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A novel sulfonic acid functionalized ionic liquid catalyzed multicomponent synthesis of 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives in water

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10,11-Dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives

ABSTRACT

Three-component reactions of 4-hydroxycoumarin, aldehydes, and cyclic 1,3-dicarbonyl compounds were prompted by novel sulfonic acid functionalized ionic liquids 1,3-dimethyl-2-oxo-1,3-bis(4-sulfobutyl)imidazolidine-1,3-diium hydrogen sulfate ([DMDBSI]·2HSO$_4$) in water at reflux temperature to provide a novel series of 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives for the first time in high yields.

Multicomponent reactions (MCRs) are important in organic and medicinal chemistry.[1] Also in combinatorial chemistry, they are predicted to exhibit negative activation volumes owing to the condensation of several molecules into a single reactive intermediate and product, thus avoiding complicated purification operations and allowing savings of both solvents and reagents.[2]

The coumarin derivatives have received considerable attention because they possess several types of pharmacological properties, such as antibacterial, anticancer, anti-HIV, anticoagulant, antioxidant, and spasmolytic activities.[3] Recently, several methods have been reported for synthesis of coumarin derivatives because of its enormous biological and industrial importance. They have been synthesized by one-pot three-component condensation of 4-hydroxycoumarin, aldehydes, and meldrum's acids or malononitrile or α-cyanocinnamonitriles in the presence of [bmim]OH,[4] HPAs,[5] TMGT,[6] MgO,[7] DAHP,[8] TBAB,[9] DBU,[10] KAl(SO$_4$)$_2$·12H$_2$O.[11] Most of the methods have their own merits. However, these procedures described the synthesis of only a narrow range of coumarin derivatives and also suffered from using of expensive catalyst, long reaction times, low yield, and poor selectivity or commercial unavailability. To the best of our knowledge, there are few reports on three-component coupling of 4-hydroxycoumarin, aldehydes and cyclic 1,3-dicarbonyl compounds to provide a novel series of coumarin derivatives[12] (Scheme 1).

Recently, sulfonic acid functionalized ionic liquids received great attention due to their unique properties like environmental compatibility, reusability, greater selectivity, and ease of isolation. They are used as dual solvent-catalyst[13] for several organic reactions, such as esterification,[14] alkylation,[15] nitration of aromatic compounds,[16] hydrolysis,[17] and heterocyclic synthesis, such as Fisher indole synthesis,[18] and Friedlander quinoline synthesis.[19] As part of our ongoing interest in green chemistry and task specific ionic liquids (TSILs) catalyzed organic reactions, we synthesized a novel SO$_3$H-functional Brønsted-acidic halogen-free TSILs that bear two butane sulfonic acid groups in 1,3-dimethyl-2-oxoimidazolidine-1,3-diium cation[21] (Scheme 2). As a mild, highly efficient, and environmentally benign catalyst, [DMDBSI]·2HSO$_4$ has been successfully applied to perform the three-component reaction of 4-hydroxycoumarin, aldehydes, and cyclic 1,3-dicarbonyl compounds (Scheme 3).

At the onset of our work, 4-hydroxycoumarin (**1a**), benzaldehyde (**2a**), and 5,5-dimethylcyclohexane-1,3-dione (**3a**) were employed as the model reactions in the presence of different catalysts to compare the catalytic performance in EtOH. It should be mentioned that besides (**4a**), a noticeable amount of (**5a**) was also obtained (Scheme 3).

As shown in Table 1, the yield of the desirable product **4a** was low and **5a** was also obtained in 42% yield when these three

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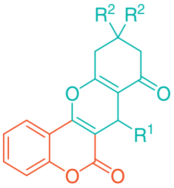
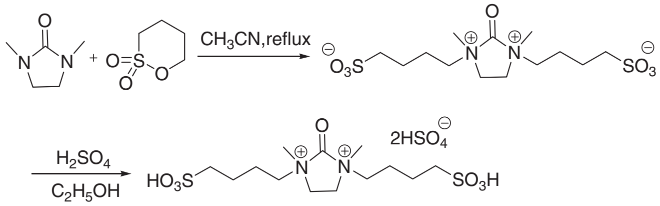


Scheme 1. 10,11-Dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-diones.

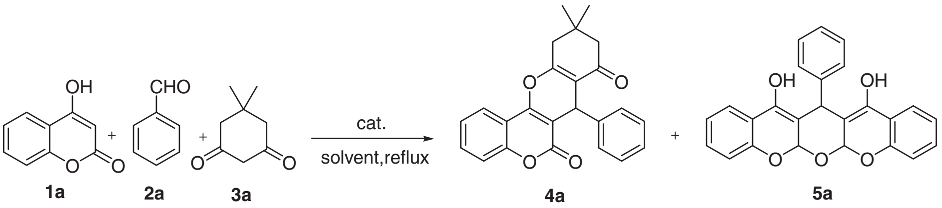


Scheme 2. Synthesis of ionic liquid [DMDBSI]·2HSO$_4$.

components were heated at reflux for 6 h in the absence of catalyst (Table 1, entry 1). To minimize the formation of **5a** and improve the yield of **4a**, PTSA, trifluoro methanesulfonate and DBU were undertaken (Table 1, entries 2–5). The yields were improved but the selectivity was also poor. Some other TSILs that bore butane sulfonic acid groups in different cations with HSO_4^- anion[20] were used, and proved to be very active, leading to 84–87% yield of **4a** in the presence of 10% TSILs (Table 1, entries 6–9). In addition, the TSILs that bore two butane sulfonic acid groups in 1,3-dimethyl-2-oxoimidazolidine-1,3-diium cation with two HSO_4^- anion were used in this three-component reaction, it gave a yield of 91% (Table 1, entry 10). Hence, [DMDBSI]·2HSO$_4$ should be the best catalyst for this multicomponent reaction.

Next, we investigated the appropriate loading amount of catalyst. It was found that 10 mol % of [DMDBSI]·2HSO$_4$ was enough to promote the reaction efficiently (Table 1, entry 12). Different organic solvents, such as DMF, CH_2Cl_2, CH_3CN were used, which afforded **4a** in moderate yields (Table 1, entries 16–19). We extremely expected the reaction to perform in aqueous media, the result was satisfactory (Table 1, entry 20). H_2O was a better solvent than the others tested. Moreover, solvent-free condition was also examined, and viscous reaction system and the yield was low (Table 1, entries 21 and 22).

In order to investigate the possibility of recycling this TSILs [DMDBSI]·2HSO$_4$, a recycling experiment was conducted using the above mentioned model reaction. After the separation of the products, the ILs-containing filtrate was reused in the next run without further purification. The TSILs as catalysts for multicomponent reaction could be reused at least five times without the apparent loss of catalytic activity (yield: 93%, 93%, 92%, 90%, 90%). The subsequent study was performed under the optimized conditions: with 10 mol % [DMDBSI]·2HSO$_4$ in H_2O at reflux, as described in Scheme 4.[22] Most of the corresponding products, 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives **4**,



Scheme 3. Reaction of 4-hydroxycoumarin, aldehydes, and cyclic 1,3-dicarbonyl compounds under different conditions.

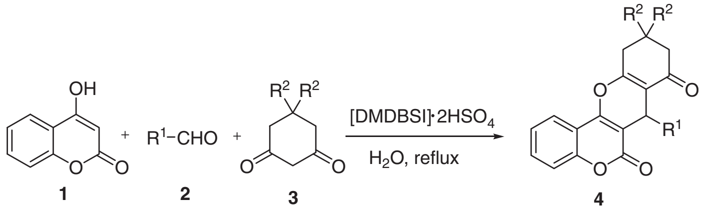
Table 1

Synthesis of 10,10-dimethyl-7-phenyl-10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione **4a** under different conditions[a]

Entry	Catalysts	Loading (mol %)	Solvents	Time (h)	Yield[b] (%)	
					4a	**5a**
1	–	–	EtOH	6	40	42
2	PTSA	10	EtOH	4	56	35
3	Y(OTf)$_3$	10	EtOH	4	72	20
4	Zn(OTf)$_2$	10	EtOH	4	75	19
5	DBU	10	EtOH	4	69	25
6	[TMBSA]·HSO$_4$	10	EtOH	4	85	Trace
7	[PyBSA]·HSO$_4$	10	EtOH	4	84	Trace
8	[MIMBSA]·HSO$_4$	10	EtOH	4	84	Trace
9	[NMPBSA]·HSO$_4$	10	EtOH	4	87	Trace
10	[DMDBSI]·2HSO$_4$	10	EtOH	4	91	Trace
11	[DMDBSI]·2HSO$_4$	5	EtOH	4	86	Trace
12	[DMDBSI]·2HSO$_4$	10	EtOH	4	91	Trace
13	[DMDBSI]·HSO$_4$	15	EtOH	4	90	Trace
14	[DMDBSI]·2HSO$_4$	20	EtOH	4	91	Trace
15	[DMDBSI]·2HSO$_4$	50	EtOH	4	90	Trace
16	[DMDBSI]·2HSO$_4$	10	DMF	4	81	Trace
17	[DMDBSI]·2HSO$_4$	10	CH_2Cl_2	4	43	20
18	[DMDBSI]·2HSO$_4$	10	CH_3CN	4	55	18
19	[DMDBSI]·2HSO$_4$	10	THF	4	60	15
20	[DMDBSI]·2HSO$_4$	10	H_2O	4	93	Trace
21	[DMDBSI]·2HSO$_4$	10	–	4	31	6
22	–	–	[DMDBSI]·2HSO$_4$	4	59	10

[a] 2 mmol 4-hydroxycoumarin, 2 mmol benzaldehyde, 2 mmol 5,5-dimethylcyclohexane-1,3-dione was carried out at reflux.

[b] Isolated yields based on **1a**.



Scheme 4. [DMDBSI]·2HSO$_4$ catalyzed condensation of 4-hydroxycoumarin, aldehydes and cyclic 1,3-dicarbonyl compounds.

Table 2
[DMDBSI]·2HSO$_4$ promoted synthesis of 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives in H_2O at reflux[a]

Entry	R^1	R^2	Time (h)	Product	Yield[b] (%)
1	Ph	Me	4	**4a**	93
2	2-ClC$_6$H$_4$	Me	4.5	**4b**	88
3	2-MeOC$_6$H$_4$	Me	4.5	**4c**	87
4	3-MeOC$_6$H$_4$	Me	3.5	**4d**	90
5	3-OHC$_6$H$_4$	Me	3.5	**4e**	91
6	3-NO$_2$C$_6$H$_4$	Me	3	**4f**	90
7	4-MeOC$_6$H$_4$	Me	3	**4g**	89
8	4-ClC$_6$H$_4$	Me	3	**4h**	92
9	4-NO$_2$C$_6$H$_4$	Me	3	**4i**	90
10	3,4-(Me)$_2$C$_6$H$_3$	Me	4	**4j**	90
11	2-F-6-ClC$_6$H$_3$	Me	4	**4k**	91
12	2,4-(Cl)$_2$C$_6$H$_3$	Me	4	**4l**	92
13	3-MeO-4-OHC$_6$H$_3$	Me	3.5	**4m**	89
14	Furan-2-yl	Me	3.5	**4n**	88
15	Thiophene-2-yl	Me	3.5	**4o**	90
16	CH$_3$CH$_2$	Me	4.5	**4p**	78
17	CH$_3$CH$_2$CH$_2$	Me	4.5	**4q**	79
18	Ph	H	3.5	**4r**	92
19	2-ClC$_6$H$_4$	H	4	**4s**	89
20	3-MeOC$_6$H$_4$	H	3	**4t**	92
21	3-NO$_2$C$_6$H$_4$	H	3	**4u**	91
22	4-ClC$_6$H$_4$	H	3	**4v**	93
23	3-MeO-4-OHC$_6$H$_3$	H	4	**4w**	90
24	2,4-(Cl)$_2$C$_6$H$_3$	H	4	**4x**	89
25	Thiophene-2-yl	H	3.5	**4y**	90
26	CH$_3$CH$_2$	H	4.5	**4z**	79

[a] All reactions were carried out on a 2 mmol 4-hydroxycoumarin with 2 mmol aldehydes, and 2 mmol cyclic 1,3-dicarbonyl compounds in the presence of 0.2 mmol [DMDBSI]·2HSO$_4$ in H_2O (3 mL) at reflux.

[b] Isolated yields based on **1a**.

were obtained in good yields, as shown in Table 2. It was observed that the protocol tolerated both electron donating and electron withdrawing groups on phenyl. When phenyl was replaced with furan-2-yl, or thiophene-2-yl the corresponding product was obtained in high yields. But when aliphatic aldehydes, such as propionaldehyde and butyraldehyde were used in this protocol under the same conditions, it led to a slight decrease in the yields due to the incomplete reaction of raw materials. Cyclic 1,3-dicarbonyl compounds with a substituent R^2 being substituted of methyl and hydrogen similarly obtained the corresponding products in satisfying yields.

In conclusion, a convenient and environmentally green methodology for the synthesis of 10,11-dihydro-chromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives via the three-component reactions of 4-hydroxycoumarin, aldehydes, and cyclic 1,3-dicarbonyl compounds has been developed. The attractive features of this protocol are simple reaction procedure, short reaction time, easy product separation, and purification, reusability of acidic ionic liquid [DMDBSI]·2HSO$_4$, and its adaptability synthesis of a broad range of 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives in moderate to high yields. To the best of our knowledge, the catalyst [DMDBSI]·2HSO$_4$ was synthesized and used in multi-component reactions for the first time, and this is the first report on the synthesis of 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-dione derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.059.

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21. *Synthesis of 1,3-dimethyl-2-oxo-1,3-bis(4-sulfobutyl) imidazolidine-1,3-diium hydrogen sulfate ([DMDBSI]·2HSO$_4$):* To a solution of 1,3-dimethyl-2-imidazolidinone (10 mmol) in CH$_3$CN (3 mL) was added 1,4-butanesultone (20 mmol) in portion within 30 min, and then the mixture was stirred at reflux for 12 h and evaporated under reduced pressure. Then H$_2$SO$_4$ (20 mmol) was added dropwise in ethanol (3 mL) in 30 min. The final solution was stirred at

50 °C for another 8 h and evaporated under reduced pressured to give [DMDBSI]·2HSO$_4$ as a viscous light brown liquid. [DMDBSI]·2HSO$_4$: viscous light brown liquid; ^{1}H NMR (400 MHz, D$_2$O): δ = 4.24 (t, J = 5.6 Hz, 4H), 3.01–2.95 (m, 8H), 2.37 (s, 6H), 1.90–1.82 (m, 4H), 1.51–1.46 (m, 4H). ^{13}C NMR (100 MHz, D$_2$O): δ = 195.8, 55.2, 51.6, 36.9, 32.5, 27.2, 20.3. MS (ESI): m/z 583 [M+1]$^+$.

22. *Typical Procedure for the synthesis of 10,10-dimethyl-7-phenyl-10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione* ***4a**:* To a mixture of 4-hydroxycoumarin **1a** (2 mmol), benzaldehyde **2a** (2 mmol) and 5,5-dimethylcyclohexane-1,3-dione **3a** (2 mmol) was added [DMDBSI]·2HSO$_4$ (0.2 mmol) in water (4 mL). The reaction mixture was stirred at reflux temperature and monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered, and washed with water, and recrystallized from ethanol/methylene chloride (12 mL, 4:1) to give the corresponding compound **4a**. Other products (**4b**–**4z**) were prepared according to the same method of **4a**. For the representative compound **4a**: white solid; mp 226–227 °C. IR (KBr): $\nu_{\max}$ = 2953, 1718, 1666, 1605, 1364, 1187, 1051 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.86 (dd, J_1 = 8.0, J_2 = 1.6 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.41–7.29 (m, 4H), 7.28–7.20 (m, 2H), 7.15 (t, J = 7.2 Hz, 1H), 4.97 (s, 1H), 2.89–2.61 (m, 2H), 2.36–2.25 (m, 2H), 1.18 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 195.6, 161.7, 160.3, 153.6, 152.3, 142.3, 132.0, 128.4 (CH × 2), 128.1 (CH × 2), 126.9, 124.1, 122.2, 116.7, 115.0, 113.5, 106.7, 50.7, 40.9, 33.4, 32.4, 29.2, 27.6. MS (ESI): m/z = 373 [M+1]$^+$. HRESI MS: calcd for $C_{24}H_{20}O_4$+Na: 395.1259; found: 395.1244.