

Clean and green synthesis of structurally diverse 4H-benzo[*b*]pyrans derivatives in water

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ABSTRACT

Magnesium sulphate has been reported as a cheap and readily available common desk reagent for the synthesis of highly functionalized 4H-benzo[*b*]pyran derivatives. The synthesis of target compounds was accomplished by one pot multicomponent reaction of aldehydes, malononitrile and dimedone or 4-hydroxycoumarin, aldehyde in under reflux temperature. The corresponding 4H-benzo[*b*]pyrane derivatives were obtained in good excellent yield under optimized reaction conditions. The methodology prescribed here was found to be adventitious over reported protocols in terms of generality, environment friendliness and economic viability.

Keywords: Magnesium sulphate, 4H-Benzo[*b*]pyran, Dimedone, Aldehyde, Malononitrile, Water medium.

I. INTRODUCTION

The multicomponent reactions for the synthesis of heterocyclic compounds has gain much attention due to their potential utility in the construction of several bonds in a single step.¹⁻⁴ In the medicinal chemistry, these type of transformations attract researchers because of their remarkable molecular diversity, good atom economy, release of minimum waste and easier purification processes.⁵⁻⁷ Therefore, researchers are attempting multicomponent protocols for the construction of C–C, C–N and C–O bonds in a single operation whenever there is requirement of more than one synthetic step to achieve the goal.⁸

The benzopyran and its derivative have gain substantial attention due to their promising biological and pharmacological properties such as spasmolytic, anticoagulant, diuretic, anticancer and antianaphyletic.⁹⁻¹⁰ They have been also used in the treatment of neurogenerative diseases, AIDS associated dementia, Down's syndrome, schizophrenia and myoclonus.¹¹ The polysubstituted 4H-benzo[*b*]pyrans constitute structural unit of the several natural products.^{12,13} Moreover, they have been used as a precursor for the preparation of numerous biologically active compounds such as pyranopyridine derivatives,¹⁴ polyazanaphthalenes,¹⁵ pyrano[2]pyrimidines,¹⁶ pyridin-2-one derivatives¹⁷ and photoactive material.¹⁸⁻²⁰

By realizing the importance of 4H-benzo[*b*]pyran derivatives, many methods have been reported for their synthesis. For instance, the conventional method involved the condensation of aldehyde, dimedone and malononitrile in acetic acid under reflux conditions.¹⁴ The various catalysts reported so far includes 1,1,3,3-*N,N,N,N*-tetramethylguanadium tetrafluoroacetate (TMGT),¹⁵ [bmIm]OH,¹⁶ dihydrogen phosphate(DAHP),¹⁷ molecular I₂,²¹ hexadecyldimethylbenzylammoniumbromide(HDMBA B),²² NaBr,²³ piperidine,^{24,25} KF-alumina²⁶ and ammonium hydrogen phosphate.²⁷ Recently, nanosize Ce₁Mg_xZr_{1-x}O₂,²⁸ electrochemical method²⁹ and microwave heating in solid state¹⁷ has been reported as an alternative methods for the synthesis of 4H-benzo[*b*]pyran derivatives. Consequently, each of the above reported method has its own merits but some of these methods are limited in terms of laborious work-up procedures, long reaction time, effluent pollution and use of luxurious catalysts. Therefore, there is scope for further development of alternative methods for the synthesis 4H-benzo[*b*]pyran derivatives under environmentally benign and economically viable procedures. In the view of the conservation of environment and current emphasis of green chemistry, the application of transition metal free, environmentally safe catalytic procedure for multicomponent reactions has always great demand. Magnesium sulphate is cheap, non-toxic and biodegradable reagent. It has been used as an efficient catalyst for various organic transformations

such as bis-(indolyl)methanes,³⁰ phenazine and quinoxaline derivatives³¹ and intermolecular Wittig reaction of dialkyl-2-(1-acetyl-2-oxopropyl)-3-(triphenylphosphoranylidene)succinates with ninhydrin.³²

Herein, the synthesis of highly functionalized 4*H*-benzo[*b*]pyran derivatives was accomplished by one pot multicomponent reaction of aldehydes, malononitrile and dimedone or 4-hydroxycoumarin, aldehyde in water under reflux conditions (Scheme 1 and 2). One of the requirements of the graduate Science, Engineering and Technology courses is that you conduct research and write a research paper on some aspects of software engineering. The paper may present original work, discuss a new technique, provide a survey and evaluation of recent work in a given area, or give comprehensive and taxonomic tutorial information. The paper must emphasize concepts and the underlying principles and should provide authentic contribution to knowledge. If your paper does not represent original work, it should have educational value by presenting a fresh perspective or a synthesis of existing knowledge. The purpose of this document is to provide you with some guidelines. You are, however, encouraged to consult additional resources that assist you in writing a professional technical paper.

II. METHODS AND MATERIAL

All chemicals were of analytical grade. The melting points were determined on the open capillary tube and were uncorrected. The IR spectra were recorded on Bomen FT-IR MB-104 Spectrophotometer with KBr disc in cm^{-1} . ^1NMR were recorded on Bruker AC-300 MHz in DMSO-d^6 . Products were all known compounds and were identified by comparison of their physical and spectral data with those of reported in literature.

General procedure for the synthesis of 4*H*-benzo[*b*]pyran derivatives

To a mixture of aldehyde (5mmol), dimedone (5mmol) or 4-hydroxy coumarin (5mmol) and malononitrile (5mmol) in water (5 mL), magnesium sulphate (20 mole %) was added. The reaction mixture was heated under reflux for specified time (Table 3 and 4). After completion of reaction (as indicated by TLC), the reaction mixture was cooled. The crystalline product

was separated which was collected by filtration and recrystallized from ethanol afforded pure crystalline 4*H*-benzo[*b*]pyran derivatives.

Spectral data of representative compounds

2-Amino-3-cyno-7,7-dimethyl-4-(phenyl)-5-oxo-4*H*-5,6,7,8-tetrahydrobenzopyran (4a):

IR(KBr): ν_{max} =3392, 3250, 2966, 2192, 1674, 1607, 1594 cm^{-1} ^1H NMR(DMSO-d^6)- δ ppm= 1.02(s,3H), 1.18 (s, 3H), 2.20-2.34(q,2H), 2.42-2.53 (m, 2H), 4.40 (s, 1H), 4.65(s, 2H), 7.20-7.40 (m, 5H) Mass (m/e): $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$ (M.W = 294) = 293.78(M^+)

2-Amino-3-cyno-7,7-dimethyl-4-(4-chlorophenyl)-5-oxo-4*H*-5,6,7,8-tetrahydrobenzopyran (4b):

IR(KBr): ν_{max} =3412, 3315, 3012, 2236, 1696, 1582 cm^{-1} ^1H NMR(DMSO-d^6)- δ ppm= 1.08(s,3H), 1.06 (s, 3H), 2.12 (d,1H) , 2.20 (d,1H,J=16Hz), 2.26 (d,1H), 2.46-2.51 (m, 2H), 4.50 (s, 1H), 6.97 (d, 2H), 7.35 (s, 2H), 7.40 (m, 2H) Mass (m/e): $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_2$ (M.W = 328.5) = 309.4(M^+).

2-Amino-3-cyno-7,7-dimethyl-4-(4-methoxyphenyl)-5-oxo-4*H*-5,6,7,8-tetrahydrobenzopyran (4d):

IR(KBr): ν_{max} = 3382, 3215, 3187, 2964, 2203, 1678, 1612, 1596 cm^{-1} ^1H NMR(DMSO-d^6)- δ ppm= 0.96(s,3H), 1.02 (s, 3H), 2.12 (d,1H) , 2.25 (d,1H), 2.43-2.58(m,2H),3.82 (s,3H), 4.46 (s, 1H), 6.82 (d, 2H), 6.88 (s, 2H), 7.08 (d, 2H) Mass (m/e): $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$ (M.W = 324) = 325.28(M^+).

2-Amino-3-cyno-7,7-dimethyl-4-(3,4-methylenedioxyphenyl)-5-oxo-4*H*-5,6,7,8-tetrahydrobenzopyran (4j):

IR(KBr): ν_{max} = 3409, 3320, 3210, 2940, 1672, 1652, 1610, 1556 cm^{-1} ^1H NMR(DMSO-d^6)- δ ppm= 0.94(s, 3H), 1.02 (s, 3H), 2.12 (d,1H) 2.24 (d,1H), 2.29 (d,1H) 2.41-2.50 (m,2H), 4.47 (s, 1H), 5.89 (s, 2H), 6.91 (s, 2H), 7.0-7.17 (m, 3H) Mass (m/e): $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$ (M.W = 350) = 351.07(M^+).

7-Amino-5-(phenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (6a):

IR(KBr): ν_{max} =3350, 3288, 3180, 2194, 1716, 1606, 1578 cm^{-1} ^1H NMR(DMSO-d^6)- δ ppm= 4.6(s,1H), 4.80 (s, 2H), 7.36 (s, 2H), 7.35-7.50(m, 6H), 7.60-7.65 (m,

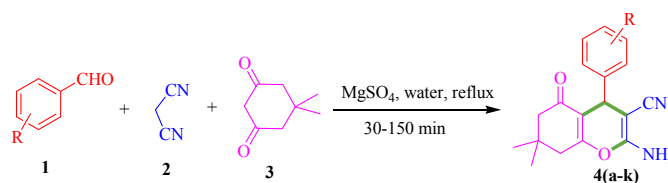
6H), 7.81-7.87 (d, 1H), 7.72 (t, 1H), 7.94 (t, 1H); Mass (m/e): C₁₉H₁₂N₂O₃ (M.W = 316) = 315.98(M⁺)

7-Amino-5-(4-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (6b):

IR(KBr): ν_{\max} =3470, 3430, 3315, 3190, 2192, 1717, 1680, 1610, 1595 cm⁻¹ H¹ NMR(DMSO-d⁶) - δ ppm= 4.60(s,1H), 7.34 (d, 2H), 7.36 (s, 2H), 7.38(s, 2H), 7.45 (d, 2H), 7.51 (s, 1H), 7.72 (t, 1H), 7.94 (t, 1H); Mass (m/e): C₁₉H₁₁ClN₂O₃ (M.W = 320) = 309.9(M⁺).

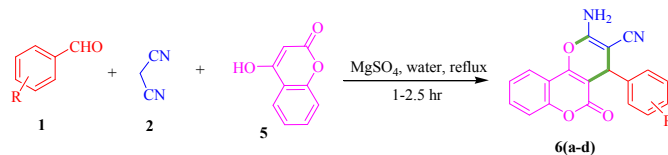
III. RESULTS AND DISCUSSION

In continuation to our ongoing research on the development of novel methods using green techniques,³³ herein we have developed an efficient method for the synthesis of 4*H*-benzo[*b*]pyran. For optimization of reaction conditions, the synthesis of 2-amino-4-phenyl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-3-carbonitrile (**4a**) was tried from the reaction of dimidone(2mmol), benzaldehyde(2 mmol) and malononitrile(2mmol) The reaction progress was studied under catalyst free conditions at room temperature, 40, 50 °C reflux temperatures, the formation of **4a** was not observed even after prolonged time in water and ethanol. When the reaction was conducted using MgSO₄(10-30 mol%) in water at reflux temperature, the product **4a** was formed in 71, 86 and >99% yield. Encouraged by the above results, the catalytic efficacy of the other metal sulphates such as Na₂SO₄, K₂SO₄, NiSO₄, Fe₂(SO₄)₃ and Al(SO₄)₃, was checked for the formation of **4a**. It has been found that the magnesium sulphate is the superior for the formation of desired product over other metal sulphates (TABLE I). With the optimized reaction conditions, we have conducted the present multicomponent reaction of by employing various aromatic aldehydes with diverse functionality. Apparently, aromatic aldehydes possessing electron-withdrawing groups (TABLE II, Entries **4a**, **4d-f**) undergo reaction in faster rates compared to aldehydes possessing electron releasing groups (TABLE II, Entries **4c**, **4i**, **4k**).The formation of good to excellent product yields for all the entries indicated the efficiency of the present method (Table 2).



Scheme 1. Synthesis of 4*H*-benzo[*b*]pyrans catalyzed by magnesium sulphate in water.

Besides, the present method was successfully employed for the multicomponent condensation of 4-hydroxycoumarin, aldehydes and malononitrile (Scheme 2). All the reactions progressed competently and the corresponding 2-amino-4-aryl-5-oxo-4*H*,5*H*-pyrano-[3,2-*c*]chromene-3-carbonitrile derivatives were obtained in good to excellent yield (Table 3, Entries **6a-d**).



Scheme 2. Magnesium sulphate catalyzed synthesis of 2-amino-4-aryl-5-oxo-4*H*,5*H*-pyrano-[3,2-*c*]chromene-3-carbonitrile in water.

Table 1. comparison of catalytic efficiency of various metal sulphates for the formation of ‘4A’

Entry	Metal sulphate	Solvent	Cat. Conc. (mol%)	Time (hr)	Yield (%) 4A
1.	Na ₂ SO ₄	Solvent free	20	4.5	- ^[a]
		EtOH	20	4.5	- ^[b]
		Water	20	4.5	72
2.	K ₂ SO ₄	Solvent free	20	4.5	- ^[a]
		EtOH	20	4.5	65
		Water	20	4.5	81
3.	NiSO ₄	Solvent free	20	4.5	- ^[a]
		EtOH	20	4.5	Sluggish ^[b]
		Water	20	4.5	- ^[b]
4.	Fe ₂ (SO ₄) ₃	Solvent free	20	3.5	- ^[a]
		EtOH	20	3.5	78
		Water	20	3.5	- ^[b]
5.	Al(SO ₄) ₃	Solvent free	20	4.0	Sluggish ^[a]

6.	MgSO ₄	EtOH	20	4.0	- ^[b]
		Water	20	4.0	- ^[b]
		Solvent free	20	2.5	- ^[a]
		EtOH	20	2.5	77
		Water	10	1.5	86
			20	1.5	91
		30	1.5	>99	
		40	1.5	>99	

[a] Reaction was conducted at 100°C temperature.

[b] Reaction was conducted at 60°C temperature.

Table 2. synthesis of 4h-benzo[b]pyran catalyzed magnesium sulphate in water (4).

Entry	Ar	Product	Time (min)	Yield (%) ^[a]	M.P.(°C)
1.	C ₆ H ₅	4a	90	>99	226-228
2.	4-ClC ₆ H ₄	4b	45	98	240-241
3.	2-ClC ₆ H ₄	4c	30	83	220-222
4.	4-NO ₂ C ₆ H ₄	4d	30	>99	177-179
5.	3-NO ₂ C ₆ H ₄	4e	30	>99	213-215
6.	2-NO ₂ C ₆ H ₄	4f	40	>99	183-185
7.	4-MeOC ₆ H ₄	4g	40	91	197-198
8.	4-OHC ₆ H ₄	4h	135	90	199-200
9.	4-MeC ₆ H ₄	4i	150	78	220-222
10.	2-Furyl	4j	50	90	194-195
11.	3,4-OCH ₂ O C ₆ H ₃	4k	120	79	218-220

[a] Yield of the isolated products and spectroscopic data was confirmed with reported data.

Table 3. Synthesis of 4H-benzo[b]pyran catalyzed Magnesium sulphate in water.

Entry	Ar	Product	Time (hr)	Yield (%) ^[a]	M.P. (°C)
1.	C ₆ H ₅	6a	2.5	89	257-259
2.	4-ClC ₆ H ₄	6b	1.5	94	261-264
3.	4-NO ₂ C ₆ H ₄	6c	1.0	>99	257-258
4.	4-MeOC ₆ H ₄	6d	2.5	92	142-143

[a] Isolated yields of the products.

The proposed mechanism of MgSO₄ catalyzed multicomponent reaction of diemidone, aldehyde and malanonitrile is represented in Figure 2. The reaction of aldehyde with malanonitrile to formed α -cynocinnamonitrile (A). The Knoevenogel reaction of

Mg(II) stabilized enol form of diemidone(B) with α -cynocinnamonitrile(A) to form intermediate 'C' which on further protonation gives 4H-benzo[b]-pyran(4)(Figure 1).

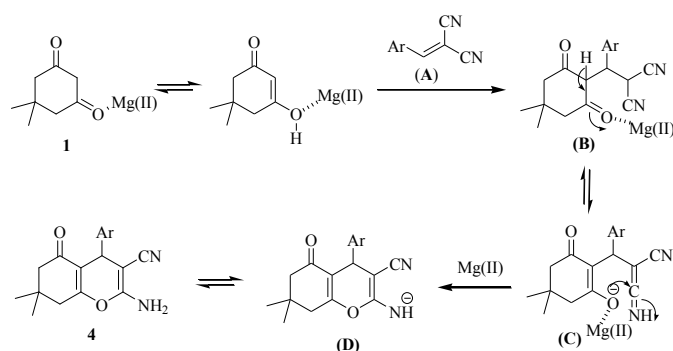


Figure 1. Proposed mechanism of MgSO₄ catalyzed synthesis of 4H-benzo[b]pyrans.

IV.CONCLUSION

In conclusion, we have described a clean and green method for the synthesis of highly functionalized 4H-benzo[b]pyran derivatives. The method presented here in valuable addition for development of green chemistry and field of catalysis. The corresponding 4H-benzo[b]pyrane derivatives were obtained in good excellent yield under optimized reaction conditions. The methodology prescribed here was found to be adventitious over reported protocols in terms of generality, environment friendliness and economic viability.

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