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OPPI BRIEF

L-Pyrrolidine-2-Carboxylic Acid Sulfate: A New Ionic Liquid for the Synthesis of Bioactive Tetrahydrobenzo[b]pyrans

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Multicomponent reactions (MCRs), a significant subclass of reactions, are one-pot processes in which three or four easily-accessible components react to form a single product. The methodology is a powerful synthetic tool for the preparation of important drugs and other biologically active compounds.¹ MCRs have been useful in the development of environmentally-friendly and less expensive procedures for the generation of libraries of heterocyclic compounds² and the development of MCRs can lead to new, efficient, synthetic methodologies. Tetrahydrobenzo[b]pyrans and their derivatives are an important class of heterocyclic compounds with anticoagulant, antitumor, spasmolytic, antibacterial, diuretic, potassium channel activating and insulin-sensitizing activities.^{3–6} 4H-Benzo[b]pyrans are usually synthesized from α -cyano cinnamionitrile derivatives with dimedone catalyzed by acid or base.⁷ Recently MCRs have been used for their preparation. As compared to the conventional linear step synthesis, they can make the process easier, reduce time, save money, energy, and raw materials, resulting in both economic and environmental benefits.^{8–9} A number of methods have been reported using dimedone, aromatic aldehydes and malononitrile in the presence of catalysts, such as $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$,¹⁰ N-methylimidazole,¹¹ tetramethyl ammonium hydroxide,¹² MgO ,¹³ amines,¹⁴ 2,2,2-trifluoroethanol,¹⁵ and TiO_2 .¹⁶ Other methods have involved microwave heating,¹⁷ ultrasonic irradiation,¹⁸ electrosynthesis,¹⁹ hexadecyldimethylbenzylammonium bromide (HDMBAB),²⁰ Na_2SeO_4 ,²¹ DABCO,²²

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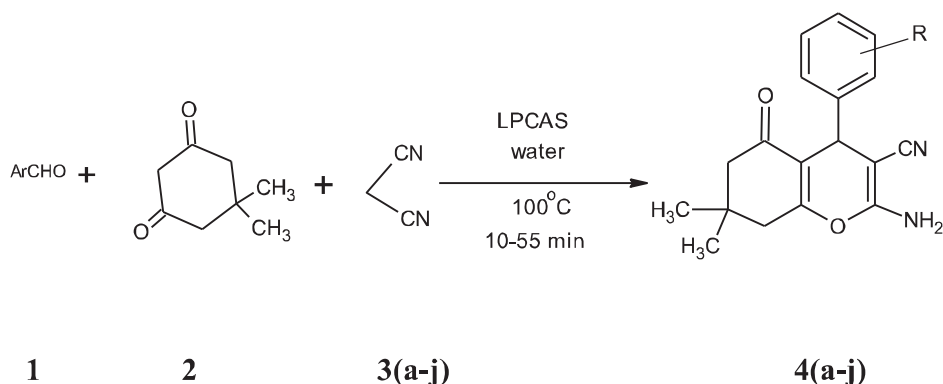
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$(\text{NH}_4)_2\text{HPO}_4$,²³ Cu(II) oxymetasilicate,²⁴ iodine,²⁵ CsF,²⁶ imidazole,²⁷ NH_4Cl ,²⁸ fructose,²⁹ and $[\text{Ch}][\text{OH}]$.³⁰

The PEG1000-DAIL/toluene³¹ temperature-dependent biphasic catalytic system has been applied. Tetrahydrobenzo[*b*]pyran derivatives have been synthesized by using tetrabutylammonium fluoride (TBAF),³² trioctylmethylammonium chloride (Aliquat® 336),³³ 4-(dimethylamino)pyridine (DMAP),³⁴ racemic aspartic acid,³⁵ (*S*)-proline³⁶ and D, L-proline.³⁷

Each of these methods has its limitations. Consequently, an alternative efficient and environmentally-friendly method for synthesis of these tetrahydrobenzo[*b*]pyrans is needed. Ionic liquid (ILs)^{38–40} act as green reaction media and catalysts and have excellent advantages, such as negligible volatility, thermal stability and remarkable solubility. Several ionic liquids are reported as catalysts for the synthesis of tetrahydrobenzo[*b*]pyrans, such as amino-functionalized ionic liquids,⁴¹ $[\text{bmIm}]\text{OH}$,⁴² *N,N*-dimethylamino-functionalized ionic liquids,⁴³ and 2-hydroxyethyl ammonium formate.⁴⁴ Unfortunately these ionic liquids show a degree of solubility in commonly used organic solvents, which causes many difficulties for product separation.

In the present work, the new Bronsted acidic ionic liquid, L-pyrrolidine-2-carboxylic acid sulfate (LPCAS)⁴⁵ has been used for first time as a catalyst in the synthesis of bioactive tetrahydrobenzo[*b*]pyran derivatives (*Scheme 1*). The distinguishing features of this methodology are high yields of products in shorter reaction times, cleaner reaction profiles, and the use of a non-toxic, inexpensive catalyst.



Scheme 1 Synthesis of tetrahydrobenzo[*b*]pyran derivatives.

To determine suitable conditions for this transformation, we examined the reaction; a mixture of benzaldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) and (LPCAS) (1 mmol) was added to a 25 ml round bottom flask and stirred at 100°C. The progress of reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and water (10 ml) was added. The content was further stirred at room temperature for 10 minutes. The separated solid was filtered, washed with excess water, dried and recrystallized from ethanol to afford pure product in good yield, characterized by IR, NMR, ¹³C-NMR and mass spectrometry. The data in *Table 1* suggest that the present method has several advantages over the existing methods for the synthesis of tetrahydrobenzo[*b*]pyrans in terms of short reaction time, excellent yield and use of an ionic liquid as a catalyst in an aqueous medium.

Most of the synthesized compounds (*Table 2*) are known and structures were confirmed by comparing their melting points with standards. One new compound was confirmed by analytical and spectroscopic data. The data in *Table 2* show that the aldehydes

Table 1

Comparison of the Present Catalytic System with Some Reported Protocols in the Model Reaction Between Benzaldehyde, Malononitrile, and Dimedone

Entry	Catalyst	Conditions	Time (min)	Yield (%)	Ref.
1	N-Methylimidazole	H ₂ O/R.T.	180	87	11
2	HDMBAB	H ₂ O/80 °C	350	84	20
3	Na ₂ SeO ₄	EtOH/Reflux	45	80	21
4	DABCO	H ₂ O/Reflux	120	95	22
5	KF–Al ₂ O ₃	DMF/ Ultrasound	60	50	18
6	CeCl ₃ ·7H ₂ O	aq. EtOH/Reflux	60	68	10
7	TMAH	aq. EtOH/50 °C	90	94	12
8	(NH ₄) ₂ HPO ₄	aq. EtOH/Reflux	30	78	23
9	Cu(II) oxymetasilicate	CH ₃ CN/Reflux	60	93	24
10	MgO	aq. EtOH/Reflux	30	93	13
11	Iodine	DMSO/ Reflux	20	94	25
12	CsF	EtOH/Reflux	15	96	26
13	TBAB	H ₂ O/Reflux	30	87	19
14	Imidazole	H ₂ O, 80 °C	30	85	27
15	Starch	Starch, 50°C	30	76–94	02
16	NH ₄ Cl	MW, 140 W	30 sec	92	28
17	Fructose	aq. EtOH/40 °C	45	98	29
18	Ethylene glycol	R.T./Ultrasound	05	72–84	10
19	[Ch][OH]	H ₂ O/80 °C	60	92	30
20	Racemic Aspartic acid	H ₂ O/Reflux	15	94	36
21	(S)-Proline	H ₂ O–EtOH /50°C	30	82	37
22	D, L–Proline	Grinding/RT	35	91	38
23	L-Pyrrolidine-2- carboxylic acid sulfate (LPCAS)	H₂O/100 °C	10	95	This work

bearing electron withdrawing and electron donating substituents reacted easily under the given conditions and the method described herein seems to be insensitive to the substituents in the substrate structure.

After completion of reaction, the reaction mass was poured onto water and the precipitated product was filtered to get the crude product. The catalyst could be recovered by concentrating the fluid from the filtrate. Reusability results of the catalyst in the case of the reaction of benzaldehyde, dimedone and malononitrile are summarized in *Table 3*. Thus the catalyst was found to be recyclable up to the third cycle without much loss of its activity.

In summary, we have developed a new eco-friendly protocol for the synthesis of tetrahydrobenzo[b]pyran derivatives via the condensation of aromatic aldehydes, malononitrile and dimedone using LPCAS ionic liquid as a catalyst in aqueous solution. This new protocol offers a simple procedure, high catalytic activity, short reaction time and excellent yields.

Table 2
Synthesis of Tetrahydrobenzo[b]pyran Derivatives Catalyzed by IL (4a-j)

Sr. No.	Aldehyde	Time (min)	Yield (%)	Melting Point (°C)		References
				Observed	Reported	
4a	Benzaldehyde	10	95	230–232	231–233	15
4b	4-hydroxybenzaldehyde	20	85	246–248	248–250	18
4c	4-Nitrobenzaldehyde	25	95	211–213	210–212	18
4d	4-chlorobenzaldehyde	15	85	160–162	159–161	18
4e	4-Methoxybenzaldehyde	30	85	195–196	195–197	29
4f	1-Naphthaldehyde	55	92	213–215	214–215	33
4g	4-Dimethylaminoben zaldehyde	10	85	210–212	210–212	35
4h	2-Hydroxy-1- naphthaldehyde	35	85	208–212	—	This work
4i	2-Chlorobenzaldehyde	20	90	216–218	217–218	32
4j	4-Hydroxy-3- methoxybenzaldehyde	10	95	236–238	238–240	34

Experimental Section

All the reagents were purchased from Aldrich/Merck and used without further purification. Melting points were obtained by using digital melting point apparatus EQ730 (Equiptronics) and are uncorrected. Progress of reactions and the purity of product were monitored on thin layer chromatography using silica gel as a stationary phase and hexane/ethyl acetate 8:2 as eluent. The products were characterized by comparing melting points and spectral data with those of authentic samples. IR spectra were recorded on a Shimadzu IR Solution 150SUI spectrophotometer using KBr pellets; values are expressed in cm^{-1} . NMR spectra were recorded on Bruker 400 MHz spectrometer using an appropriate solvent and TMS as an internal standard; chemical shifts are expressed in ppm. Mass spectra were taken on a Jeol JMSD-300 spectrometer.

General Procedure for the Synthesis of Tetrahydrobenzo[b]pyran Derivatives (4a-j)

To a mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in water (5 ml) pyrrolidine-2-carboxylic acid sulfate (ionic liquid) in catalytic amount (1 mmol) was added and the mixture was stirred at 100°C for an appropriate time as indicated in Table 2. After completion of reaction, as monitored by TLC, 10 mL water was added and the content was further stirred at room temperature for 10 minutes. The separated solid was filtered, washed with excess water, dried and recrystallized from ethanol to afford pure product.

Table 3
Recyclability of Catalyst

Recycle	Fresh	I	II	III
Yield (%)	95	91	88	84

Representative Spectra

Compound 4e FTIR (KBr) (cm^{-1}): 3379, 3270, 2195, 1666, 1622, 1234. ^1H NMR (400 MHz, DMSO): δ ppm 0.96 (s 3H), 0.1.06 (s 3H), 2.09 (d 1H), 1.08 (s 3H), 2.30 (d 1H), 2.47–2.58 (m 2H), 3.89 (s 3H), 5.80 (s 1H), 8.4 (s 2H), 6.76 (d 1H), 6.85 (d 1H), 7.07 (d 1H), 7.21 (d 1H). ^{13}C NMR (400 MHz, DMSO): 196.07, 162.63, 160.40, 133.36, 128.96, 127.38, 124.11, 115.21, 114.70, 113.19, 55.92, 54.87, 50.01, 48.65, 46.64, 31.83, 31.25, 27.78, 26.43. HRMS m/z : $[\text{M}^+] = 324.14$.

Compound 4h FTIR (KBr) (cm^{-1}): 3186, 2958, 2210, 1735, 1643, 1512, 1151. ^1H NMR (400 MHz, DMSO): δ ppm 0.91 (s 3H), 1.07 (s 3H), 2.65 (d 1H), 2.05 (d 1H), 2.24–2.41 (m 2H), 2.05–2.08 (brs 1H), 7.20 (m 1H), 7.36–7.44 (m 1H), 7.63 (dd 1H), 7.68 (dd 1H), 7.81–7.89 (m 1H), 7.81–7.89 (m 1H), 8.10 (m 1H), 8.2 (brs 2H). ^{13}C NMR (400 MHz, DMSO): 195.84, 157.95, 154.97, 149.51, 147.98, 137.12, 130.49, 129.93, 126.30, 129.93, 128.74, 127.62, 126.30, 117.26, 114.99, 112.26, 110.05, 100.71, 99.48, 50.58, 31.40, 31.69, 29.33, 25.84. HRMS m/z : $[\text{M}^+] = 360.14$.

Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.19; H, 5.62; N, 7.86.

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