Disodium Phosphate: A Highly Efficient Catalyst for One-Pot Synthesis of Substituted 3,4-Dihydropyrano[3,2-C]Chromenes

Balasaheb V. Shitolea, Nana V. Shitoleb, and Gopal K. Kakdec*

aDepartment of Chemistry, Vasant College Kaji-431518, India.
bShri Shivaji College, Parbhani-431401 MS, India.
cArts, Commerce and Science College, Dharur (Kille)-431519, India.

Article history: Received: 19 August 2016; accepted: 04 May 2017. Available online: 18 June 2017. DOI: http://dx.doi.org/10.17807/orbital.v9i3.896

Abstract: Disodium phosphate catalyzed one-pot synthesis of 3,4-dihydropyrano[3,2-c]chromenes, from aldehydes, active methylene compounds malononitrile and 4-hydroxycoumarin in ethanol:water (1:1) under reflux temperature. The attractive features of this process are inexpensive, efficient, as well as user friendly.

Keywords: chromenes; multi-component reaction; disodium phosphate; one-pot

1. INTRODUCTION

Multicomponent reactions have emerged as an efficient, powerful tool in modern organic chemistry for the generation of highly diverse, complex products from readily available substrates in a single operation, without isolation of intermediates, in minimal time, with maximum selectivity, high atom-economy, high purity and excellent yields. Multicomponent reactions are widely used in medicinal chemistry and modern organic synthesis because they are one-pot processes for assembling three or more components [1, 2]. MCRs have been successful in the synthesis of 3,4-dihydropyrano[c]chromenes and their derivatives which considerable interest due to they have pharmaceutical and biological properties [3], like spasmolytic [4], anti-inflammatory [5], anticancer [6], molluscicidal [7], diuretic [8], anti-coagulant [9].

A number of methods have been reported for the synthesis of 3,4-dihydropyrano[c]chromenes with the catalysts such as pyridine [10], K₂CO₃[11], diammonium hydrogenphosphate [12], MgO [13], TBAB [14], SiO₂PrSO₃H [15], 4-(dimethylamino)pyridine (DMAP) [16], trisodium citrate [17], ammonium acetate [18], polymer supported sulphanic acid [19], basic ionic liquid [20], CuO nanoparticles [21], p-dodecylbenzenesulfonic acid [22], amberlyst A21[23], silica-grafted ionic liquid [24] TiO₂ [25], thiourea dioxide [26], Fe₃O₄@SiO₂–imid–PMAn nanoparticles [27], and N,N-dimethylbenzylamine (DMBA) [28] have also been reported to promote this reaction. Although these methods worked nicely in many cases, some of these procedures are associated with one or more shortcomings such as long reaction time, poor yield, use of volatile organic solvents, requirement for excess reagents or catalysts, special apparatus, and harsh reaction conditions. Consequently, the development of convenient, environmentally benign, high-yielding, and clean approaches is in high demand.

Disodium phosphate is a very inexpensive, nontoxic, and commercially available compound that can be used in the laboratory without special precautions [29]. As part of our ongoing interest in the use of cheap and ecofriendly materials as catalysts for various transformations [30], we herein report a new method for the synthesis of 2-aminochromenes by the one-pot, three-component reaction of an aromatic aldehyde, malononitrile, and 4-hydroxycoumarin in the presence of a catalytic amount of disodium phosphate in ethanol water (1:1) under reflux temperature (Scheme 1).

2. MATERIAL AND METHODS

The chemicals used aldehydes, active
methylene compounds malononitrile and 4-hydroxy coumarin were of analytical reagent grade and methods used for synthesis of 3,4-dihydropyrano[3,2-C]chromenes and their derivatives. Melting points were determined in an open capillary. Melting points were determined in open capillary tubes in a paraffin bath. The progress of the reactions were monitored by TLC (Thin Layer Chromatography). IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. 1H nuclear magnetic resonance (NMR) (500 MHz) with tetramethylsilane as internal standard and dimethyl sulfoxide DMSO-d6 as solvent and chemical shift values are recorded in units δ (ppm) relative to TMS as an internal standard.

General Procedure for the Synthesis of Substituted 3,4-Dihydropyrano[3,2-C]chromenes (3a-m)

A mixture of substituted aromatic aldehyde (1 mmol), malononitrile (1 mmol) and 4-hydroxycoumarin (1 mmol) in the presence of disodium phosphate (10 mol%) as a catalyst was stirred at reflux temperature in ethanol:water (1:1) (10 mL) for 25-40 minutes. After the appropriate time, the mixture was cooled than poured on ice cold water solidified the product filtered its. The crude solid material was purified by recrystallization from ethanol (Table 3).

Spectroscopic data of synthesized some principal compounds

2-amino-4-(4-chlorophenyl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4a): IR (KBr): 3321 (NH2), 2159 (CN), 1701 (C=O) cm-1. 1H NMR (d6-DMSO, 400 MHz) δ: 4.46 (s, 1H, CH), 7.48–8.19 (m, 10H, Ar, NH2) ppm. 13C NMR (d6-DMSO, 100 MHz), δ: 57.2, 103.2, 113.3, 116.9, 119.3, 123.0, 124.1, 124.7, 125.1, 129.6, 129.7, 133.6, 147.0, 151.2, 152.7, 154.4, 158.5, 160.0 ppm.

2-amino-4-(3-chlorophenyl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4n): IR (KBr): 3321 (NH2), 2159 (CN), 1701 (C=O) cm-1. 1H NMR (d6-DMSO, 400 MHz) δ: 4.42 (s, 1H, CH), 7.21–8.71 (m, 10H, Ar, NH2) ppm. 13C NMR (d6-DMSO, 100 MHz), δ: 57.9, 104.3, 114.3, 116.2, 119.2, 122.9, 125.1, 127.0, 127.6, 127.8, 130.3, 133.8, 132.9, 146.2, 152.6, 155.4, 158.3, 158.4, 160.3 ppm.

2-amino-4-(4-methoxyphenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4j): IR (KBr): 3367 (NH2), 2887 (CH3), 2162 (CN), 1701 (C=O) cm-1. 1H NMR (d6-DMSO, 400 MHz) δ: 3.75 (s, CH3) 4.42 (s, 1H, CH), 7.33–8.22 (m, 10H, Ar, NH2) ppm. 13C NMR (d6-DMSO, 100 MHz), δ: 52.9, 58.7, 104.1, 113.1, 115.7, 116.9, 119.2, 122.9, 124.2, 124.2, 125.2, 126.7, 134.1, 138.1, 152.1, 152.5, 158.2, 159.5 ppm.

2-amino-4,5-dihydro-4-(3-nitrophenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4g): IR (KBr): 3367 (NH2), 2887 (CH3), 2162 (CN), 1701 (C=O) cm-1. 1H NMR (d6-DMSO, 400 MHz) δ: 3.75 (s, CH3) 4.42 (s, 1H, CH), 7.33–8.22 (m, 10H, Ar, NH2) ppm. 13C NMR (d6-DMSO, 100 MHz), δ: 52.9, 58.7, 104.1, 113.1, 115.7, 116.9, 119.2, 122.9, 124.2, 124.2, 125.2, 126.7, 134.1, 138.1, 152.1, 152.5, 158.2, 159.5 ppm.
NMR (d_6-DMSO, 400 MHz) δ: 4.44 (s, 1H, CH), 7.11–8.71 (m, 10H, Ar, NH_2) ppm. 13C NMR (d_6-DMSO, 100 MHz), δ: 58.4, 104.3, 112.9, 118.0, 119.2, 122.3, 122.9, 125.1, 129.8, 133.6, 135.2, 145.6, 154.5, 158.3, 158.7, 160.1 ppm.

2-amino-4,5-dihydro-4-(2-nitrophenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4m): IR (KBr): 3352 (NH_2), 2171 (CN), 1709 (C=O) cm⁻¹. 1H NMR (d_6-DMSO, 400 MHz) δ: 4.41 (s, 1H, CH), 7.21–8.52 (m, 10H, Ar, NH_2) ppm. 13C NMR (d_6-DMSO, 100 MHz), δ: 57.3, 103.2, 119.3, 117.5, 118.9, 123.8, 124.6, 125.8, 129.7, 133.3, 147.3, 151.4, 152.4, 154.4, 158.5, 161.2 ppm.

2-amino-4-(2,4-dichlorophenyl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4i): IR (KBr): 3321 (NH_2), 2157 (CN), 1702 (C=O) cm⁻¹. 1H NMR (d_6-DMSO, 400 MHz) δ: 4.44 (s, 1H, CH), 7.29–8.87 (m, 9H, Ar, NH_2) ppm. 13C NMR (d_6-DMSO, 100 MHz), δ: 34.4, 57.7, 102.9, 113.9, 117.2, 119.4, 123.2, 124.9, 128.6, 129.4, 133.1, 132.2, 133.6, 134.1, 139.1, 153.7, 154.6, 158.5, 160.4 ppm.

2-amino-4,5-dihydro-4-(3,4,5-trimethoxyphenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4c): IR (KBr): 3331 (NH_2), 2177 (CN), 1701 (C=O) cm⁻¹. 1H NMR (d_6-DMSO, 400 MHz) δ: 3.64 (s, 3H), 3.72 (s, 6H), 4.43 (s, 1H, CH), 7.29–8.87 (m, 9H, Ar, NH_2) ppm. 13C NMR (d_6-DMSO, 100 MHz), δ: 56.3, 58.3, 60.4, 104.1, 105.3, 113.5, 117.0, 119.7, 123.0, 125.1, 133.3, 137.0, 139.4, 152.6, 153.3, 153.9, 158.3, 160.1 ppm.

2-amino-4-(4-fluorophenyl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4f): IR (KBr): 3366 (NH_2), 2887 (CH_3), 2151 (CN), 1705 (C=O) cm⁻¹. 1H NMR (d_6-DMSO, 400 MHz) δ: 4.42 (s, 1H, CH), 7.41–8.22 (m, 10H, Ar, NH_2) ppm. 13C NMR (d_6-DMSO, 100 MHz), δ: 52.9, 57.6, 104.1, 113.1, 115.7, 116.9, 119.2, 122.9, 124.2, 125.2, 126.7, 134.1, 138.1, 152.1, 152.5, 154.4, 158.2, 160.5 ppm.

2-amino-4-(4-(dimethylamino)phenyl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4k): IR (KBr): 3234 (NH_2), 2187 (CN), 1702 (C=O) cm⁻¹. 1H NMR (d_6-DMSO, 400 MHz) δ: 23.1 (s, CH_3), 4.68 (s, 1H, CH), 7.37–8.11 (m, 10H, Ar, NH_2) ppm. 13C NMR (d_6-DMSO, 100 MHz), δ: 34.6, 56.2, 103.2, 113.4, 117.3, 119.3, 122.9, 124.2, 124.9, 125.2, 129.2, 128.9, 132.3, 146.7, 151.2, 152.7, 154.4, 158.5, 160.1 ppm.

3. RESULTS AND DISCUSSION

Considered as a standard model reaction as we examined the reaction 4-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxycoumarine (1 mmol) and disodium phosphate (10 mol%) as catalyst dissolved in 10 mL of ethanol:water (1:1) at reflux temperature for 25–40 min (Scheme 1). The corresponding product was obtained in excellent yield.

To determine the effect of solvent, various solvents such as water, ethanol:water (1:3,v:v), ethanol:water (1:2,v:v), ethanol:water (1:1,v:v), ethanol and methanol were used for the model reaction. The desired product was obtained in 37, 61, 71, 95, 95 and 82% yields, respectively, after 30 min at reflux condition. Water:ethanol (1:1) stand out as the solvent of choice among the solvents tested. Because of the rapid conversion and excellent yield (95%) of desired product obtained, whereas the product formed in lower yields (37–95%) by using other solvents (Table 1).

To determine the appropriate concentration of the catalyst disodium phosphate, we investigate the model reaction at different concentrations of catalyst like 2.5, 5, 7.5, 10 and 12.5 mol%. The product formed in 42, 65, 72, 95 and 95% yield, respectively. This indicates that 10 mol% of disodium phosphate is sufficient for the best result by considering the...
reaction time and yield of product (Table 2).

Table 1. Screening of solvents for synthesis of substituted 3,4-sihydropyrano[3,2-c]chromenes.

| Entry | Solvent                  | Yield (%) |
|-------|--------------------------|-----------|
| 1     | water                    | 37        |
| 2     | ethanol, water (1:3)     | 61        |
| 3     | ethanol, water (1:2)     | 71        |
| 4     | ethanol, water (1:1)     | 95        |
| 5     | ethanol                  | 95        |
| 6     | methanol                 | 82        |

To study the generality of this process, variety of examples were illustrated for the synthesis of dihydropyrano[3,2-c]chromenes and results are summarized in Table 3. The reaction is compatible for various substituents such as -CH₃, -OCH₃, -OH, -N(CH₃)₂, NO₂ and –Cl. The formation of desired product has been confirmed by ¹H NMR and IR spectroscopic analysis techniques and compared with the corresponding literature data.

Table 2. Effect of catalyst concentration.a

| Entry | Concentration (mol%) | Yield (%)b |
|-------|----------------------|------------|
| 1     | 1                    | 42         |
| 2     | 5                    | 65         |
| 3     | 7.5                  | 72         |
| 4     | 10                   | 95         |
| 5     | 12.5                 | 95         |

*Reaction conditions: 1a-m (1 mmol), 2 (1 mmol) 3 (1 mmol) and disodium phosphate in ethanol:water (1:1) at reflux temperature. *Isolated yields.

Table 3. Synthesis of dihydropyrano[3,2-c] chromenes using disodium phosphate.a

| Sr. No. | Ar-CHO | Product | Time (min) | Yieldb (%) | Found | m.p. (°C) | Reported |
|---------|--------|---------|------------|------------|-------|-----------|----------|
| 1       | 4-ClC₆H₄ | 4a      | 09         | 95         | 261-263 | 263-265   | [12]     |
| 2       | 4-CH₃C₆H₄ | 4b      | 12         | 92         | 254-267 | 253-255   | [24]     |
| 3       | 3,4,5(OCH₃)₃C₂H₄ | 4c    | 13         | 91         | 237-239 | 236-238   | [24]     |
| 4       | C₂H₅   | 4d      | 10         | 93         | 255-257 | 256-258   | [12]     |
| 5       | 4-NO₂C₂H₄ | 4e     | 08         | 95         | 256-258 | 258-260   | [12]     |
| 6       | 4-F C₂H₄ | 4f      | 09         | 94         | 257-259 | 258-259   | [20]     |
| 7       | 3-NO₂C₂H₄ | 4g     | 09         | 92         | 260-262 | 262-264   | [12]     |
| 8       | 2-ClC₂H₄ | 4h      | 11         | 89         | 243-245 | 245-246   | [20]     |
| 9       | 2,4-Cl₂C₂H₃ | 4i    | 12         | 92         | 260-262 | 257-259   | [12]     |
| 10      | 4-OH C₂H₄ | 4j     | 12         | 89         | 243-245 | 240-242   | [12]     |
| 11      | 4-(CH₃)₃NCC₂H₄ | 4k  | 14         | 92         | 262-263 | 265-267   | [20]     |
| 12      | 4-0HCH₃C₂H₄ | 4l   | 14         | 91         | 267-269 | 266-268   | [24]     |
| 13      | 2-NO₂C₂H₄ | 4m     | 10         | 87         | 259-261 | 258-260   | [24]     |
| 14      | 3-ClC₂H₄ | 4n     | 10         | 92         | 244-246 | 241-243   | [24]     |

*Reaction conditions: 1a-m (1 mmol), 2 (1 mmol) 3 (1 mmol) and disodium phosphate in ethanol:water (1:1) at reflux temperature. *Isolated yields.

4. CONCLUSION

In conclusion, this paper describes a simple and proficient approach for the synthesis of dihydropyrano[3,2-c]chromenes catalyzed by disodium phosphate in aqueous alcoholic media. Present methodology offers very attractive features such as simple experimental procedure, higher yields and economic viability.

5. ACKNOWLEDGMENTS

We are thankful to the University Grants Commission, New Delhi, for financial support which is gratefully acknowledged and the Sophisticated Instrument Facility, Punjab University, Chandigarh for providing spectroscopic data.

6. REFERENCES AND NOTES

[1] Zhu, J.; Bienayme, H. Multicomponent Reactions, Wiley-VCH: Weinheim, 2005. [CrossRef]
[2] Safari, J.; Zarnegar, Z.; Heydarian, M. J. Taibah Univ. Sci. 2013, 7, 17. [CrossRef]
[3] Katritzky, A. R.; Rees, C. W.; Scriven. E. F. V. Eds.; Pergamon Press: Oxford 1995, 5, 469.
[4] Foye, W. O. Principi Di Chemico Farmaceutica. Piccin: Padova, Italy, 1991, 416.
[5] Symeonidis, T.; Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E. Eur. J. Med. Chem. 2009, 44, 5012. [CrossRef]
[6] Ough, M.; Lewis, A.; Bey, E. A.; Gao, J.; Ritchie, J. M.; Bornmann, W. Cancer Biol. Ther. 2005, 4, 95. [CrossRef]

[7] de Andrade-Neto, V. F.; Goulart, M. O.; da Silva Filho, J. F.; da Silva, M. J.; Pinto, M. C. F. R.; Pinto, A.V.; Zalis, M. G.; Carvalho, L. H.; Krettli, A. U. Bioorg. Med. Chem. Lett. 2004, 14, 1145. [CrossRef]

[8] Andream, L. L.; Lapi, E. Bull. Chem. Farm. 1996, 51, 148.

[9] Kidwai, M.; Saxena, S. Synth. Commun. 2006, 36, 2737. [CrossRef]

[10] Shahrazad, A.; Saeed, B. Tetrahedron Lett. 2007, 48, 3299. [CrossRef]

[11] Seifi, M.; Sheibani, H. Catal. Lett. 2008, 126, 275. [CrossRef]

[12] Khurana, J. M.; Kumar, S. Tetrahedron Lett. 2009, 50, 4125. [CrossRef]

[13] Mohammadi, Z. G.; Badiei, A.; Azizi, M.; Zarabadi, P. Iran J. Chem. Eng. 2011, 30, 59.

[14] Abu, T. K.; Mohan, L.; Shahzad, A.; Md, M. K. Tetrahedron Lett. 2011, 52, 5327. [CrossRef]

[15] Jia, Z.; Yi-Qun, L. Scholars Research Library 2011, 3, 381.

[16] Kanakaraju, S.; Prasanna, B.; Srinivas, B.; Chandramouli, G. V. P. Arab. J. Chem. 2017, 10, S2705. [CrossRef]

[17] Kashmin, P.P.; Jemin, R. A.; Dipak, K. R. J. Chem. Sci. 2013, 125, 531. [CrossRef]

[18] Patel, D. S.; Avalani, J. R.; Raval, D. K. J. Saudi Chem. Soc. 2016, 20, S401. [CrossRef]

[19] Hossein, M.; Maryam, K. M. Chinese Chemical Letters 2011, 22, 1419. [CrossRef]

[20] Enayatollah, S.; Dadkhoda, G.; Vida, N. Iranian J. Catal. 2013, 3, 197.

[21] Manisha, B.; Pranjil, P. B.; Ghanashyam, B.; Hassan, A. C. R. Chim. 2013, 16, 419. [CrossRef]

[22] Niknam, K.; Piran, A. Green Sustain. Chem. 2013, 3, 1.

[23] Saeed, K.; Bahador, K.; Khalil, E.; Seyed, J. H. C.R. Chim. 2014, 17, 35. [CrossRef]

[24] Syed, S. M.; Kuppan, L.; Krishnamoorthy, A.; Prasanna, N. S. J. Taibah Univ. Sci. 2015, 9, 213. [CrossRef]

[25] Esmaeilpour, M.; Javidi, J.; Dehghanj, F.; Dodeji, F. N. RSC Adv. 2015, 5, 26625. [CrossRef]

[26] Kiyan, H.; Jalali, M. S. Comb. Chem. High T. Scr. 2016, 19, 275.

[27] Michaelis, L.; Rona P. Biochem. 1912, xivii, 447.

[28] (a) Shitole, N. V.; Shelke, K. F.; Sadaphal, S. A.; Shingate, B. B.; Shingare, M. S. Green Chem. Lett. Rev. 2010, 3, 83. [CrossRef] (b) Shitole, N. V.; Sapkal, S. B.; Shingate, B. B.; Shingare, M. S. Bull. Korean Chem. Soc. 2011, 32, 53. [CrossRef] (c) Shitole, N. V.; Shelke, K. F.; Kakade, G. K.; Shingare, M. S. Orbital: Electron. J. Chem. 2012, 4, 245. [Link] (d) Shitole, N. V.; Shitole, B. V.; Kakade, G. K.; Shingare, M. S. Orbital: Electron. J. Chem. 2013, 5, 35. [Link]