



MULTICOMPONENT ONE-POT SYNTHESIS OF 2-AMINO-3-CYANO-7-HYDROXY-4- SUBSTITUTED-4H-CHROMENE DERIVATIVES USING CAFFEINE AS A BIODEGRADABLE HOMOGENEOUS CATALYST

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ABSTRACT:

Caffeine was found to be a highly active and green catalyst for the synthesis of various 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*-chromene derivatives by the condensation of aromatic aldehydes, malononitrile and resorcinol under EtOH-H₂O (1:1) at reflux conditions. The reactions are characterized by high efficiency, short reaction time, high product yield, simple experimental procedure, availability of catalyst, and environmentally-friendly reaction conditions.

KEYWORDS: Caffeine; malanonitrile; pyrans; multicomponent reaction; one-pot synthesis

1. INTRODUCTION

Multi-component reactions (MCRs) have proven to be a valuable asset in organic and medicinal chemistry; such protocols can be used for drug design, and drug discovery because of their simplicity, efficiency, and high selectivity. MCRs are convergent reactions, in which three or more starting materials react to produce a highly complex product in one pot. Typically, purification of products resulting from MCRs is also a simple procedure, because all the organic reagents employed are consumed and incorporated into the target compound [1-4]. The development of methodologies that involve the use of inexpensive and reusable catalysts under mild and environmentally friendly reaction conditions is one of the major goals in green and

sustainable chemistry. Methodologies leading to various heterocyclic structures are in high demand for both academic and industrial applications

Pyran and its derivatives are an important class of heterocyclic compounds, which constitute the key core of various natural products as well as photochromic materials [5]. They exhibit a wide range of biological activities such as anticancer [6], Antimicrobial [7], antioxidant [8], and antiproliferative properties [9]. 4H-Pyran derivatives are also potential calcium channel antagonists, which are structurally similar to biologically active 1,4-dihydropyridines [10]. In addition, amino-4H-pyrans are often used in cosmetics and pigments, or are utilized as potentially biodegradable agrochemicals. The 4H-pyran derivatives bearing a nitrile functionality are also useful intermediates for the synthesis of various compounds such as pyridones, 1,4-dihydropyridines, lactones, pyranopyrazoles, imidoesters, and aminopyrimidines [11]. Because of the important aforementioned properties of pyran derivatives, preparation of this heterocyclic nucleus has gained great importance in organic synthesis [12]. Therefore, the synthesis of such compounds has attracted strong interest. Due to the widespread use of these compounds, a great deal of passion for the synthesis of other derivatives with more appropriate methods, such as multi-component reactions and their biological effects has emerged. The MCR method provides synthesis of them using processes with fewer process steps.

Considering the broad spectrum of biological activities of 4H-pyrans, synthetic chemists have developed numerous protocols for their syntheses. Among the different methods used for the preparation of compounds with pyran cores, multicomponent reactions of active enolates, active methylenes, and aldehydes is one of the simple and practical synthetic methods of these compounds. This reaction requires the use of acid and base catalysts and published sources have reported the use of catalysts such as thiourea dioxide [13], MgO Nanopowders [14], MgO nanoplates [15], ZnO nanoparticles [16], CuO nano-structures [17], ammonium acetate [18], snail shell [19], sodium malonate [20], and Zn(L-proline)₂ [21].

In recent years, interest in green chemistry [22-24] has developed, and a major challenge to organic chemists is to identify facile, efficient, and nonpolluting synthetic procedures that reduce the use of organic solvents and toxic reagents. In this area, use of natural materials as promising catalysts in organic reactions has received a considerable amount of attention due to their green credentials [25,26].

Use of natural materials as promising catalysts in organic reactions has received a considerable amount of attention due to their green credentials. Caffeine (trimethylxanthine (Fig. 1) is a plant alkaloid, found in numerous plant species, where it acts as a natural pesticide that paralyzes and kills certain insects feeding upon them. It is chemically related to the adenine and guanine bases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The most commonly used caffeine-containing plants are coffee, tea, and to some extent cocoa.

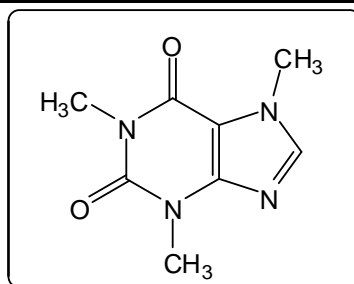
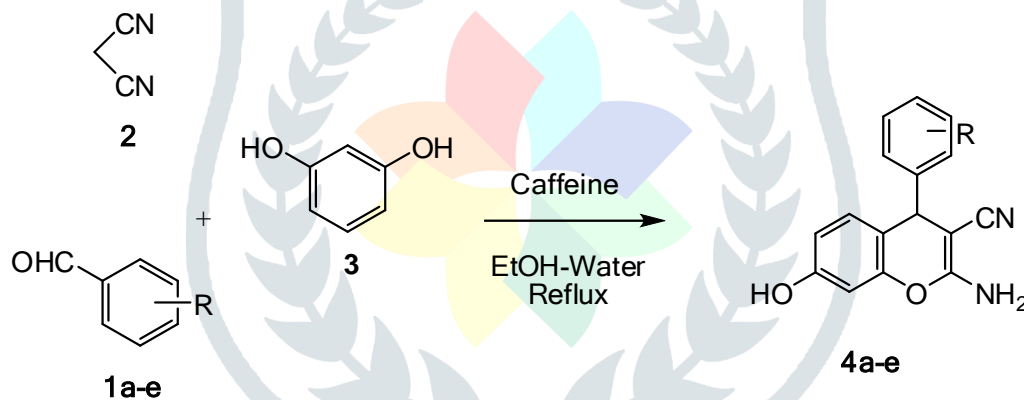


Figure 1 Structure of Caffeine

Caffeine has emerged as natural, green, cheap and efficient catalyst in various organic transformations. Caffeine was applied as a homogeneous catalyst for the one-pot synthesis of poly substituted dihydro-2-oxypyrols [27], benzo[a]pyrano[2,3-c]phenazines [28], benzo[a][1,3]oxazino[6,5-c] phenazines [29] and 1,8-dioxo-octahydro-xanthenes [30].

Considering the broad spectrum of biological activities of 4*H*-pyrans, in this manuscript, we wish to report the applicability of caffeine on the three-component reaction of aryl aldehydes, resorcinol and malononitrile for the synthesis of novel 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*-chromene derivatives in aqueous ethanol media at reflux condition (Scheme 1). This is a one-pot reaction, which is not only operationally simple but also consistently gives the corresponding products in good to excellent yields.



Scheme – 1 Synthesis of 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*-chromene derivatives

2. EXPERIMENTAL

2.1 Apparatus and analysis

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products unless otherwise stated. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained using Bruker DRX- 500 Avance at ambient temperature, using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Shimadzu spectrometer. Mass spectra were determined on a Varion - Saturn 2000 GC/MS instrument. Elemental analysis were measured by means of Perkin Elmer 2400 CHN elemental analyzer flowchart.

2.2 General procedure to synthesis of 2-amino-3-cyano-7-hydroxy-4-substituted-4H-chromene derivatives using Caffeine as catalyst

A mixture of resorcinol (1 mmol), aldehydes (1 mmol), malononitrile (1 mmol) and catalyst Caffeine, in 5 ml of EtOH-H₂O (1:1) were refluxed for appropriated time. After the TLC indicates the disappearance of starting materials, the reaction was cooled to room temperature, CH₂Cl₂ (20 ml) was added and the insoluble material was filtered to separate the catalyst. The filtrate was concentrated under vacuum and the crude residue was purified by recrystallization. 2-amino-3-cyano-7-hydroxy-4-substituted-4H-chromene derivatives was obtained as crystals. The recovered catalyst can be washed consequently with diluted acid solution, water and then acetone. After drying, it can be reused without noticeable loss of reactivity. The products were identified by IR, ¹H NMR, ¹³C NMR, mass, elemental analysis and melting points.

2.3 Spectral data for the synthesized compounds (4a-e)

2-Amino-3-cyano-7-hydroxy-4-phenyl-4H-chromene (4a)

IR (KBr, cm⁻¹): 3442 (OH), 3347 (NH₂), 2208 (CN), 1665 (C=C vinyl nitrile), 1597 (C=C aromatic); ¹H NMR (500 MHz, DMSO-*d*₆): δ 4.89 (s, 1H, CH), 6.27 (s, 2H, NH₂), 6.62 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.79 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H, Ar-H), 6.92 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.22-7.35 (m, 5H, Ar-H), 9.64 (s, 1H, OH) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): δ 30.1, 58.4, 102.9, 111.3, 117.4, 124.1, 126.1, 127.5, 129.5, 130.7, 143.7, 155.5, 159.8, 176.2 ppm. MS (ESI): *m/z* 265 (M+H)⁺. Anal. Calcd. for C₁₆H₁₂N₂O₂: C, 72.72; H, 4.54; N, 10.60 %. Found: C, 72.64; H, 4.50; N, 10.55 %.

2-Amino-3-cyano-7-hydroxy-4-(4-chlorophenyl)-4H-chromene (4b)

IR (KBr, cm⁻¹): 3444 (OH), 3340 (NH₂), 2214 (CN), 1664 (C=C vinyl nitrile), 1584 (C=C aromatic); ¹H NMR (500 MHz, DMSO-*d*₆): δ 4.89 (s, 1H, CH), 6.28 (s, 2H, NH₂), 6.65 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.75 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H, Ar-H), 6.90 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.25 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.44 (d, *J* = 7.4 Hz, 2H, Ar-H), 9.54 (s, 1H, OH) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): δ 29.4, 59.4, 104.4, 110.2, 118.2, 123.2, 125.3, 128.8, 129.4, 131.4, 144.4, 156.4, 158.4, 178.0 ppm. MS (ESI): *m/z* 299.45 (M+H)⁺. Anal. Calcd. for C₁₆H₁₁ClN₂O₂: C, 64.33; H, 3.68; N, 9.38 %. Found: C, 64.25; H, 3.63; N, 9.34 %.

2-Amino-3-cyano-7-hydroxy-4-(4-fluorophenyl)-4H-chromene (4c)

IR (KBr, cm⁻¹): 3437 (OH), 3341 (NH₂), 2200 (CN), 1672 (C=C vinyl nitrile), 1584 (C=C aromatic); ¹H NMR (500 MHz, DMSO-*d*₆): δ 5.11 (s, 1H, CH), 6.25 (s, 2H, NH₂), 6.68 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.78 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H, Ar-H), 6.98 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.28-7.49 (m, 4H, Ar-H), 9.65 (s, 1H, OH) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): δ 30.0, 59.2, 104.3, 110.3, 118.4, 123.6, 125.3, 127.4, 129.7, 130.7, 144.5, 156.5, 158.6, 178.0 ppm. MS (ESI): *m/z* 283 (M+H)⁺. Anal. Calcd. for C₁₆H₁₁FN₂O₂: C, 68.08; H, 3.90; N, 9.93 %. Found: C, 68.05; H, 3.82; N, 9.90 %.

2-Amino-3-cyano-7-hydroxy-4-(4-bromophenyl)-4H-chromene (4d)

IR (KBr, cm^{-1}): 3443 (OH), 3333 (NH_2), 2199 (CN), 1679 (C=C vinyl nitrile), 1600 (C=C aromatic); ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 4.93 (s, 1H, CH), 6.15 (s, 2H, NH_2), 6.70 (d, $J = 4.0$ Hz, 1H, Ar-H), 6.83 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar-H), 6.93 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.30-7.47 (m, 4H, Ar-H), 9.56 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ 30.5, 58.5, 103.5, 111.5, 117.5, 124.3, 126.7, 127.7, 129.5, 131.5, 143.8, 155.8, 159.6, 177.9 ppm. MS (ESI): m/z 343.6 ($\text{M}+\text{H}$)⁺. Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{BrN}_2\text{O}_2$: C, 55.99; H, 3.21; N, 8.16 %. Found: C, 55.94; H, 3.16; N, 8.09 %.

2-Amino-3-cyano-7-hydroxy-4-(4-methylphenyl)-4H-chromene (4e)

IR (KBr, cm^{-1}): 3439 (OH), 3345 (NH_2), 2215 (CN), 1671 (C=C vinyl nitrile), 1583 (C=C aromatic); ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 2.23 (s, 3H, CH_3), 4.89 (s, 1H, CH), 6.19 (s, 2H, NH_2), 6.64 (d, $J = 4.0$ Hz, 1H, Ar-H), 6.74 (dd, $J = 4.0$ Hz, $J = 8.0$ Hz, 1H, Ar-H), 6.84 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.27 (d, $J = 7.4$ Hz, 2H, Ar-H), 7.52 (d, $J = 7.4$ Hz, 2H, Ar-H), 9.66 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ 17.5, 29.3, 58.2, 103.5, 111.4, 117.3, 123.6, 126.7, 127.9, 128.5, 131.5, 143.3, 155.4, 158.6, 178.1 ppm. MS (ESI): m/z 279 ($\text{M}+\text{H}$)⁺. Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2$: C, 73.38; H, 5.03; N, 10.07 %. Found: C, 73.31; H, 4.95; N, 9.97 %.

3. RESULTS AND DISCUSSION

In order to optimize the conditions, we studied the reaction of resorcinol, 4-fluoro benzaldehyde with malonitrile and Caffeine (5 mol%) as a simple model substrate in various conditions. The reaction was performed in various solvents, temperatures, amount of catalyst and also with different catalysts. The results indicates that the use of 5 mol % of Caffeine maintaining the yield at 95%, so this amount is sufficient to promote the reaction in EtOH- H_2O (1:1) under reflux condition.

Table 1 Preparation of various 2-amino-3-cyano-7-hydroxy-4-substituted-4H-chromene derivatives^a

Entry	R1	Product	Time (min)	Yield (%) ^b	Mp (°C)
1	H	4a	75	93	194 – 195
2	4-Cl	4b	65	95	187 – 188
3	4-F	4c	75	90	160 – 162
4	4-Br	4d	75	90	181 – 183
5	4- CH_3	4e	65	92	170 – 172

^aReaction conditions: resorcinol (1 mmol), aldehyde (1 mmol) and malonitrile (1 mmol) in the presence of Caffeine (5 mol %) in EtOH- H_2O (1:1) at reflux.

^bIsolated yield.

Encouraged by this successful three-component reaction, 2-amino-3-cyano-7-hydroxy-4-substituted-4H-chromene derivatives 4a-e was undertaken. The aromatic aldehydes bearing electron-withdrawing and electron donating groups were found to be equally effective to produce 2-amino-4H-pyrans 4a-e in very good yields (Table – 1).

Recyclability of catalysts is an important aspect of a reaction from an economical and environmental point of view, and has attracted much attention in recent years. Thus the recovery and reusability of Caffeine

was investigated. After completion of the reaction, the reaction mixture was cooled to ambient temperature, CH_2Cl_2 was added, and the Caffeine was filtered off. The recycled catalyst has been examined in the next run. The Caffeine catalyst could be reused four times without any loss of its activity and yields ranged from 95 to 90 %.

4. CONCLUSION

In conclusion, a simple, efficient and green protocol was demonstrated for the synthesis of 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*-chromene derivatives *via* one-pot multicomponent reactions in EtOH-H₂O (1:1) at reflux condition. General applicability, operational simplicity, mild reaction conditions, non-toxic and inexpensive catalyst were the advantages of the present procedure.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

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