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R E S E A R C H A R T I C L E

Highly Efficient Green Synthesis and Characterization of 6-Amino Flavonones by Microwave Irradiation and Their Possible Activities

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A B S T R A C T

In today's world of competitive research it is necessary to develop newer and greener methodologies in the field of organic synthesis. Microwave serves as an efficient tool in research studies which makes the reactions cheap, solvent free, and economic in terms of time and energy. Flavonoids are explored and have potential anti-cancer, anti-tubercular, anti-malarial, anti –inflammatory, Antioxidant, anti-infective, antiviral activities etc., because of the prescence of the chromone pharmacophore. We have developed a four steps new methodology for the synthesis of 6-amino flavanones. We started with paracetamol which was acetylated and then condensed with an aldehyde to give chalcone. Further it was converted to 6 acetamino flavanone. The acetamino group was converted to amino group to give 6 amino flavanones.

Keywords: green methodology, microwave assisted synthesis, flavonoids, amino flavanones.

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C O N T E N T S

1. Introduction

In recent years there is increasing research on the development of greener methods of organic synthesis using Microwave oven [1], which are cleaner, greener, more efficient, less time consuming and solvent free when

compared to the conventional methods of organic synthesis. Naturally Flavonoids consists of polyphenolic moiety having a benzo-γ-pyrone structure and are abundantly present in plants as secondary metabolites. They are biosynthesized by phenyl propanoid pathway. Flavonoids [2] (bioflavonoids) is derived from latin word flavus meaning yellow, the natural colour and are derivatives of plant and fungus secondary metabolites. Chemically, they have the general structure [3] of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and heterocyclic ring (c). The ring A has phloroglucinol resemblance. According to the IUPAC nomenclature, they can be classified into:

- Flavonoids and bioflavonoids
- Isoflavonoids, derivatives of 3-phenyl chromen-4-one (3-phenul-1,4- benzopyrone) structure.
- Neoflavonoids, derivatives of 4- phenyl coumarine (4-phenyl-1,2- bnzopyrone) structure.

The above three classes are all ketone containing compounds and are referred as anthoxanthins or bioflavonoids (flavones and flavonols). They are polyhydroxy polyphenol compounds and are commonly called as flavonoids. With respect to the nature of defense and communication patterns adopted during evolution, flavonoids are one of the most important chemical classes of natural products. These flavonoids are synthesized by plants in response to infection by microbes [4]. Flavonoids occur mostly in plants as glycosylated derivatives and they contribute to the bright shades of blue, scarlet, yellow and orange in leaves, flowers and fruits. Apart from vegetables and fruits, flavonoids are also found in seeds, nuts, grains and various medicinal plants as well as in beverages such as wine, tea and also in beer. Above 8000 different naturally occurring flavonoids can be classified in various classes and differ in the level of oxid-ation of the c- ring of the benzo-γ-pyrone structure. Flavonoids have antioxidant activity which is shown both invivo and invitro [5, 6]. Also flavonoids have possible beneficial effects like anticancer [7], cardioprotective, antiinfective and antiaging.

2. Materials and Methods

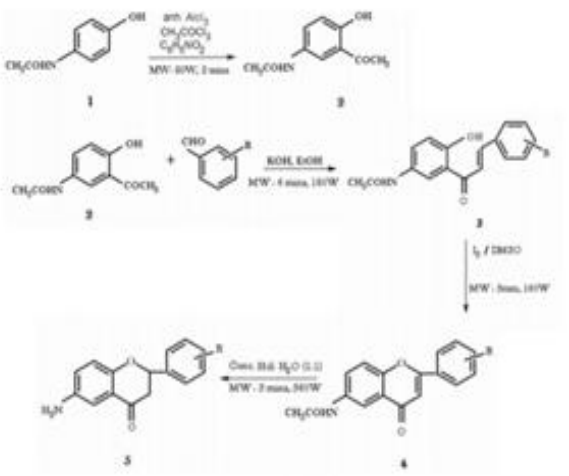
All the chemicals and reagents used are purchased from sigma aldrich and acquired from standard chemicals, Hyderabad. The melting points were determined by oil bath using thermometer and uncorrected. IR studies were done using bruker FTIR. The 1HNMR studies were done using CDCl3 on bruker and their chemical shifts were observed in ppm with tetra methyl silane(TMS) as internal standard. The progress of reaction was recorded by TLC using precoated aluminium silica gel plates. The spotting and solvent front was visualized in uv chamber or by exposure to iodine vapours.

General Procedure:

In the present investigation, it has been considered worthwhile to synthesize few 6-amino flavanone derivatives by novel microwave enhanced method with raw paracetamol as starting material. The conventional method of synthesis of 6 amino flavanones8 uses four steps and the time needed for completion of various derivatives is massive. The greener microwave method [9,10] developed utilizes lesser time.

Synthesis of 6-Aminoflavones:

The below scheme-1 was developed to synthesise 5(a-f) compounds by microwave method.



Scheme - I for the synthesis of 6-amino flavanones by Microwave assisted method

Compound Codes

Compound code	R
5a	H
5b	NO_2
5c	OCH_3
5d	Cl
5e	$C_6H_4NO_2$
5f	OC_2H_5

The present methodology has 4 steps.

Step-1 Synthesis of 5'-acetamido-2'-Hydroxy acetophenone from Paracetamol:

To a suspension of paracetamol(0.066 mol) and anhydrous aluminium chloride (0.016 mol) in nitrobenzene (10mL) was gradually added acetoyl chloride (0.066 mol) over a period of 0.5 hr. The reaction mixture was kept aside and then microwave irradiated for 30 seconds(3times) at 80 watts. After cooling, it was added to a mixture of crushed ice and 30 ml conc. HCl and stirred. It was then filtered, washed with water and then with toluene. It was recrystallized using isopropanol.

Step-2 Synthesis of 5'-Acetamido-2'-Hydroxychalcones:

Equimolar quantities (0.01 mol) of of 5'-acetamido-2'-Hydroxyacetophenone and respective aldehydes (0.001 mol) were mixed and dissolved in minimum amount (3 mL) of alcohol. To this, aqueous potassium hydroxide solution (0.003mol) was added slowly and mixed. The entire reaction mixture was microwave irradiated for about 6 minutes at 180 watts and then poured on crushed ice and acidified with 5 N HCl. The solid separated is filtered and recrystallised using ethanol.

Step-3 Synthesis of 6-Acetamidoflavones:

To 5'-Acetamido -2'-Hydroxychalcone in a flask was added catalytic amount of Iodine and 5 ml of Dimethyl Sulfoxide. The mixture was microwave irradiated for about

3 min at 360 watts and then poured on crushed ice. The excess amount of Iodine was removed using sodium thiosulphate (10%) and then filtered and crystallised using methanol.

Step-4 Synthesis of 6-Aminoflavones:

To 5'-Acetamido-2'-Hydroxychalcone in 5 ml ethanol was added a small amount of silica gel moistened with few drops of conc HCl. This was microwave irradiated for 4 minutes to get a fruity aroma 6 aminoflavanone. The product was then added to crushed ice, filtered and dried nd recrystallized using ethanol.

3. Results and Discussion

Spectral data

5a) 6-Amino-2-phenyl-4H-chromen-4-one:

IR data:1647(C=O flavones), 3250(NH_2 symstr), 3024(NH_2 asymstr), 1195 (C-N str), 3100(CH strAr); ^{1}HNMR data ($CDCl_3$) 5.4(s,2H, NH_2 at C6), 6.5(s,1H,3H),7.82(m,2H,4H)

5b) 6-Amino-2-(3'-nitrophenyl)-4H-chromen-4-one:

IR data: 1608(C=O str. flavones), 3332(NH2symstr), 3402 (NH2asymstr), 1132 (C-Nstr), 3069(CH strAr); ^{1}HNMR data ($CDCl_3$) 5.50(s,2H,NH_2 at C6), 7.02(s,3H), 7.08 (dd,1H), 7.48(d,1H)

5c) 6-Amino-2-(3'-methoxy)phenyl-4H-chromen-4-one:

IR data: 1612(C=O str. flavones), 3330(NH2symstr), 3402(NH2 asymstr), 1138 (C-N str), 3070(CH strAr); ^{1}HNMR data ($CDCl_3$) 5.4(s,2H, NH_2 at C6), 6.5(s,1H,3H),7.82(m,2H,4H)

5d) 6-Amino-2-(4'chlorophenyl)-4H-chromen-4-one:

IR data: 1608(C=O str. flavones), 3332(NH2symstr), 3402(NH2asymstr), 1132 (C-N str), 3069(CH strAr)); ^{1}HNMR data ($CDCl_3$) 5.4(s,2H, NH_2 at C6), 6.5(s,1H,3H),7.82(m,2H,4H)

4. Conclusion

Thus microwave synthesis of 6 amino flavanones is found to be undoubtedly more economic, efficient, eco-friendly and convenient than conventional reported method. Also the equipment is cheap, and reagents required are cleaner, cheaper and easily available. The reaction conditions are very simple and also yield of products are quite good. Structural features and literature review suggest potential pharmacological activites like anti-cancer, antitubercular, anti-inflammatory, antioxidant and antiproliferative activity.

Table 1: Physical data for the compounds synthesized

Compound code	Compound name	Molecular weight	M.P	% yield	Time (min)
5a	6-Amino-2-phenyl-4H-chromen-4-one	237	174	75	4
5b	6-Amino-2-(3'-nitrophenyl)-4H-chromen-4-one	289	181	70	3
5c	6-Amino-2-(3'-methoxy)phenyl-4H-chromen-4-one	261	153	82	1.5
5d	6-Amino-2-(4'chlorophenyl)-4H-chromen-4-one	271	158	80	1
5e	6-Amino-2-(3'-nitrophenyl)-4H-chromen-4-one	298	181	76	1.5
5f	6-Amino-2-(4-ethoxy)-4H-chromen-4-one	281	176	82	2

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