ENVIRONMENTALLY BENIGN PROTOCOL FOR THE SYNTHESIS OF BIOLOGICALLY SIGNIFICANT PYRANO[3,2-C]CHROMENE-3-CARBONITRILES

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ABSTRACT
An efficient and simple protocol for one pot three component synthesis of pyrano[3,2-c]chromene-3-carbonitrile derivatives is described via 4-hydroxy chromen-2-one, substituted aryl aldehydes and malononitrile using DBN as a catalyst in a scientific microwave oven at 140W. Short reaction times, environmentally friendly procedure and excellent yields are the main advantages of this procedure which makes it economical than other conventional methods.

KEYWORDS: Pyrano[3,2-c]chromene-3-carbonitrile, 4-hydroxy chromen-2-one, DBN.

INTRODUCTION
Chromene-2-one is a heterocyclic ring system consisting of a benzene ring fused to a pyran ring. It is one of the most important pharmacophores which appears as an important structure in many biologically active molecules.[1] Chromene-2-one forms the basic backbone of many polyphenols which are widely found in natural alkaloids, tocopherols, flavonoids and anthocyanins.[2] Certain natural and synthetic chromene-2-one derivatives have been found to possess some biological activities such as antimicrobial[3], antiviral[4] antivascular[5], antifungal[6], antioxidant[7], anti-inflammatory[8] and estrogenic.[9] Many of the compounds possessing the chromene-2-one moiety are also found to exhibit anticancer[10] and anti-HIV[11] activities. In addition to the wide range of biological activities, pyrano[3,2-c]chromene-3-carbonitrile are used for the treatment of neurodegenerative disorders including Alzheimer’s disease, amyotrophic lateral sclerosis, Huntington’s disease and Parkinson’s disease.[12] They are also widely employed in cosmetics, pigments[13] and are also useful as photoactive materials.[14] As a result, development of new methodology for the synthesis of pyrano[3,2-c]chromene-3-carbonitrile attracts interests from synthetic community.

The spots are visualised under ultraviolet tube. Proton nuclear magnetic resonance (1H NMR) and[13] C NMR spectra were recorded on a Bruker DPX 300 MHz spectrophotometer using tetramethylsilane (TMS) as an internal standard in DMSO-d6. Infrared spectra were recorded on a Perkin-Elmer, JASCO 4600 FTIR spectrophotometer and expressed in cm-1.

Experimental Section
General procedure for the synthesis of 2-amino-4-(aryl)-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile [Ia-j]
The mixture containing 15% DBN, aryl aldehyde [I] (1 mmol), malononitrile [II] (1 mmol), 4-hydroxy chromen-2-one [III] (1 mmol) and 5 ml ethanol in a round bottomed flask was irradiated for 3-5 min. in a scientific microwave oven at the power of 140W. The completion of reaction was monitored by pre-coated TLC plates using solvent system pet ether: ethyl acetate (7:3, v/v). After completion of the reaction, the mixture was cooled at room temperature and the product obtained was collected by filtration. The crude product obtained was recrystallized from hot ethanol to get the pure product.
Physical data of the compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular Formula</th>
<th>Formula Weight</th>
<th>Melting Point (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>C19H11ClN2O3</td>
<td>351.76</td>
<td>262</td>
<td>90</td>
</tr>
<tr>
<td>IVb</td>
<td>C19H11BrN2O3</td>
<td>395.22</td>
<td>255</td>
<td>88</td>
</tr>
<tr>
<td>IVc</td>
<td>C19H11BrN2O3</td>
<td>395.21</td>
<td>241</td>
<td>86</td>
</tr>
<tr>
<td>IVd</td>
<td>C19H11N3O5</td>
<td>361.32</td>
<td>260</td>
<td>90</td>
</tr>
<tr>
<td>IVe</td>
<td>C19H11N3O5</td>
<td>361.32</td>
<td>265</td>
<td>86</td>
</tr>
<tr>
<td>IVf</td>
<td>C19H12N2O3</td>
<td>316.32</td>
<td>253</td>
<td>91</td>
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<tr>
<td>IVg</td>
<td>C20H14N2O3</td>
<td>330.35</td>
<td>252</td>
<td>85</td>
</tr>
<tr>
<td>IVh</td>
<td>C20H14N2O4</td>
<td>346.35</td>
<td>248</td>
<td>89</td>
</tr>
<tr>
<td>IVi</td>
<td>C20H11N3O3</td>
<td>341.33</td>
<td>262</td>
<td>89</td>
</tr>
<tr>
<td>IVj</td>
<td>C17H10N2O3S</td>
<td>322.34</td>
<td>250</td>
<td>84</td>
</tr>
</tbody>
</table>

Analytical and spectral data of the compounds

2-Amino-4-(3-chloro-phenyl)-5-oxo-4H,5H-pyran-3,2-c|chromene-3-carbonitrile (IVa)

13C NMR (DMSO d6, 75 MHz): 37.18, 57.87, 103.71, 113.45, 117.00, 119.43, 123.07, 125.06, 128.65, 126.93, 127.60, 128.02, 130.77, 133.42, 133.57, 146.18, 152.70, 154.20, 158.52, 159.99 ppm Anal. Calcd.: C (65.06%), H (3.16%), N (7.99%). Found: C (65.08%), H (3.13%), N (8.01%).

2-Amino-4-(4-bromophenyl)-5-oxo-4H,5H-pyran-3,2-c|chromene-3-carbonitrile (IVb)

Anal. Calcd.: C (57.74%), H (2.81%), N (7.09%). Found: C (57.78%), H (2.86%), N (7.11%).

2-Amino-4-(3-bromophenyl)-5-oxo-4H,5H-pyran-3,2-c|chromene-3-carbonitrile (IVc)

Anal. Calcd.: C (57.74%), H (2.81%), N (7.09%). Found: C (57.79%), H (2.76%), N (7.13%).

2-Amino-4-(4-nitrophenyl)-5-oxo-4H,5H-pyran-3,2-c|chromene-3-carbonitrile (IVd)

Anal. Calcd.: C (63.16%), H (3.07%), N (11.63%). Found: C (63.12%), H (3.12%), N (11.66%).

2-Amino-4-(3-nitrophenyl)-5-oxo-4H,5H-pyran-3,2-c|chromene-3-carbonitrile (IVe)

1H NMR (DMSO d6, 300 MHz): 4.733 (s, 2H), 7.450-7.701 (m, 2H), 7.706-7.729 (t, 1H), 7.800, 7.825 (t, 1H), 7.907-7.933 (t, 1H), 7.938-8.108 (d, 1H), 8.108-8.140 (m, 2H) ppm 13C NMR (DMSO d6, 75 MHz): 37.13, 57.45, 103.36, 113.43, 117.07, 119.38, 122.73, 122.90, 123.08, 125.17, 130.53, 133.59, 135.22, 145.95, 148.34, 152.75, 154.36, 158.63, 160.06 ppm Anal. Calcd.: C (63.16%), H (3.07%), N (11.63%). Found: C (63.10%), H (3.12%), N (11.68%).

2-Amino-5-oxo-4-phenyl-4H,5H-pyran-3,2-c|chromene-3-carbonitrile (IVf)

Anal. Calcd.: C (72.15%), H (3.82%), N (8.86%). Found: C (72.12%), H (3.88%), N (8.88%).

2-Amino-4-(3-methylphenyl)-5-oxo-4H,5H-pyran-3,2-c|chromene-3-carbonitrile (IVg)

Anal. Calcd.: C (72.72%), H (4.27%), N (8.48%). Found: C (72.96%), H (4.14%), N (8.24%).

2-Amino-4-(3-methoxyphenyl)-5-oxo-4H,5H-pyran-3,2-c|chromene-3-carbonitrile (IVh)

13C NMR (DMSO d6, 75 MHz): 37.38, 55.42, 58.38, 104.37, 112.43, 113.43, 114.31, 116.95, 119.57, 120.11, 122.98, 125.01, 130.03, 133.29, 145.28, 152.62, 153.93, 158.53, 159.74, 159.96 ppm Anal. Calcd.: C (69.36%), H (4.07%), N (8.09%). Found: C (69.52%), H (4.22%), N (7.92%).

Biological prediction study of substituted pyran[3,2-c]chromene-3-carbonitrile derivatives [IV(a-j)]

The confirmed structures were subjected to computer programme PASS for the prediction of their biological activities.
<table>
<thead>
<tr>
<th>Activity</th>
<th>IVa</th>
<th>IVb</th>
<th>IVc</th>
<th>IVd</th>
<th>IVe</th>
<th>IVf</th>
<th>IVg</th>
<th>IVh</th>
<th>IVi</th>
<th>IVj</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-Cl</td>
<td>4-Br</td>
<td>3-Br</td>
<td>4-NO2</td>
<td>3-NO2</td>
<td>H</td>
<td>4-Me</td>
<td>4-QMe</td>
<td>CN</td>
<td>Thio</td>
</tr>
<tr>
<td>Catalase stimulant</td>
<td>0.823</td>
<td>0.833</td>
<td>0.834</td>
<td>0.822</td>
<td>0.815</td>
<td>0.860</td>
<td>0.814</td>
<td>0.828</td>
<td>0.842</td>
<td>0.753</td>
</tr>
<tr>
<td>Cystinyl aminopeptidase inhibitor</td>
<td>0.813</td>
<td>0.806</td>
<td>0.769</td>
<td>0.804</td>
<td>0.795</td>
<td>0.852</td>
<td>0.808</td>
<td>0.805</td>
<td>0.839</td>
<td>0.708</td>
</tr>
<tr>
<td>Excitatory amino acid transporter I inhibitor</td>
<td>0.809</td>
<td>0.817</td>
<td>0.810</td>
<td>0.713</td>
<td>0.715</td>
<td>0.872</td>
<td>0.790</td>
<td>0.761</td>
<td>0.844</td>
<td>0.683</td>
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<tr>
<td>Apoptosis agonist</td>
<td>0.782</td>
<td>0.802</td>
<td>0.799</td>
<td>0.783</td>
<td>0.769</td>
<td>0.850</td>
<td>0.802</td>
<td>0.825</td>
<td>0.832</td>
<td>0.683</td>
</tr>
<tr>
<td>CYP2A11 substrate</td>
<td>0.668</td>
<td>0.668</td>
<td>0.653</td>
<td>0.639</td>
<td>0.624</td>
<td>0.741</td>
<td>0.673</td>
<td>0.703</td>
<td>0.712</td>
<td>0.624</td>
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<tr>
<td>Potassium channel large- conductance Ca- activated activator</td>
<td>0.644</td>
<td>0.628</td>
<td>0.629</td>
<td>0.593</td>
<td>0.583</td>
<td>0.650</td>
<td>0.619</td>
<td>0.616</td>
<td>0.637</td>
<td>0.575</td>
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<tr>
<td>Systemic lupus erythematosus treatment</td>
<td>0.628</td>
<td>0.558</td>
<td>0.534</td>
<td>0.509</td>
<td>0.498</td>
<td>0.688</td>
<td>0.600</td>
<td>0.580</td>
<td>0.669</td>
<td>0.497</td>
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<td>Antiarthritic</td>
<td>0.615</td>
<td>0.541</td>
<td>0.513</td>
<td>0.494</td>
<td>0.478</td>
<td>0.646</td>
<td>0.590</td>
<td>0.612</td>
<td>0.627</td>
<td>0.466</td>
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<tr>
<td>Restenosis treatment</td>
<td>0.495</td>
<td>0.517</td>
<td>0.509</td>
<td>0.470</td>
<td>0.459</td>
<td>0.579</td>
<td>0.492</td>
<td>0.533</td>
<td>0.591</td>
<td>0.318</td>
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<tr>
<td>Hepatic disorders treatment</td>
<td>0.589</td>
<td>0.532</td>
<td>0.508</td>
<td>0.511</td>
<td>0.497</td>
<td>0.627</td>
<td>0.561</td>
<td>0.553</td>
<td>0.606</td>
<td>0.360</td>
</tr>
</tbody>
</table>

The following conclusions have been made when the compounds from this scheme were subjected to PASS programme to get the predictions.

1. All the compounds [IV(a-j)] show a variety of possible biological activities.
2. Maximum compounds have highest Pa values from 0.8 to 0.5.
3. The highest Pa value (0.860) for catalase stimulant activity is being shown by 2-amino-5-oxo-4-phenyl-4H, 5H-pyrano[3,2-c]chromene-3-carbonitrile (IVf).
4. All the derivatives [IV(a-j)] are active for all the activities from catalase stimulant to Hepatic disorders treatment.
RESULT AND DISCUSSION
The synthesis of pyran[3,2-c]chromene-3-carbonitrile moiety by several catalysts has been done before. Herein, we have reported the synthesis of various pyranochromene-2-ones using DBN catalyst via one pot multi-component reaction. As discussed in literature review the use of cyano active methylenes in our protocol it was decided to incorporate a mild organic base. Primarily, we carried out a one pot reaction from equimolar amounts of 3-nitro benzaldehyde, malononitrile and 4-hydroxy chromen-2-one in ethanol under microwave irradiations at 140W using DBN in a catalytical amount. To our beliefs the reaction progressed efficiently giving off-white colored product with 90% yield within 3.5 min. as monitored by TLC.

\[
\text{CHO} + \text{CN} + \text{O} \xrightarrow{\text{DBN}} \text{O} \]

The same reaction was then subjected to evaluation of different solvents. Initially, only water and a mixture of water with protic solvent systems were used for the reported protocol. It gave low yield in the range of <20-30% of product.

CONCLUSION
In summary, we have reported a novel one pot three component synthesis of functionalized pyran[3,2-c]chromene-3-carbonitrile derivatives using DBN as commercially available catalyst. This procedure offers several advantages including high yields, clean reaction conditions and harmless to the environment which make it useful and economically attractive process for the synthesis of these compounds.

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REFERENCES