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Anion–cation co-operative catalysis by artificial sweetener saccharine-based ionic liquid for sustainable synthesis of 3,4-dihydropyrano[c]chromenes, 4,5-dihydropyrano[4,3-b]pyran and tetrahydrobenzo[b]pyrans in aqueous medium†

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In this study, a saccharine-based ionic liquid [Bmim]Sac has been found to be a sustainable catalyst for the synthesis of 3,4-dihydropyrano[c]chromenes, 4,5-dihydropyrano[4,3-b]pyran and tetrahydrobenzo[b] pyrans scaffolds through Domino Knoevenagel–Michael reaction. The easy recovery of the catalyst and high yield of the products make the protocol attractive, sustainable and economical. A mechanistic hypothesis is discussed using the concept of cooperative catalysis based on the dual (electrophilic/ nucleophilic) activation of reactants by [Bmim]Sac. Furthermore, dual hydrogen bonding of saccharinate anions plays an important role in the activation of nucleophiles.

Introduction

Currently, ionic liquids have attracted significant attention in green organic synthesis owing to their unique properties such as low vapor pressure, wide liquid range, good conductivity and large electrochemical window.[1] In addition to these, the gold benchmark for green chemistry is functional ionic liquid-mediated synthesis (FILMs).[2] Nowadays, FILMs has become a novel approach representing an attempt to describe "design capacity of ionic liquids", which makes them an accurate working system rather than simply novel media, and their properties can be altered to suit the requirement of a particular process.[3] This unique property of the materials obtained by FILMs gives them ability to serve as catalysts. For example, ILs with acidic groups have been used in Fischer esterification, alcohol dehydrodimerization, pinacol rearrangement,[4] and Mannich reactions;[5] with basic groups, they have been utilized in Markovnikov addition,[6] Michael addition,[7] and absorption of CO_2 and SO_2.[8]

The 3,4-dihydropyrano[c]chromene and tetrahydrobenzo[b] pyran units are privileged, heterocyclic motifs that form the core of a large family of natural products with strong bioactivity profiles.[9] Multicomponent methods have been reported for the synthesis of 3,4-dihydropyrano[c]chromenes employing L-proline–melamine,[10a] magnetic nanoparticle-tagged ionic liquid,[10b] $SiO_2/H_3PW_{12}O_{40}$ nanohybrid material,[10c] [DBU][Ac],[10d]

ammonium acetate,[10e] visible light,[10f] thiourea dioxide,[10g] silica-grafted ionic liquids,[10h] crown ether complex cation ionic liquids (CECILs),[10i] SDS,[10j] [TETA]TFA,[10k] and starch solution[10l] as catalysts. Some studies on the multicomponent entry to tetrahydrobenzo[b]pyran motifs have reported employing H_2O/ PEG-400,[11a] sulfonic acid-functionalized magnetic $Fe_{3−x}Ti_xO_4$ nanoparticles,[11b] L-tyrosine,[11c] $Fe_3O_4@SiO_2$-imid-PMAn magnetic nanocatalyst,[11d] inorganic–organic hybrid magnetic nanocatalyst[11e] and magnetite-dihydrogen phosphate[11f] as catalysts.

Despite the availability of these methods, ionic liquid-mediated syntheses of 3,4-dihydropyrano[c]chromenes and tetrahydrobenzo[b]pyrans are still less explored and there remains enough scope for an efficient, high yielding, and mild approach to achieve such systems. With increasing concerns about environmental protection, synthesis of ILs from non-toxic materials is desirable. As a part of our attempt to develop synthesis of biologically important heterocycles[12] via green methodology,[13] we herein report a saccharine-based ionic liquid[14]-mediated protocol for the synthesis of 3,4-dihydropyrano[c]chromene and tetrahydrobenzo[b]pyran (Fig. 1). The saccharin group was chosen as it is less toxic than other ionic liquids.[16]

Results and discussion

[Bmim]Sac was synthesized by the reported procedure, as shown in Fig. 2.[15] Initially, the reaction between benzaldehyde (4a), malononitrile (5) and 4-hydroxycoumarin (6) was employed as the model reaction to screen ILs in water, ethanol

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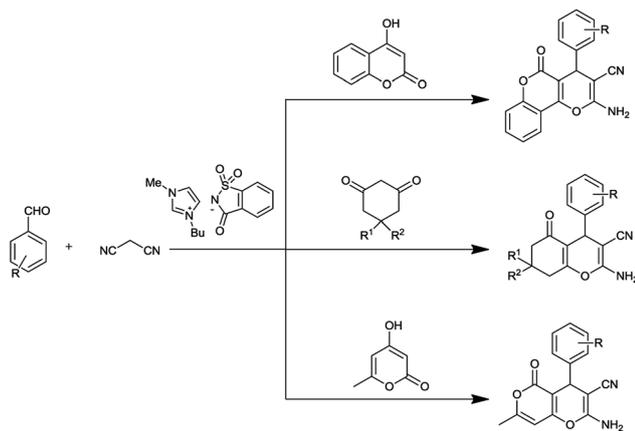
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Fig. 1 3,4-Dihydropyrano[c]chromenes, 4,5-dihydropyrano[4,3-b] pyran and tetrahydrobenzo[b]pyrans.
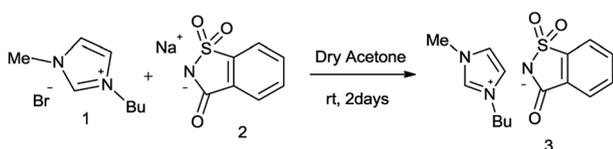

Fig. 2 Synthesis of [Bmim]Sac.

and other common solvents to develop appropriate reaction conditions.

As evident from the results summarized in Table 1, the [Bmim]-based ionic liquid with different anions could catalyse the reaction. However, the reaction of [Bmim]Sac anions proceeded very well as compared to that with others in neat as well as in water and afforded the product **7a** with moderate to excellent yield (82% and 95%), respectively. The results are summarized in Table 1. The use of water as solvent improved the yield of the desired product slightly and also reduced the amount of catalyst from 20 mol% to 5 mol% effectively (Table 1, entries 11 and 14). Higher amount of [Bmim]Sac was needed for proper mixing of reactant only in the absence of water. In the presence of imidazole, saccharine and sod saccharinate as catalysts, no product was observed (Table 1, entries 7, 8, and 9).

The influence of the reaction temperature and the amount of the ionic liquid on the catalysis performance was also studied. The reaction proceeded slowly at room temperature, and the reaction yield increased with increasing temperature to 80 °C. To show the merit of our procedure, we have compared our result for the synthesis of 3,4-dihydropyrano[c]chromenes using [Bmim]Sac with the result of some other ionic liquids reported in literature for the same transformation. The results are summarized in Table 1 (entry 15–21). As can be clearly seen from Table 1, the best result was obtained at 80 °C in the

Table 1 Optimisation conditions for 3,4-dihydropyrano[c]chromenes

S. no.	Catalyst/IL[a]	Condition	Time (min)	% yield[c]	Ref.
1	[Bmim]Br	80 °C, water	75	56	
2	[Bmim]Cl	80 °C , water	80	59	
3	[Bmim]OH	80 °C, water	90	65	
4	[Bmim]BF$_4$	80 °C, water	120	70	
5	[Bmim] SO$_3$H	80 °C, water	100	75	
6	[Bmim]PF$_6$	80 °C, water	120	62	
7	Imidazole	80 °C, water	24 h	NR	
8	Saccharine	80 °C, water	24 h	NR	
9	Sod saccharinate	80 °C, water	24 h	NR	
10	—	Water, 80 °C	24 h	NR	
11	**[BMim]Sac**	**80 °C**	**10**	**82**	
12	[Bmim]Sac	Ethanol, 80 °C	45	75	
13	[Bmim]Sac	Methanol, 65 °C	60	50	
14	**[Bmim]Sac[b]**	**Water, 80 °C**	**10**	**95**	
15	[Sipim]HSO$_4$	100 °C, 0.08 mmol	30	94	10h
16	[TETA]TFA	Ethanol–water, reflux (5 mol%)	20	86	10k
17	Starch solution	50 °C, 4 ml	25	95	10l
18	[18-C-6K][OAc]	EtOH, reflux, (30 mol%)	15	90	10i
19	NH$_4$OAc	EtOH, reflux (15 mol%)	3	94	10e
20	Thiourea dioxide	Water, 70 °C (10 mol%)	13	93	10g
21	SDS	Water, 60 °C (20 mol%)	120	85	10j

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxy coumarin (1 mmol), water (2 ml), catalyst (20 mol%). [b] Catalyst (5 mol%). [c] Isolated yield.

presence of 5 mol% of catalyst. Similar optimizations were performed for products **7b** and **9a**; in all cases, 80 °C and 5 mol% of catalyst were the optimum conditions.

Using these optimized conditions and to show the generality and scope of this methodology, reactions were explored for the synthesis of a wide variety of 3,4-dihydropyrano[*c*]chromene and tetrahydrobenzo[*b*]pyran derivatives using aldehydes, malononitriles and different 1,3-dicarbonyl compounds (4-hydroxy coumarin, 5,5-dimethyl-1,3cyclohexanedione/1,3-cyclohexanedione and 1,3-cyclohexanedione, respectively) in the presence of [Bmim]Sac (5 mol%) in an aqueous medium under reflux conditions. The results have been summarized in Tables 2 and 3. Indeed, there is no difference in reactivities among 5,5-dimethyl-1,3cyclohexanedione/1,3-cyclohexanedione, 1,3-cyclohexanedione and 4-hydroxycoumarin. The effect of electron-withdrawing substituents, electron-releasing substituents and halogens of the aromatic ring of aldehydes on the reaction results was investigated. The reaction time of aromatic aldehydes having electron-withdrawing substituents and halogens produced higher yield of products and faster reactions than that observed for their electron-rich counterparts (Table 2, entry 2).

The attempt to synthesise 3,4-dihydropyrano[*c*]chromene and tetrahydrobenzo[*b*]pyran derivatives using aliphatic aldehyde (*n*-butyraldehyde) was successful, and the results are summarized in Table 2 (entry 10) and Table 3 (entry 24 and 25). To expand the scope of the present catalytic system, we used substrate 4-hydroxy-6-methyl-2-pyrone as the cyclic 1,3-

dicarbonyl compound for the synthesis of 4,5-dihydropyrano [4,3-*b*]pyran derivatives. As expected, the reaction proceeded smoothly, giving the corresponding products in good to excellent yields with aliphatic as well as aromatic aldehydes (Table 2 , entry 11–14).

A mechanism for the probable sequence of events is given in Fig. 3. The reaction proceeds *via* three steps: Knoevenagel condensation, Michael addition, and then intramolecular cyclization, as presented in Fig. 3. The Knoevenagel adduct formed from the ionic liquid-catalyzed condensation of aldehydes and malononitrile subsequently undergoes Michael reaction with carbonyl compounds possessing a reactive methylene group (4-hydroxycoumarin, 4-hydroxy-6-methyl-2-pyrone, 5,5-dimethyl-1,3cyclohexanedione and 1,3-cyclohexanedione); after cyclization, it affords pyran annulated heterocyclic systems.

Bmim cations of ionic liquids activate electrophiles by the proton in the 2-position of the imidazolium ring through hydrogen-bond interaction with the carbonyl and nitrile groups of aldehyde and malononitrile. Simultaneously, anions of ionic liquids activate nucleophiles by accepting the hydrogen bond. The dual activation of nucleophiles and electrophiles by the cations and anions of ionic liquids is crucial to promote the reaction in high yields. As can be seen in Fig. 3, saccharinate anions also play an important role in the dual activation of 1,3-dicarbonyl intermediate nucleophile. It is proposed that an "electrophile nucleophile dual activation" phenomenon of [Bmim]Sac through "dual hydrogen bond formation by

**Table 2** Synthesis of 3,4-dihydropyrano[*c*]chromenes
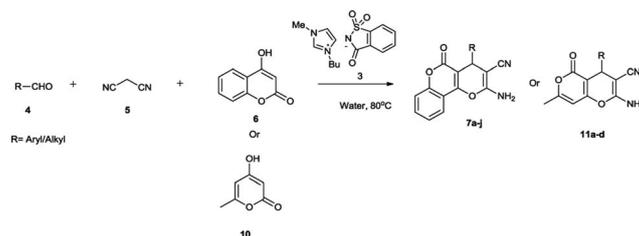
S. no.	R^a	Product	Time (min)	Yield[b]	Melting point	Literature melting point[18]
1	Ph	**7a**	10	95	262–263	260–261
2	4-MeOC$_6$H$_4$	**7b**	50	85	252–253	250–251
3	4-NO$_2$C$_6$H$_4$	**7c**	35	90	264–265	261–263
4	4-OHC$_6$H$_4$	**7d**	75	81	266–267	267–269
5	4-ClC$_6$H$_4$	**7e**	45	85	265–267	266–268
6	4-FC$_6$H$_4$	**7f**	45	84	257–258	258–259 (ref. 10*d*)
7	3-NO$_2$C$_6$H$_4$	**7g**	30	93	255–256	250–251
8	4-BrC$_6$H$_4$	**7h**	40	89	257–258	255–258
9	2-C$_5$H$_4$OS	**7i**	70	70	226–230	228–230 (ref. 19)
10	CH$_3$(CH$_2$)$_2$	**7j**	50	85	195–200	193–195 (ref. 17)
11	4-BrC$_6$H$_4$	**11a**	45	87	239–242	240–242 (ref. 11*d*)
12	CH$_3$(CH$_2$)$_2$	**11b**	40	90	218–220	220–222 (ref. 10*i*)
13	Ph	**11c**	15	93	236–238	
14	4-MeOC$_6$H$_4$	**11d**	45	88	222–224	223–225 (ref. 10*m*)

[a] Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxy coumarin/4-hydroxy-6-methyl-2-pyrone (1 mmol), water (2 ml), [Bmim]Sac (5 mol%). [b] Isolated yield.

Table 3   Synthesis of tetrahydrobenzo[b]pyrans
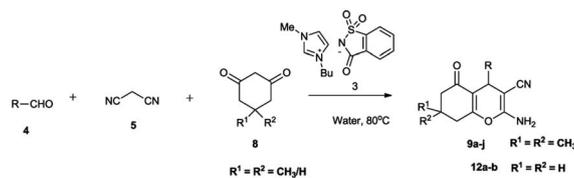
S. no.	R^a	Product	Time (min)	Yield[b]	Melting point	Literature melting point[18]
15	Ph	9a	10	96	238–240	227–228
16	4-MeOC$_6$H$_4$	9b	25	82	201–203	194–196
17	4-NO$_2$C$_6$H$_4$	9c	20	91	179–181	178–180
18	4-OHC$_6$H$_4$	9d	75	80	269–270	265–266
19	4-ClC$_6$H$_4$	9e	45	88	212–213	207–209
20	4-FC$_6$H$_4$	9f	25	92	195–197	191–193
21	3-NO$_2$C$_6$H$_4$	9g	15	94	209–211	208–211
22	4-BrC$_6$H$_4$	9h	35	90	200–201	196–198
23	2-C$_5$H$_4$OS	9i	60	88	226–228	230–231 (ref. 19)
24	CH$_3$(CH$_2$)$_2$	9j	45	89	193–194	192–193 (ref. 11h)
25	C$_6$H$_5$CH=CH	9k	60	80	200–202	205–207 (ref. 11h)
26	4-ClC$_6$H$_4$	12a	40	90	223–225	224–226 (ref. 11g)
27	Ph	12b	15	92	219–221	220–222 (ref. 10k)
28	4-BrC$_6$H$_4$	12c	40	89	196–200	—
29	4-MeOC$_6$H$_4$	12d	30	86	189–191	186–189 (ref. 10k)
30	4-MeC$_6$H$_4$	12e	30	90	228–230	—
31	CH$_3$(CH$_2$)$_2$	12f	25	92	200–205	—
32	4-FC$_6$H$_4$	12g	30	93	198–201	—

[a] Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), 5,5-dimethyl-1,3cyclohexanedione/1,3-cyclohexanedione (1 mmol), water (2 ml) [Bmim]Sac (5 mol%). [b] Isolated yield.

saccharinate anions and charge–charge interactions" occurs (Fig. 3).[16]

The reusability of ionic liquid [Bmim]Sac was also investigated using the reaction between benzaldehyde,
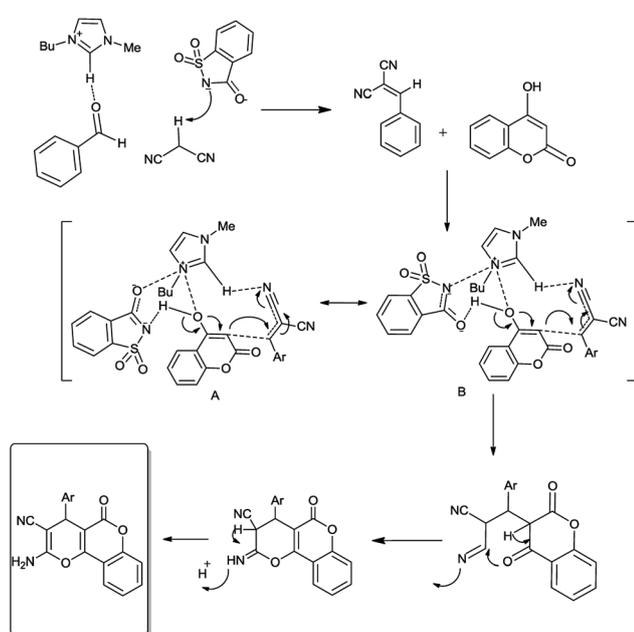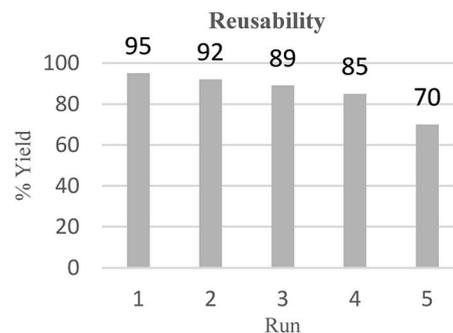

Fig. 4   Reusability of ionic liquid [Bmim]Sac.

malononitrile and 4-hydroxycoumarin as a model system. Ionic liquid can be recovered from the reaction system and it is interesting to note that the recovered IL was reused for five successive batches of reactions to afford pure products after crystallization (Fig. 4). Therefore, it can be concluded that this catalytic system has great potential in industrial applications (Fig. 4).

Conclusions

We have introduced a green domino Knoevenagel–Michael multicomponent reaction procedure for novel and highly efficient synthesis of 3,4-dihydropyrano[c]chromene and

Fig. 3   Proposed mechanism for dual activation of IL.

tetrahydrobenzo[b]pyran derivatives in the presence of [Bmim] Sac as a non-toxic and green ionic liquid in aqueous media. This procedure also offers other significant advantages including simple operation, excellent yield, short reaction time, atom economy, scaling up to multigram quantities, and ease of separation. Also, the catalyst can be easily recovered and reused for five consecutive reaction cycles without significant loss of activity.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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