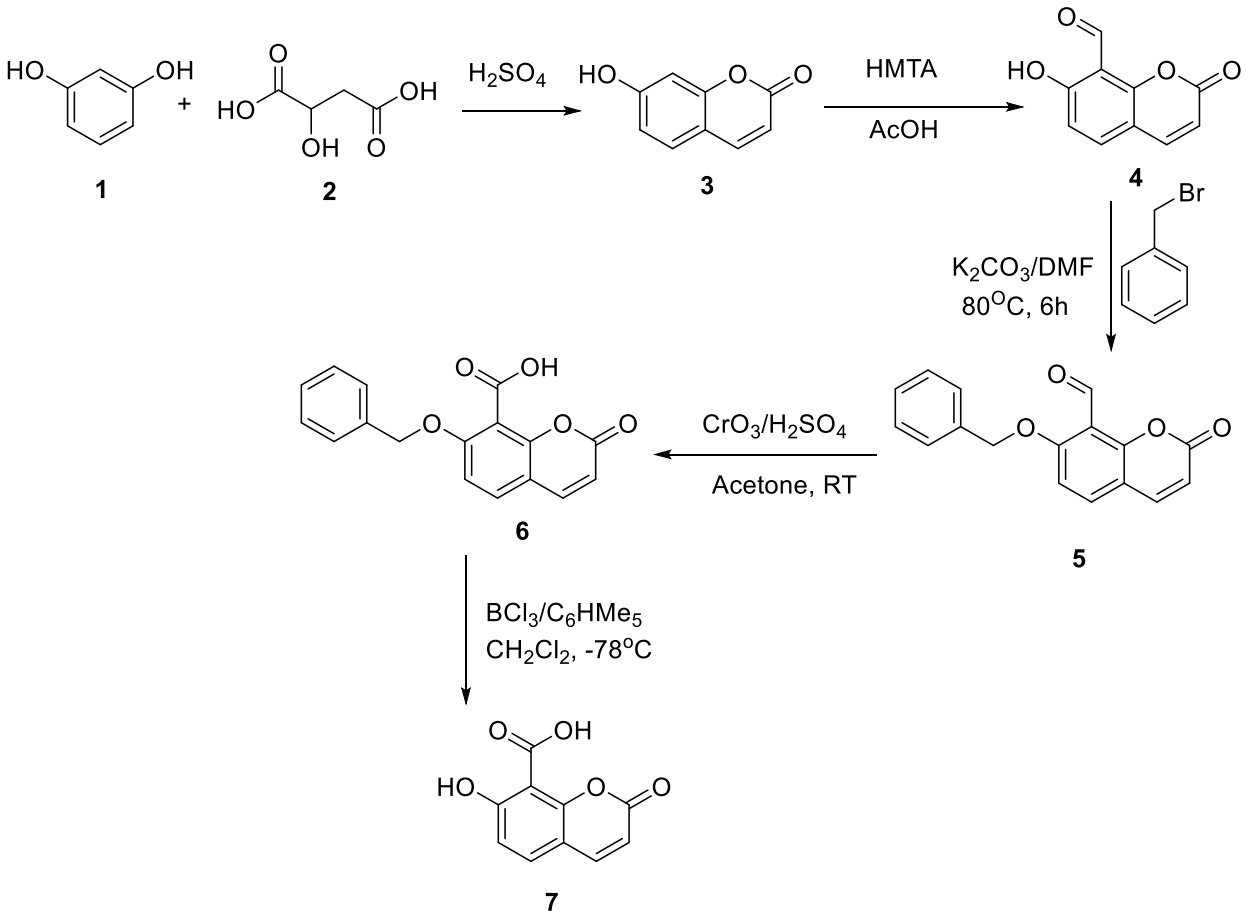
RESEARCH PROJECT REPORT

TITLE: SYNTHETIC ROUTE OPTIMIZATION OF 7-HYDROXY-2-OXO-2H-CHROMENE-8-CARBOXYLIC ACID

In the project work we describe the design and synthesis of **Synthetic route optimization of 7-hydroxy-2-oxo-2H-chromene-8-carboxylic acid** (7).

The present work involves 5 synthetics steps;

1. Synthesis of 7-hydroxy coumarin (3):
2. Synthesis of 7-hydroxy-8-formyl coumarin (4):
3. Synthesis of 7-benzyloxy-8-formyl coumarin (5):
4. Synthesis of 7-benzyloxy-2-oxo-2H-chromene-8-carboxylic acid (6):
5. Synthesis of 7-hydroxy-2-oxo-2H-chromene-8-carboxylic acid (7):



1. **Synthesis of 7-hydroxy coumarin (3):**

Resorcinol (0.2 mol) and malic acid (0.30 mol) were added to a stirred solution of concentrated sulfuric acid (400 mL) in a reaction flask equipped with a thermometer and addition funnel. The reaction mass was maintained and poured into crushed ice under vigorous stirring. The off-white solid obtained was filtered, and the crude product was further purified by re-crystallization using solvent ethanol. 68 % of yield; m.p: 187–189 C; 1 H NMR (300 MHz, CDCl3): δ 2.48 (s, 3H, C4–CH3), 6.31 (s, 1H, C3–H), 6.91 (d, 1H, C6–H, J = 9.0 Hz), 6.92 (s, 1H, C8–H), 7.61 (d, 1H, C5–H, J = 9.0 Hz). ESI-MS: 163.1(M+1).

2. **Synthesis of 7-hydroxy-8-formyl coumarin (4):**

7-hydroxy coumarin (32.40 g, 0.2 mol) was dissolved in glacial acetic acid (400 ml), and hexamethylene tetramine (84.0 g, 0.6 mol) was added in one portion. The reaction mixture was maintained for ananother 1 h, followed by extraction with diethylether, and the combined organic layer was collected, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was quenched into a pool of ice cold C_2H_5OH followed by crystallization, filtration, and drying to obtain pale yellowish crystals of 7-hydroxy-8-formyl coumarin (2). 44 % of yield; m.p. 176–178 C; 1 H NMR (300 MHz, CDCl3): δ 6.19 (s, 1H, C3-H), 6.91–6.94 (d, 1H, C6-H, J = 9 Hz), 7.89–7.91 (d, 1H, C5-H, J = 9 Hz), 10.69 (s, 1H, CHO), 12.25 (s, 1H, OH). ES-MS: 191.1(M+1).

3. **Synthesis of 7-benzyloxy-8-formyl coumarin (5):**

The compound **4** (32.0 mmol,) was dissolved in DMF and K_2CO_3 (0.1 mol, 27.0g) was added with steady stirring for about 10-15 min at ambient temperature. The mixture was then kept in cooling bath and the temperature was maintained around 0^0C. To this mixture benzyl bromide (25.0 mL) was slowly added in dropwise for about 10-15 min and mixture was stirred at 80^0C for about 6 h. At the end of the reaction, the mixture was transferred over crumbled ice and contents were thoroughly stirred for 10min. The solid formed was thus filtered off and the product was purified by column chromatographic technique. 60 % of yield; ^{1}H NMR (300 MHz, CDCl3): δ 5.20 (s, 2H), 6.17 (s, 1H, C3-H), 6.91–7.08 (d, 1H, C6-H, J = 9 Hz), 7.48-7.58 (m, 5H, Ar-H), 7.98 (d, 1H, C5-H, J = 9 Hz), 10.69 (s, 1H, CHO).

4. Synthesis of 7-benzyloxy-2-oxo-2H-chromene-8-carboxylic acid (6):

Compound **5** (75.0 mmol) was taken in acetone (120.0 mL) to which freshly made Jone's oxidizing agent (25.0 mL) was added drop wise by maintaining 0^{o}C using ice bath for about 20 min in the N_2 atmosphere. The reaction mixture was then steadily stirred using magnetic induced stirrer for 4h at room temp. The advancement of reaction was regularly checked with TLC. Once reaction completed, the quenching of oxidation was carried out using isoproponol (150.0 mL) and consequently mixture was diluted with cold water. The acid product was extracted into EtOAc and the organic layer was washed with sodium bicarbonate solution. The bicarbonate aqueous layer was acidified using hydrochloric acid (2N) to obtain the pH value at 2. The free acid **6** precipitated out was then collected by filtration and used without any further purification. 48 % of yield; ^{1}H NMR (300 MHz, CDCl3): δ 5.20 (s, 2H), 6.17 (s, 1H, C3-H), 6.92–7.09 (d, 1H, C6-H, J = 9 Hz), 7.42-7.48 (m, 5H, Ar-H), 7.96 (d, 1H, C5-H, J = 9 Hz), 10.68 (s, 1H, HCO), 12.89 (s, 1H, COOH).

5. Synthesis of 7-hydroxy-2-oxo-2H-chromene-8-carboxylic acid (7):

A 1-L oven-dried three-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar (3.5 x 1.0 cm), a rubber septum, a glass stopper, and an argon gas inlet is charged with compound (**6**) (40.0 mmol), pentamethylbenzene (120.0 mmol, 3.0 equiv), and anhydrous CH_2Cl_2 (200 mL) After the reaction mixture is cooled to -78 °C (bath temperature), 1 M boron trichloride in CH_2Cl_2 (120.0 mL, 120.0 mmol, 2.0 equiv) is added to the flask drop wise over 10 min at -78 °C. After stirring for 1h at -78 °C, the mixture is quenched by syringe addition of chloroform/methanol and is warmed to Room temperature. The solution is concentrated on a rotavapor under reduced pressure to afford crude product which was purified by silica gel column chromatography to get refined product (**7**). 67 % of yield; ^{1}H NMR (300 MHz, CDCl3): δ 6.18 (s, 1H, C3-H), 6.90 (d, 1H, C6-H, J = 9 Hz), 7.94 (d, 1H, C5-H, J = 9 Hz), 12.78 (s, 1H, COOH), 14.97 (s, 1H, OH).

References:

1. Res Chem Intermed (2015) 41:1115–1133.
2. Duff, J.C.; Bills, E.J. *J. Chem. Soc.*, **1932**, *2* , 1987.
3. *Org. Synth.* **2016**, *93*, 63-74.

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RESEARCH PROJECT COMPLETION CERTIFICATE

This is to certify that, **K.Sreedhar, 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 7-hydroxy-2-oxo-2H-chromene-8-carboxylic acid**" within a stipulated time period and all the chemicals and solvents (worth of INR Twenty Five 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: 15.04.2022

BASR Fine Chemicals Private Limited

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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 7-hydroxy-2-oxo-2H-chromene-8-carboxylic acid**" Reg.

With reference cited above, the Research project entitled -"**Synthetic route optimization of 7-hydroxy-2-oxo-2H-chromene-8-carboxylic acid**" is sanctioned to **K.Sreedhar, 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 7-hydroxy-2-oxo-2H-chromene-8-carboxylic acid.
Estimated Project Value (in INR): 25,000/- (Rs. Twenty Five thousands only-**provided in the Form of Chemicals & Solvents**).
Duration of the Project: 3 months (w.e.f. 18.01.2022).
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: 18.01.2022