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Synthesis and NMR Spectroscopic Data of Pyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin -4(1*H*)-ones: Derivatives of a Novel Tricyclic Ring System

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

Derivatives of a novel tricyclic ring system, pyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin-4(1*H*)-one**,** were prepared by reaction of either 1-substituted or 1,3-disubstituted 2-pyrazolin-5-ones and 3-chloro-2-pyrazinecarbonyl chloride in the presence of $Ca(OH)_2$ in refluxing 1,4-dioxane. In some cases the corresponding title compounds thus were obtained directly due to a spontaneous intramolecular nucleophilic substitution reaction of the intermediate 4-pyrazinoylpyrazol-5-ols. In other cases mixtures of the latter intermediates and the target compounds were obtained, which were completely converted into the desired tricycles upon treatment with HCl in a chloroform/methanol mixture. The parent system carrying no substituent in positions 1 and 3 was prepared by treatment of the 1-PMB (*p*-methoxybenzyl) protected congener with trifluoroacetic acid. Detailed NMR spectroscopic data (^{1}H, ^{13}C, ^{15}N) are presented for the title compounds.

Keywords: Pyrazolones, cyclizations, NMR spectroscopy, fused heterocyclic systems.

1. Introduction

The xanthone core is a partial structure of several biologically active compounds (Figure 1).[1] Hence, also heterocyclic analogues, in which one or both benzene rings of the parent tricyclic system is/are replaced by heteroaromatic moieties, are of considerable interest for medicinal chemists – as an example the anti-ulcer drug amlexanox (Aphthasol™, Figure 1) may serve.[2] In this respect, we recently presented a simple and generally applicable synthesis of various fused pyrano[2,3-*c*]pyrazol-4(1*H*)-ones of type **4**, which can be considered as heterocyclic analogues of xanthone (Figure 1).[3–8] In these compounds, one benzene system of the parent xanthone is replaced by a pyrazole system and the other one by a variable heteroaromatic moiety.

The synthetic approach to compounds **4** is based on the reaction of 1-substituted or 1,3-disubstituted 2-pyrazolin-5-ones (**1**) with *o*-haloheteroarenecarbonyl chlorides **2** under the conditions described by *Jensen* for the C-4 acylation of pyrazolones (calcium hydroxide, dioxane, reflux).[9] The so formed 4-acylpyrazol-5-ols **3** can be smoothly cyclized into the target compounds **4**. If the halogen atom in intermediates **3** is located in an 'activated' position (*o*- or *p*-position to a pyridine-type nitrogen atom) cyclization into **4** typically occurred under the conditions of the acylation reaction and hence the intermediate **3** was not isolated.[3,5–8] Following this approach, we have obtained compounds of type **4** carrying – amongst others – a pyridine (all positional isomers),[3] pyridazine,[5] pyrimidine,[5] quinoline,[3] quinoxaline,[6] phenanthroline,[7,8] thiophene,[4,5] and benzothiophene system[4] as the variable heteroaromatic moiety condensed to the central γ-pyrano-

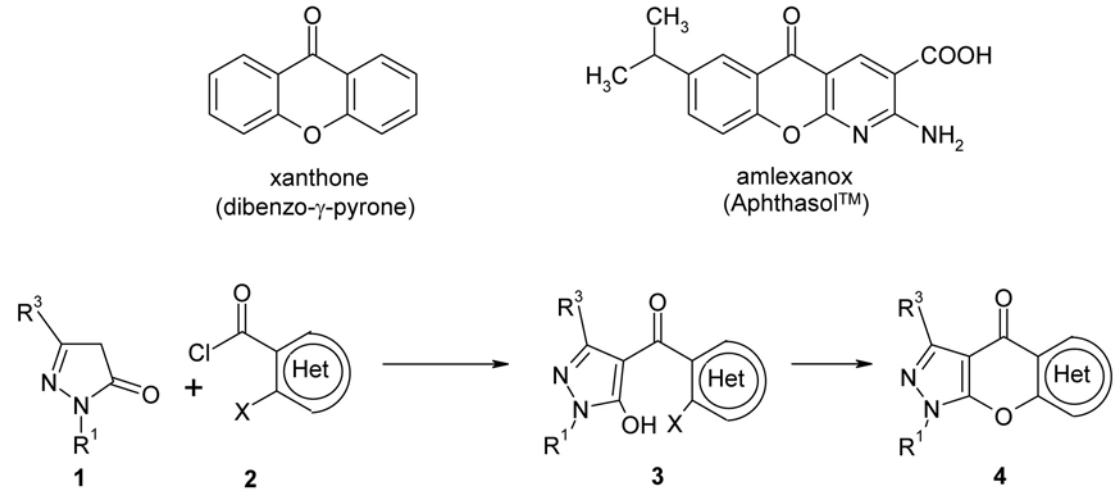


Figure 1

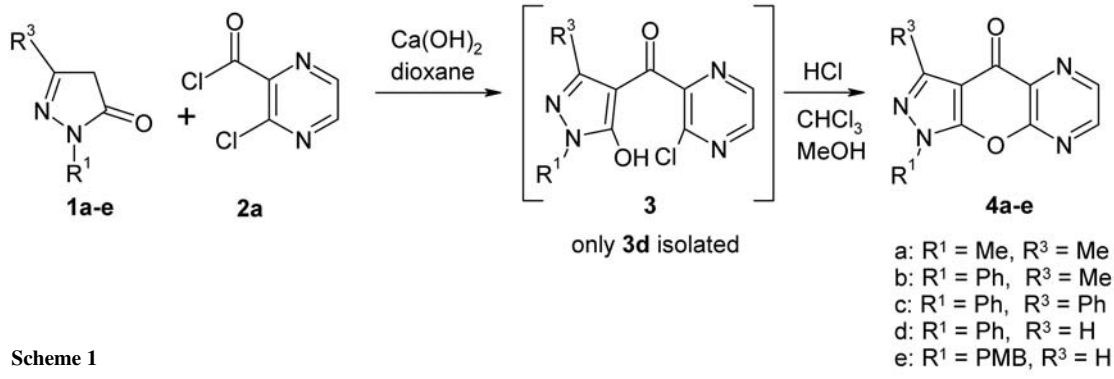
ne ring. In continuation of these investigations we here want to present the synthesis and spectroscopic data of novel, related congeners **4a**–**d** containing a pyrazine moiety (Scheme 1).

2. Results and Discussion

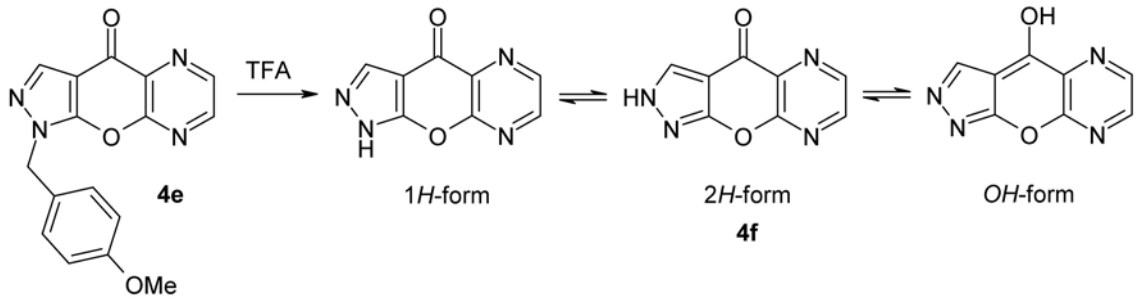
The synthetic approach to the target compounds **4a**–**e** is presented in Scheme 1, with 3-chloro-2-pyrazinecarbonyl chloride (**2a**) representing a key intermediate in this sequence. Compound **2a** – prepared by treatment of the corresponding 3-chloro-2-pyrazinecarboxylic acid with $SOCl_2$ – was immediately reacted with pyrazolones **1a**–**1e** under '*Jensen*'-conditions[9] without any further purification. Whereas in this way reaction of educts **1b** and **1c** with **2a** directly gave the target structures **4b** and **4c**, application of pyrazolones **1a, 1d** and **1e** led to mixtures of 4-aroylpyrazol-5-ols of type **3** and the corresponding tricycles of type **4**. Only in series **d** the 'open' product (**3d**) was predominating and thus was isolated from the reaction mixture (Scheme 1). Generally, the mixtures obtained upon the acylation reaction could be exhaustively converted into the corresponding target tricycles **4** upon treatment with HCl in $CHCl_3$/MeOH. Conversion of **3d** into **4d** was also carried out *via* treatment of **3d** with K_2CO_3 in refluxing DMF, however, the above mentioned cyclization method in acidic medium turned out to be more convenient and led to better yields.

Finally, the synthesis of the 'parent' compound **4f** – carrying no substituents at N-1 and C-3 – was accomplished by treatment of the N1-PMB (*p*-methoxybenzyl) protected[10] congener **4e** with trifluoroacetic acid at 70 °C (Scheme 2).

The title compounds **4a–f** were subjected to extensive multinuclear NMR spectroscopic studies. Our goal was to provide reliable data as reference material for databases used in NMR prediction programs such as CSEARCH/NMRPREDICT[11] or ACD/C+H Predictor.[12] In the last years these programs became more and more popular, especially for the prediction of ^{13}C NMR chemical shifts. However, the quality of such predictions is considerably dependent on the availability of reliable reference data of related structures. This criterion is frequently not fulfilled with less prevalent condensed heteroaromatic systems. In consideration of this fact, full and unambiguous assignments for all ^{1}H, ^{13}C and ^{15}N NMR resonances for all investigated compounds were accomplished by the combined application of standard NMR techniques.[13] Moreover, two-dimensional (δ, *J*) long-range INEPT spectra with se-



Scheme 1



Scheme 2

lective excitation[14] permitted the unequivocal mapping of $^{13}C,^{1}H$ spin coupling constants. Detailed data for each compound are given in the experimental part. As a representative example, the ^{1}H, ^{13}C and ^{15}N NMR chemicals shifts for target compound **4b** are pictured in Figure 2.

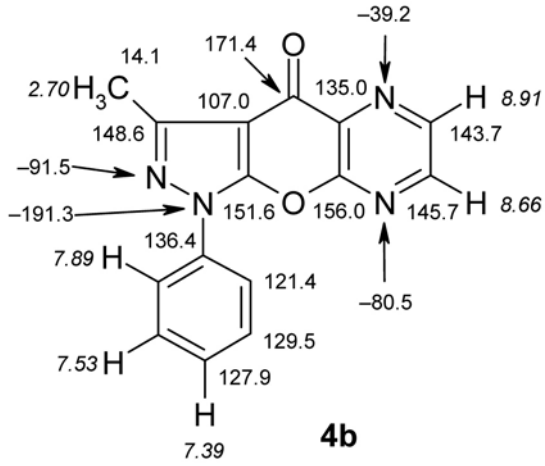


Figure 2. ^{1}H (*in italics*), ^{13}C and ^{15}N NMR chemical shifts (δ, ppm) of **4b** in $CDCl_3$

The parent compound **4f** (which is characterized by a low solubility, even in DMSO-d_6) is capable of prototropic tautomerism and shows a dynamic behavior, what is reflected by broad signal lines. Characteristic differences in the ^{13}C chemical shifts of C-3 (129.9 ppm) and C-9a (159.8 ppm) in **4f** compared to those of the corresponding N-1 PMB congener **4e** (C-3: 136.4 ppm, C-9a: 152.0 ppm) or the 1-phenyl derivative **4d** (C-3: 137.1 ppm, C-9a: 151.5 ppm) hint to a substantial contribution of the 2*H*-form to the overall tautomeric composition (Scheme 2). The presence of the third possible tautomeric form (OH-form) is improbable as the ^{13}C chemical shift of C-4 (172.9 ppm) closely resembles those of the 'fixed' ketones **4a**–**d** (170.7–171.4 ppm). For the enol C-4 in the OH-form one would expect a somewhat smaller chemical shift. The dynamic behavior of **4f** may also be jointly responsible for the fact that only one single signal (due to N-8) was found in the ^{15}N-NMR spectra.

3. Conclusion

In conclusion, we have presented a short and convenient method for the synthesis of a variety of hitherto unknown pyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin-4(1*H*)-ones starting from the corresponding pyrazolones and 3-chloro-2-pyrazinecarbonyl chloride. Moreover, we have provided valuable NMR data of the investigated fused heterocycles.

4. 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) and on a Finnigan MAT 8230 instrument (EI, 70 eV, HRMS). IR spectra were recorded on a Perkin-Elmer FTIR 1605 spectrophotometer or on a Perkin-Elmer FTIR spectrum 1000 spectrometer. Elemental analyses (C, H, N) were performed at the Microanalytical Laboratory, University of Vienna, and were in good agreement (±0.4%) with the calculated values. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The centre of the signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), δ 2.49 ppm (^{1}H in DMSO-d_6), δ 77.0 ppm (^{13}C in $CDCl_3$), and δ 39.5 ppm (^{13}C in DMSO-d_6). ^{15}N NMR spectra (gradient-selected HMBC and/or refocused INEPT) were obtained on a Bruker Avance 500 instrument with a 'directly' detecting broadband observe probe and were referenced against external nitromethane (coaxial capillary). Digital resolutions were 0.25 Hz/data point in the ^{1}H and 0.4 Hz/data point in the ^{1}H coupled ^{13}C NMR spectra (gated decoupling). Systematic names according to IUPAC recommendations were generated with ACD/Name[15] and subsequently proved manually to ensure correct nomenclature within this publication.[16] Pyrazolones **1** were commercially available and/or prepared similarly to literature procedures: **1c**,[17] **1d**,[18] **1e**.[10] 3-Chloro-2-pyrazinecarboxylic acid was purchased from Tyger Scientific Inc., Ewing, NJ, USA. Yields of products **4a**–**e** were not optimized.

3-Chloro-2-pyrazinecarbonyl chloride (**2a**): To a mixture of 3-chloro-2-pyrazinecarboxylic acid (0.50 g, 3.15 mmol), toluene (35 mL) and 3 drops of DMF was added $SOCl_2$ (2.3 mL, 31.6 mmol) and the solution was heated to reflux for 3 h. Then the solvents were removed under reduced pressure using a water aspirator, another 10 mL of toluene were added and again distilled off under reduced pressure. The remaining crude acid chloride, a brownish oil, was used in the next reaction step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, J = 2.2 Hz, H-5), 8.68 (d, J = 2.2 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.0 (C-6), 143.4 (C-2), 147.2 (C-5), 147.3 (C-3), 165.7 (CO); ^{15}N NMR (50 MHz, $CDCl_3$): δ –47.8 (N-4), –39.5 (N-1).

General procedure for the reaction of pyrazolones **1a**–**e** with acid chloride **2a**

To a suspension of pyrazolone **1a**–**e** (3.15 mmol) and $Ca(OH)_2$ (467 mg, 6.30 mmol) in 5 mL of dry 1,4-dioxane was added a solution of crude 3-chloro-2-pyrazinecarbonyl chloride (**2a**) (prepared from 3.15 mmol of **2** of the corresponding carboxylic acid as described above) in 8 mL of dry 1,4-dioxane and the mixture was heated to reflux for 3 h. After cooling to room temperature, 2N HCl was added and the pH was adjusted to ~2. The mixture was then stirred for 15 min, subsequently poured onto water (50 mL) and further treated as described below.

1,3-Dimethylpyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin-4(1*H*)-one (4a). The mixture was extracted with CH_2Cl_2 (4 × 30 mL), the combined organic layers were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to afford a mixture of **3a** (minor component) and **4a** (major component). This mixture was dissolved in $CHCl_3$–CH_3OH (7:3) (50 mL), then 2N HCl (5 mL) was added and the whole was stirred overnight at 50 °C. After removing the solvents under reduced pressure, water (50 mL) was added, the precipitated solid was filtered off, washed with water and dried to afford 0.45 g (66%) of **4a** (pure according to ^{1}H NMR). Recrystallization from EtOH gave 0.35 g (51%) of pale yellow needles; mp 264–268 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H, 3-CH_3), 3.91 (s, 3H, NCH_3), 8.62 (d, ^3J(H7,H6) = 2.2 Hz, 1H, H-7), 8.87 (d, ^3J(H6,H7) = 2.2 Hz, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (3-CH_3, ^1J = 129.3 Hz), 34.1 (NCH_3, ^1J = 141.9 Hz), 105.4 (C-3a, ^3J(C3a,3-CH_3) = 2.8 Hz), 135.0 (C-4a, ^3J(C4a,H6) = 10.5 Hz, ^4J(C4a,H7) = 1.5 Hz), 143.4 (C-6, ^1J = 188.1 Hz, ^2J(C6,H7) = 10.4 Hz), 145.3 (C-7, ^1J = 186.8 Hz, ^2J(C7,H6) = 12.5 Hz), 147.5 (C-3, ^2J(C3,3-CH_3) = 7.1 Hz), 152.5 (C-9a, ^3J(C9a,NCH_3) = 2.3 Hz), 155.8 (C-8a, ^3J(C8a,H7) = 11.8 Hz, ^4J(C8a,H6) = 1.6 Hz), 171.1 (C-4); ^{15}N NMR (50 MHz, $CDCl_3$): δ -209.4 (N-1), -89.3 (N-2), -81.7 (N-8), -38.9 (N-5); IR (KBr): ν 1677 cm^{-1} (C=O); MS *m/z* (relative intensity): 216 (M^+, 100), 67 (78), 43 (53); Anal. Calcd for $C_{10}H_8N_4O_2 \cdot 0.1\ H_2O$: C 55.10, H 3.79, N 25.70. Found: C 55.33, H 3.74, N 25.33.

3-Methyl-1-phenylpyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin-4(1*H*)-one (4b). The precipitated solid was filtered with suction, washed with water and dried to afford 0.67 g (76%) of **4b** (pure according to ^{1}H NMR). Recrystallization from EtOH gave 0.60 g (68%) of brownish crystals; mp 230–232 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.70 (s, 3H, 3-CH_3), 7.39 (m, 1H, Ph H-4), 7.53 (m, 2H, Ph H-3,5), 7.89 (m, 2H, Ph H-2,6), 8.66 (d, ^3J(H7,H6) = 2.1 Hz, 1H, H-7), 8.91 (d, ^3J(H6,H7) = 2.1 Hz, 1H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (3-CH_3, ^1J = 129.6 Hz), 107.0 (C-3a, ^3J(C3a,3-CH_3) = 2.8 Hz), 121.4 (Ph C-2,6), 127.9 (Ph C-4), 129.5 (Ph C-3,5), 135.0 (C-4a, ^3J(C4a,H6) = 10.5 Hz, ^4J(C4a,H7) = 1.5 Hz), 136.4 (Ph C-1), 143.7 (C-6, ^1J = 188.0 Hz, ^2J(C6,H7) = 10.6 Hz), 145.7 (C-7, ^1J = 186.8 Hz, ^2J(C7,H6) = 12.6 Hz), 148.6 (C-3, ^2J(C3,3-CH_3) = 7.2 Hz), 151.6 (C-9a), 156.0 (C-8a, ^3J(C8a,H7) = 11.8 Hz, ^4J(C8a,H6) = 1.6 Hz), 171.4 (C-4); ^{15}N NMR (50 MHz, $CDCl_3$): δ -191.3 (N-1), -91.5 (N-2), -80.5 (N-8), -39.2 (N-5); IR (KBr): ν 1681 cm^{-1} (C=O); MS *m/z* (relative intensity): 278 (M^+, 100), 91 (47), 77 (59), 51 (38); HRMS-EI (*m/z*): M^+ calcd for $C_{15}H_{10}N_4O_2$, 278.0804; found, 278.0800; Anal. Calcd for $C_{15}H_{10}N_4O_2$: C 64.74, H 3.62, N 20.13. Found: C 64.84, H 3.70, N 19.88.

1,3-Diphenylpyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin-4(1*H*)-one (4c). The precipitated solid was filtered with suction, washed with water and dried to afford 0.83 g (77%) of crude **4c**. Recrystallization from EtOAc gave 0.63 g (59%) of yellow crystals; mp 272–275 °C (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 2H, NPh H-4, CPh H-4), 7.52 (m, 2H, CPh H-3,5), 7.61 (m, 2H, NPh H-3,5), 8.03 (m, 2H, NPh H-2,6), 8.47 (m, 2H, CPh H-2,6), 8.70 (d, ^3J(H7,H6) = 2.1 Hz, 1H, H-7), 8.97 (d, ^3J(H6,H7) = 2.1 Hz, 1H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 105.9 (C-3a), 122.0 (NPh C-2,6), 128.4 (NPh C-4), 128.5 (CPh C-3,5), 128.6 (CPh C-2,6), 129.6 (NPh C-3,5), 129.9 (CPh C-4), 130.8 (CPh C-1), 134.9 (C-4a, ^3J(C4a,H6) = 10.5 Hz, ^4J(C4a,H7) = 1.4 Hz), 136.5 (NPh C-1), 144.0 (C-6, ^1J = 188.4 Hz, ^2J(C6,H7) = 10.4 Hz), 145.9 (C-7, ^1J = 187.0 Hz, ^2J(C7,H6) = 12.4 Hz), 150.2 (C-3), 152.4 (C-9a), 155.3 (C-8a, ^3J(C8a,H7) = 11.8 Hz, ^4J(C8a,H6) = 1.6 Hz), 170.7 (C-4); ^{15}N NMR (50 MHz, $CDCl_3$): δ -189.5 (N-1), -81.3 (N-8), -38.0 (N-5), (N-2 was not found); IR (KBr): ν 1675 cm^{-1} (C=O); MS *m/z* (relative intensity): 340 (M^+, 100), 218 (23), 77 (77), 51 (45); HRMS-EI (*m/z*): M^+ calcd for $C_{20}H_{12}N_4O_2$, 340.0960; found, 340.0953; Anal. Calcd for $C_{20}H_{12}N_4O_2$: C 70.58, H 3.55, N 16.46. Found: C 70.38, H 3.32, N 16.17.

(3-Chloropyrazin-2-yl)(5-hydroxy-1-phenyl-1*H*-pyrazol-4-yl)methanone (3d) and 1-phenylpyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin-4(1*H*)-one (4d). The precipitated solid was filtered with suction, washed with water and dried to afford 0.69 g of a mixture of **3d** and **4d** in a ~ 5:1 ratio (according to ^{1}H NMR).

3d: In a first run this mixture was repeatedly crystallized from aqueous EtOH to give 0.49 g (52%) of **3d** as yellow–brownish powder; mp 222–225 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 1H, Ph H-4), 7.49 (m, 2H, Ph H-3,5), 7.84 (m, 2H, Ph H-2,6), 8.04 (s, 1H, pyrazole H-3), 8.59 (d, ^3J(H5,H6) = 2.4 Hz, 1H, pyrazine H-5), 8.65 (d, ^3J(H6, H5) = 2.4 Hz, 1H, pyrazine H-6), 10.40 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 104.1 (pyrazole C-4), 121.4 (Ph C-2,6), 127.4 (Ph C-4), 129.2 (Ph C-3,5), 137.0 (Ph C-1), 141.2 (pyrazole C-3 and pyrazine C-6), 145.7 (pyrazine C-5), 146.9 (pyrazine C-2), 148.0 (pyrazine C-3), 159.0 (br, pyrazole C-5), 185.3 (br, CO); IR (KBr): ν 1634 cm^{-1} (C=O); MS *m/z* (relative intensity): 302 (M^+, 5), 300 (M^+,19), 264 (28), 141 (37), 113 (30), 91 (28), 77 (100), 53 (31), 52 (29), 51 (78); HRMS-EI (*m/z*): M^+ calcd for $C_{14}H_9ClN_4O_2$, 300.0414; found, 300.0412.

4d: In a second run the 5:1 mixture of **3d** and **4d** (0.69 g) was dissolved in $CHCl_3$-CH_3OH (7:3) (50 mL), then 2N HCl (5 mL) was added and the whole was stirred overnight at 50 °C. After removing the solvents under reduced pressure the residue was recrystallized from EtOH to give 0.43 g (52%) of a brownish powder; mp 226–228 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (m, 1H, Ph H-4), 7.56 (m, 2H, Ph H-3,5), 7.92 (m, 2H, Ph H-2,6), 8.31 (s, 1H, H-3), 8.70 (br s, 1H, H-7), 8.94 (br s, 1H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.6 (C-3a, ^2J(C3a,H3) = 10.3 Hz), 121.5 (Ph C-2,6), 128.3 (Ph C-4), 129.6 (Ph C-3,5), 134.5 (C-4a, ^3J(C4a,H6) = 10.4 Hz), 136.4 (Ph C-1), 137.1 (C-3, ^1J = 196.3 Hz), 143.9 (C-6, ^1J = 188.4 Hz, ^2J(C6,H7) = 10.5 Hz), 146.1 (C-7, ^1J = 187.0 Hz, ^2J(C7,H6) = 12.6 Hz), 151.5 (C-9a, ^3J(C9a,H3) = 4.8 Hz), 155.9 (C-8a, ^3J(C8a,H7) = 11.9 Hz), 170.9 (C-4); ^{15}N NMR (50 MHz, $CDCl_3$): δ -185.1 (N-1), -83.7 (N-2), -80.1 (N-8), -39.1 (N-5); IR (KBr): ν 1678 cm^{-1} (C=O); MS *m/z* (relative intensity): 264 (M^+, 65), 91 (36), 77 (100), 51 (96); Anal. Calcd for $C_{14}H_8N_4O_2 \cdot 0.3\ H_2O$: C 62.36, H 3.21, N 20.78. Found: C 62.59, H 3.20, N 20.55.

Cyclization of 3d under basic conditions. Under anhydrous conditions, compound **3d** (200 mg, 0.66 mmol) was dissolved in dry DMF (4 mL) and K_2CO_3 (93 mg, 0.66 mmol) was added to the mixture. The reaction mixture was refluxed overnight. Then the solvent was evaporated under reduced pressure, H_2O (2 mL) was added to the residue and the mixture stirred for 15 minutes. The precipitate was filtered off, washed with H_2O and recrystallized from EtOH to afford 101 mg (57%) of **4d**.

1-(4-Methoxybenzyl)pyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin-4(1*H*)-one (4e). The mixture was extracted with CH_2Cl_2 (4 × 30 mL), the combined organic layers were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to afford a mixture of **3e** (minor component) and **4e** (major component). This mixture was dissolved in $CHCl_3$–CH_3OH (7:3) (50 mL), then 2N HCl (5 mL) was added and the whole was stirred overnight at 50 °C. After removing the solvents under reduced pressure, water (50 mL) was added, the precipitated solid was filtered off, washed with water and dried to afford 0.77 g (79%) of **4e** (pure according to ^{1}H NMR). Recrystallization from EtOH gave 0.40 g (41%) of brownish crystals; mp 200–201 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H, OMe), 5.43 (s, 2H, NCH_2), 6.87 (m, 2H, Ph H-3,5), 7.36 (m, 2H, Ph H-2,6), 8.16 (s, 1H, H-3), 8.68 (d, ^3J(H7,H6) = 2.1 Hz, 1H, H-7), 8.92 (d, ^3J(H6,H7) = 2.1 Hz, 1H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.3 (OCH_3, ^1J = 144.0 Hz), 51.5 (NCH_2, ^1J = 141.3 Hz, ^3J(NCH_2,Ph H-2,6) = 4.6 Hz), 107.4 (C-3a, ^2J(C3a,H3) = 10.4 Hz), 114.3 (Ph C-3,5), 126.3 (Ph C-1), 129.7 (Ph C-2,6), 134.7 (C-4a, ^3J(C4a,H6) = 10.5 Hz, ^4J(C4a,H7) = 1.5 Hz), 136.4 (C-3, ^1J = 195.6 Hz), 143.6 (C-6, ^1J = 188.2 Hz, ^2J(C6,H7) = 10.5 Hz), 145.8 (C-7, ^1J = 186.8 Hz, ^2J(C7,H6) = 12.6 Hz), 152.0 (C-9a, ^3J(C9a,H3) = 5.0 Hz, ^3J(C9a,NCH_2 = 2.5 Hz), 155.8 (C-8a, ^3J(C8a,H7) = 11.8 Hz, ^4J(C8a,H6) = 1.7 Hz), 159.8 (Ph C-4), 170.7 (C-4); ^{15}N NMR (50 MHz, $CDCl_3$): δ -189.4 (N-1), -82.9 (N-2), -81.0 (N-8), -38.9 (N-5); IR (KBr): ν 1679 cm^{-1} (C=O); MS *m/z* (relative intensity): 308 (M^+, 10), 121 (100), 78 (14), 77 (13); Anal. Calcd for $C_{16}H_{12}N_4O_3$: C 62.33, H 3.92, N 18.17. Found: C 62.08, H 3.84, N 18.13.

Pyrazolo[4',3':5,6]pyrano[2,3-*b*]pyrazin-4(1*H*)-one (4f). A solution of **4e** (180 mg, 0.58 mmol) in trifluoroacetic acid (TFA) (10 mL) was stirred for 24 h at 70 °C. After removal of excess TFA under reduced pressure the residue was dried over solid KOH for 1 h. Then it was digested with ice-cold Et_2O-acetone (2:1, 5 mL) and filtered with suction. The remaining solid was washed with Et_2O and dried to afford crude **4f** in quantitative yield (109 mg). The unsoluble product was further purified by refluxing in $CHCl_3$ (30 mL), the suspension was then filtered with suction and the residue dried *in vacuo*. Yield: 99 mg (90%) of a brownish powder; mp > 350 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71 (br s, 1H, H-3), 8.79 (br s, H-7), 8.87 (br s, H-6), 14.0 (br s, NH); ^{13}C NMR (125 MHz, DMSO-d_6): 107.3 (C-3a), 129.9 (C-3), 133.8 (C-4a), 142.4 (C-6), 146.6 (C-7), 157.4 (C-8a), 159.8 (C-9a), 172.9 (C-4); ^{15}N NMR (50 MHz, DMSO-d_6): δ -81.0 (N-8), N-1, N-2 and N-5 were not found; IR (KBr): ν 1670 (C=O), 3152 cm^{-1} (NH); MS *m/z* (relative intensity): 188 (M^+, 100), 110 (46), 78 (18), 67 (18), 54 (15), 53 (52), 52 (16), 51 (18); HRMS-EI (*m/z*): M^+ calcd for $C_8H_4N_4O_2$, 188.0334; found, 188.0332.

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Povzetek

Opisana je sinteza derivatov [4',3':5,6]pirano[2,3-*b*]pirazin-4(1*H*)-ona kot novega tricikličnega sistema iz 1,3-disubstituiranih 2-pirazolin-5-onov in 3-kloro-2-pirazinkarbonil klorida v prisotnosti $Ca(OH)_2$. V nekaterih primerih so bile končne spojine dobljene direktno, ko posledica spontane intramolekularne ciklizacije 5-hidroksi-4-pirazinoilpirazolskega intermediate, v ostasli primerih pa je bilo potrebno ciklizacijo omenjenih intermediatov izvesti pod kislimi pogoji. Osnovni system brez substituentov na položajih 1 in 3 je bil pripreavljen v reakciji 1-(4-metoksifenil) substituiranega derivata s trifluoroocetno kislino. Predstavljeni so tudi detajlni NMR spektroskopski podatki (^{1}H, ^{13}C, ^{15}N) končnih produktov.