

Highly efficient synthesis of tetrahydrobenzo[b]pyrans promoted by cesium carbonate under visible light

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Abstract

Multi-component reaction (MCR) is a powerful synthetic tool for the synthesis of biologically active compounds. Development of such multi-component reaction strategies in visible light has been of considerable interest, as they provide simple and rapid access to a large number of organic molecules through a sustainable path. An efficient and green protocol for the synthesis of tetrahydrobenzo[b]pyran derivatives by one-pot, three component coupling reaction of aromatic aldehyde, malononitrile, and dimedone has been developed using readily available cesium carbonate as the catalyst under visible light. This efficient procedure has the advantages of giving the target compounds in high yields, short reaction times, simple work-up procedure, use of cheap and easily available catalyst, and environmentally benign conditions.

Keywords: Cesium carbonate; aldehydes; one-pot three-component; visible light; malononitrile.

Introduction

Tetrahydrobenzo[b]pyrans bearing oxygen atom has received an increasing interest because of attractive pharmacological and biological properties [1,2]. They are class of drugs which work as antianaphylactin, anticoagulant, anticancer, diuretic, and spasmolytic agents [3,4] and can be used as cognitive enhancers for the treatment of neurodegenerative disease, including Alzheimer's disease, Huntington's disease, Parkinson's disease, Down's syndrome and schizophrenia [5,6]. Furthermore, these compounds occur in a series of natural

products [7,8] and some of these have photochemical activities[9].

The most general method for the preparation of tetrahydrobenzo[b]pyrans involves the one-pot reaction of aldehydes, malononitrile and dimedone in the presence of a Lewis/ mineral acid and base catalysts [10-31]. Although synthesis of tetrahydrobenzo[b]pyrans using several reagents have been previously reported, most of the present procedures have disadvantages such as long reaction time, use of strongly acidic condition or organic solvents, unsatisfactory product yield, and

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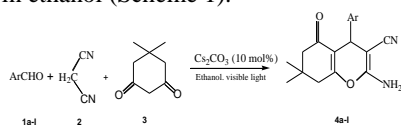
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formation of side products. Therefore, alternative approaches to these products need to be developed.

An attractive area in organic synthesis involves photochemical reactions particularly using visible light in environment-friendly solvents like water or aqueous-ethanol and is generally considered as a clean and green procedure. This type of photoactivation of substrates very often minimizes the formation of by-products and requires less time compared to thermal methods and for this reason, photochemical reactions occupy an interesting position and various reviews [32,33] have been published in this area.

In recent years, cesium carbonate has found wide applications as an excellent base for a variety of synthetic transformations [34-41] and has received even industrial acceptance. In this research, we describe a highly efficient and practical method for the synthesis of 4*H*-benzo[*b*]pyrans (**4a-l**) by three component reaction of aldehydes (**1a-l**), malononitrile (**2**) and dimedone (**3**) under visible light irradiation using readily available and non-toxic cesium carbonate as catalyst in ethanol (Scheme 1).



Scheme 1. Photochemical synthesis of tetrahydrobenzo[*b*]pyrans

Experimental

General

All reagents and solvents purchased from Sigma-Aldrich were used without further purification. Melting points

were measured on the programmable melting point apparatus and are uncorrected. The progress of the reaction was monitored by thin layer chromatography (TLC) which performed in the presence petroleum ether and ethyl acetate (8:2) on silica plates. Infrared (IR) spectra were recorded on a Bruker equinox-55 spectrometer using KBr discs, ¹H NMR spectra were recorded at 400 MHz using CDCl₃ or DMSO-*d*₆ as solvent and the presence of TMS as an internal standard.

General procedure for the synthesis of tetrahydrobenzo[*b*]pyran derivatives

Cesium carbonate (10 mol%) was added to mixture of aromatic aldehyde (1mmol), malononitrile (1.2mmol) and dimedone (1 mmol) in 5 mL of ethanol and irradiated with 200 W tungsten lamp (Philips India Ltd). The reaction progress was monitored by TLC in 5 min interval. Upon completion of the reaction, the reaction mixture was cooled and the crystalline product so obtained was filtered, washed with water, and dried in *vacuo*. The desired compounds, tetrahydrobenzo[*b*]pyrans (**4a-l**) were isolated in high yields in essentially pure form.

Spectral data for the selected compounds

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(phenyl)-5-oxo-4*H*-benzopyran(4a): IR (KBr) cm⁻¹: 3388, 2964, 2197, 1655, 1601; ¹H NMR (DMSO-*d*₆, 400 MHz), δ 0.97(s, 3H, CH₃), 1.06(s, 3H, CH₃), 2.10(d, 1H, *J*=16.1 Hz), 2.24(d, 1H, *J*=16.1 Hz), 4.19 (s, 1H), 6.80 (s, 2H), 7.13-7.27(m, 5H).

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4(4-nitrophenyl)-5-oxobenzopyran(4c)

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IR (KBr) cm^{-1} : 3369, 2980, 2189, 1656, 1602, 1513; $^1\text{H NMR}$ (DMSO- d_6 , 400 MHz), δ 0.96(s, 3H, CH₃), 1.05(s, 3H, CH₃), 2.09(d, 1H, $J=15.8$ Hz), 2.26(d, 1H, $J=16$ Hz), 2.52(s, 2H), 4.36(s, 1H), 7.11(s, 2H), 7.45(d, 2H, $J=8.64$ Hz), 8.16(d, 2H, $J=8.64$ Hz).

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4(4-Chlorophenyl)-5-oxo-benzopyran(4e)

IR (KBr) cm^{-1} : 3379, 2961, 2188, 1674, 1631; $^1\text{H NMR}$ (DMSO- d_6 , 400 MHz), δ 0.96(s, 3H, CH₃), 1.05(s, 3H, CH₃), 2.12(d, 1H, $J=16.1$ Hz), 2.22(d, 1H, $J=16.1$ Hz), 4.50(s, 2H), 4.19(s, 1H), 6.83(s, 2H), 7.14(d, 2H, $J=8.4$ Hz), 7.27(d, 2H, $J=8.4$ Hz).

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4(4-hydroxyphenyl)-5-oxo-benzopyran(4g)

IR (KBr) cm^{-1} : 3474, 2965, 2200, 1655, 1615, 1213; $^1\text{H NMR}$ (DMSO- d_6 , 400 MHz), δ 0.95(s, 3H, CH₃), 1.05(s, 3H, CH₃), 2.09(d, 1H, $J=16.1$ Hz), 2.26(d, 1H, $J=16.1$ Hz), 2.40-2.51(m, 2H), 4.08(s, 1H), 6.66(d, 2H, $J=8.4$ Hz), 6.91-6.94(m, 4H), 9.10(s, 1H).

Results and discussion

Initially, we have screened the reaction of benzaldehyde (**1a**), malononitrile(**2**) and dimedone (**3**) under visible light in presence of cesium carbonate (10 mol%) as a simple model substrate in various conditions. First, we tested the effect of various solvents. When using aprotic polar solvents such as CH₃CN, CH₂Cl₂ and CHCl₃, the reactions afforded the corresponding 4H-benzopyran (**4a**) with modest yields after 6 h under visible light (Table 1, Entries 1-3). However, the reactions in refluxing protic solvents such as H₂O or EtOH gave better yields (Table 1, Entries 4 and 5) in short reaction times. In the absence of catalyst, reaction was not completed even after 15 h under visible light (Table 1, Entry 6).

Similarly, the reaction without any solvent under visible light was not very successful (Table 1, Entry 7). In the absence of visible light, the reaction was sluggish and completed in 10 h with moderate yield (Table 1, Entry 8). The ethanol is proven to be the most suitable solvent for this condensation in terms of yield and reaction time (Table 1, Entry 5).

Next, we evaluated the amount of cesium carbonate required for the reaction. It was found that when decreasing the amount of the catalyst from 10 to 5 mol%, the yield decreased from 85 to 78% (Table 1, Entry 9). A reduced yield was observed when the amount of cesium carbonate was increased (Table 1, Entries 10-11). Thus, the best result was obtained with 10 mol % of catalyst in ethanol under visible light condition. Subsequent screening of other bases revealed that Cs₂CO₃ was superior over others in terms of yield and time (Table 1, Entries 12-14).

Table 1: Synthesis of tetrahydrobenzo[b]pyrans under various reaction conditions

Entry	Catalyst(mol%)	Solvent	Time (h)	Yield ^a (%)
1	Cs ₂ CO ₃ /(10)	CH ₃ CN	6	55
2	Cs ₂ CO ₃ /(10)	CH ₂ Cl ₂	6	45
3	Cs ₂ CO ₃ /(10)	CHCl ₃	6	52
4	Cs ₂ CO ₃ /(10)	H ₂ O	4	81
5	Cs ₂ CO ₃ /(10)	EtOH	3	85
6	-	EtOH	15	68
7	Cs ₂ CO ₃ /(10)	-	15	37
8	Cs ₂ CO ₃ /(10)	EtOH	10	55
9	Cs ₂ CO ₃ /(5)	EtOH	3	78
10	Cs ₂ CO ₃ /(15)	EtOH	3	75
11	Cs ₂ CO ₃ /(20)	EtOH	3	74
12	K ₂ CO ₃ /(10)	EtOH	5	76
13	Na ₂ CO ₃ /(10)	EtOH	5	78
14	NaH/(10)	EtOH	5	75

^aIsolated yield

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To explore the scope and generality of this reaction, we extended the reaction to various aromatic aldehydes. All reactions delivered good to excellent products yields and accommodated a wide range of aromatic aldehydes containing electron-donating and electron-withdrawing groups (Table 2, Entries **4a-n**) without any significant substituent effect. This three-

component condensation reaction also proceeded with heteroaromatic aldehyde, such as 2-furaldehyde and give the corresponding product in high yield (Table 2, Entry **4m**). The scope of this one-pot reaction was further extended to α,β -unsaturated aldehyde and the corresponding functionalized 4H-benzo[*b*]pyran was produced in good yield (Table 2, Entry **4l**).

Table 2: Visible light irradiated synthesis of tetrahydrobenzo[*b*]pyrans

Entry	Ar	Time (h)	Yield ^{a,b} (%)
4a	C ₆ H ₅	1	85
4b	3-NO ₂ C ₆ H ₄	1.5	88
4c	4-NO ₂ C ₆ H ₄	1	92
4d	3-ClC ₆ H ₄	2	89
4e	4-ClC ₆ H ₄	1	93
4f	3-OHC ₆ H ₄	3	87
4g	4-OHC ₆ H ₄	2.5	90
4h	3-CH ₃ C ₆ H ₄	3	80
4i	3-OCH ₃ C ₆ H ₄	3	88
4j	4-BrC ₆ H ₄	2	91
4k	2-OCH ₃ C ₆ H ₄	3	85
4n	4-Me ₂ N-C ₆ H ₄	3	78
4m	2-Furyl	2	87
4l	C ₆ H ₅ CH=CH	2.5	82

^aIsolated yields. ^bProducts are characterized by IR, and ¹H NMR spectra.

In order to check the efficacy of the visible light, the one-pot multicomponent reaction was performed with benzaldehyde (**1a**), malononitrile (**2**) and dimedone (**3**) in presence of cesium carbonate (10 mol%) using ethanol as solvent under refluxing condition for 4 h in the absence of tungsten lamp. The reaction mixture became sticky after dilution with water and the product (**4a**) was

obtained by column chromatography in only 27% yield. However, the same combination of substrates under an identical condition in the presence of visible light afforded **4a** in much higher yield (85%) in a significantly less time (1 h). This clearly shows that the present photochemical method is much superior to the conventional thermal one.

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Conclusion

In conclusion, we have developed an efficient, environmentally friendly, one-pot three-component reaction for the synthesis of tetrahydrobenzo[b]pyrans in ethanol. The present method has some advantages such as devoid of any unwanted side reactions, simple work-up procedure, use of easily available catalyst, and presence of visible light from low cost tungsten lamp. The present work may be considered as an excellent improvement over the existing methods.

Acknowledgements

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