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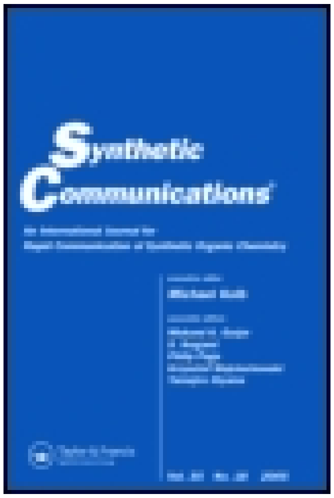

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Efficient and Green Preparation of 2-Amino-4H-chromenes by a Room Temperature, Na_2CO_3-Catalysed, Three-Component Reaction of Malononitrile, Benzaldehydes, and Phloroglucinol or Resorcinol in Aqueous Medium

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Efficient and green preparation of 2-amino-4H-chromenes by a room temperature, Na_2CO_3-catalysed, three-component reaction of malononitrile, benzaldehydes, and phloroglucinol or resorcinol in aqueous medium

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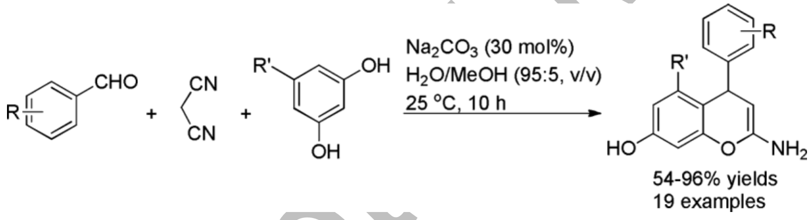
Abstract

The preparation of substituted 2-amino-4H-chromenes by a Na_2CO_3-catalysed 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, phloroglucinol, resorcinol, malononitrile

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 high atom economy 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 environmental benign, nonflammable and naturally available solvent and therefore the obvious choice. Water also offers the benefit of cheaper 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 Na_2CO_3-catalysed 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 due to their activity against human inflammatory diseases and cancer.[9, 14-18]

RESULTS AND DISCUSSION

In our model reaction, an equimolar mixture of benzaldehyde **1**, malonitrile **2** and phloroglucinol **3** was dissolved in MeOH (1 ml). To this solution was then added an aqueous solution of Na_2CO_3 (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 Na_2CO_3 is produced in large quantities in Sua town, Botswana and has extensive domestic use therefore 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**. Cyclisation of intermediate **6** proceed 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 Na_2CO_3, the model reaction was carried out using various amounts. Thus, when the reaction was carried out with less than 30 ml% of Na_2CO_3, a complex mixture was obtained. In the absence of the catalyst, only the starting materials were detected by TLC. Increasing the Na_2CO_3 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 simple allowing the reaction mixture to stand at room temperature for about 30 minutes, filtering off the resulting solid and washing it with ice cold methanol.

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 above 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 **21**, **22** and **23** 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 broadness 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 high 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 malononotrile and benzylaldehydes in the presence of access K_2CO_3 and under microwave irradiation.[21] 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**, **11**, **12**, **13**, **14**, **15** and **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 low 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 in this paper.

EXPERIMENTAL

Laboratory grade chemicals and solvents were procured from Sigma-Aldrich and used without any further purification. Reactions were monitored by 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 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 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 cm^3) in a round bottom flask. A solution of Na_2CO_3 (0.09 g, 0.8 mmol) in water (19.0 cm^3) was then added to the round bottom flask and the resulting suspension was stirred at room temperature for 10 hours. The solid formed was filtered off, washed with water followed by cold methanol and dried in an oven at 100 ^{o}C to give 2-amino-3-cyano-5,7-dihydroxy-4-phenyl-4H-chromene as a white powder in 65% yield. mp 162-164 ^{o}C; IR (neat) ν: 3331,3203, 2188, 1654, 1618, 1468 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 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, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) 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 $C_{16}H_{12}N_2O_3$: 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,[7,22,23] 29,[22] 33,[7,22] 34, and 35,[22,22].

CONCLUSION

In conclusion we have described an efficient green synthesis of 2-amino-4H-chromenes by the three-component Na_2CO_3-catalysed 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_2CO_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.

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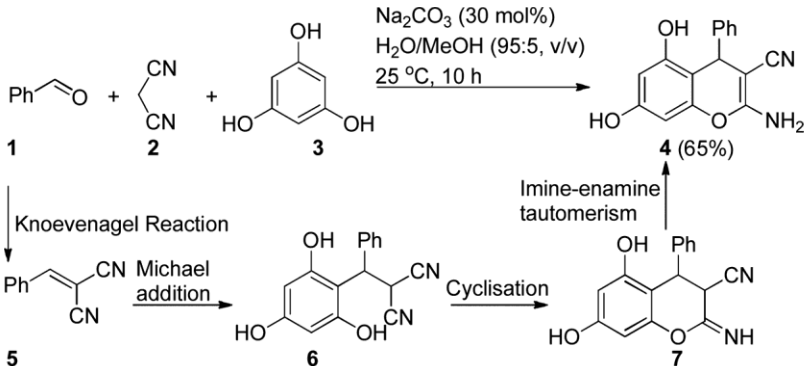
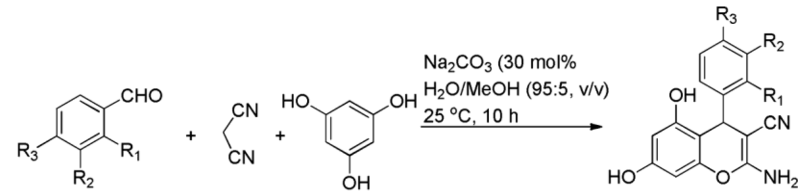
Scheme 1: The model three-component reaction

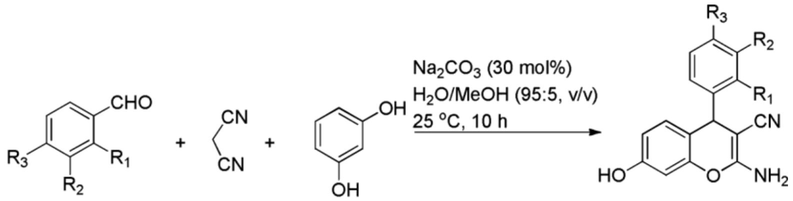


Scheme 2: MCRs of substituted benzaldehydes, malononitrile and phloroglucinol



8 ($R_1 = R_2 = H, R_3 = OMe$)	**2**	**3**	**17** (75%)
9 ($R_1 = R_2 = H, R_3 = OH$)			**18** (79%)
10 ($R_1 = H, R_2\text{-}R_3 = OCH_2O$)			**19** (72%)
11 ($R_1 = H, R_2 = OMe, R_3 = OH$)			**20** (70%)
12 ($R_1 = Me, R_2 = R_3 = H$)			**21** (78%)
13 ($R_1 = R_3 = H, R_2 = Me$)			**22** (83%)
14 ($R_1 = R_2 = H, R_3 = Me$)			**23** (79%)
15 ($R_1 = R_2 = H, R_3 = NO_2$)			**24** (96%)
16 ($R_1 = R_2 = H, R_3 = Cl$)			**25** (73%)

Scheme 3: MCRs of substituted benzaldehydes, malononitrile and resorcinol



1 ($R_1 = R_2 = R_3 = H$)	**2**	**26**	**27** (72%)
8 ($R_1 = R_2 = H$, $R_3 = OMe$)			**28** (56%)
9 ($R_1 = R_2 = H$, $R_3 = OH$)			**29** (77%)
11 ($R_1 = H$, $R_2 = OMe$, $R_3 = OH$)			**30** (70%)
12 ($R_1 = Me$, $R_2 = R_3 = H$)			**31** (54%)
13 ($R_1 = R_3 = H$, $R_2 = Me$)			**32** (87%)
14 ($R_1 = R_2 = H$, $R_3 = Me$)			**33** (74%)
15 ($R_1 = R_2 = H$, $R_3 = NO_2$)			**34** (89%)
16 ($R_1 = R_2 = H$, $R_3 = Cl$)			**35** (80%)