

# MnSO<sub>4</sub>·4H<sub>2</sub>O: A Novel and Inexpensive Catalyst for the One-pot Multicomponent Synthesis of 4H-benzo[b]pyran Derivatives

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## Abstract

New and efficient synthesis of 4H-benzo[b]pyran derivatives is accomplished by a one-pot three-component condensation of dimedone, malononitrile (or ethyl cyanoacetate) and aromatic aldehydes in the presence of MnSO<sub>4</sub>·4H<sub>2</sub>O as a catalyst in aqueous media at 70 °C. Several types of aromatic aldehyde, containing electron-withdrawing groups as well as electron-donating groups, were used in the reaction and in all cases the desired products were synthesized successfully and 4H-benzo[b]pyran derivatives were obtained in short time and excellent yield (86%–98%). Simple and easy work-up, low cost, green process, inexpensive catalyst, short reaction times and excellent yields of the products are the advantages of this procedure.

**Keywords:** 4H-benzo[b]pyrans, MnSO<sub>4</sub>·4H<sub>2</sub>O, Dimedone, Malononitrile, ethyl cyanoacetate, Aromatic aldehydes

## 1. Introduction

Over the years, multicomponent reactions (MCRs) have been proven to be a very elegant and rapid way to synthesize structurally diverse bioactive heterocyclic compounds in a single synthetic operation from simple building blocks. They have been receiving much attention because of their wide range of applications in medicinal chemistry and drug discovery. The major advantages of multicomponent reactions are high atom-economy, operational simplicity, high selectivity, due to substantial minimization of waste, time, labor and cost [1-4].

Recently, much attention has been evoked towards the synthesis of 4H-benzo[b]pyran derivatives owing to their pronounced pharmacological and biological activities [5]. They have spasmolytic, diuretic [6], antiallergic, antibacterial [7], anticoagulant, anticancer and anti-anaphylactic activities [8], as well as their use in therapy [9]. The synthesis of 4H-benzo[b]pyran derivatives has been achieved by the reaction of aromatic aldehydes, malononitrile (or ethyl cyanoacetate) and dimedone in the presence of a catalysts, such as tetra-methyl ammonium hydroxide (TMAH) [10], sodium selenate (Na<sub>2</sub>SeO<sub>4</sub>) [11], phenylboronic acid (PhB(OH)<sub>2</sub>) [12], tetrabutylammonium bromide (TBAB) [13], sodium bromide (NaBr) [14],

trisodium citrate [15], Zn(Phen)<sub>2</sub>Cl<sub>2</sub> [16], acyclic acidic ionic liquids (TSILs) [17], sulfonic acid functionalized silica (SiO<sub>2</sub>-Pr-SO<sub>3</sub>H) [18], nickel nitrate hexahydrate (Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O) [19], mesoporous silica nanoparticles (MSNs) [20], potassium phthalimide-N-oxyl (POPINO) [21], starch solution [22], tetrabutylammonium fluoride (TBAF) [23] and Aminopropylated silica gel(AP-SiO<sub>2</sub>) [24]. However, these methods show varying degrees of success as well as limitations such as prolonged reaction times, unsatisfactory yield, use of toxic solvents and catalysts, requirement of large amounts of expensive reagents and catalysts, laborious work-up procedures and harsh reaction conditions. Thus, the development of an alternate milder and clean procedure is highly demanding for the synthesis of 4H-benzo[b]pyran derivatives, which surpasses those limitations.

In view of our ongoing efforts to explore newer reactions for synthesis of heterocyclic compounds [25], in this work, in regard of some reports on the application of manganese (II) sulfate tetrahydrate in organic transformations, we decided to introduce a new application of manganese (II) sulfate tetrahydrate as a highly efficient and inexpensive catalyst in synthesis of 4H-benzo[b]pyran derivatives.

## 2. Experimental

### 2.1 General

All reagents were purchased from Merck, Fluka and Aldrich with high-grade quality, and used without any purification. The reactions were monitored by TLC. Visualization of the developed chromatogram was performed by UV light (254 nm). All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR, <sup>1</sup>H NMR spectra). The NMR spectra were recorded on a Bruker Avance 250 MHz instruments. The spectra were measured in DMSO-d<sub>6</sub> relative to TMS (0.00 ppm). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. Melting points were measured by using the capillary tube method with IA 9000 series thermal analyzer.

## 2.2 General procedure for synthesis of 4H-benzo[b]pyran derivatives

A solution of an aromatic aldehyde (1 mmol), malononitrile (or ethyl cyanoacetate) (1.2 mmol), dimedone (1 mmol) and  $\text{MnSO}_4 \cdot 4\text{H}_2\text{O}$  (15 mol%) in 5 mL aqueous ethanol (1:1,  $\text{H}_2\text{O}$ -EtOH) was stirred at 70 °C for the appropriate time. After completion of the reaction which was monitored by TLC, the reaction mixture was cooled to 25 °C, the solid product was collected by filtration, washed with (5 ml  $\times$  3) distilled water and *n*-hexane to obtain pure products. As the catalyst is completely soluble in distilled water, it was easily separated from the reaction mixture. Compounds were characterized by IR and  $^1\text{H}$  NMR spectroscopy.

## 3.3 Spectral data for selected compound

### 2-amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4a).

White solid, mp: 227–229 °C, IR (KBr)  $\nu_{\text{max}}$  3395, 3324, 3212, 2962, 2199, 1680, 1661, 1603, 1370, 1214, 1139, 1036  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (250 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  0.92 (s, 3H), 1.01 (s, 3H), 2.07 (d, 1H,  $J = 15$  Hz), 2.23 (d, 1H,  $J = 15$  Hz), 2.47 (s, 2H), 4.14 (s, 1H), 7 (s, 2H), 7.09–7.18 (m, 3H), 7.26 (t, 2H,  $J = 7.5$  Hz) ppm.

### 2-amino-3-cyano-4-(4'-chlorobenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8 tetrahydrobenzo[b]pyran (4f).

White solid, mp: 215–217 °C, IR (KBr)  $\nu_{\text{max}}$  3396, 3212, 2964, 2193, 1684, 1655, 1605, 1368, 1214  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (250 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  0.92 (s, 3H), 1.00 (s, 3H), 2.07 (d, 1H,  $J = 15$  Hz), 2.23 (d, 1H,  $J = 15$  Hz), 2.48 (s, 2H), 4.17 (s, 1H), 7.05–7.34 (m, 6H) ppm.

### 2-amino-3-cyano-4-(4'-nitrobenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8 tetrahydrobenzo[b]pyran (4h).

Yellow solid, mp: 172–174 °C, IR (KBr)  $\nu_{\text{max}}$  3400, 3324, 3210, 2192, 1658, 1595, 1519, 1346, 1214, 1038  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (250 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  0.93 (s, 3H), 1.01 (s, 3H), 2.08 (d, 1H,  $J = 15$  Hz), 2.24 (d, 1H,  $J = 15$  Hz), 2.48 (s, 2H), 4.34 (s, 1H), 7.17 (s, 2H), 7.42 (d, 2H,  $J = 7.5$  Hz), 8.14 (d, 2H,  $J = 7.5$  Hz) ppm.

### 2-amino-3-cyano-4-(4'-methoxybenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4k).

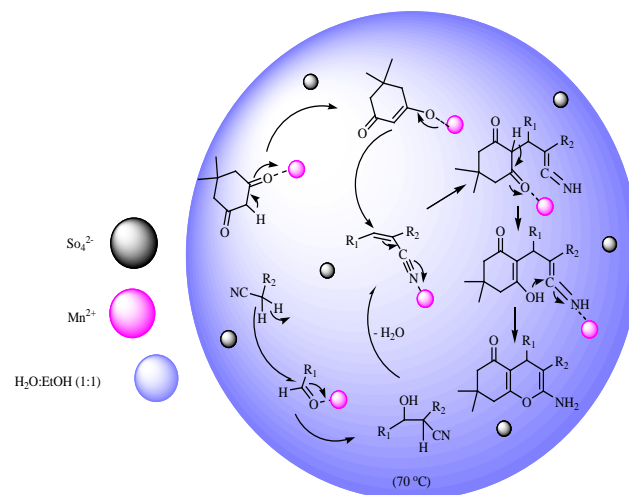
Yellow solid, mp: 199–201 °C, IR (KBr)  $\nu_{\text{max}}$  3376, 3319, 3185, 2960, 2190, 1682, 1657, 1606, 1510, 1368, 1256, 1212, 1033  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (250 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  0.92 (s, 3H), 1.00 (s, 3H), 2.06 (d, 1H,  $J = 15$  Hz), 2.22 (d, 1H,  $J = 15$  Hz), 2.50 (s, 2H), 3.68 (s, 3H), 4.09 (s, 1H), 6.81 (d,

2H,  $J = 7.5$  Hz), 6.94 (s, 2H), 7.02 (d, 2H,  $J = 7.5$  Hz) ppm.

## 3. Results and discussion

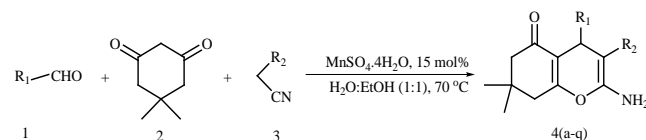
In order to optimize the conditions, initially the effect of the reaction solvent, reaction temperature, the amounts of catalyst and the reaction time were tested. For this study, a reaction between dimedone (1 mmol), malononitrile (1.2 mmol), 4-chlorobenzaldehyde (1 mmol) were examined as the model reaction in the presence of  $\text{MnSO}_4 \cdot 4\text{H}_2\text{O}$ .

Initial studies showed that better results could be obtained in the presence of (15 mol%)  $\text{MnSO}_4 \cdot 4\text{H}_2\text{O}$  in aqueous ethanol (1:1,  $\text{H}_2\text{O}$ -EtOH) at 70 °C. We proposed a plausible mechanism for the synthesis of 4H-benzo[b]pyrans in Figure 1.



**Fig. 1** Plausible mechanism for the synthesis of 4H-benzo[b]pyrans catalyzed by  $\text{MnSO}_4 \cdot 4\text{H}_2\text{O}$ .

Encouraged by these results, the generality and synthetic scope of this protocol were demonstrated by synthesizing a series of 4H-benzo[b]pyran derivatives. Several aromatic aldehydes with different functional groups were subjected to the condensation reaction and the desired products were synthesized in good to high yields and short reaction time (Figure 2).



**Fig. 2** The synthesis of 4H-benzo[b]pyran derivatives from dimedone, malononitrile (or ethyl cyanoacetate) and aromatic aldehydes using  $\text{MnSO}_4 \cdot 4\text{H}_2\text{O}$  as a catalyst.

As shown in Table 1, aromatic aldehydes bearing electron-donating or electron-withdrawing substituents gave the desired 4H-benzo[b]pyran derivatives in high yields.

 Table 1: MnSO<sub>4</sub>.4H<sub>2</sub>O catalyzed synthesis of 4H-benzo[b]pyran derivatives<sup>a</sup>.

Entry	R <sub>1</sub>	R <sub>2</sub>	Product	Time (min)	Yield <sup>b</sup> (%)	Mp (°C)	
						Found	Reported [Ref]
1	C <sub>6</sub> H <sub>5</sub>	CN	<b>4a</b>	4	86	227-229	228-230 [10]
2	3-ClC <sub>6</sub> H <sub>4</sub>	CN	<b>4b</b>	5	97	190-191	191-192 [23]
3	4-FC <sub>6</sub> H <sub>4</sub>	CN	<b>4c</b>	3	98	211-213	210-211 [23]
4	4-BrC <sub>6</sub> H <sub>4</sub>	CN	<b>4d</b>	3	98	206-208	210-211 [23]
5	4-CNC <sub>6</sub> H <sub>4</sub>	CN	<b>4e</b>	3	96	222-224	225-228 [10]
6	4-ClC <sub>6</sub> H <sub>4</sub>	CN	<b>4f</b>	2	97	215-217	215-217 [10]
7	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	CN	<b>4g</b>	1	95	210-212	211-214 [10]
8	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	CN	<b>4h</b>	1	98	172-174	177-179 [10]
9	2,4-ClC <sub>6</sub> H <sub>3</sub>	CN	<b>4i</b>	2	95	181-183	180-182 [10]
10	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CN	<b>4j</b>	3	92	211-213	210-213 [10]
11	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CN	<b>4k</b>	5	89	199-201	201-202 [23]
12	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CN	<b>4l</b>	6	86	192-194	194-196 [12]
13	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	CN	<b>4m</b>	5	90	182-184	188-190 [16]
14	C <sub>6</sub> H <sub>5</sub>	CO <sub>2</sub> Et	<b>4n</b>	6	86	155-157	156 [11]
15	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>4o</b>	3	90	183-184	185-188 [11]
16	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>4p</b>	3	95	180-182	184 [11]
17	4-ClC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	<b>4q</b>	5	93	154-156	157 [11]

<sup>a</sup>Reaction conditions: aromatic aldehyde (1 mmol), malononitrile (or ethyl cyanoacetate) (1.2 mmol), dimedone (1 mmol), MnSO<sub>4</sub>.4H<sub>2</sub>O (15 mol%), aqueous ethanol (5 mL), at 70 °C.

<sup>b</sup>Yields refer to isolated products.

To show the merit of the present work in comparison with the reported results in the literature, we summarized some of the results for the preparation of 4H-benzo[b]pyran derivatives in Table 2, which shows that MnSO<sub>4</sub>.4H<sub>2</sub>O can act as suitable catalyst with respect to the reaction time and temperature and exhibits broad applicability in terms of yield.

 Table 2: Comparison of the efficiency of MnSO<sub>4</sub>.4H<sub>2</sub>O with other catalysts for the synthesis 4H-benzo[b]pyran derivatives.

Entry	Catalyst	Conditions	Time	Yield (%) [Ref]
1	TFE, 2 Ml	Reflux	5 (h)	80-95 [7]
2	Na <sub>2</sub> SeO <sub>4</sub> , 0.1 g	EtOH/H <sub>2</sub> O, reflux	0.66-3 (h)	80-98 [11]
3	PhB(OH) <sub>2</sub> , 5 mol%	EtOH/H <sub>2</sub> O, reflux	0.5–2.5 (h)	38-88 [12]
4	TBAB, 10 mol%	H <sub>2</sub> O, reflux	30-45 (min)	89-95 [13]
5	Trisodium citrate, 5 mol%	EtOH/H <sub>2</sub> O, reflux	5-120 (min)	80-96 [15]
6	POPINO, 7.5 mol%	H <sub>2</sub> O, reflux	10-40 (min)	88-98 [21]
7	Starch solution, 4mL	50 °C	30-75(min)	82-95 [22]
8	TBAF, 10 mol%, 5mL	H <sub>2</sub> O, reflux	10-300 (min)	73-98 [23]
9	(AP-SiO <sub>2</sub> ), 10 mol%	H <sub>2</sub> O, 70 °C	45-120(min)	87-96 [24]
10	MnSO <sub>4</sub> .4H <sub>2</sub> O, 15 mol%	EtOH/H <sub>2</sub> O, 70 °C	1-6 (min)	86-98 [This work]

## 4. Conclusions

In conclusion this paper describes a highly efficient and environmentally green process for the synthesis of 4H-benzo[b]pyran derivatives via the one pot three-component reactions of dimedone, aromatic aldehydes and malononitrile (or ethyl cyanoacetate) in the presence of catalytic amount of  $\text{MnSO}_4 \cdot 4\text{H}_2\text{O}$  at 70 °C in aqueous media. Simple reaction procedure, inexpensive catalyst, high yields of the products, short reaction time, easy product separation, generality and cost efficiency make our methodology a valid contribution to the existing processes in the field of 4H-benzo[b]pyran derivatives synthesis.

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