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Synthesis and structural characterization of pyrazol-1′-ylpyrazolo[1,5-*a*]pyrimidines by multinuclear NMR spectroscopy

Ranjana Aggarwal [a,*], Garima Sumran [a], Rosa M. Claramunt [b], Dionisia Sanz [b,*], J. Elguero [c]

[a] Department of Chemistry, Kurukshetra University, Kurukshetra-136 119, India
[b] Departamento de Química y Bio-orgánica, Facultad de Ciencias, UNED, Senda del Rey 9, E-28040 Madrid, Spain
[c] Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain

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ABSTRACT

3(5)-Amino-5(3)-hydrazinopyrazole dihydrochloride (**8**) reacts with pentane-2,4-dione (**9a**) to afford 2-(3′,5′-dimethylpyrazol-1′-yl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**10a**) instead of the 3-(3′,5′-dimethylpyrazol-1′-yl)-4,6-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine isomer (**11**). Similarly, the reaction of **8** with phenyl-1,3-butanedione (**9b**) resulted into the formation of 2-(3′-methyl-5′-phenylpyrazol-1′-yl)-5-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (**10b**) out of the four possible regioisomers. The structure of the reaction products **10a** and **b** was established by analysis of high-resolution ^{1}H NMR spectra. Complete spectral analysis has been achieved utilizing (^{1}H–^{13}C) HMQC as well as (^{1}H–^{13}C) and (^{1}H–^{15}N) HMBC experiments.

1. Introduction

Amino-1*H*-pyrazoles are useful synthons and building blocks for many heterocyclic products particularly for pyrazolo[1,5-*a*]pyrimidines. The presence of both primary and secondary amine functionalities in 3-amino-1*H*-pyrazoles is conveniently utilized in making pyrazolo[1,5-*a*]pyrimidines *via* reacting them with bidentate electrophiles [1–10]. Formation of exclusively one isomeric pyrazolo[3,4-*b*]pyridine has been reported by us when several unsubstituted 5-aminopyrazoles were reacted with trifluoromethyl-β-diketones [11]. Joshi et al. [12] have also reported the formation of two isomeric products, 1*H*-pyrazolo[3,4-*b*]pyridines (**3**) and pyrazolo[1,5-*a*]pyrimidines (**4**), when 5-amino-3-aryl-1*H*-pyrazoles (**1**) were treated with 1-(4′-fluorophenyl)-butane-1,3-dione (**2**) (Scheme 1).

Furthermore, a perusal of literature reveals that where there is clear evidence of the exclusive formation of pyrazolo[1,5-*a*]pyrimidines, there are contradictory reports [3,4] about the position of CH_3 group at position-5 and/or -7. Novinson et al. [3] have reported peaks at 2.56 (C_7–CH_3) and 2.73 ppm (C_5–CH_3) in the ^{1}H NMR spectrum of 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5**) (Scheme 2). On the contrary, Almansa et al. [4] have described that the CH_3 group of 3-(4-fluorophenyl)-2-(4-methyl-sulfonylphenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine (**6**) at position-5 resonates upfield, at 2.63 ppm, as compared to CH_3 group at position-7 of 3-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine (**7**) at 2.88 ppm, respectively (Scheme 2).

Thus, having the above reported uncertainties in mind and in continuation of our efforts to synthesize pyrazolo[1,5-*a*]pyrimidines [13] with potential biological activity, we become interested in investigating and establishing the structure of the reaction products obtained by the condensation of 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**8**) with symmetrical and unsymmetrical β-diketones.

Reaction of 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**8**) with pentane-2,4-dione (**9a**) resulted in exclusive formation of a single isomer that may have structures either of pyrazol-1′-ylpyrazolo[1,5-*a*]pyrimidine (**10a**) or pyrazol-1′-ylpyrazolo[3,4-*b*]pyridine (**11**) (Scheme 3). The challenge was to differentiate and determine its structure by NMR spectroscopy. Similarly, phenyl-1,3-butanedione (**9b**) on reaction with **8** afforded a single isomer of fused pyrazolo[1,5-*a*]pyrimidine which may have one of the four possible regioisomeric structures (Scheme 4). To assign the structure of isolated regioisomers unambiguously and to solve the discrepancy reported in the literature [3,4], we have made use of high-resolution ^{1}H NMR as well as multinuclear (^{13}C and ^{15}N) NMR spectroscopy.

* Corresponding authors.
E-mail addresses: ranjana67in@yahoo.com (R. Aggarwal), dsanz@ccia.uned.es (D. Sanz).

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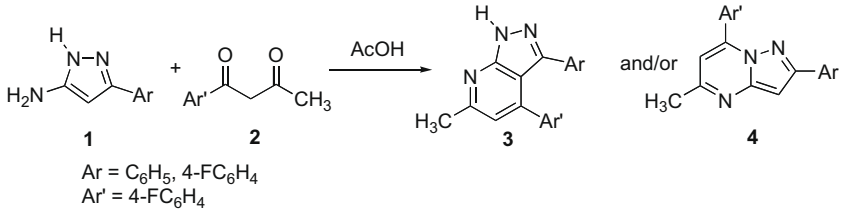
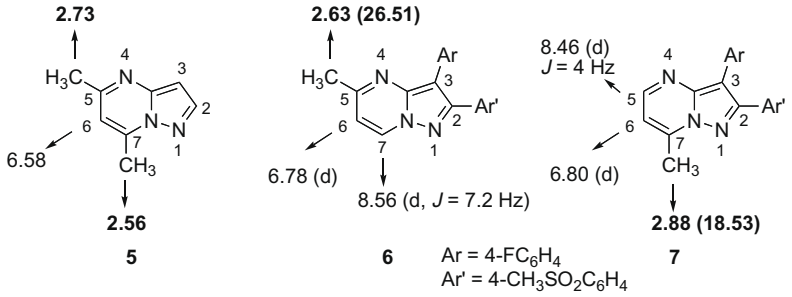
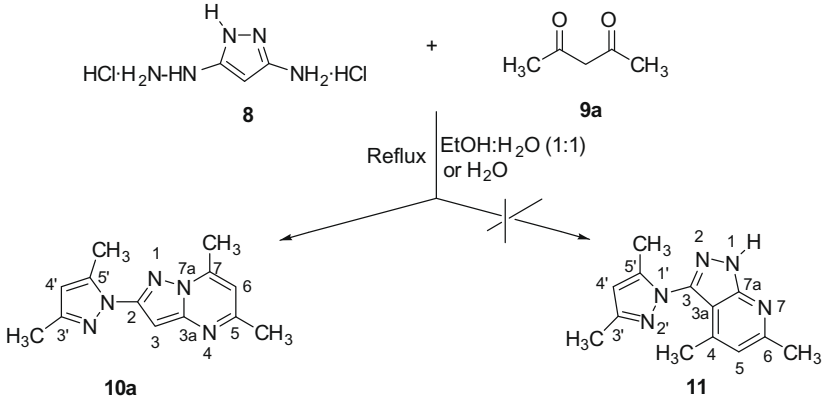


Scheme 1. Synthesis of compounds **3** and **4** [12].



Scheme 2. Literature results (in parentheses ^{13}C chemical shifts).



Scheme 3. Synthesis of **10a**.

2. Experimental

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer in KBr pellets (ν max in cm^{-1}). High-resolution mass spectra (HRMS) were measured in EI mode on a Kratos MS-50 spectrometer. The reactions were monitored by the TLC carried out on pre-coated silica gel glass plates. Pentane-2,4-dione and 1-phenyl-1,3-butanedione are commercially available. The required 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**8**) was synthesized by treating one equivalent of malononitrile with two equivalents of hydrazine hydrate according to literature procedure [14].

*2.1. Synthesis of 2-(3′,5′-dimethylpyrazol-1′-yl)-5,7-dimethylpyrazolo[1,5-a]pyrimidine (**10a**)*

A solution of 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**8**) (0.93 g, 0.005 mol) and pentane-2,4-dione (**9a**) (0.5 g, 0.005 mol) in H_2O (20 mL) was heated under reflux for 4 h. After the reaction was complete (from TLC), the mixture was cooled and excess of H_2O was distilled off under reduced pressure and the residue was recrystallized from EtOH–H_2O.

M.p. 128–130 °C; yield[1] 0.96 g, 80%. IR (cm^{-1}): 2921, 1629, 1573, 1533, 1424. ^1H NMR (400 MHz) ($CDCl_3$, δ): 2.31 (s, 3H, C_3'–CH_3), 2.54 (s, 3H, C_5–CH_3), 2.57 (d, 3H, ^4J = 0.8 Hz, C_5'–CH_3), 2.70 (d, 3H, ^4J = 1.0 Hz, C_7–CH_3), 5.99 (bs, 1H, C_4'–H), 6.55 (q, 1H, ^4J = 1.0 Hz, C_6–H), 6.69 (s, 1H, C_3–H). HRMS (m/z): 241.1329 (M^+) ($C_{13}H_{15}N_5$ requires 241.1327). Elemental Analysis: Found: C, 64.81; H, 6.45; N, 29.01%; $C_{13}H_{15}N_5$ requires C, 64.73; H, 6.22, N, 29.04%.

*2.2. Synthesis of 2-(3′-methyl-5′-phenylpyrazol-1′-yl)-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidine (**10b**)*

To H_2O (20 mL) was added 3(5)-amino-5(3)-hydrazinopyrazole dihydrochloride (**8**) (0.93 g, 0.005 mol) and 1-phenyl-1,3-butanedione (**9b**) (0.81 g, 0.005 mol) and the reaction mixture was boiled under reflux for 4 h. The progress of reaction mixture was moni-

[1] Theoretically 1 eq. of **8** is reacting with 2 eq. of **9a** and **b**. However, yields are calculated assuming 1 eq. of diketone.