in which we used the E-factor to evaluate the magnitude of waste generated by a wide range of cyclocondensation reactions carried out under solvent-free conditions on a laboratorial scale [23]. The E-factor was determined for each individual compound, and the E-factor was obtained as an average value for a series of individual E-factors. We found that reactions involving both synthesis (SYS) and isolation steps (PIS) of compounds showed E-factors in a range of 24.2–388.9. In this review, we also evaluate the impact of excluding the mass of water formed in solvent-free cyclocondensation reactions on the E-factor. The data obtained showed that the exclusion of the mass of water from E-factors for cyclocondensation reactions that led to the formation of water in the reaction medium brought about a reduction in the range of 0.01–1 units in E-factor values; therefore, we do not consider it relevant to present this calculation in this paper.

In this work, we found that the E-factor values for all protocols are in the range of 59.3–91.3, which falls within the range found in the review for the SYS + PIS E-factor

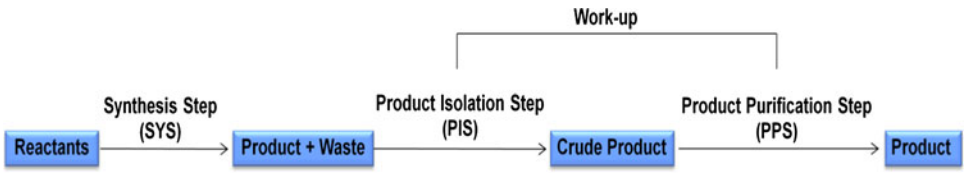


Fig. 1 Synthetic procedure steps to obtain products

$$\text{E - factor} = \frac{m_{\text{reactants}} - m_{\text{products}}}{m_{\text{products}}}$$

Fig. 2 Equation used for the E-factor calculation

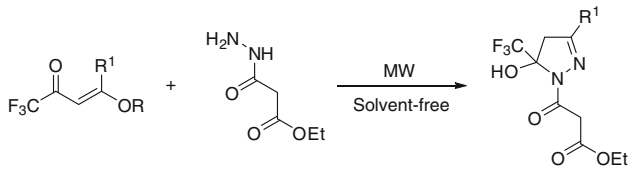
Table 2 E-Factors for the synthesis of compounds **3a** and **3b**

Method	E-factor	
	3a	**3b**
CM/EtOH	91.3	79.9
CM/SF	76.9	78.1
MW/EtOH	88.7	80.9
MW/SF	64.1	59.3

and falls within the range of fine chemical and pharmaceuticals industry segments (<25–100) [23].

After checking the best reaction conditions to obtain the 4,5-dihydro-1*H*-pyrazoles **3a**, **3b**, new compounds with different substituents were synthesized. The scope of this solvent-free microwave irradiation method for the synthesis of 4,5-dihydro-1*H*-pyrazoles **3a–3l** was demonstrated by the use of enones with various substituents (R^1) as shown in Table 3. The results obtained show that the presence of a substituent R^1 at the 4-position of the enone was sensitive to the reaction conditions. Enones containing 4-alkyl were more reactive and presented lower reaction temperatures, whereas 4-aryl substituents required higher reaction temperatures. These results are presented in Table 3.

Table 3 Reaction conditions for the synthesis of 4,5-dihydro-1*H*-pyrazoles **3a–3l**



1a-1l **2** **3a-3l**

Product	R	R^1	T (°C)	Time (min)	Yield (%)
3a	Et	H	50	6	78
3b	Me	Me	50	6	80
3c	Me	Et	50	6	85
3d	Me	Pr	50	6	87
3e	Me	*i*-Bu	50	6	83
3f	Me	Ph	100	6	80
3g	Me	4-Me-C_6H_4	100	6	79
3h	Me	4-F-C_6H_4	100	6	83
3i	Me	4-Cl-C_6H_4	100	6	77
3j	Me	fur-2-yl	100	6	72
3k	Me	Naphth-2-yl	100	6	87
3l	Me	Biphenyl-4-yl	100	6	78

4,5-Dihydro-1*H*-pyrazoles **3** showed sets of ^{1}H and ^{13}C NMR data that correspond to the proposed structures. Compound **3** showed ^{1}H NMR chemical shifts of the diastereotopic methylene protons (H-4a and H-4b) as a characteristic AB system and as a doublet at the range of 3.09–3.86 ppm, respectively, with a geminal coupling constant at the range of $^2J = 18.6$–19.7 Hz. Previous studies have demonstrated that the doublet in the low field corresponds to the hydrogen *cis* in relation to the hydroxyl group [24]. Interestingly, the protons present between the carbonyl groups at position 1 of the pyrazole ring also showed different chemical shifts as a doublet at the range of 3.65–3.91 ppm, with a geminal coupling constant in the range of $^2J = 16$–17 Hz. The same compounds showed ^{13}C NMR spectra with typical chemical shifts at the ranges of 145.2–159.6 (C-3), 42.3–42.8 (C-4), 89.9–91.8 (C-5), and 122.9–123.0 (CF_3).

The mechanism of formation of 4,5-dihydro-1*H*-pyrazoles involves a cyclocondensation reaction. The reaction proceeds by a Michael addition/elimination on the β-carbon atom of the enone [25] by the more nucleophilic function of hydrazide. The enamino ketone intermediate formed undergoes cyclization by the addition of the second NH function at the carbonyl group to provide 4,5-dihydro-1*H*-pyrazoles **3a–3l**.

In conclusion, we developed an efficient method for obtaining a new series of fluorine-containing 4,5-dihydro-1*H*-pyrazoles using microwave irradiation and solvent-free conditions. The efficiency of this methodology was also verified by the lower E-factor values found herein. The products were obtained in good yields and under mild conditions.

Experimental

Microwave experiments were performed in a CEM Discover using the simultaneous cooling mode of operation. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) and Bruker DPX-200 (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) in $CDCl_3$/TMS solutions at 298 K. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, cross-linked to a HP-5 capillary column (30 m, 0.32 mm i.d.), and helium was used as the carrier gas. The melting points were measured using a Microquímica MQAPF 301. Elemental analyses were performed on a Perkin Elmer CHN elemental analyzer and results agreed favorably with calculated values.

*General procedure for the preparation of compounds **3a**, **3b** by conventional methods*

Enone **1a**, **1b** (1 mmol), hydrazine **2** (1.2 mmol), and when required 5 cm^3 of EtOH were placed in a round-bottomed flask. The mixture was kept under magnetic stirring at the time and temperature indicated in Table 1. Then 10 cm^3 dichloromethane was added, and the reaction mixture was washed with water (3 × 15 cm^3). The organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure.

*General procedure for the preparation of compounds **3a–3l** under microwave irradiation*

A 10 cm^3 microwave vessel equipped with a standard cap (commercially furnished with a vessel by CEM Discover) was filled with enone **1a–1l** (1 mmol), hydrazine **2** (1.2 mmol), and when necessary 5 cm^3 of EtOH. After the vessel was sealed, the sample was irradiated for the time and temperature indicated in Table 3. The data were then plotted in Synergies Version 3.5.9 software applying a maximum irradiation level of 200 W and a maximum level of internal vessel pressure of 250 psi. The reactions were carried out at 50–100 °C with simultaneous cooling. The reaction mixture was subsequently cooled to 50 °C by compressed air. Then, 10 cm^3 dichloromethane was added, and the reaction mixture was washed with water (3 × 15 cm^3). The organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to furnish the products **3a–3l**.

Ethyl 4,5-dihydro-5-hydroxy-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate (**3a**, $C_9H_{11}F_3N_2O_4$)
Yield 78%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, 3H, H10), 3.20 (d,1H, ^2J = 19.7 Hz, H4a), 3.39 (d, 1H, ^2J = 19.7 Hz, H4b), 3.69 (d, 1H, ^2J = 16.1 Hz, H7a), 3.78 (d, 1H, ^2J = 16.1 Hz, H7b), 4.20 (q, 2H, H9), 6.98 (s, 1H, H3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (C10), 42.6 (C4), 44.9 (C7), 61.6 (C9), 89.9 (q, ^2J = 35 Hz, C5), 122.9 (q, ^1J = 287 Hz, CF_3), 145.3 (C3), 166.5 (C6, C=O), 168.0 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 268 (M^+, 10), 223 (41), 181 (4), 115 (66), 85 (100).

Ethyl 4,5-dihydro-5-hydroxy-3-methyl-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3b**, $C_{10}H_{13}F_3N_2O_4$)
Yield 80%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, 3H, H10), 2.05 (s, 3H, CH_3), 3.13 (d, 1H, ^2J = 19.6 Hz, H4a), 3.27 (d, 1H, ^2J = 19.1 Hz, H4b), 3.69 (d, 1H, ^2J = 16.1 Hz, H7a), 3.74 (d, 1H, ^2J = 16.1 Hz, H7b), 4.20 (q, 2H, H9) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (C10), 15.4 (C11), 42.3 (C4), 46.9 (C7), 61.3 (C9), 91.1 (q, ^2J = 34 Hz, C5), 122.9 (q, ^1J = 287 Hz, CF_3), 155.2 (C3), 166.6 (C6, C=O), 167.3 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 282 (M^+, 3), 237 (9), 168 (39), 99 (100).

Ethyl 3-ethyl-4,5-dihydro-5-hydroxy-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3c**, $C_{11}H_{15}F_3N_2O_4$)
Yield 85%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16 (t, 3H, H12), 1.26 (t, 3H, H10), 2.37 (q, 2H, H11), 3.12 (d,1H, ^2J = 18.6 Hz, H4a), 3.27 (d, 1H, ^2J = 18.6 Hz, H4b), 3.66 (d, 1H, ^2J = 16.1 Hz, H7a), 3.75 (d, 1H, ^2J = 16.1 Hz, H7b), 4.20 (q, 2H, H9), 6.01 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.0 (C12), 13.9 (C10), 23.2 (C11), 42.5 (C4), 45.5 (C7), 61.3 (C9), 91.1 (q, ^2J = 34 Hz, C5), 123.0 (q, ^1J = 287 Hz, CF_3), 159.6 (C3), 166.6 (C6, C=O), 167.6 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 296 (M^+, 5), 251 (17), 182 (49), 113 (100).

Ethyl 4,5-dihydro-5-hydroxy-β-oxo-3-propyl-5-(trifluoromethyl)-1H-pyrazole-1-propanoate (**3d**, $C_{12}H_{17}F_3N_2O_4$)
Yield 87%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (t, 3H, H13), 1.26 (t, 3H, H10), 1.61 (st, 2H, H12), 2.32 (t, 2H, H11), 3.08 (d, 1H, ^2J = 19.1 Hz, H4a), 3.26 (d, 1H, ^2J = 18.9 Hz, H4b), 3.65 (d, 1H, ^2J = 16.1 Hz, H7a), 3.75 (d, 1H, ^2J = 16.1 Hz, H7b), 4.19 (q, 2H, H9), 6.03 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4 (C13), 13.9 (C10), 19.2 (C12), 31.6 (C11), 42.5 (C4), 45.6 (C7), 61.3 (C9), 91.0 (q, ^2J = 34 Hz, C5), 123.0 (q, ^1J = 284 Hz, CF_3), 158.7 (C3), 166.7 (C6, C=O), 167.6 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 310 (M^+, 18), 265 (35), 196 (89), 127 (100).

Ethyl 4,5-dihydro-5-hydroxy-3-(2-methylpropyl)-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3e**, $C_{13}H_{19}F_3N_2O_4$)
Yield 83%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95–0.98 (m, 6H, H13, H13'), 1.26 (t, 3H, H10), 1.93 (sp, 1H, H12), 2.21 (d, 2H, H11), 3.14 (d, 1H, ^2J = 18 Hz, H4a), 3.26 (d, 1H, ^2J = 18 Hz, H4b), 3.65 (d, 1H, ^2J = 16.1 Hz, H7a), 3.76 (d, 1H, ^2J = 16.1 Hz, H7b), 4.21 (q, 2H, H9), 6.00 (br s, 1H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (C10), 21.9 (C13), 22.1 (C13'), 26.0 (C12), 38.4 (C11), 42.4 (C4), 45.9 (C7), 61.1 (C9), 90.8 (q, ^2J = 34 Hz, C5), 123.0 (q, ^1J = 287 Hz, CF_3), 158.0 (C3), 166.5 (C6, C=O), 167.2 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 324 (M^+, 3), 279 (9), 210 (38), 141 (100).

Ethyl 4,5-dihydro-5-hydroxy-β-oxo-3-phenyl-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3f**, $C_{15}H_{15}F_3N_2O_4$)
Yield 80%; m.p.: 60–63 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, 3H, H10), 3.55 (d, 1H, ^2J = 18.7 Hz, H4a), 3.72 (d, 1H, ^2J = 18.7 Hz, H4b), 3.77 (d, 1H, ^2J = 16.0 Hz, H7a), 3.86 (d, 1H, ^2J = 16.0 Hz, H7b),

4.20 (q, 2H, H9), 7.44–7.70 (m, 5H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (C10), 42.8 (C4), 43.5 (C7), 61.5 (C9), 91.7 (q, ^2J = 34 Hz, C5), 123.0 (q, ^1J = 287 Hz, CF_3), 126.6, 128.9, 129.5, 131.3 (C–Ar), 153.6 (C3), 166.6 (C6, C=O), 167.7 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 344 (M^+, 19), 299 (12), 230 (84), 161 (100), 103 (13).

Ethyl 4,5-dihydro-5-hydroxy-3-(4-methylphenyl)-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3g**, $C_{16}H_{17}F_3N_2O_4$)
Yield 79%; m.p.: 58–60 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, 3H, H10), 2.40 (s, 3H, CH_3), 3.53 (d, 1H, ^2J = 18.5 Hz, H4a), 3.70 (d, 1H, ^2J = 18.7 Hz, H4b), 3.76 (d, 1H, ^2J = 16.1 Hz, H7a), 3.85 (d, 1H, ^2J = 16.1 Hz, H7b), 4.20 (q, 2H, H9), 6.00 (br s, 1H, OH), 7.24 (d, ^3J = 8 Hz, 2H, H–Ar), 7.56 (d, ^3J = 8 Hz, 2H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (C10), 21.4 (C15), 42.8 (C4), 43.5 (C7), 61.4 (C9), 91.6 (q, ^2J = 34 Hz, C5), 123.0 (q, ^1J = 287 Hz, CF_3), 126.6, 126.8, 129.5, 141.8 (C–Ar), 153.6 (C3), 166.6 (C6, C=O), 167.6 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 358 (M^+, 23), 313 (12), 244 (97), 175 (100).

Ethyl 3-(4-fluorophenyl)-4,5-dihydro-5-hydroxy-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3h**, $C_{15}H_{14}F_4N_2O_4$)
Yield 83%; m.p.: 82–84 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, 3H, H10), 3.54 (d, 1H, ^2J = 19 Hz, H4a), 3.70 (d, 1H, ^2J = 19 Hz, H4b), 3.76 (d, 1H, ^2J = 16.1 Hz, H7a), 3.85 (d, 1H, ^2J = 16.1 Hz, H7b), 4.20 (q, 2H, H9), 5.98 (br s, 1H, OH), 7.09–7.64 (m, 4H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (C10), 42.8 (C4), 43.5 (C7), 61.5 (C9), 91.8 (q, ^2J = 34 Hz, C5), 116.2 (d, ^2J = 22.7 Hz, C–Ar), 123.0 (q, ^1J = 287 Hz, CF_3), 125.9 (d, ^4J = 2.9 Hz, C–Ar), 128.8 (d, ^3J = 8.8 Hz, C–Ar), 152.6 (C3), 164.5 (d, ^1J = 253.2 Hz, C14), 165.8 (C6, C=O), 167.7 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 362 (M^+, 5), 317 (5), 248 (63), 179 (100), 121 (15).

Ethyl 3-(4-chlorophenyl)-4,5-dihydro-5-hydroxy-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3i**, $C_{15}H_{14}ClF_3N_2O_4$)
Yield 77%; m.p.: 79–82 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, 3H, H10), 3.53 (d, 1H, ^2J = 19 Hz, H4a), 3.70 (d, 1H, ^2J = 19 Hz, H4b), 3.76 (d, 1H, ^2J = 16 Hz, H7a), 3.85 (d, 1H, ^2J = 16 Hz, H7b), 4.20 (q, 2H, H9), 5.97 (br s, 1H, OH), 7.42 (d, ^3J = 9 Hz, 2H, H–Ar), 7.61 (d, ^3J = 9 Hz, 2H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (C10), 42.7 (C4), 43.4 (C7), 61.5 (C9), 91.8 (q, ^2J = 34 Hz, C5), 123.0 (q, ^1J = 287 Hz, CF_3), 127.8, 128.0, 129.2, 137.4 (C–Ar), 152.5 (C3), 166.5 (C6, C=O), 167.6 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 378 (M^+, 19), 333 (13), 264 (100), 195 (83).

Ethyl 3-(2-furanyl)-4,5-dihydro-5-hydroxy-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3j**, $C_{13}H_{13}F_3N_2O_5$)
Yield 72%; m.p.: 91–93 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, 3H, H10), 3.51 (d, 1H, ^2J = 18.6 Hz, H4a), 3.68 (d, 1H, ^2J = 18.6 Hz, H4b), 3.76 (d, 1H, ^2J = 17.1 Hz, H7a), 3.85 (d, 1H, ^2J = 16.1 Hz, H7b), 4.21 (q, 2H, H9), 6.04 (br s, 1H, OH), 6.55 (q, 1H, H13), 6.86 (d, 1H, H12), 7.58 (d, 1H, H14) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (C10), 42.4 (C4), 43.2 (C7), 61.4 (C9), 91.2 (q, ^2J = 35 Hz, C5), 123.0 (q, ^1J = 288 Hz, CF_3), 112.2, 113.6, 145.1, 145.4 (2-furanyl), 145.2 (C3), 166.5 (C6, C=O), 167.8 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 334 (M^+, 25), 289 (11), 220 (100), 151 (79).

Ethyl 4,5-dihydro-5-hydroxy-3-(naphthalen-2-yl)-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3k**, $C_{19}H_{17}F_3N_2O_4$)
Yield 87%; m.p.: 110–113 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, 3H, H10), 3.68 (d,1H, ^2J = 18.9 Hz, H4a), 3.86 (d, 1H, ^2J = 18.7 Hz, H4b), 3.81 (d, 1H, ^2J = 16.1 Hz, H7a), 3.91 (d, 1H, ^2J = 16.1 Hz, H7b), 4.22 (q, 2H, H9), 6.01 (br s, 1H, OH), 7.51-7.93 (m, 7H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (C10), 42.8 (C4), 43.4 (C7), 61.5 (C9), 91.8 (q, ^2J = 34 Hz, C5), 123.0 (q, ^1J = 287 Hz, CF_3),122.6, 127.0, 127.1, 127.7, 127.8, 127.9, 128.5, 128.8, 132.7, 134.4 (C–Ar), 153.6 (C3), 166.6 (C6, C=O), 167.7 (C8, C=O) ppm; MS (EI, 70 eV): *m/z* (%) = 394 (M^+, 35), 349 (10), 280 (100), 211 (79), 153 (18).

Ethyl 3-(biphenyl-4-yl)-4,5-dihydro-5-hydroxy-β-oxo-5-(trifluoromethyl)-1H-pyrazole-1-propanoate
(**3l**, $C_{21}H_{19}F_3N_2O_4$)
Yield 78%; m.p.: 101–104 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, 3H, H10), 3.58 (d, 1H, ^2J = 18.8 Hz, H4a), 3.75 (d, 1H, ^2J = 18.6 Hz, H4b), 3.79 (d, 1H, ^2J = 16.1 Hz, H7a), 3.88 (d, 1H, ^2J = 16.0 Hz, H7b), 4.22 (q, 2H, H9), 6.00 (br s, 1H, OH), 7.40–7.77 (m, 9H, H–Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (C10), 42.8 (C4), 43.5 (C7), 61.5 (C9), 91.4 (q, ^2J = 34 Hz, C5), 123.0 (q, ^1J = 287 Hz, CF_3), 127.0, 127.1, 127.5, 128.2, 128.4, 128.5, 128.9, 139.7, 144.1 (C–Ar), 153.4 (C3), 166.6 (C6, C=O), 167.8 (C8, C=O) ppm; MS (EI,70 eV): *m/z* (%) = 420 (M^+, 39), 375 (14), 306 (100), 237 (91), 178 (26).

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