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A facile and efficient synthesis of tetrahydrobenzo[*b*]pyrans using lactose as a green catalyst

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Abstract Lactose has been used as a mild, efficient, green, and inexpensive catalyst for the synthesis of tetrahydrobenzo[*b*]pyran derivatives via a one-pot, three-component condensation between aryl aldehydes, malononitrile, and dimedone in H_2O:EtOH at 60 °C. This method offers a considerable number of advantages including short reaction time, high to quantitative yields, low cost, easy accesses, and simple work-up.

Keywords Lactose · Tetrahydrobenzo[*b*]pyran · Malononitrile · Dimedone

Introduction

Multi-component reactions (MCRs) have recently received a good deal of attention because of several new bonds in a one-pot reaction, low number of reaction and purification steps, selectivity, synthetic convergence, high atom economy, simplicity, synthetic efficiency, short reaction time, facility of workup, and high yield of products [1, 2]. Recently, MCRs have been the best way for the synthesis of heterocycles, which have great value in design and discovery of biologically new active compounds [1, 3–5]. Among them, Pyran annulated heterocylic derivatives represent an important class of oxygen-containing heterocycles being the main components of many naturally occurring products, and they are widely employed in cosmetics and pigments [1]. 4*H*-Benzo[*b*]pyrans have occupied a vital place in drug research because of their various biological and pharmacological activities such as spasmolytic, diuretic, anticoagulant, anticancer, antianaphylactic antioxidant, antileishmanial, antibacterial, antifungal, hypotensive, antiviral, antiallergenic,

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and antitumor activities [6–11]. Furthermore, they can be used as cognitive enhancers for the treatment of neurodegenerative disease, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS-associated dementia, and Down's syndrome, as well as for the treatment of schizophrenia and myoclonus [12]. Finally, some of 4*H*-benzo[*b*]pyrans are useful as photoactive materials [13]. Consequently, many methods for the synthesis of these compounds have been reported including the use of microwaves [14], ultrasonic irradiations [15], sodium bromide [15], hexadecyldimethylbenzyl ammonium bromide [16], tetramethyl ammonium hydroxide [17], diammonium hydrogen phosphate [18], fluoride ion [19], magnesium oxide [20], sodium selenite [21], iodine [22], $H_6P_2W_{12}O_{62}.H_2O$ [23], tetrabutylammonium bromide [24], cerium(III) chloride [25], lithium bromide [26], $RE(PFO)_3$ [27], amberlite IRA-40 (OH) [28], acidic ion liquids [29], L-proline [30], ZnO-beta zeolite [31], trisodium citrate [32], and basic ionic liquids [33]. Most of these synthetic methods suffer from drawbacks such as employing toxic catalysts, strong basic conditions, expensive and complex catalysts or reagents, many tedious steps, low yields of the products, and long reaction times in most cases, which restricts their usages in practical applications.

Recently, organic reactions in green solvents such as water, ethanol, and their mixtures, devoid of harmful organic solvents in the presence of green catalysts, have attracted a great deal of attention, as these solvents are inexpensive, safe, and environmentally benign [34, 35]. In continuation of our research on using inexpensive, easy-access, biodegradable, green catalysts, and solvents [36–39], we focused our investigation to develop new synthetic methods for the preparation of tetrahydrobenzo[*b*]pyrans using aryl aldehydes, malononitrile, and dimedone in the presence of lactose as a catalyst (Fig. 1) in H_2O/EtOH at 60 °C (Scheme 1). This is a one-pot, three-component reaction in H_2O/EtOH, which is not only operationally simple, clean, and efficient, but also consistently gives the corresponding products in good to excellent yields.

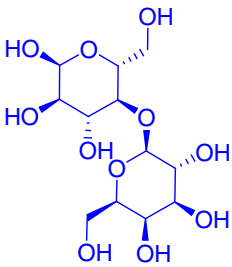
Experimental

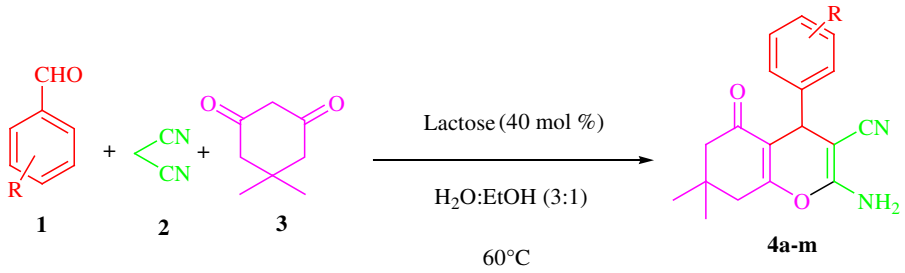
Melting points and IR spectra of all compounds were measured on an Electro thermal 9100 apparatus and FT-IR-JASCO-460 plus spectrometer. The ^{1}H NMR spectra were obtained on Bruker DRX-400 Avance instruments with DMSO and acetone as a solvent. All reagents and solvents were obtained from Fluka and Merck and used without further purification.

General procedure for the preparation of tetrahydrobenzo[*b*]pyrans

Lactose (40 mol%) was dissolved in H_2O:EtOH (3:1) then aromatic aldehyde (1 mmol), malononitrile (1 mmol), and dimedone (1 mmol) was added to mentioned solution at 60 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and the products were isolated by filtration and washed with water and recrystallized from

Fig. 1 Structure of lactose





Scheme 1 Synthesis of tetrahydrobenzo[*b*]pyran derivatives in the presence of lactose in H_2O:EtOH at 60 °C

ethanol (95 %) to afford pure products. Selected spectroscopic data of some products are given in the following sections.

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile (Table 4, entry 1)

IR (KBr, cm^{-1}): 3,390, 3,245, 2,960, 2,190, 1,676, 1,209; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.07 (s, 3H), 1.14 (s, 3H), 2.25 (dd, $J = 16.4$ Hz, 2H,), 2.48, (s, 2H), 4.43 (s, 1H), 4.55 (s, 2H), 7.2, 7.3 (m, 5H).

2-Amino-5,6,7,8-tetrahydro-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (Table 4, entry 5)

IR (KBr, cm^{-1}): 3,285, 3,160, 2,960, 2,185, 1,675, 1,209; ^{1}H NMR (400 MHz, (DMSO-d_6): δ (ppm): 1.055(s, 3H), 1.12 (s, 3H), 2.25 (dd, $J = 16.4$ Hz, 2H), 2.463 (s, 2H), 4.36 (s, 1H), 4.53(s, 2H), 5.26 (s, 1H), 6.728–7.103 (dd, $J = 8.4$, 4H).

2-Amino-5,6,7,8-tetrahydro-4-(2,3-dimethoxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (Table 4, entry 7)

IR (KBr, cm^{-1}): 3,305, 3,205, 2,945, 2,175, 1,676, 1,212; ^{1}H NMR (400 MHz, (DMSO-d_6): δ (ppm) = 1.08 (s, 3H), 1.12 (s, 3H), 2.22 (dd, $J = 16$ Hz, 2H), 2.44

(dd, $J = 17.6$, 2H), 3.85 (s, 3H), 3.95 (s, 3H), 4.52(s, 2H), 4.74(s, 1H), 6.716–6.809 (dd, $J = 8$, 2H), 6.972 (t, $J = 8$, 1H).

2-Amino-5,6,7,8-tetrahydro-4-(4-methyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (Table 4, entry 11)

IR (KBr, cm^{-1}): 3465, 3320, 2955, 2190, 1676, 1247; ^1H NMR (400 MHz, (DMSO-d_6): δ (ppm) = 1.08 (s, 3H), 1.12 (s, 3H), 2.23 (dd, $J = 16.4$ Hz, 2H), 2.30 (s, 3H), 2.40 (dd, $J = 17.6$, 2H), 4.52(s, 2H), 4.74(s, 1H), 6.716–6.809 (m, 2H), 6.972 (t, 1H).

Results and discussion

In order to optimize the reaction conditions, we studied the reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), and dimedone (1 mmol). As can be seen in Tables 1 and 2, the best results were obtained at 60 °C in the presence of 0.012 g (40 mol%) lactose in H_2O:EtOH (3:1). Also, we used sucrose and glucose as a catalyst under the optimized reaction conditions and the results are summarized in Table 3.

Table 1 Effect of amount of catalyst for the synthesis of tetrahydrobenzo[*b*]pyran

Entry	Catalyst loading (mol%)	Yield (%)
1	5	52
2	10	62
3	20	63
4	30	79
5	**40**	**89**
6	50	80

The optimize conditions are in bold

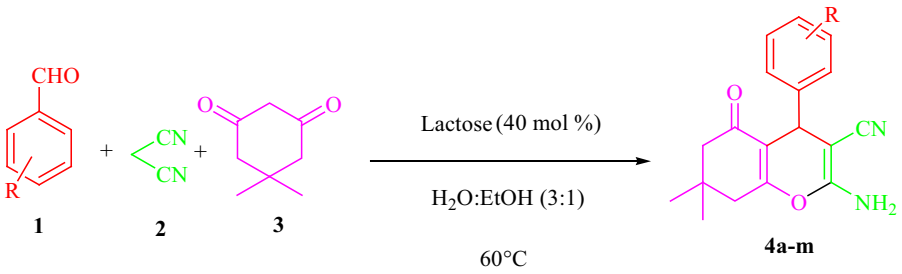
Table 2 Influence of different solvents and temperature on the synthesis of tetrahydrobenzo[*b*]pyrans in the presence of lactose (40 mol%)

Entry	Solvent	Temperature (°C)	Yield (%)
1	H_2O	70	79
2	H_2O:EtOH(2:1)	70	73
3	H_2O:EtOH(3:1)	70	82
4	H_2O:EtOH(4:1)	70	68
5	H_2O:EtOH(3:1)	r.t	–
6	H_2O:EtOH(3:1)	40	46
7	H_2O:EtOH(3:1)	50	71
8	**H_2O:EtOH(3:1)**	**60**	**89**

The optimize conditions are in bold

Table 3 Different catalytic systems and catalytic activity evaluation for the synthesis of tetrahydrobenzo[*b*]pyrans in the presence of lactose in H_2O:EtOH (3:1) at 60 °C

Entry	Catalyst	Mol%	Time (min)	Yield (%)
1	Sucrose	40	30	58
2	Lactose	40	30	63
3	Glucose	40	35	54

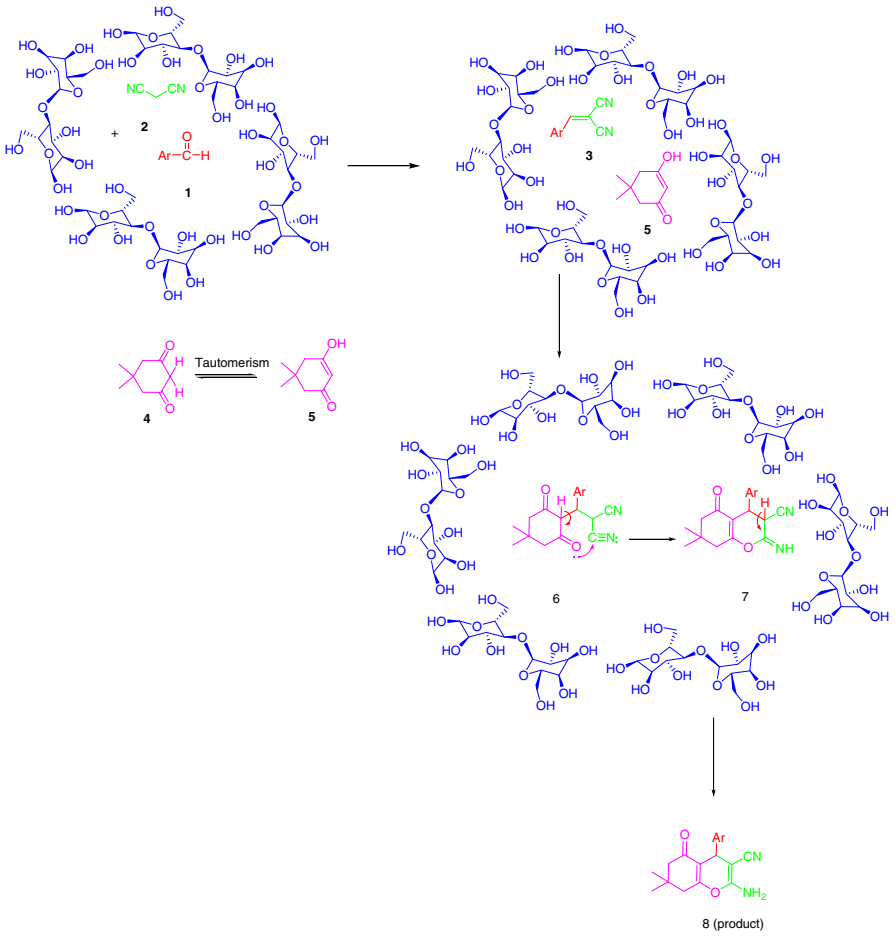


Scheme 2 Synthesis of tetrahydrobenzo[*b*]pyrans derivatives in the presence of lactose in H_2O:EtOH (3:1) at 60 °C

Table 4 Synthesis of tetrahydrobenzo[*b*]pyrans derivatives **4a–m** via the condensation of aryl aldehydes **1**, malononitrile **2**, and dimedone **3** in the presence of lactose (40 mol%) in H_2O:EtOH (3:1) at 60 °C

Entry	Aromatic aldehyde	Product	Time (min)	Yield (%)	MP (Obsd) (°C)	MP (Lit) (°C)
1	C_6H_5CHO	**4a**	25	89	229–232	233–234 [19]
2	4-CL C_6H_4CHO	**4b**	30	97	208–211	215–217 [31]
3	2-CL C_6H_4CHO	**4c**	35	91	196–198	214–215 [40]
4	2,4-$(CL)_2$ C_6H_3CHO	**4d**	30	89	120–123	115–117 [27]
5	4-OH C_6H_4CHO	**4e**	40	89	213–215	205–207 [31]
6	4-$N(Me)_2$ C_6H_4CHO	**4f**	45	95	198–200	198–200 [19]
7	2,3-$(OMe)_2$ C_6H_3CHO	**4g**	50	94	214–216	217–219 [41]
8	2-NO_2 C_6H_5CHO	**4h**	25	89	218–220	224–226 [40]
9	3-NO_2 C_6H_5CHO	**4i**	30	97	209–211	208–211 [20]
10	4-NO_2 C_6H_5CHO	**4j**	35	98	170–175	169–171 [31]
11	4-Me C_6H_5CHO	**4k**	35	84	208–211	214–216 [17]
12	2-Furaldehyde	**4l**	25	96	215–217	222–224 [19]
13	Thiophene-2-carbaldehyde	**4m**	25	97	215–219	210–212 [42]

Using this optimized reaction, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of substituted tetrahydrobenzo[*b*]pyrans using aryl aldehydes, malononitrile, and dimedone (Scheme 2). The results are summarized in Table 4.



Scheme 3 Suggested mechanism for lactose-catalyzed synthesis of tetrahydrobenzo[*b*]pyran derivatives

All reactions delivered good-to-excellent product yields and accommodated a wide range of aromatic aldehydes containing electron-donating and electron-withdrawing groups (Table 4, entries 1–11) without any significant substituent effects. This three-component condensation reaction also proceeded with hetero-aromatic aldehyde, such as 2-furaldehyde and thiophene-2-carbaldehyde and gave the corresponding product in high yield (entries 12 and 13).

We proposed a mechanism for the synthesis of tetrahydrobenzo[*b*]pyran derivatives in the presence of lactose as a catalyst. First, Knoevenagel condensation between **1** and **2** produced 2-benzylidenemalononitrile **3**, Michael addition of **3** with **5** (1,3-dicarbonyl compound), and followed cyclization, and tautomerization afforded the corresponding product. We suggested that the lactose hydroxys group has activated the carbonyl and nitrile groups (Scheme 3).

Conclusions

In summary, we report an eco-friendly and straightforward one-pot, three-component condensation for the synthesis of 4*H*-tetrahydrobenzo[*b*]pyran derivatives in the presence of lactose as a highly effective, green, and homogenous catalyst. It is clear that lactose is an effective catalyst and it provides a facile and useful method for the synthesis of 4*H*-tetrahydrobenzo[*b*]pyrans by condensation of aromatic aldehydes, malononitrile, and dimedone. Lactose is inexpensive, clean, safe, nontoxic, and it is easily obtained. Moreover, this method has several other advantages including, high yields, operational simplicity, and clean and neutral reaction conditions, which makes it a useful and attractive process for the synthesis of a wide variety of biologically active compounds.

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