The One-Pot Synthesis of Pyrano[2,3-d]pyrimidinone Derivatives with 1,4-diazabicyclo[2.2.2]octane in Aqueous Media

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ABSTRACT

1,4-diazabicyclo[2.2.2]octane (DABCO) was used as a catalyst for one-pot, three-component condensation reactions consisting of aromatic aldehydes, malononitrile and thiobarbituric acid in aqueous ethanol at room temperature. This method has the advantages of a simple operation, mild reaction conditions, high yields, by using a less toxic and low cost chemical as a catalyst.

Keywords: thiobarbuturic acid, malononitrile, DABCO, Aldehyde, Catalyst.

INTRODUCTION

Owing to their pharmacological activity, Barbituric (BA) and Thiobarbituric (TBA) acids, as well as their various substituted derivatives, are very important compounds in biological chemistry and medicine. Their biological activity is mainly related to tautomerism and acid-base equilibria and, in turn, to the nature of substituents 1-3. It is known that barbituric acid itself has no affect on the central nervous system 4, however it is a precursor to medical barbiturates which can be lethal in excessive amounts 5. Other work has shown that in mice, barbituric acid will cause liver and kidney weight increase 6. Barbituric acid is also a precursor to derivates that have been shown to have antibacterial activity 7,8 and for tumor inhibitory agents 9. Therefore, determination of trace amounts of barbituric acid is very important both in studies of biological and industrial processes.

In this paper we focus on the preparation of pyranopyrimidinone derivatives 4 (Scheme 1) in aqueous media. Due to the diverse biological properties of this compound class, there is a widespread interest in their synthesis. Compounds
with an uracil moiety antitumor, antibacterial, antihypertensive, vasodilator, bronchodilator, hepatoprotective, cardiotonic, and antiallergic activities. Some of them exhibit antimalarial, antifungal analgesics, and herbicidal properties 10–17.

Previous methods for the synthesis of 7-amino-6-cyano-5-(aryl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone derivatives have been reported in which a two-component reaction between arylidene malononitrile with barbituric acid occurred under harsh thermal conditions 18. Also, a microwave-assisted one-pot three-component cyclocondensation of barbituric acids, benzaldehyde derivatives, and alkylnitrile in the absence or presence of triethylamine Diammonium hydrogen phosphate (DAHP) 19-20 has been reported. These methods exhibit some disadvantages such as: harsh conditions, long reaction times, low yields, and effluent pollution.

EXPERIMENTAL

All of the chemical materials used in this work were purchased from Merck and Fluka and used without further purification. Melting points were determined with an Electro thermal 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR (FTLA 2000) spectrometer. 1H NMR and 13C NMR spectra were recorded on a Bruker DRX-500 AVANCE at 500 and 125MHz (respectively) using TMS as internal standard and DMSO-δ6 as solvent. Mass spectra data were obtained using a GC-MS Hewlett Packard (EI, 20 eV) instrument.

Synthesis 7-Amino-6-cyano-5-(aryl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone

A solution of aromatic aldehyde 1 (1 mmol), malononitrile 2 (1.2 mmol), barbituric acid 3 (1 mmol), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (10 mol%) in H2O (10 ml) and EtOH (10 ml) was stirred at room temperature for 2 h. After completion of the reaction, the solid product was collected by filtration and purified with washing with aqueous ethanol.

7-Amino-6-cyano-5-(4-bromophenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4a)

White color powder, m.p. 236°C (dec.). IR (KBr) (νmax/cm⁻¹): 3370 (NH2), 3189 (NH), 2220 (Ca=N), 1684 (C=O), 1567 cm⁻¹. 1H-NMR: δ=4.26 (s, 1H, H-5), 7.20 (d, 2H, JHH= 8.2Hz, H-Ar), 7.48 (d, 2H, JHH=8.2Hz, H-Ar), 7.86 (brs, 2H, NH2), 12.45 (brs, 1H, NH), 13.66 (brs, 1H, NH) ppm. 13C-NMR: δ=35.28 (CH), 58.48 (C-CN), 82.76 (C), 118.99 (Ca=N), 120.00 (C-Br), 129.91 (2 CH), 132.19 (2 CH), 132.74 (C), 143.04 (C-NH2), 157.42 (C=O), 160.34 (C), 173.97 (C=S) ppm.

7-amino-6-cyano-5-(3-chlorophenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4b)

White color powder, m.p. 236°C (dec.). IR (KBr) (νmax/cm⁻¹): 3370, 3196 (NH2), 3199, 3061 (NH), 2203 (Ca=N), 1683 (C=O), 1569 cm⁻¹. 1H-NMR: δ=4.29 (s, 1H,H-5), 7.19 (brs, 2H,NH2), 7.21–7.35 (m, 4 H, H-Ar), 12.45 (brs, 1H, NH), 13.50 (brs, 1H, NH) ppm. 13C-NMR: δ=35.28 (CH), 58.48 (C-CN), 82.76 (C), 118.99 (Ca=N), 120.00 (C-Br), 129.91 (2 CH), 132.19 (2 CH), 132.74 (C), 143.04 (C-NH2), 157.42 (C=O), 160.34 (C), 173.97 (C=S) ppm.

Scheme 1: synthesis of pyrano-pyrimidinone derivatives in aqueous media
7-Amino-6-cyano-5-(2,3-dichloro phenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4c)

White color powder, m.p. 257–258 °C. IR (KBr) (ν max/cm -1): 3460, 3316 (NH 2), 3172, 3064 (NH), 2190 (Ca=N), 1671, 1574 cm -1 . 1H-NMR: δ =34.03 (CH), 57.45 (C-CN), 93.29 (C), 119.35 (Ca=N), 129.20 (2 CH), 130.00 (CH), 131.26 (C-Cl), 132.59 (C-Cl), 144.00 (C), 153.10 (CNH2), 158.57 (C=O), 160.93 (C), 174.87 (C=S) ppm. Mass: (C14H9ClN4O2S) m/z(%)=370 (0.1, M 4+), 368 (0.4, M2+), 366 (0.7, M +), 265 (100), 267 (41), 222 (18), 206(2), 187(23).

RESULTS AND DISCUSSION

Herein we report a simple synthesis of 7-amino-6-cyano-5-aryl-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinones as a domino Knoevenagel–Michael condensation 21, catalyzed by 10% DABCO in aqueous media at room temperature (Scheme 1). Although we have not yet established the mechanism of the one-pot reaction between benzaldehyde derivatives, malononitrile and thiobarbituric acid in the presence of DABCO, a possible explanation is presented in Scheme 2.

We suggest that DABCO is an effective catalyst for the formation. The higher reactivity of the iminium group is utilized to facilitate Knoevenagel condensation between aryl aldehyde 1 and malononitrile 2, which proceeds via intermediate 5 and, after dehydration, olefin 7 is produced. DABCO also catalyzes the generation of a proposed carbonium thiobarbituric acid and this intermediate adds to olefin 6 to generate 4, after proton transfer,
tautomerization and hydrolysis of intermediate 8 (Scheme 2).

The structures of compounds 4(a-g) were deduced from their $^1$H NMR, $^{13}$C NMR and IR spectral data and their molecular weight confirmed by mass spectrometry. $^1$HNMR and $^{13}$C NMR spectroscopy were especially useful to elucidate the structures of products. Thus, all of the products exhibited a singlet peak at about $\delta = 4.22–4.85$ ppm for H-5 in the $^1$H NMR spectra, and also a distinctive signal at $\delta = 35–36$ ppm for C-5 in the $^{13}$C NMR spectra. The mass spectra of these compounds detected the expected molecular ion signals. Selected spectroscopic data have been given in general procedure section.

Table 1 shows the results obtained in the reaction of a series of representative aldehydes with malononitrile and thiobarbitoric acid. The effect of

Scheme 2. The proposed mechanism for the synthesis of 7-Amino-6-cyano-5-(Aryl)4-oxo-2-thioxo-5H-pyano[2,3-d] pyrimidinone in aqueous media catalyzed by 1,4-diazabicyclo[2.2.2] octane (DABCO).
substituents on the aromatic ring did not show special effects in terms of yields under these reaction conditions.

CONCLUSION

We have developed an easier, practically convenient, novel, ecologically safe method for the synthesis of pyrano[2,3-d]pyrimidinone derivatives using a green chemistry protocol. The use of DABCO as a green catalyst not only gave high yields of products but also provided a procedure that does not use harmful organic solvents.

REFERENCES


