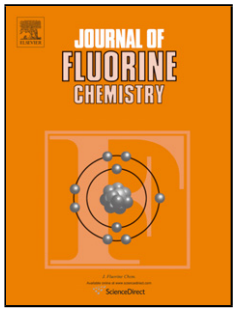

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Synthesis of 2,2,2-trifluoroethyl 1*H*-pyrazole carboxylates: insight into the mechanism of trichloromethyl group hydrolysis

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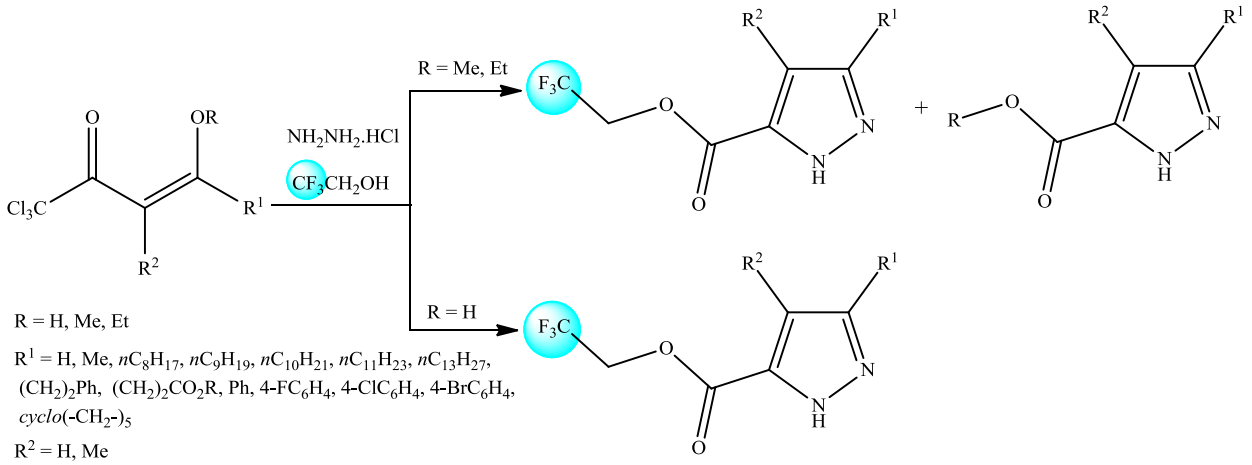
Graphical Abstract



Synthesis of novel 2,2,2-trifluoroethyl 1*H*-pyrazol-5(3)-carboxylates from cyclocondensation between hydrazine hydrochloride and 1,1,1-trichloro-4-alkoxy-3-alken-2-ones and trichloromethyl-1,3-diketones in TFE.

Highlights

- Use of green trifluoroethanol;
- Easy diversification of products from trichloromethyl-substituted precursors;
- The route proposed allows to obtain novel products with trifluoroethyl chain;
- The products obtained are all unpublished and with high potential biological activity.

Abstract – This paper reports one-pot synthesis of 2,2,2-trifluoroethyl *1H*-pyrazole-5(3)-carboxylates via cyclocondensation of 1,1,1-trichloro-4-alkoxy-3-alken-2-ones [$Cl_3CC(O)C(R^2)=C(R^1)OMe$, where R^1 = H, CH_3, *n*-octyl, *n*-nonyl, *n*-undecyl, *n*-undecyl, *n*-tridecyl, -$(CH_2)_2$Ph, 4-ClC_6H_4, 4-BrC_6H_4 and R^2 = H] and 1,1,1-trichloro-2,4-alkanediones, 1-aryl-4,4,4-trichloro-1,3-butanediones [$Cl_3CC(O)CHR^2C(O)R^1$, where R^1 = H, CH_3, -$(CH_2)_2$Ph, Ph, 4-FC_6H_4, 4-BrC_6H_4, R^2 = H, R^1 = Ph and R^2 = CH_3 and R^1, R^2 = cyclo-$(CH_2)_5$-] with hydrazine hydrochloride in 2,2,2-trifluoroethanol (TFE). Considering the low nucleophilicity of TFE in relation to methanol or ethanol, the results provide evidence for the mechanism of hydrolysis of the trichloromethyl group attached to the 1*H*-pyrazol ring.

Keywords: 2,2,2-trifluoroethyl 1H-pyrazole-5(3)-carboxylates; 2,2,2- trifluoroethanol; 1H-pyrazoles; 1,1,1-trichloromethyl-4-alkoxy-3-alken-2-ones

1. Introduction

The synthesis of CF_3-containing compounds is largely done because they have enhanced biological activity and can be used as pharmaceuticals and agricultural chemicals, in addition to their role in the development of new technological materials [1]. The geometrical similarities between the methyl and trifluoromethyl groups are well known, but compounds in the latter group modify the physicochemical profiles of chemicals, increasing their lipophilicity and metabolic stability [2]. In addition, fluorinated solvents have attracted increasing interest in the context of green synthesis, having been introduced as alternative green reaction media because of their unique chemical and physical properties; for example, they exhibit significant regiochemistry control, allowing facile recovery of solvents by distillation [3].

1*H*-pyrazole rings are versatile moieties present in many synthetic physiologically active substances, including commercial crop broad-spectrum fungicides, the herbicide Fluazolate, and the anti-inflammatory COX-2 inhibitor Celecoxib [4]. Owing to their versatile bioactivity, a large amount of research has focused on these nuclei [5].

On the other hand, we have studied the synthesis of 1,1,1-trichloro-4-methoxy-3-alken-2-ones and trichloromethyl-1,3-diketones as building blocks for the production of a diversity of heterocycles, including 1*H*-pyrazole-carboxylate derivatives [6]. This paper reports the results of [3 + 2] cyclocondensation of a series of 1,1,1-trichloro-4-methoxy-3-alken-2-ones (**1**) and 1,1,1-trichloro-2,4-alkanediones (**2**) with hydrazine in environmental friendliness 2,2,2-trifluoroethanol (TFE), a synthetic approach to producing new 2,2,2-trifluoroethyl 1*H*-pyrazole-carboxylates (**3**).

2. Results and Discussion

A series of 1,1,1-trichloro-4-methoxy-3-alken-2-ones **1** and trichloromethyl-1,3-diketones **2** were obtained via trichloroacetylation of the respective enol ether or acetal derivative [6, 7].

Initially the reaction between **1h** and NH_2NH_2.HCl in 10 mL TFE was conducted at 50°C for 12 h. Then TFE was distilled off and the solid residue was characterized by ^{1}H NMR as a mixture of two products, 2,2,2-trifluoroethyl 3-phenethyl-1*H*-pyrazole-5-carboxylate (**3h**) and methyl 3-phenethyl-5-pyrazole carboxylate (**4h**) (Figure 1). To find the best reaction conditions, considering the yield and product purity of **3h**, we tested different reaction conditions, varying the temperature, reaction time, and amount of TFE. The [3 + 2] cyclocondensation was performed in an alcohol solvent according to a previously described method, leading initially to the aromatic 5(3)-trichloromethyl-1*H*-pyrazoles; thereafter, the trichloromethyl group was hydrolyzed, leading to the 1*H*-pyrazole-5(3)-carboxylates [6a]. We propose that the key intermediate in this mechanism is a carboxylic acid chloride, which is attacked by nucleophilic solvent (Scheme 1). Then, using TFE as the solvent, the nucleophilic attack occurs preferentially from methanol that forms *in situ* after the cyclocondensation of the 1,1,1-trichloro-4-methoxy-4-phenethyl-3-hexen-2-one (**1h**). When the proportion of TFE was increased in the reaction medium from 10 to 25 mL, or when a more concentrated 5 mL TFE reaction solution was used, yields and the mixture rate remained in the same range, as shown in Table 1. The formation only of the product derivative of the alcohol generated *in situ* from the dielectrophilic substrate probably does not occur due to the 100ºC reaction temperature, at which both methanol or ethanol are in the highest concentration in the vapor phase.

Attempts to replace hydrazine hydrochloride with inexpensive hydrazine sulfate were unsuccessful, because even under reflux of TFE, it did not dissolve and did not react with dielectrophilic trichloromethyl-substituted substrates [8].

The reaction conditions shown in entry 5 of Table 1 were extended to cyclocondensations between series **1a-i**, **1m**, **n**, and hydrazine hydrochloride in TFE solvent to afford an almost equimolar mixture of two products, which were identified as 2,2,2-trifluoroethyl 1*H*-pyrazole-5(3)-carboxylates **3a-i**, **3m, n**, and respective ethyl or methyl 1*H*-pyrazole-5(3)-carboxylates **4a-i**, **4m**, **n** (Scheme 2). The ratio of these two products in each reaction was measured by ^{1}H NMR spectroscopy of the crude reaction mixture (Table 1). The formation of products **3** and **4** was confirmed on the basis of their ^{1}H, ^{13}C, ^{19}F and LC-MS/MS spectra (Supplementary Information).

The strategy to circumvent the formation of nucleophilic alcohol in the reaction medium was to use the previously developed trichloromethyl-β-diketones as 1,3-dielectrophilic precursors in the cyclocondensation process. We have previously demonstrated the synthesis of trichloroacetyl-cycloalkanones and 4,4,4-trichloro-1-aryl-1,3-butanediones[9].Then 1,1,1-trichloro-6-phenyl-2,4-hexanedione (**2h**) was synthesized via acid hydrolysis of the 1,1,1-trichloro-4-methoxy-6-phenyl-3-hexen-2-one (**1h**), and cyclocondensation was conducted as described in entry 5 of Table 1. After the reaction, the residual white solid was identified as pure 2,2,2-trifluoroethyl 3-phenethyl-1*H*-pyrazole-5-carboxylate (**3h**) (Fig. 2). This reaction was extended to the series of trichloromethyl-1,3-diketones **2a**, **2b**, **2j**, **2k**, **2l**, **2n**, and **2o**, leading to the respective 2,2,2-trifluoroethyl 1*H*-pyrazole-5-carboxylates in good yields (Scheme 3).

All isolated products were identified by NMR spectroscopy and LC-MS/MS data. The ^{1}H NMR spectra for 1*H*-pyrazole-5(3)-carboxylates **3** showed a general feature, displaying the signals related to methylene from the 2,2,2-trifluoroethyl chain at 4.6–4.9 ppm and the H-4 from the pyrazole ring at 6.5–7.5 ppm. The ^{13}C NMR spectra showed the characteristic signals for each derivative series. The quartet related to the CF_3 group was displayed at about δ 125 ppm with J_{CF} 277 Hz, that related to 2,2,2-trifluoroethyl methylene was at about δ 60 ppm with $^{3}J_{CF}$ 36 Hz, and that related to C=O from the carboxyl group was at about δ 160 ppm.

3. Conclusion

We developed an efficient method to synthesize 2,2,2-trifluoroethyl 1*H*-pyrazol-5(3)-carboxylates with good yields and purity. The results demonstrate the efficiency and versatility of the precursors 1,1,1-trichloro-4-alkoxy-3-alken-2-ones and trichloromethyl-β-diketones for 1*H*-pyrazol-5(3)-carboxylate synthesis, and furthermore provide data that endorse the proposed mechanism of hydrolysis of the trichloromethyl group attached to the 1*H*-pyrazole ring of carboxylic ester, with confirmation of a step that depends on the nucleophilicity of the alcohol solvent.

4. Experimental

^{1}H and ^{13}C NMR spectra were collected at 305 K on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz, ^{13}C at 100.62 MHz) using a 5 mm dual probe. Chemical shifts (δ) are quoted in ppm from tetramethylsilane (TMS), and coupling constants (J) are given in Hz. ^{19}F NMR spectra were collected at 376.5 MHz on a Bruker Ascend Avance III 400 spectrometer using a 5 mm dual probe. The ESI mass spectra were obtained on an Agilent 6460 Triple Quadrupole connected to a 1200 series LC and equipped with a solvent degasser, binary pump, column oven, auto-sampler, and an ESI source. The Agilent QQQ 6460 tandem mass spectrometer was operated in positive jet stream electrospray ionization (ESI) mode. Nitrogen was used as the nebulizer, turbo (heater) gas, curtain gas, and collision-activated dissociation gas. The capillary voltage was set at +3500 V and the nozzle voltage was at +500 V. The ion source gas temperature was 300°C with a flow rate of 5 L/min. The jet stream sheath gas temperature was 250°C with a flow rate of 11 L/min. All samples were infused into the ESI source at a 5 μL/min flow rate. Data were acquired in positive MS total ion scan mode (mass scan range *m/z* 50–650) and in positive MS/MS product ion scan mode. The mass spectra recorded were evaluated using the Qualitative Analysis software from Agilent Technologies.

4.1. General procedure for 2,2,2-trifluoroethyl 1H-pyrazol-5-carboxylates

A solution of 1,1,1-trichloro-2,4-alkanedione or 4,4,4-trichloro-1-aryl-1,3-butanedione **2** (3 mmol) and NH_2NH_2.HCl (3.1 mmol) in 5 mL TFE was stirred at 100°C until complete dissolution, and the resulting mixture was stirred for 16 h. TFE was removed and residue was dissolved in CH_2Cl_2 (30 mL); the organic solution was washed with water (1 × 30 mL) and dried with Na_2SO_4. The solvent was evaporated, resulting in product **3**. Products were analyzed without further purification. Spectroscopic data are shown in the Supplementary Information.

2,2,2-Trifluoroethyl 1H-pyrazol-5(3)-carboxylate (**3a**) was obtained (74%) as a yellowish white solid (CH_2Cl_2). It decomposes above 135°C. ^{1}H NMR (CD_3CN): δ 4.81 (q,$^3J_{HF}$ 8.8 Hz, 2H, CH_2), 6.91 (d, $^3J_{HH}$ 2.4, 1H, H-4), 7.74 (d, 1H, $^3J_{HH}$ 2.4 Hz, 1H, H-3); ^{13}C NMR(CD_3CN): δ 60.1 (q, $^2J_{CF}$ 36.1 Hz, CH_2), 108.3 (C-4), 123.5 (q, J_{CF} 276 Hz, CF_3), 131.5 (C-3), 140.8 (C-5), 160.3 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.5 (t, $^3J_{FH}$ 7.5 Hz). $C_6H_5F_3N_2O_2$ calcd. mass 194.0303 g.mol^{-1}. Found: 195.0340 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(5)-methyl-1H-pyrazol-5(3)-carboxylate (**3b**) was obtained (81%) as a yellowish white solid (CH_2Cl_2). It decomposes above 150°C. ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H), 4.64 (q,$^3J_{HF}$ 8.4 Hz, 2H, CH_2), 6.56 (s, 1H, H-4); ^{13}C NMR($CDCl_3$): δ 10.4 (CH_3), 60.1 (q, $^2J_{CF}$ 37.2 Hz, CH_2), 107.4 (C-4), 122.8 (q, J_{CF} 277 Hz, CF_3), 131.5 (C-3), 140.8 (C-5), 160.3 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.7 (t, $^3J_{FH}$ 7.5 Hz). $C_7H_7F_3N_2O_2$ calcd. mass 208.0460 g.mol^{-1}. Found: 209.0519 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(5)-octyl-1H-pyrazol-5(3)-carboxylate (**3c**) was obtained (30%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, $^3J_{HH}$ 6,8 Hz 3H, CH_3), 1.29 (m, 10H), 1.62 (m, 2H), 2.69 (m, 2H), 4.67 (q,$^3J_{HF}$ 8.4 Hz, 2H, CH_2), 6.62 (s, 1H, H-4); ^{13}C NMR($CDCl_3$): δ 13.9 (CH_3), 22.5, 25.6, 28.9, 29.1, 31.7 (CH_2), 60.1 (q, $^2J_{CF}$ 36.2 Hz, CH_2), 106.7 (C-4), 122.9 (q, J_{CF} 277.5 Hz, CF_3), 140.7 (C-3), 147.6 (C-5), 160.5 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.6 (t, $^3J_{FH}$ 7.5 Hz). $C_{14}H_{21}F_3N_2O_2$ calcd. mass 306.1555 g.mol^{-1}. Found 307.1632.mol^{-1}.

2,2,2-Trifluoroethyl 3(5)-nonyl-1H-pyrazol-5(3)-carboxylate (**3d**) was obtained (33%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, $^3J_{HH}$ 6,8 Hz 3H, CH_3), 1.31 (m, 10H), 1.64 (m, 2H), 2.69 (m, 2H), 4.67 (q,$^3J_{HF}$ 8.4 Hz, 2H, CH_2), 6.63 (s, 1H, H-4); ^{13}C NMR($CDCl_3$): δ 13.8 (CH_3), 22.5, 25.7, 28.9, 29.2, 29.3, 31.7 (CH_2), 60.1 (q, $^2J_{CF}$ 36.2 Hz, CH_2), 106.7 (C-4), 122.9 (q, J_{CF} 277.2 Hz, CF_3), 141.2 (C-3), 148.1 (C-5), 160.3 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.6 (t, $^3J_{FH}$ 7.5 Hz). $C_{15}H_{23}F_3N_2O_2$ calcd. mass 320.1712 g.mol^{-1}. Found 321.1632.mol^{-1}.

2,2,2-Trifluoroethyl 3(5)-decyl-1H-pyrazol-5(3)-carboxylate (**3e**) was obtained (22%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, $^3J_{HH}$ 6,8 Hz 3H, CH_3), 1.26 (m, 14H), 1.63 (m, 2H), 2.69 (m, 2H), 4.65 (q,$^3J_{HF}$ 8.4 Hz, 2H, CH_2), 6.60 (s, 1H, H-4); ^{13}C NMR($CDCl_3$): δ 13.8 (CH_3), 22.5, 25.6, 28.9, 29.2, 29.3, 29.4, 31.7 (CH_2), 60.3 (q, $^2J_{CF}$ 37 Hz, CH_2), 106.6 (C-4), 123.0 (q, J_{CF} 278 Hz, CF_3), 140.4 (C-3), 147.3 (C-5), 160.3 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.6 (t, $^3J_{FH}$ 7.5 Hz). $C_{16}H_{25}F_3N_2O_2$ calcd. mass 334.1868 g.mol^{-1}. Found 335.1936 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(5)-undecyl-1H-pyrazol-5(3)-carboxylate (**3f**) was obtained (41.2%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, $^3J_{HH}$ 6,8 Hz 3H, CH_3), 1.29 (m, 14H), 1.66 (m,

2H), 2.70 (m, 2H), 4.68 (q,$^{3}J_{HF}$ 8.4 Hz, 2H, CH_2), 6.64 (s, 1H, H-4); ^{13}C NMR($CDCl_3$): δ 13.8 (CH_3), 22.5, 25.6, 28.9, 29.2, 29.3, 29.4, 31.7 (CH_2), 60.3 (q, $^{2}J_{CF}$ 37 Hz, CH_2), 106.8 (C-4), 123.0 (q, J_{CF} 277 Hz, CF_3), 140.3 (C-3), 147.7 (C-5), 160.2 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.6 (t, $^{3}J_{FH}$ 7.5 Hz). $C_{17}H_{27}F_3N_2O_2$ calcd. mass 348.2025 g.mol^{-1}. Found 349.2085 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(*5*)*-tridecyl-1H-pyrazol-5*(*3*)*-carboxylate* (**3g**) was obtained (41.2%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, $^{3}J_{HH}$ 6,8 Hz 3H, CH_3), 1.29 (m, 20H), 1.66 (m, 2H), 2.70 (m, 2H), 4.68 (q,$^{3}J_{HF}$ 8.4 Hz, 2H, CH_2), 6.65 (s, 1H, H-4); ^{13}C NMR($CDCl_3$): δ 13.8 (CH_3), 22.5, 25.6, 28.9, 29.2, 29.3, 29.4, 31.7 (CH_2), 60.3 (q, $^{2}J_{CF}$ 37 Hz, CH_2), 106.8 (C-4), 123.0 (q, J_{CF} 277 Hz, CF_3), 140.2 (C-3), 147.5 (C-5), 160.2 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.6 (t, $^{3}J_{FH}$ 7.5 Hz). $C_{19}H_{31}F_3N_2O_2$ calcd. mass 376.2338 g.mol^{-1}. Found 377.2408 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(*5*)*-phenethyl-1H-pyrazol-5*(*3*)*-carboxylate* (**3h**) was obtained (97%) as a white solid, m.p. 119–120°C. ^{1}H NMR ($CDCl_3$): δ 2.97 (m, 2H, CH_2), 3.07 (m, 2H, CH_2), 4.63 (q,$^{3}J_{HF}$ 8.4 Hz, 2H, CH_2), 6.67 (s, 1H, H-4), 7.18 (m, 2H, Ph), 7.23 (m, 1H, Ph), 7.32 (m, 2H, Ph); ^{13}C NMR($CDCl_3$): δ 27.5 (CH_2), 35.3 (CH_2), 60.4 (q, $^{2}J_{CF}$ 37 Hz, CH_2), 107.2 (C-4), 122.9 (q, J_{CF} 277 Hz, CF_3), 126.4, 128.3, 128.5, 140.4 (Ph), 140.5 (C-3), 146.6 (C-5), 160.3 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm:–73.6 (t, $^{3}J_{FH}$ 7.5 Hz). $C_{19}H_{31}F_3N_2O_2$ calcd. mass 298.0929 g.mol^{-1}. Found 299.0991 g.mol^{-1}.

3-(*5*(*3*)(*2,2,2-trifluoroethoxycarbonyl*)*-1H-pyrazol-3*(*5*)*-yl*)*-propanoic acid* (**3i**) was obtained (51%) as a white solid. ^{1}H NMR (DMSO-d6): δ 2.58 (m, 2H, CH_2), 2.86 (m, 2H, CH_2), 4.88 (q,$^{3}J_{HF}$ 8.8 Hz, 2H, CH_2), 6.61 (s, 1H, H-4); ^{13}C NMR(DMSO-d6): δ 21.2 (CH_2), 33.3 (CH_2), 60.1 (q, $^{2}J_{CF}$ 36 Hz, CH_2), 106.9 (C-4), 123.9 (q, J_{CF} 278 Hz, CF_3), 140.5 (C-3), 145.7 (C-5), 160.5 (C=O), 173.7 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm:–73.6 (t, $^{3}J_{FH}$ 7.5 Hz). $C_9H_9F_3N_2O_2$ calcd. mass 266.0514 g.mol^{-1}. Found 267.0575 g.mol^{-1}.

2,2,2-trifluoroethyl 2,4,5,6,7,8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (**3j**) was obtained (87%) as a white solid, m.p. 180–182°C. ^{1}H NMR ($CDCl_3$): δ 1.68 (m, 4H, $2CH_2$), 1.85 (m, 2H, CH_2), 2.78 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 4.66 (q,$^{3}J_{HF}$ 8.4 Hz, 2H, CH_2) ^{13}C NMR($CDCl_3$): δ 24.2, 26.9, 27.6, 28.1, 31.7 (CH_2), 60.1 (q, $^{2}J_{CF}$ 37 Hz, CH_2), 123.0 (q, J_{CF} 278 Hz, CF_3), 125.2 (C-4), 134.2 (C-3), 149.7 (C-5), 160.1 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm:–75.2 (t, $^{3}J_{FH}$ 9.4 Hz). $C_{11}H_{13}F_3N_2O_2$ calcd. mass 262.0929 g.mol^{-1}. Found 263.1000 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(*5*)*-phenyl-1H-pyrazol-5*(*3*)*-carboxylate* (**3k**) was obtained (92%) as a white solid, m.p. 96–97°C. ^{1}H NMR ($CDCl_3$): δ 4.59 (q,$^{3}J_{HF}$ 8.4 Hz, 2H, CH_2), 7.1 (s, 1H, H-4), 7.41 (m, 3H, Ph), 7.71 (m, 2H, Ph); ^{13}C NMR($CDCl_3$): δ 60.6 (q, $^{2}J_{CF}$ 37 Hz, CH_2), 106.5 (C-4), 122.8 (q, J_{CF} 277 Hz, CF_3), 125.7, 128.9, 129.0, 129.5 (Ph), 139.1 (C-3), 148.1 (C-5),

158.2 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.5 (t, $^3J_{FH}$ 7.5 Hz). $C_{12}H_9F_3N_2O_2$ calcd. mass 270.0616 g.mol^{-1}. Found 271.0683 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(*5*)-(*4-fluorophenyl*)-*1H-pyrazol-5*(*3*)-*carboxylate* (**3l**) was obtained (94%) as a white solid, m.p. 96–97°C. ^{1}H NMR ($CDCl_3$): δ 4.69 (q,$^3J_{HF}$ 8.4 Hz, 2H, CH_2), 7.03 (s, 1H, H-4), 7.10 (t, 2H, Ph), 7.78 (m, 2H, Ph); ^{13}C NMR($CDCl_3$): δ 60.5 (q, $^2J_{CF}$ 37 Hz, CH_2), 105.6 (C-4), 116.0 (d,$^3J_{CF}$ 22 Hz, Ph), 122.9 (q, J_{CF} 277 Hz, CF_3), 125.5 (Ph), 127.8 (d,$^3J_{CF}$ 2 Hz, Ph), 139.7 (C-3), 146.3 (C-5), 159.7 (C=O), 163.1 (d, J_{CF} 248 Hz, Ph); ^{19}F NMR ($CDCl_3$) δ ppm: –73.6 (t, $^3J_{FH}$ 7.5 Hz, CF_3), -112.0 (m, *p*-F). $C_{12}H_8F_4N_2O_2$ calcd. mass 288.0522 g.mol^{-1}. Found 289.0591 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(*5*)-(*4-chlorophenyl*)-*1H-pyrazol-5*(*3*)-*carboxylate* (**3m**) was obtained (51%) as a brown solid. ^{1}H NMR (DMSO-d6): δ 4.95 (q,$^3J_{HF}$ 9.2 Hz, 2H, CH_2), 7.29 (s, 1H, H-4), 7.46 (m, 2H, Ph), 7.85 (m, 2H, Ph); ^{13}C NMR(DMSO-d6): δ 60.3 (q, $^2J_{CF}$ 35 Hz, CH_2), 106.5 (C-4), 123.8 (q, J_{CF} 278 Hz, CF_3), 127.7, 128.8, 129.4, 133.6 (Ph), 139.8 (C-3), 145.7 (C-5), 159.8 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm: –73.6 (t, $^3J_{FH}$ 7.5 Hz). $C_{12}H_8ClF_3N_2O_2$ calcd. mass 304.0226 g.mol^{-1}. Found 305.0300 g.mol^{-1}.

2,2,2-Trifluoroethyl 3(*5*)-(*4-bromophenyl*)-*1H-pyrazol-5*(*3*)-*carboxylate* (**3n**) was obtained (89%) as a brown solid, m.p. 138–140°C. ^{1}H NMR (DMSO-d6): δ 4.95 (q,$^3J_{HF}$ 9.2 Hz, 2H, CH_2), 7.28 (s, 1H, H-4), 7.60 (m, 2H, Ph), 7.78 (m, 2H, Ph); ^{13}C NMR(DMSO-d6): δ 60.3 (q, $^2J_{CF}$ 35 Hz, CH_2), 106.5 (C-4), 122.1 (Ph), 123.9 (q, J_{CF} 277 Hz, CF_3), 127.9, 129.2, 132.3 (Ph), 139.8 (C-3), 145.8 (C-5), 159.8 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm:–73.6 (t, $^3J_{FH}$ 7.5 Hz). $C_{12}H_8BrF_3N_2O_2$ calcd. mass 304.0226 g.mol^{-1}. Found 305.0300 g.mol^{-1}.

2,2,2-Trifluoroethyl 4-methyl-3(*5*)-(*phenyl*)-*1H-pyrazol-5*(*3*)-*carboxylate* (**3o**) was obtained (89%) as a brown solid, m.p. 138–140°C. ^{1}H NMR (DMSO-d6): δ 4.95 (q,$^3J_{HF}$ 9.2 Hz, 2H, CH_2), 7.28 (s, 1H, H-4), 7.60 (m, 2H, Ph), 7.78 (m, 2H, Ph); ^{13}C NMR(DMSO-d6): δ 9.5 (CH_3), 60.1 (q, $^2J_{CF}$ 37 Hz, CH_2), 118.0 (C-4), 122.9 (q, J_{CF} 277 Hz, CF_3), 127.6, 128.3, 128.7, 129.9 (Ph), 136.9 (C-3), 145.0 (C-5), 159.9 (C=O); ^{19}F NMR ($CDCl_3$) δ ppm:–72.6 (t, $^3J_{FH}$ 7.5 Hz). $C_{13}H_{11}F_3N_2O_2$ calcd. mass 284.0788 g.mol^{-1}. Found 285.0846 g.mol^{-1}.

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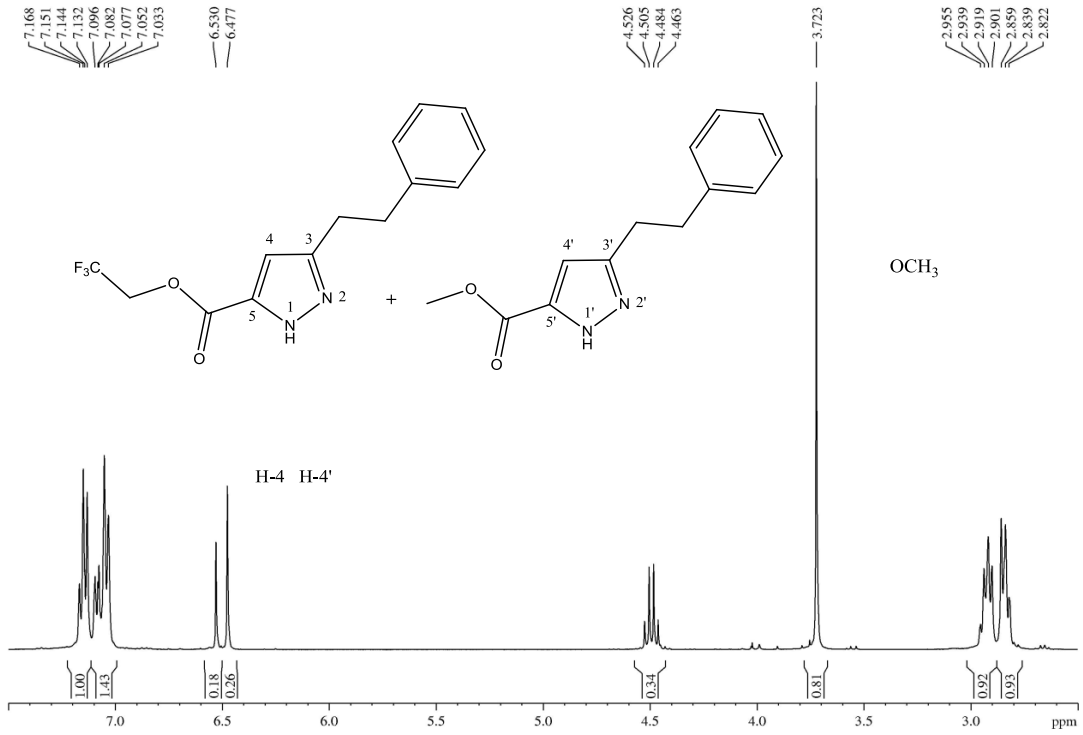


Figure 1. ^{1}H NMR spectrum of the cyclocondensation product obtained from **1h** and $NH_2NH_2.HCl$.

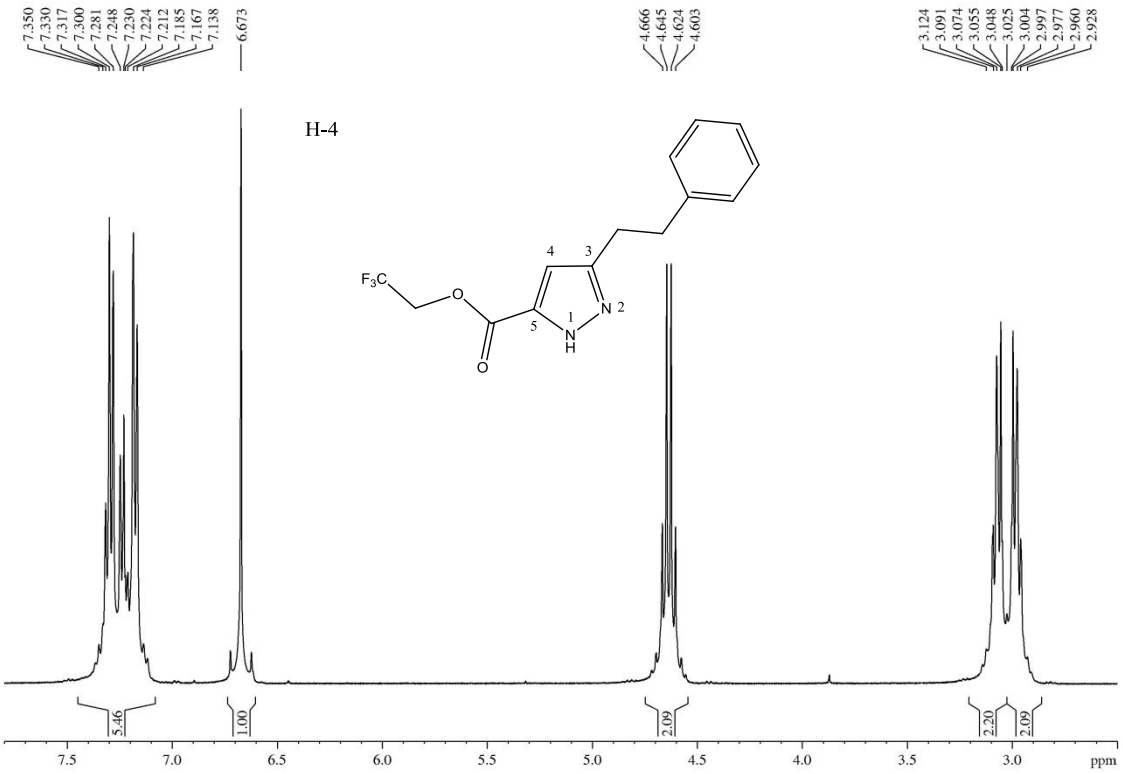
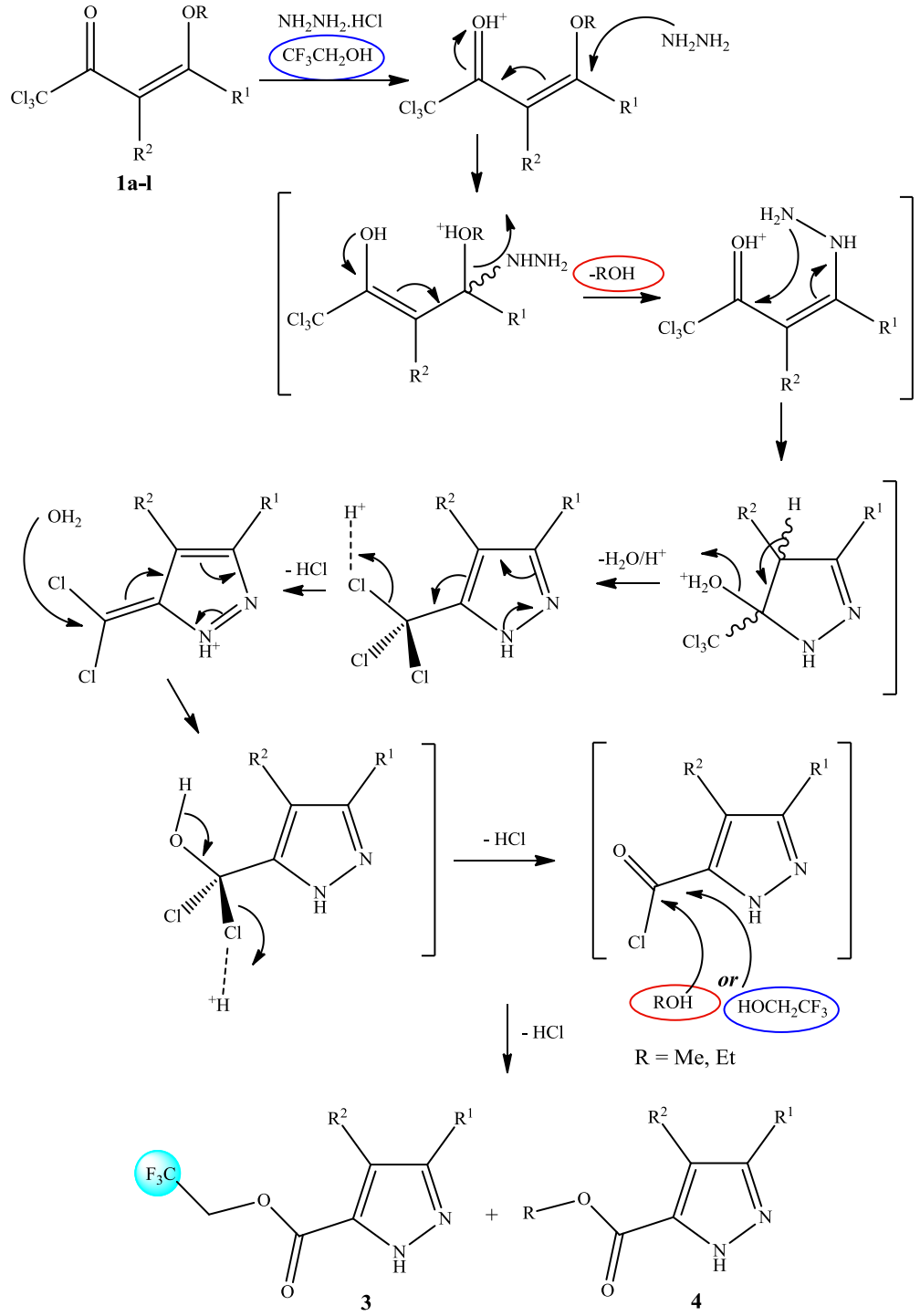
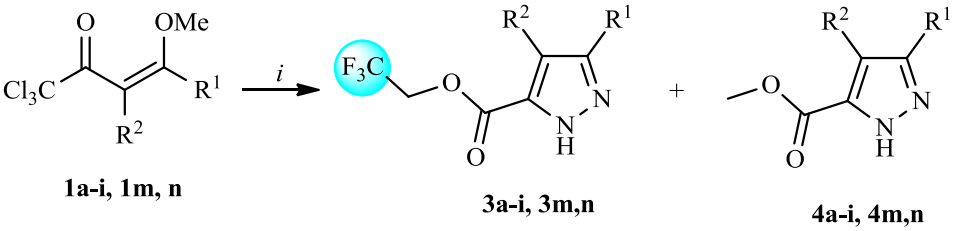


Figure 2. ^{1}H NMR spectrum of the cyclocondensation product obtained from **2h** and $NH_2NH_2.HCl$.



Scheme 1. Mechanism proposed to [CCC + NN] cyclocondensation followed of trichloromethyl

hydrolysis for 1*H*-pyrazole-5(3)-carboxylates **3** or **4**.



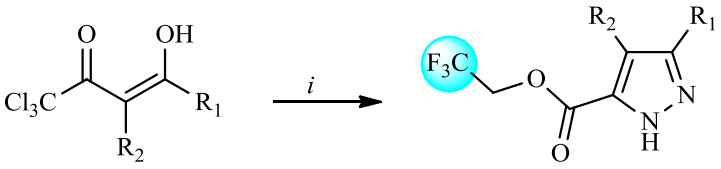
1a-i, 1m, n **3a-i, 3m,n** **4a-i, 4m,n**

i= NH_2NH_2.HCl, CF_3CH_2OH, 24h, 100 ºC

3, 4	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**
R^1	H	Me	nC_8H_{11}	nC_9H_{15}	$nC_{10}H_{17}$	$nC_{11}H_{19}$	$nC_{13}H_{21}$	$(CH_2)_2Ph$	$(CH_2)_2CO_2H$
R^2	H	H	H	H	H	H	H	H	H

3, 4	**m**	**n**
R^1	4-ClC_6H_4	4-BrC_6H_4
R^2	H	H

Scheme 2. Synthesis of mixtures of 2,2,2-trifluoroethyl 1*H*-pyrazole-5(3)-carboxylate (**3**) and (ethyl) methyl 1*H*-pyrazole-5(3)-carboxylate (**4**).



2a, 2b, 2h, 2j-l, 2n, 2o **3a, 3b, 3h, 3j-l, 3n, 3o**

i= NH_2NH_2.HCl, CF_3CH_2OH, 24h, 100 ºC

	a	b	h	j	k	l	n	o
R_1	H	Me	$(CH_2)_2Ph$	$-(CH_2)_5-$	Ph,	4-FC_6H_4,	4-BrC_6H_4,	Ph,
R_2	H	H	H		H	H	H	Me

Scheme 3. Synthesis of the 2,2,2-trifluoroethyl 1*H*-pyrazole-5(3)-carboxylate (**3**).

Table 1. Yields, isomer ratio, and reaction conditions for cyclocondensation between **1h** and NH_2NH_2.HX

Entry	HX	Temperature (°C)	solvent volume (mL)	time (h)	yield (%)
1	HCl	25	5	16	-[a]
2	HCl	25	15	24	-[a]
3	HCl	50	20	24	84 (41:59)
4	HCl	100	15	12	81 (42:58)
5	HCl	100	5	16	97 (41:59)
6	H_2SO_4	100	5	24	-[a]
7	H_2SO_4	100	15	24	-[a]

[a] Recovery of starting reagents.

Table 2. Yields and ratio **3**:**4** obtained for cyclocondensation between **1a-i, 1m, n**, and NH_2NH_2.HCl in 5 mL TFE

Precursor	R[a]	Yield (%)	Ratio **3:4**[b]
1a	H	75	47:53
1b	CH_3	79	51:49
1c	*n*-octyl	64	45:55
1d	*n*-nonyl	69	48:52
1e	*n*-decyl	67	33:67
1f	*n*-undecyl	71	58:42
1g	*n*-tridecyl	67	55:45
1h	$Ph(CH_2)_2$	97	41:59
1i	$HO_2C(CH_2)_2$	93	55:45
1m	$4\text{-}ClC_6H_4$	86	59: 41
1n	$4\text{-}BrC_6H_4$	92	34:66

[a] R in 1*H*-pyrazol-5carboxylate; [b] from ^{1}H NMR integral of H-4 signals.