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Microwave Assisted, Cesium Carbonate Catalyzed Mild and Efficient Synthesis of Pyranochromenes

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ABSTRACT

A mild and efficient domino protocol successfully developed for the synthesis of 3,4-dihydropyrano[c]chromenes from 4-hydroxy coumarin, malononitrile and aldehydes by using highly efficient cesium carbonate in ethanol under microwave irradiation. Several advantages associated with this protocol such as high yields, easy accessibility, wide substrate scope and short reaction time. This methodology might prove as a better alternative to the existing literature methods.

Keywords: Pyranochromenes, Cesium carbonate, Microwave, Multicomponent reaction, Green chemistry

INTRODUCTION

Heterocycles, an important class of organic compounds, constitute more than 70% of promising bioactive and drug molecules presently available in literature. Among these widespread heterocyclic compounds, oxygen heterocycles occupy a distinct position because of their extensive natural abundance and broad biological as well as pharmaceutical importance. Fused heterocyclic compounds have attracted the attention of chemists due to their unique important characteristics and wide applications in drug discovery and material sciences [1].

The legend of coumarin was started in 1820 when Vogel extracted it from Tonka beans. Coumarin is a natural product that occurring in plants and it chemically consists of a benzene ring fused to a lactone ring [2]. Coumarins showed important biological activities such as anti-cancer [3], anti-viral [4], anti-inflammatory, anti-oxidant [5] and anti-microbial [6]. Recently coumarins have been indicated to increase central nervous system activity [7]. Coumarins were utilized as flavoring agents in, toothpastes, foods, detergents, tobaccos, alcoholic and beverages [8]. In industry, coumarin derivatives were commonly used as laser dyes due to their emission properties [9].

The chromene skeleton belongs to the privileged structural motifs in the field of natural products as well as in the area of pharmaceutically active compounds which exhibit. It is widely present in natural alkaloids, flavonoids, tocopherols, and anthocyanins [10]. Moreover, in recent years, functionalized chromenes have played an ever-increasing role in the synthetic approaches to promising compounds in the field of medicinal chemistry [11]. Among the different types of chromene systems, 2-amino-4H-chromenes broad spectrum of significant biological activities such as anticancer, anti HIV, antibacterial and many more [12].

The first multicomponent reaction was reported by Strecker in 1853 for the synthesis of α -amino acids [13]. Since then, for more than a century or so, the field of multicomponent synthesis appeared dormant, but more recently the last two decades have enormous developments in this field [14]. These developments were mainly aimed either at the design of new multicomponent reactions or towards making advancements in existing methodologies for known multicomponent reactions [15]. Multicomponent reactions are advantageous over multistep reaction like high atom economy, short reaction times, high yields, low costs and minimization of waste, labor, energy and avoidance of complex or tedious processes. These reactions are valuable assets in the organic synthesis and pharmaceutical chemistry due to their wide range of usage in the preparation of various structural scaffolds and discovery of new drugs [16].

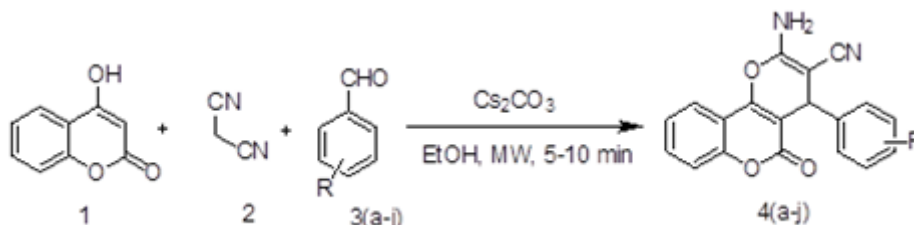
Pyranocoumarins and their related heterocyclic compounds usually occur in natural products as well as in synthetic molecules, exhibiting a broad spectrum of biological activities such as antibacterial, anticancer, anti-inflammatory, antifungal, antioxidant, anti-allergic, acetyl cholinesterase inhibitors, xanthine oxidase inhibitors Src kinase inhibitors etc. [17].

The concept of "green chemistry" occurred in the early 1990s [18] and now broadly accepted to cover the fundamental scientific challenges to protect the environment and human health while simultaneously achieving commercial feasibility. Non-conventional methods following the principles of green chemistry [19] reduce or even eliminate the generation of hazardous substances [20] as well as minimize the use of conventional volatile organic solvents. There have been remarkable successes in the synthesis of various heterocyclic compounds and in the development of new protocol under clean, environmentally benign methodologies that are sustainable for a long time.

Microwave radiation is converted into heat with high efficiency, so that "superheating" becomes possible at ambient pressure. Enormous accelerations in reaction time can be achieved, if superheating is performed in closed vessels under high pressure. Microwave-assisted organic synthesis is an efficient approach in order to improve reaction efficiencies, in terms of the product quality, reaction rate and time in addition it offers several unique advantages such as cleaner reactions, drastic acceleration of complex transformations, enhanced yields etc. [21]

MATERIALS AND METHODS

All chemical and reagents are purchased from SD Fine chemical company with high purity and used without further purification. Melting points are determined in open capillaries using an Electrothermal Mk3 apparatus. Infrared (IR) spectra in KBr were recorded using a Perkin-Elmer spectrum 65 FT-IR spectrometer. ¹H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in DMSO or CDCl₃ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me₄Si) as an internal standard. The microwave irradiation was carried out in a scientific microwave oven (CATA-4R-Model No. QW-99, India makes), 2450 MHz Frequency, with power output of 140-700 W. The progress of reaction was monitored by TLC (Thin Layer Chromatography) (Scheme 1).



Scheme 1: General procedure for synthesis of 3,4-dihydropyranocoumarins using cesium carbonate under mw irradiations

A mixture of malononitrile (1 mmol), aromatic aldehyde (1 mmol), 4-hydroxy coumarin (1 mmol), ethanol (2 ml) and cesium carbonate (10 mole %), was added in a capped 10 mL microwave vessel and kept in irradiation cavity. The mixture was irradiated with microwaves at the power of 140 W. The total period of microwave irradiation was 5-10 min. The progress of reaction was monitored by TLC (ethyl acetate: hexane 4:1). After completion of reaction, the reaction mixture was cooled to room temperature and poured on 10 ml ice cold water. The separated solid was filtered and washed with water. The residue was dried and recrystallized from ethanol to get the corresponding 3,4-dihydropyranocoumarins. The products were confirmed by comparison with authentic samples, IR, ¹H NMR, mass spectra and melting points.

RESULTS AND DISCUSSION

Initially, reaction between 4-nitrobenzaldehyde, malononitrile and 4-hydroxy coumarin was investigated in different polar solvent under microwave by using cesium carbonate catalyst and the results are listed in Table 1. It was observed that in all used solvents, reaction afforded the desired product. However ethanol gave the best in terms of yield of the desired product within short reaction time.

Table 1: Optimization of solvents

| S. No. | Solvent | Time (min) | Yield % |
|--------|------------------|------------|---------|
| 1 | DMF | 30 | 38 |
| 2 | Acetonitrile | 30 | 45 |
| 3 | MeOH | 30 | 70 |
| 4 | EtOH | 5 | 92 |
| 5 | H ₂ O | 15 | 80 |

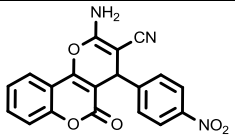
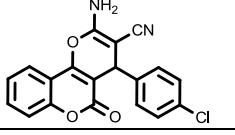
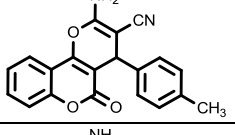
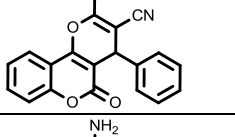
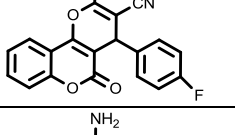
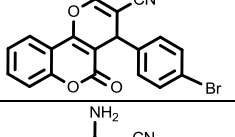
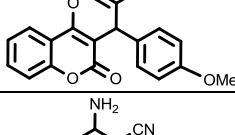
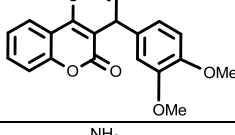
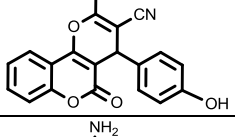
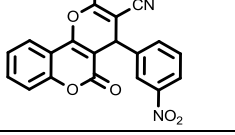
In order to determine the mol % of catalyst we have carried out model reaction with different amount of catalyst and found the optimum catalyst loading of cesium carbonate to be 10 mol %. By decreasing the amount of catalyst to 5 mol % the yield of product 4a was reduced; however, by increasing the amount of catalyst from 10 to 15 mol %, no appreciable change in the yield of product was observed (Table 2).

Table 2: Optimization of catalyst loading

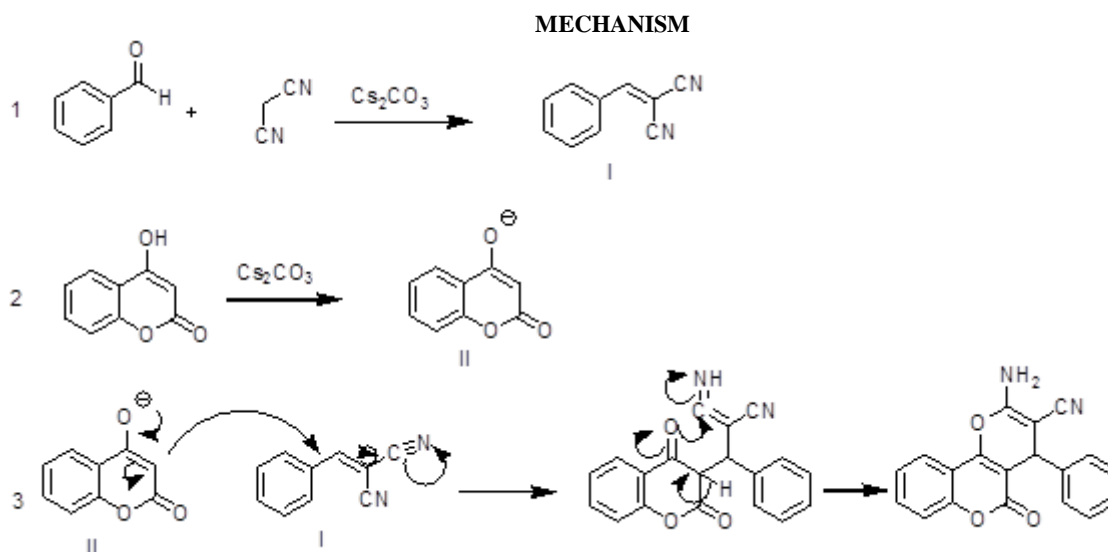
| S. No | Amount of catalyst (mol %) | Time (min) | Yield % |
|-------|----------------------------|------------|---------|
| 1 | - | 60 | 40 |
| 2 | 5 | 15 | 75 |
| 3 | 10 | 5 | 92 |
| 4 | 15 | 5 | 90 |
| 5 | 20 | 5 | 85 |

Next, in order to investigate the substrate scope of the reaction; a variety of substituted benzaldehydes were used employing the present optimized reaction conditions. The yield and reaction were found to be fairly equal and good (Table 3).

Table 3: Cs₂CO₃ catalyzed three-component synthesis of dihydropyrano[3,2-c]chromenes

| Entry | Aldehyde | Product 4(a-j) | Time (min) | Yield % | MP (°C) | MP (ref) |
|-------|-------------------|---|------------|---------|---------|--------------|
| a | 4-NO ₂ |  | 5 | 92 | 260-262 | 260-261 [22] |
| b | 4-Cl |  | 7 | 90 | 262-264 | 259-260 [22] |
| c | 4-Me |  | 6 | 91 | 250-252 | 253-255 [22] |
| d | H |  | 10 | 85 | 260-262 | 257-259 [23] |
| e | 4-F |  | 6 | 88 | 256-258 | 258-259 [22] |
| f | 4-Br |  | 7 | 89 | 250-252 | 252-254 [23] |
| g | 4-OMe |  | 8 | 86 | 244-246 | 240-242 [22] |
| h | 3,4-di OMe |  | 10 | 84 | 230-232 | 227-229 [22] |
| i | 4-OH |  | 10 | 86 | 260-262 | 261-262 [23] |
| j | 3-NO ₂ |  | 5 | 91 | 255-257 | 256-258 [23] |

A tentative mechanism is proposed (Scheme 2). Initially the Knoevenagel reaction occurs between aldehyde and malononitrile in presence of cesium carbonate to form adduct I. Then cesium carbonate abstract proton from hydroxyl group of coumarin to form oxide anion. In last Michael addition of oxide anion on adduct I, followed by the cyclization to form desired product 4a.



Scheme 2: Mechanism

Spectral data

2-amino-4,5-dihydro-4-(4-nitrophenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4a)

Melting point: 247-249°C. IR (KBr) cm^{-1} : 3431 (NH_2), 2979 and 2942 (C-H), 2259 (CN), 1679 (C=O), 1598 (C=C), 1579, 1449, 1403, 1367, 1260, 1215. $^1\text{H NMR}$ (DMSO-d_6 , 400 MHz, δ ppm): 7.89 (d, 1H, Ar-H), 7.69 (d, 1H, Ar-H), 7.49 (m, 3H, Ar-H), 7.45 (m, 3H, Ar-H), 7.23 (s, 2H, NH_2), 4.47 (s, 1H, CH).

2-amino-4-(4-bromophenyl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile (4f)

Melting point: 247-249°C. IR (KBr) cm^{-1} : 3436 (NH_2), 2986 and 2939 (C-H), 2259 (CN), 1668 (C=O), 1594 (C=C), 1513, 1464, 1413, 1363, 1312, 1259, 1225. $^1\text{H NMR}$ (DMSO-d_6 , 400 MHz, δ ppm): 7.98 (s, 1H, Ar-H), 7.64 (s, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 7.34 (m, 1H, Ar-H), 7.27 (m, 4H, Ar-H), 7.01 (s, 2H, NH_2), 4.47 (s, 1H, CH).

CONCLUSION

In summary, we have successfully developed a highly efficient cesium carbonate promoted protocol via one-pot three component reaction to synthesize medicinally and biologically relevant pyranochromenes. There are several advantages associated with this method (i) High yields, (ii) Easy accessibility, (iii) Wide substrate scope and (iv) Short reaction time. This methodology might prove as a better alternative to the existing literature methods.

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