

A new method for synthesis of tetrahydrobenzo[*b*]pyrans and dihydropyrano[*c*]chromenes using *p*-dodecylbenzenesulfonic acid as catalyst in water

Enayatollah Sheikhhosseini*, Dadkhoda Ghazanfari, Vida Nezamabadi

Department of Chemistry, Faculty of Science, Kerman Branch, Islamic Azad University, Kerman, Iran.

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ABSTRACT

p-Dodecylbenzenesulfonic acid (DBSA) was used as a catalyst for a simple and efficient one-pot synthesis of aryl substituted tetrahydrobenzo[*b*]pyrans and dihydropyrano[*c*]chromens via initial Knoevenagel, subsequent Michael and final heterocyclization reactions of aryl aldehyde, malononitrile and 4-hydroxycoumarin/dimedone in moderate to excellent yields. The present method was operationally simple and use of water as the reaction medium made the process environmentally benign.

Keywords: Green media, Dihydropyrano[*c*]chromen, *p*-Dodecylbenzenesulfonic acid (DBSA), Tetrahydrobenzo[*b*]pyran.

1. Introduction

Tetrahydrobenzo[*b*]pyran and dihydropyrano[*c*]chromene derivatives have attracted great interest due to their widespread biological properties of being spasmolytic, diuretic, antibacterial, antimicrobial, anti-coagulant, anti-cancer, anti-HIV and anti-anaphylactic. Moreover, they can also be employed as cognitive enhancers for treatment of neurodegenerative diseases including Parkinson's, Alzheimer's, amyotrophic lateral sclerosis, schizophrenia and myoclonus [1-9]. Also, synthesis of these 4*H*-pyrans and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products [10] contain these heterocyclic molecules. A number of 2-amino-4*H*-pyrans are useful as photoactive materials [11].

The importance of tetrahydrobenzo[*b*]pyran and dihydropyrano[*c*]chromene has led many workers to synthesize them using methods including electrolysis [12] microwave and ultrasonic irradiation [13, 14] by piperidine/pyridine in ethanol [15], diammonium hydrogen phosphate or (S)-proline, tetrabutylammonium bromide, copper oxide nanoparticles, sodium Dodecyl sulfate (SDS), Trisodium citrate,

selectfluor, triethylbenzylammonium chloride DABCO in aqueous media [16-23]. Tetramethylguanidinium trifluoroacetate (TMGT) [24], rare earth perfluorooctanoates [25], Na₂SeO₄ [26], SiO₂-Pr-SO₃ [27], sulfonic acid functionalized silica [28], Hexamethylenetetramine [29], Fe₂O₃ nanoparticles [30], silica gel [31] and Ru (II) complexes [32] as catalysts in one-pot reactions. Each of the above methods has its own merits while some are plagued by limitations of poor yields, use of expensive catalyst, difficult work-up and toxic effluents.

Recently, use of water as a green medium has been of interest. Compared with organic solvents, water has advantages such as low cost, safety and environmental friendliness [33, 34]. Reactions in aqueous media have less carcinogenic effects with a simple work-up that are especially important in the industry.

The surfactant is stable in water and can make organic materials solubility or form colloidal dispersions [35], so it can solve the above drawbacks of the reactions and can be used as a good catalyst in water. *p*-Dodecylbenzenesulfonic acid (DBSA) is a Brønsted acid-surfactant-combined catalyst, composed of an acidic group and a hydrophobic moiety that has been studied as a catalyst in organic chemistry [36]. It could be explained that the inside of emulsion droplets composed of substrate and DBSA is hydrophobic

* Corresponding author: E-mail: sheikhhosseiny@gmail.com, Tel.: +98 341 3201357; Fax: +98 341 3211405.

enough to exclude water molecules. Thus, surfactant catalyzed organic reactions in water have become one of the most challenging research topics.

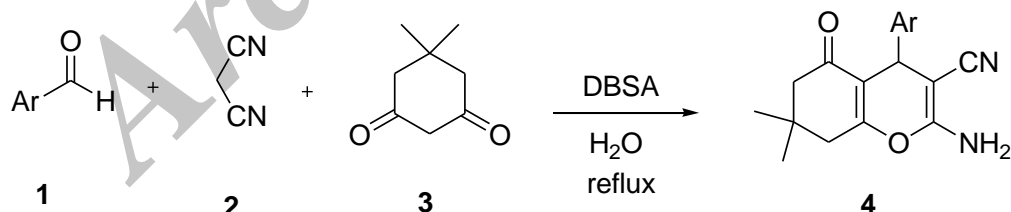
Behavior of DBSA as a catalyst has been studied in Mannich type reactions, Biginelli reaction, synthesis of bis(indol-3-yl)alkanes, xanthenes derivatives and also esterification of various carboxylic acids and alcohols [37-41]. In this study, the present results were reported for the synthesis of 4*H*-pyran derivatives using DBSA in environmentally benign conditions.

2. Experimental

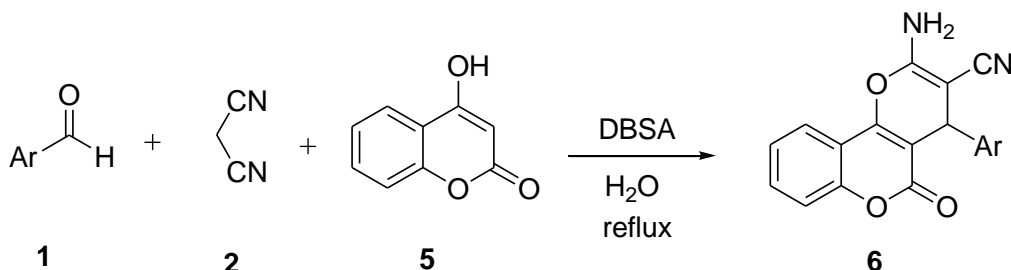
IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer (KBr). ¹H NMR spectra were recorded on a varian 400 MHz spectrometer. Melting points were determined using an Electrothermal 9100 and were uncorrected. The reactions were monitored by thin layer chromatography and the products were identified fully or by comparison of melting points and spectroscopic data with the previously reported ones.

2.1. General procedure for synthesis of tetrahydrobenzo[*b*]pyran and dihydropyrano[*c*]chromene using DBSA (in water):

A mixture of malononitrile (2.2 mmol), substituted benzaldehydes (2 mmol), 4-hydroxycoumarin/dimedone (2 mmol) and DBSA (0.4 mmol) in water (5 mL) was heated at reflux for 4-7 h in order to synthesize 3,4-dihydropyrano[*c*]chromenes and 4-6 h to synthesize tetrahydrobenzo[*b*]pyran. Progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was allowed to cool down to room temperature. The solid was filtered off, washed with water and purified by recrystallization from ethanol.



Scheme 1. Preparation of tetrahydrobenzo[*b*]pyrans.



Scheme 2. Preparation of dihydropyrano[*c*]chromenes.

Selected spectral data:

Compound (4a): 2-amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran
m.p. 226-228 °C. IR (KBr, cm⁻¹): 3395, 3212, 2960, 2199, 1680. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 0.96 (s, 3H, Me), 1.05 (s, 3H, Me), 2.11 (d, *J* = 16.1 Hz, 1H, CH₂), 2.26 (d, *J* = 16.1 Hz, 1H, CH₂), 2.53 (s, 2H, CH₂), 4.18 (s, 1H, CH), 7.02 (s, 2H, NH₂), 7.14-7.21 (m, 3H, H-Ar) 7.29 (t, *J* = 7.5 Hz, 2H, H-Ar)

Compound (6a): 2-Amino-4-phenyl-3-cyano-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one
m.p. 255-257 °C. IR (KBr, cm⁻¹): 3375, 3180, 2197, 1709. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 4.46 (s, 1H, CH), 7.22-7.27 (m, 3H, H-Ar) 7.30-7.34 (m, 2H, H-Ar), 7.42 (br s, 2H, NH₂), 7.46 (d, 1H, *J* = 8.3 Hz, H-Ar), 7.50 (td, 1H, *J* = 7.6, 0.9 Hz, H-Ar), 7.72 (td, 1H, *J* = 7.8, 1.6 Hz, H-Ar), 7.91 (dd, 1H, *J* = 7.9, 1.4 Hz, H-Ar) ppm.

3. Results and Discussion

To the best knowledge of the present authors, a reliable method for three-component condensation of an aromatic aldehyde, malonitrile and dimedone/4-hydroxycoumarin in the present DBSA as catalyst in green media has not been reported. DBSA was used as a source of H⁺ to catalyze this reaction and it was found to be a good catalyst for the preparation of tetrahydrobenzo[*b*]pyran and dihydropyrano[*c*]chromene derivatives (Schemes 1 and 2).

To optimize the conditions, reaction of benzaldehyde, malonitrile and dimedone was selected as the model to examine effects of the DBSA catalyst (5–30 mol%) at several temperatures in water (Table 1).

Table 1. Optimization of conditions for the reaction of benzaldehyde, malononitrile and dimedone.

Entry	Catalyst	Temperature	Time (h)	Yield (%) ^a
1	Catalyst free	r.t	24	No reaction
2	DBSA (10%)	r.t.	24	trace
2	DBSA (10%)	50 °C	24	25
3	DBSA (10%)	reflux	10	35
7	DBSA (15%)	reflux	5	60
8	DBSA (20%)	reflux	5	75
9	DBSA (25%)	reflux	4	90
10	DBSA (30%)	reflux	4	90

^a Isolated yield.

The present optimization studies revealed that yield smoothly increased with the catalyst load up to 25 mol % and use of larger amounts of the catalyst did not improve the yields while decreasing the amount of catalyst led to decreased yields. The negligible amount of the product was formed in the absence of catalyst. The optimized conditions were found to be reflux for 4h (Table 1). Afterward, concentration was on the scope of this reaction with a variety of aldehydes (Scheme 1) to check the viability of this protocol in obtaining a library of tetrahydrobenzo[*b*]pyrans derivatives (Table 2).

As Table 2 shows, in all the cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups smoothly underwent the reaction

and gave the products in good yields under the optimized reaction conditions. To extend scope of the DBSA catalyzed multi-component reaction, 3,4-dihydropyrano[*c*]chromene derivatives (6a-e) were successfully synthesized when using 4-hydroxy coumarin instead of dimedone in these MCRs under the mentioned optimal conditions. The results are given in Table 3.

All the aforementioned reactions (Table 3) delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both electro-donating and electro-withdrawing substituents. The comparison of the time duration showed that time of this reaction was 1-2 h more than the time needed for tetrahydrobenzo[*b*]pyran preparation.

Table 2. Preparation of tetrahydrobenzo[*b*]pyrans catalyzed by DBSA at reflux in water.

Entry	Ar	Product	Yield (%) ^a	m.p. (°C)		Ref.
				Found	Reported	
1	C ₆ H ₅ -	4a	90	226-228	224	[12]
2	3-NO ₂ C ₆ H ₄ -	4b	80	204-206	210	[12]
3	4-NO ₂ C ₆ H ₄ -	4c	75	177-179	178	[12]
4	4-BrC ₆ H ₅ -	4d	70	196-198	205-207	[19]
5	4-ClC ₆ H ₄ -	4e	69	203-205	206	[12]
6	4-MeOC ₆ H ₄ -	4f	70	199-201	201	[12]
7	4-MeC ₆ H ₄ -	4g	75	210-212	214-216	[27]
8	3,4-(MeO) ₂ C ₆ H ₃ -	4h	71	168-170	170-172	[27]

^a Isolated yield.**Table 3.** Preparation of dihydropyrano[*c*]chromene catalyzed by DBSA at reflux in water.

Entry	Ar	Product	Yield (%) ^a	m.p. (°C)		Ref.
				Found	Reported	
1	C ₆ H ₅ -	6a	88	255-257	256-258	[16]
2	3-NO ₂ C ₆ H ₄ -	6b	90	266-268	262-264	[16]
3	4-NO ₂ C ₆ H ₄ -	6c	81	256-258	258-260	[16]
4	4-BrC ₆ H ₅ -	6d	75	252-254	247-249	[24]
5	4-ClC ₆ H ₄ -	6e	87	259-261	263-265	[16]
6	4-MeOC ₆ H ₄ -	6f	80	240-242	240-242	[16]
7	4-MeC ₆ H ₄ -	6g	75	250-252	251-253	[20]
8	2,4-(MeO) ₂ C ₆ H ₃ -	6h	71	230-232	236-238	[20]

^a Isolated yield.

Table 4. Comparison of our results with some of those reported in the literature for the reaction of benzaldehyde, malononitrile and 4-hydroxycoumarin.

Entry	Reaction conditions	Yield (%)	Time	Ref.
1	DAHP (10 mol%), ethanol-water, r.t.	85	6h	[16]
2	Nano aluminum oxide (Al ₂ O ₃) (10 mol%), ethanol, reflux	71	2h	[28]
3	S-pyroline (10 mol%), ethanol-water, reflux	78	3h	[16]
4	SDS (20 mol%), water, reflux	88	2.5h	[20]
5	RuBr ₂ (PPh ₃) ₄ , water, reflux	trace	60 min	[32]
6	RuBr ₂ (PPh ₃) ₄ , ethanol, reflux	45	45min	[32]
7	RuBr ₂ (PPh ₃) ₄ , methanol, reflux	80	3min	[32]
8	Silica gel, ethanol, r.t.	95	4h	[31]
9	Triethylbenzylammonium chloride, water, reflux	96	10h	[23]
10	DBSA (25 mol%), water, reflux	90	4h	this work

To show the efficiency of the selected method, Table 4 compares the results obtained in the present study with some of those reported in the literature.

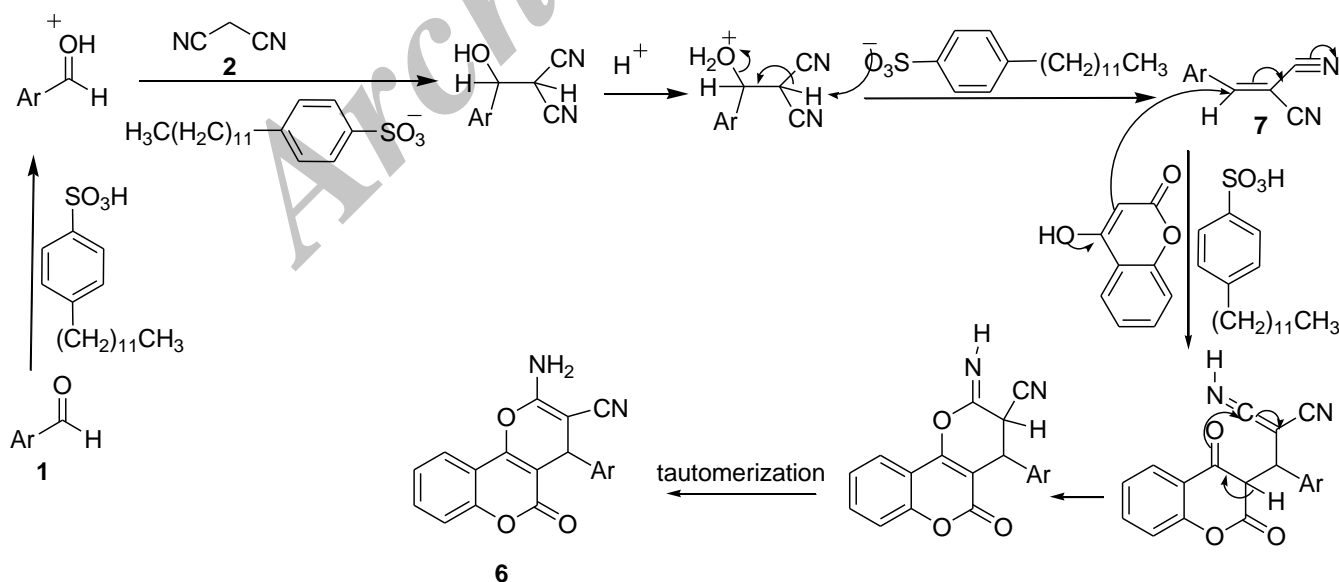
Although this reaction in presence of the other kinds of catalyst reacted more rapidly as reported in some previous studies, using DBSA as surfactant-type Brønsted acid, inexpensive, ecofriendly, non-toxic, water-soluble catalyst in aqueous media is the key advantage over some reports [16, 23, 28, 32 and 31]. In addition, no harmful organic solvents are used.

The proposed mechanism is described in Scheme 3. The Knoevenagel reaction occurred in the presence of DBSA via an initial formation of α -cyanocinnamionitrile derivatives **7** by condensation of protonated aromatic aldehyde with malononitrile **2**.

Then, Michael addition of 4-hydroxy coumarin/dimedone to the arylmethylidene malononitrile **7** followed by cyclization and rearrangement provided the desired products.

4. Conclusions

In conclusion, a simple, efficient and green protocol was demonstrated for the synthesis of tetrahydrobenzo[*b*]pyran and dihydropyrano[*c*]chromene derivatives via one-pot multicomponent reactions in neat water. General applicability, operational simplicity, mild reaction conditions, non-toxic and inexpensive catalyst and green reaction media were the advantages of the present procedure.

**Scheme 3.** Proposed mechanism.

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