Catalyst-free Multicomponent Synthesis of Novel Chromene Carbonitriles from Pyrazole Aldehydes using Ethanol

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ABSTRACT

A catalyst-free synthetic strategy to chromene carbonitriles by Multi-Component reaction of pyrazole aldehydes, 5,5-dimethylcyclohexane-1,3-dione and malononitrile with ethanol, at room temperature is reported. Screening of solvents and purification of the compounds were also performed. The newly synthesized novel compound’s (4H-chromene-3-carbonitriles) structures were authenticated by the spectral techniques viz. (¹H, ¹³C) Nuclear Magnetic Resonance, FT-IR, and LC-MS analysis.

Keywords: 4H-chromene-3-carbonitrile, Multicomponent, Catalyst-free, Ethanol, Multi-Drug Resistant, RT-Room Temperature, Tetra Methyl Silane, Ethyl Acetate, Petroleum Ether.

INTRODUCTION

Multi-drug resistant varieties of many pathogens threaten health as well as economy. Ugi-Multicomponent Reaction has played a vital part in pharmaceutical chemistry. Traditional Ugi-MCRs provide one-step synthesis of molecules with peptide core. Ugi-MCRs with a number of modifications were made available which enabled medicinal chemists to design diverse molecular scaffolds and have enlarged its application in modern drug evolution tremendously. The multicomponent reaction’s applications in drug design like molecules were notable¹³. MCRs also play a vital role in agrochemical industries. Several studies have revealed the importance of innovative synthetic organic methods via one-pot multi-component reactions (MCRs)⁴. Simple protocols, environmentally friendly principles, usage of readily available low-cost reactants and greater product yields were the advantages of one-pot synthesis compared to conventional multistep synthesis⁶. These reactions enable the production of variety of heterocyclic compounds without the necessity for isolation of intermediates⁵. Reduced reaction time, simple workup method, greater selectivity, high atom economy and the ability to employ green solvents are all the added advantages of MCRs⁷.
The vast majority of marketed pharmaceuticals contain heterocycles as common fragments and hence heterocycles play essential role in modern drug synthesis. They played a crucial influence in the contemporary organic synthesis development. Heterocycles were largest diverse class of synthesized compounds with notable biomedical, commercial and chemical uses. Large number of natural products, diverse drugs and biologically active substances contain heterocycles in their structures. Considering the importance of heterocycles, substantial attentions were paid to strategize various eminent methods for their synthesis. Heterocyclic chemistry has its origin in organic synthesis and medicinal chemistry.

Chromenes were a group of heterocycles containing oxygen atom, bicyclic, formed by fusion of a pyran ring with that of a benzene ring. They were most common types of naturally occurring heterocyclic compounds with diverse spectrum of biological activities. They were found in plants, bacteria, fungi and animals. Chromenes were important cores in medicinal chemistry, since they exhibit a myriad of biological activities like β-secretase inhibition, anti-dyslipidemic and anti-neoplastic behaviour. Chemotherapeutic chromenes such as EPC2407, LY290181 and LY290191 are well known for their anticancer activities.

4-Aryl-4H-Chromene possessed ER-antagonists activity against MCF-7 cell line and phenyl benzo[h]chromene have shown inhibitory activation against tumour cell lines. Bis chromene derivatives were prepared and their anti-influenza virus activities were studied.

2-aryl-4H-chromene was prepared and its prominent α-glucosidase inhibitory activities were studied. 2-Amino-4H-Chromenes possess a broad range of medicinal activities. Vinyl-2H-chromene-3-carbonitriles, prepared by Knoevenagel condensation were found to have enhanced optical properties and could be used as dyes. Optically active nitro-2H-chromenes containing best antibacterial properties were reported. 4H-chromene-3-carboxylates were synthesized and their potential elastase inhibitory action was found to be predominant.

Various catalysts were utilized in the synthesis of chromenes over the past few decades and are as follows, Fe3O4 nanoparticles, L-Proline, DABCO, Bi-functional organocatalysts, 1-[(3,5-bis(tri-fluoromethyl)phenyl)]thiourea, squaramide organocatalysts by Tandem-Michael cyclization, tandem Michael-asymmetric reaction using chiral squaramide catalysts, morpholine, TMEDA, L-cysteine functionalized magnetic nanoparticles, meglumine, Catalyst-free synthesis under ultrasound irradiation, NaOtBu, CuFe2O4 nanocatalyst, Na2CO3, piperidine, chitosan catalysed microwave assisted, eco-friendly synthesis under ultrasonication, Polystyrene-supported p-toluene sulfonic acid and K2CO3.

The lack of literatures with synthesis of chromene cores imbibing pyrazole aldehydes have been the driving force for the synthesis of these compounds. In our aim to build a novel library of biologically active targets, we discuss the catalyst-free, one-step, three-component synthesis of functionalized chromene carbonitriles process in RT.
T.L Chromatography. Silica gel of 230-400 mesh size (Merck, India) was used for performing column chromatography.

**Analytical equipment**

FT-IR spectra were recorded with a Lambda spectrophotometer. Using DMSO, NMR spectra (1H and 13C) of the compounds were acquired at 400MHz and 100MHz respectively with spectrometer of BRUKER Company with TMS as standard. QTRAP system (4000) [LC/MS/MS (UPLC)-hybrid triple quadruple/Linear Ion trap] was used for recording the mass spectra.

**General Procedure—Synthesis of 4-(2-amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chrom-4yl)-1-phenyl-1H-pyrazole-3-carboxylates 4a-4l**

At room temperature, reaction mixture containing 5,5-dimethylcyclohexane-1,3-dione (0.25 g), malononitrile (0.11 g) and pyrazole aldehyde (0.2 g) was stirred in ethanol (10 mL) for 2 hours. Thin layer chromatographic technique was used to confirm the reaction progress. Formed precipitate was filtered, purified by column chromatography [20% E.A: 80% P.E mixture] and pure product was obtained. 1H, 13C NMR, FT-IR and LC-M.S spectroscopic techniques were utilized to characterize the prepared compounds and results were tabulated 2.

**RESULTS AND DISCUSSION**

Using water, methanol and ethanol, solvent screening was carried out. It was found that, poor yield was obtained in water; better results were obtained while using methanol and excellent yield were seen with ethanol. The obtained results were given in Table 1.

**Table 1: Solvent-Screening**

| Derivatives | Reaction Time (h) | Water | Methanol | Ethanol |
|-------------|------------------|-------|----------|---------|
| 4a          | 2.0              | 45    | 65       | 94      |
| 4b          | 2.5              | 38    | 60       | 93      |
| 4c          | 2.0              | 41    | 61       | 95      |
| 4d          | 2.2              | 45    | 71       | 96      |
| 4e          | 2.5              | 33    | 55       | 91      |
| 4f          | 3.5              | 30    | 54       | 89      |
| 4g          | 2.0              | 32    | 59       | 92      |
| 4h          | 2.5              | 33    | 55       | 92      |
| 4i          | 3.0              | 43    | 62       | 94      |
| 4j          | 2.2              | 34    | 54       | 88      |
| 4k          | 2.1              | 41    | 60       | 91      |
| 4l          | 2.2              | 45    | 61       | 92      |

aIsolated yield

The proton NMR spectrum of product-4e shows a 6 protons singlet in 1.36ppm must be due to the presence of two methyl(-CH3) group. 2 protons singlet at 2.94ppm was due protons at C-8 position and two protons singlet at 3.40ppm was assigned to C-6 position. 1 proton singlet in 5.11ppm was attributed for chromene [pyran]ring proton C-4 position. The ten protons multiplet at 7.47–7.94ppm was attributed to aromatic protons. The singlet 8.21ppm was assigned to proton of pyrazole ring. Two protons singlet in 9.22ppm assigned to presence of amine (-NH2).
In the $^{13}$C NMR spectra, the peaks ranges between 114.3–138.8ppm were because of aromatic ring carbons. Peak at 24.5ppm was attributed for 2 methyl carbon. Peak at 32.5, 34.5, 42.4, 54.7 and 79.1ppm was assigned to C-7, C-4, C-8, C-6 and C-3. Carbon at position 3', 4' and 5' of pyrazole ring are appeared at 153.0, 115.0 and 120.3ppm respectively. The peak at 114.8ppm showed to Carbon of nitrile group. Peak at 155.3ppm was assigned for C-2. Peak at 196.5ppm was due to carbonyl (-C=O) carbon. [M+H]$^+$ of LC-MS spectrum revealed molecular ion peak at m/z 437.

Table 2: Preparation of Chromenes (4a-4l)

| Sr. No | Product (4a-4l)* | Yield (%)b | Time (h) |
|--------|------------------|------------|----------|
| 1      | ![Image](image1) | 95         | 2        |
| 2      | ![Image](image2) | 92         | 2.5      |
| 3      | ![Image](image3) | 94         | 2        |
| 4      | ![Image](image4) | 96         | 2        |
| 5      | ![Image](image5) | 90         | 2.5      |
| 6      | ![Image](image6) | 88         | 3        |
| 7      | ![Image](image7) | 92         | 2        |
| 8      | ![Image](image8) | 90         | 2.5      |
| 9      | ![Image](image9) | 94         | 3        |
| 10     | ![Image](image10) | 86         | 2        |
| 11     | ![Image](image11) | 90         | 2        |
| 12     | ![Image](image12) | 92         | 2        |

*All the synthesized compounds were characterized by FTIR, $^1$HNMR, $^{13}$CNMR and LC-MS.

bIsolated yield after the compounds being purified by column chromatography

In the $^{13}$C NMR spectra, the peaks ranges between 114.3–138.8ppm were because of aromatic ring carbons. Peak at 24.5ppm was attributed for 2 methyl carbon. Peak at 32.5, 34.5, 42.4, 54.7 and 79.1ppm was assigned to C-7, C-4, C-8, C-6
## Table 3: Molecular mass and Physical properties of synthesized compounds 4a-4l

| Compound | Molecular mass | m/z(m+h)+ | Colour & appearance | Nature | Retention factor(20% e.A:p.E) |
|----------|----------------|-----------|---------------------|--------|-----------------------------|
| 4a       | 432.89         | 433       | Pale yellow         | solid  | 0.40                        |
| 4b       | 522.78         | 523       | Yellow              | solid  | 0.43                        |
| 4c       | 418.89         | 419       | Pale yellow         | solid  | 0.38                        |
| 4d       | 508.85         | 509       | Dark yellow         | solid  | 0.36                        |
| 4e       | 436.89         | 437       | Light yellow        | solid  | 0.41                        |
| 4f       | 469.79         | 471       | White               | solid  | 0.39                        |
| 4g       | 514.88         | 515       | Pale Orange         | solid  | 0.48                        |
| 4h       | 466.96         | 467       | Whitish Orange      | solid  | 0.52                        |
| 4i       | 480.86         | 481       | Brownish yellow     | solid  | 0.58                        |
| 4j       | 560.77         | 561       | Light Orange        | solid  | 0.42                        |
| 4k       | 604.86         | 605       | Pale yellow         | solid  | 0.46                        |
| 4l       | 556.95         | 557       | Reddish yellow      | solid  | 0.47                        |

## Table 4: Elemental analysis data for compounds 4a-4l

| Compound | Molecular formula | % of C  | % of H  | % of N  | % of O  | % of Br | % of Cl |
|----------|-------------------|---------|---------|---------|---------|---------|---------|
| 4a       | C_{24}H_{24}N_{4}O_{4} | Calculated | 66.65   | 5.59    | 12.96   | 14.80   |         |
|          | Found             |         | 66.62   | 5.56    | 12.94   | 14.74   |         |
| 4b       | C_{24}H_{22}N_{6}O_{8} | Calculated | 55.17   | 4.24    | 16.09   | 24.50   |         |
|          | Found             |         | 55.13   | 4.20    | 16.06   | 24.44   |         |
| 4c       | C_{23}H_{22}N_{4}O_{4} | Calculated | 66.02   | 5.30    | 13.39   | 15.29   |         |
|          | Found             |         | 66.00   | 5.28    | 13.36   | 15.27   |         |
| 4d       | C_{23}H_{20}N_{6}O_{8} | Calculated | 54.33   | 3.96    | 16.53   | 25.17   |         |
|          | Found             |         | 54.29   | 3.93    | 16.48   | 25.14   |         |
| 4e       | C_{27}H_{24}N_{4}O_{2} | Calculated | 74.29   | 5.54    | 12.84   | 7.33    |         |
|          | Found             |         | 74.22   | 5.52    | 12.80   | 7.28    |         |
| 4f       | C_{27}H_{23}ClN_{4}O_{2} | Calculated | 74.29   | 5.54    | 12.84   | 7.33    |         |
|          | Found             |         | 74.22   | 5.52    | 12.80   | 7.28    |         |

## Table 5: Spectral data for newly prepared compounds 4a-4l

| Product | °H NMR: 400MHz, DMSO, δppm | °C NMR: 100MHz, DMSO, δppm | FT-IR [KBr, cm⁻¹] |
|---------|------------------------------|----------------------------|-------------------|
| 4a      | 1.03(s, 3H ), 1.10 (s, 3 H), 1.41 | 4.4, 26.2, 27.5, 28.9, | 14.4, 26, 27, 28.9, 29.9 | 3758.07, 3142.77, |
|          | (t, 3 H, J = 7.2 Hz), 2.19 (s, 2 H), | 32.0, 40.6, 50.7, 58.0, | 32.0, 40.4, 50.4, 58.3, | 2184.51, 1710.95, |
|          | 2.44 (s, 2 H ), 4.36 (q, 2H, J = 7.1 Hz), 4.64 ( s, 2 H ), 4.88 (s, 1H), 7.26-7.71(m, 5 H ), 7.88 (s, 1 H ); | 61.1, 61.5, 111.9, 118.9, 121.0, 127.6, 127.9, | 61.4, 61.9, 112.6, 117.6, | 1640.22, 1409.86, |
|          | 128.8, 129.4, 129.9, 128.9, 1319.9, 1157.03, 1291.99, 1157.03, 1289.99, 1157.03, | 139.4, 141.7, 158.2, 158.5, 162.2, 162.3, 196.1, | 162.2, 162.3, 196.1 | 1608.48, 932.03, |
|          | 139.4, 141.7, 158.2, 162.2, 162.3, 196.1 | 139.4, 141.7, 158.2, | 162.2, 162.3, 196.1 | 751.63, 692.48, |
|          | 619.27, 555.36 | 751.63, 692.48 | 619.27, 555.36 | 751.63, 692.48 |
| 4b      | 1.13 (s, 3H), 1.20 (s, 3H), 1.43 | 14.2, 26.4, 27.8, 28.8, | 128.9, 129.3, 129.9, 137.4 | 931.13, 752.53, |
|          | (t, 3H, J = 7.3 Hz ), 2.20( s, 2H), 2.46 (s , 2 H ), 4.34(q, 2H, 7.2 Hz), 4.66 ( s, 2H ), 4.89 (s, 1H), 7.90 | 32.0, 40.4, 50.4, 58.3, | 128.9, 129.3, 129.9, 137.4, | 2183.50, 1711.93, |
|          | (s, 1 H ), 8.23 (d, 1 H, J = 8.4 Hz), | 61.4, 61.9, 112.6, 117.6, | 128.9, 129.3, 129.9, 137.4, | 2183.50, 1711.93, |
|          | 121.1, 127.3, 127.7, 1156.33, 1067.45, | 128.9, 129.3, 129.9, 137.4, | 128.9, 129.3, 129.9, 137.4, | 931.13, 752.53, |
CONCLUSION

In summary, we have presented an unique, catalyst-free three component reaction which provides a simple methodology for synthesising chromene derivatives using pyrazole aldehydes, malononitrile and dimedone using various solvents. Regarding solvents, ethanol was found to be the most suitable solvent. The current method is advantageous for it’s milder cum quicker reaction procedure, high desired compounds yield, eco-friendly, simple experimental and purification procedures, making it an efficient synthetic scenario to the 4H-chromene-3-carbonitriles. Our future perspective is to carry out single-crystal XRD and evaluate various pharmaceutical activities for 4H-chromene-3-carbonitrile derivatives.

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