

## One-pot pseudo-five-component synthesis of dihydropyrano[2,3-g] chromenes using sodium phthalimide/[BMIM]BF<sub>4</sub> as high efficient catalytic system

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Received 24 November 2016; received in revised form 21 April 2017; accepted 24 May 2017

### ABSTRACT

An efficient route for the synthesis of dihydropyrano[2,3-g] chromenes via one-pot pseudo-five component cyclization reaction of an aldehyde, malononitrile and 2,5-dihydroxy-1,4-benzoquinone in the presence of an effective and mild catalytic system containing sodium phthalimide and 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF<sub>4</sub>) ionic liquid (SPI/IL) was studied. The reaction products were characterized using <sup>1</sup>H NMR, <sup>13</sup>C NMR, FTIR, Mass spectroscopy and elemental analysis. Environmentally eco-friendly catalyst, clean reaction with easy work-up (through simple filtration) and high yield products with no more purification are the main merits of this protocol. Presented method can be used for the synthesis of mentioned products (with pharmacology and Biologic properties) in large scales.

**Keywords:** Dihydropyrano[2,3-g] chromenes, [BMIM]BF<sub>4</sub>, Sodium phthalimide, Heterocycles, One-pot synthesis, Multicomponent reaction.

### 1. Introduction

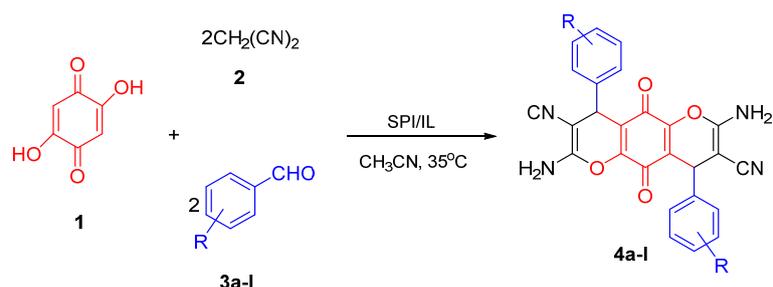
Multi component reactions (MCRs) are a powerful synthetic strategy because of their productivity, simple procedures and facile execution [1]. These reactions are very beneficial, because of three or more starting materials react to give a highly complex product that incorporate substantial portions of all the reactants in one pot [2]. Typically, purification of products resulting from MCRs is simple because all the organic reagents employed, are consumed and incorporated into the target compound [3].

In recent years, considerable interest has been focused on Chromenes (Benzopyrans) and benzo[g]chromenes due to the diverse biological properties such as antimicrobial, antioxidant, antitumor, antifungal, anticancer, anti-HIV and anti-inflammatory activities [4-8]. Also 2-Amino-4H-benzo[g]chromenes found as the main components of many natural products employed as cosmetics, pigments and pharmacological aspect, such as anticoagulants, spasmolytic and anticancer [9-13].

Recently, one of the important challenges in organic synthesis was the development of efficient catalytic systems as well as inexpensive, reusable, clean and eco-friendly. In this way, some of nano materials including nano metal oxides and their modified derivatives [14-17], as well as Ionic liquids [18-23] have been investigated extensively as catalyst in organic structures and chromene synthesis. On the other hand, using the basic organo salts has been developed as new catalytic systems. Potassium phthalimide as a mild, green, inexpensive, commercially available and stable reagent is used recently as an effective basic catalyst in organic reactions [24-28]. There are wide variety of synthetic methods for the synthesis of chromenes in the presence of different catalyst and reaction conditions; but in case of the preparation of dihydropyrano [2,3-g] chromenes, only one report was released on 2009 by A. Shaabani et al. [29]. Authors used NEt<sub>3</sub> as homogeneous catalyst for the synthesis of dihydropyrano [2,3-g] chromenes. Products were obtained in 62-73% yield after 24 hours.

We now report a new efficient and simple method for the synthesis of dihydropyrano[2,3-g]chromene derivatives, via the addition of condensation product of

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**Scheme 1.** Synthesis of dihydropyrano[2,3-g]chromene derivatives catalyzed by SPI/IL

an aldehyde and malononitrile to 2,5-dihydroxy-1,4-benzoquinone and subsequently cyclization in the presence of a dually catalyst containing sodium phthalimide and [BMIM]BF<sub>4</sub> (SPI/IL). Obtained results show that SPI/IL as a mild, green and high efficient catalyst can be used for the synthesis of dihydropyrano[2,3-g]chromene derivatives in high to excellent yields (Scheme 1).

## 2. Experimental

All chemicals were obtained from Merck, Sigma-Aldrich and Alfa Aesar companies and used as received. Melting points were determined in an open capillary using a Thermo Scientific 9300 apparatus. Infrared (IR) spectra were recorded with a Perkin-Elmer FTIR 550 spectrometer. <sup>1</sup>HNMR and <sup>13</sup>CNMR spectra were recorded in DMSO-d<sub>6</sub> using Bruker DRX-400 and 100 MHz, respectively. The elemental analyses (CHN) were obtained from a Carlo ERBA model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer and Mass spectra were recorded on a Finnigan MAT 44S by Electron Ionization (EI) mode with an ionization voltage of 70 eV.

### 2.1. General procedure for the synthesis of dihydropyrano [2,3-g] chromenes

To a magnetically stirred mixture of benzaldehyde derivatives (2.0 mmol) and malononitrile (0.13 g, 2.0 mmol) in CH<sub>3</sub>CN (5 ml), a catalytic amount of SPI (10 mol%) and IL (0.01 g) was added and stirred for 30 min at 35°C. Then, 2,5-dihydroxy-1,4-benzoquinone (0.14 g, 1.0 mmol) was added. The reaction mixture was stirred for appropriate time. After completion of reaction (monitored by TLC), the precipitated product was separated from the reaction mixture by filtration and washed with *n*-hexane and dried. All of dihydropyrano [2,3-g] chromene derivatives were identified by physical and spectral data (See supplementary data).

## 3. Results and Discussion

In this study, we try to introduce a simple and efficient method for the synthesis of dihydropyrano [2,3-g]chromenes using the reaction of 2,5-dihydroxy-1,4-benzoquinone, malononitrile and benzaldehyde derivatives by SPI/IL at 35°C (in CH<sub>3</sub>CN). The reaction products were obtained in good to excellent yields under mild conditions through a clean and easy process. Products were obtained in high yields using simple filtration. Also, SPI/IL can be mentioned as a basic efficient and eco-friendly catalyst.

The effect of sodium phthalimide amounts (in various temperatures) on the reaction process was investigated on the reaction of 2,5-dihydroxy-1,4-benzoquinone, malononitrile and 4-nitrobenzaldehyde as model reaction. Obtained results were collected in Table 1. As indicated in this Table, the highest yield of product (4a) was achieved in the presence of 10 mol% of sodium phthalimide at 35°C and from the reaction without SPI, only 35% of product was produced (entry 1).

After the optimization of sodium phthalimide and temperature, we try to study on the ionic liquid amounts on the yield of the model reaction product (4a) in the presence of 10 mol% of SPI and 35°C. Results depicted in Table 2 shown that 0.01 g of IL is the optimized amount in 35°C. Also in the absence of SPI, only 50% of product was obtained (entry 3).

It is clear that [BMIM]BF<sub>4</sub> as a neutral ionic liquid with imidazolium ring can activate the carbonyl groups of benzaldehyde derivatives through hydrogen bonding of ionic liquid and carbonyl group of aldehyde. On the other hand, the role of SPI (as a base) in absorption of acidic hydrogen of malononitrile, improve the efficiency of catalytic system and also the yield and rate of the reaction.

Solvent effect on reaction performance was investigated using model reaction in various solvents in the presence of 10 mol% of SPI and 0.01 g of IL at 35°C. As shown in Table 3, the reaction performed very efficiently in CH<sub>3</sub>CN.

**Table 1.** The effect of SPI amounts and temperature on yield of (4a)<sup>a</sup>.

Entry	SPI (mol%)	Temp. (°C)	Time (h)	Yield (%) <sup>b</sup>
1	-	35	25	35
2	5	35	22	60
3	10	35	22	85
4	10	50	25	45
5	10	70	25	40
6	15	35	22	80
7	20	35	22	75

<sup>a</sup>1 mmol of **1**, 2 mmol of **2** and **3a** in 5 ml of CH<sub>3</sub>CN.<sup>b</sup>Isolated yield.**Table 2.** The effect of various amounts of IL on the yield of (4a)<sup>a</sup>.

Entry	IL (g)	Time (h)	Yield (%) <sup>b</sup>
1	0.005 <sup>c</sup>	24	30
2	0.01	21	95
3	0.01 <sup>c</sup>	28	50
4	0.015	21	85

<sup>a</sup>1 mmol of **1**, 2 mmol of **2** and **3a** in the presence of 10 mol% of SPI in 5 ml of CH<sub>3</sub>CN and 35°C.<sup>b</sup>Isolated yield<sup>c</sup>1 mmol of **1**, 2 mmol of **2** and **3a** in 5 ml of CH<sub>3</sub>CN (without SPI) at 35°C.**Table 3.** Comparison of the various solvent effects on the yield and time of (4a)<sup>a</sup>.

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%) <sup>b</sup>
1	H <sub>2</sub> O	35	24	30
2	EtOH	35	24	30
3	EtOH/H <sub>2</sub> O	35	24	80
4	CH <sub>2</sub> Cl <sub>2</sub>	35	24	45
5	CH <sub>2</sub> Cl <sub>2</sub>	50	24	37
6	CH <sub>3</sub> CN	70	25	70
7	CH <sub>3</sub> CN	35	21	95

<sup>a</sup>1 mmol of **1**, 2 mmol of **2** and **3a** in the presence of 10 mol% of SPI and 0.01 g of IL.<sup>b</sup>Isolated yield.

After determining the optimized conditions of model reaction, in order to study on the scope and limitation of proposed reaction, various benzaldehyde derivatives were employed under similar conditions (such as model reaction). Reactions proceed very efficiently, and led to the formation of dihydropyrano[2,3-g] chromene derivatives (4a-l) in good yields. The structure of products was deduced from their FTIR, Mass spectroscopy,  $^1\text{H}$ NMR,  $^{13}\text{C}$ NMR and elemental analysis (CHN) data.

Obtained results in Table 4 show that aldehydes with electron withdrawing groups lead to formation of products in higher yields. Although in all entries, the yield of reaction is high to excellent.

A plausible mechanism of the reaction is presented in Scheme 2. Although the mechanism of this reaction has not been studied experimentally, the formation of product can be rationalized by initial condensation reaction between an activated aldehyde (with IL) and carbanion from the effect of SPI on malononitrile.

Then, obtained intermediate (I) has been attacked by 2,5-dihydroxy-1,4-benzo quinone, which lead to the intermediate (II). Such addition intermediate may contribute in a cyclization and then tautomerization, to produce dihydropyrano [2,3-g] chromenes (4a-l).

The structures of products were analyzed by melting point and spectroscopic methods such as FTIR,  $^1\text{H}$  NMR,  $^{13}\text{C}$ NMR, Mass spectroscopy and elemental analysis (CHN). In the FTIR spectra, the stretching frequency of functional groups such as  $-\text{NH}_2$ , CN, C=O and aromatic C=C were appeared at about 3340, 2190, 3215 and 1599  $\text{cm}^{-1}$  respectively. In  $^1\text{H}$  NMR spectra of synthetic materials, aliphatic C-H, aromatic C-H and hydrogen of  $\text{NH}_2$  groups were appeared in about 4.8 and 7-8.30 ppm respectively.

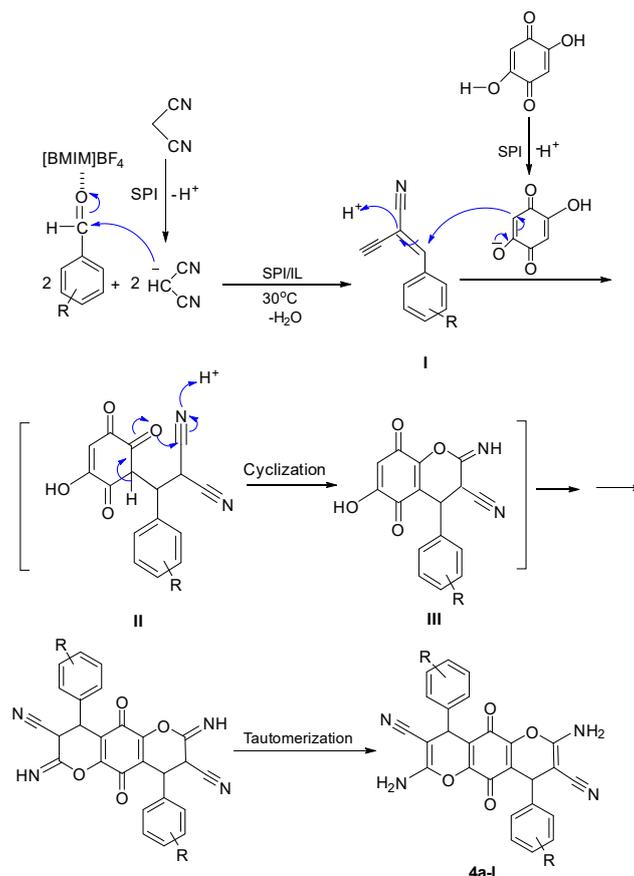
Mass spectra of 4k depicted in Fig. 1. As shown in this pattern, the sign with  $m/z = 538$  related to molecular ion, was confirmed the chemical structure of this compound. The compounds of 4g-4l are new and their structures have been deduced from  $^1\text{H}$ NMR, FTIR, elemental analysis and mass spectral data.

**Table 4.** Pseudo-five-component synthesis of dihydropyrano[2,3-g] chromene derivatives<sup>a</sup>.

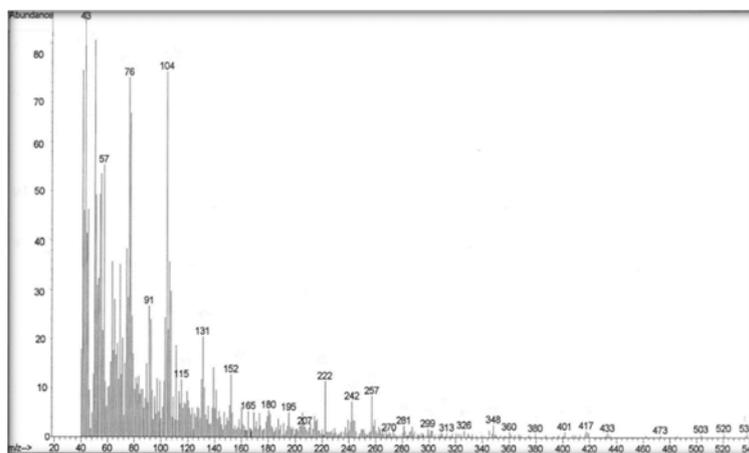
Product	RCHO	Time (h)	Yield (%) <sup>b</sup>	m.p. (°C)	Ref.
4a	4-NO <sub>2</sub>	21	92	290-293	[29]
4b	4-Cl	21	85	273-275	[29]
4c	4-Br	21	80	264-266	[29]
4d	2-OH	22	75	246-248	[29]
4e	2-CH <sub>3</sub>	24	72	280-282	[29]
4f	H	22	90	287-289	[29]
4g	4-OH	22	80	208-210	This work
4h	4-CH <sub>3</sub>	22	78	260-263	This work
4i	4-OCH <sub>3</sub>	24	70	>300	This work
4j	2,4-dichloro	22	80	263-265	This work
4k	3-NO <sub>2</sub>	22	95	242-244	This work
4l	2-thienyl	24	90	258-290	This work

<sup>a</sup>1 mmol of **1**, 2 mmol of **2** and **3** in the presence of 10 mol% of SPI and 0.01 g of IL.

<sup>b</sup>Isolated yield.



**Scheme 2.** Proposed mechanism for the synthesis of dihydropyrano [2,3-g] chromenes in the presence of SPI/IL.



**Fig. 1.** Mass spectra of 4k.

#### 4. Conclusion

We have developed an efficient method for the synthesis of dihydropyrano[2,3-g] chromenes in good to excellent yields. The procedure provides several advantages such as clean reaction with easy work-up (through simple filtration) and high yields with no more purification.

#### Acknowledgements

We gratefully acknowledge the chemistry department of university of Kashan for supporting this work.

#### References

- [1] J. Collins, *J. Chem. Educ.* 72 (1995) 965-970.
- [2] M.M. Hooper, B.D. Boef, *J. Chem. Educ.* 86 (2009) 1077-1097.

- [3] I. Ugi, *Pure Appl. Chem.* 73 (2001) 187-191.
- [4] W.S. Shehab, A.A. Ghoneim, *Arab. J. Chem.* 9 (2016) S966-S970.
- [5] S.R. Parker, H.C. Cutler, J.M. Jacyno, R.A. Hill, *J. Agric. Food Chem.* 45 (1997) 2774-2776.
- [6] R.C. Gadwood, B.V. Kamdar, L.A. Cipkus Dubary, M.L. Wolf, M.P. Smith, W. Watt, S.A. Mizensak, V.E. Groppi, *J. Med. Chem.* 36 (1993) 1480-1487.
- [7] H. Mehrabi, M.K. Mireki, *Chinese. Chem. Lett.* 22 (2011) 1419-1422.
- [8] N. Hazeri, M.T. Maghsoodlou, F. Mir, M. Kngani, H. Saravani, E. Molashahi, *Chinese J. Catal.* 35 (2014) 391-395.
- [9] S. Kanakaraju, B. Prasanna, Srinivas Basavoju, G.V.P. Chandramouli, *Arab. J. Chem.* (2013) DOI: 10.1016/j.arabjc.2013.10.014.
- [10] Y.W. Dong, G.W. Wang, L. Wang, *Tetrahedron* 64 (2008) 10148-10154.
- [11] B. Maleki, S. Babaee, R. Tayebee, *Appl. Org. Chem.* 29 (2015) 408-411.
- [12] J. Safari, M. Heydarian, Z. Zarnegar, *Arab. J. Chem.* (2013) DOI: 10.1016/j.arabjc.2013.11.038.
- [13] R.L. Magar, P.B. Thorat, V.B. Jadhav, S.U. Tekake, S.A. Dake, B.R. Patil, R.P. Pawar, *J. Mol. Catal. A: Chem.* 374-375 (2013) 118-124.
- [14] L. Kheirkhah, M. Mamaghani, N. Mahmoodi, A. Yahyazadeh, S. S. Mirmezami Ziabari, *J. Chem. Res.* 41 (2016) 21-24.
- [15] B. Maleki, *Org. Prep. Proced. Int.* 48 (2016) 81-87.
- [16] M. Khoobia, L. Ma'mani, F. Rezazadeh, Z. Zareie, A. Foroumadi, A. Ramazani, A. Shafieec, *J. Mol. Catal. A: Chem.* 359 (2012) 74-80.
- [17] K. Niknam, A. Piran, *Green Sustainable Chem.* 3 (2013) 1-8.
- [18] H. Xue, R. Verna, J.M. Shreeve, *J. Fluorine Chem.* 127 (2006) 159-176.
- [19] H. Zhao, Sh. Xia, P. Ma, *J. Chem. Technol. Biotechnol.* 80 (2005) 1089-1096.
- [20] A. Somes, P.C. Howlett, D.R. Macfarlane, M. Forsyth, *Lubricants* 1 (2013) 3-21.
- [21] R.P. Singh, R.D. Verma, D.T. Meshri, J.M. Shreev, *Angew. Chem. Int. Ed.* 45 (2006) 3584-3601.
- [22] J. Lu, J.M. Lazzaroni, J.P. Hallet, A.S. Bommarius, L.L. Charles, C.A. Eckert, *Ind. Eng. Chem. Res.* 43 (2004) 1586-1590.
- [23] D. Habibi, A. Shamsian, D. Nematollahi, *Chem. Pap.* 69 (2015) 586-595.
- [24] H. Kiyani, F. Ghorbani, *Chem. Pap.* 68 (2014) 1104-1112.
- [25] H. Kiyani, F. Ghorbani, *Res. Chem. Intermed.* 41 (2015) 4031-4046.
- [26] H. Kiyani, M. Ghiasi, *Res. Chem. Intermed.* 41 (2015) 5177-5203.
- [27] H. Kiyani, F. Ghorbani, *J. Saudi Chem. Soc.* 21 (2017) S112-S119.
- [28] H. Kiyani, F. Ghorbani, *J. Saudi Chem. Soc.* 18 (2014) 689-701.
- [29] A. Shaabani, R. Ghadari, S. Ghasemi, M. Pedarpour, A.H. Rezayan, A. Sarvary, S.W. Ng, *J. Comb. Chem.* 11 (2009) 956-959.