

A GREENSYNTHESIS OF THIOXOPYRANO[2, 3-*d*]PYRIMIDINE USING IRON ORE PELLET AS NATURAL AND REUSABLE CATALYST

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Abstract

Iron ore pellet is used as natural and reusable catalyst for a simple and efficient one-pot synthesis of thioxopyrano[2,3-*d*]pyrimidine derivatives via initial Knoevenagel, subsequent Micheal and final heterocyclization reactions of aryl aldehyde, malononitrile and thiobarbituricacidingood to excellent yields. The present method is operationally simple and the use of water as the reaction medium makes the process environmentally benign.

Keywords

Natural catalyst, Iron ore pellet, Thioxopyrano[2,3-*d*]pyrimidine, Green media, Multicomponent reactions

Introduction

With green chemistry becoming a central issue in both academic and industrial research in the 21st century¹, development of environmentally benign and clean synthetic procedures has become the goal of today's organic synthesis. Many organic solvents are harmful and their use should be therefore minimized as far as possible or even excluded altogether. Green alternatives which have been investigated for organic reactions include water², supercritical fluids, in particular CO₂³, and solvent-free condition (SFC)⁴. Use of water as the reaction medium exhibits a remarkable benefit, because this green solvent is highly polar, and therefore immiscible with most of the organic compounds. Moreover, the water-soluble catalyst resides and operates in the aqueous media and separation of organic compounds is thus easy. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, comparatively cheaper to operate, and especially important in the industry and has a simple work up procedure⁵. Thus, there is a need for developing multicomponent reactions (MCR) in water without using any harmful organic solvents.

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-based equilibria and, in turn, to the nature of substituents⁶. It is known that barbituric acid itself has no effect on the central nervous system⁷, however, it is a precursor to medical barbiturates which can be lethal in excessive amounts⁸. Other works have demonstrated that, in mice, barbituric acid will cause liver and kidney weight increase⁹. Barbituric acid is also a precursor to the derivatives that have been shown to have antibacterial activity¹⁰ and for

tumor inhibitory agents¹¹. Therefore, determining the trace amounts of barbituric acid is very important in studies of biological and industrial processes.

Pyrano[2,3-*d*]pyrimidine moieties are clubbed into one molecule; then, the resultant derivative enhances its pharmaceutical activity because of being abundant in biologically active compounds such as Antitumour¹², cardiotoxic¹³ and antifungal activity¹⁴. Some of them exhibit antihypertensive activity¹⁵, antagonist, antimalarial, antimetabolite¹⁶ and antiviral evaluation properties¹⁷. Pyrano[2,3-*d*]pyrimidines are the building blocks used to evaluate their antibacterial activities¹⁸ and various derived natural products are also used as drugs for insomnia treatment¹⁹.

The importance of pyrano[2,3-*d*]pyrimidine derivatives has led many researchers to synthesize them using methods including traditional thermal condition²⁰⁻²², ultrasonic²³, and microwave irradiation^{24,25}. Different catalysts such as L-proline^{26,27}, *N*-methyl-morpholine²⁸, H₁₄[NaP₅W₃₀O₁₁₀]²⁹, triethylamine³⁰, 1,4-dioxane³¹, (SBA-Pr-SO₃H)³², [BMIm]BF₄³³, and [KAl(SO₄)₂] under heating³⁴ and diammonium hydrogen phosphate (DAHP)³⁵ have been studied in terms of the synthesis of pyrano[2,3-*d*]pyrimidine derivatives.

Each of the above methods has their own merit, with at least one of the limitations of drastic conditions as applying novel conditions, having long reaction times, and causing effluent pollution. Thus, new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to those heterocycles and their diverse biological properties. Application of inorganic solid catalysts as an effective heterogeneous catalyst could receive considerable attention in organic synthesis owing to their unique physical and chemical properties in terms of shape, porous solid possessing acid and Lewis basic sites, selectivity and thermal stability. Advantages of these catalyst systems over homogeneous ones are well-known and include stability, ease of handling, lack of corrosion, and other environmental hazards, cleaner product, and manipulative simplicity, ease of recovery and regeneration. As a part of the present program for applying novel catalysts to multi-component reactions, an efficient one-pot three-component synthesis of thioxopyrano [2,3-*d*]pyrimidine derivatives was reported which was catalyzed by iron ore pellet in aqueous media.

Result and discussion

The natural iron ore pellet catalyst used in this work was obtained in the southern Sirjan region, Iran³⁶. Prior to use, this material required initial treatments such as winnowing and washing. This catalyst had the following chemical composition: Fe (67-68 %), FeO (5 %), SiO₂ (1.5 %), MgO (1.2 %), CaO (≤0.6 %), Al₂O₃ (≤0.46 %), TiO₂ (0.01 %), (0.36%) and several metals (Mn, S, C, P) in the range of ppm and physical property: cold crushing strength (C. C. S = 270 Kg/pellet), abrasion index (A. I. 5.4 %), porosity (20-22%) and gradation (8-16 mm).

The original shape of this catalyst was approximately spherical with the diameter varying between 8 and 16 mm (Fig. 1). Morphology of the solid surface was observed in scanning electron micrograph (SEM) images (Fig. 2). The erratic shaped primary holes were agglomerated and size was in the order 100-200 μm.



Fig. 1. Image of iron ore pellet

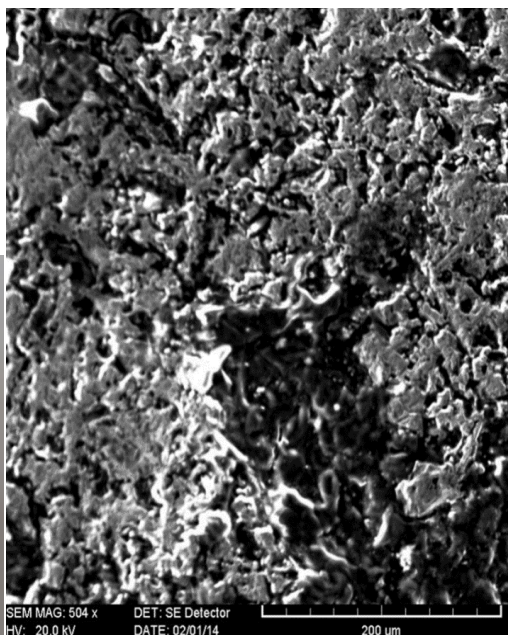
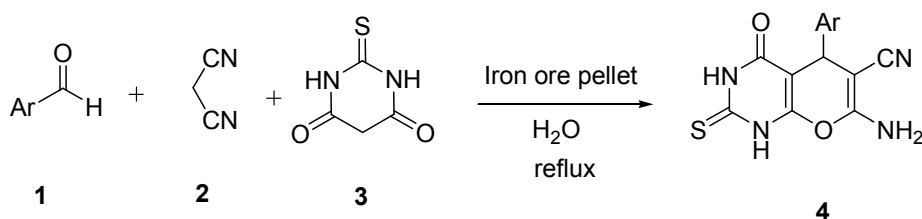


Fig. 2. SEM image of iron ore pellet

Attempts were made to report a green, efficient, convenient, and facile method for three component reaction of an aromatic aldehyde, malonitrile, and thiobarbituric acid, leading to thioxopyrano[2,3-*d*]pyrimidinone derivatives in the presence of iron ore pellet as a heterogeneous catalyst. It was found as a good catalyst for preparing these products.



Scheme 1. Synthesis of pyrano-pyrimidinone derivatives in aqueous media

Initially, the focus was on the systematic evaluation of different solvents for the model reaction of benzaldehyde, malonitrile, and thiobarbituric acid in the presence of iron ore pellet. Attempts for studying and optimizing the reaction conditions showed that carrying out the reaction in H₂O as the media had satisfactory results, revealing that the highest yield was obtained in water (Table 1, entry 6).

Table 1. Reactions of benzaldehyde, malonitrile and thiobarbituric acid in the presence of iron ore pellet in different solvent.

Entry	Solvent	Temperature	Time (min)	Yield(%) ^a
1	EtOH	reflux	8	76
2	MeOH	reflux	8	79
3	EtOH:H ₂ O (1:1)	reflux	8	77
4	MeOH:H ₂ O (1:1)	reflux	8	81
5	H ₂ O	r.t.	60	trace
6	H ₂ O	reflux	889	

^a)Isolated yield

Afterward, concentration was on the scope of this reaction with a variety of aldehydes (Scheme 1) to check the viability of this protocol in obtaining a library of thioxopyrano-pyrimidinone derivatives (Table 2).

Table 2. Preparation of thioxopyrano-pyrimidinone catalyzed by iore pellet at reflux in water

Entry	Ar	Time / min	product	Yield / % ^a m.p. (°C)
1	C ₆ H ₅	84a	89218-220	
2	2-OH-C ₆ H ₄	8	4b	88186-190
3	2-MeO-C ₆ H ₄	10	4d	84244-245
4	4-MeO-C ₆ H ₄	124e		82266-267
5	2,4-MeO-C ₆ H ₃	4f85		295-299
6	3,4,5-MeO-C ₆ H ₂	84g		79243-245
7	2,4-Cl-C ₆ H ₃	4h84		240-242
8	3-NO ₂ -C ₆ H ₄	4i86		239-240
9	4-NO ₂ -C ₆ H ₄	64j	86229-230	
10	2-Cl-C ₆ H ₄	84k	79291-292	
11	2,6-Cl-C ₆ H ₃	15	4l65	250-252
12	2-Br-C ₆ H ₄	164m		78228-230
13	3-Me-C ₆ H ₄	4n72		290-292
14	2-OH-5-Br-C ₆ H ₃	20	4o68	218-220

^a) Isolated yield.

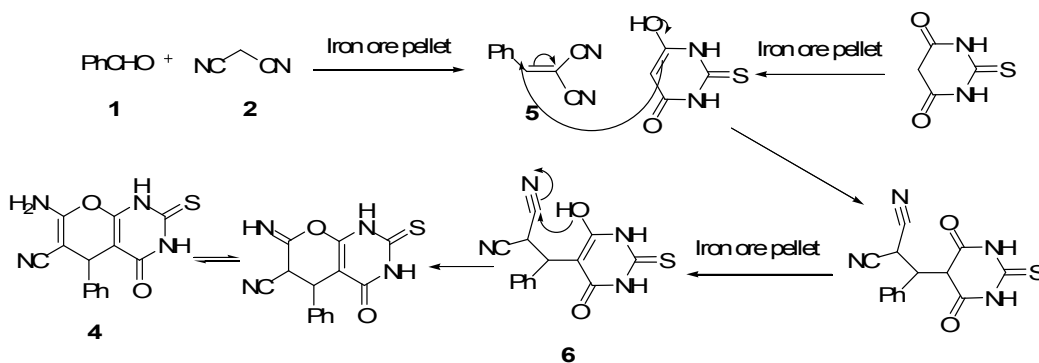
As can be seen in Table 2, in all the cases, aromatic aldehydes, substituted with either electron-donating or electron-withdrawing groups, smoothly underwent the reaction and gave the products in high-excellent yields under the optimized reaction conditions.

This natural solid catalyst could become particularly interesting when it can be regenerated. In a typical experiment, after completing the reaction, iron ore pellet was isolated by simple filtration, washed with water (10 mL) and DMSO (5 mL) for three times, dried, and successively used several times without the loss of activity. In fact, the reaction of benzaldehyde with malononitrile and thiobarbituric acid was repeated six times using the same catalyst with the respectably high yields of 85-89%.

Table 3. Reusability of catalyst at reflux

Run	1	2	3	4	5	6
Yeild (%)	89	87	88	88	87	85

Although the mechanism of the one-pot reaction between benzaldehyde derivatives, malononitrile, and barbituric acid was not established in the presence of iron ore pellet, it was estimated that the surface of the catalyst could present multicatalytic active sites. The basic sites polarize the C-H bond of the active methylene compound. The acidic surface probably coordinates with the oxygen of the carbonyl carbon, on which a partial positive charge appears. A possible explanation is presented in Scheme 2.



Scheme 2. Proposed mechanism

Higher reactivity of the iminium group is utilized to facilitate Knoevenagel condensation between aryl aldehyde **1** and malononitrile **2**, which produces intermediate **5**. Iron ore pellet also catalyzes the generation of a proposed enolicbarbituric acid and this intermediate adds to olefin **5** to generate **4**, after cyclization, proton transfer and tautomerization of intermediate **6**. In conclusion, using iron ore pellet as a natural, inexpensive, ecofriendly, non-toxic, and heterogeneous catalyst in aqueous media which has short reaction time and high-excellent yield are the key advantages of this work over some other reports. In addition, no harmful organic solvents were used.

Experimental

IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer (KBr). ^1H NMR spectra were recorded on a varian 400 MHz spectrometer. Melting points were determined using an Electrothermal 9100 and were uncorrected. The reactions were monitored by thin layer chromatography and the products were identified fully or by comparison of melting points and spectroscopic data with the previously reported ones.

General procedure for synthesis of thioxopyrano[2,3-d]pyrimidine derivatives using iron ore pellet (in water):

A mixture of malononitrile (2.2 mmol), substituted benzaldehydes (2 mmol), thiobarbituric acid (2 mmol) and iron ore pellet in water (10 ml) was heated at reflux for 8-30 min order to synthesize thioxopyrano[2,3-d]pyrimidine derivatives. Progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was allowed to cool down to room temperature. The solid was filtered off, washed with water and purified by recrystallization from ethanol. Spectral data of the selected compound is given below:

7-amino-5-(5-bromo-2-hydroxyphenyl)-2,3,4,5-tetrahydro-4-oxo-2-thioxo-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (4p). Yield 68%. M.p. = 218-220 °C. IR (KBr, cm^{-1}): 3418, 3319, 3198, 2853, 2191, 1711, 1661. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 4.98 (s, 1H, CH), 6.88 (d, $J = 8.8$ Hz, 1H-arom), 6.97 (br s, 1H, OH), 7.10 (br s, 2H, NH_2), 7.28 (dd, $J = 8.6, 2$ Hz, 1H, H-arom), 7.75 (t, $J = 7.6$, 1H, H-arom), 7.32 (s, 1H, H-arom), 12.01 (s, 1H, NH), 13.02 (s, 1H, NH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 32.5, 58.2, 83.3, 118.3, 119.6, 121.5, 122.9, 130.6, 136.8, 148.2, 150.3, 152.6, 163.5, 179.4.

Acknowledgments

The authors gratefully acknowledges the financial support from Islamic Azad University, Kerman Branch.

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Received on December 15, 2014.