EFFICIENT AND GREEN PREPARATION OF 2-AMINO-4H-CHROMENES BY A ROOM-TEMPERATURE, Na₂CO₃-CATALYZED, THREE-COMPONENT REACTION OF MALONONITRILE, BENZALDEHYDES, AND PHLOROGLUCINOL OR RESORCINOL IN AQUEOUS MEDIUM

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GRAPHICAL ABSTRACT

Abstract The preparation of substituted 2-amino-4H-chromenes by a Na₂CO₃-catalyzed reaction of malononitrile, benzaldehydes, and phloroglucinol or resorcinol in aqueous medium and at room temperature is reported. The merits of this procedure include limited use of organic solvents, easy workup technique, and high purity of products. The 2-amino-4H-chromenes were prepared in yields of 54–96%.

Keywords 2-Amino-4H-chromenes; green reaction; malononitrile; phloroglucinol; resorcinol

INTRODUCTION

Multicomponent coupling reactions (MCRs) in aqueous medium and at room temperature are of great interest to synthetic chemists because they provide access to a large number of organic molecules through a highly atom economical and environmentally benign route.¹⁻⁹ It is important to also note that the replacement of hazardous solvents with relatively benign solvents is an important aspect of green chemistry. Water is the most environmentally benign, nonflammable, and naturally

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available solvent and therefore the obvious choice. Water also offers the benefit of inexpensive and simple workup and purification that can be carried out by phase-separation techniques. Organic reactions in aqueous media are therefore an attractive area in green chemistry.

As part of our broad interest in green chemistry[10] and the synthesis of organic compounds with the chromene moiety,[11–13] we report the synthesis of 2-aminochromenes by a Na₂CO₃-catalyzed reaction of benzaldehydes, malononitrile, and phloroglucinol or resorcinol in aqueous media at room temperature. The synthesis of substituted 2-amino-4H-chromenes is of currently interest mainly because of their activity against human inflammatory diseases and cancer.[9,14–18]

RESULTS AND DISCUSSION

In our model reaction, an equimolar mixture of benzaldehyde 1, malononitrile 2, and phloroglucinol 3 was dissolved in MeOH (1 ml). To this solution was then added an aqueous solution of Na₂CO₃ (19 ml, 30 mol%) and the suspension was stirred at room temperature for 10 h to give 2-amino-4H-chromene 4 in 65% (Scheme 1). It is important to note that Na₂CO₃ is produced in large quantities in Suatown, Botswana, has extensive domestic use, and is relatively safe.

The mechanism of the reaction involves a Knoevenagel reaction of benzaldehyde 1 and malononitrile 2 to give 5. Subsequent Michael addition of 3 to intermediate 5 gives 6. Cyclization of intermediate 6 proceeds to give imine 7 followed by imine-enamine tautomerism to afford the desired product 4 (Scheme 1).[3,5,19,20]

To determine the optimal amount of Na₂CO₃, the model reaction was carried out using various amounts. Thus, when the reaction was carried out with less than 30 ml% of Na₂CO₃, a complex mixture was obtained. In the absence of the catalyst, only the starting materials were detected by thin-layer chromatography (TLC). Increasing the Na₂CO₃ amount beyond the 30 mol% threshold had no significant effect on the product yield. It was therefore concluded that the optimum amount of the catalyst was 30 mol%. The pure product was recovered by simply allowing the reaction mixture to stand at room temperature for about 30 min, filtering off the resulting solid, and washing it with ice-cold methanol.

Scheme 1. Model three-component reaction.
With the optimal amount of catalyst for the reaction in hand, various substituted benzaldehydes were used in the three-component procedure and were found to be well tolerated. Thus, 4-methoxybenzaldehyde 8 and 4-hydroxybenzaldehyde 9 reacted with malononitrile 2 and phloroglucinol 3 to give 2-amino-4H-chromenes 17 and 18 respectively in yields greater than 75%. In addition, disubstituted aldehydes 10 and 11 reacted with malononitrile 2 and phloroglucinol 3 under the described reaction conditions to give the corresponding 2-amino-4H-chromenes 19 and 20 in 72 and 70% yields respectively. Methyl substituted aldehydes 12, 13, and 14 also participated in the three-component reaction to afford 2-amino-4H-chromenes 19, 20, and 21 in yields of 79% and better (Scheme 2). The results discussed thus far involved the use of benzaldehydes with electron-donating substituents. To further test the breadth of the tolerance of this three-component reaction, benzaldehydes 15 and 16 with electron-withdrawing nitro and chloro groups respectively were subjected to the three-component reaction conditions to afford the corresponding 2-amino-4H-chromenes 24 and 25 in good yields (Scheme 2).

The scope and generality of the present method were further expanded to resorcinol 26 instead of phloroglucinol 3. It is instructive to note that there is literature precedent of the reaction of resorcinol with malononitrile and benzaldehydes in the presence of access K2CO3 and under microwave irradiation. In the context of our procedure, it was established that resorcinol 26 participated in the MCR with malononitrile 2 and benzaldehyde 1 to give 2-amino-4H-chromene 27 in 72% yield. Substituted benzaldehydes 8, 9, and 11–16 also participated in the three-component reaction to give the corresponding chromenes in 54–89% yields (Scheme 3). It is worthwhile to mention that benzaldehydes with both electron-donating and electron-withdrawing groups reacted smoothly with malononitrile 2 and resorcinol 26 to give the corresponding products in moderate to excellent yields. While the relatively poor yield for 31 can be attributed to steric hindrance in the Knoevenagel reaction due to the nearness of the methyl group to the carbonyl group, it is not obvious to what the lower yield of 28 should be attributed, so no rational is offered here.

Scheme 2. MCRs of substituted benzaldehydes, malononitrile, and phloroglucinol.
Laboratory-grade chemicals and solvents were procured from Sigma-Aldrich and used without any further purification. Reactions were monitored by thin-layer chromatography (TLC) using Merck's TLC silica gel 60 F254 aluminium sheets. Melting-point measurements were determined on a Stuart melting-point apparatus and are uncorrected. Infrared spectra were recorded neat on a Perkins Elmer FT-IR spectrophotometer 1000. High-resolution mass spectra (HRMS) were recorded on a GCT Premier mass spectrometer (Waters) with an ionization energy of 70 eV. NMR spectra were recorded on a Bruker Avance DPX 300-MHz NMR spectrometer with tetramethylsilane (TMS) as an internal standard.

**Typical Procedure for the Synthesis of 2-Amino-3-cyano-5,7-dihydroxy-4-phenyl-4H-chromene (4)**

A mixture of benzaldehyde (0.30 g, 2.8 mmol), malononitrile (0.19 g, 2.8 mmol), and phloroglucinol (0.36 g, 2.8 mmol) was dissolved in methanol (1.0 cm³) in a round-bottomed flask. A solution of Na₂CO₃ (0.09 g, 0.8 mmol) in water (19.0 cm³) was then added to the round-bottomed flask, and the resulting suspension was stirred at room temperature for 10 h. The solid formed was filtered off, washed with water followed by cold methanol, and dried in an oven at 100 °C to give 2-amino-3-cyano-5,7-dihydroxy-4-phenyl-4H-chromene as a white powder in 65% yield. Mp 162–164 °C; IR (neat) ν: 3311, 3203, 2188, 1654, 1618, 1468 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 4.48 (1H, s, H-4), 5.98 (1H, d, J = 1.5 Hz, H-6), 6.06 (1H, d, J = 1.5 Hz, H-8), 6.78 (2H, s, 2OH), 7.20 (5H, m, ArH), 9.57 (2H, br, NH₂); ¹³C NMR (75 MHz, DMSO-d₆) δ 36.8 (C-4), 58.0 (C-3), 94.2 (C-8), 99.3 (C-6), 102.8 (C-4a), 121.3 (CN), 126.6 (C-4'), 127.5 (C-2' and 6'), 128.6 (C-3' and 5'), 146.8 (C-1'), 150.9 (C-8a), 155.8 (C-7), 157.9 (C-5), 160.9 (C-2). HRMS-EI (m/z) calcd. for C₁₆H₁₂N₂O₅: 280.2848; found, 280.2853.

The following 2-amino-4H-chromenes that were prepared are known compounds and were characterized on the basis of data that matched literature data: 27, 28, 29, 30, 31, 32, 33, 34, and 35.

**Scheme 3**. MCRs of substituted benzaldehydes, malononitrile, and resorcinol.

![Scheme 3](image-url)
CONCLUSION

In conclusion we have described an efficient green synthesis of 2-amino-4H-chromenes by the three-component Na$_2$CO$_3$-catalyzed reaction of benzaldehydes, malononitrile, and phloroglucinol or resorcinol at room temperature. The most striking features of this route to 2-amino-4H-chromenes are use of water as a solvent, reliance on use of relatively safe Na$_2$CO$_3$ as a catalyst, and the easy workup method.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

REFERENCES

1. Azizian, J.; Delbari, A. S.; Yadollahzadeh, K. Synth. Commun. 2014, 44, 3277–3286.
2. Fatma, S.; Singh, D.; Ankit, P.; Mishra, P.; Singh, M. Singh, J. Tetrahedron Lett. 2014, 55, 2201–2207.
3. Behbahani, F. K.; Maryam, S. J. Korean Chem. Soc. 2013, 57, 357–360.
4. Ghorbani-Vaghei, R.; Toghraei-Semiromi, Z.; Karimi-Nami, R. J. Braz. Chem. Soc. 2011, 22, 905–909.
5. Kiyani, H.; Ghorbani, F. J. Saudi Chem. Soc. 2014, 18, 689–701.
6. Ranjbar-Karimi, R.; Hashemi-Uderji, S.; Mousavi, M. J. Iran. Chem. Soc. 2011, 8, 193–197.
7. Safari, J.; Zarnegar, Z.; Heydarian, M. J. Taibah Univ. Sci. 2013, 7, 17–25.
8. Solhy, A.; Elmakssoudi, A.; Tahir, R.; Karkouri, M.; Larzek, M.; Bousminaa, M.; Zahouily, M. Green Chem. 2010, 12, 2261–2267.
9. Zonouzi, A.; Mirzazadeh, R.; Safavi, M.; Ardestani, S. K.; Emami, S.; Foroumadi, A. Iranian J. Pharm. Res. 2013, 12, 679–685.
10. Masesane, I. B.; Murithi, E.; Tabane, T. H. Bull. Chem. Soc. Ethiop. 2014, 28, 301–304.
11. Masesane, I. B.; Mazimba, O. Bull. Chem. Soc. Ethiop. 2014, 28, 289–294.
12. Masesane, I. B.; Desta, Z. Y. Beilstein J. Org. Chem. 2012, 8, 2166–2175.
13. Mazimba, O.; Masesane, I. B. Majinda, R. R. T. Tetrahedron Lett. 2011, 52, 6716–6718.
14. Thomas, N.; Zachariah, S. M. Asian J. Pharm. Clin. Res. 2013, 6, 11–15.
15. Adibi, H.; Khodarahmi, R.; Mansouri, K.; Khaleghi, M.; Magsoudi, S. Pharmaceut. Sci. 2013, 19, 23–30.
16. Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Zhao, J.; Crogan-Grundy, C.; Xu, L.; Lamothe, S.; Gourdeau, H.; Denis, R.; Tseng, B.; Kasibhatla, S.; Cai, S. X. J. Med. Chem. 2007, 50, 2858–2864.
17. Osyanin, V. A.; Osipov, D. V.; Klimochkin, Y. N. *Tetrahedron* 2012, 68, 5612–5618.
18. Keerthy, H. K.; Garg, M.; Mohan, C. D.; Madan, V.; Kanojia, D.; Shobith, R.; Nanjundaswamy, S.; Mason, D. J.; Bender, A.; Basappa; Rangappa, K. S.; Koeffler, H. P. *PLoS One* 2014, 9, 107–118.
19. Zhou, Z.; Yang, F.; Wu, L.; Zhang, A. *Chem. Sci. Trans.* 2012, 1, 57–60.
20. Karami, B.; Khodabakhshi, S.; Eskandari, K. *Tetrahedron Lett.* 2012, 53, 1445–1446.
21. Kidwai, M.; Saxena, S.; Khan, M. K. R.; Thukral, S. S. *Bioorg. Med. Chem. Lett.* 2005, 15, 4295–4298.
22. Albadi, J.; Razeghi, A.; Mansournezhad, A.; Azarian, Z. *J. Nanostr. Chem.* 2013, 3, 85.
23. El-Maghraby, A. M. *Org. Chem. Int.* 2013, Article ID 715091.