RESEARCH PROJECT REPORT

TITLE: SYNTHETIC ROUTE OPTIMIZATION OF 2,3-DIMETHYL-7-HYDROXY-CHROMONE-8-CARBOXYLIC ACID

In the project work we describe the design and synthesis of **2,3-dimethyl-7-hydroxy-Chromone-8-carboxylic acid** (**8**).

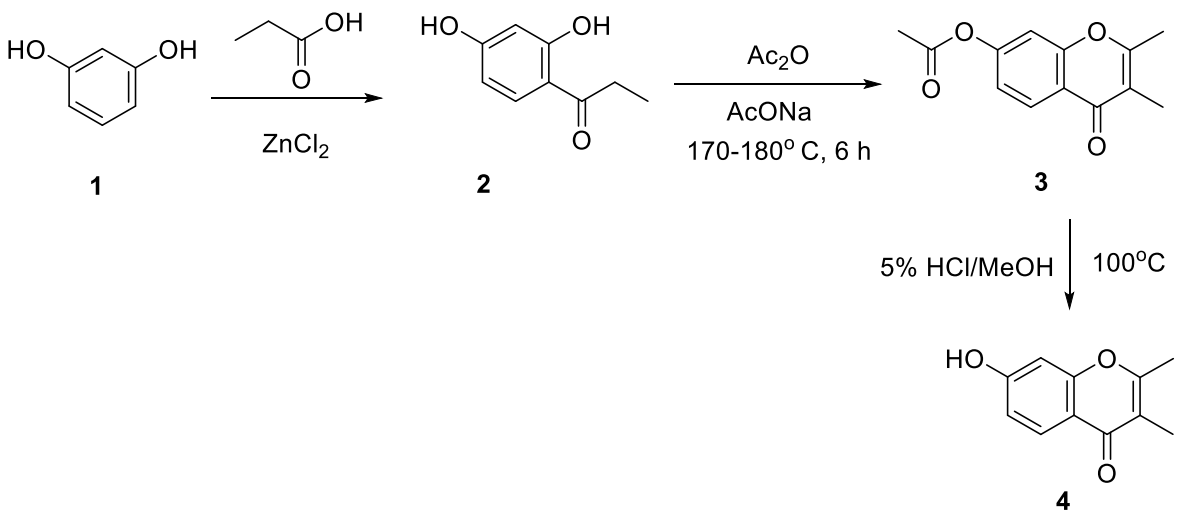
The present work involves 5 synthetics steps;

1. Synthesis of 7-hydroxy-2,3-dimethyl-4H-chromen-4-one (**4**)
2. Synthesis of 7-hydroxy-2,3-dimethyl-4-oxo-4H-chromene-8-carboxaldehyde (**5**)
3. Synthesis of 7-(benzyloxy)-2,3-dimethyl-4-oxo-4H-chromene-8-carboxaldehyde (**6**)
4. Synthesis of 7-(benzyloxy)-2,3-dimethyl-4-oxo-4H-chromene-8-carboxylic acid (**7**)
5. Synthesis of 7-(benzyloxy)-2,3-dimethyl-4-oxo-n-aryl/benzyl-4H-chromene-8-carboxamides (**8**)

1. Synthesis of 7-hydroxy-2,3-dimethyl-4H-chromen-4-one (4)

To construct the intended chromone-8-carboxylic acid **7** we focused our attention to formulate functional chromone-precursor bearing hydroxyl group at a strategic C-7 position and followed by formylation at C-8 position of chromone scaffold.[1] The multistep preparation started with $ZnCl_2$ mediated propanoylation of 1,3 dihydroxy benzene using ethylformic acid to give 1-(2,4-dihydroxyphenyl)propan-1-one (**2**) which was then cyclocondensed *via* Modified Baker-Venkataraman reaction[2] to afford intermediate **3**, which upon acid hydrolysis using 5% hydrochloric acid in MeOH at 100^0C gave 2,3-dimethyl-7-hydroxy-chromone (**4**)**.** Compound **4** was characterized by its spectral analysis.

Scheme-1: Synthesis of 7-hydroxy-2,3-dimethyl-4H-chromen-4-one (**4**)



In the FTIR spectrum (KBr-pellet) of 2,3-dimethyl-*7-hydroxy* chromone *(***4**), C=O group stretching absorption frequency was recorded as sharp band at 1634 cm^{-1} where as 7-hydroxy group gave broad band at 3209 cm^{-1}.

In the ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of 2,3-dimethyl-7-hydroxychromone **4** broad signal at δ 5.37 due to OH proton The signals in the aliphatic region i.e. at δ 2.03(s) and 2.38(s) were comparable to the methyl protons at C-2 and C-3 positions respectively while the aromatic ring protons of chromone gave complex signal pattern due to unequal spin-spin coupling. The H-5 proton appeared at δ 8.09 (d, *J*=9.0 Hz, 1H, H-5), whereas, H-8 proton and H-6 protons appeared at δ 6.77 (d, *J*=2.1 Hz, 1H, H-8) and 6.83 (dd, *J*=2.4, 8.6 Hz, 1H, H-6) respectively.

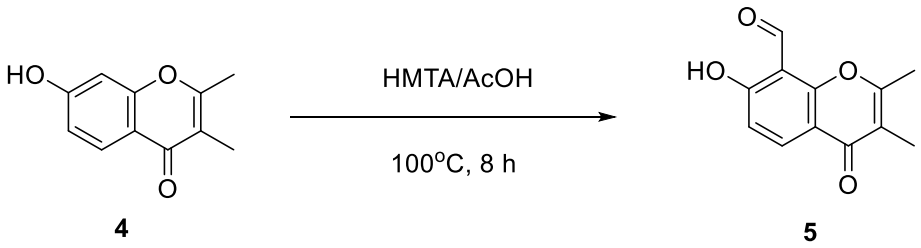
In ^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of **4** the characteristic C=O group signal appeared at very low field δ 176.8 (C=O) and C-7 carbon signal resonated at δ 161.6. The methyl group carbons resonated in high field region at δ 9.4 (C3-CH_3) and δ 17.9 (C3-CH_3). The signals of other chromone-skeleton carbons found at δ160.5(C-2), 157.0 (C-8a), 126.4 (C-5), 115.3 (C-6), 115.0 (C-4a), 114.0 (C-3), 101.5 (C-8).

In the ESI-MS of **4**, the quasi molecular ion peak was recorded at m/z 191.1[M+H].

2. Synthesis of 7-hydroxy-2,3-dimethyl-4-oxo-4H-chromene-8-carboxaldehyde (5)

The Duff formylation[45] of 7-hydroxychromone **4** using HMTA/AcOH afforded regioselective 7-hydroxy-chromone-8-carboxaldehyde **5 (Scheme-2).**

*Scheme-2: Synthesis of 7-hydroxy-2,3-dimethyl-4-oxo-4H-chromene-8-carboxaldehyde***(5)**



The FTIR (KBr pellet) spectrum of *7-hydroxy* chromone-8-carboxaldehyde **5**, showed C=O stretching frequency of formyl functional group at 1654cm^{-1} whereas a sharp band from C=O group of chromone found at 1628 cm^{-1}, while 7-hydroxy group gave broad band at 3419 cm^{-1}.

In the ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of **5** the singlet signal in very low field region at δ 12.40 from OH proton, while the signals in the aliphatic region i.e. at δ 2.06(s) and 2.45(s) were from C-2 and C-3 methyl groups. The benzenoid ring protons of chromone resonated at δ 6.95 (d, *J*=9.0 Hz, 1H, H-6) and 8.32 (d, *J*=9.0 Hz, 1H, H-5), whereas the diagnostic aldehyde proton signal was found in low field region at δ 10.54 as singlet which indicated regioselective formylation at C-8 position.

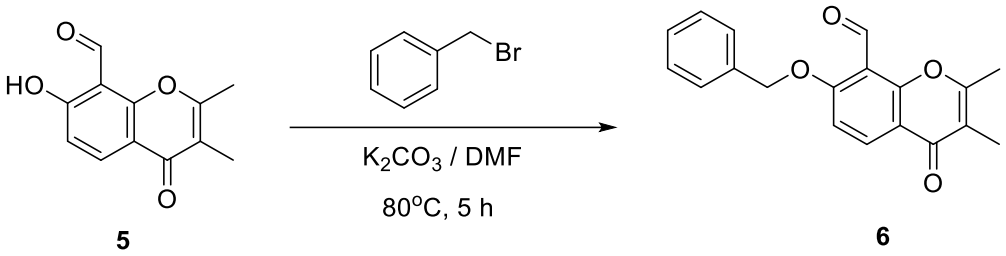
In ^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of **5** the characteristic CHO group carbon signal resonated at very low field at δ 192.0 and C=O of chromone carbon signal found at δ 175.7. The methyl group carbons resonated in high field region at δ 9.7 (C3-CH_3) and δ 18.1 (C2-CH_3). The signals owing to other chromone-skeleton carbons found at δ 166.7 (C-7), 160.5 (C-2), 157.3 (C-8a), 134.9 (C-5), 117.8 (C-4a), 115.4 (C-8), 114.8 (C-6), 108.0 (C-3).

In the ESI-MS of compound **5**, the quasi molecular ion peak was observed at m/z 219.1[M+H].

3. Synthesis of 7-(benzyloxy)-2,3-dimethyl-4-oxo-4H-chromene-8-carboxaldehyde (6)

O-Benzylation of 2,3-dimethyl-7-hydroxy-chromone-8-carboxaldehyde (**5**) was performed by using benzyl bromide in the presence of potassium carbonate in DMF at 80^0C to afford the benzyloxy-tethered chromone-8-carboxaldehyde **6**, which was then used as a precursor for subsequent reactions.

*Scheme-3: Synthesis of 7-O- benzyloxy-tethered chromone-8-carboxaldehyde **(6)***



5 **6**

The FTIR spectrum recorded using KBr pellet of *7-O*-benzyloxy-tethered chromone-8-carboxaldehyde **6**, showed strong band at 1694 cm^{-1} which was assigned to aldehyde C=O group, where as chromone carbonyl (C=O) band appeared at 1635 cm^{-1}.

In the ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *7-O*- benzyloxy-tethered chromone-8-carboxaldehyde **6** the signal at δ 5.32 due to OCH_2- protons clearly implied the O-benzylation of the hydroxy-compound **5**. The signals in the aliphatic region at δ 2.04 and 2.46 were corresponding to the methyl protons at C-2 and C-3 positions respectively. The benzonoid ring protons of chromone resonated at δ 7.10 (d, *J*=8.8 Hz, 1H, H-6) and 8.37 (d, *J*=8.8 Hz, 1H, H-5) as doublet with *J*=8.8Hz, whereas the aromatic protons of benzyl group resonate in the range of δ 7.36 to 7.47 as complex multiplet. The aldehyde proton signal was found in very low field region at δ 10.68 as singlet.

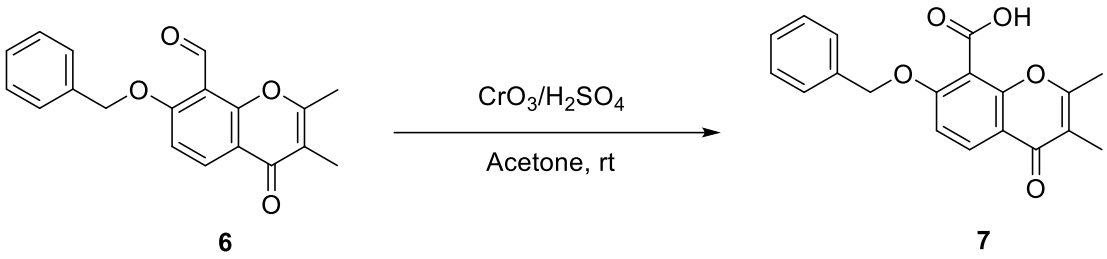
In ^{13}C NMR (DMSO-d_6, 125 MHz) spectrum of compound **6** the diagnostic OCH_2 carbon signal found at δ 71.2, while the C=O group signals were arose at δ 175.7 (C=O) and 187.2 (CHO). The methyl group carbons resonated at high field δ 10.0 (C3-CH_3) and δ 18.6 (C2-CH_3). The benzylic carbons displayed signals in between δ127.9 to 136.3. The signals of chromone-framework carbons found at δ 164.3(C-7), 162.6 (C-2), 155.8 (C-8a), 133.0 (C-5), 116.8 (C-4a), 116.3 (C-8), 112.7 (C-6), 111.8 (C-3).

In the ESI-MS of **6**, the quasi molecular ion peak was recorded at m/z 309.2[M+H].

4. Synthesis of 7-Benzyloxy-2,3-dimethyl-4-oxo-4H-chromene-8-carboxylic acid (7)

Selective oxidation of formyl group of compound **6** into carboxylic acid **7** was performed by employing Jones oxidation method at room temperature.

*Scheme-4: Synthesis of 2,3-dimethyl-7-O- benzyloxy- chromone-8-carboxylicacid **(7)***



6 **7**

The FTIR(KBr) spectrum of *7-O*-benzyloxy-tethered-2,3-dimethyl-chromone-8-carboxylic acid **7**, strong band at 1719cm^{-1} for carboxylic C=O group and a broad band was observed around 3428cm^{-1} due to –OH of carboxylic acid functional group, meanwhile chromone carbonyl (C=O) band appeared at 1639cm^{-1}.

In the ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of **7** six signals were traced out which represented 16 protons. The signal in the extremely low field region i.e. at δ 13.51 suggested the presence of acid group proton in the compound **7**. The signals in the aliphatic region with chemical shifts δ 1.93, δ 2.36 and 5.33 were assigned to the methyl group (at C-2 and C-3 position) and –OCH_2 protons respectively. The H-5 proton of chromone skeleton was appeared as doublets at δ 8.02 with J=9.0 Hz whereas H-6 proton was resonated along with benzylic protons in the aromatic range of δ 7.32 to 7.46 as a part of complex multiplet.

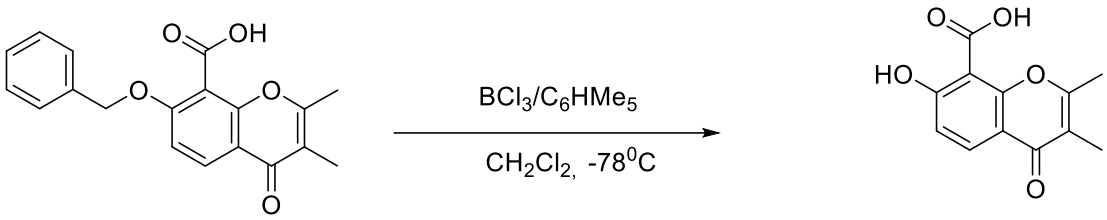
In ^{13}C NMR (DMSO-d_6, 100 MHz) spectrum of **7** the characteristic COOH carbon signal appeared at δ 168.9, chromone C=O group resonated at δ 175.4. The methyl group signals appeared with slight shift towards high field i.e. at δ 9.5 (C3-CH_3) and δ 18.2 (C2-CH_3). The benzylic CH_2 carbon showed the signals at δ 70.1, meanwhile the aromatic benzyl ring carbons resonated in the range of δ 127.3 to 136.1. The chromone skeletal carbons resonated at δ 164.7 (C-7), 161.8 (C-2), 158.0 (C-8a), 136.1 (C-1'), 134.7 (C-5), 115.8 (C-4a), 115.7 (C-8), 113.4 (C-6), 110.9 (C-3).

In the ESI-MS of **7**, the quasi molecular ion peak was observed at m/z 325.1[M+H].

5. Synthesis of 7-Benzyloxy-2,3-dimethyl-4-oxo-4H-chromene-8-carboxylic acid (7)

Deprotection of benzyloxy chromone-carboxylic acid **7** to target molecule i.e. **2,3-dimethyl-7-hydroxy-Chromone-8-carboxylic acid (8)** was achieved by using stoichiometric amount of lewis acid BCl_3 in Pentamethyl benzene and CH_2Cl_2 at reduced temperature under inert conditions.

*Scheme-5: Synthesis of 2,3-dimethyl-7-hydroxy- chromone-8-carboxylicacid **(8)***



7 **8**

In the ^1H NMR (DMSO-d_6, 400 MHz) spectrum of **8** six signals were traced out which represented 10 protons. The signal in the extremely low field region i.e. at δ 12.71 suggested the presence of acid group proton in the compound **8**. The signals in the aliphatic region with chemical shifts δ 1.98 and δ 2.39 were assigned to the methyl groups (at C-2 and C-3 position). The H-5 proton of chromone skeleton was appeared as doublets at δ 8.17 with J=9.0 Hz whereas H-6 proton was resonated at δ 7.19 as doublet whereas free hydroxyl proton resonates at δ 15.89.

In the ESI-MS of **8**, the quasi molecular ion peak was observed at m/z 235.1[M+H].

References:

1. Rao, Y.J.; Krupadanam, G.L.D. *Indian J. Chem.*, **2000**, *39B*, 610.
2. Reddy, B.P.; Krupadanam, G.L.D. *J.Heterocycl.Chem.*,**1996**, *33(6)*, 1561.
3. Duff, J.C.; Bills, E.J. *J. Chem. Soc.*, **1932**, *2* , 1987.
4. *Org. Synth.* **2016**, *93*, 63-74.

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From
The Chief Manager,
BASR Fine Chemicals Pvt. Ltd.
Hyderabad-55.

To
The Principal
Tara Government College, Sangareddy (A)
Sangareddy-502001.

Sir/Madam,

Sub: Sanctioning of the Research Project titled-"**Synthetic route optimization of 2,3-dimethyl-7-hydroxy-Chromone-8-carboxylic acid**" Reg.

With reference cited above, the Research project entitled -"**Synthetic route optimization of 2,3-dimethyl-7-hydroxy-Chromone-8-carboxylic acid**" is sanctioned to **Dr.Abhijit Kantankar, Asst. Professor of Chemistry & Principal Investigator**, Department of Chemistry, Tara Government College, Sangareddy (A), Sangareddy. The main motif of the projects is to build the strong Industry-Academia relations.

THE PROJECT SPECIFICATIONS AS FOLLOWS:

Title of the Project: Synthetic route optimization of 2,3-dimethyl-7-hydroxy-Chromone-8-carboxylic acid.
Estimated Project Value (in INR): 26,000/- (Rs. Twenty Six thousands only-**provided in the Form of Chemicals & Solvents**).
Duration of the Project: 3 months (w.e.f. 28.01.2022).
Purity of the Target Molecule: >95% (through HPLC).

Thanking you.
With regards,

BASR Fine Chemicals Pvt. Ltd., Hyderabad-55.

For BASR Fine Chemicals Pvt. Ltd.

Authorised Signatory

Authorized Signatory
Date: 28.01.2022

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RESEARCH PROJECT COMPLETION CERTIFICATE

This is to certify that, **Dr.Abhijit Kantankar, Asst. Professor of Chemistry & Principal Investigator**, Department of Chemistry, Tara Government College, Sangareddy (A), Sangareddy has successfully completed and submitted the sanction project i.e. "**Synthetic route optimization of 2,3-dimethyl-7-hydroxy-Chromone-8-carboxylic acid**" within a stipulated time period and all the chemicals and solvents (worth of INR Twenty Six thousands only) provided by BASR Fine Chemicals Pvt. Ltd., have been utilized on purpose of the project without any deviation.

BASR Fine Chemicals Pvt. Ltd., Hyderabad-55.

For BASR Fine Chemicals Pvt. Ltd.

Authorised Signatory

Authorized Signatory

Date: 18.04.2022