Silica-bonded N-propyl sulfamic acid: a recyclable catalyst for microwave-assisted synthesis of various dihydropyrano[3,2-c]chromenes

A. Gharib 1,2*, N. Noroozi Pesyan 3, L. Vojdani Fard 4, M. Roshani 1

1 Department of Chemistry, Islamic Azad University, Mashhad, IRAN
2 Agricultural Researches and Services Center, Mashhad, IRAN
3 Department of Chemistry, Faculty of Science, Urmia University, 57159 Urmia, IRAN
4 Education Ministry, Education Organization of Razavi Khorasan, Mashhad, IRAN

Received March 13, 2012; Revised February 13, 2013

A novel and simple method for the synthesis of dihydropyrano[3,2-c]chromenes is reported. The products are obtained in good to excellent yields by a simple, mild and efficient procedure using silica-bonded N-propyl sulfamic acid (SBNPSA) as a catalyst under microwave irradiation conditions.

Keywords: Silica-bonded N-propyl sulfamic acid (SBNPSA); chromenes; dihydropyrano[3,2-c]chromenes; Irradiation microwave

INTRODUCTION

Chromones constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents [1]. Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer) [2-4], neuroprotective [5], HIV-inhibitory [6], antimicrobial [7,8], antifungal [9] and antioxidant activity [10]. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans [11]. The synthesis of chromone derivatives is a research field of great interest and long history [12]. In general, chromones are synthesized by the cyclodehydration of 1-(o-hydroxyaryl)-1,3-diketones or equivalent intermediates catalyzed by strong acids or strong bases (Vilsmeier-Haack reaction) [13]. They have been prepared on a large scale by the Allan-Robinson synthesis involving acylation-rearrangement, and subsequent cyclization [14]. This methodology has been followed in the synthesis of chromone derivatives with quaternary ammonium functionalities which show not only activity of cosmetic interest but also for hair sustainability, as well as in the asymmetric synthesis of optically active 4-chromone derivatives [15]. In the Baker-Venkataraman synthesis [16], internal Claisen condensation of 2-aryloxy-1-acetylenes is employed as a key step. More recently the synthesis of chromone derivatives was accomplished by intramolecular ester carbonyl olefination [17] or Pd-catalyzed regiospecific carboxylative annulation of o-iodophenol acetates and acetylenes [1, 18]. 3-Cyanochromones have been synthesized in a mild and facile way from oximes derived from 3-formyl chromones using dimethyl formamide/thioly1 chloride complex [19]. As for aminochromones, useful for the prevention of allergic and asthmatic reactions in mammals, as indicated by tests in rats, they have been synthesized either by rearrangement of isoxazoles [20] or from chlorinated salicylic acids and malononitrile in aqueous NaOH or NaH [21]. 2-Amino-4H-chromenes and their derivatives are of considerable interest as they possess a wide range of biological properties [22], such as spasmolytic, diuretic, anticoagulant, anticancer and antianaphylactic activity [23]. In addition, they can be used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease, Parkinson’s disease, AIDS associated dementia and Down’s syndrome as well as for the treatment of schizophrenia and myoclonus [24].

The development of multi-component reactions (MCRs) has attracted much attention from the vantage point of combinatorial and medicinal chemistry [25]. Many important heterocycle syntheses are multi-component reactions. Recently, the synthesis of 4H-chromenes and dihydropyrano[3,2-c]chromenes derivatives has attracted great interest to their biological and pharmacological activities [26]. The 4H-chromene derivatives show various pharmacological properties such as spasmolytic, diuretic,
anticoagulant, anticancer, and antianaphylactic activities [26]. Substituted 4H-chromenes are particularly versatile compounds that bind Bcl-2 protein (B-cell lymphoma 2) and induce apoptosis in tumor cells.

EXPERIMENTAL

All materials and solvents were purchased from Merck and Fluka. Melting points were determined in open capillary tubes in an Electrothermal IA 9700 melting point apparatus. 1H NMR spectra were recorded on a Bruker-300 MHz instrument using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Irradiation was carried out in a domestic microwave oven (Electra, 2450 MHz, 700 W) for optimized time. All yields refer to isolated products. Silica bonded N-propyl sulfamic acid (SBNPSA) was prepared according to our previously reported procedure [27].

General procedure for the preparation of 2-amino-5-oxo-dihydropyrano[3,2-c]chromenes: A mixture of aldehyde (12 mmol), malononitrile (0.1 g) in H2O (5 mL) and EtOH (5 mL) was stirred and irradiated in a microwave oven at 700 W for optimized time. All yields refer to isolated products. Silica bonded N-propyl sulfamic acid (SBNPSA) was prepared according to our previously reported procedure [27].

Selected spectral data:

**2-amino-5-oxo-4-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrano[3,2-c]chromene (Table 1, entry 1):** m.p. 224-226 °C; (m.p. 224-226 °C [28,29]); IR (KBr) νmax/cm-1: 3425, 3321, 2191, 1672, 1595, 1375, 1154. 1H NMR (DMSO-d6, 300 MHz) δ: 3.63 (s, 3H, CH3), 3.71 (s, 6H, CH3), 4.43 (s, 1H, H), 6.52 (s, 2H, NH2), 7.42 (t, 2H, aromatic), 7.65 (t, 2H, aromatic), 7.87 (2d, 3H, aromatic). 13C NMR (DMSO-d6, 250 MHz) δ: 160.1, 158.5, 154.0, 153.3, 152.6, 139.4, 137.1, 125.1, 123.6, 121.3, 119.7, 117.0, 113.6, 105.4, 104.1, 60.4, 58.4, 56.0, 37.7. MS (m/z): 404. Anal. Calc. C, 65.02; H, 4.46; N, 6.89%. Found: C, 65.0; H, 4.27; N, 6.93%.

**2-amino-4-(2,6-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene (Table 1, entry 2):** m.p. 254-256 °C, (m.p. 254-256 °C [29]); IR (KBr) νmax/cm-1: 3420, 3320, 2190, 1677, 1595, 1377, 1152. 1H NMR (DMSO-d6, 300 MHz) δ: 4.27 (s, 1H, H), 6.83 (s, 2H, NH2), 7.45 (t, 2H, aromatic), 7.67 (t, 2H, aromatic), 7.80 (2d, 3H, aromatic). 13C NMR (DMSO-d6, 250 MHz) δ: 161.3, 160.6, 159.4, 152.6, 139.5, 138.4, 135.7, 128.2, 127.4, 123.6, 119.2, 116.6, 115.3, 113.5, 105.4, 58.3. MS (m/z): 384. Anal. Calc. C, 59.24; H, 2.62; N, 7.27%. Found: C, 59.20; H, 2.65; N, 7.26%.

**2-amino-4-(2,4-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene (Table 1, entry 3):** m.p. 274-276 °C, (m.p. 274-276 °C [29]); IR (KBr) νmax/cm-1: 3423, 3320, 2192, 1675, 1595, 1377, 1150. 1H NMR (DMSO-d6, 300 MHz) δ: 4.29 (s, 1H, H), 6.85 (s, 2H, NH2), 7.43 (t, 2H, aromatic), 7.66 (t, 2H, aromatic), 7.84 (2d, 3H, aromatic). 13C NMR (DMSO-d6, 250 MHz) δ: 161.1, 160.7, 159.4, 152.5, 139.5, 138.4, 135.7, 128.2, 127.4, 123.6, 119.2, 116.6, 115.3, 113.5, 105.4, 58.3. MS (m/z): 384. Anal. Calc. C, 59.24; H, 2.62; N, 7.27%. Found: C, 59.20; H, 2.65; N, 7.26%.

**2-amino-4-(3-bromophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene (Table 1, entry 4):** m.p. 254-256 °C, (m.p. 255-258 °C [29]); IR (KBr) νmax/cm-1: 3420, 3322, 2190, 1677, 1595, 1377, 1152. 1H NMR (DMSO-d6, 300 MHz) δ: 4.27 (s, 1H, H), 6.83 (s, 2H, NH2), 7.45 (t, 2H, aromatic), 7.67 (t, 2H, aromatic), 7.80 (2d, 3H, aromatic). 13C NMR (DMSO-d6, 250 MHz) δ: 161.3, 160.5, 159.4, 152.6, 139.5, 138.4, 135.7, 128.2, 127.4, 123.6, 119.2, 116.6, 115.3, 113.5, 105.4, 58.3. MS (m/z): 384. Anal. Calc. C, 59.24; H, 2.62; N, 7.27%. Found: C, 59.20; H, 2.65; N, 7.26%.

**2-amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene (Table 1, entry 5):** m.p. 254-256 °C, (m.p. 255-257 °C [29]); IR (KBr) νmax/cm-1: 3423, 3321, 2190, 1678, 1595, 1375, 1152. 1H NMR (DMSO-d6, 300 MHz) δ: 4.28 (s, 1H, H), 6.81 (s, 2H, NH2), 7.42 (t, 2H, aromatic), 7.44 (t, 2H, aromatic), 7.66 (t, 2H, aromatic), 7.81 (2d, 3H, aromatic). 13C NMR (DMSO-d6, 250 MHz) δ: 161.9, 160.7, 159.3, 152.6, 139.5, 138.7, 135.4, 128.2, 127.5, 123.6, 119.2, 116.6, 115.3, 113.5, 105.4, 58.3. MS (m/z): 384. Anal. Calc. C, 59.24; H, 2.62; N, 7.01%. Found: C, 57.55; H, 2.75; N, 7.01%.

**2-amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene (Table 1, entry 6):** m.p. 255-258 °C, (m.p. 256-259 °C [29]); IR (KBr) νmax/cm-1: 3423, 3321, 2190, 1678, 1595, 1375, 1152. 1H NMR (DMSO-d6, 300 MHz) δ: 4.26 (s, 1H, H), 6.82 (s, 2H, NH2), 7.46 (t, 2H, aromatic), 7.44 (t, 2H, aromatic), 7.68 (t, 2H, aromatic).
2-amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 1, entry 7): m.p. 256-259 °C, (m.p. 255-258 °C [29]); IR (KBr) ν_max/cm⁻¹: 3422, 3320, 2195, 1677, 1591, 1376, 1152. 1H NMR (DMSO-d6, 300 MHz) δ: 4.24 (s, 1H, H), 6.82 (s, 2H, NH₂), 7.44 (t, 2H, aromatic), 7.69 (t, 2H, aromatic), 7.83 (2d, 3H, aromatic). 13C NMR (DMSO-d6, 250 MHz) δ: 161.7, 160.7, 159.5, 152.8, 139.2, 138.6, 135.6, 128.3, 127.4, 123.6, 120.1, 115.6, 116.7, 113.5, 105.4, 58.3. MS (m/z): 361. Anal. Calc. C, 63.16; H, 3.07; N, 11.63%. Found: C, 63.03; H, 3.14; N, 11.63%.

2-amino-4-(4-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (Table 1, entry 9): m.p. 244-247 °C, (m.p. 246-249 °C [29]); IR (KBr) ν_max/cm⁻¹: 3421, 3326, 2199, 1676, 1590, 1377, 1154. 1H NMR (DMSO-d6, 300 MHz) δ: 3.83 (s, 1H, CH₃), 4.28 (s, 1H, H), 6.80 (s, 2H, NH₂), 7.14 (s, 1H, aromatic ), 7.44 (t, 2H, aromatic), 7.66 (t, 2H, aromatic), 7.82 (2d, 3H, aromatic). 13C NMR (DMSO-d6, 250 MHz) δ: 161.9, 160.2, 159.2, 152.8, 144.1, 135.5, 127.7, 128.6, 123.3, 125.7, 119.1, 115.3, 116.4, 105.3, 58.1, 39.8. MS (m/z): 346. Anal. Calc. C, 72.15; H, 3.82; N, 8.86%. Found: C, 72.04; H, 3.72; N, 8.94%.

RESULTS AND DISCUSSION

We performed the synthesis of 2-amino-4H-chromenes and/or dihydropyrano[3,2-c]chromenes through a three-component reaction employing silica-bonded N-propyl sulfamic acid (SBNPSA) acid as a catalyst. The synthesis of 2-amino-4H-chromenes and/or dihydropyrano[3,2-c]chromenes was achieved by three-component condensation of an aromatic aldehyde, malononitrile and 4-hydroxycoumarin in the presence of SBNPSA as a catalyst. The reaction was carried out in aqueous ethanol under microwave irradiation conditions to give products in good to high yields (Scheme 1 and Table 1).
Table 1. Synthesis of various dihydropyran[3,2-c]chromenes were run at microwave conditions and in the presence of silica-bonded N-propyl sulfamic acid (SBNPSA) as catalyst, H2O:EtOH (1:1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,4,5-(OCH3)3-C6H4CHO</td>
<td>![Product Image]</td>
<td>47</td>
<td>94.5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2,6-Cl2-C6H4CHO</td>
<td>![Product Image]</td>
<td>34</td>
<td>96</td>
<td>[28]</td>
</tr>
<tr>
<td>3</td>
<td>2,3-Cl2-C6H4CHO</td>
<td>![Product Image]</td>
<td>30</td>
<td>92.5</td>
<td>[29]</td>
</tr>
<tr>
<td>4</td>
<td>2,4-Cl2-C6H4CHO</td>
<td>![Product Image]</td>
<td>32</td>
<td>85</td>
<td>[29]</td>
</tr>
<tr>
<td>5</td>
<td>4-Br-C6H4CHO</td>
<td>![Product Image]</td>
<td>38</td>
<td>95.5</td>
<td>[29]</td>
</tr>
<tr>
<td>6</td>
<td>3-NO2-C6H4CHO</td>
<td>![Product Image]</td>
<td>40</td>
<td>94.5</td>
<td>[29]</td>
</tr>
<tr>
<td>7</td>
<td>4-NO2-C6H4CHO</td>
<td>![Product Image]</td>
<td>41</td>
<td>98</td>
<td>[29]</td>
</tr>
<tr>
<td>8</td>
<td>4-CH3-C6H4CHO</td>
<td>![Product Image]</td>
<td>43</td>
<td>93</td>
<td>[30]</td>
</tr>
<tr>
<td>9</td>
<td>4-OCH3-C6H4CHO</td>
<td>![Product Image]</td>
<td>24</td>
<td>84.5</td>
<td>[29]</td>
</tr>
<tr>
<td>10</td>
<td>4-Cl-C6H4CHO</td>
<td>![Product Image]</td>
<td>29</td>
<td>83</td>
<td>[29]</td>
</tr>
<tr>
<td>11</td>
<td>C6H5CHO</td>
<td>![Product Image]</td>
<td>44</td>
<td>92.5</td>
<td>[29]</td>
</tr>
</tbody>
</table>

*Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods.
Table 2. Synthesis of various dihydropyrano[3,2-c]chromenes were run under reflux (Conventional heating conditions) and in the presence of silica-bonded N-propyl sulfamic acid (SBNPASA) as catalyst, H₂O:EtOH (1:1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,4,5-(OCH₃)₃-C₆H₄CHO</td>
<td><img src="image1" alt="Product 1" /></td>
<td>65</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>2,6-Cl₂-C₆H₄CHO</td>
<td><img src="image2" alt="Product 2" /></td>
<td>47</td>
<td>86.5</td>
</tr>
<tr>
<td>3</td>
<td>2,3-Cl₂-C₆H₄CHO</td>
<td><img src="image3" alt="Product 3" /></td>
<td>49</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>2,4-Cl₂-C₆H₄CHO</td>
<td><img src="image4" alt="Product 4" /></td>
<td>51</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>4-Br-C₆H₄CHO</td>
<td><img src="image5" alt="Product 5" /></td>
<td>48</td>
<td>74.5</td>
</tr>
<tr>
<td>6</td>
<td>3-NO₂-C₆H₄CHO</td>
<td><img src="image6" alt="Product 6" /></td>
<td>63</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>4-NO₂-C₆H₄CHO</td>
<td><img src="image7" alt="Product 7" /></td>
<td>58</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>4-CH₃-C₆H₄CHO</td>
<td><img src="image8" alt="Product 8" /></td>
<td>61</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>4-OCH₃-C₆H₄CHO</td>
<td><img src="image9" alt="Product 9" /></td>
<td>47</td>
<td>68.5</td>
</tr>
<tr>
<td>10</td>
<td>4-Cl-C₆H₄CHO</td>
<td><img src="image10" alt="Product 10" /></td>
<td>41</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>C₆H₅CHO</td>
<td><img src="image11" alt="Product 11" /></td>
<td>59</td>
<td>78.5</td>
</tr>
</tbody>
</table>

*Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods.*
Scheme 2. The mechanism of the synthesis of various dihydropyrano[3,2-c]chromenes in the presence of silica-bonded N-propyl sulfamic acid (SBNPSA) as catalyst under irradiation microwave conditions.

As shown in Table 1, the results of the reactions of the aromatic aldehyde, malononitrile with 4-hydroxycoumarin indicate that the application of microwave irradiation can considerably increase the efficiency of these reactions to produce entries 1-11 in satisfactory yields (83-98%) and reduce the reaction times when compared with the conventional thermal conditions (68-88%) (Table 2).

2-Amino-4H-chromenes are generally prepared by refluxing malononitrile, aldehyde and activated phenol in the presence of hazardous organic bases like piperidine for several hours [31]. A literature survey revealed that several modified procedures using CTACl [32], TEBA [33], and γ-alumina [34] as catalysts have been recently reported but all these methods require long refluxing hours. Based on previous studies, new heterogeneous catalyst systems for fine chemical preparation were developed [35]. The suggested mechanism for the SBNPSA-catalyzed transformations is shown in Scheme 2. As reported in the literature [36], the Knoevenagel coupling of aldehydes with malononitrile gives the intermediate (5). Then, the subsequent 1,4-conjugate addition of 4-hydroxycoumarin to the intermediate (I) followed by cyclization, affords the corresponding products [37,38]. A mechanism for this reaction has been suggested in Scheme 2.

The catalysts were recovered by evaporation of the solvent and washing of the solid with chloroform. When the reaction was completed, the mixture was filtered, the solid residue was washed with warm ethanol and the catalyst was reused in the subsequent reaction. The recycled catalyst could be reused four times without any additional treatment. No appreciable loss in the catalytic activity of SBNPSA was observed (Table 3).

Table 3. Recyclability of SBNPSA catalyst for the synthesis of compound (Table 1, 7) (2-amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile).

<table>
<thead>
<tr>
<th>Run</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>94</td>
</tr>
</tbody>
</table>

* Isolated yield.
* Yield of catalyst recycled four times.

CONCLUSION

In conclusion, we have developed an efficient procedure for the synthesis of 2-amino-4H-chromene and/or dihydropyrano[3,2-c]chromene derivatives in 1:1 EtOH-water mixture using silica-bonded N-propyl sulfamic acid (SBNPSA) as a catalyst. This method offers several advantages such as inexpensive catalysts, easy synthetic procedure, high yields, simple work-up procedure and easy product isolation. The microwave irradiation reduced the reaction times in this synthesis.

REFERENCES


N-ПРОПИЛ-СУЛФАМИНОВА КИСЕЛИНА ВЪРХУ НОСИТЕЛ ОТ СИЛИЦИЕВ ДИОКСИД: РЕЦИКЛИРУЕМ КАТАЛИЗАТОР ЗА СИНТЕЗИ НА РАЗЛИЧНИ ДИХИДРОПРОПАНОЛ [3,2-C] – ХРОМЕН ПРИ МИКРОВЪЛНОНО ЛЪЧENIE

А. Гариб 1,2*, Н. Норузи Песян 3, Л. Вождани Фард 4, М. Рощани 1

1 Департамент по химия, Исламски университет Азад, Машхад, Иран
2 Център за земеделски изследвания и услуги, Машхад, Иран
3 Департамент по химия, Научен факултет, Университет в Урмия, 57159 Урмия, Иран
4 Министерство на образованието, Организация за образованието Разави, Хоразан,, Машхад, Иран


(Резюме) Съществува се за нов и прост метод за синтезата на диоксидпропанол [3,2-C] – хромени при микровълново лъчение.