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Condition based divergence in synthesis of tetrahydrobenzo[*b*]pyrans

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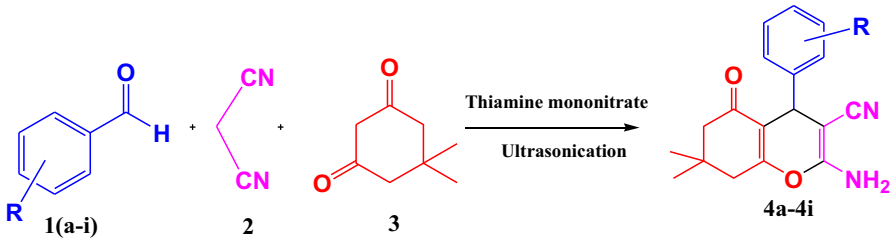
Abstract An environmentally benign novel strategy is developed for the synthesis of tetrahydrobenzo[*b*]pyrans by using thiamine mononitrate as a green catalyst, with the help of a conventional as well as non-conventional energy source. Synthesis of tetrahydrobenzo[*b*]pyrans is achieved by one pot condensation of aromatic aldehydes, malononitrile and dimedone in a water–ethanol system. Use of aqueous reaction media, mild conditions, water stable catalyst and energy plummeting process as well as excellent yield, are the key features in completing the reaction. This method excludes the use of volatile organic solvents, tedious workup and column chromatographic purification of compounds, making the method greener, convenient and superior.

Graphical Abstract



Keywords Aromatic aldehydes · Malononitrile · Dimedone · Ultrasonication · Green chemistry · Tetrahydrobenzo[*b*]pyrans

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Introduction

As green chemistry is becoming a central issue in both academic and industrial research in the twenty-first century, the development of environmentally benign and clean synthetic procedures have become the goal of present day of organic synthesis [1]. In order to achieve the goal of green sustainable technology, one pot multicomponent reactions have become a developing green tool. Such reactions can provide synthetic efficiency, high convergence, atom economy and uncomplicated procedure [2]. A rapid and efficient way of generating potentially active molecules in a one pot single step reaction, as well as multiplicity in the reaction, can be accomplished by varying the components of reaction [3].

Multicomponent reactions (MCRs) are useful in developing different heterocyclic scaffolds using the same reaction components by merely changing the reaction conditions, e.g. by using specific catalyst, reaction media or some different additives that promote the reaction and can make the pathway distinct. Condition-based divergence builds up a way of directing the reaction to be very rapid and resourceful.

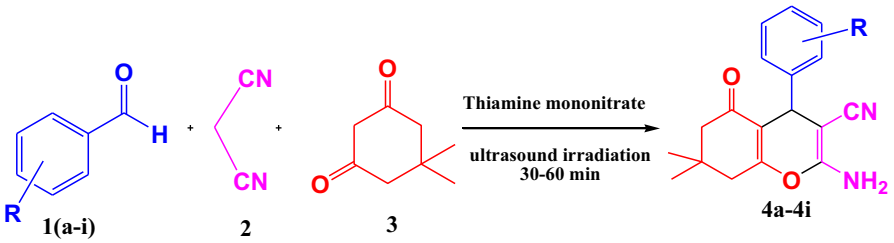
The development of biologically active agents has been pursued using a number of diverse pharmacological approaches. The search for safe and effective bioactive agents continues in order to develop drugs with novel pharmacological profiles with maximal therapeutic benefits. Literature survey has shown that tetrahydrobenzo[b]pyran derivatives have been listed to possess potential therapeutics activity. The pyrans and their fused derivatives recently stimulated extensive interest for anticoagulant, anti-HIV, anticancer, antimicrobial, antitubercular, antitumor and antioxidant agents [4]. Moreover, substituted pyrans are significant because of their optical properties and their constitution of a structural unit of a series of natural products [5].

Literature survey reveals that various methods reported for the synthesis of tetrahydrobenzo[b]pyrans that include potassium sodium tartrate [6], TiO_2 [7], ionic liquid [8], infrared irradiation [9], lactose [10], (*S*)-proline [11], L-proline [12], sodium selenate, starch [13], molecular sieves, sodium bromide, hexadecyldimethylbenzyl ammonium bromide [14], hydrogen phosphate, tetramethyl ammonium hydroxide, diammonium fluoride ion, MgO [15, 16], ZnO-beta zeolite, iodine, tetrabutylammonium bromide [17], amberlite IRA-40, cerium(III) chloride, lithium bromide [18], ionic liquid [19], etc.

All these protocols are gaining recognition for shortcomings such as insensitive reaction conditions and lack of attentiveness towards the environment. Hence, there is a vital need to develop a glowingly organized, simple and yield elevating protocol for the synthesis of tetrahydrobenzo[b]pyrans.

As a part of our continual efforts toward the development of efficient, economical and new methods using green catalysts and solvents [20], we investigated the activity of the readily available, renewable, recyclable and environmentally benign thiamine mononitrate as catalyst for synthesis of tetrahydrobenzo[b]pyrans under ultrasound irradiation (Scheme 1).

Reactions in aqueous media are gaining more significance because of their noncarcinogenic effects, low volatility, unique reactivity and selectivity, as well as being nonflammable and nontoxic. These features make the reaction eco-friendly, as



Scheme 1 Synthesis of tetrahydrobenzo[b]pyran derivatives

is the law in green chemistry. On the other hand, water soluble catalyst also plays a crucial role in speeding up the reaction and its heterogeneous nature facilitates an easy workup procedure by avoiding further purification processes.

Organic catalyst is a good option for selection because of its direct use in organic reaction. Thiamine occurs widely in nature, and the use of thiamine (Vitamin B1) in its hydrochloride form has been reported for many multicomponent reactions [21, 22] such as knoevenagel condensation, michael addition and cyclization and in constructing carbon–carbon and carbon–heteroatom bonds because of its potent catalyzing activity. It is used in the synthesis of octahydroquinazolinone [23], pyridines, dihydropyridine [24], benzoimidazol [25] etc. Thiamine mononitrate is one of the analogs of vitamin B1 that assist the reaction proficiently by providing catalytic sites closer to the reaction component without solvating itself. Its non toxicity, inexpensive and easy handling make the catalyst green (Fig. 1).

Therefore, we have made genuine efforts for the development of a greener protocol with condition-based divergence for the synthesis of tetrahydrobenzo[b]pyran. We report one pot, three component condensation of aromatic aldehyde, malononitrile and dimedone using thiamine mononitrate and water–ethanol system. With the help of ultrasound irradiation, it gives the desired product in excellent yield, within a short reaction time.

General experimental procedure for synthesis of tetrahydrobenzopyran (4a-i)

Conventional method

A mixture of aromatic aldehyde (1 mmol) and malononitrile (1 mmol) were taken into a 10-mL (4:1 water:ethanol) system and a catalytic amount of catalyst thiamine

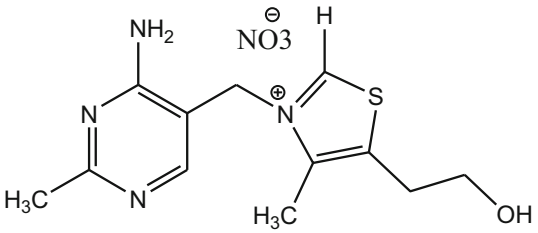


Fig. 1 Structure of thiamine mononitrate

mononitrate (10 mol %) was added. Precipitation occurred after 10 min, as the outcome of knovengel condensation. To this reaction mass, dimedone (1 mmol) was added. It was heated at 40 °C for a specific reaction time, as mentioned in Table 4. Progress of reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the crude mass was separated out and poured on crushed ice and kept at room temperature. The water soluble catalyst dissolved in water, which was further recycled and the solid product obtained was purified by crystallization using ethanol as solvent.

Ultrasound method

A mixture of aromatic aldehyde (1 mmol) and malononitrile (1 mmol) were taken into a 10-mL (4:1 water:ethanol) system and a catalytic amount of catalyst thiamine mononitrate (10 mol %) was added. This was subjected to ultrasound irradiation. After 3–5 min, dimedone (1 mmol) was added and it was irradiated further for a time specified in Table 4 until the complete conversion occurred. Reaction progress was monitored by TLC. After completion of the reaction, the reaction mass was poured on crushed ice and stirred well. It was separated by simple filtration and crude product was recrystallized using ethanol as solvent.

Spectral data of selected compounds

*2-Amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (***4a***): IR (KBr, cm^{-1})* 3369.5, 3310.8, 3182.5, 2963.5, 2835.2, 2188.8, 1734.6, 1654.5, 1601, 1504.9, 1371.3, 1243, 1029.**^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.15 (*d*, J = 8.6 Hz, 2H), 6.81 (*d*, J = 8.6 Hz, 2H), 4.54(brs, 2H, –NH_2), 4.35(s, 1H), 3.76(s, 3H, –OCH_3), 2.43(s, 2H), 2.21 (AB system, J_{AB} = 16.2 Hz), 1.10(s, 3H), 1.02(s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$):** 196.1, 161.4, 158.7, 157.5, 135.6, 133.6, 128.7, 118.9, 114.3, 114.1, 55.3, 50.8, 40.8, 34.9, 32.3, 29.0, 27.8. **Mass M$^+$Na,** 347.13 (100 %).

Results and discussion

The present manuscript deals with the synthesis of tetrahydrobenzo[b]pyran, considering the increased attention towards greener and non conventional techniques. We have found a unique, synthetic combining route to provide a greener protocol for medicinally important heterocyclic scaffolds with the help of water, which is cheap, safe and environment friendly as a reaction medium. In the preliminary experiments, we found optimum reaction conditions regarding the selection of catalyst, solvent and temperature of the reaction. For this optimization, anisaldehyde, malononitrile and dimedone were selected as model substrates.

For the selection of catalyst, various catalysts were implemented to carry out the model reaction. The results showed the need of a catalyst, since the reaction was incomplete without catalyst and only knovengel product was obtained. In order to get the appropriate catalyst result, we deliberately took all types of catalysts, such as

sulfonated species, Lewis acid, simple salts and organocatalyst (VB1). Initially, we explored a one pot model reaction of tetrahydrobenzo[b]pyran without using catalyst; it did not go to completion. Realizing the need for catalyst, we introduced sulfonated alumina; however, the yield of the product was found to not be satisfactory. Neutral species alumina was not eligible to carry out the reaction. However, Lewis acid ($ZnCl_2$) gave a better yield as compared to neutral salts (NaCl and ammonium acetate). When thiamine mononitrate was used as stable organocatalyst, the product was obtained in excellent yield within a short reaction time (Table 1).

In order to demonstrate the crucial role of solvent, the model reaction was carried out in various solvents by using thiamine mononitrate. The effects of various solvents with different criteria such as polarity and proticity were used in the model reaction to optimize the reaction conditions. We started the solvent study in non polar solvent 1,4-Dioxane. The reaction in non polar solvent yields only a 50 % yield in a long time span. As we were aware that the reaction proceeds via knovengel condensation and polar solvents are feasible for such condensations, we selected acetonitrile, DMF, and DCM as polar aprotic solvents, which resulted in enhancing the yield of product as compared to non polar solvents. The polar protic solvents like ethanol, water and methanol are well known for 1,2 elimination reactions, so we performed the model reaction in these solvents, which resulted in

Table 1 Effect of catalyst

Entry	Catalyst	Time (h)	Yield (%)[a]
1.	Without catalyst	10	No reaction
2.	Al_2O_3-SO_3H	5	56
3.	Al_2O_3	10	No reaction
4.	$ZnCl_2$	4	80
5.	NaCl	8	60
6.	Ammonium acetate	4	65
7.	Thiamine mononitrate	1	92

Rreaction condition: anisaldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol), thiamine mononitrate catalyst (10 mol %) in ethanol 10 mL at reflux

[a] Isolated yields

Table 2 Effect of solvents

Entry	Solvent	Time (min)	Yield (%)[a]
1.	Dioxane	240	50
2.	Acetonitrile	200	65
3.	DCM	240	60
4.	DMF	180	72
5.	Methanol	120	80
6.	Ethanol	75	85
7.	Water	80	90
8.	H_2O:Ethanol(1:1)	60	88
9.	H_2O:Ethanol (2:1)	60	90
10.	H_2O:Ethanol (4:1)	**45**	**90**

Rreaction condition: anisaldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol), thiamine mononitrate catalyst (15 mol %) in 10 mL solvent, reflux

[a] Isolated yields

moderate yield (Table 2).Water and ethanol show a comparable percentage of yield. In order to investigate and assess their exact roles, we carried out model reactions in various proportions of water:ethanol system (Table 2, entry 8, 9, 10). The (4:1) water:ethanol system was found to be an excellent solvent system for synthesis of tetrahydrobenzopyran.

Thiamine mononitrate is the salt of pyrimidine ring and a thiazole ring is linked by a methylene bridge with nitric acid. In order to show the scope and applicability of our catalyst, we used the above-mentioned optimized condition to evaluate the concentration of catalyst and temperature. The reaction was performed at reflux temperature and 15 mol % of thiamine mononitrate catalyst gives 80 % yield of product. Therefore, with the hope of increasing the yield and minimizing the reaction time, the same reaction was tested at lower temperatures (Table 3, entry 2, 3, 4 and 7). As a result, the best catalytic activity of thiamine mononitrate was found at 40 °C temperature favoring the higher yield.

In calculating the optimum concentration of catalyst, model reaction was carried out at 15, 10, and 5 mol % (Table 3, entry 4, 5, 6) of thiamine mononitrate in (4:1 water:ethanol) media. The product was obtained at 90, 94, 90 % respectively, at 40 °C temperature. Thus, it is concluded that 10 mol % thiamine mononitrate catalyst is sufficient for a good result. Finally, all reactions were scaled up with various substituted aromatic aldehydes by using 10 mol % catalyst and water:-ethanol (4:1).

Thiamine hydrochloride is hygroscopic, whereas the mononitrate form has almost no hygroscopic properties. For this reason, we selected mononitrate as the more stable form of vitamin B1. It is well known fact that thiamine is one of the coenzymes in biochemical reactions in aqueous media that involve some aldol type of condensations. Ultimately, being a cofactor of an enzyme, it enhances the rate of reaction, and this effect can be better seen in the presence of a water:ethanol system. The medium for the reaction is explained on the basis that solvent affects the transition state and when water soluble species are used as catalyst, substrates are activated for synthesis and polar protic solvents help the intermediates for salvation of the transition state, thereby increasing rate of reaction, which ultimately increases the product yield. Also, ethanol, like polar water miscible solvent, disperses the catalyst.

Table 3 Effect of the concentration of catalyst and temperature

Entry	Temp.	Thiamine mononitrate catalyst (mole %)	Yield (%)[a]
1.	Reflux	15	80
2.	80 °C	15	80
3.	60 °C	15	85
4.	40 °C	15	90
5.	40 °C	10	94
6.	40 °C	05	90
7.	RT	10	70
8.	RT	05	65

Reaction condition: anisaldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol). Thiamine mononitrate catalyst in 4:1 (water:ethanol), 10 mL

[a] Isolated yields

In an attempt to understand the mechanism of this reaction, the simplest analogy to be made is that the thiamine in its salt form behaves like Lewis acid [26] and thiazolium ion is acidic and provides the hydrogen, because the carbon atom between the sulfur and nitrogen atoms on thiazole ring thiamine has an acidic H^+ which acts as the functional part of the thiazolium ring. This hydrogen gets close enough to the aromatic aldehyde and provides an acidic environment. The thiamine also acts as an electron sink [27].

As pointed out in the mechanism, there is a possibility that thiamine also stabilizes the minor tauto-enol form of dimedone, and this enolic nucleophile constitutes the michael addition followed by intramolecular cyclization to manage the final product (Fig. 2).

After completing optimization of the reaction, the same set of reactions was carried out using a nonconventional energy source i.e., in ultrasonic bath. The influence of ultrasound irradiation was found to be very effectual in finishing the reaction within a short time, with excellent yield. This phenomenon encourages integrating the synthesis of derivatives by means of sonochemistry and conventional energy source (Table 4).

Various aldehydes were selected to synthesize the tetrahydrobenzopyran and it was established that this protocol is improved and highly efficient in obtaining excellent yield of desired product. The entire range of compounds was characterized

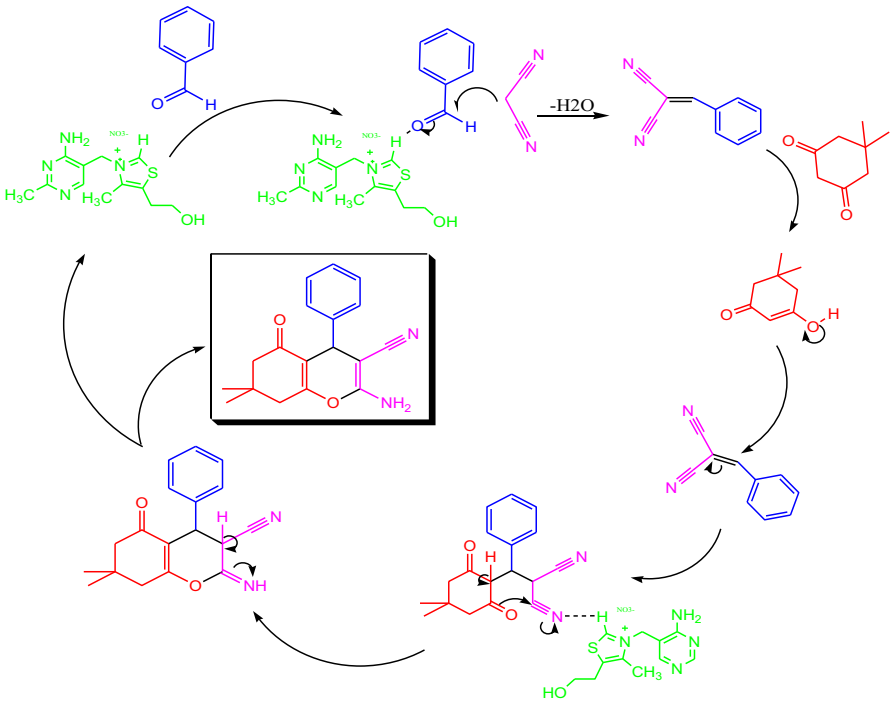


Fig. 2 Mechanism

Table 4 Synthesis of tetrahydrobenzopyran

Products	R	Conventional[a]		Nonconventional (ultrasoundirradiation)[b]	
		Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
4a	4-OCH_3	45	85	30	94
4b	H	60	80	20	82
4c	4-OH	50	85	20	90
4d	4-Cl	60	82	25	85
4e	2-NO_2	90	75	60	80
4f	4-$N(CH_3)_2$	50	90	30	92
4g	Cinnamal	120	82	45	82
4h	6-methoxy napthalene	80	80	45	85
4i	4-F	45	82	25	90

[a] Conventional reaction: aromatic aldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol), thiamine mononitrate catalyst(10 mol %) in 4:1(water:ethanol) 10 ml at 40 °C

[b] Nonconventional reaction: Aromatic aldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol), thiamine mononitrate catalyst (10 mol %) in 4:1(water:ethanol) 10 mL, ultrasound irradiation

[c] Isolated yields

by comparing the spectral data of (IR, ^{1}H NMR,^{13}C NMRand mass) with the valid results. This comparative study shows that synthesized compounds are precisely matched with the reported compounds. This method is very convenient, much better and highly competent in the area of green chemistry.

Conclusion

In summary, we report a simple, eco-friendly, three-component, one pot reaction for the synthesis of tetrahydrobenzopyran using thiamine mononitrate as a catalyst under ultrasound irradiation. This protocol offers several advantages, such as short reaction time, simple workup and simple reaction condition. Use of water as an eco-friendly solvent makes this method much better than other reported methods.

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