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An easy synthetic access to new pyrazole spiro derivatives from 3-amino-1-phenyl-2-pyrazolin-5-one

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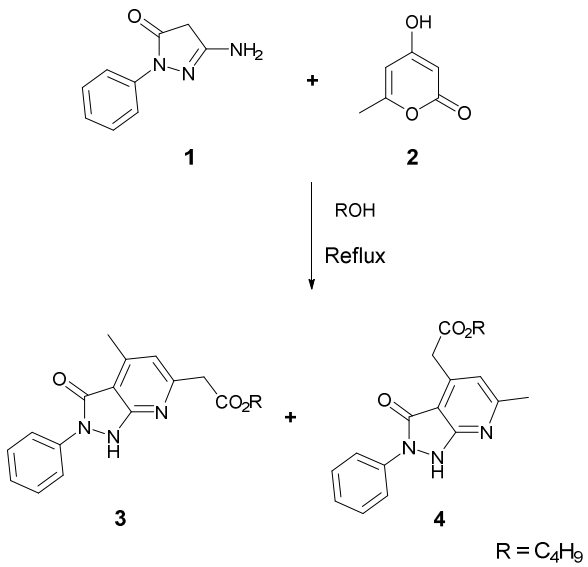
Pyrazole and pyrazolone moieties have shown important biological activities. For this reason, the synthesis of new derivatives has attracted the interest of the scientific community. Herein we report the formation of two unexpected spiro compounds containing pyrazole moieties from a tandem process involving the initial condensation of 3-amino-1-phenyl-2-pyrazolin-5-one with benzaldehyde followed by dimerization.

The importance given by the pharmaceutical industry and by the scientific community to pyrazole and pyrazolone derivatives is related to their role in medicine as analgesic, antipyretic and anti-inflammatory drugs among others.1 The pyrazole nucleus is found in many other drugs like muzolimine, sulfaphenazole, betazole and recently, their in vitro and in vivo trypanosomicidal activity were reported.2 Compounds containing the pyrazole core are also appropriate precursors for industrial preparation of for instance herbicides,3 thermal-stable polymers,4 and color developing agents for photography.5 In addition, spiro-compounds although less investigated show also very promising biological activities such as anticancer agents and antimicrobial agents.6 Pyrazoles and their derivatives are commonly prepared by reaction of hydrazines with either 1,3-dicarbonyl compounds or α,β-unsaturated aldehydes or ketones.7-9 Nevertheless, the preparation of pyrazoles have been also accomplished via electrophilic cyclization of α,β-alkyne hydrazones,10,11 as well as by 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with alkenes or alkynes.12-14 The dehydroacetic acid is another synthon for the synthesis of pyrazoles by reaction with mono-substituted hydrazines.[15] In addition, pyrazolo[3,4-b]pyridines were prepared by condensation of 3-amino-1-phenyl-2-pyrazolin-5-one **1** with α,β-unsaturated carbonyl compounds.[16]

In this context, we have been intensively investigating the preparation of pyrazolo[3,4-b]pyridines (**3** and **4**), through the condensation of 3-amino-1-phenyl-2-pyrazolin-5-one **1** with 4-hydroxy-6-methylpyran-2-one **2** (Scheme 1).[17-19]



Scheme 1 Synthetic route to pyrazolo[3,4-b]pyridines from condensation of 3-amino-1-phenyl-2-pyrazolin-5-one **1** with 4-hydroxy-6-methylpyran-2-one **2**

Following our research interests in exploring the commercially available synthon 1 for preparing new heterocycles, we decided to evaluate its reactivity with aromatic aldehydes under Knoevenagel conditions to obtain new α,β-unsaturated carbonyl compounds. Noteworthy, T. R. Sobahi isolated pyranodipyrazole derivatives in moderate yields (53-61%) by

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Electronic Supplementary Information (ESI) available: NMR spectra (^{1}H, ^{13}C, DEPT 135, COSY, NOESY, HSQC and HMBC), ESI-MS mass spectra of compounds **5** and **6** and single crystal X-ray Diffraction Studies of compound **5**. See
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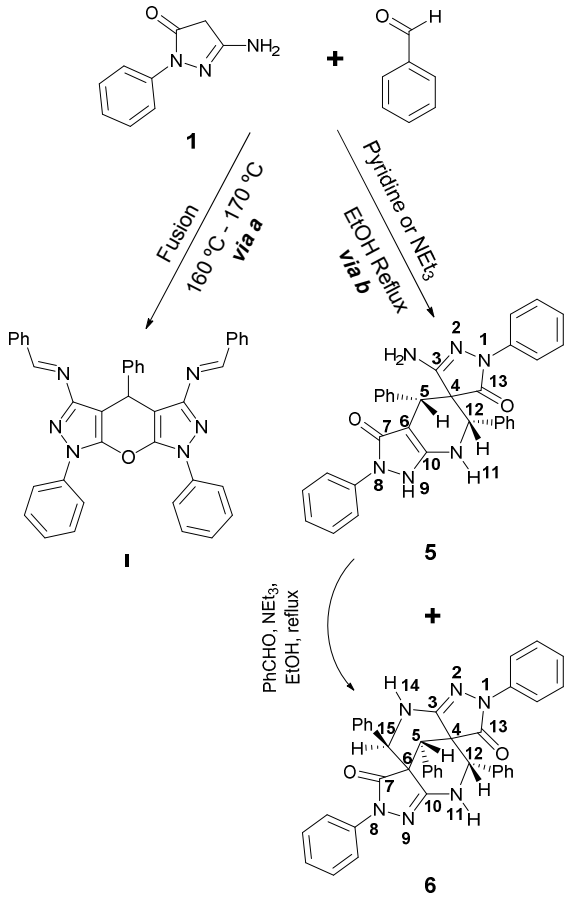
reacting 1 with different aromatic aldehydes in the absence of solvent, and heating the reaction mixture at 160-170 °C (via a, Scheme 2, compound I was obtained using benzaldehyde).20 In order to favor the Knoevenagel condensation we decided to start our studies by reacting 1 with benzaldehyde in refluxing ethanol, in the presence of a base (pyridine or triethylamine) (Scheme 2, via b).



Scheme 2 Reactivity of 3-amino-1-phenyl-2-pyrazolin-5-one **1** with benzaldehyde under different experimental conditions

Surprisingly we found that under these conditions compound 1 is converted into a new spiro derivative **5** (*ca.* 45% in pyridine and 35% in triethylamine). Further reacting with an extra molecule of benzaldehyde affords the new adduct **6**. Spectroscopic data of the new derivatives are strikingly distinct from those reported by T. R. Sobahi, and did not agree with the expected product from Knoevenagel condensation.

The identification of the structures of these new spiro compounds was facilitated by the successfully crystallization of **5** from a mixture of chloroform and acetone affording a material composed of very thin colourless plates whose structure was unveiled from single-crystal X-ray diffraction (vide infra). This result, accompanied by a careful analysis of their NMR (^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY) and MS (see in the ESI) allowed us to establish the structure of compounds **5** and **6** and to identify all their proton and carbon resonances. Additionally, the molecular formulae of the new compounds were also confirmed by elemental analysis.

The electrospray mass spectra (ESI-MS) of **5** and **6** show the expected $[M+H]^+$ ions at, respectively, *m/z* 527 and 615; the difference of 88 Da between these two molecular ions agrees with the presence of an extra benzaldehyde unit and one molecule of water less in compound **6**. The ^{1}H NMR spectrum of **5** (Figure S3 in the ESI) shows a very simple aliphatic region being the two singlets at δ 4.68 and δ 4.98 ppm assigned to the resonances of H-5 and H-12, respectively. The assignment of the most important carbon resonances was possible based on HSQC analysis (Figure S5 in the ESI). The aliphatic carbons C-5 and C-12 appear, respectively, at δ 44.4 and δ 61.6 ppm, and the spiro carbon C-4 appears at δ 61.1 ppm. From HMBC analysis, the resonances at δ 169.4, 158.6 and 156.2 ppm were assigned to the amide C-7, imino C-3 and amide C-13 carbons.

The aliphatic region of the 1H NMR spectrum of 6 displays a singlet at δ 4.04 ppm corresponding to the resonance of H-5 and four broad doublets. By HSQC analysis it was found that the doublets at δ 5.09 and δ 5.32 ppm are not correlated with any carbon, and were assigned to the NH protons (Figure 1). The COSY correlation between the doublets at δ 5.05 and δ 5.09 ppm and of those at δ 5.15 and δ 5.32 ppm allowed their identification as H-12 and H-11, and of H-15 and H-14 resonances, respectively (Figure S8 in the ESI). The NOESY spectrum shows NOE cross peaks between the doublets at H-5 (δ 4.04) and H-12 (δ 5.05) indicating that these protons are in the same plane, which agrees with the proposed structure and the previous assignments (Figure S9 in the ESI). The analysis of HSQC and HMBC spectra allowed the identification of the carbon resonances of the spiro carbons C-4 and C-6 (δ 56.9 and δ 54.5 ppm), the carbons of the imino groups C-3 and C-10 (δ 166.0 and δ 166.6 ppm), the carbons of the amide groups C-7 and C-13 (δ 157.4 and δ 157.5 ppm) and the aliphatic carbons C-5, C-12 and C-15 (δ 46.9, δ 67.7 and δ 61.0 ppm). Additionally, the resonances of the quaternary carbons were confirmed by the DEPT 135 spectrum.

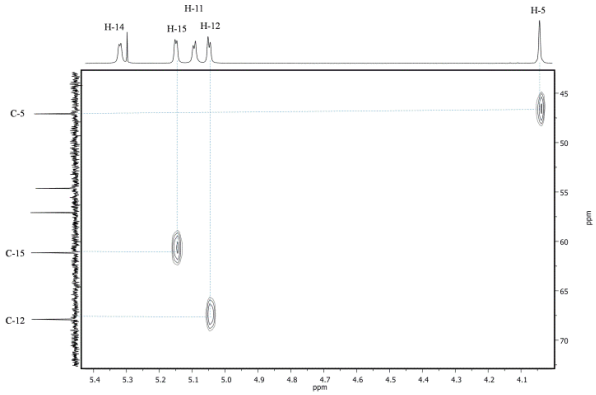


Figure 1 Partial HSQC (^{1}H/^{13}C) spectrum of compound **6**.

Compound **5** was isolated as a crystalline material composed of very thin colourless plates which were studied using single-

crystal X-ray diffraction (see ESI for additional technical details on the performed studies). As expected, the reaction led to the isolation of a pair of enantiomers for the three chiral consecutive carbon centers, *S*,*R*,*S* and *R*,*S*,*R*, with this being transposed into the asymmetric unit of the crystal structure which contains two of such molecules (see Figure S14 in the ESI). It is important to emphasize that the centering of the triclinic unit cell could, just by itself, generate the aforementioned pair of enantiomers but, as depicted in Figure S14b, one molecule further exhibits a considerable structural disorder which led, in this way, to the presence of two molecules in the asymmetric unit.

The possibility of the proton transfer between the nitrogen and the oxygen atoms composing the pyrazolone groups could be immediately discarded from the performed crystallographic studies. As described in the technical section of these investigations (see in the ESI), all hydrogen atoms associated with nitrogen, including those of these pyrazolone groups, were markedly visible in difference Fourier maps. Moreover, the refined internuclear distances for the two molecules clearly indicate the presence of a carbonyl moiety and a single bond for the N-N connection in the pyrazolone groups (data not shown – see CIF file for additional geometrical details).

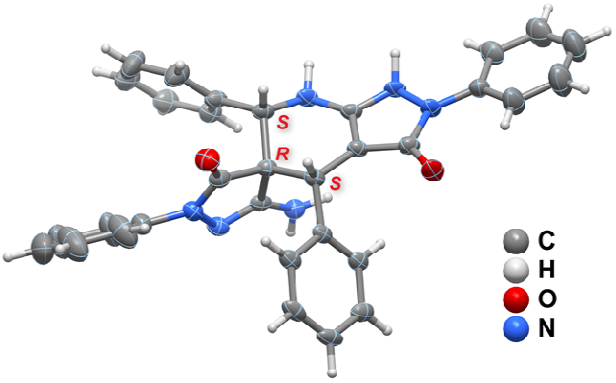
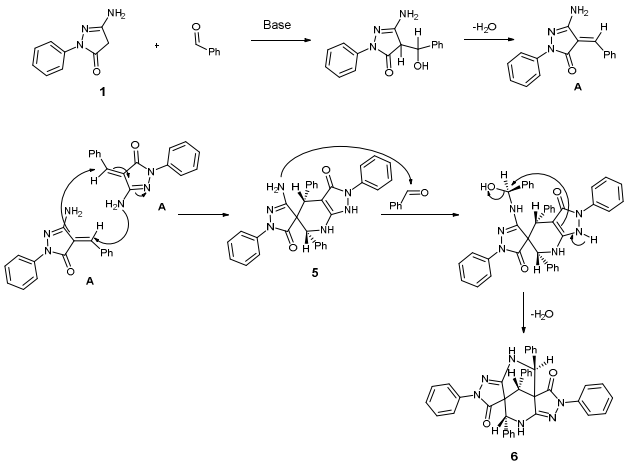


Figure 2 Schematic representation of the *S*,*R*,*S* enantiomer present in the asymmetric unit of compound **5**. Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level and hydrogen atoms are depicted as small spheres with arbitrary radii. For a representation of the *R*,*S*,*R* enantiomer (including the extensive disorder associated with this chemical moiety) see Figure S14 in the Electronic Supporting Information

The molecule is rich in both donor and acceptor groups capable of forming strong and highly directional hydrogen bonds (see Figure S14 in the ESI showing the atomic labelling for these groups). In this way, adjacent pairs of enantiomers are mutually engaged in both strong N–H···O and N–H···O hydrogen bonds leading to a ladder-type supramolecular chain parallel to the *a*-axis as depicted in Figure S15 in the ESI. This ladder is composed of two graph set motifs as shown in Figure S16 (ESI):[21] on the one hand, $\mathbf{R}^1_2(6)$ connects adjacent enantiomers along the *a*-axis, forming the lateral of the aforementioned supramolecular ladder; on the other, $\mathbf{R}^2_2(8)$ promotes strong connections between these lateral chains, forming the central bridge of the ladder and arising solely from one of the two molecules composing the asymmetric unit. Noteworthy, this latter supramolecular connection also arises as one of the strongest in the crystal structural, with an almost linear interaction angle which indicates a much more directional bond than all remaining ones (see Table S2 for geometrical details in the ESI).

The formation of the tricyclic compound **5** can be justified according with the tandem process depicted in Scheme 3 and starts with the expected Knoevenagel type condensation between **1** and the benzaldehyde leading to the α,β-unsaturated derivative **A** (Scheme 3). Then a Michael addition involving two molecules of A affords the tricyclic spiro compound **5**. Further condensation between the primary amine group of **5** with an extra molecule of benzaldehyde can explain the formation of the tetracyclic compound **6**. This last step was supported by the formation of compound **6** from the reaction of **5** with benzaldehyde in the presence of triethylamine in refluxing ethanol (Scheme 2).



Scheme 3 Putative mechanism for the formation of spiro compounds **5** and **6**

In summary, novel and unexpected spiro compounds containing pyrazole moieties have been easily obtained from the reaction of 3-amino-1-phenylpyrazolin-5-one **1** with benzaldehyde in the presence of a base. We plan to extend this strategy to other aldehydes to obtain an extended series of new spiro derivatives.

Experimental:

General procedure: To a solution of 3-amino-1-phenyl-2-pyrazolin-5-one **1** (200 mg, 1.14 mmol) in ethanol (ca. 10 mL) was added the benzaldehyde (0.3 mL, 2.5 mmol) and 0.5-1 equivalents of base (triethylamine or pyridine). Then, the mixture was refluxed in an oil-bath under stirring for 1 h when compound **6** started to precipitate and the TLC monitoring showed the total consumption of the starting materials. After cooling to room temperature the resulting precipitate was separated from the mother liquor. The obtained solid was purified by recrystallization in a mixture of chloroform and hexane yielding 10% of compound **6** when triethylamine was used as base and 12% in the case of pyridine. Compound **5** was obtained after removing the solvent of the mother liquor

under vacuum in a rotary evaporator. Then, the resulting residue was purified by chromatography over a silica gel column using a mixture of ethyl acetate/hexane (3:7). Compound **5** after recrystallized in a mixture of acetone and chloroform was obtained in 35% when triethylamine was used as base and in 45% in the case of pyridine. No real improvement was achieved when the reaction time was increased to 24 h.

Compound **5**: m.p. 214 °C dec.; ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz,) δ 7.65 (dd, J = 8.7 and 1.1 Hz, 2H, o-Ph-12), 7.56-7.53 (m, 2H, o-Ph-5), 7.42-7.37 (m, 3H, Ph), 7.30-7.28 (m, 5H, Ph), 7.22-7.14 (m, 6H, Ph), 7.10-7.05 (m, 2H, Ph), 4.98 (s, 1 H, H-12), 4.68 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD) δ 169.4 (C-7), 158.6 and 156.2 (C-3 and C-13), 138.6 and 137.2 (C-1-NPh-1 and C-1-NPh-8), 135.3 (C-1-Ph-12), 134.5 (C-1-Ph-5),129.5 (Ph or C-10), 129.4 (Ph), 129.1 (Ph), 128.9 (Ph), 128.8 (Ph), 128.7 (Ph), 128.3 (Ph), 128.2 (Ph), 128.0 (Ph or C-10) 126.0 (Ph), 125.0 (Ph), 121.1 (Ph), 120.0 (Ph), 84.1 (C-6), 61.6 (C-12), 61.1 (C-4), 44.4 (C-5). MS (ESI): found $[M+H]^+$ 527, $M+Na]^+$ 549; $C_{32}H_{26}N_6O_2 \cdot 1/2\ C_2H_5OH$: calcd. C 72.11, H 5.32, N 15.29; found C 72.11, H 5.32, N 15.20.

Compound 6: m.p. 168 °C dec.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2H, o-Ph-12), 7.59-7.56 (m, 2H, o-Ph-15), 7.40-7.35 (m, 7H, Ph including o-Ph-5), 7.29-7.16 (m, 12H, Ph including p-Ph-12 and p-Ph-15), 7.07-7.01 (m, 2H, Ph), 5.32 (br d, J = 1.6 Hz, 1H, H-14), 5.15 (br d, J = 1.6 Hz, 1H, H-15), 5.09 (br d, J = 2.0 Hz, 1H, H-11), 5.05 (br d, J = 2.0 Hz, 1H, H-12), 4.04 (s, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 and 166.0 (C-3 and C-10), 157.5 (C-13), 157.4 (C-7), 137.1 and 137.0 (C-1-NPh-1 and C-1-NPh-8), 134.49 and 134.47 (C-1-Ph-12 and C-1-Ph-15), 132.3 (C-1-Ph-5), 129.6 (p-Ph-12), 129.5 (p-Ph-15), 129.0 (o-Ph-5), 128.4 (Ph), 128.34 (Ph), 128.31 (Ph), 127.9 (o-Ph-15), 127.8 (o-Ph-12), 124.9 (Ph), 124.7 (Ph), 119.4 (Ph), 118.8 (Ph), 67.7 (C-12), 61.0 (C-15), 56.9 (C-4), 54.5 (C-6), 46.9 (C-5). MS (ESI): found $[M+H]^+$ 615, $[M+Na]^+$ 637; $C_{39}H_{30}N_6O_2 \cdot 2C_2H_5OH$: calcd. C 73.03, H 5.99, N 11.89; found C 73.30, H 5.80, N 12.00.

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