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A Facile and Efficient Synthesis of Tetrahydrobenzo[*b*]pyrans Using Sucrose as Green, Inexpensive, Natural and Biodegradable Catalyst

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A very efficient one-pot three-component synthesis of pyran derivatives has been improved by condensation of aldehydes and malononitrile with dimedone under 80 °C using sucrose as natural and biodegradable catalyst in water. This method offers some advantages including inexpensive, high to quantitative yields, short reaction time, and easy work-up. Therefore, this methodology is entirely green and environmentally benign protocol for the preparation of tetrahydrobenzo[*b*]pyran derivatives.

Keywords: Sucrose, Malononitrile, Multi-component reactions (MCRs), Tetrahydrobenzo[*b*]pyran

INTRODUCTION

Development of environmentally benign and green synthetic methods is the aim of modern organic synthesis. Water acts as a fundamental role in life processes and also as a medium for organic reactions [1]. Development of multi-component reactions (MCR's) in water with suitable conditions such as an appropriate catalyst and use of any harmful organic solvents is need. Pyrans derivatives are interesting because of their wide range of biological activities [2], such as diuretic, anti-cancer, anti-coagulant, spasmolytic and anti-ancaphylactia activity [3]. In addition, they can be used as cognitive enhancers, for the treatment of neurodegenerative disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's diseases, including Alzheimer's disease, Down's syndrome and AIDS associated dementia as well as for the treatment of myoclonus and schizophrenia [4]. 4*H*-Pyrans also comprise the structural unit of a series of natural products [5]. A number of 2-amino-4*H*-pyrans are used as photoactive materials [6]. Consequently, several procedures have been reported for the synthesis of these compounds, including the use of microwave [7] and a variety of reagents like tetramethyl ammonium hydroxide [8], magnesium oxide [9], fluoride ion [10], sodium selenate [11], Amberlite IRA-400 (OH^-) [12], trisodium citrate [13], $H_6P_2W_{12}O_{62}.H_2O$ [14], ionic liquids [15] and ZnO-beta Zeolite [16]. However, these methods suffer mainly from the drawbacks of long reaction time, low yields, anhydrous organic solvents, elevated temperatures, tedious work-up, acidic or basic catalysts, and the use of stoichiometric and/or relatively expensive reagents. In recent years, the use of organic catalysts has received enormous attention in organic synthesis, because organocatalysis has some important advantages, such as the possibility of carrying out reactions in the presence of acid sensitive substrates, performing reactions in milder reaction conditions, and selectivity [17]. Also, the use of green solvent is of the great importance in organic synthesis such as water. Carrying out organic synthesis in aqueous phase is highly challenging both from the impact of the environmental pollution and also from the synthetic view point. Apart from being environmentally friendly, water possesses some unique properties different from other solvents which make it a very good reaction medium for organic synthesis.

In continuation our interest in developing green and efficient synthetic methodologies for the synthesis of important compounds [18-25], herein we want to report commercially available sucrose (Fig. 1), as highly efficient

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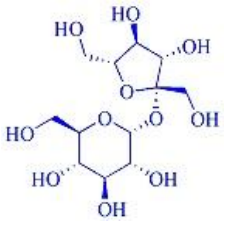
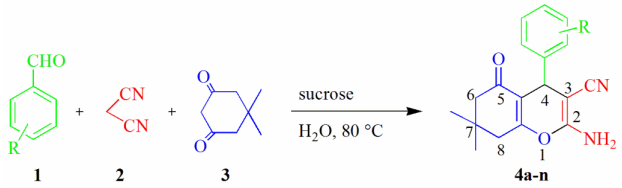


Fig. 1. Structure of sucrose.



Scheme 1. Synthesis of tetrahydrobenzo[*b*]pyran derivatives using sucrose as a natural catalyst

and natural organocatalyst, for the synthesis of pyran derivatives **4** *via* one-pot three-component reaction of aldehydes **1**, dimedone **2** and malonitrile **3** in aqueous media at 80 °C (Scheme 1).

EXPERIMENTAL

General

Melting points and IR spectra of all compounds were measured on an Electro thermal 9100 apparatus and FT-IR-JASCO-460 plus spectrometer, respectively. ^{1}H NMR spectra of compounds were recorded on a Bruker DRX-400 Avance instrument in $CDCl_3$ at 400 MHz. All reagents were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland).

General Procedure for the Preparation of Tetrahydrobenzo[b]pyrans

First, sucrose was dissolved in water (3 ml) then aldehyde (1 mmol), dimedone (1 mmol) and malononitrile (1 mmol) were added in sucrose solution (40 mol%, 0.14 g) and stirred at 80 °C for the time indicated in Tables 3. After completion of the reaction, as indicated by TLC, the products were isolated by simple filtration to yield the highly pure tetrahydrobenzo[*b*]pyran derivatives. Also, the catalyst was removed by simple filtration during the mixture reaction filtration. The pure product was characterized by conventional spectroscopic methods. Spectral data for the selected compounds **4a**, **4e**, **4h** and **4l**:

Compound 4a. IR (KBr), (ν_{max} (cm^{-1})): 3390, 3245, 2960, 2190, 1676, 1209; ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 1.07 (3H, s, CH_3), 1.14 (3H, s, CH_3), 2.25 (2H, dd, *J* = 24.0, 16.4 Hz, H-8), 2.48 (2H, s, H-6), 4.43 (1H, s, H-4), 4.55 (2H, s, NH_2), 7.21-7.33 (5H, m, ArH).

Compound 4e: IR (KBr), (ν_{max} (cm^{-1})): 3285, 3160, 2960, 2185, 1675, 1209; ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 1.05 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.24 (2H, dd, *J* = 20.0, 16.4 Hz, H-8), 2.46 (2H, t, *J* = 19.2 Hz, H-6), 4.36 (1H, s, H-4), 4.53 (2H, s, NH_2), 5.26 (1H, s, OH), 6.71-6.74 (2H, m, ArH), 7.08-7.12 (2H, m, ArH)

Compound 4h. IR (KBr), (ν_{max} (cm^{-1})): 3305, 3205, 2945, 2175, 1676, 1212; ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 1.08 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.21 (2H, dd, *J* = 20.0, 16.0 Hz, H-8), 2.39-2.51 (2H, m, H-6), 3.85 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.52 (1H, s, H-4), 4.74 (2H, s, NH_2), 6.72 (1H, dd, *J* = 8.0, 1.2 Hz, ArH), 6.79 (1H, dd, *J* = 1.6, 8.0 Hz, ArH), 6.97 (1H, t, *J* = 8.0 Hz, ArH).

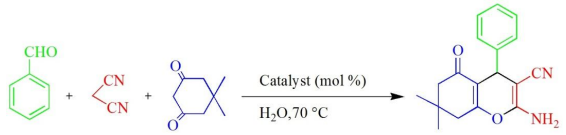
Compound 4l. IR (KBr), (ν_{max} (cm^{-1})): 3465, 3320, 2955, 2190, 1676, 1247; ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 1.06 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.23 (2H, dd, *J* = 20.0, 16.4 Hz, H-8), 2.30 (3H, s, CH_3), 2.46 (2H, s, H-6), 4.38 (1H, s, H-4), 4.54 (2H, s, NH_2), 7.10 (2H, d, *J* = 7.6 Hz, ArH), 7.12-7.14 (2H, m, ArH).

RESULTS AND DISCUSSION

Initially, we selected the reaction of benzaldehyde and dimedone with malonitrile in the presence of sucrose as a reaction model in water, which the results are shown in Table 1. As a preliminary study, different amounts of sucrose were used for the model reaction in water at temperature 70 °C to choose the catalytic amount of catalyst. Further experiments revealed that the optimum amount of catalyst should be 40 mol%. As shown in Table 1, 40 mol% of sucrose maintain the yield at 85% (Table1, Entry 7), so this amount of catalyst is sufficient to advance the reaction.

Next, we tested influence of different temperatures on the synthesis of tetrahydrobenzo[*b*]pyrans in the presence of sucrose (40 mol%) in aqueous media, the results are shown in Table 2. It was found that the best results are obtained at

Table 1. Catalytic Activity Evaluation for the Synthesis of Tetrahydrobenzo[*b*]pyran[a]

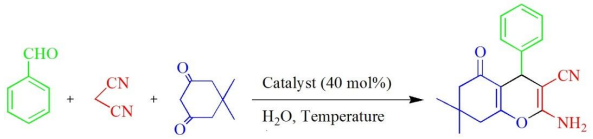


4a

Entry	Catalyst	Catalyst loading (mol%)	Solvent	Time (min)	Yield (%)
1	Sucrose	5	Water	60	60
2	Sucrose	7.5	water	55	62
3	Sucrose	10	water	53	79
4	Sucrose	20	Water	48	68
5	Sucrose	30	Water	45	77
6	Sucrose	35	Water	41	73
7	**Sucrose**	**40**	**Water**	**29**	**85**
8	Sucrose	50	Water	35	81

[a]Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol) and malonitrile (1 mmol) in water at 70 °C.

Table 2. Influence of Different Temprature on the Synthesis of Tetrahydrobenzo [b]pyrans in the Presense of Sucrose (40 mol%) in Aqueous Media



4a

Entry	Solvent	Temp.	Time (min)	Yield (%)
1	Water	r.t	120	-
2	water	40	50	59
3	water	50	45	58
4	Water	60	38	69
5	Water	70	29	85
6	**Water**	**80**	**17**	**91**
7	Water	90	25	68
8	Water	100	27	57

[a]Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol) and malonitrile (1 mmol) in water.

Table 3. Synthesis of Tetrahydrobenzopyran Derivatives Using Sucrose

Entry	R	Product	Time (min)	Yield (%)[a]	M.P. (°C)	Lit. m.p. (°C)[Ref.]
1	H	**4a**	17	91	229-232	233-234 [9]
2	4-Cl	**4b**	30	94	214-217	215-217 [14]
3	2-Cl	**4c**	35	96	217-219	214-215 [30]
4	2,4-Cl_2	**4d**	30	75	120-122	115-117 [29]
5	4-HO	**4e**	20	84	208-210	205-207 [14]
6	4-Me_2N	**4f**	30	81	202-204	198-200 [9]
7	4-HO-3-MeO	**4g**	30	87	230-234	230-238 [27]
8	2,3-$(MeO)_2$	**4h**	35	81	214-216	217-219 [30]
9	2-O_2N	**4i**	25	83	228-230	224-226 [17]
10	3-O_2N	**4j**	30	81	206-208	208-211 [10]
11	4-O_2N	**4k**	35	82	174-178	169-171 [14]
12	4-Me	**4l**	30	80	212-214	214-216 [8]
13	2-Furaldehyde	**4m**	25	85	217-221	222-224 [9]
14	Thiophene-2-carbaldehyde	**4n**	25	84	205-207	205-206 [26]

[a]Yields refer to the pure isolated products.

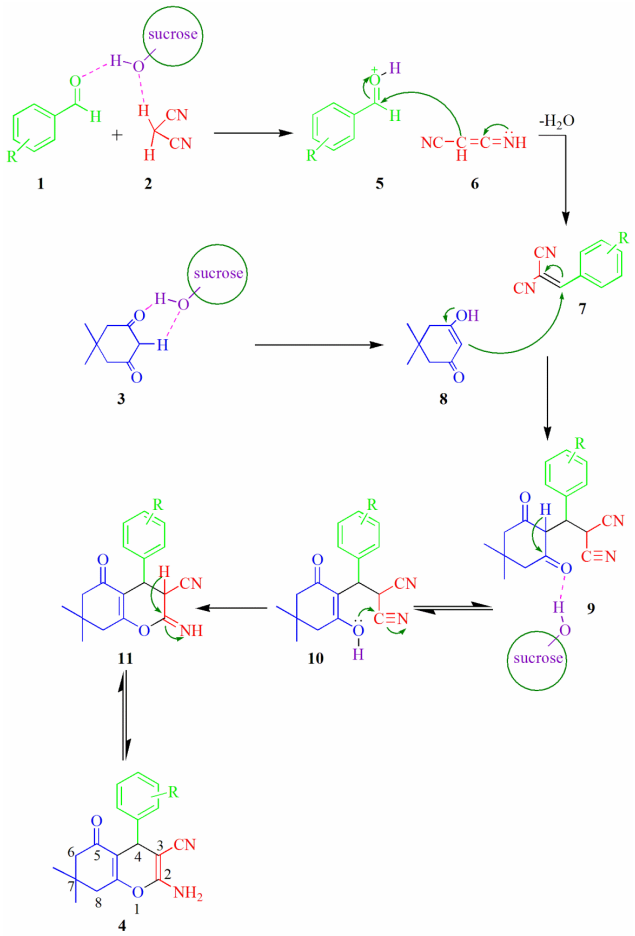
80 °C. Efficiency of 91% was generated (Table 2, Entry 6) at the higher temperature did not increase the reaction yield (Table 2, Entries 7 and 8). Also, it is worthy of notice that, the reaction did not progress even after 48 h at the room temperature (Table 2, Entry 1).

All reactions gave good-to-excellent product yields and accommodated a wide range of aromatic aldehydes containing electron-withdrawing and electron-donating groups (Table 3, Entries 1-12) without any significant substituent effect. Also, this three-component condensation reaction is proceeded with heteroaromatic aldehydes such as 2-furaldehyde and thiophene-2-carbaldehyde and produce the corresponding products in desirable yields (Table 3, Entries 13 and 14).

The formation of **4** can be explained by the possible mechanism presented in Scheme 1. The reaction can occur *via* the initial formation of the α,β-unsaturated compound **6**, from the Knoevenagel condensation reaction between aldehyde **1** and malononitrile **2**, which undergoes nucleophilic attack of the enole **8** of dimedone **3** to give the Michael adduct **9**. Then, the latter promotes the cyclization to intermediate **11**, and subsequent tautomerization to afford the 4H-tetrahydrobenzo[*b*]pyrans **4**.

CONCLUSIONS

In conclusion, we have shown a one-pot three-component reaction of aromatic aldehydes malononitrile, and dimedone in the presence of sucrose as a biodegradable catalyst. This methodology has some advantages, including readily available starting materials, eco-friendliness, operational simplicity, easy work-up, short times and that the products are isolated with good yields in high purity without the need for column chromatography. Therefore, we report a general and highly efficient one-pot multi-component reaction in aqueous media using an inexpensive, green, natural, biodegradable, safe and environmentally and commercially available sucrose catalyst which make it a useful and attractive process for the synthesis of a wide variety of biologically and pharmaceutically active



Scheme 2. Proposed mechanism for the synthesis of pyrans **4**

compounds.

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