Synthesis of Substituted 3-Phenyl-6*H*-pyrazolo[4,3-d]isoxazoles from Corresponding 4-Benzoyl-5-hydroxypyrazoles

Wolfgang Holzer* and Katharina Hahn

Department of Pharmaceutical Chemistry, University of Vienna, Pharmaziezentrum, Althanstrasse 14, A-1090 Vienna, Austria

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Treatment of 1,(3)-(di)substituted 4-benzoyl-5-hydroxypyrazoles with phosphorus oxychloride affords the corresponding 4-benzoyl-5-chloropyrazoles. Reaction of the latter with hydroxylamine leads to oximes, which can be cyclized to novel 3-phenyl-6*H*-pyrazolo[4,3-*d*]isoxazoles by treatment with sodium hydride in dimethyl formamide. Detailed nmr spectroscopic studies (^{1}H, ^{13}C) with all obtained compounds are presented.

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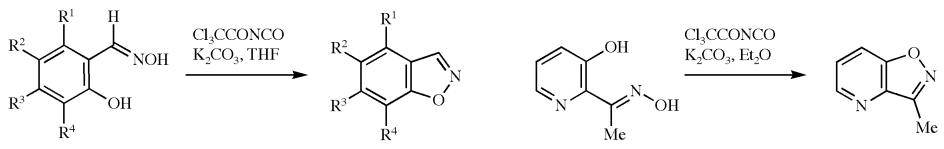
As some 1,2-benzisoxazole derivatives show interesting pharmacological activities - the anticonvulsant and antiepileptic drug Zonisamide may serve as an example [1] - also some attention has been addressed to hetero-annulated isoxazoles. However, only a few publications are dealing with the synthesis of 6*H*-pyrazolo[4,3-*d*]isoxazoles and a considerably small number of representatives containing this core has been hitherto obtained. For the synthesis of such systems one approach is based on pyrazole ring closure *via* reaction of 4-benzoyl-3-methyl-5-hydroxyisoxazole (or the corresponding 5-chloro derivative) with hydrazine or phenylhydrazine [2], the other consists in construction of the isoxazole ring starting from appropriately substituted pyrazole derivatives. Thus, it is claimed that a one-pot reaction of 5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde (or its 1-phenyl derivative, **5e** in Scheme 4) and hydroxylamine smoothly leads to 4-methyl-6*H*-pyrazolo[4,3-*d*]isoxazole or 4-methyl-6-phenyl-6*H*-pyrazolo[4,3-*d*]isoxazole (**3e** in Scheme 4), respectively [3-5]. However, these reports seem rather mystic as neither experimental procedure nor spectroscopic data of the reaction products are provided [3-5]. Moreover, there is a considerable discrepancy concerning the reported melting point for reaction product **3e** (lit [5] mp 95°, lit [3] mp 131°), the latter value being similar to that given for 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime (**6e** in Scheme 4) which has a mp of 134-136° [6] or 140-141° [7]. When we repeated one of the mentioned reactions under the insinuated conditions, *i.e.* treatment of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**5e**) with hydroxylamine hydrochloride and catalytic amounts of a base (sodium hydroxide or piperidine) [5] in refluxing ethanol, we always obtained the corresponding oxime **6e**, but we could never observe cyclization into the bicyclic system **3e** (Scheme 4). Another respresentative, namely 3,4-dimethyl-6-phenyl-6*H*-pyrazolo[4,3-*d*]isoxazole has been mentioned in the literature; again, neither a synthesis nor any data are given [8]. To sum up, it is questionable if all these supposed pyrazolo[4,3-*d*]isoxazoles really have been in the hands of the authors.

Thus, to overcome the lack of data regarding 6*H*-pyrazolo[4,3-*d*]isoxazoles and in continuation to our previous studies concerning the tautomerism, the synthetic and biological potential of pyrazolones (5-hydroxypyrazoles) [9-14] we here report a synthetic route to the title compounds starting from 1-substituted 4-benzoyl-5-hydroxypyrazoles.

Synthesis.

For the synthesis of 1,2-benzisoxazoles one of the most important methods consists in the dehydrating cyclization of oximes derived from salicylaldehydes or alkyl (aryl) 2-hydroxyphenyl ketones [15]. For this purpose, amongst conditions such as, for instance, heating the educts with potassium hydroxide or sodium acetate in ethanol, treatment with polyphosphoric acid, thionyl chloride/pyridine or acetic anhydride/sulfuric acid [15] also the mild and effective reaction system trichloroacetyl isocyanate/potassium carbonate in dry tetrahydrofuran has been successfully applied, for instance for the cyclization of salicylaldehyde oximes (Scheme 1) [16]. Similarly, 3-methylisoxazolo[4,5-*b*]pyridine was conveniently prepared applying this reaction system (Scheme 1) [17].

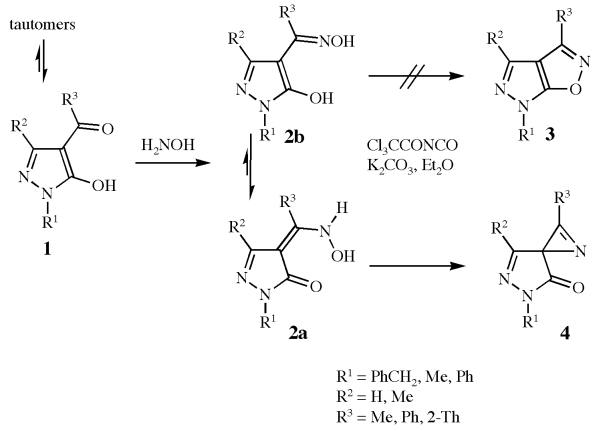
Scheme 1



However, attempted application of a similar synthetic concept for the synthesis of 6*H*-pyrazolo[4,3-*d*]isoxazoles (**3**), namely starting from 4-acetyl or 4-aroyl-5-hydroxypyrazoles

(**1**) failed: Whereas under most of the above mentioned 'standard' conditions the corresponding oximes **2** did not react, upon treatment with trichloroacetyl isocyanate/potassium carbonate the educts were completely consumed. Nevertheless, cyclization to bicyclic compounds **3** did not occur. Instead, the formation of spiro compounds **4** was observed (Scheme 2) [18]. This particular reaction behaviour can be explained by the exclusive presence of 'oximes' **2** in an enaminopyrazolone form (**2a**), which was unambiguously confirmed by detailed NMR-spectroscopic investigations as well as by X-ray structure analyses with compounds **2** and their methylation products [19]. The complete absence of the hydroxypyrazole form **2b** obviously prevents cyclization to 6*H*-pyrazolo[4,3-*d*]isoxazoles **3**.

Scheme 2



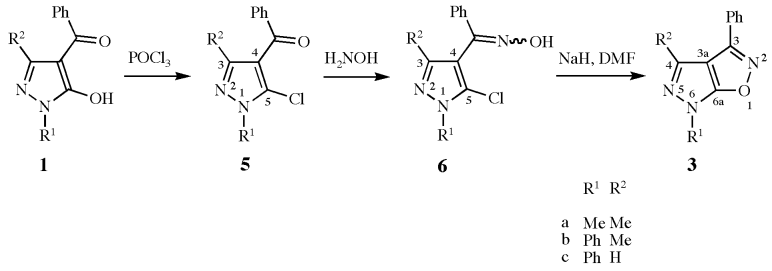
To overcome the above mentioned problems of unwanted tautomerism the 5-hydroxypyrazoles (tautomer to pyrazolones) **1** (R^3 = Ph) were heated with phosphorus oxychloride to smoothly afford the corresponding 4-benzoyl-5-chloropyrazoles **5** (Scheme 3) [20].

Treatment of ketones **5** with hydroxylamine hydrochloride in ethanol/pyridine in the following gave the oximes **6**. Compounds **6a** and **6b** were obtained as (*E*)/(*Z*)-mixtures with the (*Z*)-isomer predominating, **6c** was isolated as a single isomer to which according to ^{1}H and ^{13}C nmr experiments (*E*)-configuration was assigned (see below). Finally, treatment of oximes **6a-c** with sodium hydride in dimethyl formamide led to the target compounds **3a-c** in high yields. Whereas cyclization of **6b** and **6c** proceeded at ambient temperature, with **6a** heating to 60° was required. In contrast, under such reaction conditions cyclization of the aldehyde-derived oxime **6d** into the corresponding bicyclic compound **3d** failed, only unreacted starting material was isolated from the reaction mixture (Scheme 4). Likewise, heating of aldoxime **6e** in ethanol/NaOH or in pyridine did not afford the corresponding ring closure product **3e**. A possible explanation for the failure of ring closure with **6d** and **6e** is the exclusive presence of these oximes in the 'wrong' (*E*)-configuration being not suitable for isoxazole ring formation (see NMR-spectroscopic investigations and Figure 1). It is well known that the configuration of the starting oximes plays a crucial role in such cyclization reactions [15,21,22]. Obviously, under the applied reaction conditions with **6d** and **6e** isomerisation to the corresponding (*Z*)-isomers does not occur, with only the latter species being anticipated to be suitable for cyclization into condensed systems **3**.

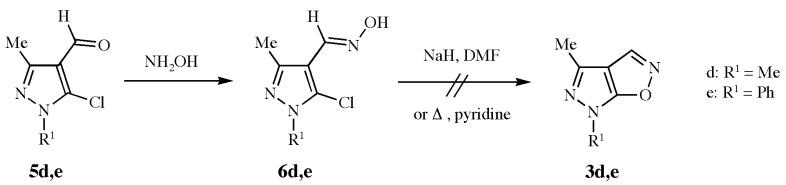
NMR-Spectroscopic Investigations.

Unambiguous assignment for all proton and carbon resonances was achieved on basis of NOE-difference [23] and 1D-TOCSY [24] experiments, fully ^{1}H-coupled ^{13}C nmr spectra, APT [25], HMQC [26], 1D-HETCOR [27] and long-range INEPT spectra with selective excitation [28,29].

Scheme 3



Scheme 4



Discrimination between (*Z*)- and (*E*)-forms of oximes **6a** and **6b** was carried out by comparison of the ^{13}C nmr chemical shifts of both isomers considering γ-effects. Carbon atoms in γ-position (α to C=N) to a *syn* located oxime oxygen atom suffer an upfield shift compared to the γ-C-atoms in the *anti*-position due to steric compression [30,31]. Thus, the signal of pyrazole C-4 in (*Z*)-**6b** (δ 111.6 ppm, *syn*-position to the oxime O-atom) is shifted 3.6 ppm upfield compared to the corresponding pyrazole C-4 resonance in (*E*)-**6b** (δ 115.2 ppm). Reversely, the signal of C-phenyl C-1 in (*Z*)-**6b** (δ 134.9 ppm) is shifted to higher frequencies compared to that in (*E*)-**6b** (δ 132.1 ppm) (Figure 1). Oxime **6c**, present as a single isomer in deuteriochloroform solution, was assigned to have (*E*)-configuration by comparison with the closely related pair (*Z/E*)-**6b**. The stereochemistry in aldoximes **6d** and **6e**, which were obtained as single isomers, was unequivocally determined by NOE-difference experiments which revealed spatial closeness of N=CH and NOH proton and thus (*E*)-configuration [32]. This assignment is confirmed by the magnitude of the one-bond $^{13}C,^{1}H$ coupling constant of the N=CH moiety in **6d** (^{1}J = 162.9 Hz) and **6e** (^{1}J = 165.0 Hz), which is known to be strongly dependent from the orientation of the nitrogens' lone-pair [33]. Thus, (*Z*)-configuration should lead to a considerably larger coupling constant in the range of 177 Hz [33].

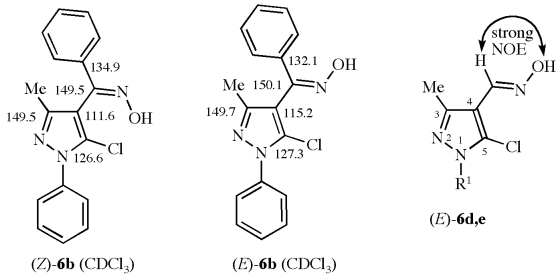


Figure 1

Figure 1. Discrimination between (*Z*)-**6b** and (*E*)-**6b** *via* γ-effects regarding ^{13}C nmr chemical shifts (in deuteriochloroform); determination of (*E*)-configuration in **6d** and **6e** *via* a strong NOE between N=CH and N-OH.

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV), infrared spectra on a Perkin-Elmer FTIR 1605 spectrophotometer. The nmr spectra were obtained on a Varian UnityPlus 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28°. The centre of the solvent signal was used as an internal standard which was related to tetramethylsilane with δ 7.26 ppm (^{1}H in deuteriochloroform), δ 2.49 ppm (^{1}H in deuteriodimethyl sulfoxide), δ 77.0 ppm (^{13}C in deuteriochloroform), δ 39.5 ppm (^{13}C in deuteriodimethyl sulfoxide). Compounds **1b** ((3-methyl-5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone = 4-benzoyl-3-methyl-1-phenyl-5-pyrazolinone), **5d** (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-carbaldehyde) and **5e** (5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-carbaldehyde) are commercially available.

(5-Chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)phenylmethanone (**5a**).

A mixture of (1,3-dimethyl-5-hydroxy-1*H*-pyrazol-4-yl)-phenylmethanone (**1a**) [34] (2.162 g, 10 mmoles) and phosphorus oxychloride (3.067 g, 20 mmoles) was heated to reflux for 2 hours. Then the mixture was poured onto ice-water (50 ml) and neutralized with 40% aqueous sodium hydroxide. After extraction with ether (3×20 ml) the combined organic phases were washed with water, dried (sodium sulfate) and evaporated under reduced pressure to afford 2.018 g (86%) of an orange oil which solidified on standing, lit. [35] mp 49-52°; ^{1}H nmr (deuteriochloroform): δ 7.72 (m, 2H, Ph H-2,6), 7.55 (m, 1H, Ph H-4), 7.44 (m, 2H, Ph H-3,5), 3.83 (s, 3H, N-Me), 2.28 (s, 3H, 3-Me); ^{13}C nmr (deuteriochloroform): δ 190.0 (C=O), 150.2 (pyrazole C-3, ^{2}J(C-3,3-Me) = 6.9 Hz), 138.4 (Ph C-1), 132.6 (Ph C-4), 129.9 (pyrazole C-5), 129.2 (Ph C-2,6), 128.3 (Ph C-3,5), 116.8 (pyrazole C-4, ^{3}J(C4,3-Me) = 2.8 Hz), 36.1 (N-Me, ^{1}J = 141.6 Hz), 13.9 (3-Me, ^{1}J = 129.0 Hz).

(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)phenyl-methanone (**5b**).

Compound **5b** was prepared similiarly as described for the synthesis of **5a** starting from (3-methyl-5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (**1b**) (2.783 g, 10 mmoles) and phosphorus oxychloride (3.067 g, 20 mmoles). The obtained raw product (2.929 g) was recrystallized from ethanol-water to afford 1.751 g (59%) of colorless needles , mp 87° (lit [36] mp 88°); ^{1}H nmr (deuteriochloroform): δ 7.83 (m, 2H, C-Ph H-2,6), 7.59 (m, 1H, C-Ph H-4), 7.56 (m, 2H, N-Ph H-2,6), 7.49 (m, 4H, C-Ph H-3,5 and N-Ph H-3,5), 7.44 (m, 1H, N-Ph H-4), 2.37 (s, 3H, 3-Me); ^{13}C nmr (deuteriochloroform): δ 190.2 (C=O), 151.3 (pyrazole C-3, ^{2}J(C-3, 3-Me) = 6.9 Hz), 138.2 (C-Ph C-1), 137.5 (N-Ph C-1), 132.8 (C-Ph C-4), 129.4 (C-Ph C-2,6), 129.2 (pyrazole C-5), 129.1 (N-Ph C-3,5), 128.8 (N-Ph C-4), 128.4 (C-Ph C-3,5), 125.4 (N-Ph C-2,6), 118.3 (pyrazole C-4, ^{3}J(C-4,3-Me) = 2.8 Hz), 14.0 (3-Me, ^{1}J = 129.0 Hz).

(5-Chloro-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (**5c**).

A mixture of (5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)phenyl-methanone (**1c**) [37] (2.643 g, 10 mmoles) and phosphorus oxychloride (3.067 g, 20 mmoles) was heated to reflux for 2 hours. Then the mixture was poured onto ice-water (50 ml) and neutralized with 40% aqueous sodium hydroxide. The aquous phase was exhaustively extracted with ether and then with dichloromethane. The combined etheral and dichloromethane phases were separately washed with water, dried (sodium sulfate) and evaporated. The combined residues were recrystallized from ethanol to afford 1.583 g (56%) of colorless crystals, mp 110°; ir (potassium bromide): 1648 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.99 (s, 1H, pyrazole H-3), 7.89 (m, 2H, C-Ph H-2,6), 7.61 (m, 1H, C-Ph H-4), 7.59 (m, 2H, N-Ph H-2,6), 7.54 (m, 2H, N-Ph H-3,5), 7.52 (m, 2H, C-Ph H-3,5), 7.49 (m, 1H, N-Ph H-4); ^{13}C nmr (deuteriochloroform): δ 188.0 (C=O), 142.9 (pyrazole C-3, ^{1}J = 191.9 Hz), 138.3 (C-Ph C-1), 137.4 (N-Ph C-1), 132.7 (C-Ph C-4), 131.1 (pyrazole

C-5), 129.24 (N-Ph C-4), 129.2 (N-Ph C-3,5 and C-Ph C-2,6), 128.5 (C-Ph C-3,5), 125.5 (N-Ph C-2,6), 118.9 (pyrazole C-4, ^{2}J(C-4,H-3) = 9.9 Hz); ms: m/z (%) 284 (13), 283 (M^+, 6), 282 (32), 207 (29), 205 (100), 105 (17), 89 (10), 77 (87), 51 (40).

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.89; H, 3.91; N, 9.81.

(*E*/*Z*)-(5-Chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)phenylmethanone Oxime (**6a**).

A mixture of (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)phenylmethanone (**5a**) (2.347 g, 10 mmoles), hydroxylamine hydrochloride (2.780 g, 40 mmoles), pyridine (2.4 ml) and ethanol (17 ml) was heated to reflux for 5 hours. Then the mixture was poured onto water (110 ml), the precipitated solid was collected by filtration, washed several times with water and dried to afford 2.222 g (89%) of colorless crystals (ratio *Z*/*E* ~ 3.7:1 according to ^{1}H nmr). An analytical sample was obtained upon recrystallization from ethanol, mp 188-190°; ir (potassium bromide): 3134, 2848 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): (*Z*)-isomer: δ 9.94 (s, 1H, NOH), 7.52 (m, 2H, Ph H-2,6), 7.37 (m, 2H, Ph H-3,5), 7.36 (m, 1H, Ph H-4), 3.87 (s, 3H, N-Me), 2.14 (s, 3H, 3-Me); (*E*)-isomer: δ 9.94 (s, 1H, NOH), 7.53 (m, 2H, Ph H-2,6), 7.41 (m, 3H, Ph H-3,4,5), 3.80 (s, 3H, N-Me), 2.05 (s, 3H, 3-Me); ^{13}C nmr (deuteriochloroform): (*Z*)-isomer: δ 149.6 (C=NOH), 148.0 (pyrazole C-3, ^{2}J(C-3,3-Me) = 6.8 Hz), 135.0 (Ph C-1), 129.5 (Ph C-4), 128.5 (Ph C-3,5), 127.2 (pyrazole C-5, ^{3}J(C5,NMe) = 2.8 Hz), 127.0 (Ph C-2,6), 109.5 (pyrazole C-4, ^{3}J(C4,3-Me) = 3.3 Hz), 36.1 (N-Me, ^{1}J = 141.1 Hz), 13.6 (3-Me, ^{1}J = 128.3 Hz); (*E*)-isomer: δ 150.1 (C=NOH), 148.1 (pyrazole C-3, ^{2}J(C-3,3-Me) = 6.8 Hz), 132.3 (Ph C-1), 129.4 (Ph C-2,6), 129.3 (Ph C-4), 128.1 (Ph C-3,5), 127.7 (pyrazole C-5, ^{3}J(C5,NMe) = 2.8 Hz), 113.4 (pyrazole C-4, ^{3}J(C4,3-Me) = 3.2 Hz), 36.0 (N-Me, ^{1}J = 141.2 Hz), 13.4 (3-Me, ^{1}J = 128.4 Hz); ms: m/z (%) 251 (14), 250 (M^+, 11), 249 (44), 232 (40), 214 (72), 156 (17), 154 (39), 142 (16), 136 (19), 132 (32), 130 (100), 129 (18), 95 (20), 77 (53), 51 (39).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.83. Found: C, 58.02; H, 4.72; N, 16.79.

(*E*/*Z*)-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone Oxime (**6b**).

A mixture of (5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (**5b**) (2.968 g, 10 mmoles), hydroxylamine hydrochloride (2.780 g, 40 mmoles), pyridine (2.4 ml) and ethanol (20 ml) was heated to reflux for 4 hours and was then stirred at room temperature overnight. The mixture was poured onto water (150 ml) and was then extracted with dichloromethane (3×40 ml). The combined organic phases were washed several times with water (to remove traces of pyridine), dried (sodium sulfate) and evaporated under reduced pressure to afford 1.933 g (62%) of an almost colorless powder (ratio *Z*/*E* ~ 2:1 according to ^{1}H nmr). An analytical sample was obtained upon recrystallization from ethanol-water, mp 131°; ir (potassium bromide): 3218 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): (*Z*)-isomer: δ 9.73 (s, 1H, NOH), 7.62 (N-Ph H-2,6), 7.58 (m, 2H, C-Ph H-2,6), 7.52-7.38 (m, 6H, N-Ph H-3,4,5 and C-Ph H-3,4,5), 2.24 (s, 3H, 3-Me); (*E*)-isomer: δ 9.73 (s, 1H, NOH), 7.64-7.55 (m, 2H, N-Ph H-2,6), 7.60 (m, 2H, C-Ph H-2,6), 7.52-7.38 (m, 6H, N-Ph H-3,4,5 and C-Ph H-3,4,5), 2.16 (s, 3H, 3-Me); ^{13}C nmr (deuteriochloroform): (*Z*)-isomer: δ 149.5 (C=NOH), 149.5 (pyrazole C-3, ^{2}J(C-3,3-Me) = 6.9 Hz), 138.0 (N-Ph C-1), 134.9 (C-Ph C-1), 129.6 (C-Ph C-4), 128.9 (N-Ph C-3,5), 128.6 (C-Ph C-3,5), 128.2 (N-Ph C-4), 127.1 (C-Ph C-2,6), 126.6 (pyrazole C-5), 125.0 (N-Ph C-2,6), 111.6 (pyrazole C-4, ^{3}J(C4,3-Me) = 3.3 Hz), 13.7 (3-Me, ^{1}J = 128.6 Hz); (*E*)-isomer: δ 150.1 (C=NOH), 149.7 (pyrazole C-3, ^{2}J(C-3,3-Me) = 6.9 Hz), 137.9 (N-Ph C-1), 132.1 (C-Ph C-1), 129.4 (C-Ph C-2,6 and C-Ph C-4), 128.9 (N-Ph C-3,5), 128.3 (N-Ph C-4), 128.1 (C-Ph C-3,5), 127.3 (pyrazole C-5), 125.2 (N-Ph C-2,6), 115.2 (pyrazole C-4, ^{3}J(C4,3-Me) = 3.0 Hz), 13.5 (3-Me, ^{1}J = 128.6 Hz); ms: m/z (%) 313 (13), 312 (M^+,10), 311 (44), 294 (21), 276 (40), 216 (16), 204 (15), 198 (14), 194 (20), 192 (64), 157 (15), 104 (13), 102 (14), 91 (10), 77 (100), 51 (70), 50 (16).

Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.25; H, 4.47; N, 13.24.

(*E*)-(5-Chloro-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone Oxime (**6c**).

Compound **6c** was prepared from (5-chloro-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone (**5c**) (2.827 g, 10 mmoles) and hydroxylamine hydrochloride (2.780 g, 40 mmoles) similarly as described for the synthesis of **6b**. Recrystallization of the whole raw product from ethanol afforded 2.144 g (72%) of colorless needles, mp 170-172°; ir (potassium bromide): 3250, 3203 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform) [38]: (*E*)-isomer: δ 8.82 (s, 1H, NOH), 7.63 (s, 1H, pyrazole H-3), 7.57-7.44 (m, 10H, Ph-H); ^{13}C nmr (deuteriochloroform): (*E*)-isomer: δ 150.6 (C=NOH), 141.2 (pyrazole C-3, ^{1}J = 191.4 Hz), 137.9 (N-Ph C-1), 131.9 (C-Ph C-1), 129.4 (C-Ph C-4), 129.0 (N-Ph C-3,5 and C-Ph C-2,6), 128.7 (N-Ph C-4), 128.3 (C-Ph C-3,5), 126.4 (pyrazole C-5), 125.4 (N-Ph C-2,6), 116.5 (pyrazole C-4, ^{2}J(C4,H3) = 9.0 Hz); ms: m/z (%) 299 (17), 298 (M^+, 11), 297 (54), 180 (34), 178 (100), 102 (10), 77 (85), 51 (42).

Anal. Calcd. for $C_{16}H_{12}ClN_3O \cdot 0.2\ H_2O$: C, 63.77; H, 4.15; N, 13.94. Found: C, 63.63; H, 4.04; N, 13.77.

(*E*)-5-Chloro-1,3-dimethyl-1*H*-pyrazol-4-carbaldehyde Oxime (**6d**).

A mixture of 5-chloro-1,3-dimethyl-1*H*-pyrazol-4-carbaldehyde (**5d**) (317 mg, 2 mmoles) and hydroxylamine hydrochloride (167 mg, 2.4 mmoles) in methanol (3 ml) was slightly warmed until the solution became clear. After stirring at room temperature for 20 hours water (8 ml) was added and the mixture was left for additional 3 hours. The precipitated solid was collected by filtration, washed with water and dried to afford 330 mg (95%) of colorless needles, mp 163-165° (lit [39] mp 164-165°); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 11.06 (s, 1H. NOH), 7.89 (s, 1H, N=CH), 3.72 (s, 3H, N-Me), 2.24 (s, 3H, 3-Me); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 145.7 (pyrazole C-3, ^{2}J(C3,3-Me) = 7.0 Hz, ^{3}J(C3,N=CH) = 5.0 Hz), 140.0 (N=CH, ^{1}J = 162.9 Hz, ^{3}J(N=CH,OH) = 9.8 Hz), 125.9 (pyrazole C-5), 109.4 (pyrazole C-4, ^{2}J(C4,N=CH) = 6.5 Hz, ^{3}J(C4,3-Me) = 3.0 Hz), 35.8 (N-Me, ^{1}J = 141.4 Hz), 13.9 (3-Me, ^{1}J = 128.1 Hz); ms: m/z (%) 175/173 (M^+, 31/100), 158/156 (20/63), 138 (76), 121 (49), 120 (70), 93 (76), 76 (37), 66 (67), 52 (37).

Anal. Calcd. for $C_6H_8ClN_3O$: C, 41.51; H, 4.64; N, 24.20. Found: C, 41.47; H, 4.43; N, 23.98.

(*E*)-5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-carbaldehyde Oxime (**6e**).

A mixture of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-carbaldehyde (**5e**) (221 mg, 1 mmole) and hydroxylamine hydrochloride (114 mg, 1.64 mmoles) in ethanol (3 ml) was

slightly warmed until the solution became clear. After stirring at room temperature for 3 hours water (10 ml) and saturated sodium bicarbonate solution (5 ml) was added, the precipitated solid was collected by filtration, washed several times with water and dried to afford 220 mg (93%) of a colorless powder, mp 138-140° (lit [6] mp 134-136°, lit [7] mp 140-141°]); ^{1}H nmr (deuteriochloroform): δ 8.93 (s, 1H, NOH), 8.14 (s, 1H, N=CH), 7.58-7.36 (m, 5H, Ph-H), 2.47 (s, 3H, 3-Me); ^{13}C nmr (deuteriochloroform): δ 149.0 (pyrazole C-3, ^{2}J(C3,3-Me) = 6.9 Hz, ^{3}J(C3,N=CH) = 5.0 Hz), 142.3 (N=CH, ^{1}J = 165.0 Hz), 137.6 (Ph C-1), 129.1 (Ph C-3,5), 128.6 (Ph C-4), 127.6 (pyrazole C-5), 125.0 (Ph C-2,6), 111.2 (pyrazole C-4, ^{2}J(C4,N=CH) = 6.0 Hz, ^{3}J(C4,3-Me) = 2.9 Hz), 14.5 (3-Me, ^{1}J = 128.8 Hz).

Anal. Calcd. for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; N, 17.83. Found: C, 55.94; H, 4.51; N, 17.61.

4,6-Dimethyl-3-phenyl-6*H*-pyrazolo[4,3-*d*]isoxazole (**3a**).

To sodium hydride (80% suspension in mineral oil, 35 mg, 1.17 mmoles) in dry dimethyl formamide (3 ml) was added a solution of (5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)phenylmethanone oxime (**6a**) (250 mg, 1 mmol) in dry DMF (1 ml) *via* a syringe and the mixture was stirred for 1.5 hours at 60°. Then it was poured onto water (10 ml), the precipitated solid was collected by filtration, washed with water and dried to afford 188 mg (88%) of colorless crystals. An analytical sample was obtained upon recrystallization from ethanol, mp 100°; ^{1}H nmr (deuteriochloroform): δ 7.84 (m, 2H, Ph H-2,6), 7.48 (m, 3H, Ph H-3,4,5), 3.82 (s, 3H, N-Me), 2.46 (s, 3H, 4-Me); ^{13}C nmr (deuteriochloroform): δ 168.2 (C-6a), 155.9 (C-3, ^{3}J(C-3,Ph H-2,6) = 4.5 Hz), 137.8 (C-4, ^{2}J(C-4,4-Me) = 7.0 Hz), 130.5 (Ph C-4), 128.9 (Ph C-3,5), 128.2 (Ph C-1), 127.8 (Ph C-2,6), 108.6 (C-3a, ^{3}J(C-3a,4-Me) = 3.4 Hz), 34.8 (N-Me, ^{1}J = 140.9 Hz), 14.8 (4-Me, ^{1}J = 128.3 Hz); ms: m/z (%) 214 (26), 213 (M^+, 100), 212 (69), 149 (14), 142 (32), 105 (37), 77 (63), 70 (14), 67 (49), 51 (32).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.44; H, 5.03; N, 19.52.

3,6-Diphenyl-4-methyl-6*H*-pyrazolo[4,3-*d*]isoxazole (**3b**).

The synthesis of **3b** starting from 5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone oxime (**6b**) (312 mg, 1 mmol) was carried out similarly as described for the synthesis of **3a** except that the reaction was carried out at room temperature. After work-up 242 mg (88%) of colorless crystals were obtained. An analytical sample was obtained upon recrystallization from diisopropyl ether, mp 141-143°; ^{1}H nmr (deuteriochloroform): δ 7.90 (m, 2H, C-Ph H-2,6), 7.85 (m, 2H, N-Ph H-2,6), 7.53 (m, 1H, C-Ph H-4), 7.52 (m, 2H, C-Ph H-3,5), 7.50 (m, 2H, N-Ph H-3,5), 7.27 (m, 1H, N-Ph H-4), 2.59 (s, 3H, 4-Me); ^{13}C nmr (deuteriochloroform): δ 166.8 (C-6a), 155.7 (C-3, ^{3}J(C-3,Ph H-2,6) = 4.4 Hz), 139.5 (C-4, ^{2}J(C-4,4-Me) = 7.0 Hz), 137.3 (N-Ph C-1), 130.7 (C-Ph C-4), 129.5 (N-Ph C-3,5), 129.1 (C-Ph C-3,5), 128.0 (C-Ph C-2,6), 127.9 (C-Ph C-1), 125.8 (N-Ph C-4), 117.1 (N-Ph C-2,6), 110.8 (C-3a, ^{3}J(C-3a,4-Me) = 3.3 Hz), 15.1 (4-Me, ^{1}J = 128.6 Hz); ms: m/z (%) 276 (20), 275 (M^+, 79), 274 (22), 142 (17), 105 (59), 91 (58), 77 (100), 69 (27), 67 (45), 51 (52).

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.16; H, 4.73; N, 15.09.

3,6-Diphenyl-6*H*-pyrazolo[4,3-*d*]isoxazole (**3c**).

The synthesis of **3c** starting from 5-chloro-1-phenyl-1*H*-pyrazol-4-yl)phenylmethanone oxime (**6c**) (298 mg, 1 mmol) was carried out similarly as described for the synthesis of **3b**. The almost colorless solid obtained after work-up (209 mg, 80%) was crystallized from ethanol to afford 138 mg (53%) of thin, colorless needles, mp 160-161°; ^{1}H nmr (deuteriochloroform): δ 7.94 (m, 2H, C-Ph H-2,6), 7.90 (m, 2H, N-Ph H-2,6), 7.79 (s, 1H, H-4), 7.53 (m, 3H, C-Ph H-3,4,5), 7.52 (m, 2H, N-Ph H-3,5), 7.32 (m, 1H, N-Ph H-4); ^{13}C nmr (deuteriochloroform): δ 166.4 (C-6a, ^{3}J(C-6a,H-4) = 4.5 Hz), 154.8 (C-3), 137.3 (N-Ph C-1), 131.0 (C-Ph C-4), 129.7 (C-4, ^{1}J(C-4,H-4) = 194.0 Hz), 129.6 (N-Ph C-3,5), 129.1 (C-Ph C-3,5), 127.6 (C-Ph C-1 and C-Ph C-2,6), 126.4 (N-Ph C-4), 117.5 (N-Ph C-2,6), 111.9 (C-3a, ^{2}J (C-3a, H-4) = 10.9 Hz); ms: m/z (%) 261 (M^+, 69), 260 (49), 128 (29), 105 (50), 91 (29), 77 (100), 53 (20), 51 (46).

Anal. Calcd. for $C_{16}H_{11}N_3O\bullet 0.2H_2O$: C, 72.55; H, 4.34; N, 15.86. Found: C, 72.78; H, 4.20; N, 15.75.

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