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Mild and efficient synthesis of 5, 7-dihydroxy-6-methoxy-2-phenyl-4H-chromen-4-one

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ABSTRACT

Mild and efficient synthesis of 5, 7-dihydroxy-6-methoxy-2-phenyl-4H-chromen-4-one (Oroxylin A) has been reported. MEM is used as protecting group to get Oroxylin A. Screening of protecting groups and solvents system are described in detail. Optimal reaction conditions towards achieving maximum selectivity are discussed. Oroxylin A is characterized by NMR and Mass spectroscopy.

Introduction

Oroxylin A is found in the extract of *Oroxylum indicum*[1], *Colebrookea oppositifolia*[2] and *Gomphrena martiana*[3]. It has medicinal value such as anti gastric ulcer and anti-oxidant properties [4]. 7-OAcyl and glycoside derivative of Oroxylin A has potent anti bacterial and anti gastric ulcer activity [5]. Derivatives of baicalein (*5, 6, 7-trihydroxy-2-phenyl-4H-chromen-4-one*), an intermediate of Oroxylin A also exhibits various activities [6-8]. Selectivity is of crucial importance in the synthesis of Oroxylin A.

The methods for the synthesis of Oroxylin A involve multiple steps including selective protection and deprotection. These methods involve harsh reaction conditions which results in degradation of molecule thereby reducing the yield. Moreover selectivity is not obtained by any of the methods. All the known processes involve column chromatography purification which further decreases the yield probably due to adsorption of Oroxylin A on silica.

Reaction of 3,4,5 trimethoxy phenol with cinnamoyl chloride in BF_3-Ether at reflux condition gave Chalcone, which on oxidative cyclisation with I_2/DMSO give flavone. Further demethylation of flavone in 47 % HBr and glacial acetic acid yield monodemethylated product. This is not matching with naturally occurring Oroxylin A, this indicate that these processes not yielding Oroxylin A [9-10]. This gives possibly isomer of Oroxylin A (Negletein) as major product and not Oroxylin A. Demethylation using Lewis acid is not feasible [11] and reaction with HBr in acetic acid, HCl, H_2SO_4 does not yield Oroxylin A.

Very few reports are available for synthesis of Oroxylin A from Baicalein[12-14]. Method involves selective benzylation of Baicalein. This process gives poor yield of Oroxylin A (6% yield) and involves the use of lachrymator benzyl bromide, which is hazardous to human health and environment. Selectivity for benzylation is less, reaction require further long maintaining in scale up, removal of dibenzylated and unwanted mono benzylated impurities is also not possible by crystallization techniques. Other protecting group like methoxy methyl ether (MOM) is also reported [15], but the process not described in details, yields and reagents are not clearly mentioned with their mole ratio. Process is not reproducible and shows variable selectivity on altering batch size and selectivity is not substantial to yield Oroxylin A.

Thus, after investigating these previous methods of synthesis of Oroxylin A in details and identifying its shortcoming, development of detail synthesis of Oroxylin is needed.

Result and Discussion

To begin with, we worked on the method of benzylation [12-13] as reported, we wish to report the following observations. Selective benzylation depends upon the nature of group attached to benzyl bromide/chloride **(BzX).** Experimental evidence shows that electron withdrawing group on **BzX** facilitate the selectivity **(Table 1, entry 5)** while electron donating group react with all the available phenolic site in baicalein (**Table 1, entry 4**). Benzylation in dry acetone at ambient condition does not provide sufficient activation energy for the completion of reaction while at reflux conditions acetone losses its ability to solvate the phenolic group.

We screened different solvents and good results were obtained with *N, N*-Dimethylformamide which has better coordinating site to solvate phenolic group at ambient condition. Choice of base also plays significant role on selectivity. Use of potassium carbonate leads to formation of unwanted mono and dibenzylated by product **(Table 1, entry 2).** Maximum selectivity of 60 % along with dibenzylated byproduct was obtained with sodium bicarbonate **(Table 1, entry 3).** Though protection using benzoyl chloride gave good selectivity and very less by product, its deprotection is not feasible. Acetyl chloride (**Table 1, entry 7)** shows no selectivity towards C_7 phenolic –OH group and forms diacetylated baicalein as major product. Other commonly used protecting agent such as trityl chloride, tetra hydro pyranyl and pivolyl chloride did not yield result.

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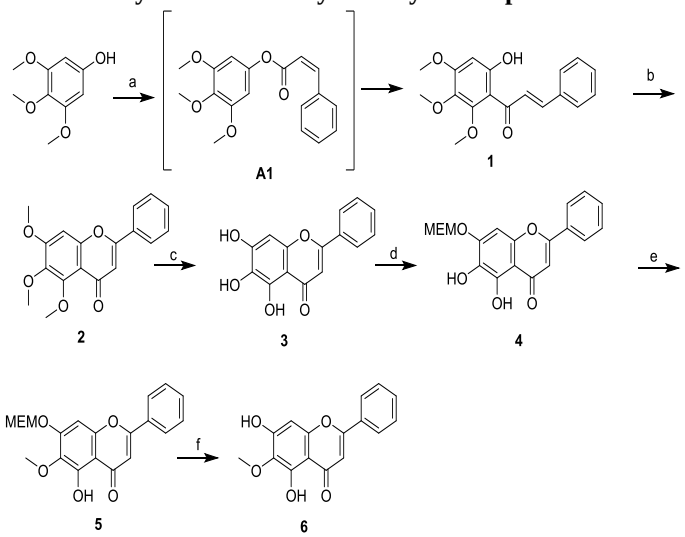
Table 1. Study of selective protection of baicalein.

Sr. no	Protecting agent	Reaction Conditions	% Selectivity	% conversion
1	Benzyl chloride	Acetone/NaI/$NaHCO_3$ Reflux	15	45
2	Benzyl bromide	DMF/NaI/K_2CO_3 /25-30 °C	18	53
3	Benzyl bromide	DMF/NaI/$NaHCO_3$ /25-30 °C	60	70
4	4-Methoxy benzyl chloride	DMF/NaI/$NaHCO_3$ /25-30 °C	20	45
5	4- Nitro benzyl bromide	DMF/NaI/$NaHCO_3$ /25-30 °C	62	80
6	Benzoyl chloride	DMF/NaI/$NaHCO_3$ /25-30 °C	64	67
7	Acetyl chloride	Et_3N /CH_2Cl_2/25-30 °C	02	84
8	Pivolyl chloride	DMF/NaI/$NaHCO_3$ /25-30 °C	00	00
9	Pivolyl chloride	DMF/NaI /Et_3N/25-30 °C	00	00
10	Trityl chloride	DMF/NaI/$NaHCO_3$ /25-30 °C	00	00
11	Tetra hydro pyranyl	PPTS/CH_3CN /25-30 °C	00	00
12	MEM chloride	K_2CO_3/DMF/0-5 °C	94	96

PPTS=Pyridinium para toluene sulphonate, Pr = Protecting group, MEM chloride = Methoxy ethoxy methyl chloride

Scheme caption

Scheme I. Synthesis of Oroxylin A by MEM protection.



Reaction conditions: a) Cinnamoyl chloride, BF_3-etherate; b) I_2/DMSO; c) 47 % HBr; d) MEM=$CH_3OCH_2CH_2OCH_2$-Cl; K_2CO_3, DMF; e) Acetone, hexane, Dimethyl sulphate, K_2CO_3; f) THF, HCl.

In our attempt towards improvisation of these existing approaches, we made use of MEM chloride as protecting group of C_7-OH of baicalein. MEM chloride has advantages over benzyl bromide/chloride as protecting group due to its less hazardous nature. It gave maximum selectivity. Deprotection of MEM group is achieved at ambient condition which is not reported earlier **(Table 1, entry 12)**. We observed that carrying out reaction in DMF and employing potassium carbonate as base at 0-5 °C gave maximum selectivity and conversion (94 % and 96 % respectively). We further noticed that protection of hydroxyl functionality with MEM chloride is highly sensitive towards reaction conditions such as temperature, solvent polarity and concentration of solvent. Utilization of Aliquat-336 catalyst for demethylation of flavone reduces the stoichiometric proportions of HBr whose per mole quantity increases while scale up of the process.

After protection of hydroxyl group of baicalein with MEM chloride at C_7, C_5 and C_6 position hydroxyl group are available for methylation. C_6-OH has to be methylated selectively. Though C_5-OH group is hydrogen bonded with C_4 carbonyl, in solvent system it becomes readily available as free reactive hydroxyl group. In highly polar solvent DMF, there is very less selectivity towards methylation, while in relatively lesser polar solvent acetone 60 % selectivity was obtained. We tried to carry out reaction in different non polar solvent but reaction remained incomplete even after maintaining reaction for long hours under different conditions. To know the effect of the required polarity and solvation on selectivity, we carried out reaction with mixture of different solvent system and best results were obtained with 25 % acetone and 75 % hexane which gave maximum selectivity (93-94 %) of **5.**

We herein investigated in detail the complete synthesis of Oroxylin A and rediscovered the convenient ecofriendly pathway for large scale synthesis of Oroxylin A which replace harsh reaction conditions, give maximum atom economy for each step. As depicted in scheme 2, Baicalein was dissolved in anhydrous acetone and treated with sodium iodide, sodium bicarbonate and benzyl chloride .The mixture was refluxed for 24 h to give 7-benzoyloxy-5,6-dihydroxy flavones **(s)** which was taken in anhydrous acetone and refluxed with potassium carbonate and dimethyl sulphate to give 7-benzoyloxy-6-methoxy-5-hydroxy flavones **(t).** Deprotection of **(t)** was carried out in concentrated HCl and glacial acetic acid at boiling water temperature to give Oroxylin A [12-13].

Experimental

Commercially available solvents, reagents, Aliquat-336(*N*-Methyl-N,N-dioctyloctan-1-ammonium chloride) were used without any further purification. ^1H and ^{13}C NMR Spectra were recorded in $CDCl_3$, DMSO on a Brucker 400 MHz NMR spectrometer. Chemical shift of ^1H spectra are reported in δ PPM downfield from tetramethyl silane. Mass spectra were recorded on Thermo-Finnigan LCQ Advantage of ion trap type. TLC was carried out on TLC silica gel 60 T_{254} of Merck made. Evaporation of solvent was accomplished with Buchi rota evaporator. Drying of organic extract during workup of reaction was performed over anhydrous sodium sulfate.

7-((2-methoxyethoxy) methoxy) 5, 6-dihydroxy-2-phenyl-4H-chromen-4-one (4)

To a stirred solution of **3** (5 g, 18.5 mmol) and DMF (50 mL), potassium carbonate (2.85 g, 20 mmol) was added. After stirring for 15 min, reaction mixture was cooled to 0-5 °C. To this, methoxy ethoxy methyl chloride (2.3 g, 18.5 mmol) in 10 mL DMF was added slowly. After 8 hours, reaction mass

was filtered, DMF was distilled out under vacuum and reaction mass was quenched with 200 mL distilled water. After stirring for 1 hour at 0-5 °C, reaction mass was filtered, washed with 50 mL water to obtain **4.**

Yield: 84 % (5.5g); Anal Calcd. For $C_{19}H_{18}O_7$**:** C, 63.68; H, 5.06; O, 31.25 %. Found: C, 63.61; H, 5.12; O, 31.21 %; ^{1}H-NMR (400 MHz, DMSO-d_6 δ / ppm): 12.57 (1H, *s*), 8.91(1H, *s*), 8.11-8.09(2H, t, *J*=8.04 Hz), 7.62-7.57(3H, *dd*, *J*=8.04 Hz), 7.03(1H, *s*), 7.01(1H, *s*), 5.44-5.42(2H, *s*), 3.88-3.78(2H, m), 3.55-3.49(2H, m); ^{13}C-NMR (100 MHz, DMSO-d_6 δ / ppm): 182.9(-C=O), 164.1(-C), 156.5(-C), 152.9(-C), 152.7(-C), 133.1(-C), 132.6(-C), 131.0(-C), 129.6(-CH), 126.9(-CH), 106.3(-CH), 105.3(-CH), 94.5(-CH), 93.8(-CH), 71.3(-CH), 68.5(-CH), 60.6(-CH_2), 60.4(-CH_2), 58.4(-CH_2); MS (EI) m/z 358 (M^+).

7-((2-methoxyethoxy)methoxy)-5-hydroxy-6-methoxy-2-phenyl-4H-chromen-4-0ne (5)

Acetone (50 mL) and hexane (150 mL) mixture was prepared. To the prepared solvent mixture, 4 (5.5 g, 15 mmol), potassium carbonate (2.3 g, 16 mmol) and dimethyl sulphate (1.93 g, 15 mmol) was added and heated to reflux for 4 hours, filtered and washed with acetone. Solvent was distilled out under vacuum to obtain crystals of **5**.

Yield: 90 % (5.25g); Anal Calcd. For $C_{20}H_{20}O_7$: C, 64.51; H, 5.41; O, 30.08 %. Found: C, 64.46; H, 5.45; O, 30.12 %; ^{1}H-NMR (400 MHz, $CDCl_3$ δ / ppm) 12.75(1H, *s*), 7.93-7.91 (2H, *dd*), 7.58- 7.54(3H, *m*), 6.93 (1H, *s*), 6.70 (1H, *s*), 5.46 (2H, *s*), 3.95 (3H, *s*), 3.94-3.91(2H, m), 3.62-3.60 (2H, *t*), 3.41(3H, *s*); ^{13}C-NMR (100 MHz, $CDCl_3$ δ / ppm): 182.9(-C=O), 164.2(-C), 156.4(-C), 153.4(-C), 152.9(-C), 133.2(-C), 131.9(-C), 131.2(-C), 129.1(-CH), 126.3(-CH), 106.9(-CH), 105.4(-CH), 94.0(-CH), 93.9(-CH), 71.4(-CH_2), 68.3(-CH_2), 60.9(-CH_3), 59(-CH_3); MS (EI) m/z 372 (M^+).

5, 7-dihydroxy-6-methoxy-2-phenyl-4H-chromen-4-one (6)

To a solution of **5** (5.25 g, 14 mmol), THF (52.5 mL) and 11N HCl (5.25 mL) was added. After stirring for 6 hours at ambient temperature, 210 mL distilled water was added to precipitate out **6**, the reaction was stirred for 30 minute, filtered and subsequently recrystallised with 1: 2 ethylacetate:hexane to give **Oroxylin A.**

Yield: 94 % (3.76 g); Anal Calcd. For $C_{16}H_{12}O_5$: C, 67.60; H, 4.25; O, 28.14 %. Found: C, 67.63; H, 4.29; O, 28.19 %; ^{1}H-NMR (400 MHz, DMSO-d_6 δ / ppm) 12.93 (1H, *s*), 10.9 (1H, *s*), 8.07-8.05 (2H, *d*, *J* = 8.0 Hz), 7.61-7.54 (3H, *m*), 6.97 (1H, *s*), 6.64 (1H,*s*), 3.76 (3H, *s*); ^{13}C-NMR (100 MHz, DMSO-d_6 δ / ppm): 182.7(-C=O), 163.7(-C), 158.1(-C), 153.2(-C), 153.0(-C), 153.0(-C), 132.5(-C), 131.9(-C), 131.2(-CH), 129.6(-CH), 126.9(-CH), 126.9(-CH), 105.1(-CH), 104.8(-CH), 94.9(-CH), 60.4(-CH_3); MS (EI) m/z 285 (M^+).

Conclusions

In conclusion we have developed and described a process for synthesis of Oroxylin A using MEM chloride, which gave 94% selectivity as a protecting group. The method is devoid of harsh reaction conditions. The deprotection was achieved at ambient conditions. This convenient and ecofriendly pathway gave good yields of 5, 7-dihydroxy-6-methoxy-2-phenyl-4H-chromen-4-one (Oroxylin A).

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