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# Regioselectivity in Benzylation of Chrysin

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A regioselective monobenzylation of the 7-hydroxyl group of 5,7-dihydroxy flavone (**I**) under extremely mild basic conditions (anhydrous $NaHCO_3$) and polar solvent ($CH_3CN$) has been developed. The selective debenzylation of 5,7-*bis* benzyloxy flavone (**III**) to obtain 7-benzyloxy-5-hydroxy flavone (**II**) is also reported.

**Key Words: Regioselectivity, Benzylation, 5,7-*Bis* benzyloxy flavone, 7-Benzyloxy,5-hydroxy flavone.**

## INTRODUCTION

Protection and deprotection are the common practices in multistep synthesis allowing the reaction in one functionality at the cost of another[1]. Among various groups of phytochemicals, hydroxy flavones and flavonolignans have been reported to possess several pharmacological activities[2,3] such as anticancer, antitumor, antiinflammation, antiageing, antioxidants, *etc*. Several flavones *e.g.* chrysin, baicalein, wogonin, oroxylin-A *etc*. also show inhibitory activities[4] against iNOS, COX-2 and PGE2 productions.

In ongoing program on the synthesis of naturally occurring flavonolignans[5], it is needed a selectivity in the benzylation of chrysin (5,7- dihydroxy flavone) (**I**). The aim was to benzylate at the 7-position of the flavone and debenzylate it at the appropriate stage. 7-Benzyloxy chrysin (**II**) is an important substrate for many reactions in flavonoid chemistry[2] as well as natural product synthesis[3]. The available literature methods[4,6-8] for (**II**) include either $K_2CO_3$/>=O system (where no product composition or detailed work up processes and yield are mentioned) or $K_2CO_3$/DMF/TBAB system where microwave is used and the product was purified by column chromatography. Hence, it is decided to investigate an easiest, mild and convenient procedure for the mono benzylation of chrysin.

## EXPERIMENTAL

Benzyl chloride was obtained from BDH chemicals and used without further purification. Chrysin was prepared from phloroacetophenone by a little modification of Baker-Venkataraman rearrangement[9]. Potassium carbonate was obtained from Qualigen chemicals, ignited for 6 h and cooled in desiccator prior to use. Sodium bicarbonate (Speckpure chemicals) was dried in desiccator ($CaCl_2$) for 24 h before

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use. Acetone (SD Fine Chemicals) was refluxed in the presence of $KMnO_4$ till the permanganate colour sustained, distilled and stored over anhydrous $K_2CO_3$ for 15 d with intermittent shaking before use. Acetonitrile (Merck) was stored over $CaCl_2$ and distilled over $P_2O_5$ prior to use. Benzene and ethyl acetate (SD Fine Chemicals) were used as such.

IR spectra were recorded on Perkin-Elmer spectrum 2000 infrared spectrophotometer. $^1H$ NMR spectra were recorded on Varian-60 spectrophotometer. EI mass spectra were taken on Jeol JMS-DX 303 mass spectrophotometer.

**Benzylation of chrysin by $K_2CO_3$/acetone system (Run 2):** Chrysin (2.3 g, 0.009 mol), benzyl chloride (1.26 g, 0.0099 mol), freshly ignited and cooled $K_2CO_3$ (6.25 g, 0.0452 mol), dry acetone (200 mL) and a catalytic amount of NaI (0.12 g) were refluxed for 4 h. The reaction mixture was cooled to room temperature and the acetone portion after filtration was concentrated to give a reddish brown solid which was chromatographed on a silica gel column eluting with benzene. The initial fractions gave a viscous liquid which solidified later melting at 177 ºC (lit.[10] m.p. 177-178 ºC) and was characterized to be 7-O-benzyl chrysin (**II**) (1.00 g, 33 %). It gave a positive $FeCl_3$ test.

IR (KBr, $\nu_{max}$):1058, 1595, 1645, 3450 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, $\delta$): 5.2 (S, 2H, $-CH_2$-Ph), 6.6 (S, 1H, H-6), 6.7 (S, 1H, H-8), 6.8 (s, 1H, H-3), 7.5 (m, 8H, H-3', H-4', H-5' and $-CH_2$-Ph), 8.0 (m, 2H, H-2' and H-6'), 12.5 (S, 1H, -OH). EIMS (m/z, R.A.): 344 ($M^+$, 11.0), 209 (11.4), 119 (14.6), 105 (15.4), 91 (35.2), 84 (10.6), 77 (15.3), 65 (4.3), 40 (100), 49 (11.7).

The later fractions gave a white solid melting at 165 ºC (lit.[10] m.p. 165-167 ºC) and giving a bluish fluorescence on UV light (1.4 g, 36 %). It was characterized to be 5,7-O,O'-bisbenzyl chrysin (**III**).

IR (KBr, $\nu_{max}$):1055, 1596, 1646 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, $\delta$): 5.2 (S, 2H, 5-$OCH_2$-Ph), 5.3 (S, 2H, 7-$OCH_2$-Ph) 6.65 (S, 1H, H-6), 6.75 (S, 1H, H-8), 6.8 (s, 1H, H-3), 7.5 (m, 13H, H-3', H-4', H-5' and 2 × $CH_2$-Ph), 8.1 (m, 2H, H-2' and H-6'). EIMS (m/z, R.A.): 433($M^+$-1, 11.0), 432 ($M^+$-2, 5.1), 403 (4.9), 129 (5.2), 105 (23.8), 91(100.0).

The above data are in agreement with the data given in literature[10].

**Benzylation of chrysin by $NaHCO_3$/$CH_3CN$ system (Run 9):** In a 100 mL flask, chrysin (**I**, 2.3 g, 0.0090 mol), benzyl chloride (1.26 g, 0.0099 mol), anhydrous $NaHCO_3$ (3.8 g, 0.0452 mol) were refluxed in 50 mL dry acetonitrile for 20 h. The reaction mixture was filtered with hot acetone washings and the filtrate was evaporated to dryness at 50 ºC under reduced pressure to give a brownish viscous mass (2.86 g, 92 %) which solidified later. It was matched in all the properties of (**II**) and there was no starting material (**I**) or bisbenzyl product (**III**) at all as checked by TLC, $^1H$ NMR and mass spectra.

**Debenzylation of (III) to (II):** In a 100 mL dry round bottom flask, anhydrous $AlCl_3$ (1.00 g, 0.0074 mol) was stirred with 30 mL of dry acetonitrile for 15 min during which the yellow colour was disappeared and the reaction mixture became whitish. Dibenzyl chrysin (**III**, 1.40 g, 0.0032 mol) dissolved in in 20 mL of acetonitrile was added. The reaction mixture again became yellowish and it was refluxed for 4 h. After acetonitrile was evaporated completely, crushed ice (20.0 g) was added to the flask and kept on ice bath. To this mixture conc. HCl (10 mL) was added slowly. The sticked solid was macerated thoroughly which was filtered at the pump and dried to give a bright yellow coloured solid (2.40 g). The crude solid was dissolved in EtOAc (50 mL) whish was extracted with cold conc. HCl (20 mL), washed thoroughly with water (3 mL × 20 mL) and dried over anhydrous $Na_2SO_4$. The EtOAc was evaporated completely at 50 ºC under reduced pressure to give a sticky mass which solidified later (1 g, 90 %). Its physical and spectral data was in agreement with the data of 7-O-benzyl chrysin (**II**).

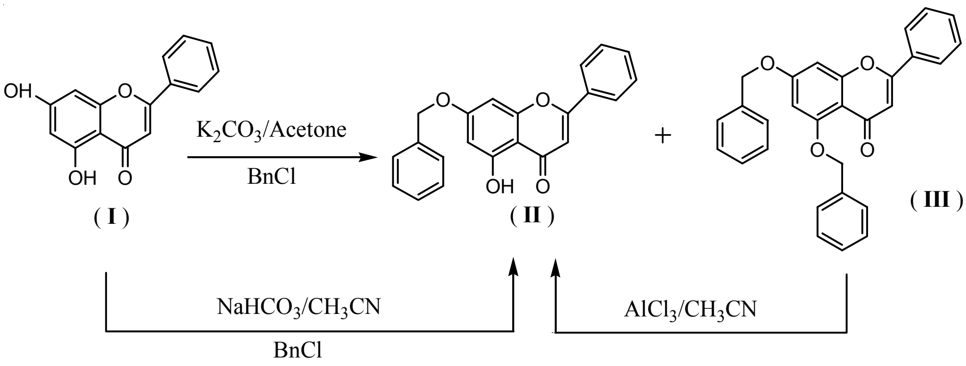
## RESULTS AND DISCUSSION

All the reactions attempted (run 1 to run 9), reagents used, conditions and results are listed in Table-1.

TABLE-1
BENZYLATION OF CHRYSIN

| Run | Reagent | Molar ratio | Solvent | Reflux time (h) | Observations |
|---|---|---|---|---|---|
| 1 | $K_2CO_3$ (Cat. NaI) | 1:5 | >=O | 4 | The progress of the reaction was monitored hourly by TLC. Up to 3 h presence of **I** was detected along with **II** & **III.** Reaction was completed after 4 h yielding **II** & **III.** |
| 2 | Run 1 was repeated to check the reproducibility of result | | | 4 | Reaction was completed after 4 h yielding **II (33 %)** & **III (36 %).** |
| 3 | $NaHCO_3$ | 1:1.2 | >=O | 48 | The progress of the reaction was monitored 6 hourly by TLC. After 48 h, mostly **I** was present with little % of **II.** |
| 4 | $NaHCO_3$ (Cat. NaI) | 1:1.2 | >=O | 48 | Same observation as run 3, but **III** was also present along with unreacted **I** & **II.** |
| 5 | $NaHCO_3$ | 1:5 | >=O | 48 | Same observations as run 3.No **III** was present. |
| 6 | $NaHCO_3$ | 1:10 | >=O | 48 | Same observations as run 3.No **III** was present. |
| 7 | $K_2CO_3$ | 1:5 | >=O | 48 | Same observations as run 3.No **III** was present. |
| 8 | $NaHCO_3$ | 1:1.2 | $CH_3CN$ | 24 | The progress of the reaction was monitored 6 hourly by TLC. Up to 18 h presence of **I** was detected along with **II.** After 24 h **I** was finished and only **II** present. Yield 91% |
| 9 | $NaHCO_3$ | 1:5 | $CH_3CN$ | 20 | The progress of the reaction was monitored 6 hourly by TLC. Up to 12 h presence of **I** was detected along with **II.** After 20h **I** was finished and only **II** present. Yield 92% |
| 10 | $NaHCO_3$ | 1:10 | $CH_3CN$ | 18 | The progress of the reaction was monitored 6 hourly by TLC. With the progress of time, % of **I** went on decreasing and % of **II** went on increasing till 18h after which only **II** present. Yield 92% |

Firstly, the traditional method of refluxing the substrate and benzyl chloride was tried with acetone in the presence of anhydrous $K_2CO_3$ and a catalytic amount of NaI (run 1 and run 2). The course of the reaction was hourly monitored by TLC (eluant = benzene: EtOAc, 95:5, v/v) which showed the completeness of the reaction after 4 h giving 2 products which were identified to be monobenzyl chrysin (**II**) and dibenzyl chrysin (**III**) after purification (**Scheme-I**).



**Scheme-I**

Since $K_2CO_3$ is a stronger base, it favoured dibenzylation in acetone medium as seen from the Table-1 (run 1 and run 2). Hence we took a little more than 1 mole (1.2 mole equivalent than the substrate) of anhydrous $NaHCO_3$ and refluxed in dry acetone monitoring after every 6 h (run 3), but we got mostly the starting material along with a little % of mono product even after 48 h reflux. Then repeated the same reaction in the presence of NaI, thinking it could accelerate the reaction (run 4), but surprisingly after 8 h reflux TLC showed the presence of (**III**) along with (**II**) and unreacted (**I**).The status of the reaction was same even after 24 h. As the addition of NaI enhanced the bisbenzyl product formation, run 3 was repeated with increased amount of $NaHCO_3$. 5 and 10 mole equivalents of $NaHCO_3$ were employed in run 5 and run 6, respectively, but the starting flavone was not finished even after 48 h reflux although we got (**II**) only and not (**III**) in both the cases.

From all the experiments above, it is concluded that NaI favours *bis*benzylation and $NaHCO_3$ in acetone was not able to complete the reaction. So anhydrous $K_2CO_3$ (5 mole eqv) was taken in dry acetone (run 7) and monitored the progress. Although there was only monobenzyl product, starting material was not finished even after 48 h reflux. Therefore, it is decided to change the solvent and benzylated chrysin (**I**) in acetonitrile in the presence of $NaHCO_3$ (1.2 mol eqv) (run 8). Until 18 h there was only monobenzyl chrysin along with unreacted starting material and surprisingly after 24 h the reaction was completed showing the absence of starting material in TLC and we got pure (**II**) in 91 % yield after work up.

Hence, the $NaHCO_3/CH_3CN$ is the best system for achieving regioselective monobenzylation. To reduce the time as in run 8, we increased the quantity (5 mole eqv) of $NaHCO_3$ (run 9) and found that the reaction was complete in 20 h giving exclusively the mono benzyl product. Increasing the amount of $NaHCO_3$ (10 mole eqv, run 10) did not reduce the reaction time significantly. Therefore, this (run 9) is a very simple and easiest method for achieving regioselective 7-benzyloxy chrysin from chrysin.

To confirm the product structures, the *bis*benzyl chrysin (**III**) obtained from run 2 was refluxed with dry $CH_3CN$ and anhydrous $AlCl_3$ to get exclusively 7-benzyloxy chrysin (**II**) in 93 % yield (**Scheme-I**).

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