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One-pot synthesis of tetrahydro benzo[*b*]pyran derivatives using iron ore pellet as natural, efficient and reusable heterogeneous catalyst in aqueous media

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Abstract: An efficient synthesis of tetrahydro benzo[*b*]pyran derivatives is achieved via a tree-component reaction of aldehydes, dimedone and malononitrile in the presence of iron ore pellet as natural catalyst in water. The key advantages are the short reaction time, high yields, simple workup, and green media. The catalyst can be recovered by simple filtration and reused at least seven cycles without losing its activities.

Keywords: Tetrahydro benzo[*b*]pyran, Natural catalyst, Iron ore pellet, Green media, Multicomponent reactions.

Introduction

Heterogeneous catalysis is an important application of porous solids possessing acid and Lewis basic sites. Studies on solid acid catalysts are enormous. Though little attention is devoted to basic catalysts in comparison with solid acid catalysts, high activities and selectivities are often obtained for numerous reactions [1]. Many reactions including isomerizations, alkylations, cyclizations and additions are carried out industrially using liquid bases as catalysts. The advantages of heterogeneous catalysis over conventional homogeneous reactions are that it provides greater selectivity, enhanced reaction rates, cleaner product and manipulative simplicity. For these reasons, heterogeneous catalysis can be considered as a new attempt to develop the notion of 'clean chemistry'.

Design of efficient chemical reaction sequence that furnishes maximum structural complexity and diversity with a minimum number of synthetic steps to provide compounds with increasing properties is a major challenge of modern drug discovery [2]. Recently, multicomponent reaction has emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom-economy and convergent character, the simplicity of one-pot procedure, the possible structural variation, the accessible complexion of the molecule, and the very large number of accessible compounds are among the described advantages of multicomponent reaction [3]. Thus, they are perfectly amenable to automation for combinatorial synthesis [4].

Benzopyrans and polyfunctionalized benzopyrans, in particular have shown many biological and pharmacological properties including spasmolytic, antianaphylactin, diuretic, antisterility, anticancer agents, cosmetics, pigments and biodegradable agrochemicals [5, 6]. They are also used for the treatment of neurodegenerative disease, downes syndrome and AIDS associated dementia as well as for treatment of myoclonus and schizophrenia [7]. Also, 4*H*-benzopyrans are major skeleton in many natural products [8] and 2-amino-4H-benzo[b]pyrans are useful as photo active materials [9]

Due to their applications, the syntheses of heterocyclic compounds including these ring systems

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have great importance in medicinal and organic chemistry. Strategies for the synthesis of these compounds have varied from one-pot to multi-step approaches [10].

The simplest method involves one-pot, three-component condensation of malononitrile, an aldehyde and dimedone in different conditions. Various catalysts such as Na_2SeO_4 [11], hexadecyldimethylbenzyl ammonium bromide [12], Ru(II) complexes [13], NaBr [14], trisodium citrate [15] tetramethyl ammonium hydroxide $(CH3)_4N^+OH^-$ [16], TEBA [17], KF-montmorillonite [18], KF-alumina[19], ionic liquid [20, 21], organocatalysts [22], TFE [23], $Yb(PFO)_3$ [24], TBAB [25], SiO_2-Pr-SO_3H [26] acetic acid [27], diammonium hydrogen phosphate [28], potasim phosphate [29], Silica Nanopatticles [30], DBSA [31] and without catalyst [32] have been used in this synthesis.

Each method has own advantages and disadvantages, however, because of wide range of biological activities of tetrahydrobenzo[*b*]pyran derivatives, we would like to explore the catalytic activity of Iron ore pellet as heterogenous nanoporous acid catalyst towards the synthesis of these products.

Results and discussion

To Natural iron ore pellet catalyst used in this work was obtained in the southern Sirjan region (Iran) [33]. Prior to use this material requires initial treatments such as winnowing and washing. This catalyst has following chemical composition: Fe (67-68 %), FeO (5 %), SiO_2 (1.5 %), MgO (1.2 %), CaO ((≤0.6 %), Al_2O_3 (≤0.46 %), TiO_2 (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 (Figure **1)**. The morphology of the solid surface was observed in scanning electron micrograph (SEM) images (Figure **2**). The erratic shaped primary holes are agglomerated and size in the order 100-200μm.

Attempts were made to report a green, efficient, convenient and facile method for tree component reaction of an aromatic aldehyde, malonitrile and 5, 5-dimethylcyclohexane-1,3-dione leading to tetrahydrobenzo[*b*]pyran derivatives in the presence of iron ore pellet as a heterogenous catalyst (Scheme **1**). It was found to be a good catalyst for preparation of these products.

Figure 1: Image of iron ore pellet.

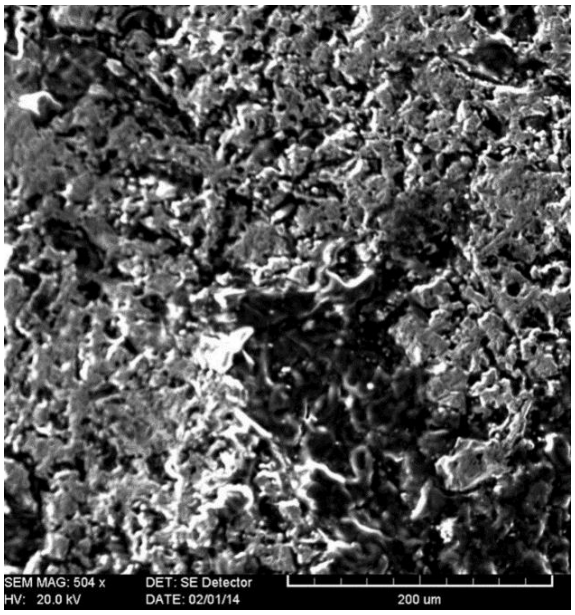


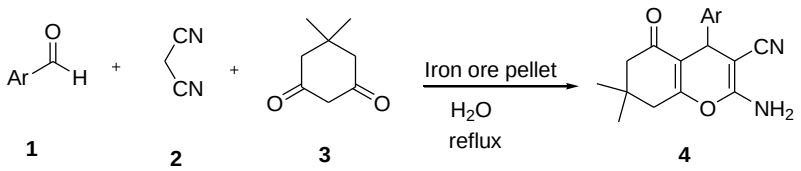
Figure 2: SEM image of iron ore pellet.

Initially, the focus was on systematic evaluation of different solvents for the model reaction of 4-chlorobenzaldehyde, malonitrile and dimedone in the presence of iron ore pellet. The attempts for studying and optimizing the reaction conditions showed that carrying out the reaction in H_2O as media had satisfactory results (Table **1**, entry 5).

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 tetrahydrobenzo[b]pyran derivatives (Table **2**).

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 becomes particularly interesting when it can be regenerated. In a typical experiment, after completion of the reaction, iron ore pellet was isolated by simple filtration, washed with water and

DMSO three times, dried and successively used several times without the loss of activity. In fact, the reaction 4-chlorobenzaldehyde with malononitrile and dimedone has been repeated five times using the same catalyst with respectably high yields: 85-90%.



Scheme 1: Synthesis of tetrahydrobenzo[*b*]pyrans derivatives in aqueous media.

Table 1: Reactions of 4-chlorobenzaldehyde, malonitrile and dimedone in the presence of iron ore pellet in different solvent.

Entry	Solvent	Temperature	Time (min)	Yield(%)[a]
1	EtOH	reflux	30	80
2	EtOH:H_2O (1:1)	reflux	15	80
3	MeOH	reflux	60	70
4	MeOH:H_2O (1:1)	reflux	40	80
5	H_2O	reflux	7	90

a) Isolated yield.

Table 2: Preparation of tetrahydrobenzo[*b*]pyran derivatives catalyzed by iron pellet at reflux in water.

					M.p. (°C)	
Entry	Ar	Time (min)	Product	Yield[a] (%)	Found	Reported
1	C_6H_5	20	4a	90	225-228	227-229 [25]
2	3-NO_2- C_6H_4	20	4b	90	200-202	210-211 [25]
3	4-NO_2- C_6H_4	20	4c	84	170-177	177-180 [25]
4	2-MeO-C_6H_4	10	4d	91	195-200	200-201 [34]
5	4-MeO-C_6H_4	18	4e	76	200-201	201-203 [25]
6	3,4,5-$(MeO)_3$-C_6H_2	10	4f	67	175-180	------
7	4-Me-C_6H_4	15	4g	75	212-215	210-212 [31]
8	4-$N(Me)_2$-C_6H_4	15	4h	85	228-231	223-225 [25]
9	4-Cl-C_6H_4	7	4i	90	210-214	212-214 [25]
10	2,4-Cl-C_6H_3	25	4j	85	110	118-119 [26]
11	3-OH-C_6H_4	15	4k	88	235-240	229-231 [25]
12	4-propyl-C_6H_4	15	4m	86	170-175	168-170 [21]

[a]) Isolated yield.

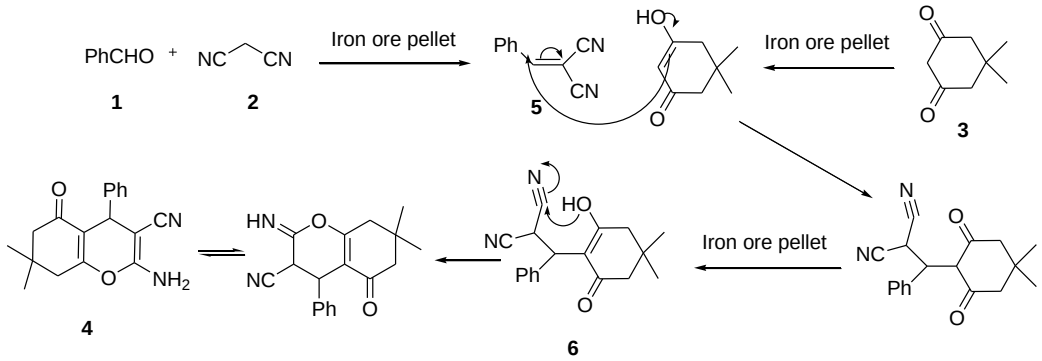
To show the efficiency of the selected method, Table **3** compares the results obtained in the present study with some of those reported in the literature.

Although we have not yet established the mechanism of the one-pot reaction between benzaldehyde derivatives, malononitrile and dimedone in the presence of iron ore pellet, we estimate that the surface of the catalyst presents 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**.

Table 3: Comparison of our results with some of those reported in the literature for the reaction of benzaldehyde, malononitrile and dimedone.

Entry	Reaction condition	Yield (%)	Time	Ref.
1	TFE, reflux	90	5 h	[23]
2	$Yb(PFO)_3$ (5 mol%), 60 °C, ethanol	90	5 h	[24]
3	TMGT, TBAB, 60 °C	80	50 min	[20]
4	TBAB (10 mol%), water, reflux	90	40 min	[25]
5	SiO_2NPs (5 mg), EtOH, r.t.	98	20 min	[30]
6	Na_2SeO_4, EtOH/H_2O, reflux	97	1 h	[11]
7	H_2O, reflux	81-99	3.5 h	[32]
8	Iron ore pellet, Water, reflux	90	20 min	this work



Scheme 2: Proposed mechanism for synthesis of tetrahydrobenzo[*b*]pyrans derivatives.

The C–C bond formation is facilitated and knoevenagel product is obtained by the transfer of a proton followed by dehydration. Then, Michael addition of dimedone **3** to the arylmethylidene malononitrile **5** followed by cyclization **6** and rearrangement provided the desired products **4**.

Conclusion

In conclusion, we have developed a novel and highly efficient method for the synthesis of tetrahydrobenzo[b]pyran by treatment of aromaticaldehydes with malononitrile and dimedone in the presence of iron ore pellet as an effective catalyst in water. The significant advantages of this methodology are high yields, green media, short reaction times and a simple work-up procedure. Iron ore pellet as a catalyst is important from an environmental point of view and from the view point of economic considerations. It also has excellent activity on an industrial scale and in most cases can be recovered from reaction mixtures and reused without loss activity.

Experimental

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

General procedure for synthesis of tetrahydrobenzo[b]pyran using iron ore pellet (in water):

A mixture of malononitrile (2.2 mmol), substituted benzaldehydes (2 mmol), dimedone (2 mmol) and iron ore pellet (1 number) in water (8 mL) was heated at reflux for 10-25 min order to synthesize

tetrahydrobenzo[b]pyran 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 recrystalization from ethanol. Spectral data of the selected compounds are given below:

*2-amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo [b]pyran (**4f**):*

M.p. 175-180 °C. IR (KBr, cm^{-1}): 3395, 3212, 3180, 2194, 1682. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.03 (s, 3H, Me), 1.06 (s, 3H, Me), 2.14 (d, J = 16.0 Hz, 1H, CH_2), 2.29 (d, J = 16.0 Hz, 1H, CH_2), 2.50-2.59 (m, 2H, CH_2), 3.63(s, 3H, OMe), 3.72 (s, 6H, 2OMe), 4.14 (s, 1H, CH), 6.38 (s, 2H, H-Ar), 7.01 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 26.5, 28.6, 31.7, 35.6, 49.9, 55.7, 58.2, 59.9, 104.0, 108.4, 112.3, 119.7, 136.0, 140.5, 152.7, 158.3, 162.8, 195.7.

*2-amino-3-cyano-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo [b]pyran (**4i**):*

M.p. 210-214 °C. IR (KBr, cm^{-1}): 3391, 3290, 2970, 2191, 1665. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.95 (s, 3H, Me), 1.04 (s, 3H, Me), 2.11 (d, J = 16.0 Hz, 2H, CH_2), 2.25 (d, J = 16.0 Hz, 2H, CH_2), 4.20 (s, 1H, CH), 7.06 (br s, 2H, NH_2), 7.17 (d, J = 8.4 Hz, 2H, H-Ar), 7.35 (d, J = 8.4 Hz, 2H, H-Ar).

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