Synthesis of Substituted-4-Chloromethylcoumarines of Anticipated Antifungal Activity by Microwave or Infrared (IR) Irradiations

Ali Ibrahim AL-Jobury
College of Pharmacy, University of Tikrit, Tikrit, Iraq

Received 10/3/2010 Accepted 22/4/2010

Abstract

Rapid and selective free radical monochlorination of the substituted -4-methyl coumarines (1a-d) was achieved using sodium hypochlorite under microwave conditions to synthesize substituted-4-chloromethyl coumarines(2a-d)of anticipated antifungal activity,while irradiation using the assistance of IR lamp was failed to chlorinate these derivatives. The advantages of Microwave irradiation provide shorter reaction times, and higher yields . The structures of these compounds were confirmed by IR&UV Spectrophotometer.

تحضير معوضات4- كلوريد مثيل الكيومارين المتوقع إن تكون ذات فعالية مضادة للفطريات بالتشعيع بالميكروويف أو مصباح الأشعة تحت الحمراء

على ابراهيم مصطفى الجبورى

المستخلص

تم استخدام طريقة سريعة وانتقائية بمساعدة التشعيع بالميكروويف لكلورة معوضات4-مثيل الكيومارين (d-a1) لتحضير مشتقات 4- كلوريد مثيل الكيومارين (d-a2) التي يتوقع إن تكون فعالة كمضادات للفطريات. فشلت طريقة التشعيع باستخدام مصباح الأشعة تحت الحمراء لكلورة هذه المشتقات.ان محاسن استخدام التشعيع هي وقت تفاعل اقصر و ناتجا اعلى. تم إثبات التراكيب الكيميائية للمركبات بوساطة أطيافها في منطقة الأشعة تحت الحمراء وفوق البنفسجية .

Introduction

Coumarin and its derivatives occur widely in nature, and have been exploited in biological, chemical and physical fields. They are one of the most important classes of organic compounds and they are found to possess several biological activities[1-2]. The 4-(4-tert-butylphenoxy)methyl and 4-(4-nitrophenoxy)methyl analogues possessed greatest toxicity towards the majority of the tested fungi[3] Conventional routes for the synthesis of coumarin-containing compounds involve the Pechmann reaction – condensation of phenols and β–keto esters. In some cases reaction mixtures were allowed to stand overnight or for a number of days or were heated above 150 C^0[4]. Substituted-chloromethyl coumarines were versatile starting materials that were widely used in synthetic organic chemistry, as further manipulation of the chloride may lead to other functional groups and a desired functionalization for the synthesis of natural products[5]. 4-Chlorocoumarin was prepared from 4-hydroxycoumarin using $POCl_3$ because of its herbicidal activity[6] 2-Methyl-1,3,4-thiadiazole can be chlorinated under free radical conditions. Trichloro- and tribromomethyl-1,3,4-thiadiazoles have been obtained by this method[7].Rapid and selective free radical monochlorination of the 2-mercapto-5-methyl-1,3,4-thiadiazole was achieved using sodium hypochlorite under microwave conditions [8]. As part of continuous program directed toward the studies with organic compounds[9], it was became of interest to investigate preparative routes to chlorinate substituted-4-methyl coumarines of anticipated antifungal activity by irradiations with microwave or IR lamp.

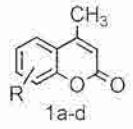
Material and methods

All melting points were determined on a Gallen Kamp and Electro thermal 1A9300 Digital-Series (1998)apparatus and were uncorrected. The IR – spectra (λmax cm^{-1}) were recorded on Perkin – Elmer 590B Spectrophotometer. UV- Shimadzu UV-160 spectrophotometer using EtOH as solvent.

General procedure for the synthesis of substituted-4-methyl coumarines: [10]

To a mixture of (0.01mole of proper phenol in (1.1gm,0.01mole) ethylacetoacetate) 2ml of conc. H_2SO_4 was added drop wise at 0-10 C^0.The mixture was stirred for 1 hour at this temperature, then 4hours at ambient temperature. An aqueous solution of 1 ml ethanol and 3ml water was added, and stirred for further 30 minutes. The precipitate was filtered off and dried, crystallized from ethanol gave compounds(1a-d). %Yields and physical properties of the title compounds were listed in Table (1).

Table (1): Percentage yields and physical properties of compounds (1a-d)



1a-d

Compd. No.2	R	% Yield	mp °C	IR, KBr ,Cm -1		UV λ max(nm) MeOH
				C=O Stretching	C-O Stretching	
a	7OH	60	190-91	1695	1070	300
b	7-OMe	75	160-61	1720	1130	300
c	5,6-diMe	65	160-62	1710	1155	320
d	5,7-diMe -	65	170-72	1730	1145	312

Synthesis of Substituted-4-Chloromethyl coumarines (2a-d)

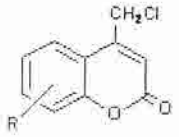
Method (A) (Microwave irradiation): [11]

Appropriate substituted -4-methyl coumarines (1a-d) (0.01mole) was mixed with 30ml. concentrated sodium hypochlorite. The reaction mixture was placed in a conical flask in a specification of domestic microwave oven and irradiated for 2 minutes .The reaction mixture was cooled at room temperature the product was dissolved in ethanol and solvent was removed under reduced pressure, which yield the corresponding title compounds, which were crystallized from ethanol %Yields and physical properties of the title compounds were listed in Table (2). To a solution of 30 ml concentrated sodium hypochlorite in a 100 ml conical flask was added appropriate substituted -4-methyl coumarines (1a-d)(0.01mole). The reaction mixture was placed under focused microwaves in an unmodified domestic microwave oven for 2 minutes. The reaction mixture was poured into water. The solid obtained was filtered off, washed with water and dried to give the product(2a–d), which was crystallized from ethanol %Yields and physical properties of the title compounds were listed in Table (2).

Method (B) (IR Lamp irradiation)

Appropriate substituted -4-methyl coumarines (1a-d) (0.01mole) was mixed with 10ml. sodium hypochlorite. The reaction mixture was placed in an open conical flask and irradiated for (2,4and 6 hrs) using IR lamp .No reaction was taken place

Table (2): Percentage yields and physical properties of compounds (2a-d)

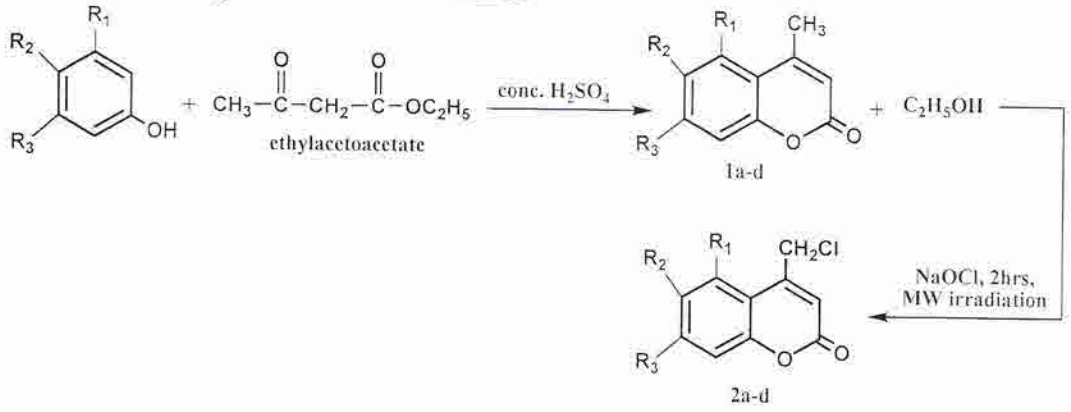


2a-d

Compd. No.2	R	% Yield	mp °C	IR, KBr ,Cm -1			UV λ max(nm) MeOH
				C=O Stretching	C-O Stretching	C-Cl Stretching	
a	7OH	70	215-217	1690	1100	790	310
B	7-OMe	75	186-187	1730	1110	790	350
C	5,6-diMe	88	188-189	1720	1105	795	330
D	5,7-diMe-	85	207-208	1730	1145	790	332

Results and Discussion

Schemes (1) summarizes the route followed for the synthesis of substituted 4-methylcoumarines(1a-d) and their chlorination using microwave irradiation to prepared substituted-4-chloromethyl coumarines (2a-d).



Scheme (1)

R_1, R_2 = methyl , R_3 = OH , OMe , Methyl

Synthesis of substituted 4-chloromethyl coumarin

Coumarines were prepared by the modification of Pechman-Duisberge condensation of phenols with β-ketoester (ethyl acetoacetate) by using sulfuric acid[12] The structures of these compounds were confirmed by IR&UV Spectrophotometery Tables 1 .These compounds have absorption bands at(300-320nm) in uv λmax value of the first $\pi \rightarrow \pi^*$ transition bands duo to conjugation in the coumarine nucleolus which lowered the exited state energy and gave red shift. The IR frequencies of these compounds showed the presence of conjugated carbonyl group at (1695-1730 cm^{-1}).The decrease in the C=O stretching to 1695-1730 cm^{-1},(in comparison with that of carbonyl compounds) was due to the decrease of the force constant resulted from the resonance (produced by the conjugation effects of unsaturated pyran-2-one ring) [12] Rapid and selective free radical monochlorination of the substituted -4-methyl coumarines (1a-d) was achieved using sodium hypochlorite under microwave conditions [8],while irradiation using the assistance of IR lamp failed to chlorinate these derivatives, may be due to law energy supplied. The structures of these compounds were confirmed by IR&UV Spectrophotometery Tables 2.The IR absorption showed the presence of a characteristic band at (790-795 cm^{-1}) for C-Cl strutting[8] The reaction involves free radical monohalogenation without affecting other substituent's. Note that the heat of formation of 7-hydroxychloromethylcoumarine (2a-d) which was chosen as representative for new products was -87, 87, 14 kcal/mole using the MOPAC Data-File format by computer - generated representation which has been minimized with the MM2 force field, and was drawn by Chem 3D Ultra Molecular Modeling and Analysis Version 8.0.3.Also this computational study showed that the compound was essentially planar, Fig (1).

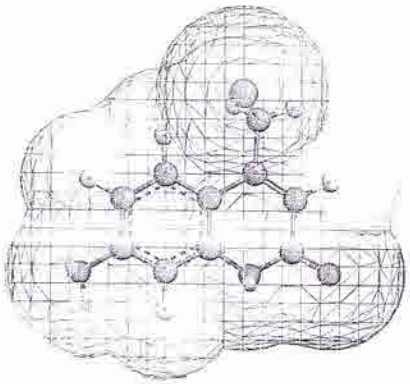


Fig (1)

Model of 7-Hydroxychloromethylcoumarine(2a-d) as representative for new products which indicated that the compound was essentially planar as drawn by Chem3D with solvent accessible surface : wire mesh type and atom colors map property

The advantages of this work were the safe and simple reaction with a good product yield, short reaction time and the avoid of using volatile and toxic solvents.

References

1-Fylaktakidou,K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. Natural and synthetic coumarin derivatives with anti inflammatory activities. . *Curr.Pharm. Design* 2004,*10*, 3813-3833

2- Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhainl, A. T.; Lee, K. H. Catalyzed efficient synthesis 4-substituted qumarins . *J. Med. Chem.* 2001, *44*, 664."

3- Tushar Batra, Raj V. Singh, Naresh K. Sangwan, Mangel S. Malik, Om. P. Malik' Studies on pesticides based on coumarin IV: Synthesis and antifungal activity of twelve 4-(substituted phenoxy)methyl-6-methyl coumarins "Pest Manegment Scince; Volume 25 Issue 1, Pages 53 – 58(2006)]

4- Xie, L.; Yu, D, Wild C. Allways, Turo, Swith PC; Lee & A. *Bioorg.* "Microwave-assisted synthesis of fluorinated coumarino sulfonamides".. *Med. Chem. Lett.* 2000, *10*, 1003-1005.

5- Diego S. Pisoni; Douglas Gamba; Carlos V. Fonseca; Jesse S. da Costa; Cesar L. Petzhold; Eduardo R. de Oliveira; Marco A. Ceschi;"$InCl_3$/NaClO: A reagent for allylic chlorination of terminal olefins "J. Braz. Chem. Soc. vol.17 no.2 São Paulo Mar./Apr. 2006.

6- Martin Kováč,I Andrea Sabatié, and Ľubomír Floch"Synthesis of coumarin sulfonamides and sulfonylurea"; ARKIVOC 2001 (vi) 100-108.

7- H. Hagen, R. D. Kohler, and H. Fleig, Leibigs Ann. Chem., 1980, 1216.

8- M. Kidwai, S. Kohli, and P. Kumar, " Rapid Side Chain Chlorination Of Heterocyclic Compound Using Focused Microwave Irradiation", J. Chem. Res. (S), 1998, 9, 586-587.

9-A.I.M.AL-Joboury "Synthesis of 1-(1-phenylcyclohexyl) piperidine derivatives &analogues iii(BJOH Prpject),MSc Thesis, College of Pharmacy, Dept. of Pharmaceutical Chemistry, University of Baghdad,Iraq.1986.

10-S.Balint;Hung.tolose hv(pat.);46;315;(Cl,C07.D311/08) 2008.

11- A.Vogel,"A Text Book of Practical Organic Chemistry"5th edtion;1989.

12- Saied,S.M .;1983"Synthesis of some heterocyclic derv. of anticipated insecticidal activity"; M.Sc. Thesis ,College of pharmacy, University. of Baghdad ,Iraq]