The molecular structure of 1,3-dimethyl-4-phenyl-1*H*-pyrazole-5-carboxylic acid

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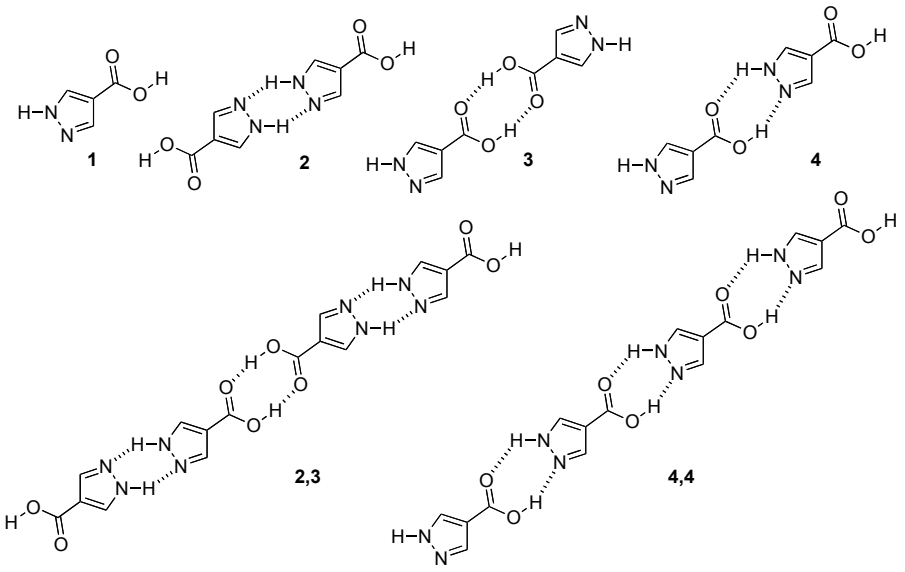
Dedicated to our good friend Professor Arlette Solladié-Cavallo on her 70th birthday

Abstract
The synthesis, NMR study and X-ray structure determination of the title compound are reported together with B3LYP/6-311++G** calculations. The chemical shifts have been compared with absolute shieldings calculated using the GIAO approximation. An analysis of the structures of pyrazole carboxylic acids found in the Cambridge Structural Data Base has been carried out.

Keywords: Pyrazole, carboxylic acids, X-ray crystallography, GIAO/B3LYP/6-311++G** calculations

Introduction

N-Unsubstituted pyrazoles bearing carboxylic groups at positions 3, 4 or 5 are interesting molecules from a structural point of view due to the fact that both functional groups are able to associate through hydrogen bonds (HB). For instance, 1*H*-pyrazole-4-carboxylic acid (**1**) can form dimers of both the homo **2** and **3** and hetero chiral configuration **4** (Scheme 1). These, in turn, can associate to form chains (catemers) of either the **2,3** or the **4,4** type. In particular, compound **1** crystallizes in catemers of the **2,3** kind (TIDLIB).[1,2]



Scheme 1

An examination of the structures reported in the Cambridge Structural Database (CSD, not including metals),[1] shows that there are four 4-COOH derivatives, two 3-COOH derivatives, five 5-COOH derivatives, one 3(5)-COOH, two 3,5-diCOOH, and twenty salts derived from the monoanion of pyrazole-3,5-dicarboxylic acid (Scheme 2). In addition, one further 3(5)-COOH pyrazole has been described, albeit too recently to be included in the lastest version of the CSD.[1]

The secondary structure observed in most of these compounds is more complicated than that shown in Scheme 1. This is due to the fact that these molecules present hydrogen bond donor (HBD) and acceptor (HBA) atoms other than those of the carboxylic and pyrazole functional groups. We have reported that the crystal structures become more stable as the number of donor and acceptor groups involved in the hydrogen bond network increases.[3]

Among the 35 carboxylic-pyrazole derivatives, there are 9 *N*R-pyrazoles, with the remainder consisting of 26 *N*H-pyrazoles. The former do not present the possibility of forming the infinite chains explicated in Scheme 1. Two of these (PADBAX and SAYWUL) present dimers of type 3 (Scheme 1). DEVVIK, DPYZCX, HACTAG and INENAQ form infinite chains through $OH_{COOH}\cdots N_{pz}$ whereas in the last two the interaction is assisted by a water molecule as per $OH_{COOH}\cdots OH_{H2O}\cdots N_{pz}$.

The infinite chains observed in DPYZCX and in the title structure overlap perfectly (Fig. 1). Twenty three out of the twenty six NH-pyrazoles cocrystallize with molecules that participate in the strong hydrogen bonds observed in their crystal structures. Particularly deserving of mention are the 3(5)-COOH pyrazole derivatives (WEHKEA and ref. 3) and the 3,5-dicarboxylic pyrazole (SEPNUX and WOCREL). Both 3(5)-COOH pyrazoles are seen to exist as the 3-COOH tautomer as per their crystal structure. The secondary structure of WEHKEA can be considered to be an infinite chain of the 4,4 type (Scheme 2) assisted by one water molecule (Fig. 2). The 3-phenyl-1*H*-pyrazole-5-carboxylic acid[3] exibits a 2D hydrogen bonded

substructure linked through CH···O and CH(ph)···π(ph) interactions in the formation of the associated crystal lattice. Finally, the most important difference at the molecular level between SEPNUX and WOCREL is observed in the conformation of the carboxylic group at position 3, which is in *trans* conformation with respect to the carboxylic in position 5 in SEPNUX and in *cis* conformation in WOCREL. This molecular difference allows two different crystal packings. In SEPNUX a stacking of planar layers is observed while in WOCREL the crystal includes water molecules which are able to form four hydrogen bonds,[4] thus allowing the formation of a strong 3D hydrogen bonded structure.

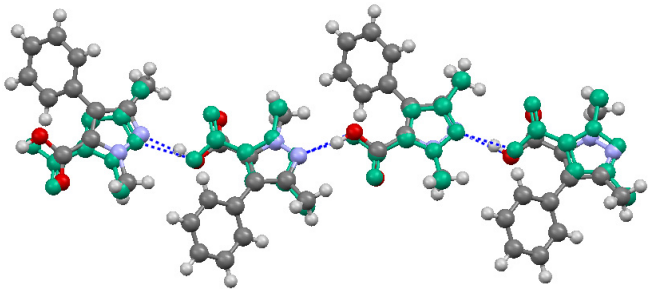


Figure 1. Secondary structure superposition of DPYZCX (green color) and the title compound (atoms color).

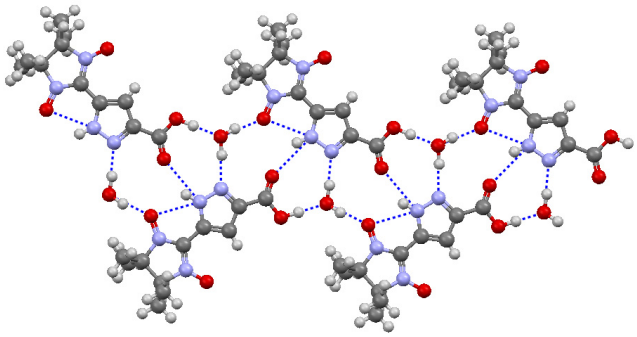
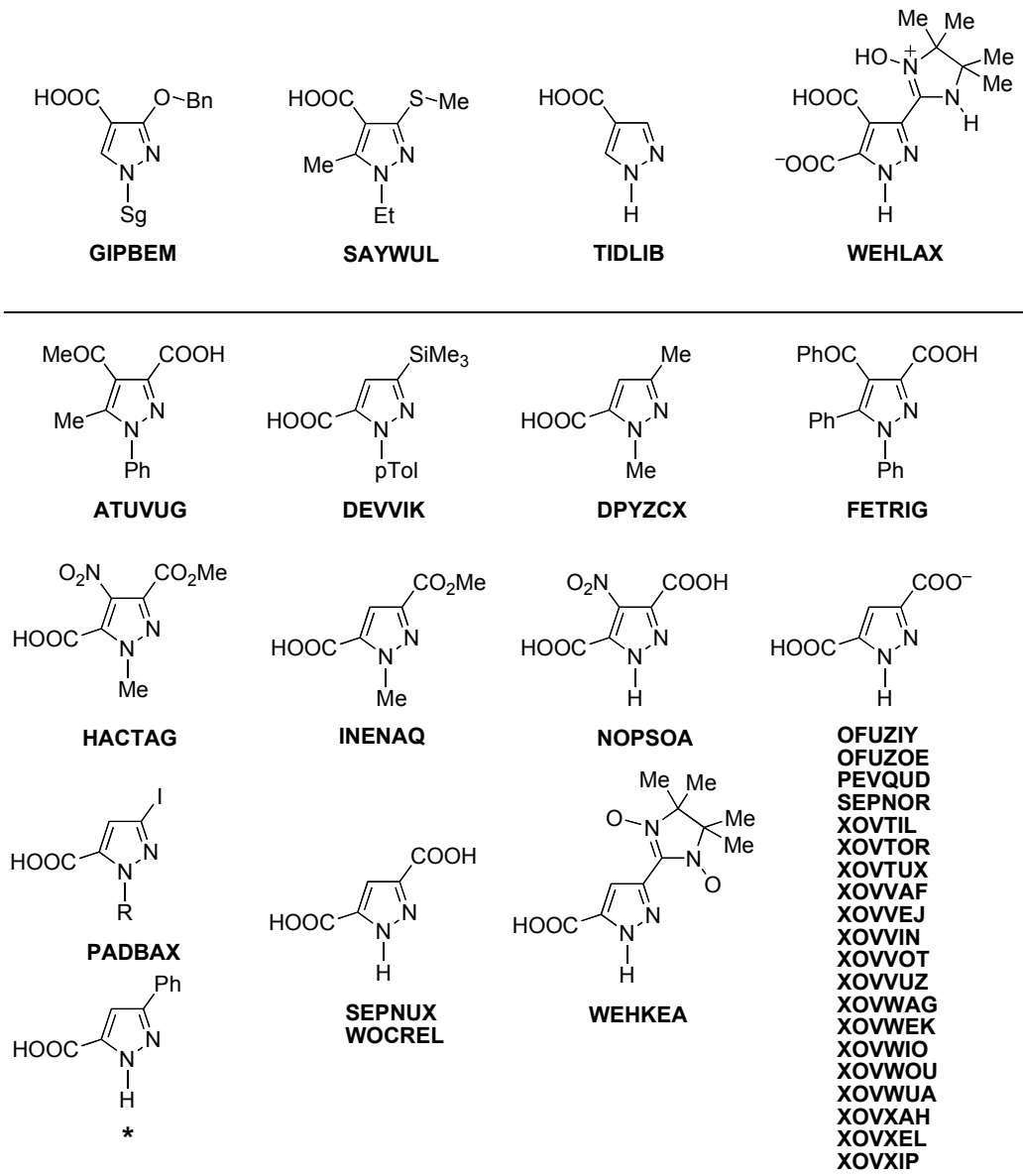


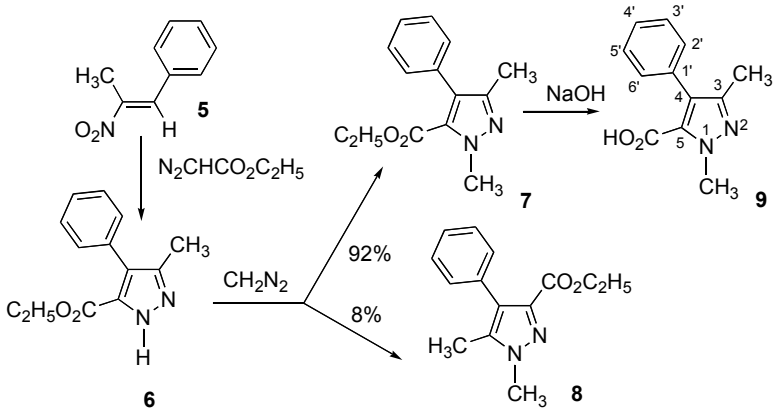
Figure 2. Secondary structure of the compound CSD refcode: WEHKEA.



Scheme 2. *This compound[1] has still not been included in the CSD.

Results and Discussion

Although originally we have intended to prepare a series of pyrazolecarboxylic acids, the only crystal we succeeded in growing conveniently was 1,3-dimethyl-4-phenyl-1*H*-pyrazole-5-carboxylic acid (**9**). This compound was prepared by the sequence of reactions reported in Scheme 3.



Scheme 3

The crystals of this compound are found to contain two independent molecules (1 and 2) in the unit cell (Figure 3). In both molecules, practically all of the bond distances and angles have present the expected values. Although the pyrazole ring of molecule 1 is planar, in the case of molecule 2 there is a significant distortion from the planarity ($\chi^2 = 129.49$ *vs*. the tabulated value of 5.99). The carbon atoms bonded to the pyrazole ring do not deviate from the mean-square pyrazole planes, except for those of the phenyl ring in molecule 1 [0.117(1) Å] and that of the carboxylic group in molecule 2 [0.111(1) Å]. Moreover, one further unusual feature of this structure is that the C1-C2-C6 and C1'-C2'-C6' angles (125.5º and 124.5º, respectively) are much reduced in comparison with those found in other phenylpyrazole derivatives, wherein the average value for this angle is 128±1.2º (calculated with Mogul[5] using data derived from the CSD).

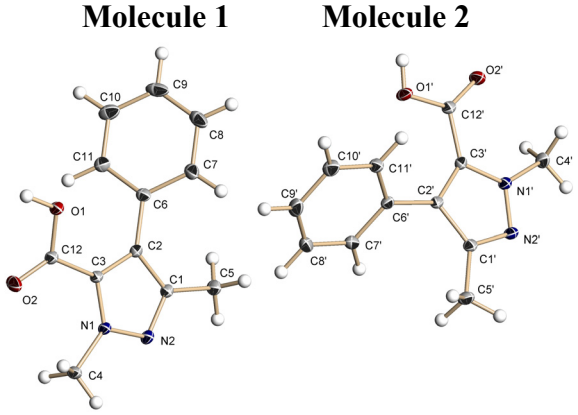


Figure 3. The molecular structure of **9**, showing the two independent molecules of the asymmetric unit together with the atom-labeling scheme for each molecule. Displacement ellipsoids are drawn at the 50% probability level; H atoms are shown as circles of arbitrary size.

The principle difference between the two molecules lies in two related parameters: the dihedral angle between the planes of the phenyl and pyrazole rings (48.7° and 51.5° in the molecule 1 and 2 respectively), and the torsional angle between the planes of the pyrazole ring and of the carboxylic group (17.6°, 1; 6.0°, 2). The more coplanar the orientation of the COOH group with the pyrazole ring is, the more perpendicular the orientation of the phenyl ring becomes.

The secondary structure of **9** is formed by infinite chains, each one consisting of molecules 1 and 2 arranged in an alternating manner and linked through O-H···N hydrogen bonds (Figure 4 and Table 1). The hydrogen bond between the O1 and N2' is slightly shorter and more linear than that formed between O1' and N2.

Table 1. Geometry of the hydrogen bonds for the compound **9**

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
O1-H1···N2'	0.910 Å	1.789 Å	2.679 Å	165.5°
O1'-H1'···N2	0.882 Å	1.840 Å	2.694 Å	162.3°

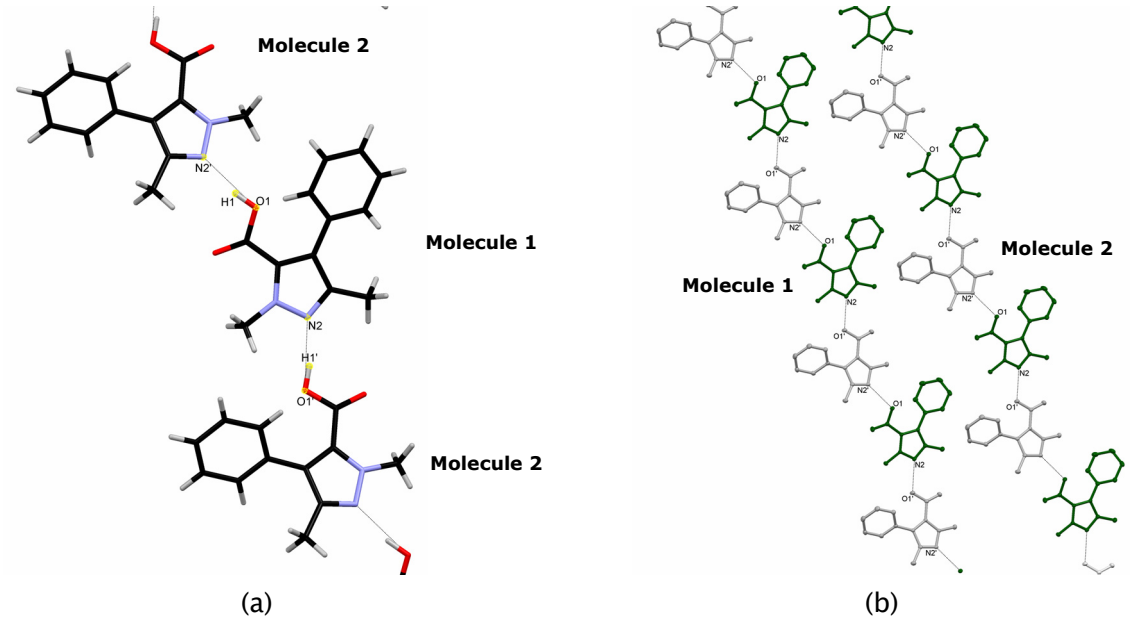


Figure 4. (a) Secondary structure of compound **9** showing, (a) the O-H···N hydrogen bonds between molecules 1 and 2, (b) infinitely extended ribbons from the two independent molecules (molecule 1, green, molecule 2, grey, of the asymmetric unit).

These chains are related via an inversion centre (Figure 5). They grow along the [110] direction and are connected through van der Waals interactions to form the observed 3D structure.

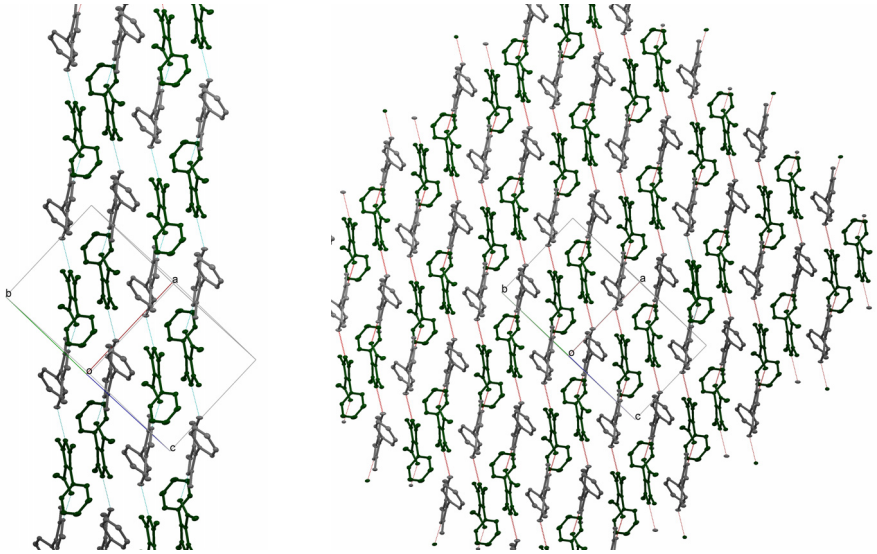


Figure 5. Crystal packing of **9** along the [110] direction.

Using this structure as a starting point, we have carried out an optimization at the B3LYP/6-311++G** level. The dihedral angles of rotable bonds are the most sensitive parameters and thus, sizeable differences are to be expected for the two different environments, ie. for the gas phase (calculations) and for the solid state (X-ray results). The results obtained for the dihedral angles that define the relative disposition of the two rings and those that indicate the disposition of the carboxylic group *vs*. the pyrazole group have been gathered in Table 2. These results show that the packing reduces the dihedral angle between the two rings, making the system flatter while at the same time increasing the dihedral angle between the acid group and the pyrazole ring, most probably to better accommodate the intermolecular hydrogen bonds absent in these calculations.

Table 2. Dihedral angles (º) obtained in the B3LYP/6-311++G(d,p) calculation and in the two independent molecules of the unit cell

	Calculations	Molecule 1	Molecule 2
Pz-COOH angle	4.2	17.6	6.0
Ph/Pz angle	65.6	48.7	51.5

The absolute shieldings, σ, of **9** were calculated with the GIAO approximation and compared with the experimental chemical shifts (see Experimental Section). The agreement is excellent in both the ^{1}H and in the ^{13}C NMR cases (all in ppm):

Exp. ^{1}H (δ) = (30.76±0.16) – (0.960±0.006) Calc. ^{1}H (σ), n = 5, r^2 = 1.000

Exp. ^{13}C (δ) = (176.6±0.8) – (0.974±0.009) Calc. ^{13}C (σ), n = 9, r^2 = 0.999

These results prove that in $CDCl_3$ solution compound **9** exists in its neutral form and not as a zwitterion (pyrazolium carboxylate inner salt).

Conclusions

The present study of compound **9** increases the number of pyrazolecarboxylic acids whose structure has been characterized and determined (Scheme 2). These compounds are precursors of amides and hydrazides which have both been described as having important pharmaceutical applications.[6-9]

Experimental Section

General Procedures. ^{1}H-NMR spectra were recorded at 300 or 500 MHz and ^{13}C-NMR spectra at 75 or 125 MHz on Bruker 300 and Varian 500 unity spectrometers. Chemical shifts are reported in ppm using TMS as the internal standard. *J* values are reported in Hz. Melting points (uncorrected) were determined with a Reichert Jung Thermovar apparatus. Mass spectra were recorded using electrospray positive mode. Flash column chromatographies were run on silica gel 60 (230-400 mesh) or on a medium pressure flash system with a prepacked silica gel cartridge (Isolute Flash Si II 50g/150mL). TLC was carried out on Merck $60F_{254}$ silica plates.

Ethyl 3(5)-methyl-4-phenyl-1*H*-pyrazole-5(3)-carboxylate (**6**). To a solution of *trans*-methyl-nitrostyrene (**5**, 5.00 g, 30.6 mmol) in toluene (12 mL) was added ethyldiazoacetate (5.00 g, 43.8 mmol) under nitrogen atmosphere. The mixture was heated to reflux for 14 hours. The solvent was evaporated under reduced pressure to give 8.14 g of crude product. Purification by flash column chromatography (cyclohexane/ethyl acetate/dichloromethane 3:2:1) afforded 3.17 g (49% yield) of the compound **6** as a yellow oil. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H, aromatics), 4.25 (q, J = 7.0 Hz, 2H, OCH_2), 1.52 (s, 3H, CH_3 pyrazole), 1.25 (t, J = 7.0 Hz, 3H, CH_3).

Ethyl 1,3-dimethyl-4-phenyl-1*H*-pyrazole-5-carboxylate (7) and ethyl 1,5-dimethyl-4-phenyl-1*H*-pyrazole-3-carboxylate (8). To a solution of **6** (3.17 g, 13.8 mmol) in dichloromethane (15 mL) was added a solution of diazomethane (distilled from 3.00 g Diazald®) in ether. The reaction mixture was stirred at room temperature overnight. The products were purified by medium pressure column chromatography (cyclohexane/dichloromethane/ethyl acetate 9:2:1) to give 1.13 g of compound **7** (34% yield) and 0.11 g of compound **8** (3% yield). Compound **7**: ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H, aromatics), 4.15 (m, 5H, ethyl CH_2 and *N*-CH_3), 2.18 (s, 3H, CH_3-pyrazole), 1.03 (t, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 160.6 (C=O), 146 (3), 133.6 (5), 130.4 (1'), 130.3 (3'), 127.9 (2'), 127.3 (4'), 125.7 (4), 60.9 (CH_2), 39.8 (*N*-CH_3), 13.9 (ethyl CH_3), 12.2 (CH_3 pyrazole); ME (ES^+) m/z = 245 (100%)

$[M+H]^+$. Compound **8**: ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 7.33 (t, J = 7.2 Hz, 2H, 3´), 7.25 (m, 3H, 2',4'), 4.22 (q, J = 7.1 Hz, 2H, CH_2), 3.85 (s, 3H, N-CH_3), 2.14 (s, 3H, CH_3-pyrazole), 1.19 (t, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 162.2 (C=O), 138.8 (5), 138.0 (3), 132.4 (1'), 130.0 (3'), 127.6 (2'), 126.8 (4'), 123.5 (4), 60.3 (CH_2), 37.0 (N-CH_3), 13.9 (CH_3 of ethyl), 9.7 (CH_3-pyrazole); ME (ES^+) m/z = 245 (100%) $[M+H]^+$.

1,3-Dimethyl-4-phenyl-1*H*-pyrazole-5-carboxylic acid (9). NaOH (1.63 g, 40.9 mmol) was added to a solution of **7** (1.00 g, 4.1 mmol) in ethanol/water (40 mL/40 mL). The solution was stirred for 3 hours. The reaction mixture was acidified with diluted HCl and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine (1 x 100 mL), dried over $MgSO_4$, and evaporated in vacuum to give 952 mg (99%) of the compound **9** as a white solid. Mp = 240 ºC. ^{1}H NMR (499.81 MHz, $CDCl_3$) δ 7.35 (t, J = 7.1 Hz, 2H, 3'), 7.30 (d, J = 7.1 Hz, 1H, 4'), 7.25 (d, J = 7.1 Hz, 2H, 2'), 4.10 (s, 3H, N-CH_3), 2.10 (s, 3H, CH_3-pyrazole). ^{13}C NMR ($CDCl_3$) δ 162.8 (C=O), 146.9 (3), 134.2 (1'), 132.1 (4), 131.2 (2'), 128.8 (3'), 128.1 (4'), 126.6 (5), 39.7 (N-CH_3), 11.8 (3-CH_3); ME (ES^+) m/z = 217 (100%) $[M+H]^+$; HPLC t_R = 3.13 min. (99%), eluent: 60% CH_3CN and 40% H_2O (H_3PO_4 0.01%), flow 1 mL min^{-1}, detection: λ = 214 nm. Isotropic shieldings (σ): ^{1}H: N-Me 27.81, 3-Me 29.82, H2',6' 24.49, H3',5' 24.37, H4' 24.42 ppm; ^{13}C: N-Me 139.98, C-Me 169.39, C3 30.33, C4 47.28, C5 49.73, C1' 41.28, C2',C6' 47.08, C3',C5' 50.10, C4' 50.93 ppm.

X-Ray crystal structure analyses of 9

Colorless crystals of the compound **9** were recrystallized in 0.5 mm capillaries by counterdiffusion of water into a methanol-dichloromethane solution of the compound. A suitable crystal of dimensions 0.64 x 0.33 x 0.28 was mounted in a glass fiber covered with perfluoropolyether oil (FOMBLIN®, Aldrich). Intensity data were collected on a Bruker-AXSX8Kappa diffractometer equipped with an Apex-II CCD area detector, using a graphite monochromator Mo $K_{\alpha 1}$ (λ=0.71073 Å) and a Bruker Cryo-Flex low-temperature device. Data collection was carried out with APEX-W2D-NT (Bruker, 2004), cell refinement with SAINT-Plus (Bruker, 2004) and data reduction with SAINT-Plus (Bruker, 2004). The structure was solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. The position of the hydrogen atoms was determined by difference Fourier synthesis and refined, together their isotropic thermal parameter, by least-squares procedures. Weighted R factors (wR) and all goodness-of-fit (S) are based on F^2, conventional R factors (R) are based on F. The SHELXTL software package[10] (based on SHELXS and SHELXL) was used for structure solution and refinement.

A summary of the fundamental crystal and refinement data (Table S1), atomic coordinates (Table S2), bond lengths and angles (Table S3) and anisotropic displacement parameters (Table S4) are given in the Supporting Information.

Computational details

The optimization of the geometry was carried out at the B3LYP/6-311++G** computational level[11-13] within the Gaussian-03 package.[14] Frequency calculations were employed to confirm that the obtained structures correspond to energetic minima. GIAO absolute shieldings[15] were calculated using the B3LYP/6-311++G** optimized geometries.

Supplementary Information Available

CCDC-664608 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; e-mail: deposit@ccdc.cam.uk.

Acknowledgements

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