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Short Note

6-(4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydro-pyrimidin-5-yl)-3,6-dimethyl-2-(methylthio)-6,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidine-4,5-dione

Pablo E. Romo [1], Jairo Quiroga [1,*], Braulio Insuasty [1], Manuel Nogueras [2] and Justo Cobo [2]

[1] Heterocyclic Compound Research Group, Department of Chemistry, Universidad del Valle, A.A. 25360 Cali, Colombia; E-Mails: pabloromo13@gmail.com (P.E.R.); braulio.insuasty@correounivalle.edu.co (B.I.)

[2] Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain; E-Mails: mmontiel@ujaen.es (M.N.); jcobo@ujaen.es (J.C.)

* Author to whom correspondence should be addressed; E-Mail: jairo.quiroga@correounivalle.edu.co; Tel.: +57-2-3393248; Fax: +57-2-3392444.

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Abstract: The title compound 6-(4-amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydro-pyrimidin-5-yl)-3,6-dimethyl-2-(methylthio)-6,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidine-4,5-dione was synthesized in 60% yield by a microwave-induced cyclocondensation reaction of aminopyrimidine with pyruvic acid in the presence of cerium ammonium nitrate (CAN) as catalyst.

Keywords: pyrrolo[2,3-*d*]pyrimidine; microwave irradiation; cerium ammonium nitrate

Introduction

Nitrogen heterocycles have received a great deal of attention in the literature as a result of their role as pharmacophores of great historical significance. Among these heterocyclic systems, those containing pyrimidine in particular have been the subject of expanding research efforts in heteroaromatic and biological chemistry.

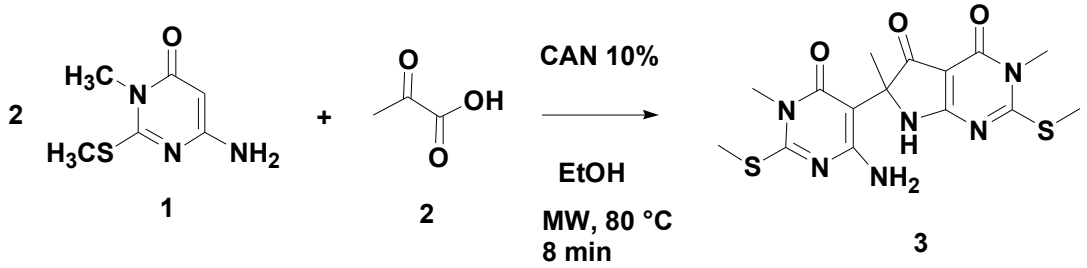
The structural diversity and biological importance of pyrimidines have made them attractive synthesis targets for many years. The pyrimidine is a widespread heterocyclic moiety, present in numerous

natural products as well as synthetic pharmacophores with biological activities [1–4]. Substituted pyrimidines, particularly with amino groups at the 2 and 4 positions, are known pharmacophores in several structure-based drug design approaches in medicinal chemistry [5–7]. Pyrimidines and their fused derivatives have been studied continuously because they exhibit broad biological activity as antitumor [8–11], antifungal [12,13], antibacterial [12,14–16], anti-HIV agents [17–19]. The synthesis of pyrrolopyrimidines is of high interest in medicinal chemistry, because some of them possess biological and pharmacological activities, such as anti-leukemia [20], tyrosine kinase inhibitors [20–23], anti-HIV-1 [24], antibiotic [25], antiangiogenic and antitumor properties [20]. Syntheses of pyrrolopyrimidines have been reported by several authors. Generally an aminopyrimidine reacts with either an α-halo-aldehyde [26,27], α-halo-ketone [28,29] or α-halo-acid chloride [29].

In continuation of our previous studies of the synthesis of heterocyclic compounds from heterocyclic amines [30–36], in this work a novel pyrrolo[2,3-*d*]pyrimidine synthesis was performed, where the target compound was obtained by the reaction between the aminopyrimidine and pyruvic acid (an α-keto-acid) using a microwave irradiation and cerium ammonium nitrate (CAN) as catalyst.

Results and Discussion

The synthesis of 6-(4-amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl)-3,6-dimethyl-2-(methylthio)-6,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidine-4,5-dione involves the reaction of aminopyrimidine **1** (2 eq.) with pyruvic acid (**2**, 1 eq.) in ethanol (Scheme 1). The reaction mixture was irradiated with microwaves at 80 ° C for 8 minutes; cerium ammonium nitrate (CAN) was used as the catalyst. The reaction was monitored using thin layer chromatography. The yellow cream solid formed was filtered under reduced pressure and did not require further purification.

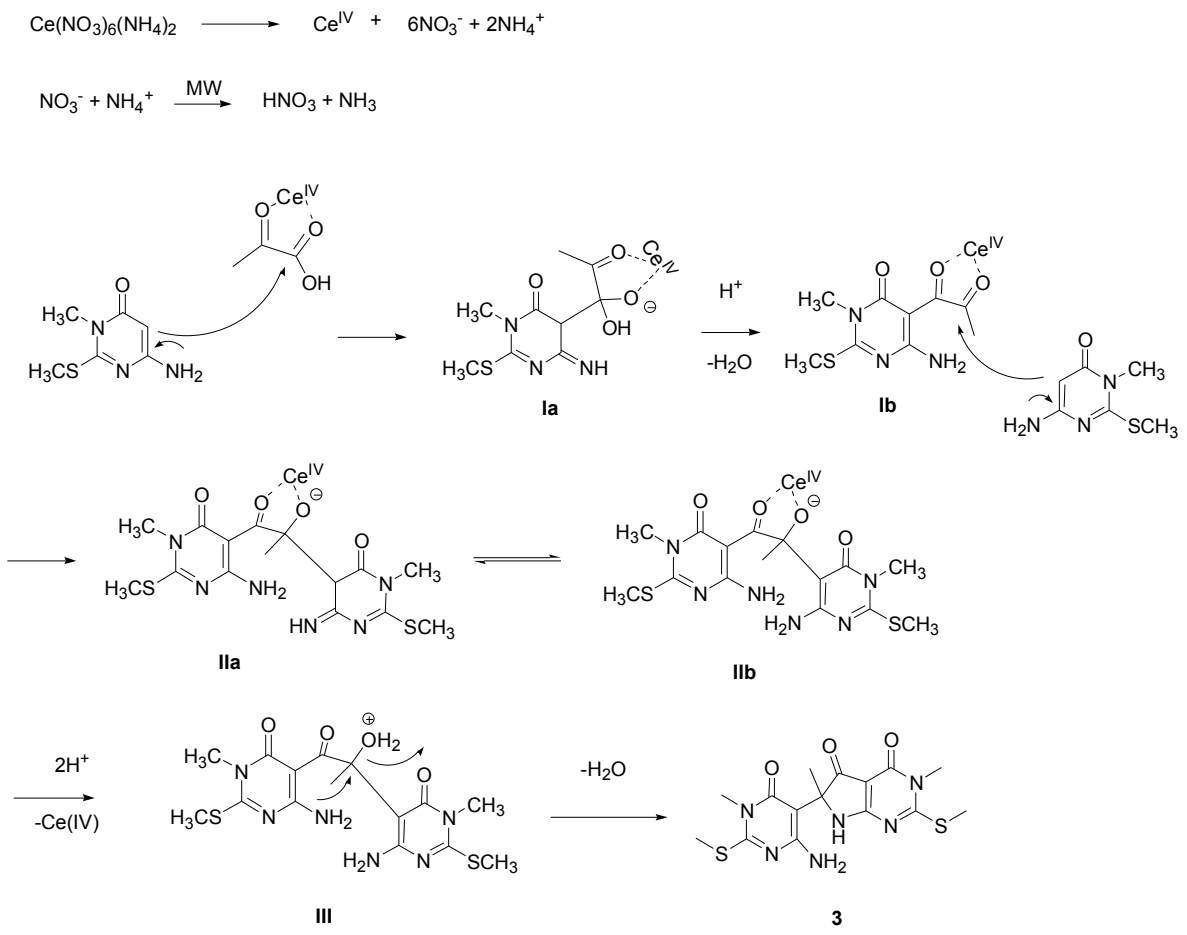


Scheme 1. Synthesis of 6-(4-amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl)-3,6-dimethyl-2-(methylthio)-6,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidine-4,5-dione.

The structure of the compound **3** was determined by spectroscopic techniques and mass spectrometry. The proton NMR spectrum showed signals for nonequivalent SCH_3 and NCH_3 groups at 2.54, 2.60, 3.20 and 3.39 ppm as a singlets, respectively, whereas a singlet at δ 1.55 ppm was assigned to the 6-CH_3 protons and two singlets at 6.45 and 10.83 ppm correspond to the NH_2 group and NH of the pyrrole ring. The IR spectrum analysis showed the NH band at 3402 and 3329 cm^{-1}, and carbonyl bands at 1751 and 1632 cm^{-1}.

A plausible mechanism is shown in Scheme 2. Initially the CAN, dissociates into its constituents. It is known that the nitrate anion and the ammonium cation can react to form nitric acid and ammonia. The Ce(IV) is coordinated with the carbonyl groups [37] of pyruvic acid, and the C-5 carbon of the

aminopyrimidine performs a nucleophilic attack on the carbonyl group of the carboxylic acid to form intermediate **Ia**, which loses water and forms **Ib**. Compound **Ib** subsequently reacts with another mole of aminopyrimidine to form **IIa-b**, and the acidic medium promotes the decoupling of the Ce(IV) from the carbonyl groups and allows a second dehydration, followed by the cyclization of the second amino group to form the desired pyrrolo[2,3-*d*]pyrimidine **3**.



Scheme 2. Plausible mechanism for the formation of the new pyrrolo[2,3-*d*]pyrimidine.

Experimental

General Information

The reaction progress was monitored by precoated TLC plates of silica gel 60GF254 of 0.2 μm thickness (Merck, Darmstadt, Germany). Melting points were measured using a Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were obtained with an IR Affinity-1 instrument (Shimadzu, Kyoto, Japan) equipped with an ATR accessory. The ^{1}H and ^{13}C-NMR spectra were run on a DPX 400 spectrometer (Bruker, Bruker BioSpin GmbH, Rheinstetten, Germany) operating at 400 and 101 MHz respectively, using dimethyl sulfoxide-d_6 as solvent and TMS as internal standard. The mass spectrum was obtained on a Shimadzu-GCMS-QP2010 spectrometer operating at 70 eV. Microwave experiments were carried out in a CEM Discover System^{TM} 300 W focused microwave reactor (manufacturer, Charlotte, NC, USA).

Procedure for the Synthesis of 6-(4-Amino-1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-5-yl)-3,6-dimethyl-2-(methylthio)-6,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-4,5-dione

A mixture of 6-aminopyrimidine **1** (2 mmol) and pyruvic acid (**2**, 1 mmol) and CAN 10% mol in ethanol (1 mL) was heated by microwave irradiation for 8 minutes (80 °C). The solid was filtered under reduced pressure and washed with ethanol. Compound **3** was obtained in high purity (according to TLC and the corresponding NMR spectrum) and did not require further recrystallization. Yellow cream solid, Yield: 60% M.p.: 254 °C (dec). IR (ATR) (cm^{-1}): 3402 (NH), 3329 (NH), 3217 (C-H), 1751 (C=O), 1632 (C=O). ^{1}H-NMR (DMSO-d_6) δ ppm: 1.55 (s, 3H, C$\underline{H_3}$), 2.54 (s, 3H, SC$\underline{H_3}$), 2.60 (s, 3H, SC$\underline{H_3}$), 3.20 (s, 3H, N-C$\underline{H_3}$), 3.39 (s, 3H,N-C$\underline{H_3}$), 6.45 (s, 2H, N$\underline{H_2}$), 10.83 (s, 1H, N$\underline{H}$). ^{13}C-NMR (DMSO-d_6) δ ppm: 14.5 (SCH_3), 15.2 (SCH_3), 20.2 (CH_3), 29.9 (N-CH_3), 30.2 (N-CH_3), 47.2 (C), 94.4 (C), 101.6 (C), 157.9 (C), 158.9 (C), 159.9 (C), 160.9 (C), 165.0 (C), 181.9 (C). MS (EI): *m/z* 394 (57, [M^+]), 379 (77, M^+ - CH_3). Anal. Calcd. For $C_{15}H_{18}N_6O_3S_2$ (394.47): C: 45.67; H: 4.60; N: 21.31; Found: C: 45.51; H: 4.49; N: 21.44.

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Author Contributions

The authors PER, JQ, BI, MN and JC designed and accomplished research. Also, they analyzed data and wrote the paper together. Finally, all authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest

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