Efficient Syntheses of Some Versatile 3,5-Bifunctional Pyrazole Building Blocks

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Abstract: A series of convenient synthetic procedures are reported for pyrazole derivatives with carbonyl or ester groups in the 3- and 5-positions and variable substitution pattern at C4 and at the functional side arms. All compounds have been characterized by ^{1}H and ^{13}C NMR spectroscopy, elemental analyses, and mass spectrometry. In addition, the structures of several pyrazole derivatives have been determined by single crystal X-ray diffraction, which provides insight into the effect of functional side arms on the hydrogen-bonded supramolecular motifs of NH-pyrazoles.

Key words: pyrazoles, N-heterocycles, X-ray crystal structure, H-bonding

Pyrazoles are considered as extremely versatile building blocks in organic chemistry.[1] They constitute key fragments in active pharmaceutical and agrochemical ingredients, which have found widespread use as ligands for transition-metal complexes.[2,3] Decoration of the pyrazole core often requires the attachment of functional substituents at the 3- and 5-positions of the heterocycle, which can then be further manipulated. Recent examples of valuable 3,5-difunctionalized pyrazoles comprise aminopyrazole derivatives as nonpeptidic templates capable of recognizing β-sheet structures,[4] and compartmental pyrazole/imine ligand scaffolds that form binuclear Pd and Ni complexes for catalytic olefin polymerization.[5]

The most common methods for the preparation of pyrazoles are the reaction of hydrazines with β-dicarbonyl compounds, and 1,3-dipolar cycloadditions of diazo compounds onto triple bonds.[6] The former process, usually considered to be the best and most versatile method, involves the double condensation of 1,3-diketones with hydrazine or its derivates. While this works well for simple pyrazoles bearing various alkyl or aryl substituents in the 3- and 5-positions, however, most electrophilic functional groups such as aldehydes, nitriles, esters, and alkyl halides do not survive such transformation. On the other hand, there is a paucity of 3,5-bifunctional pyrazole compounds that would allow facile subsequent derivatization. These should be amenable via high-yielding and straightforward syntheses, which is particularly true for N-unsubstituted pyrazoles.[7,8] Established pyrazole building blocks include dialdehyde **A**[9] and diacid dichloride **B**[10] as well as diester **C**[11] (Figure 1), all of which have proven useful for the preparation of, for example, macrocycles and multidentate ligand scaffolds incorporating one or more pyrazole moieties.[3]

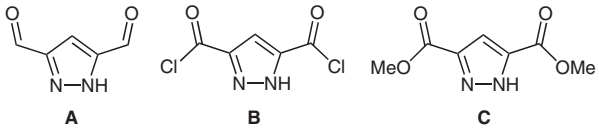

Figure 1 Established 3,5-bifunctionalized pyrazole synthons.

In order to broaden the scope of these systems, we set out to develop efficient syntheses for a variety of new 1*H*-pyrazole derivatives related to **A**–**C** with carbonyl or ester groups in the 3- and 5-positions, but with different substitution pattern both at the pyrazole-C4 position and the side arm carbonyl functions. For the synthetic approaches it was aimed to avoid toxic hydrazine or its derivatives. Finally, it was deemed interesting to study the solid-state structures of such pyrazole synthons that are decorated with functional groups, since the presence of multiple H-bonding donor and acceptor sites may give rise to complex aggregation patterns, distinct from those of simple pyrazoles.[12] The new compounds reported here are collected in Table 1.

The potassium salt of pyrazole-3,5-dicarboxylic acid **D** as well as the diester **C** are readily accessible from commercially available 3,5-dimethylpyrazole by oxidation with $KMnO_4$ and subsequent esterification using MeOH and gaseous HCl.[11] We found that treatment of **D** with MeLi in THF directly gave 3,5-diacetylpyrazole (**1**) in 60% yield (Scheme 1). While the low solubility of the starting material **D** in THF or diethyl ether apparently has a detrimental effect on the yield, this method still represents an improvement over the two procedures reported previously for **1**, one of which has not been optimized and gives only a mixture of products.[13] In order to open the potential for substituting at C4 via, for example, Pd-catalyzed cross-coupling reactions, 4-iodo-1*H*-pyrazole-3,5-dicarboxylic acid dimethyl ester (**2**) was prepared in 95% yield by the reaction of **C** with I_2 in the presence of ammonium cerium(IV) nitrate, following a procedure developed by Rodríguez-Franco.[14]

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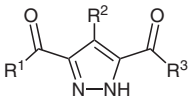
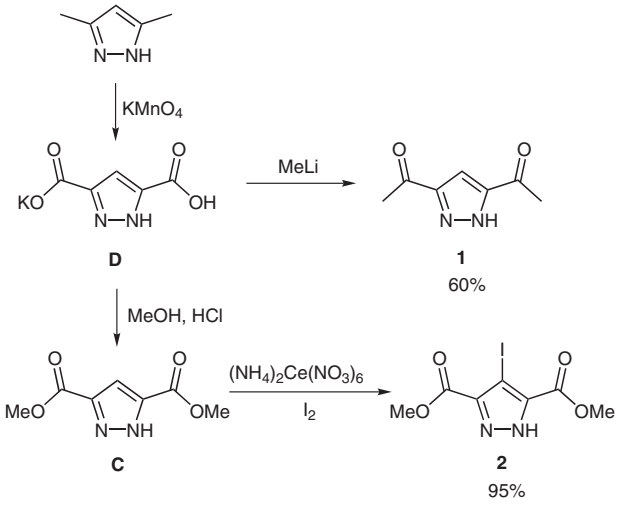
Table 1 3,5-Bifunctional Pyrazoles Prepared



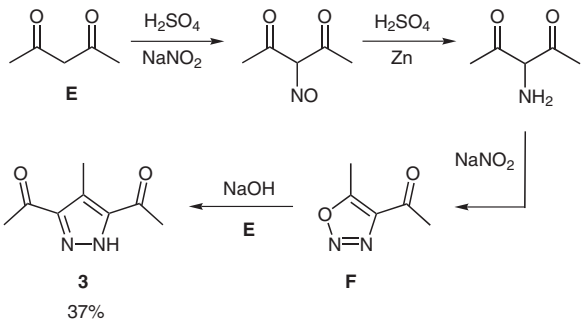
Product	R^1	R^2	R^3
1	Me	H	Me
2	OMe	I	OMe
3	Me	Me	Me
5	OMe	Ph	OMe
7	H	Ph	H
8	Ph	Ph	Ph
9	Me	Me	OH
10	Me	Ph	Ph



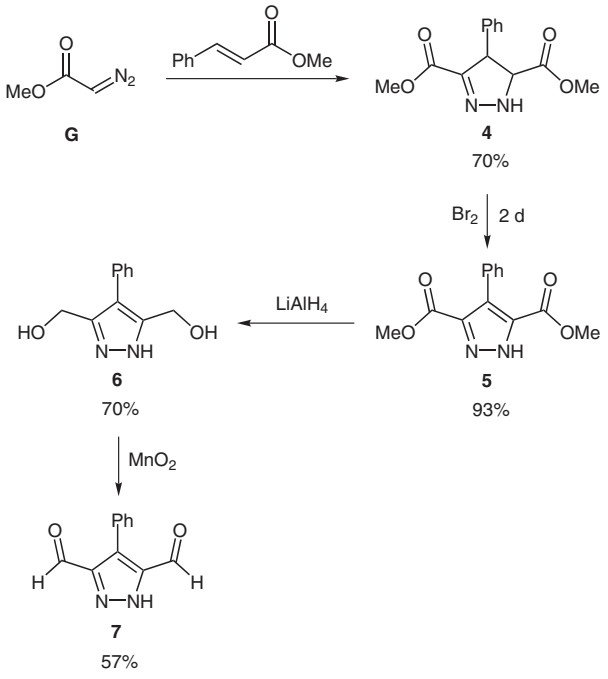
Scheme 1 Synthesis of pyrazole derivatives **1** and **2**.

The 3,5-diacetylpyrazole (**1**) represents a modification of **A** with acetyl instead of formyl groups as side arms. The fully methylated derivative **3** can be prepared according to a procedure reported by Wolff in 1902 (Scheme 2).[15] However, this method proved to be quite unreliable, since the 4-acetyl-5-methyl[1,2,3]oxadiazole **F** is rather unstable and its yield is often very low. A better synthesis of **3** has been developed here (see below).

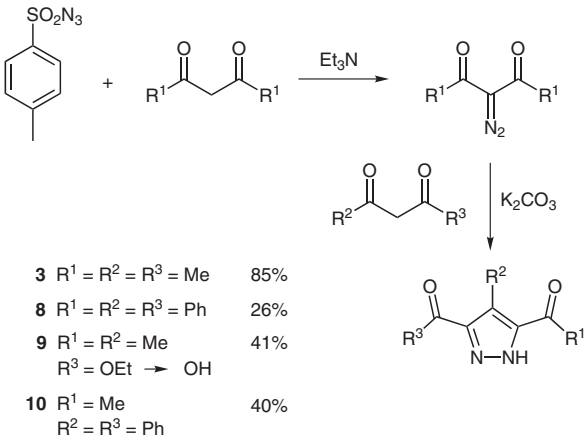
A four-step procedure has been followed to introduce a single phenyl group at the pyrazole-C4. 4-Phenyl-1*H*-pyrazole-3,5-dicarbaldehyde (**7**) was synthesized from methyl diazoacetate via modification of a procedure reported by Buchner and co-workers in 1902 (Scheme 3).[16] Dipolar cycloaddition of diazoglycine methyl ester with the methyl ester of cinnamic acid forms pyrazoline **4**. Pyrazolines have often been described as fairly unstable compounds that are not easy to purify and handle, but **4** can be isolated in 70% yield after recrystallization from diethyl ether at –30 °C. Oxidation with bromine then affords the pyrazole diester **5**, and subsequent reduction



Scheme 2 Original synthesis of **3**; the yield given is the overall yield for four steps (which may vary; see text).



Scheme 3 Synthetic route to 4-phenyl-1*H*-pyrazole-3,5-dicarbaldehyde (**7**).



Scheme 4 New synthetic route to 3,5-dicarbonyl-1*H*-pyrazoles with variable substitution pattern; overall yields for two steps.

with $LiAlH_4$ gives dialcohol **6**. Reoxidation with MnO_2 then leads to the sought-after product **7**. The final step

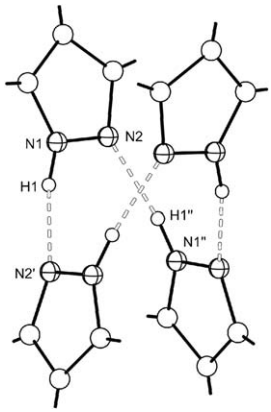


Figure 2 View of the hydrogen-bond structure of **8**. Selected atom distances (Å) and angles (°): N1···N2′ 2.841(2); N1–H1···N2′ 167(2). Symmetry transformations used to generate equivalent atoms: (′) *y*, 1–*x*, 2–*z*; (″) 1–*y*, *x*, 2–*z*.

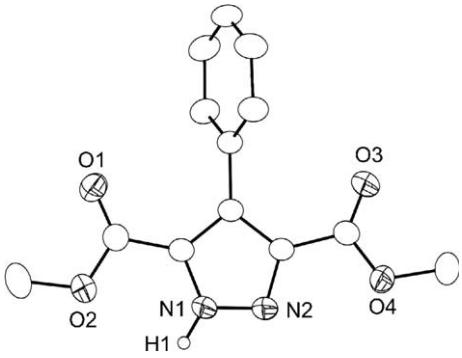


Figure 3 ORTEP plot (30% probability thermal ellipsoids) of the cationic part of **5**. For the sake of clarity, most hydrogen atoms have been omitted.

proceeds only to 57%, giving a modest overall yield of 26% for the combined four steps.

While ^{13}C NMR spectra of all 3,5-disubstituted pyrazoles usually show a single broad resonance for the C3/5 atoms of the heterocycle due to fast NH tautomerism, two broad signals are observed for **6** at 140.0 and 149.0 ppm. In addition, ^{13}C resonances for the side arm methylene groups are significantly broadened, suggesting that tautomerism is slowed down in this particular compound. Involvement of the side arm hydroxyl groups in hydrogen bonding interactions might be assumed as a likely reason.

An alternative synthetic route was developed to provide a more general approach towards 3,5-dicarbonyl pyrazoles with variable substitution pattern (Scheme4). Diazotization of a β-diketone with *p*-toluenesulfonyl azide and subsequent treatment with a second equivalent of β-diketone, which may be the same or different from the first one, provides a series of trisubstituted pyrazoles, with R^1, R^2 and R^3 depending on the β-diketones.

For **3**, this method is a significant improvement over the laborious synthesis described above (Scheme2). Compound **3** and the triphenyl derivative **8** are obtained in 85% and 26% yield, respectively. High regioselectivity is observed when using ethyl acetoacetate as an unsymmetric β-diketone in the second step, and pure 5-acetyl-4-methyl-1*H*-pyrazole-3-carboxylic acid (**9**) is conveniently isolated in 41% yield from the reaction mixture. This implies hydrolysis of the ester moiety under the reaction conditions to give a carboxylic acid function in the product.

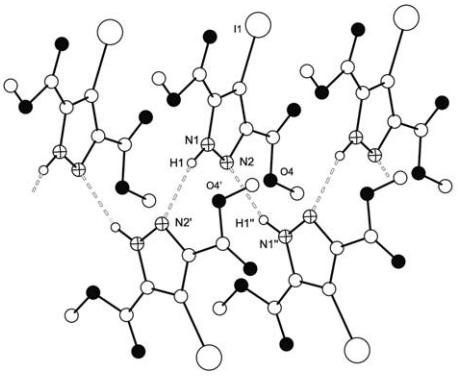


Figure 4 View of the hydrogen bond structure of **2**. Selected atom distances (Å) and angles (°): N1···N2′ 2.890(2), N1···O4′ 3.200(2); N1–H1···N2′ 148(2), N1–H1···O4′ 127(3). Symmetry transformations used to generate equivalent atoms: (′) –1/2+*x*, 3/2–*y*, 1–*z*; (″) 1/2+*x*, 3/2–*y*, 1–*z*.

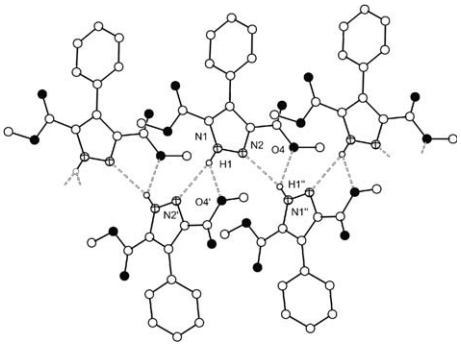


Figure 5 View of the hydrogen bond structure of **5**. Selected atom distances (Å) and angles (°): N1···N2′ 3.120(2), N1···O4′ 3.084(2); N1–H1···N2′ 146(2), N1–H1···O4′ 138(2). Symmetry transformations used to generate equivalent atoms: (′) –1/2+*x*, 3/2–*y*, –*z*; (″) 1/2+*x*, 3/2–*y*, –*z*.

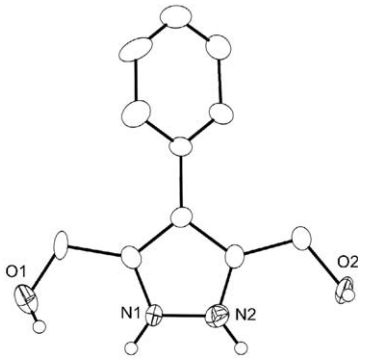


Figure 6 ORTEP plot (30% probability thermal ellipsoids) of the cationic part of **6**·HCl. For the sake of clarity, most hydrogen atoms have been omitted.

Table 2 Crystal Data and Refinement Details for Compounds **2**, **5**, **6**, and **8**

	2	**5**	**6**	**8**
Formula	$C_7H_7IN_2O_4$	$C_{13}H_{12}N_2O_4$	$C_{11}H_{12}N_2O_2$, $C_{11}H_{13}N_2O_2^+$, Br^-, 0.5 CH_4O, 0.5 H_2O	$C_{23}H_{16}N_2O_2$, 0.5 C_3H_6O
M_r	310.05	260.25	514.40	381.42
crystal size [mm]	0.49 × 0.04 × 0.04	0.47 × 0.34 × 0.31	0.30 × 0.21 × 0.11	0.48 × 0.37 × 0.25
crystal system	orthorhombic	orthorhombic	triclinic	tetragonal
space group	$P2_12_12_1$ (No. 19)	$P2_12_12_1$ (No. 19)	$P\bar{1}$ (No. 2)	$I\bar{4}$ (No. 82)
a [Å]	4.5086(2)	6.2569(3)	9.4338(14)	12.9187(5)
b [Å]	12.6705(6)	14.1156(9)	9.7537(13)	12.9187(5)
c [Å]	17.1726(10)	14.5255(8)	13.6894(18)	24.7001(13)
α [°]	90	90	101.433(11)	90
β [°]	90	90	108.673(11)	90
γ [°]	90	90	100.573(11)	90
V [Å^3]	981.01(9)	1282.89(12)	1127.5(3)	4122.3(3)
Z	4	4	2	8
$\rho_{calcd.}$ [g cm^{-3}]	2.099	1.347	1.515	1.229
F(000)	592	544	532	1600
μ [mm^{-1}]	3.255	0.102	1.866	0.080
T_{max}/T_{min}	0.9181/0.4158	–	0.8213/0.7027	–
hkl range	–5 to 4, ± 16, ± 21	–8 to 7, ± 18, ± 18	–11 to 10, ± 11, –16 to 15	± 16, ± 16, ± 31
θ range [°]	2.00–26.94	2.01–27.35	2.21–24.82	1.65–27.42
measured refl.	9592	25226	7117	31940
unique refl. [R_{int}]	2128 [0.0405]	2897 [0.0490]	2248 [0.0658]	4678 [0.0503]
observed refl. ($I>2\sigma(I)$)	2035	2285	1234	4082
ref. param./ restraints	133/0	178/0	293/3	267/5
goodness-of-fit	1.013	1.028	1.165	1.007
Abs. structure param.	–0.029(17)	0.3(13)	–	0.5(12)
*R*1, *wR*2 [$I>2\sigma(I)$]	0.0151, 0.0373	0.0408, 0.1115	0.1053, 0.2958	0.0413, 0.1109
*R*1, *wR*2 (all data)	0.0165, 0.0378	0.0516, 0.1165	0.1638, 0.3402	0.0476, 0.1144
resid. el. dens. [e Å^{-3}]	0.249/–0.709	0.182/–0.187	0.618/–0.732	0.411/–0.300

The variety of synthetic procedures shown in Schemes 1–4 now provides convenient access to differently substituted 3,5-dicarbonyl pyrazoles, which should prove valuable synthons for subsequent transformations.

The solid-state structures of N-unsubstituted pyrazoles have received considerable attention over the last years, in particular their hydrogen-bonded supramolecular arrangements[12,17] and their annular tautomerism.[18] At least five different structural motifs are known to exist, comprising of dimers, trimers, tetramers, hexamers, and catemers.[17] A relationship between the size of C-substituents attached to the heterocycle and the aggregation patterns has been proposed,[12] and neural networks as well as theoretical methods have been used in order to predict the secondary structures.[19,20] Since those previous studies have mostly focused on NH-pyrazoles with purely alkyl or aryl substituents, it appeared interesting to investigate the effect of functional groups that might act as hydrogen bond donor or acceptor, such as the appended carbonyl and hydroxyl groups of the present NH-pyrazole derivatives.

X-ray crystallographic studies were performed on crystalline compounds **2**, **5**, **6**·HBr and **8**, and the results are presented in Figures 2–6. Compound **8** that bears benzoyl groups in the 3- and 5-positions features the common S_4-symmetric tetrameric arrangement with intermolecular N–H···N hydrogen bonds, without any involvement of the side arm carbonyl groups. Compounds **2** and **5** both have methyl ester groups but differ in their C4 substituents, which is iodine in **2** versus a phenyl group in **5**. Molecular structures of **2** and **5** emphasizing the H-bonding patterns are provided in Figures 4 and 5. In both cases infinite zigzag chains of pyrazole ester molecules are formed via intermolecular N–H···N linkages. Further interactions with the ester oxygen atoms can be taken into account, but these are clearly weaker in **2** [d(N1···O4′) = 3.200(2) Å] than in **5** [d(N1···O4′) = 3.084(2) Å]. Interestingly, a stronger involvement of the side arm acceptor induces a significant lengthening of the N1···N2′ distances [2.890(2) Å in **2** versus 3.120(2) Å in **5**]. The crystallographic analysis of **6**·HBr confirms the identity of the dialcohol (Figure 6). However, due to twinning and disorder the quality of the structure determination is rather low, which precludes a detailed discussion of metric parameters.

In summary, we have developed or improved a variety of straightforward synthetic procedures that make available pyrazole derivatives with carbonyl or ester functions in the 3- and 5-positions and different backbone substituents. These compounds will serve as valuable starting materials for new pyrazole-based ligands, receptors, etc. Solid-state structures of some of the functionalized pyrazoles reveal a subtle interplay between intra- and intermolecular H-bonding in their supramolecular arrangements.

Melting points/decomposition temperatures were determined with an OptiMelt system (Stanford Research Systems, Inc.) using open capillaries; values are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500, a Bruker Avance 300, or a Bruker 200 spectrometer. ^{13}C resonances were obtained with broad-band proton decoupling, spectra were recorded at 298 K. ^{1}H NMR and ^{13}C NMR chemical shifts were referenced internally to solvent signals. Mass spectra were recorded using a Finnigan MAT 95 (EI) or Bruker APEX IV (HRMS, ESI). IR spectra from KBr peletts were recorded on a Digilab Excalibur Series FTS 3000 spectrometer. Elemental analyses were performed by the analytical laboratory of the Institut of Inorganic Chemistry, University of Göttingen using a Heraeus CHN-O-RAPID instrument or an Elementar vario EL III instrument. All reagents were purchased from commercial sources and employed without further treatment. 1*H*-Pyrazole-3,5-dicarboxylic acid dimethyl ester **C**,[11] pyrazole-3,5-dicarboxylic acid monopotassium salt **D**,[11] methyl diazoacetate **G**,[21] diazoacetylacetone,[22] and 2-diazo-1,3-diphenylpropane-1,3-dione[22] were prepared according to literature methods.

3,5-Diacetyl-1*H*-pyrazole (1)

To a –78 °C cold suspension of the monopotassium salt of pyrazole-3,5-dicarboxylic acid (1.0 g, 5.2 mmol) in THF (200 mL) was added dropwise MeLi in Et_2O (1.6 M, 16 mmol). After stirring for 1 h at –78 °C, the suspension was allowed to warm to r.t. and stirring was continued for 2 d. Unreacted MeLi was carefully hydrolyzed with H_2O. The resulting suspension was extracted with CH_2Cl_2 (2 × 100 mL), washed with aq Na_2CO_3 (2 × 50 mL), and dried ($MgSO_4$). The pure product was obtained as a white solid; yield: 0.40 g (60%); mp 146 °C.

IR (KBr): 3433, 3296, 3206, 3126, 3001, 2919, 1668, 1602, 1561, 1497, 1567, 1430, 1375,1306, 1261, 1236,1220, 1205, 1140, 1097, 1016, 999, 962, 946, 867, 796, 705, 661, 622, 531, 507, 483 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 6 H, CH_3), 7.29 (s, 1 H, CH^{pz4}), 11.42 (br, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.8 (CH_3), 108.9 (C^{pz4}), 147.5 (br, $C^{pz3/5}$), 191.3 (C=O).

MS (EI, 70 eV): m/z (%) = 152 (51, $[M]^+$), 137 (100, $[M – Me]^+$).

HRMS-(ESI–): m/z calcd for $C_7H_7N_2O_2$ $[M – H]^–$: 151.05130; found: 151.05129.

4-Iodo-1*H*-pyrazole-3,5-dicarboxylic Acid Dimethyl Ester (2)

A solution of the hydrochloride salt of 1*H*-pyrazole-3,5-dicarboxylic acid dimethyl ester (3.7 g, 17 mmol), I_2 (5.5 g, 22 mmol), and $(NH_4)_2Ce(NO_3)_6$ (10.0 g, 19 mmol) in MeCN (500 mL) was heated to reflux for 3 d. After evaporation of the solvent and addition of EtOAc (300 mL), the excess of I_2 was destroyed by adding a 5% aq $Na_2S_2O_3$ solution. The mixture was washed with brine (50 mL), dried ($MgSO_4$), and the solvent evaporated. The crude product was finally recrystallized from $CHCl_3$ to give pure **2**; yield: 5.0 g (95%); white solid; mp 157 °C.

IR (KBr): 3444, 3196, 3050, 2958, 2009, 1951, 1878, 1739, 1533, 1467, 1420, 1376, 1283, 1246, 1201, 1173, 1060, 1019, 940, 816, 776, 633, 569, 506 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.97 (s, 6 H, CH_3), 8.48 (br, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.6 (CH_3), 65.3 (C^{pz4}), 141.1 ($C^{pz3/5}$), 159.8 (C=O).

MS (EI, 70 eV): m/z (%) = 310 (100, $[M]^+$), 279 (67, $[M – OMe]^+$),

Anal. Calcd for $C_7H_7IN_2O_4$: C, 27.10; H, 2.28; N, 9.04. Found: C, 27.38; H, 2.46; N, 8.88.

3,5-Diacetyl-4-methyl-1*H*-pyrazole (3)

A solution of diazoacetylacetone (25 g, 0.20 mol) in MeOH (100 mL) was added to a solution of acetylacetone (20 g, 0.20 mol) and K_2CO_3 (55 g, 0.40 mol) in MeOH (100 mL) at r.t. The mixture was stirred for 2 h, and H_2O (200 mL) was then added. After removal of MeOH under reduced pressure, the pH was adjusted to 2 by the slow addition of aq 12 M HCl. The resulting solid was separated by filtration and recrystallized from CH_2Cl_2; yield: 28 g (85%); white solid; mp 113 °C.

IR (KBr): 3293, 3013, 2925, 1690, 1648, 1570, 1544, 1484, 1434, 1411, 1395, 1354, 1303, 1243, 1206, 1188, 1057, 1014, 980, 936, 803, 687, 561, 545, 486 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.59 (s, 6 H, O=CCH_3), 2.62 (s, 3 H, CH_3^{pz4}).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.3 (CH_3^{pz4}), 28.4 (O=C*C*H_3), 121.8 (C^{pz4}), 156.0 ($C^{pz3,5}$), 195.1 (O=*C*CH_3).

MS (EI, 70 eV): m/z (%) = 166 (100, $[M]^+$), 151 (95, $[M – Me]^+$).

Anal. Calcd for $C_{32}H_{16}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.75; H, 6.00; N, 16.78.

4-Phenyl-4,5-Dihydro-1*H*-pyrazole-3,5-dicarboxylic Acid Dimethyl Ester (4)

A mixture of diazoacetic acid methyl ester (6.0 g, 0.06 mol) and methyl cinnamate (9.7 g, 0.06 mol) was kept between 60 and 90 °C for 18 h (heating rate 5 °C per 30 min). The crude product was recrystallized from Et_2O at –30 °C; yield: 10.9 g (70%); white solid; mp 106 °C.

IR (KBr): 3446, 3308, 3066, 3028, 3004, 2954, 2846, 2089, 2020, 1955, 1732, 1694, 1601, 1532, 1494, 1445, 1416, 1349, 1258, 1204, 1153, 1114, 1047, 1013, 973, 908, 893, 870, 827, 793, 773, 750, 700, 621, 611, 525, 492, 474 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, CH_3), 3.81 (s, 3 H, CH_3), 4.31 (d, *J* = 3.8 Hz, 1 H, CH), 4.65 (d, *J* = 3.8 Hz, 1 H, CH), 7.19–7.32 (m, 5 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.2 (OCH_3), 53.0 (OCH_3), 53.4 (CH), 69.9 (CH), 127.1 (CH, Ar-*p*), 127.9 (CH, Ar-*o*), 129.1 (CH, Ar-*m*), 138.8 (C, Ar-*i*), 145.2 (N=C), 161.8 (=C*C*=O), 171.4 (HC*C*=O).

MS (EI, 70 eV): *m*/*z* (%) = 262 (18, $[M]^+$), 231 (7, $[M - OMe]^+$), 203 (100, $[M - MeOC=O]^+$), 171 (83, $[M - MeOC=O, –MeO]^+$), 159 (30, $[M - MeOC=O, –MeOC]^+$), 144 (11, $[M - 2MeOC=O]^+$).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.26; H, 5.47; N, 10.49.

4-Phenyl-1*H*-pyrazole-3,5-dicarboxylic Acid Dimethyl Ester (5)

Br_2 (14.7 g, 0.092 mol) was added dropwise to a cooled solution of 4-phenyl-4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylic acid dimethyl ester (22.0 g, 0.084 mol) in $CHCl_3$ (250 mL). After stirring for 2 d, the solution was washed with aq $Na_2S_2O_3$ to eliminate the excess of Br_2. Extraction with $CHCl_3$ (2 × 200 mL), drying (Na_2SO_4), and evaporation of the solvent leads to the pure product; yield: 20.3 g (93%); white solid; mp 130 °C.

IR (KBr): 3447, 3264, 3065, 3008, 2957, 1964, 1894, 1746,1729, 1582, 1561, 1508, 1459, 1441, 1416, 1381, 1280, 1226, 1195, 1172, 1144, 1077, 1019, 1009, 942, 821, 801, 781, 766, 749, 699, 684, 646, 611, 509, 476 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.82 (s, 6 H, CH_3), 7.32–7.43 (m, 5 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.2 (OCH_3), 127.5 (CH, Ar-*p*), 128.0 (CH, Ar-*o*), 130.2 (CH, Ar-*m*), 130.3 (C, Ar-*i*), 138.0 (br, $C^{pz3/5}$), 160.9 (C=O), C^{pz4} was not observed.

MS (EI, 70 eV): *m*/*z* (%) = 260 (100, $[M]^+$), 229 (27, [M – OMe]).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.98; H, 4.65; N, 10.77. Found: C, 59.85; H, 4.67; N, 10.75.

3,5-Bis(hydroxymethyl)-4-phenyl-1*H*-pyrazole (6)

To a suspension of $LiAlH_4$ (2.6 g, 69 mmol) in Et_2O (250 mL) was added dropwise a solution of **5** (3.4 g, 13 mmol) in THF (50 mL) at –78 °C. After stirring at –78 °C for 2 h, the suspension was allowed to warm to 0 °C and was carefully hydrolyzed with H_2O. The solvent was evaporated under reduced pressure and the residual solid dissolved in MeOH (250 mL). Carbon monoxide was bubbled through the suspension for 10 min, the mixture stirred overnight and then filtered. The pure product was obtained after recrystallization from MeOH; yield: 2.4 g (70%); white solid; mp 197 °C.

IR (KBr): 3435, 2954, 2924, 2854, 2360, 2341, 1636, 1520, 1454, 1383, 1235, 1212, 1175, 1081, 1056, 1006, 922, 811, 783, 758, 704, 679, 557, 494 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 4.42 (s, 4 H, CH_2), 4.81–5.38 (br, 2 H, OH), 7.38–7.55 (m, 5 H, ArH), 12.74 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 53.6 (br, CH_2), 55.6 (br, CH_2), 117.6 (C^{pz4}), 125.9 (CH, Ar-*p*), 128.3 (CH, Ar-*o*), 128.9 (CH, Ar-*m*), 133.4 (C, Ar-*i*), 140.0 (br, $C^{pz3/5}$), 149.0 (br, $C^{pz5/3}$).

MS (EI, 70 eV): *m*/*z* (%) = 204 (100, $[M]^+$), 169 (18, $M - CH_2OH]^+$).

Anal. Calcd for $(C_{11}H_{12}N_2O_2)_2$·HBr: C, 54.00; H, 5.15; N, 11.45. Found: C, 54.17; H, 5.72; N, 11.48.

4-Phenyl-1*H*-pyrazole-3,5-dicarbaldehyde (7)

A suspension of **6** (2.5 g, 17 mmol) and MnO_2 (4.8 g, 170 mmol) in 1,2-dimethoxyethane (500 mL) was heated to reflux for 4 h. After hot filtration over Celite, washing with hot MeOH (100 mL), and evaporation of the solvent, the crude product was recrystallized from light petroleum (bp 40–60 °C); yield: 1.9 g (57%); light brown solid; mp 60 °C.

IR (KBr): 3384, 3245, 3059, 2954, 2856, 2360, 2340, 1699, 1609, 1493, 1436, 1398, 1289, 1204, 1158, 1067, 1016, 930, 868, 770, 698, 537 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.38–7.61 (m, 5 H, ArH), 9.82 (s, 2 H, O=CH), 14.99 (br, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 124.2 (C^{pz4}), 128.0 (CH, Ar-*p*), 128.2 (CH, Ar-*o*), 130.4 (CH, Ar-*m*), 136.2 (C, Ar-*i*), 143.3 ($C^{pz3/5}$), 183.8 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 200 (100, $[M]^+$).

HRMS (ESI–): *m*/*z* calcd for $C_{11}H_9N_2O_2$ $[M + H]^+$: 201.06584; found: 201.06585.

3,5-Dibenzoyl-4-phenyl-1*H*-pyrazole (8)

To a solution of 1,3-diphenylpropane-1,3-dione (3.2 g, 14 mmol) in MeOH (200 mL) were added 2-diazo-1,3-diphenylpropane-1,3-dione (4.7 g, 19 mmol) and K_2CO_3 (3.9 g, 28 mmol). After stirring for 2 d at r.t. were added H_2O (50 mL) and HCl (10 mL). The organic phase was extracted with Et_2O (2 × 150 mL), and the combined Et_2O phases were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by chromatography on silica gel (hexane–EtOAc, 7:1, DC 3:1) and recrystallized from acetone; yield: 1.3 g (26%); white solid; mp 154 °C.

IR (KBr): 3264, 3201, 3056, 1958, 1811, 1729, 1669, 1648, 1598, 1578, 1500, 1449, 1418, 1375, 1310, 1284, 1226, 1177, 1075, 1048, 1024, 1015, 1001, 911, 799, 769, 740, 691, 568, 524 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.01–7.81 (m, 15 H, ArH), 9.98 (br, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 127.3 (C^{pz4}), 127.4 (CH, Ar), 127.6 (CH, Ar), 127.9 (CH, Ar), 130.0 (CH, Ar), 130.3 (C, Ar), 130.5 (CH, Ar), 132.9 (CH, Ar), 136.4 (C, Ar), 143.6 ($C^{pz3/5}$), 188.0 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 352 (100, $[M]^+$).

Anal. Calcd for $C_{32}H_{16}N_2O_2$: C, 78.38; H, 4.58; N, 7.95. Found: C, 78.06; H, 4.56; N, 8.03.

5-Acetyl-4-methyl-1*H*-pyrazole-3-carboxylic Acid (9)

To a solution of ethyl acetoacetate (23.4 g, 0.18 mol) in MeOH (200 mL) were added diazoacetylacetone (22.8 g,0.18 mol) and K_2CO_3 (46.7 g, 0.36 mol). After stirring for 2 h at r.t., the solvent was partially evaporated (to a volume of ca. 200 mL) and H_2O (250 mL) was added. The precipitate was dissolved in EtOH (150 mL) and H_2O (250 mL) was added. The pH was first adjusted to 11 by the addition of aq KOH and then adjusted to 2 by the addition of aq 5 M HCl. The resulting pure product was collected by filtration and washed with H_2O (50 mL); yield: 12.4 g (41%); mp 115 °C.

IR (KBr): 3721, 3290, 3012, 1666, 1650, 1392, 1225, 1188, 936, 787, 671 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 2.55 (s, 6 H, CH_3), 14.15 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.6 (CH_3^{pz4}), 28.0 ($CH_3C=O$), 120.4 (C^{pz4}), 148.7 ($C^{pz3/5}$), 175.8 (COOH), 190.5 (O=*C*CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 167 (100, $[M - H]^+$).

Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; N, 16.66; H, 4.80. Found: C, 50.11; N, 16.56; H, 4.89.

5-Acetyl-4-phenyl-1*H*-pyrazole-3-yl-phenylmethanone (10)
To a solution of 1,3-diphenylpropane-1,3-dione (2.8 g, 13 mmol) in MeOH (20 mL) were added a solution of diazoacetylacetone (1.6 g, 13 mmol) in MeOH (20mL) and solid K_2CO_3 (2.5 g, 18 mmol). After stirring for 28 h at r.t., the solvent was partially evaporated (to a volume of ca. 20 mL) and H_2O (40 mL) was added. The pH was adjusted to 5 by the addition of aq 5 M HCl. The aqueous phase was extracted with Et_2O (2 × 25 mL), dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (CH_2Cl_2–*i*-PrOH, 95:5, R_f = 0.30) and ($CHCl_3$–EtOAc, 98:2, R_f = 0.41); yield: 1.3 g (20%); light brown solid; mp 130 °C.

IR (KBr): 3205, 1958, 1913, 1817, 1773, 1682, 1659, 1595, 1578, 1549, 1506, 1468, 1448, 1428, 1382, 1352, 1308, 1284, 1213, 1175, 1166, 1142, 1075, 1045, 1031, 1020, 1000, 957, 907, 809, 797, 772, 750, 706, 692, 663, 606, 562, 491, 414 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 7.29–7.89 (m, 10 H, ArH), 9.52 (br, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.7 (CH_3), 127.3 (C^{pz4}), 128.3 (CH-Ar), 128.4 (CH-Ar), 128.5 (CH-Ar), 130.4 (CH-Ar), 130.5 (CH-Ar), 131.1 (CH-Ar), 133.3 (C-Ar), 136.8 (C-Ar), 142.4 ($C^{pz3/5}$), 188.0 (Ph*C*=O), 191.4 (CH_3*C*=O).

MS (EI, 70 eV): *m*/*z* (%) = 290 (100, $[M]^+$), 275 (17, $[M – Me]^+$).

Anal. Calcd for $C_{32}H_{16}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.64; H, 5.13; N, 9.49.

X-ray Crystal Structure Determination
X-ray data were collected on a STOE IPDS II diffractometer (graphite monochromated Mo-Kα radiation, λ = 0.71073 Å) by use of ω scans at r.t. (**5**, **6**) or at –140 °C (**2**, **8**) (Table 2). The structures were solved by direct methods and refined on F^2 using all reflections with SHELX-97.[23a,b] The nonhydrogen atoms were refined anisotropically, except those in disordered parts. Most hydrogen atoms were placed in calculated positions and assigned to an isotropic displacement parameter of 0.08 $Å^2$. Crystals of **6** are nonmerohedrally twinned (ratio of the two twin components approximately 60:40, twinlaw –1, 0, 0/0, –1, 0/–1.07, 0.74, 1) and the reflection data for refinement were prepared using the program X-AREA.[23c] One side-arm in **6** was found to be disordered about two positions [occupancy factors 0.54(2)/0.46(2)] and was refined by using DFIX ($d_{C–O}$ = 1.41 Å) restraints. Furthermore, H_2O and MeOH (DFIX restraint, $d_{C–O}$ = 1.41 Å) solvent molecules are disordered about a center of inversion and were refined with a fixed occupancy factor of 0.5. In **6a** an acetone molecule is disordered about a two-fold rotation axis and was refined a fixed occupancy factor of 0.5. DFIX ($d_{C–C}$ = 1.51 Å, $d_{C=O}$ = 1.21 Å), SADI ($d_{C···O}$) and FLAT restraints were used to model the disorder. The positional and isotropic displacement parameters of the nitrogen-bound hydrogen atoms in **5**, **2**, and **8** were refined without any restraints or constraints. Face-indexed absorption corrections for **2** and **6** were performed numerically with the program X-RED.[23d,24]

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(24) CCDC-664760 (**2**), CCDC-664761 (**5**), CCDC-664762 (**6**), and CCDC-664763 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at 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.ac.uk].