

Phenyl and Pyridyl Bis-Pyrazoles: Synthesis from the Bis(β -diketone) Precursors and Characterization by Analytical and Spectroscopic Methods

Josefina Pons*, Arafa Chadghan, Jordi García-Antón and Josep Ros

Departament de Química, Unitat de Química Inorgànica, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain

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Abstract: The bis(β -diketone) compounds, 3,3'-(pyridine-2,6-diyl)bis(1-phenylpropane-1,3-dione) monohydrated (**1a**·H₂O) and 3,3'-(pyridine-2,6-diyl)bis(1-(pyridin-2-yl)propane-1,3-dione) monohydrated (**1b**·H₂O) were prepared by Claisen condensation of the appropriate ketone and dimethyl pyridine-2,6-dicarboxylate ester. Compounds 2,6-bis(5-phenyl-1H-pyrazol-3-yl)pyridine dihydrated (**2a**·2H₂O) and 2,6-bis(5-(pyridin-2-yl)-1H-pyrazol-3-yl)pyridine monohydrated (**2b**·H₂O) were synthesized by reaction of the appropriate bis(β -diketone) compounds and hydrazine monohydrate.

Keywords: Nitrogen heterocycles, bis-pyrazole, bis(β -diketone), NMR spectroscopy.

INTRODUCTION

In recent years, considerable attention has been paid to pyrazoles, pyrimidines and related *N*-containing heterocyclic derivatives. The chemistry of the pyrazole and its derivatives is well established [1]. A multitude of synthetic routes have been worked out during the last few decades, as some members of the pyrazole family play an economically important role in pharmacy [2] and agrochemistry [3]. They are also of particular interest to the chemical community because they exhibit pesticide properties [4].

Recently, our group has developed general synthesis and characterisation of 3,5-substituted pyrazole [5], and 1,3,5-substituted pyrazole derived ligands [6], which have in the 3 and 5 positions methyl, phenyl, pyridyl and trifluoromethyl groups and in the *N*1 position ethyl, octyl and alkylamino groups. These compounds are obtained by treatment of hydrazine with 1,3-diketone compounds. The preparation of pyrazole derivatives is well documented for simple β -diketone precursors [7], but there are only limited reports of bis(β -diketones) being employed as precursors for bis-pyrazole derivatives [8].

In this paper, we research the synthesis and characterization of two new bis(β -diketone) and, by reaction with hydrazine, two new bis-pyrazole compounds (Scheme 1). The reaction of 3,3'-(pyridine-2,6-diyl)bis(1-phenylpropane-1,3-dione) monohydrated (**1a**·H₂O) or 3,3'-(pyridine-2,6-diyl)bis(1-(pyridin-2-yl)propane-1,3-dione) monohydrated (**1b**·H₂O) with hydrazine hydrate are investigated.

RESULTS AND DISCUSSION

The bis(β -diketone) compounds **1a**·H₂O and **1b**·H₂O have been synthesized following a Claisen condensation of

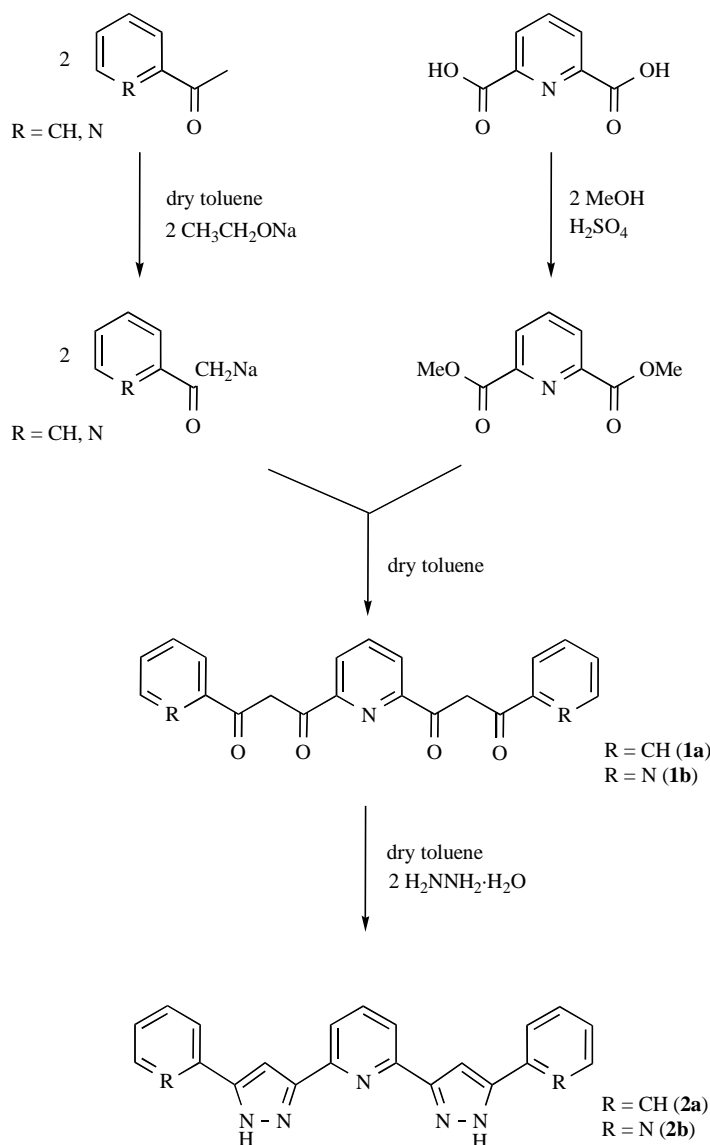
the appropriate ketones and esters. In particular, **1a**·H₂O was prepared by reaction of methylphenylketone and dimethyl pyridine-2,6-dicarboxylate in toluene at room temperature during 12 h, and **1b**·H₂O was prepared by reaction of methyl-(2-pyridyl)ketone and dimethyl pyridine-2,6-dicarboxylate in toluene at room temperature during 12 h. Nucleophilic attack of two equivalents of hydrazine monohydrate on the required bis(β -diketone) precursor (**1a**·H₂O and **1b**·H₂O) in toluene and under reflux for 18 h, led to formation of the desired bis-pyrazoles. These products are 2,6-bis(5-phenyl-1H-pyrazol-3-yl)pyridine dihydrated (**2a**·2H₂O) and 2,6-bis(5-(pyridin-2-yl)-1H-pyrazol-3-yl)pyridine monohydrated (**2b**·H₂O), with yields of 74 and 44 %, respectively (Scheme 1).

In DMSO-*d*₆ solution, the bis- β (diketone) compounds (**1a**·H₂O and **1b**·H₂O) described here are in equilibrium with the corresponding ketoenols [9]. These last species are the dominant ones, in an approximate ratio of 60% ketoenol:40% β -diketone. The ratio of the forms has been calculated through ¹H NMR experiments, especially from the integration of the signals HOC=CH-C(O) and (O)C-CH₂-C(O).

Both bis(β -diketone) (**1a**·H₂O and **1b**·H₂O) and both bis-pyrazole (**2a**·2H₂O and **2b**·H₂O) compounds were characterized by melting point, elemental analyses, mass spectrometry, IR, ¹H, ¹³C{¹H} and HSQC spectroscopies.

Elemental analyses confirm the proposed stoichiometry. Molecular weight of **1a**·H₂O, **1b**·H₂O, **2a**·2H₂O, and **2b**·H₂O were confirmed by mass spectrometry studies. For **1a**·H₂O, the peaks at 371 and 105 correspond to [**1a**]⁺ and [phCO]⁺, respectively, and for **1b**·H₂O, the peaks at 374, 226, 148 and 78 correspond to [**1b**+H]⁺, [py-CO-CH₂-CO-py]⁺, [py-CO-CH₂-CO]⁺ and [C₅H₄N]⁺, respectively. For the compounds **2a**·2H₂O and **2b**·H₂O, peaks at 363 and 365 have been observed, and they correspond to [**2a**]⁺ and [**2b**]⁺, respectively.

*Address correspondence to this author at the Departament de Química, Universitat Autònoma de Barcelona, 08193-Bellaterra-Cerdanyola, Barcelona, Spain; Tel: 34-935812895; Fax: 34-935813101; E-mail: Josefina.Pons@uab.cat



Scheme 1. Formation of bis(β -diketone) (**1a**, **1b**) and bis-pyrazole (**2a**, **2b**) compounds.

The IR spectra in the range $4000\text{--}400 \text{ cm}^{-1}$, for **1a**·H₂O and **1b**·H₂O, show bands attributable to $\nu(\text{C}=\text{O})$, $\nu(\text{C}=\text{C})$, and $\delta(\text{C-H})_{\text{oop}}$. Moreover, for **1b**·H₂O we can observe the band $\nu(\text{C}=\text{N})$. The IR spectra of **2a**·2H₂O, and **2b**·H₂O show the bands $\nu(\text{C}=\text{C})$, $\nu(\text{C}=\text{N})$, and $\delta(\text{C-H})_{\text{oop}}$ [10].

The ^1H , $^{13}\text{C}\{^1\text{H}\}$ and HMQC spectra for **1a**·H₂O, **1b**·H₂O, **2a**·2H₂O, and **2b**·H₂O were recorded in DMSO-*d*₆ [10]. HSQC spectra were used to assign signals of most of the hydrogen and carbon atoms.

For **1a**·H₂O and **1b**·H₂O, ^1H NMR spectra display signals between 8.36–7.40 ppm (**1a**·H₂O) and 9.00–7.80 ppm (**1b**·H₂O), attributable to H_{ph} and H_{py} . The signals corresponding to $\text{HOC}=\text{CH}-\text{C}(\text{O})$ and $(\text{O})\text{C}-\text{CH}_2-\text{C}(\text{O})$ are observed in each case at 7.22 and 5.01 ppm (**1a**·H₂O) and 7.45 and 4.92 ppm (**1b**·H₂O). The proportion of the keto/enol tautomers is 45/55 and 35/65, for **1a**·H₂O and **1b**·H₂O, respectively. These values have been calculated from the ^1H NMR spectra. The $^{13}\text{C}\{^1\text{H}\}$ NMR spectra display signals between 190.0–120.0 ppm (**1a**·H₂O) and 185.0–121.0 ppm

(**1b**·H₂O), attributable to C_{ph} and C_{py} . The signals corresponding to $\text{HOC}=\text{CH}-\text{C}(\text{O})$ and $(\text{O})\text{C}-\text{CH}_2-\text{C}(\text{O})$ are observed, in each case, at 93.4 and 48.5 ppm (**1a**·H₂O) and 94.4 and 48.3 ppm (**1b**·H₂O),

For compounds **2a**·2H₂O and **2b**·H₂O, ^1H NMR spectra display one broad band at 11.0 and 11.7 ppm, respectively, attributable to $\text{N}_{\text{pz}}-\text{H}$. The signals corresponding to H_{ph} and H_{py} are observed, in each case, at 8.10–7.70 ppm (**2a**·2H₂O) and 8.64–7.55 ppm (**2b**·H₂O). Finally, at 7.18 ppm (**2a**·2H₂O) and 7.36 ppm (**2b**·H₂O) appears a singlet attributable to CH_{pz} . The $^{13}\text{C}\{^1\text{H}\}$ NMR spectra display signals between 166.0–118.0 ppm (**2a**·2H₂O) and 149.5–123.3 ppm (**2b**·H₂O), attributable to C_{ph} and C_{py} . At 101.2 ppm (**2a**·2H₂O) and 102.6 ppm (**2b**·H₂O), the signal corresponding to CH_{pz} is observed.

CONCLUSION

In summary, we have presented the synthesis and characterization of two new bis(β -diketones) (**1a** and **1b**),

and the corresponding bis-pyrazoles (**2a** and **2b**). The bis-pyrazoles have been obtained, in good yields, by reaction of the bis(β -diketone) precursors and hydrazine hydrate.

EXPERIMENTAL

General

All reagents were commercial grade materials and were used without further purification. All solvents (ethanol and toluene) were previously deoxygenated in a vacuum line and all reactions were routinely carried out under nitrogen atmosphere.

The elemental analyses (C, H, N) were carried out by the staff of the Chemical Analyses Service of the Universitat Autònoma de Barcelona on a Carlo Erba CHNS EA-1108 instrument. Infrared spectra were run on a Perkin-Elmer FT spectrophotometer series 2000 cm^{-1} as KBr pellets in the range 4000–400 cm^{-1} under a nitrogen atmosphere. The ^1H , $^{13}\text{C}\{^1\text{H}\}$ NMR and HSQC spectra were run on a NMR-FT Bruker 250 MHz spectrometer in DMSO- d_6 solutions and room temperature. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR chemical shifts (δ) were determined relative to internal TMS and are given in ppm. Electronic impact mass spectra were measured on a Hewlett-Packard HP-5989A apparatus (GC/MS).

3,3'-(Pyridine-2,6-diyl)bis(1-phenylpropane-1,3-dione) monohydrated (**1a**·H₂O)

Under a nitrogen atmosphere, a 250 ml Schlenk flask was charged with sodium (60.9 mmol, 1.40 g). Deoxygenated ethanol (40 ml) was added and the mixture was stirred until all the sodium was consumed. The ethanol was eliminated under vacuum. Dry toluene (25–30 ml), dimethyl pyridine-2,6-dicarboxylate (20.8 mmol, 4.05 g) and methylphenylketone (80.5 mmol, 9.66 g) were added, in this order, always slowly, to the white residuum of sodium ethanolate. The mixture was stirred until a yellowish precipitate was formed (2h), and then it was gently warmed until the sodium salt of bis(β -diketone) was formed (12 h). The salt was filtered off and dried under vacuum. The resulting solid was slowly added to a vigorously stirred solution of ethanoic acid (30 ml), water (30 ml) and ice (100 g), yielding a white solid, which was filtered and dried under vacuum.

Yield: 76% (6.16 g), mp 150–152°. IR (KBr, cm^{-1}) 3063 $\nu(\text{C-H})_{\text{ar}}$, 1629 $\nu(\text{C=O})_{\text{as}}$, 1566 ($\nu(\text{C=C})$, $\nu(\text{C=N})_{\text{ar}}$), 1490 ($\delta(\text{C=C})$, $\delta(\text{C=N})_{\text{ar}}$), 1300 $\nu(\text{C=O})_{\text{s}}$, 1072 $\delta(\text{C-H})_{\text{ip}}$, 774, 685 $\delta(\text{C-H})_{\text{oop}}$. ^1H NMR (DMSO- d_6 solution, 250 MHz) δ : 8.36–7.40 (13H, m, H_{py} , H_{ph}), 7.22 (HOC=CH-C(O)), 5.01 ((O)C-CH₂-C(O)) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 solution, 63 MHz) δ : 190.0–120.0 (C_{py} , C_{ph}), 93.4 (HOC=CH-C(O)), 48.5 ((O)C-CH₂-C(O)) ppm. Found: C, 71.16; H, 4.75; N, 3.82; Calc. for C₂₃H₁₇NO₄·H₂O: C, 70.94; H, 4.92; N, 3.60%. MS(EI): m/z (%) 371 [(1a)⁺, 27], 105 [phCO⁺, 100].

3,3'-(Pyridine-2,6-diyl)bis(1-(pyridin-2-yl)propane-1,3-dione) monohydrated (**1b**·H₂O)

Under a nitrogen atmosphere, a 250 ml Schlenk flask was charged with sodium (60.9 mmol, 1.40 g). Deoxygenated ethanol (40 ml) was added and the mixture was stirred until all the sodium was consumed. The ethanol was eliminated

under vacuum. Dry toluene (25–30 ml), dimethyl pyridine-2,6-dicarboxylate (20.8 mmol, 4.05 g) and methyl-(2-pyridyl)ketone (81.8 mmol, 9.90 g) were added, in this order, always slowly, to the white residuum of sodium ethanolate. The mixture was stirred until a yellowish precipitate separated (2h), and then it was gently warmed until the sodium salt of bis(β -diketone) was formed (12 h). The salt was filtered off and dried under vacuum. The resulting solid was slowly added to a vigorously stirred solution of ethanoic acid (30 ml), water (30 ml) and ice (100 g), yielding a white solid, which was filtered and dried under vacuum.

Yield: 58% (4.70 g), mp 155–157°. IR (KBr, cm^{-1}) 3056 $\nu(\text{C-H})_{\text{ar}}$, 1615 $\nu(\text{C=O})_{\text{as}}$, 1566 ($\nu(\text{C=C})$, $\nu(\text{C=N})_{\text{ar}}$), 1437 ($\delta(\text{C=C})$, $\delta(\text{C=N})_{\text{ar}}$), 1290 $\nu(\text{C=O})_{\text{s}}$, 1075 $\delta(\text{C-H})_{\text{ip}}$, 971, 746 $\delta(\text{C-H})_{\text{oop}}$. ^1H NMR (DMSO- d_6 solution, 250 MHz) δ : 9.00–7.80 (11H, m, H_{py} , H_{ph}), 7.45 (HOC=CH-C(O)), 4.92 ((O)C-CH₂-C(O)) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 solution, 63 MHz) δ : 185.0–121.0 (C_{py} , C_{ph}), 94.4 (HOC=CH-C(O)), 48.3 ((O)C-CH₂-C(O)) ppm. Found: C, 64.20; H, 4.12; N, 10.53; Calc. for C₂₁H₁₅N₃O₄·H₂O: C, 64.45; H, 4.38; N, 10.74%. MS(EI): m/z (%) 374 [(1b+H)⁺, < 1], 226 [py-CO-CH₂-CO-py⁺, 9], 148 [py-CO-CH₂-CO⁺, 61], 78 [C₅H₄N⁺, 100].

2,6-Bis(5-phenyl-1H-pyrazol-3-yl)pyridine dihydrated (**2a**·2H₂O)

A 100 ml Schlenk flask connected to a Dean-Stark apparatus was charged with 3,3'-(pyridine-2,6-diyl)bis(1-phenylpropane-1,3-dione) monohydrated (2.57 mmol, 1.00 g) and hydrazine monohydrated (4.00 mmol, 0.20 g). Toluene (30–40 ml) was added, and the mixture was then refluxed for 18 h. After this time, the solution was allowed to cool to room temperature and then filtered, obtaining the desired product as a white solid.

Yield: 74% (0.59 g), mp 155–157°. IR (KBr, cm^{-1}) 3256 $\nu(\text{N-H})$, 3064 $\nu(\text{C-H})_{\text{ar}}$, 1599, 1563 ($\nu(\text{C=C})$, $\nu(\text{C=N})_{\text{ar}}$), 1470, 1453 ($\delta(\text{C=C})$, $\delta(\text{C=N})_{\text{ar}}$), 1074 $\delta(\text{C-H})_{\text{ip}}$, 764, 695 $\delta(\text{C-H})_{\text{oop}}$. ^1H NMR (DMSO- d_6 solution, 250 MHz) δ : 11.0 (br, N_{py}H), 8.10–7.70 (13H, m, H_{py} , H_{ph}), 7.18 (2H, s, CH_{pz}) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 solution, 63 MHz) δ : 166.0–118.0 (C_{py} , C_{ph}), 101.2 (CH_{pz}) ppm. Found: C, 69.20; H, 5.28; N, 17.60; Calc. for C₂₃H₁₇N₅·2H₂O: C, 69.16; H, 5.30; N, 17.53%. MS(EI): m/z (%) 363 [(2a)⁺, 100].

2,6-Bis(5-(pyridin-2-yl)-1H-pyrazol-3-yl)pyridine monohydrated (**2b**·H₂O)

A 100 ml Schlenk flask connected to a Dean-Stark apparatus was charged with 3,3'-(pyridine-2,6-diyl)bis(1-(pyridin-2-yl)propane-1,3-dione) monohydrated (2.56 mmol, 1.00 g) and hydrazine monohydrated (4.00 mmol, 0.20 g). Toluene (30–40 ml) was added, and the mixture was then refluxed for 18 h. After this time, the solution was allowed to cool to room temperature and then filtered, obtaining the desired product as a white solid.

Yield: 44% (0.34 g), mp 156–158°. IR (KBr, cm^{-1}) 3191 $\nu(\text{N-H})$, 3060 $\nu(\text{C-H})_{\text{ar}}$, 1598, 1567 ($\nu(\text{C=C})$, $\nu(\text{C=N})_{\text{ar}}$), 1456, 1378 ($\delta(\text{C=C})$, $\delta(\text{C=N})_{\text{ar}}$), 1091 $\delta(\text{C-H})_{\text{ip}}$, 780, 745 $\delta(\text{C-H})_{\text{oop}}$. ^1H NMR (DMSO- d_6 solution, 250 MHz) δ : 11.7 (br, N_{py}H), 8.64 (2H, d, o-H_{py}), 8.50–7.55 (11H, m, H_{py} , H_{ph}), 7.36 (2H, s, CH_{pz}) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (DMSO- d_6 solution, 63 MHz) δ : 149.5–123.3 (C_{py} , C_{ph}), 102.6 (CH_{pz}) ppm. Found: C, 65.67; H, 4.43; N, 25.42; Calc. for C₂₁H₁₅N₇·H₂O:

C, 65.79; H, 4.47; N, 25.57%. MS(EI): m/z (%) 365 [(2b)⁺, 51], 222 [py-pz-py⁺, 100], 78 [C₅H₄N⁺, 29].

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