Preparations of 4-Substituted 3-Carboxypyrazoles

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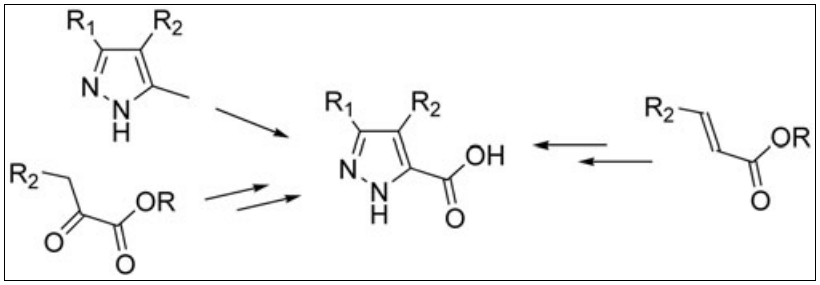

The scopes of three synthetic methods reported for the preparation of an array of 3-pyrazolecarboxylates featuring substituents on position 4 were investigated. The first one is based on the potassium permanganate oxidation of methylpyrazoles. The second starts with the condensation between DMF dimethylacetal and ethyl pyruvate and is followed by the addition of hydrazine hydrochloride. The last one makes use of the cycloaddition of diazomethane on acrylate esters followed by a bromine-based oxidative rearrangement into 4-substituted 3-pyrazole esters.

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In the course of our work [1–7] on the design of chemical libraries with a potential against infectious disease, we were led to synthesize 3-pyrazolecarboxylic acid derivatives preferably lacking a substituent on carbon 5. From the available synthetic methods reported [8–10], three different approaches were used. The controlled oxidation of 3-methylpyrazoles derivatives **1a–e** into acids **2a–e** using potassium permanganate was first investigated [11–15] (Scheme 1). It appeared that this method is limited by some decarboxylation taking place in refluxing water. Moreover, the lack of solubility of potential reaction substrates, at RT, often prevented less stringent methyl oxidation. Further purification by recrystallization of the rather water-soluble acids was often found necessary and thus led to pure compounds **2a–e** in yields no higher than 16%.

We then investigated the recently reported preparation of ethyl-3-pyrazolecarboxylate from ethylpyruvate [16]. From the reaction between DMF dimethylacetal and the two pyruvate derivatives **3a–b**, followed by addition of hydrazine hydrochloride on the resulting Mannich bases **4a–b**, we could extend this original method and prepare esters **5a–b** (Scheme 2). The quite low yields obtained are due to the occurrence of many unidentified side compounds. From the benzyl-bearing substrate **3a**, we could isolate in 18% yield and fully characterize the furan derivative **6**. This side compound, which results from a dimerization of compound **3a** under the reaction conditions, illustrates the difficulties we encountered with this synthetic method. A related preparation of such furan derivative has actually been reported [17]. From esters **5a–b**, an acidic hydrolysis led to sizable amount (75%) of the target acids **7c** but much smaller (5%) amount of the diacid **7d**.

Far more pyrazole derivatives were made by the well-described cycloaddition of diazomethane on α,β-unsaturated esters [18–20]. From the acrylates **8a–k**, this cycloaddition led to the intermediates **9a–k**. No attempts were made to isolate these compounds, and the following oxidative rearrangement into 4-substituted 3-pyrazole esters **10a–k** was achieved with bromine. As described in the experimental part, the commercially unavailable α,β-unsaturated esters were prepared by acid-catalyzed esterification of the available acids or by using the greatly optimized condensation of malonic acid monoethylester on aldehydes [21]. To minimize the handling of the carcinogenic as well as explosive diazomethane, we used a comparatively safer one-pot protocol starting from the also carcinogenic *N*-methylnitrosourea [22]. A noteworthy phase-separation step, based on the freezing of the aqueous phase, led fairly safely to a dry ether solution of diazomethane, which was immediately used without any other purification. The hydrolysis of the resulting esters **10a–k** in boiling hydrochloric acid provided acids **11a–k** in acceptable overall yield (from 20 to 35%) (Scheme 3).

In conclusion, this work allowed the preparation of many known as well as previously undescribed 4-subtituted 3-carboxypyrazoles. By far, the last method, based on the diazomethane cycloaddition on acrylates, provided the most

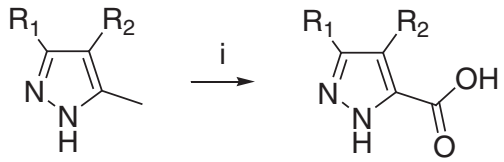
diverse set of compounds. However, the inherent hazards of this approach point at the fact that the optimization or the design of alternative synthetic accesses could be of interest, especially if a large scale production is required.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively. Shifts (δ) are given in parts per million with respect to the TMS signal, and coupling constants (*J*) are given in Hertz. Column chromatography were performed over Merck silica gel 60 (0.035–0.070 mm), using a solvent pump operating at a pressure between 2 and 7 bar (25–50 mL/mn) and an automated collecting system driven by a UV detector set to 254 nm, unless stated otherwise. Melting points were measured on a Koffler apparatus. Mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric ESI system, a C18 column, a gradient of water, and either acetonitrile containing 0.07% of formic acid or, more often, methanol containing 0.07% of ammonium formate.

Note concerning the ^{13}C NMR data: In some cases, an equilibrium existing between the two forms of the pyrazole nucleus and/or the carboxyester group conformation prevented the determination of the carbons 2 and 5 ^{13}C NMR signals value as they were spread on a too large frequency band and probably overlapped in some cases. Quite often these two signals were observed as a large peak with a width of as much as 4 ppm. If a higher concentration of the sample was used for NMR experiments, two almost complete set of signals were then observed in ^{1}H as well as ^{13}C NMR spectra, and their respective proportion varied according to the solvent used. This phenomenon is likely to be due to some kind of self-organization taking place via intermolecular interactions.

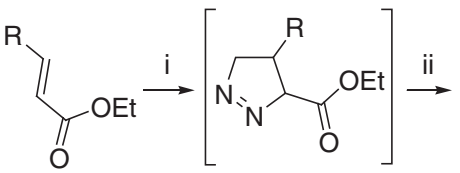
Scheme 1. i: $KMnO_4$, H_2O, 25°C, or reflux.



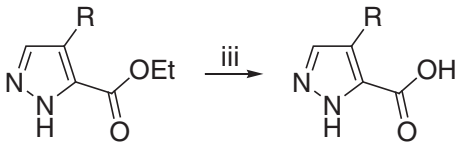
1a-e **2a-e**

a: R_1, R_2 = H, H
b: R_1, R_2 = H, Cl
c: R_1, R_2 = H, Br
d: R_1, R_2 = Me, H
e: R_1, R_2 = Me, Cl

Scheme 3. i: CH_2N_2, Et_2O. ii: Br_2. iii: hydrochloric acid, reflux.



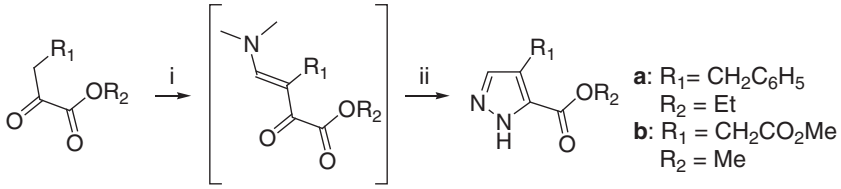
8a-k **9a-k**



10a-k **11a-k**

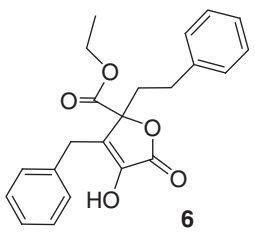
a: R = CH_3
b: R = CF_3
c: R = Et
d: R = Pr
e: R = iPr
f: R = CH_2iPr
g: R = *n*pentyl
h: R = phenyl
i: R = 2-pyridyl
j: R = 3-pyridyl
k: R = 4-pyridyl

Scheme 2. i: DMF dimethylacetal. ii: NH_2NH_2, HCl. iii: hydrochloric acid, reflux.



3a-b **4a-b** **5a-b**

a: R_1= $CH_2C_6H_5$
R_2 = Et
b: R_1 = CH_2CO_2Me
R_2 = Me



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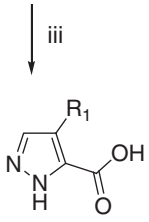

7c-d

c: R_1= $CH_2C_6H_5$
d: R_1 = CH_2CO_2H

Preparation of acids 2a–e. The 3-methyl pyrazoles **1a–e** (0.003 mol) were dispersed in water (30 mL), and potassium permanganate (1.4 g; 0.009 mol.) was added. The resulting suspension was stirred at RT or refluxed for the requisite time as described in the succeeding sections. The manganese oxide was filtered, and the filtrate was made acid using concentrated acid hydrochloric acid 2*N*. The resulting precipitate was filtered, washed with cold water, and further purified as described in the following.

1H-Pyrazole-3-carboxylic acid (2a). This compound was obtained in a 10% yield after 4 h at reflux. The precipitate was purified by a recrystallization in acetic acid. mp = 212°C (lit. [15] = 213–215°C). ^{1}H (MeOD): 5.01 (s (br), 2H); 6.83 (d, 1H, J = 1.5 Hz); 7.70 (d, 1H, J = 1.5 Hz). ^{13}C (MeOD): 109.4; 134.1; 143.1; 165.1. LC/MS: m/z = 113 $(M + H)^+$.

4-Chloro-1H-pyrazole-3-carboxylic acid (2b). From 4-chloro-3-methylpyrazole (made by the chlorination of 3-methyl-1*H*-pyrazole with NCS and still containing succinimide), this compound was obtained in a 10% yield after 4 h at reflux. The precipitate was purified by a recrystallization in acetic acid. mp = 250°C (lit. [15] = 244–245°C). ^{1}H (MeOD): 4.95 (s (br), 2H); 7.73. ^{13}C (MeOD): 114.7; 135.0 (br); 163.0. LC/MS: m/z = 145/ 147 $(M - H)^-$.

4-Bromo-1H-pyrazole-3-carboxylic acid (2c). From 4-bromo-3-methylpyrazole [23], this compound was obtained in a 12% yield after 4 h at reflux. The precipitate was purified by a recrystallization in acetic acid. mp = 260°C (lit. [15] = 250–251°C). ^{1}H (MeOD): 4.96 (s (br), 2H); 7.76 (s, 1H). ^{13}C (MeOD): 98.1; 138 (br); 163.1. LC/MS: m/z = 189/191 $(M - H)^-$.

5-Methyl-1H-pyrazole-3-carboxylic acid (2d). This compound was obtained in a 16% yield after 4 days of reaction at RT. The precipitate was purified by a recrystallization in hydrochloric acid 0.2*N* and two supplementary recrystallizations, which were necessary to fully remove the traces of the corresponding diacid also occurring in the reaction. mp = 245°C (lit. [24] = 241–243°C). ^{1}H (DMSO-d_6): 2.24 (s, 3H); 6.45 (s, 2H); 12.87 (s (br), 1H). ^{13}C (DMSO-d_6): 11.9; 107.6; 142.2; 143.8; 163.7. LC/MS: m/z = 125 $(M - H)^-$.

4-Chloro-5-methyl-1H-pyrazole-3-carboxylic acid (2e). From 4-chloro-3,5-dimethylpyrazole (made by the chlorination of 3,5-dimethyl-1*H*-pyrazole with N-chlorosuccinimide and still containing succinimide), this compound was obtained in a 7% yield after 3 weeks of reaction at RT. The precipitate was purified by recrystallization in acetic acid. mp = 260°C (lit. [25] = 259°C). ^{1}H (MeOD): 2.28 (s, 3H); 4.97 (s (br), 2H). ^{13}C (MeOD): 10.0; 112.7; 137.4; 143.3; 163.3. LC/MS: m/z = 161/163 $(M + H)^+$; weak signal.

Preparation of esters 2a–e. To the pyruvates **3a–b** (0.01 mol), dissolved in dichloromethane (100 mL), was added DMF dimethyl acetal (1.33 mL; 0.01 mol). This was stirred at 25°C for 2 h and concentrated to dryness without heating. The residue was dissolved in ethanol (or methanol according to the ester used) (100 mL), and hydrazine hydrochloride was added (0.68 g; 0.01 mol). This was heated to reflux for 8 h and concentrated to dryness. The residue was then purified as described in the succeeding sections.

4-Benzyl-1H-pyrazole-3-carboxylic acid ethyl ester (5a). This compound was obtained in a 12% yield after the corresponding chromatographic fraction (silica gel elution with cyclohexane/ethyl acetate 4:1) was further purified by recrystallization in cyclohexane. mp = 129°C. ^{1}H (DMSO-d_6): 1.24 (t, 3H, J = 6.9 Hz); 4.03 (s, 2H); 4.19 (m, 2H); 7.20 (m, 5H); 7.60 (s(br), 1H). ^{13}C (DMSO-d_6): 15.0; 27.2; 30.4; 60.6 (br); 123.5 (br); 126.6; 129.08; 129.13; 130.3 (br); 141.9. LC/MS: m/z = 231 $(M + H)^+$.

3-Benzyl-4-hydroxy-5-oxo-2-phenethyl-2,5-dihydrofuran-2-carboxylic acid ethyl ester (6). This compound was obtained in a 18% yield after the corresponding chromatographic fraction (silica gel elution with cyclohexane/ethyl acetate 4:1) was further purified by recrystallization in cyclohexane. mp = 120°C. ^{1}H ($CDCl_3$): 1.69 (t, 3H, J = 7.1 Hz); 2.15 (m, 1H); 2.39 (m, 1H); 2.48 (m, 2H); 3.7 (s, 2H); 3.96 (q, 2H, J = 7.1 Hz); 6.25 (s, 1H); 7.19 (m, 2H); 7.28 (m, 8H). ^{13}C ($CDCl_3$): 14.2; 29.5; 30.4; 36.3; 62.9; 87.5; 126.6; 127.4; 128.8; 128.83; 129.14; 129.4; 131.4; 136.5; 139.5; 140.6; 168.3; 169.5. LC/MS: m/z = 384 $(M + NH_4)^+$.

4-(Carboxymethyl)-1H-pyrazole-3-carboxylic acid dimethyl ester (5b). This compound was obtained in a 13% yield after the corresponding chromatographic fraction (silica gel elution with dichloromethane/methanol 98:2) was further purified by recrystallization in a toluene/cyclohexane mixture. mp = 120°C (lit. [26] = 139–140°C). ^{1}H (MeOD): 3.70 (s, 3H); 3.83 (s, 2H); 3.87 (s, 3H); 7.55 and 7.72 (2s, 1H overall). ^{13}C (MeOD): 31.0; 52.4; 52.8; 118.1; 131.9; 142.5; 164.9; 174.1. LC/MS: m/z = 199 $(M + H)^+$.

Hydrolysis of esters 5a–b. The corresponding ester was dispersed in 35% hydrochloric acid (10 mL for 0.5 g) and refluxed for 3 h. The resulting solution was concentrated to dryness and the residue further purified as described in what follows.

4-Benzyl-1H-pyrazole-3-carboxylic acid (7a). This compound was obtained in a 75% yield after dispersion in boiling water. mp = 235°C. ^{1}H (DMSO-d_6): 4.04 (s, 2H); 7.19 (m, 5H); 7.47 (s, 1H). ^{13}C (DMSO-d_6): 30.3; 124.0; 126.6; 129.1; 129.2; 136.0; 142.0; 163.5. LC/MS: m/z = 203 $(M + H)^+$.

4-(Carboxymethyl)-1H-pyrazole-3-carboxylic acid (7b). This compound was obtained in a 5% yield after a recrystallization in water. mp > 250°C (dec.) [lit. [26] = 241–243°C (dec.)]. ^{1}H (DMSO-d_6): 3.66 (s, 2H); 7.62 (s, 1H); 12.8 (s (br), 1H). ^{13}C (DMSO-d_6): 30.5; 117.8; 135.8; 163.5; 173.2. LC/MS: m/z = 171 $(M + H)^+$; weak signal.

Preparation of the α,β-unsaturated ethyl esters 8g and 8j–k by esterification. The α,β-unsaturated acid (0.007 mol) was dissolved in ethanol (100 mL), and concentrated (95%) sulfuric acid (1.5 mL in the case of pyridinyl acrylic acids or 10 drops in the case of alkylacrylic acid) was added. This was heated to reflux for 36 h, concentrated, diluted in water, and extracted with dichloromethane. The organic phase was washed with 1*N* sodium hydroxide and water, and dried over sodium sulfate. The resulting esters were used directly in the cycloaddition step.

Preparation of the α,β-unsaturated esters 8c and 8i by condensation of malonic acid monoethylester. Following the reported procedure [21], the corresponding aldehyde (0.018 mol), malonic acid monoethylester (3.3 mL; 0.028 mol), 4-dimethylaminopyridine (0.22 g, 0.0018 mol), and piperidine (0.15 mL; 0.0018 mol; just for the preparation of the pyridyl acrylate) were dissolved in dry DMF (100 mL, dried over 4-Å molecular sieves). The solution was stirred at RT for 24 h. In the case of the nonvolatile pyridyl acrylate, the solution was concentrated to dryness, and the residue was dissolved in ethyl acetate and washed with 1*N* sodium hydrogenocarbonate twice and water five times. The organic layer was dried over sodium sulfate and concentrated to dryness. In the case of the ethyl acrylate, the solution was diluted in ether (500 mL) and washed with 1*N* ammonium chloride twice, 1*N* sodium hydrogenocarbonate

twice, and water thrice before drying it over sodium sulfate and a cautious concentration to dryness. The resulting esters were used in the next step without further purification.

Preparation of the pyrazole esters 10a–k. CAUTION: due precautions must be taken when working with the carcinogenic diazomethane or *N*-methyl-*N*-nitrosourea. Any residue of *N*-methyl-*N*-nitrosourea can be neutralized with a 1:1 solution of acetone and sodium hydroxide 1*N*; any solution of diazomethane can be quenched with acetic acid. Under a well-ventilated hood, in a 250-mL Erlenmeyer "free of defaults and devoid of a ground glass joint", potassium hydroxide (3.8 g, 0.057 mol) was dissolved in water (45 mL). After cooling to 0°C, diethyl ether (45 mL) was added followed by *N*-methyl-*N*-nitrosourea (2 g; 0.019 mol; contains acetic acid as a stabilizer). The biphasic suspension was well stirred at 0°C for 10 min. The stirring of the resulting yellow biphasic solution was stopped, and after it settled, the bottom layer was frozen at −78°C using an acetone and dry ice bath. The cold yellow top layer was quickly filtered using a large cotton-plugged ("not glass wool") funnel, and the filtrate was allowed to drop directly into a cooled (0°C) solution of the α,β-unsaturated ethyl ester (0.0096 mol; in three instances, a methyl ester was used) in diethyl ether (45 mL). This was stirred overnight while allowing the temperature to rise to 25°C, and bromine (0.5 mL; 0.0096 mol) was then added. The solution was stirred for 10 min, washed successively with 1*N* solutions of sodium sulfite, sodium carbonate, and water, dried over sodium sulfate, and concentrated to dryness. Note: in few cases described in the succeeding sections, dichloromethane was used to improve the extraction of the reaction product. The resulting residues were then purified as described in the following.

4-Methyl-1H-pyrazole-3-carboxylic acid ethyl ester (10a). This compound was obtained in a 25% yield after an extraction of the aqueous phase first with ether then with dichloromethane. The residue, resulting from the concentration to dryness of these organic phases, was then dispersed in boiling cyclohexane before filtering it at RT. mp = 156°C (lit. [27] = 156–157°C). ^{1}H (MeOD): two sets of signals 1.39 (t, 3H, J = 7.1 Hz); 2.29 (s, 3H); 4.36 (q, 2H, J = 7.1 Hz); 7.41 and 7.53 (2s, 1H overall). ^{13}C (MeOD): two sets of signals 9.9; 10.2; 61.9; 62.0; 121.0; 122.5; 130.8; 142.4; 165.0. LC/MS: m/z = 155 $(M+H)^+$.

4-(Trifluoromethyl)-1H-pyrazole-3-carboxylic acid ethyl ester (10b). This compound was obtained in a 35% yield after an extraction of the aqueous phase first with ether then with dichloromethane The residue, resulting from the concentration to dryness of these organic phases, was then recrystallized in cyclohexane. mp = 163°C. ^{1}H (MeOD): 1.39 (t, 3H, J = 7.1 Hz); 4.40 (q, 2H, J = 7.1 Hz); 8.16 (s (br), 1H). ^{13}C (MeOD): 14.9; 63.0; 115.4 (q, J = 32 Hz); 123.0 (q, J = 264 Hz); 132.9 (br); 142.3 (br); 163.0 (br). LC/MS: m/z = 209 $(M+H)^+$ and 226 $(M+NH_4)^+$.

4-Ethyl-1H-pyrazole-3-carboxylic acid ethyl ester (10c). This compound was obtained as a solid in a 30% yield after purification by a chromatography over silica gel (dichloromethane/ethanol 98:2). mp = 102°C (lit. [19] = 102°C). ^{1}H (DMSO-d_6): two sets of signals 1.13 (m, 3H); 1.28 (m, 3H); 2.66 (m, 2H); 4.25 (m, 2H); 7.49 (s, 1/3H) 7.65 (s, 2/3H). ^{13}C (DMSO-d_6): two sets of signals 15.0; 15.6; 17.9; 18.1; 60.4; 61.1; 126.3; 127.7; 128.9; 129.9; 140.3; 140.5; 160.4; 163.6. LC/MS: m/z = 169 $(M+H)^+$.

4-Propyl-1H-pyrazole-3-carboxylic acid ethyl ester (10d). This compound was obtained as a solid in a 44% yield after purification by a chromatography over silica gel (dichloromethane/ethanol 98:2). mp = 77°C (lit. [19] = 81–82°C). ^{1}H (DMSO-d_6): two sets of signals 0.88 (t, 3H, J = 7.3 Hz); 1.30 (m, 3H); 1.53 (m, 2H); 2.63 (m, 2H); 4.30 (m, 2H); 7.47 and 7.65 (2s, 1H overall); 13.19 and 13.6 (s (br) 1H overall). ^{13}C (DMSO-d_6): two sets of signals 14.5; 14.6; 14.95; 15.04; 24.12; 24.16; 26.46; 26.78; 60.42; 61.16; 124.4; 125.97; 129.2; 129.4; 130.1; 140.6; 140.9; 160.4; 163.6. LC/MS: m/z = 183 $(M+H)^+$.

4-Isopropyl-1H-pyrazole-3-carboxylic acid methyl ester (10e). This compound was obtained as a solid in a 20% yield, from the corresponding methyl acrylate, after purification by a chromatography over silica gel (dichloromethane/ethanol 98:2). mp = 96°C). ^{1}H (DMSO-d_6): 1.27 (d, 6H, J = 6.9 Hz); 3.45 (sept, 1H, J = 6.9 Hz); 3.96 (s, 3H); 7.56 (s, 1H). ^{13}C (DMSO-d_6): 24.0; 24.5; 52.1; 131.2 (br); 132.9; 162.7. LC/MS: m/z = 169 $(M+H)^+$.

4-Isobutyl-1H-pyrazole-3-carboxylic acid methyl ester (10f). This compound was obtained as a solid in a 50% yield, from the corresponding methyl acrylate, after purification by a chromatography over silica gel (dichloromethane/ethanol from 99:1 to 98:2). mp = 80°C. ^{1}H (DMSO-d_6): two sets of signals 0.84 (d, 6H, J = 6.8 Hz); 1.79 (sept, 1H, J = 6.8 Hz); 2.55 (m, 2H); 3.76 and 3.82 (2s, 1H overall); 7.45 and 7.65 (2s, 1H overall). ^{13}C (DMSO-d_6): two sets of signals 23.01; 23.03; 29.6; 29.8; 33.2; 33.5; 51.8; 52.4; 123.3; 125.1; 130.0; 130.2; 140.7; 141.5; 160.8; 164.1. LC/MS: m/z = 183 $(M+H)^+$.

4-Pentyl-1H-pyrazole-3-carboxylic acid ethyl ester (10g). This compound was obtained as a solid in a 47% yield after purification by a chromatography over silica gel (dichloromethane/ethanol 98:2). mp = 107°C. ^{1}H (DMSO-d_6): two sets of signals 0.86 (t, 3H, J = 6.5 Hz); 1.28 (m, 7H); 1.52 (m, 2H); 2.63 (t, 2H, J = 7.3 Hz); 4.28 (m, 2H); 7.46 and 7.65 (2s (br), 1H overall). ^{13}C (DMSO-d_6): two sets of signals 14.76; 14.79; 15.0; 22.7; 24.6; 30.6; 31.87; 31.9; 60.4; 61.1; 124.6; 126.2; 129.2; 129.4; 130.1; 140.6; 140.9; 160.4; 163.6. LC/MS: m/z = 211 $(M+H)^+$.

4-Phenyl-1H-pyrazole-3-carboxylic acid methyl ester (10h). This compound was obtained as a solid in a 25% yield, from the corresponding methyl cinnamate, by filtration of the material precipitating at the interface between the water and ether layers in the course of the extraction step. mp = 191°C (lit. [23] = 185°C). ^{1}H (DMSO-*d*6): 3.76 (s, 3H); 7.29 (m, 1H); 7.37 (m, 2H); 7.50 (m, 2H); 7.95 (s, 1H). ^{13}C (MeOD): 52.5; 127.2; 128.7; 129.4; 130.7; 133.7; 135.7; 163.7. LC/MS: m/z = 203 $(M+H)^+$.

4-(Pyridin-2-yl)-1H-pyrazole-3-carboxylic acid ethyl ester (10i). This compound was obtained as a solid in a 12% yield after purification by a chromatography over silica gel (dichloromethane/cyclohexane 95:5). mp = 134°C. ^{1}H (MeOD): 1.29 (m, 3H); 4.33 (m, 2H); 7.36 (m, 1H); 7.79 (s (br), 1H); 7.86 (m, 1H); 7.92 (s (br), 1H); 8.55 (m, 1H). ^{13}C (MeOD): 15.1; 62.9 (br); 124.4; 126.2 (br); 126.9; 132.6; 138.8; 138.9; 143 (br); 150.4; 153.3. LC/MS: m/z = 218 $(M+H)^+$.

4-(Pyridin-3-yl)-1H-pyrazole-3-carboxylic acid ethyl ester (10j). This compound was obtained as a solid in a 20% yield after purification by a chromatography over silica gel (dichloromethane/ethanol from 98:2 to 95:5) followed by washing the solid obtained in boiling cyclohexane. mp = 135°C. ^{1}H (MeOD): two sets of signals 1.21 (m, 3H); 4.13 (m, 2H); 7.47 (m, 1H); 7.83 and 7.99 (2s (br), 2H overall); 8.44 (m, 1H); 8.67 and 8.75 (2s (br), 1H overall). ^{13}C (MeOD): two sets of signals 14.8; 62.4; 62.5; 123.0; 125.05; 130.9; 131.7; 139.4; 141.8 (br); 148.8; 150.7. LC/MS: m/z = 218 $(M+H)^+$.

4-(Pyridin-4-yl)-1H-pyrazole-3-carboxylic acid ethyl ester (10k). This compound was obtained as a solid in a 20% yield after purification by a chromatography over silica gel (dichloromethane/ethanol from 98:2 to 95:5) followed by a recrystallization in

toluene. mp = 191°C. ^{1}H (DMSO-d_6): two set of signals 1.24 (t, 3H, J = 7.0 Hz); 4.26 (q, 2H, J = 7.0 Hz); 7.54 (m, 2H); 8.19 (s (br), 1H). ^{13}C (DMSO-d_6): 14.8; 61.3; 124.3; 131.4; 140.6 (br); 150.1. LC/MS: m/z = 218 $(M + H)^+$.

Hydrolysis of esters 10a–k. The corresponding ester was dispersed in 35% hydrochloric acid (10 mL for 0.5 g) and refluxed for 3 h. The resulting solution was concentrated to dryness and the residue further purified as described in the following.

4-Methyl-1H-pyrazole-3-carboxylic acid (11a). This compound was obtained as a solid in 93% yield after dispersion in ether. mp = 210°C (lit. [27] = 218–220°C).. ^{1}H (DMSO-d_6): 2.18 (s, 3H); 7.51 (s, 1H). ^{13}C (DMSO-d_6): 10.2; 119.8; 135.7; 136.5; 163.5. LC/MS: m/z = 155 $(M + H)^+$.

4-(Trifluoromethyl)-1H-pyrazole-3-carboxylic acid (11b). This compound was obtained as a solid in a 77% yield after dispersion in water. mp = 236°C (dec.). ^{1}H (DMSO-d_6): 8.37 (s(br), 1H); 13.05 (s (br), 1H); 13.98 (s (br), 1H). ^{13}C (DMSO-d_6): 113.2 (q, J = 37 Hz); 123.0 (q, J = 264 Hz); 133.7 (br); 141.3 (br); 161.9 (br). LC/MS: m/z = 179 $(M - H)^-$.

4-Ethyl-1H-pyrazole-3-carboxylic acid (11c). This compound was obtained as a solid in a 75% yield after recrystallization in water. mp = 206°C (lit. [19] = 214–215°C). ^{1}H (DMSO-d_6): 1.13 (t, 3H, J = 7.5 Hz); 2.66 (q, 2H, J = 7.5 Hz); 7.54 (s, 1H); 13.0 (s (br), 1H). ^{13}C (DMSO-d_6): 15.8; 18.0; 126.8; 129.0 (br); 165.5. LC/MS: m/z = 141 $(M + H)^+$.

4-Propyl-1H-pyrazole-3-carboxylic acid (11d). This compound was obtained as a solid in a 98% yield after recrystallization in water. mp = 214°C (lit. [19] = 214–245°C). ^{1}H (DMSO-d_6): 0.88 (t, 3H, J = 7.3 Hz); 1.54 (m, 2H); 2.62 (t, 2H, J = 7.4 Hz); 7.52 (s, 1H). ^{13}C (DMSO-d_6): 14.6; 24.0; 26.5; 125.0; 135.0 (br); 163.5. LC/MS: m/z = 155 $(M + H)^+$.

4-Isopropyl-1H-pyrazole-3-carboxylic acid (11e). This compound was obtained as a solid in a 71% yield after recrystallization in water. mp = 201°C. ^{1}H (DMSO-d_6): 1.16 (d, 6H, J = 6.9 Hz); 3.32 (sept, 1H, J = 6.9 Hz); 7.57 (s, 1H). ^{13}C (DMSO-d_6): 24.3; 24.5; 123.6; 132.3; 145.8; 163.5. LC/MS: m/z = 155 $(M + H)^+$.

4-Isobutyl-1H-pyrazole-3-carboxylic acid (11f). This compound was obtained as a solid in a 70% yield after dispersion in boiling water. mp = 195°C. ^{1}H (DMSO-d_6): 0.84 (d, 6H, J = 6.6 Hz); 1.79 (m, 1H); 2.54 (d, 2H, J = 7.0 Hz); 7.50 (s, 1H). ^{13}C (DMSO-d_6): 23.0; 29.7; 33.4; 123.9; 136.1 (br); 163.4. LC/MS: m/z = 169 $(M + H)^+$.

4-Pentyl-1H-pyrazole-3-carboxylic acid (11g). This compound was obtained as a solid in a 93% yield after dispersion in boiling water. mp = 165°C. ^{1}H (DMSO-d_6): 0.85 (t, 3H, J = 6.8 Hz); 1.28 (m, 4H); 1.53 (m, 2H); 2.64 (t, 2H, J = 7.5 Hz); 7.52 (s, 1H). ^{13}C (DMSO-d_6): 14.7; 22.7; 24.4; 30.5; 31.8; 125.2; 135.0; 163.5. LC/MS: m/z = 183 $(M + H)^+$.

4-Phenyl-1H-pyrazole-3-carboxylic acid (11h). This compound was obtained as a solid in a 75% yield after recrystallization in water. mp > 260°C (lit. [28] = 251–253°C (dec.)). ^{1}H (DMSO-d_6): 7.28 (m, 1H); 7.36 (m, 2H); 7.55 (m, 2H); 7.87 (s, 1H); 13.3 (s (br), 2H). ^{13}C (MeOD): 127.1; 128.6; 129.4; 130.7; 133.7; 136.3 (br); 164.4. LC/MS: m/z = 189 $(M + H)^+$.

4-(Pyridin-2-yl)-1H-pyrazole-3-carboxylic acid (11i). This compound was obtained as a solid in a 74% yield after a recrystallization in water. mp > 200°C (dec.). ^{1}H (DMSO-d_6): 7.55 (m, 1H); 8.23 (m, 2H); 8.54 (s (br), 1H); 8.62 (m, 1H); 14.14 (s (br), 1H). ^{13}C (DMSO-d_6): 118.5; 122.6; 123.9; 135.6 (br); 140.3 (br); 140.3 (br); 141.9; 145.6; 149.3; 161.0 (br). LC/MS: m/z = 190 $(M + H)^+$.

4-(Pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (11j). This compound was obtained as a solid in a 94% yield after dispersion in ether. mp > 260°C (lit. [29] = 250–251°C). ^{1}H (DMSO-d_6): 7.95 (dd, 1H, J = 5.5 and 8.1 Hz); 8.20 (m, 1H); 8.76 (dd, 1H, J = 1.2 and 5.5 Hz); 9.08 (d, 1H, J = 1.9 Hz). ^{13}C (DMSO-d_6): 118.6; 127.1; 132.4; 136.0; 140.9; 142.4; 145.5; 163.1. LC/MS: m/z = 190 $(M + H)^+$.

4-(Pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (11k). This compound was obtained as a solid in a 94% yield after dispersion in ether. mp > 260°C (lit. [29] = 255–256°C). ^{1}H (DMSO-d_6): 8.28 (d, 2H, J = 6.8 Hz); 8.49 (s (br), 1H); 8.86 (d, 2H, J = 6.8 Hz). ^{13}C (DMSO-d_6): 119.6; 126.3; 136.2; 141.9; 149.9; 164.4 (br). LC/MS: m/z = 190 $(M + H)^+$.

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