

SHORT COMMUNICATION

GREEN AND PRACTICAL SYNTHESIS OF BENZOPYRAN AND 3-SUBSTITUTED COUMARIN DERIVATIVES BY BRØNSTED ACID IONIC LIQUID [(CH₂)₄SO₃HMIM][HSO₄]

Majid M. Heravi^{1*}, Parvaneh Ansari¹, Mina Saeedi^{1*}, Narges Karimi¹ and Niloofar Tavakoli-Hosseini²

¹Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran, Iran

²Department of Chemistry, Faculty of Sciences, Islamic Azad University, Mashhad Branch, Mashhad, Iran

(Received July 21, 2010; revised November 22, 2010)

ABSTRACT. Different benzopyran and 3-substituted coumarin derivatives were synthesized by a green and practical procedure in the presence of catalytic amount of Brønsted acid ionic liquid (BAIL) [(CH₂)₄SO₃HMIM][HSO₄] in water.

KEY WORDS: Benzopyran derivatives, 3-Substituted coumarin derivatives, Brønsted acid ionic liquid, 1-(4-Sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate

INTRODUCTION

In recent years, finding creative ways to reduce hazard and waste has been the goal of many organic chemists. It has been focused on reducing, recycling or eliminating the use of toxic chemicals and solvents to minimize the human and environmental impact without stifling scientific progress. So as to achieve this goal, water-based organic synthesis has been in an astonishing field. Utilizing water instead of common organic solvents which mostly are toxic, offers green moiety and eco-friendly procedures in organic synthesis. In addition to this great advantage, it can affect the rate and selectivity of organic reactions as well. Breslow and co-workers reported acceleration of the Diels-Alder reaction in water with the reaction performed at very high dilution to dissolve the reactants [1]. Most recently, the progress in the field of ionic liquids (ILs) are gaining significance due to their unique properties and it plays dual role as a solvent and catalyst [2], and also its importance from a green chemistry perspective can not be ignored. Among different kinds of ILs, protic ILs exhibit significant catalytic effects. Efficiency and effectiveness of 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate as a Brønsted acid ionic liquid (BAIL) in organic synthesis have been established [3].

Much attention has been paid to the development of new methods for synthesis of benzopyran and coumarin derivatives due to their imperative biological activities. Benzopyran derivatives act as selective thrombin (THR) inhibitors [4], potassium channel opener [5], PPAR α/γ agonists [6], anti-*Helicobacter pylori* agents [7] and estrogen receptors [8]. Coumarin derivatives display very important biological activities such as antimicrobial [9], antifungal [10] and anti-HIV [11] properties.

Knoevenagel reaction has been an important synthetic method to synthesize coumarin derivatives [12]. Recently, some benzopyran derivatives have been synthesized by the reaction of substituted salicylaldehydes with dimedone using different catalysts such as KF/Al₂O₃ [13], triethylbenzylammonium chloride [14] and 2,4,6-trichloro-1,3,5-triazine [15]. Knoevenagel condensation of salicylic aldehydes with other active methylene compounds such as malonitrile

*Corresponding author. E-mail: saeedi.mina@gmail.com

and ethylacetoacetate has been reported as well. Brufola *et al.* developed some 3-cyanocoumarin derivatives by the Knoevenagel reaction of *o*-hydroxyaryl aldehydes and *o*-hydroxyacetophenone with acetonitriles [16]. In recent years, different catalysts such as *L*-proline [17a], Ti(O-*i*-Pr)₄ [17b], MCM-41 [17c] and ZrOCl₂·8H₂O have been reported for the synthesis of various 3-substituted coumarins. In the present work, 1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate, was chosen not only as an efficient catalyst but also as environmentally benign and user-friendly catalyst for synthesis of different benzopyran and 3-substituted coumarin derivatives.

EXPERIMENTAL

General

All the chemicals were purchased from Merck. Melting points were measured using Barnstead Electro thermal. GC/Mass analysis was performed using Agilent 6890 GC system Hp-5 capillary 30 m × 530 μm × 1.5 μm nominal. IR spectra were recorded as KBr disc on the FT-IR Bruker Tensor 27 spectrometer. ¹H NMR spectra were recorded on a Bruker AQS-AVANCE spectrometer at 500 MHz, using TMS as an internal standard (DMSO-*d*₆, CDCl₃ solution).

Typical procedure for the synthesis of BAIL

Brønsted acid IL ([[(CH₂)₄SO₃HMIM][HSO₄]) was synthesized according to the procedures reported in literature [3a].

Typical procedure for the synthesis of different benzopyran derivatives

1-(4-Sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate (0.1 g, 31.6 mol%), 1,3-cyclohexanedione derivatives (2 mmol), and substituted salicylaldehyde **1** (1 mmol) were added to 5 mL of water (Scheme 1) and the reaction was stirred for the appropriate time at 85 °C (Table 1). The progress of the reaction was monitored by TLC using petroleum ether-ethyl acetate (4:1) as eluent. After the completion of the reaction, the mixture was filtered, and the resulting crude product was recrystallized from ethanol.

3b. M.p. 252-254 °C (lit. [15] 251-253 °C); IR (KBr) (ν_{\max} , cm⁻¹): 3415, 3101, 2959, 1616, 1473, 1374; ¹H NMR (DMSO-*d*₆, 500 MHz) δ_{H} (ppm): 0.84 (6H, s, CH₃), 0.99 (3H, s, CH₃), 1.11 (3H, s, CH₃), 1.96-2.60 (8H, m, CH₂), 4.98 (1H, s, CH), 6.88-7.23 (3H, ArH), 10.51 (1H, s, OH).

Typical procedure for the synthesis of different 3-substituted coumarin derivatives

1-(4-Sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate (0.1 g, 31.6 mol%), an appropriate salicylic aldehyde **1** (1 mmol) and reactive methylene compound **2** (1 mmol) were added to 5 mL of water (Scheme 2) and the reaction was stirred for the appropriate time at 85 °C (Table 2). The progress of the reaction was monitored by TLC using petroleum ether-ethyl acetate (7:3) as eluent. After the completion of the reaction, the mixture was filtered, and the resulting crude product was recrystallized from ethanol.

5b. M.p. 92-94 °C (lit. [17a] 92 °C); IR (KBr) (ν_{\max} , cm⁻¹): 3050, 2940, 1765, 1681, 1565; ¹H NMR (CDCl₃, 500 MHz) δ_{H} (ppm): 1.43 (3H, t, *J* = 7.2 Hz, CH₃), 4.43 (2H, q, *J* = 7.2 Hz, CH₂), 7.39-7.32 (2H, m, ArCH), 7.61-7.69 (2H, m, ArCH), 8.54 (1H, s, CH).

Table 1. Synthesis of benzopyran derivatives catalyzed by BAIL in water.

Entry	R ₁	R ₂	R	Product	Time (h)	Yield (%) ^a	M.p. (°C)	
							Found	Reported
1	H	H	CH ₃	3a	2	95	210-211	210-212 [16]
2	H	Br	CH ₃	3b	2.5	95	252-254	251-253 [15]
3	H	NO ₂	CH ₃	3c	2	98	204-205	203-205 [15]
4	OCH ₃	H	CH ₃	3d	3	97	227-231	229-231 [15]
5	H	Cl	CH ₃	3e	3	94	235-237	236-238 [15]
6	Cl	Cl	CH ₃	3f	3	92	235-237	236-237 [15]
7	H	H	H	3g	3	81	246-248	245-247 [15]
8	H	Br	H	3h	3	84	238-240	238-239 [15]
9	H	NO ₂	H	3i	3	84	244-245	245-246 [14]
10	H	Cl	H	3j	3	82	244-245	244-245 [15]

^a Isolated yield.

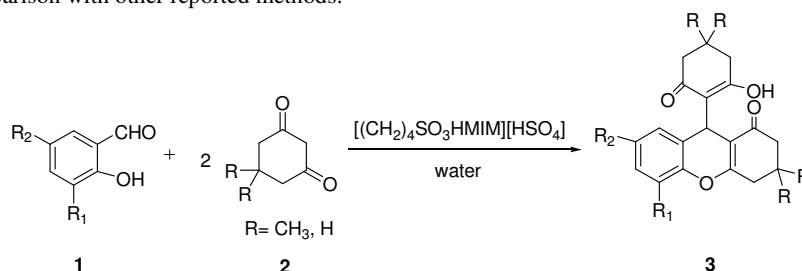
Table 2. Synthesis of 3-substituted coumarin derivatives catalyzed by BAIL in water.

Entry	R ₁	R ₂	Z ₁	Z ₂	Product	Time (min)	Yield (%) ^a	M.p. (°C)	
								Found	Reported
1	H	H	CN	CN	5a	40	91	165-167	164-165 [17a]
2	H	H	COOEt	COOEt	5b	45	89	92-94	92 [17a]
3	H	H	COOEt	CN	5c	55	92	180-182	182 [17a]
4	OCH ₃	H	CN	CN	5d	60	90	173-175	172-173 [17a]
5	OCH ₃	H	COOEt	CN	5e	65	88	224-225	224-225 [17a]
6	H	Br	CN	CN	5f	55	89	196	198-199 [17b]
7	H	OH	CN	CN	5g	60	92	283-285	>260 [17b]
8	OH	H	CN	CN	5h	65	85	293-295	>260 [17b]

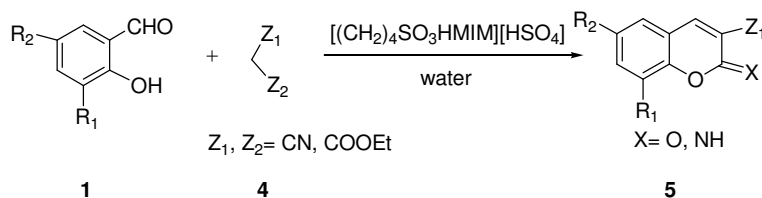
^a Isolated yield.

RESULTS AND DISCUSSION

In continuation of our efforts on the synthesis of heterocyclic compounds using ionic liquids [3b,c,d] and also organic synthesis in water [18], herein, we wish to report a green and practical method for synthesis of benzopyran and 3-substituted coumarin derivatives in the presence of catalytic amount of BAIL [(CH₂)₄SO₃HMIM][HSO₄] (Schemes 1 and 2). This protocol and the BAIL used in this work not only avoid the problems associated with handling and contamination but also afford the products in high yields and shorter reaction time in comparison with other reported methods.



Scheme 1



Scheme 2

To determine optimum reaction condition, a model reaction including treatment of 1 mmol salicylaldehyde and 2 mmol dimedone in the presence of BAIL in water was conducted. It was found that the highest yield was obtained at 85 °C and 0.1 g (31.6 mol%) of catalyst. And corresponding benzopyran derivative was afforded in 95% yield (Table 1, entry 1). In similar manner, substituted salicylaldehydes **1** and 1,3-cyclohexanediones **2** under the mentioned reaction conditions to give corresponding benzopyran derivatives **3** (Table 1). However with 1,3-cyclohexanedione, lower yield of products were witnessed (entry 7-10). It should be noted that the model reaction was achieved in different organic solvents including polar and non-polar. As shown in Table 3, water was found much better than organic solvents and poor yields, long reaction time and by-products were observed by using non-polar organic solvents. It can be interpreted with much better solubility of catalyst in water.

Table 3. Effect of solvent in model reaction (1 mmol salicylaldehyde and 2 mmol dimedone).

Entry	Solvent	Time (h)	Yield (%) ^a
1	C ₂ H ₅ OH	18	50
2	CH ₃ CN	20	22
3	CH ₂ Cl ₂	24	12
4	Toluene	36	10
5	H ₂ O	2	95

^a Isolated yield.

Another model reaction was conducted for the reaction of 1 mmol salicylaldehyde and 1 mmol malonitrile in the presence of BAIL in water to obtain corresponding 3-substituted coumarin. The optimum condition was achieved at 85 °C and 0.1 g (31.6 mol%) of catalyst. In similar procedure, substituted salicylaldehydes **1** and reactive methylene compounds **2** under the mentioned reaction conditions give related 3-substituted coumarin derivatives **3** (Table 2). The model reaction was examined in different solvents and the best results were achieved in water (Table 4).

Table 4. Effect of solvent in model reaction (1 mmol salicylaldehyde and 1 mmol malonitrile).

Entry	Solvent	Time (min)	Yield (%) ^a
1	C ₂ H ₅ OH	50	90
2	CH ₃ CN	120	88
3	CH ₂ Cl ₂	140	62
4	Toluene	24	30
5	H ₂ O	40	91

^a Isolated yield.

To examine the recycle-ability of the catalyst, after completion of reaction, the mixture was filtered to separate the product. After washing the IL with the appropriate solvent (diethyl ether), it was dried at 50 °C, under vacuum for 1 h, and reused in another reaction. The catalyst has been recovered and reused for the synthesis of **3a** and the product was obtained with only a modest loss in yield (89 %).

It should be noted that all compounds were known and their physical data were compared with those of authentic compounds and found to be identical.

In conclusion, we have developed an efficient and straightforward method for synthesis of benzopyran and 3-substituted coumarin derivatives in the presence of catalytic amount of Brønsted acid ionic liquid (BAIL) [(CH₂)₄SO₃HMIM][HSO₄] in water. Present methodology offers encouraged results such as reduced reaction time, higher yields, green procedure and user-friendly process.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Alzahra University for partial financial support.

REFERENCES

1. (a) Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, 102, 7816. (b) Breslow, R. *Acc. Chem. Res.* 1991, 24, 159.
2. Greaves, T.L.; Drummond, C.J. *Chem. Rev.* **2008**, 108, 206.
3. (a) Wang, W.; Shao, L.; Cheng, W.; Yang, J.; He, M. *Catal. Commun.* **2008**, 9, 337. (b) Heravi, M.M.; Saeedi, M.; Karimi, N.; Zakeri, M.; Beheshtiha, Y.S.; Davoodnia, A. *Synth. Commun.* **2010**, 40, 523. (c) Beheshtiha, Y.S.; Heravi, M.M.; Saeedi, M.; Karimi, N.; Zakeri, M.; Tavakolli-Hosseini N. *Synth. Commun.* **2010**, 40, 1216. (d) Heravi, M.M.; Zakeri, M.; Karimi, N.; Saeedi, M.; Oskooie, H.A.; Tavakolli-Hosseini N. *Synth. Commun.* **2010**, 40, 1998. (e) Davoodnia, A.; Heravi, M.M.; Rezaei-Daghigh, L.; Tavakoli-Hoseini, N. *Chin. J. Chem.* **2010**, 28, 429.
4. Frederick, R.; Robert, S.; Charlier, C.; Wouters, J.; Masereel, B.; Pochet, L. *J. Med. Chem.* **2007**, 50, 3645.
5. Gadwood, R.C.; Kamdar, B.V.; Dubray, L.A.C.; Wolfe, M.L.; Smith, M.P.; Watt, W.; Mizsak, S.A.; Groppit, V.E. *J. Med. Chem.* **1995**, 36, 1480.
6. Yu, J.; Tang, L.; Tang, Y.; Ji, R. *Eur. J. Med. Chem.* **2008**, 43, 2428.
7. Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Carradori, S.; Granese, A.; Rivanera, D.; Lilli, D.; Scaltrito, M.M.; Brenciaglia, M.I. *Eur. J. Med. Chem.* **2006**, 41, 208.
8. Richardson, T.I.; Dodge, J.A.; Durst, G.L.; Pfeifer, L.A.; Shah, J.; Wang, Y.; Durbin, J.D.; Krishnan, V.; Norman, B.H. *Bioorg. Med. Chem. Lett.* **2007**, 17, 4824.
9. Cacic, M.; Trkovnik, M.; Cacic, F.; Has-Schon, E. *Molecules* **2006**, 11, 134.
10. Reddy, Y.D.; Somayajulu, V.V. *J. Indian Chem. Soc.* **1981**, 58, 500.
11. Kashman, Y.; Gustafson, K.R.; Fuller, R.; Cardellina, J.H.; McMahon, J.B.; Currens, M.J.; Buckheit, R.; Hughes, S.H.; Cragg, G.M.; Boyd, M.R. *J. Med. Chem.* **1992**, 35, 2735.
12. Shaabani, A.; Ghadari, R.; Rahmati, A.; Rezayan, A.H. *J. Iran. Chem. Soc.* **2009**, 6, 710.
13. Li, Y.-L.; Chen, H.; Zeng, Z.-S.; Wang, X.-S.; Shi, D.-Q.; Tu, S.-J. *Chin. J. Org. Chem.* **2005**, 25, 846.
14. Wang, X.-S.; Shi, D.-Q.; Li, Y.-L.; Chen, H.; Wei, X.-Y.; Zong, Z.-M. *Synth. Commun.* **2005**, 35, 97.
15. Zhang, P.; Yu, Y.-D.; Zhang, Z.-H. *Synth. Commun.* **2008**, 38, 4474.
16. Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, 43, 1257.

17. (a) Karade, N.N.; Gampawar, S.V.; Shinde, S.V.; Jadhav, W.N. *Chin. J. Chem.* **2007**, *25*, 1686. (b) Volmajer, J.; Toplak, R.; Leban, I.; Marechal, A. M.L. *Tetrahedron Lett.* **2005**, *61*, 7012. (c) Heravi, M.M.; Poormohammad, N.; Beheshtiha, Y.S.; Baghernejad, B.; Malakooti, R. *Bull. Chem. Soc. Ethiop.* **2010**, *24*, 273. (d) Moghaddam1, F.M.; Mirjafary1, Z.; Saeidian1, H. *Transactions C: Chem. Chem. Engin.* **2009**, *16*, 12.
18. (a) Heravi, M.M.; Bakhtiari, K.; Zadsirjan, V.; Bamoharram, F.F.; Heravi, O. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4262. (b) Heravi, M.M.; Baghernejad, B.; Oskooie, H.A. *Mol. Divers.* **2009**, *13*, 385. (c) Heravi, M.M.; Derikvand, F.; Haghighi, M.; Bakhtiari, K. *Lett. Org. Chem.* **2006**, *3*, 297. (d) Heravi, M.M.; Taheri, S.; Bakhtiari, K.; Oskooie, H.A. *Catal. Commun.* **2007**, *8*, 211.