MICROWAVE-ASSITED SYNTHESIS OF COUMARIN DERIVATIVES

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ABSTRACT

Some coumarin derivatives possess high biological activities, such as antispasmodic effects, dilating the coronary arteries, anticoagulants, psoriasis treatment, and antibacterial, antifungal and anti-inflammatory activity. Some derivatives also exert inhibitory effect on HIV. In this study, we performed a microwave- assisted solvent-free synthesis of coumarins from using conjugate nucleophilic reactions with various amines and achieved 55-70% efficiency. Th products synthesized exhibit antibacterial and antifungal activity.

Keywords: Coumarin, synthesis, antibacterial and antifungal activity.

Tổng hợp một số dẫn xuất coumarin bằng phương pháp sử dụng lò vi sóng

TÓM TẮT

Một số dẫn xuất của coumarin có hoạt tính sinh học cao, như tác dụng chống co thắt, làm giãn nở động mạch vành, chống đông máu, chữa bệnh vẩy nến, kháng khuẩn, chống nấm, chống viêm,... một số có tác dụng ức chế HIV.Trong nghiên cứu này chúng tôi thực hiện việc tổng hợp một số dẫn xuất coumarin theo phương pháp không dung môi trong lò vi sóng bằng phản ứng cộng hợp nucleophin với các amin khác nhau, cho hiệu suất đạt từ 55-70%. Các sản phẩm coumarin cũng đã được khảo sát hoạt tính sinh học, kết quả cho thấy các sản phẩm tổng hợp được đều có tính kháng khuẩn, chống nấm cao.

Từ khóa: Coumarin, tổng hợp, kháng khuẩn, kháng nấm

1. INTRODUCTION

Coumarins are an important group of organic compounds that are used as additives to food and cosmetics. They have high biological, antifungal and anti-inflammatory activities, optical brightening agents and dispersed fluorescence and laser dyes (Deniz *et al.* (2014), Zaheer-ul-Haq *et al.* (2008)). The derivatives of coumarin usually occur as secondary metabolites present in seeds, roots and leaves of many plant species. Their function is far from clear, though suggestions include waste products, plant growth regulators, fungistats and bacteriostats (Deniz *et al.*, 2014; Moussaoui *et al.*, 2007; Bayer *et al.,* 1982; Mahesh *et al.*, 2016; Fatunsin, 2010). It is, therefore, of utmost importance that the synthesis of coumarin and its derivatives should be achieved by a simple and effective method. Coumarins can be synthesised by methods such as Claisen rearrangement, Perkin reaction and Pechmann reaction as well as Knoevenagel condensation.

It was recently shown that the Pechman reaction could be quickly achieved using microwave irradiation of the reagents in a household microwave oven. For reasons of economy and pollution, solvent-free methods are of great interest in order to modernize classical procedures making them cleaner, safer

and easier to perform. These methodologies can more over be improved to take advantage of microwave activation as a beneficial alternative to conventional heating under safe and efficient conditions with large enhancements in yields and saving in time.

In the present study, we report the synthesis of coumarins using microwave oven and the evaluation of their biological activity.

2. MATERIALS AND METHODS

2.1. Materials

All reagents and solvents used were obtained from the supplier (Merck, Germany). The melting points of the products were determined by open capillary method. The FTIR-spectra were recorded on Magna 760 FT-IR Spectrometer (NICOLET, USA) in the mixture with KBr and using reflex-measured method. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Avance DRX 500 Bruker, Germany (500.13 MHz and 125,76 MHz, respectively) spectrometer in DMSO-d6, and the chemical shifts (δ) are given in ppm relative to the signal for TMS as internal standard. The homogeneity of the compounds was determined by thin layer chromatography (TLC) on silica gel plate 60 F_{254} No. 5715 ((Merck, Germany) using eluent benzene: acetone (9:1). The migrated compounds were visualized by dragendorff reagent. The physical data of all these compounds are summarized in Table 1.

2.2. General procedures for the preparation of compounds

2.2.1. Synthesis of 3-acetyl-6-substituted-2H-chromen-2-one (3): general procedure

A mixture of 5-substituted salicylaldehyde (1) (0.1 mol) and ethylacetoacetate (0.11 mol) was taken in a conical flask, stirred and cooled. To this mixture, 0,5 ml of piperidine was added with shaking. The mixture was then maintained at freezing temperature for 2 to 3 h, and then a yellow coloured solid mass was separated out. The lumps were broken in cold ethanol and filtered. The solid was washed with cold ethanol and dried which gave satisfactory yields. The products were recrystallized from ethanol to give pure compounds (3a-c). These products have melting point (Mp) 115-117ºC, IR (KBr, cm-1): 1732.8 and 1670.1 (C=O), 1550.66 (C=C); 1210.3 (aryl ether, C-O-C)^{1}HNMR (DMSO-d_6, δ, ppm): 2.58 (s, 3H, CH3), 8,07 (s, 1H, CH), 7.49-8,07 (aromatic proton)

2.2.2. Synthesis of compounds (4a-4f): general procedure

3-Acetyl-6-substituted-2*H*-chromen-2-one (3) (2.5mmol) and amines (2) (5 mmol) were thoroughly mixed without solvent in an MW tube and irradiated by using the MW program as follows: power: 120 W; hold time: 3-5 minutes; and temperature: 100°C. After completion of the reaction, the mixture was treated with water (10 ml), and the precipitate was washed with water (50 ml), then with diisopropyl ethanol/toluene (30 mL) and dried to yield pure chromenes (4a-f)

Synthesis 3-[(1-Naphthylimino) ethyl]- 2H-chromen-2-one (4a)

From compound (3a) and α-aphthylamine to form 3-[(1-Naphthylimino) ethyl]- 2H-chromen-2-one (4a). It has some characteristic: IR (KBr, cm^{-1}): 1750.15(C=O), 1656.55 (C=N), 1575 (C=C), 1203 (C-O-C). ^{1}HNMR (DMSO-d_6, δ, ppm):8.6 (s, 1H, CH), 7.4-7.9 (m, 11H, aromatic proton), 2.59 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, δ, ppm): 30.0, 116.0, 118.1, 124.4, 124.8, 130.7, 134.4, 146.9, 154.4, 158.34, 195.0

Synthesis 3-[(Phenylimino) ethyl]- 2H-chromen-2-one (4b)

From compound (3a) and phenylamine to form 3-[(Phenylimino) ethyl]- 2H-chromen-2-one (4b). It has some characteristic: IR (KBr, cm^{-1}): 1740 (C=O), 1596 (C=N), 1475 (C=C), 1103 (C-O-C).). ^{1}H NMR (DMSO-d_6, δ, ppm):8.5(s, 1H, CH), 7.6 - 7.9 (m, 9H, aromatic proton), 2.54 (s, 3H, CH_3).).^{13}C NMR (DMSO-d_6, δ, ppm): 159,1 (C=O); 175,6(C=N); 153,5 (C-O); 136,1 (C-N); 116,1-132,7 (aromatic carbons); 19,5 (CH_3).

Synthesis 6- Chloro -3-[(phenylimino) ethyl]- 2H-chromen-2-one (4c)

From compound (3b) with phenylamine to form 6- Chloro -3-[(phenylimino) ethyl]- 2H-chromen-2-one (4c). It has some characteristic. IR (KBr, cm^{-1}): IR (KBr, cm^{-1}): 1742 (C=O), 1675.02 (C=N), 1556 (C=C), 1201.(C-O-C).). ^{1}H NMR (DMSO-d_6, δ, ppm):8.21 (s, 1H, H4), 7.53-7.46 (m, 7H, aromatic proton), 2,52 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, δ, ppm): 159,3 (C=O); 182,1(C=N); 151,5 (C-O); 136,2 (C-N); 113,4-132,9 (aromatic carbons); 19,5 (CH_3).

Synthesis 6- chloro -3-[(α -naphthylimino)) ethyl]- 2H-chromen-2-one (4d)

From compound (3b) and α –naphthylamine to form 6- chloro -3-[(α -naphthylimino)) ethyl]- 2H-chromen-2-one (4d). It has some characteristic: IR (KBr, cm^{-1}): 1742 (C=O), 1645 (C=N), 1553 (C=C), 1169 (C-O-C). ^{1}H NMR (DMSO-d_6, δ, ppm):8.31 (s, 1H, H4), 7.43-7.88 (m, 9H, aromatic proton), 2.47 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, δ, ppm): 159,3 (C=O); 182,1(C=N); 151,5 (C-O); 136,2 (C-N); 113,4-132,9 (aromatic carbons); 19,5 (CH_3).

Synthesis 6- Bromo -3-[(phenylimino) ethyl]- 2H-chromen-2-one (4e)

From compound (3c) with phenylamine to form 6- Bromo -3-[(phenylimino) ethyl]- 2H-chromen-2-one (4e). It has some characteristic IR (KBr, cm^{-1}): IR (KBr, cm^{-1}): 1752 (C=O), 1663 (C=N), 1523,69 (C=C), 1211 (C-O-C). ^{1}H NMR (DMSO-d_6, δ, ppm):8.22 (s, 1H, H4), 7.33-7.65 (m, 7H, aromatic proton), 2.52 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, δ, ppm): 159,5 (C=O); 179,1(C=N); 152,5 (C-O); 136,0 (C-N); 113,4-134,3 (aromatic carbons); 19,7 (CH_3)

Synthesis 6- Bromo-3-[(α -naphthylimino)) ethyl]- 2H-chromen-2-one (4f):

From compound (3c) with α-naphthylamine. to form 6- Bromo-3-[(α -naphthylimino)) ethyl]- 2H-chromen-2-one (4f):. It has some characteristic IR (KBr, cm^{-1}): 1734.52 (C=O), 1675.30 (C=N), 1545,59 (C=C), 1159.25 (C-O-C). ^{1}HNMR (DMSO-d_6, δ, ppm):8.61 (s, 1H, H4), 7.43-7.67 (m, 9H, aromatic proton), 2.35 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, δ, ppm): 159,6 (C=O); 189,5(C=N); 152,5 (C-O); 147,7 (C-N); 115,1-139,4 (aromatic carbons); 19,7 (CH_3)

3. RESULTS AND DISCUSSION

The derivatives of coumarins (4) could be easily synthesized by the nucleophilic addition of corresponding amine compounds (2) on 3-acetyl-6-substituted-2*H*-chrome-2-one (3). We performed this reaction by microwave- assisted solvent-free method, for several minutes. Reaction yields were quite high (55-70%). All coumarins obtained are soluble in common organic solvents (such as ethanol, toluene, benzene, DMF,…) but insoluble in water. Their structure have been confirmed by spectroscopic data (such as IR-, 1H-NMR- and ^{13}C-NMR-spectra). The proposed mechanism for the formation of 4a-f:

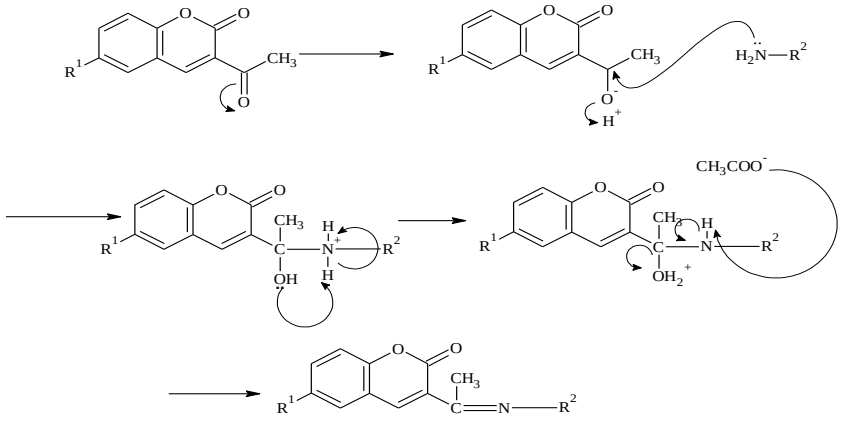


Figure 1. The proposed mechanism for the formation of coumarins

The IR spectra of coumarins 4a-f, the stretching absorption band of C=O linkage was observed at 1734-1752 cm-1. Absorption bands at regions of 1543-1575 cm^{-1} and 1159-1210 cm^{-1} were characterized for stretching vibration of C=C double bond and C-O-C groups, respectively. In addition, absorption band appeared at 1643-1675 indicating the presence of C=N functional group in the synthesized coumarins. ^{1}H-NMR spectra showed resonance signals which were specified for protons H_4 are in region δ=δ8,21-8,65 ppm (singlet). Some resonance signals were in region δ=7.435-7.962 ppm belonging to aromatic protons. Protons in CH_3 had some resonance peaks with chemical shifts from 2,49 ppm to 2,58 ppm (Figure 1). ^{13}C-NMR spectra showed four-parted regions. The magnetic resonance signals of the carbonyl bonds C=O appeared in the down-field regions at δ195.02ppm. In addition, there were some resonance peaks in up-field region at δ 29.92 - 39.99 ppm indicating the presence of methyl groups and δ 146. 93-158.34 ppm belonging to C=C aromatic carbon-13.

Compounds (4a-f) were screened for their antibacterial and antifungal activities against *E. coli, S. aureus* and *Candida albicans* by the disc diffusion method (Table 2). Almost all compounds 4 had remarkable biological activity at 150μg/ml concentration. Compounds (4a) showed highest antibacterial and antifungal activity. Coumarins (4a-c) have significant biological activities against *S. aureus* concentration of 100μg/ml. Except compound 4d, 4f which exhibited no antifungal activity against *S. aureus*. All coumarins 4 have no biological activities against *E. coli*, *S. aureus*, and *C. albicans* at 100 μg/ml concentration.

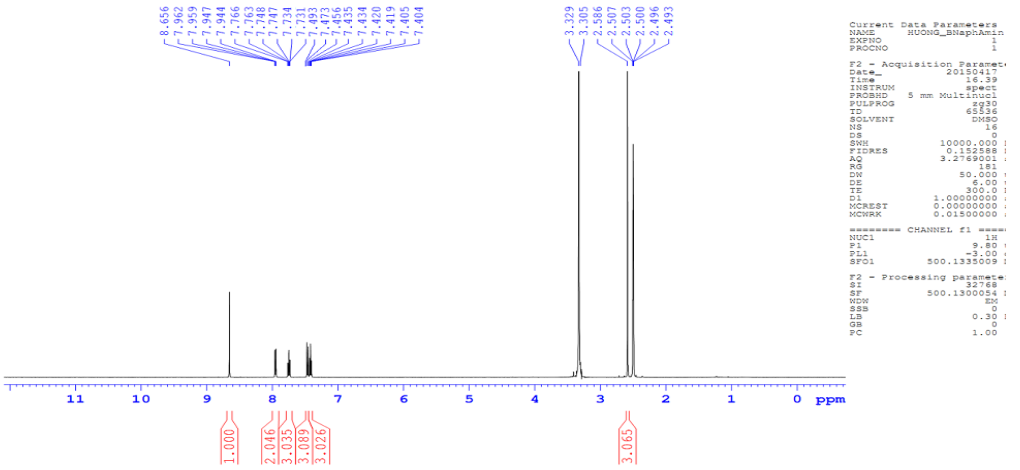


Figure 2. ^{1}H-NMR spectra of 3-[(α-naphthylimino) ethyl]- 2*H*-chromen-2-one (4a)

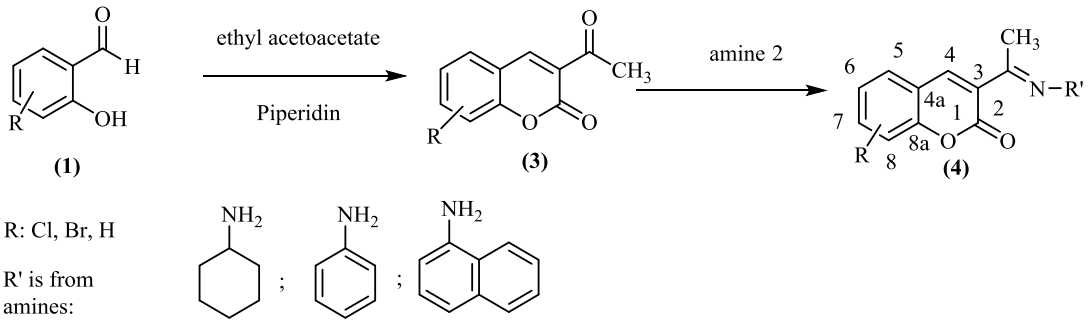


Figure 3. Summary diagram for the synthesis of coumarins

Table 1. Physical parameters of compounds 4(a-f)

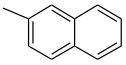
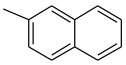
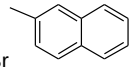
Compound	R^1	R^2	Yield (%)	Mt (^oC)
4a	-H		58	230-233
4b	-H		55	218-221
4c	-Cl		70	220-221
4d	-Cl		55	225-226
4e	-Br		56	224-225
4f	-Br		67	233-235

Table 2. Response of various micro-organisms to substituted coumarins 4(a–f)

(Diameter of zone inhibition (mm))

Entry	*E.coli*		*S.aureus*		*C.abicans*	
	100μg/ml	150μg/ml	100μg/ml	150μg/ml	100μg/ml	150μg/ml
4a	-	17	15	18	35	40
4b	-	15	17	19	23	32
4c	-	16	13	15	27	32
4d	-	16	-	15	22	27
4e	-	-	-	17	19	22
4f	-	16	-	14	22	30

4. CONCLUSIONS

Six coumarin derivatives were synthesized by microwave-assisted solvent-free method from from 3-acetyl-6-substituted-*2H*-chromen-2-one using conjugate nucleophilic reactions with various amines with 55-70% efficiency. The highest efficiency is 4c compounds. The microwave-assisted solvent-free synthesis of coumarins has many advantages: closed reaction system, solvent free, no use of heat sources, etc..... all these reduce evaporation and dispersion of substances into the environment, greatly reducing toxic effects on humans and the environment. Currently, this method are classified as green synthesis methods in chemistry. The synthesized products have antibacterial and antifungal activity.

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