



AN EXPEDITIOUS AND GREEN APPROACH FOR THE SYNTHESIS OF 2-AMINO-4H-CHROMENES USING A CATALYST OF NATURAL ORIGIN

H. D. Bhosale,^[a] S. U. Shisodia,^[a] R. D. Ingle,^{[a]*} P. S. Kendrekar,^{[b]*} A. U. Shisodia,^[a] László Kótai,^[c] and R. P. Pawar^{[a]*}

Keywords: Green synthesis; benzaldehyde; malononitrile; catalyst of natural origin; ultrasound; 2-amino-4H-chromenes.

A highly efficient three-component one step system for the synthesis of 2-amino-4H-chromenes is developed. Excellent yields were obtained simply by mixing malononitrile, aromatic aldehyde and α -naphthol in lemon juice as a catalyst of natural origin and solvent, avoiding using hazardous organic solvents. The main advantages of this method are its green method character, short reaction time and simple workup procedures and the lack of using any metal containing catalysts.

* Corresponding Authors

E-Mail: rppawar@yahoo.com, rajitaingle@yahoo.in, kkpravin@gmail.com

[a] Department of Chemistry, Deogiri College, Station Road, Aurangabad, Maharashtra- 431005, Maharashtra, India

[b] Departmental Health Science, Central University of Technology, Bloemfontein 9300, Free State, South Africa

[c] Research Centre for Natural Sciences, Hungarian Academy of Sciences, P. O. Box 17, HU-1525, Budapest, Hungary

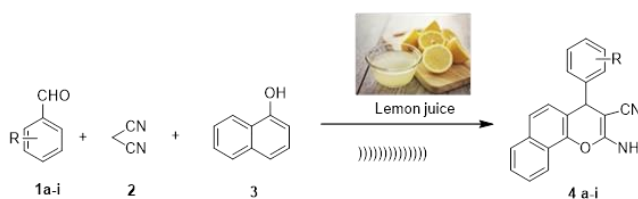
Introduction

Heterocyclic compounds containing chromene moieties are of considerable interest as they are a class of natural and synthetic compounds that possess a great variety of biological as well as pharmaceutical activities.¹⁻⁵ Chromene derivatives having a wide range of valuable pharmacological properties, such as diuretic, spasmolytic, analgesic, anticoagulant, anti-anaphylactic, anti-tumor activities.⁶⁻⁸ Some among them are extremely effective against such kind of diseases which influenced by nitrogen-activated protein kinase enzyme inhibitors. Some of them have antimicrobial activity,¹¹ cytotoxic effect against human cancer cells,¹² antiallergic activity,¹³ central nervous system influencing activity,¹⁴ antiproliferation activity.¹⁵ Several derivatives are also widely used as agrochemicals,¹⁶ antioxidant¹⁷ and anti-inflammatory agent.¹⁸

Literature survey revealed the several reports on one pot three components system for the synthesis of 2-amino-4H-chromenes. This reaction can be catalyzed by both basic as well as by acidic compounds. As acid catalyst can be used heteropoly acids like H₁₄[NaP₅W₃₀O₁₁₀],¹⁹ methanesulfonic acid (MSA),²⁰ p-toluenesulfonic acid (PTSA),²¹ tungstic acid functionalized mesoporous SBA-15 silica,²² Fe₃O₄@sulphochitosan nanoparticles (CS-SO₃H NPs),²³ sulfonic acid-functionalized metal-organic frameworks like MIL-101(Cr),²⁴ etc.

Recently, reactions carried out in green solvent like water have attracted much attention of researchers for environmentally benign. In the continuation of our previous

work on the synthesis of 2-amino-4H-chromenes,²⁵⁻²⁷ here we report three component one pot synthesis of biologically important substituted 2-amino-4H-chromenes using lemon juice as green catalyst and solvent under ultrasound waves irradiation.



Scheme 1. Synthesis of 2-amino-(substituted phenyl)-4H-benzo[h]chromene-3-carbonitriles

Experimental

All starting materials and chemical reagents were purchased from SD fine chemical company and used without further purification; melting points were determined in open capillaries using electrochemical MK3 apparatus. IR spectra were recorded using Perkin-Elmer FT-IR spectrometer by using KBr pellets, ¹H & ¹³C NMR spectra were recorded on Bruker 250 MHz NMR spectrometer in CDCl₃ and chemical shift values were recorded in δ (ppm) by using tetramethylsilane (Me₄Si) as an internal standard.

General procedure for the synthesis of 2-amino-4H-chromenes

In a single neck round bottom flask, p-methoxy benzaldehyde 1 (1 mmol), malononitrile 2 (1.2 mmol), α -naphthol 3 (1 mmol) were taken and in it lemon juice (extract) 10 mL was added and this resulting reaction mixture was irradiated to ultrasound for 20-30 minutes. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, the reaction mixture was poured on crushed ice and the solid obtained was filtered, washed with cold water and recrystallized from

methanol to afford pure product. The obtained product was characterized by using ^1H NMR and ^{13}C NMR spectroscopy. The NMR spectroscopic data of the known compounds (**4a-4i**) are agreed well with the literature data.²⁸⁻³⁰

2-Amino-4-(4-nitrophenyl)-4H-benzo[h]chromene-3-carbonitrile (**4g**)

^1H NMR (250 MHz, CDCl_3) δ (ppm): 8.25 (d, 1H, ArH), 7.79 (t, 1H, Ar-H), 7.51 (m, 3H, Ar-H), 7.43 (d, 2H, Ar-H), 7.15 (d, 2H, ArH), 7.01 (d, 1H, ArH), 6.92 (s, 2H, NH_2), 4.83 (s, 1H, CH).

2-Amino-4-(2-bromophenyl)-4H-benzo[h]chromene-3-carbonitrile (**4i**)

^1H NMR (250 MHz, CDCl_3) δ (ppm): 8.21 (d, 1H, ArH), 7.81 (d, 1H, Ar-H), 7.51 (m, 3H, Ar-H), 7.49 (m, 2H, Ar-H), 7.23 (m, 3H, ArH), 6.96 (s, 2H, NH_2), 4.87 (s, 1H, CH).

Results and discussion

In this communication, we have reported the use of lemon juice as a catalyst and solvent for the synthesis of 2-amino-(substituted phenyl)-4H-benzo[h]chromene-3-carbonitrile

derivatives (Scheme 1). We have performed the three-component condensation reaction using lemon juice under sonification conditions (45 °C). We got better result regarding purity and product yield of synthesized compounds.

We have carried out the standard model reaction of p-methoxybenzaldehyde, malononitrile and α -naphthol in presence of lemon juice. In order to optimize reaction conditions we have carried out reaction at room temperature, 80 °C and under ultrasonication conditions at (45 °C) and found that reaction carried out under sonification condition have given good yield in short reaction time (Table 1).

Table 1. Model reaction of p-methoxybenzaldehyde, malononitrile and α -naphthol in presence of lemon juice

Reaction condition	T, °C	Time, h	Yield, %
Without catalyst	50 °C	7	00
Room temperature	30 °C	10	70
Heating	80 °C	6	78
Sonification	45 °C	1/3	84

The scope of catalyst on different substituted benzaldehydes has been examined such as electron donating or withdrawing groups, all the results obtained are presented in (Table 2).

Table 2. Synthesis of 2-amino-(substituted phenyl)-4H-benzo[h]chromene-3-carbonitrile (**4a-i**)

Arylaldehyde	Product	Time, min	Yield, %	Melting point, °C	
				Observed	Reported
Benzaldehyde	4a	30	76	274-275	205-207 ²⁸
<i>o</i> -Chlorobenzaldehyde	4b	28	77	231-232	253-254 ²⁸
<i>p</i> -Chlorobenzaldehyde	4c	27	78	210-212	229-200 ²⁸
<i>m</i> -Methoxybenzaldehyde	4d	29	74	247-248	248-250 ²⁹
<i>p</i> -Methoxybenzaldehyde	4e	20	76	187-189	193-194 ²⁸
<i>m</i> -Nitrobenzaldehyde	4f	25	82	233-237	212-214 ³⁰
<i>p</i> -Nitrobenzaldehyde	4g	28	84	240-241	238-239 ²⁸
<i>p</i> -Hydroxybenzaldehyde	4h	29	76	242-243	244-245 ²⁸
<i>p</i> -Bromobenzaldehyde	4i	27	72	238-239	240-241 ²⁸

Reaction works well for all substituted benzaldehydes which means reaction is compatible with this catalytic system. However, ortho substituted derivatives have shown less yield as compare to the meta and para substituted due to electronic effect.

Conclusion

In conclusion, we have successfully synthesized, 2-amino-4H-chromens by using ultrasound waves from malononitrile, benzaldehyde and α -naphthol by using lemon juice as a biocatalyst as well as it acts as solvent, it show high catalytic activity and clean reaction procedure, easy workup, with high yields of products and purity.

Acknowledgment

The authors are thankful to the Dr. S. N. Thore, Principal Deogiri College for continuous encouragement and providing laboratory facilities.

References

- Curini, M., Cravotto, G., Epofano, F., Chemistry and Biological Activity of Natural and Synthetic Prenyloxycoumarins, *Curr. Med. Chem.*, **2006**, *13*, 199-222. DOI: [10.2174/092986706775197890](https://doi.org/10.2174/092986706775197890).
- Litvinov, Y. M., Shestopalov, A. M., Synthesis, Structure, Chemical Reactivity, and Practical Significance of 2-Amino-4H-pyrans, *Adv. Heterocycl. Chem.*, **2011**, *103*, 175-260. DOI: [10.1016/B978-0-12-386011-8.00003-4](https://doi.org/10.1016/B978-0-12-386011-8.00003-4).

- ³Desimone, R. W., Currie, K. S., Mitchell, S. A., Darrow, J. W., Pippin, D. A., Privileged Structures: Applications in Drug Discovery, *Comb. Chem. High Throughput Screen.*, **2004**, *7*, 473–794. DOI: [10.2174/1386207043328544](https://doi.org/10.2174/1386207043328544)
- ⁴Patchett A. A., Nargund R. P., Privileged structures – an update, *Ann. Rep. Med. Chem.*, **2000**, *35*, 289–298. [https://doi.org/10.1016/S0065-7743\(00\)35027-8](https://doi.org/10.1016/S0065-7743(00)35027-8)
- ⁵Kemnitzer W., Kasibhatla S., Jiang S., Zhang, H., Zhao, J., Jia, S., Xu, L., Crogan-Grundy, C., Denis, R., Barriault, N., Vaillancourt, L., Charron, S., Dodd, J., Attardo, G., Labrecque, D., Lamothe, S., Gourdeau, H., Tseng, B., Drewe, J., Cai, S. X., Discovery of 4-aryl-4H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. 2. Structure-activity relationships of the 7- and 5-, 6-, 8-positions, *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 4745–4751. DOI: [10.1016/j.bmcl.2005.07.066](https://doi.org/10.1016/j.bmcl.2005.07.066).
- ⁶Hafez, E. A., Elnagdi, M. H., Elagamey, A. G. A., El Taweel, F. M. A. A., Nitriles in Heterocyclic Synthesis: Novel Synthesis of Benzo[c]coumarin and of Benzo[c]pyrano[3,2-c]quinoline Derivatives, *Heterocycles*, **1987**, *26*, 903–907. DOI: [10.3987/R-1987-04-0903](https://doi.org/10.3987/R-1987-04-0903).
- ⁷Sofan, M. A., El-Taweel, F. M. A. A., Elnagdi, M. H., Studies on Cinnamitriles: The Reaction of Cinnamitriles with Cyclopentanone, *Liebigs Ann. Chem.* **1989**, 935–936. DOI: [10.1002/jlac.198919890246](https://doi.org/10.1002/jlac.198919890246)
- ⁸Bonsignore L., Loy G., Secci D., Calignano A., Synthesis and pharmacological activity of 2-oxo-(2H) 1-benzopyran-3-carboxamide derivatives, *Eur. J. Med. Chem.* **1993**, *28*, 517–520. DOI: [10.1016/0223-5234\(93\)90020-F](https://doi.org/10.1016/0223-5234(93)90020-F)
- ⁹Kidwai, M., Saxena, S., Khan, M. K. R. and Thukral, S. S., Aqua mediated synthesis of substituted 2-amino-4H-chromenes and in vitro study as antibacterial agents, *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 4295. DOI: [10.1016/j.bmcl.2005.06.041](https://doi.org/10.1016/j.bmcl.2005.06.041)
- ¹⁰Anderson, D. R., Hegde, S., Reinhard, E., Gomez, L., Vernier, W. F., Lee L., Liu, S., Sambandam, A., Snider, P. A., Masih, L., Aminocyanopyridine inhibitors of mitogen activated protein kinase-activated protein kinase 2 (MK-2), *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1587. DOI: [10.1016/j.bmcl.2005.01.067](https://doi.org/10.1016/j.bmcl.2005.01.067).
- ¹¹Naimi-Jamal, M. R., Mashkouri, S., Sharifi, A., An efficient, multicomponent approach for solvent-free synthesis of 2-amino-4H-chromene scaffold, *Mol. Divers.*, **2010**, *14*, 473–477. DOI: [10.1007/s11030-010-9246-5](https://doi.org/10.1007/s11030-010-9246-5)
- ¹²Kemnitzer, W., Kasibhatla, S., Jiang, S. C., Zhang, H., Zhao, J. H., Jia, S. J., Xu, L. F., Crogan-Grundy, C., Denis, R., Barriault, N., Vaillancourt, L., Charron, S., Dodd, J., Attardo, G., Labrecque, D., Lamothe, S., Gourdeau, H., Tseng, B., Drewe, J. and Cai, S. X., Discovery of 4-aryl-4H-chromenes as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. 2. Structure-activity relationships of the 7- and 5-, 6-, 8-positions, *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 4745–4751. DOI: [10.1016/j.bmcl.2005.07.066](https://doi.org/10.1016/j.bmcl.2005.07.066).
- ¹³Ling, R., Yoshida, M., Mariano, P. S., Exploratory Investigations Probing a Preparatively Versatile, Pyridinium Salt Photoelectrocyclization–Solvolytic Aziridine Ring Opening Sequence, *J. Org. Chem.*, **1996**, *61*, 4439–4449. DOI: [10.1021/jo960316i](https://doi.org/10.1021/jo960316i).
- ¹⁴Anderson, D. R., Hegde, S., Reinhard, E., Gomez, L., Vernier, W. F., Lee, L., Liu, S., Sambandam, A., Snider, P. A., Masih, L., Aminocyanopyridine inhibitors of mitogen activated protein kinase-activated protein kinase 2 (MK-2), *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 1587–1590. DOI: [10.1016/j.bmcl.2005.01.067](https://doi.org/10.1016/j.bmcl.2005.01.067)
- ¹⁵Dell, C. P., Williams, A. C., Pyrano[3,2-h]quinolines for treating restenosis, European Patent Appl EP 1004584, **1993**.
- ¹⁶Hafez, E. A., Elnagdi, M. H., Elagamey, A. G. A., El-Taweel, F. M. A., Nitriles in Heterocyclic Synthesis: Novel Synthesis of Benzo[c]coumarin and of Benzo[c]pyrano[3,2-c]quinoline Derivatives, *Heterocycles*, **1987**, *26*, 903–907. DOI: [10.3987/R-1987-04-0903](https://doi.org/10.3987/R-1987-04-0903)
- ¹⁷Vats, P., Hadjimitova, V., Yoncheva, K., Kathuria, A., Sharma, A., Chand, K., Duraisamy, A. J., Sharma, A. K., Sharma, A. K., Saso, L., Sharma, S. K., Chromenone and quinolinone derivatives as potent antioxidant agents, *Med. Chem. Res.*, **2014**, *23*, 4907. DOI: [10.1007/s00044-014-1054-5](https://doi.org/10.1007/s00044-014-1054-5)
- ¹⁸Hiramoto, K., Nasuhara, A., Michiloshi, K., Kato, T., Kikugawa, K., DNA strand-breaking activity and mutagenicity of 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP), a Maillard reaction product of glucose and glycine, *Mutat. Res.*, **1997**, *395*, 47–56. DOI: [10.1016/S1383-5718\(97\)00141-1](https://doi.org/10.1016/S1383-5718(97)00141-1)
- ¹⁹Heravi, M. M., Bakhtiari, K., Zadsirjan, V., Bamoharram, F. F., Heravic, O. M., Aqua mediated synthesis of substituted 2-amino-4H-chromenes catalyzed by green and reusable Preyssler heteropolyacid, *Biol. Med. Chem. Lett.*, **2007**, *17*, 4262–4265. DOI: [10.1016/j.bmcl.2007.05.023](https://doi.org/10.1016/j.bmcl.2007.05.023)
- ²⁰Heravi, M. M., Baghernejad, B., Oskooie, H. A., A Novel and Efficient Catalyst to One - Pot Synthesis of 2-Amino-4H-chromenes by Methanesulfonic Acid, *J. Chin. Chem. Soc.* **2008**, *55*, 659–662. DOI: [10.1002/jccs.200800098](https://doi.org/10.1002/jccs.200800098)
- ²¹Baghernejad, B., Heravi, M. M., Oskooie, H. A., A Novel and Efficient Catalyst to One-Pot Synthesis of 2-Amino-4H-chromenes by p-Toluenesulfonic Acid, *Korean J. Chem. Soc.*, **2009**, *53*, 631–634.
- ²²Kundu, S. K., Mondal, J., Bhaumik, A., *Dalton Trans.*, **2013**, *42*, 10515–10524. DOI: [10.1039/C3DT50947H](https://doi.org/10.1039/C3DT50947H)
- ²³Mohammadi, R., Kassae, M. Z., Sulfochitosan encapsulated nano-Fe₃O₄ as an efficient and reusable magnetic catalyst for green synthesis of 2-amino-4H-chromen-4-yl phosphonates, *J. Mol. Catal. A. Chem.*, **2013**, *380*, 152–158. DOI: [10.1016/j.molcata.2013.09.027](https://doi.org/10.1016/j.molcata.2013.09.027)
- ²⁴Saikia, M., Saikia, L., Sulfonic acid-functionalized MIL-101(Cr) as a highly efficient heterogeneous catalyst for one-pot synthesis of 2-amino-4H-chromenes in aqueous medium, *RSC Adv.*, **2016**, *6*, 15846–15853. DOI: [10.1039/C5RA28135K](https://doi.org/10.1039/C5RA28135K)
- ²⁵Throat, V. V., Dake, S. A., Katariya, M. V., Pawar, R. P., Cesium carbonate as a heterogeneous reusable and efficient catalyst for the synthesis of 2-amino-4H-chromene derivatives, *Der Chemica Sinica*, **2015**, *6(6)*, 37–50.
- ²⁶Khandare, P. M., Ingale, R. D., Taware, A. S., Shisodia, S. U., Pawar, S. S., Kotai, L. and Pawar, R. P., One-pot synthesis and biological evaluation of pyranopyrazoles in aqueous medium, *Eur. Chem. Bull.*, **2017**, *6(9)*, 410–414. DOI: [10.17628/ecb.2017.6.410-414](https://doi.org/10.17628/ecb.2017.6.410-414).
- ²⁷Joshi, V. M., Magar, R. L., Throat, P. B., Tekale, S. U., Patil B. R., Kale, M. P., Pawar, R. P., Novel one-pot synthesis of 4H-chromene derivatives using amino functionalized silica gel catalyst, *Chin. Chem. Lett.*, **2014**, *25(3)*, 455–458. DOI: [10.1016/j.ccl.2013.12.016](https://doi.org/10.1016/j.ccl.2013.12.016).
- ²⁸Shinde, S., Damate, S., Morbale, S., Patil M., Patil, S. S., Aegle marmelos in heterocyclization: greener, highly efficient, one-pot three-component protocol for the synthesis of highly functionalized 4H-benzochromenes and 4H-chromenes, *RSC Adv.*, **2017**, *7*, 7315–7328. DOI: [10.1039/c6ra28779d](https://doi.org/10.1039/c6ra28779d).
- ²⁹Mohammad Nikpassand, Leila Zare Fekri, Parvin Ahmadi., Grinding synthesis of 2-amino-4H-chromenes using 3,3-(butane 1,4-diyl) bis (1,2-dimethyl-1H-imidazole-3-ium)Br⁻ can as a novel reagent, *J. Chilean Chem. Soc.*, **2017**, *62(1)*, 3399–3402. DOI: [10.4067/S0717-97072017000100019](https://doi.org/10.4067/S0717-97072017000100019).
- ³⁰Kumbhar, Arjun, Jadhav, Sanjay, Shejwal, Rajendra, Rashinkar, Gajanan, Salunkhe, Rajshri, Application of novel multi-cationic ionic liquids in microwave assisted 2-amino-4H-chromene synthesis, *RSC Adv.*, **2016**, *6*, 19612–19619. DOI: [10.1039/c6ra01062h](https://doi.org/10.1039/c6ra01062h).

Received: 10.05.2018.

Accepted: 13.06.2018.