Synthesis of Functionalized Coumarins

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ABSTRACT: *The synthesis of functionalized 2-oxo-2H-coumarin derivatives has been studied by a one-pot reaction of o-hydroxybenzaldehyde, ethyl 2-bromoacetate and triphenylphosphine in the presence of catalytic amount of triethyl amine in EtOAc, water or under solvent free conditions. We have found the best results obtained under solvent free condition.*

KEY WORDS: *Coumarin, Wittig reaction, O-hydroxybenzaldehyde, Ethyl 2-bromoacetate, Triphenylphosphine.*

INTRODUCTION

Coumarins form a vast class of natural products. They occur widely as secondary plant metabolites and are known to exhibit numerous interesting biological activities. Their applications range from additives in food, perfumes, cosmetics, pharmaceuticals and in the preparation of insecticides, optical brighteners and dispersed fluorescent and tunable laser dyes. So, coumarins have various bioactivities, for example, inhibition of platelet aggregation, anticancer and inhibition of steroid 5α-reductase. These properties have made coumarins into interesting targets for organic chemists. The last decade witnessed a series of publications on the development of synthetic protocols for this important heterocyclic scaffold. Thus, it is clearly evident that the need for the development of new and flexible protocols is required; especially when they accommodate important functionalities and are broad in scope [1-6]. In the past, coumarins have been synthesized by several routes including *Pechmann* [7], *Perkin* [8], *Knoevenagel* [9], and *Reformatsky* [10]. These reactions often require strongly acidic or strongly basic reaction conditions and high temperature for longer reaction times, which makes them less suitable for the synthesis of coumarins with complex substitution patterns [11-13]. Moreover, they mostly lead to coumarins with subsistent in the 3- or 4-position [14]. A good alternative for the synthesis of 3,4-unsubstituted coumarins is the two-step Wittig reaction [15]. In general, the synthetic strategy consists of synthesizing the suitable *o*-hydroxybenzaldehydes and Wittig reagent, which can be converted to the corresponding coumarins via a Wittig reaction protocol.

Coumarin synthesis, require harsh reaction conditions and catalyst like bismuth(III) nitrate [21]. For example in synthesis of coumarin through the Wittig reaction *o*-hydroxybenzaldehydes or o-hydroxyacetophenones with ethoxylcarbonyl triphenylphosphorous, the reaction times up to 17-34 h under refluxing conditions in benzene or xylene as very toxic solvents [22,23].

During the course of our studies toward the development of new routes to the synthesis of organic compounds [16-18] and our interest in synthesis of coumarins [19,20], we wish to modify the Wittig reaction to synthesis coumarin derivatives by simple one-pot condensation of ethyl bromoacetate and *o*-hydroxybenzaldehyde in the presence of PPh_3 at 80°C (Scheme 1).

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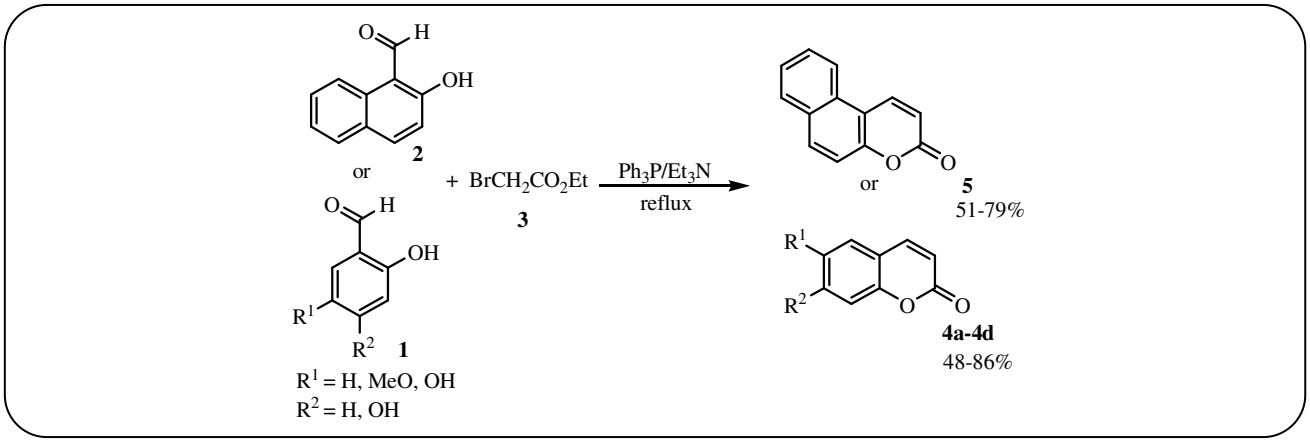
1021-9986/11/4/19 4/$/2.40



Scheme 1: Synthesis of products 4a-d and 5.

EXPERIMENTAL SECTION

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained on solutions in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Merck and Fluka chemical companies.

All the products are known compounds, which were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral data and their melting points were compared with literature reports [25-27].

Typical procedure for the synthesis of 2H-chromen-2-one (4a)

Triphenylphosphine (3 mmol, 0.78 g), ethylbromoacetate (3 mmol, 0.16 g), salicylaldehyde (3 mmol, 0.36 g) and triethylamine (0.1 mmol, 0.10 g) was added to screw caped tube and heated under classical heating conditions for 90 min or refluxed in water or ethyl acetate for 150 min. Progress of reaction was monitored by TLC. After completion of reaction, pure product was obtained from reaction mixture by column (10cm) chromatography (EtOAc:n-Hexane, 6:4).

RESULTS AND DISCUSSION

As can be seen from Table 1, coumarins are produced with high yields varying from 48-86% under classical heating conditions. However, the reaction times are reduced from a day to several minutes. As a consequence, it is possible to select the most appropriate conditions for particular applications. If time is of little of importance, the reaction can be completed without expenditure of additional energy. Also, solvent free conditions and using water as solvent are nature friendly and prevent from environmental pollutions.

We can see from Table 1 that yields under solvent free-classical heating condition is better than other conditions; but if we want to scale-up the reaction, heat built-up in some points of reaction mixture and difficulty of heat transfer in solid phase, cause degradation of reagent and product that decrease the yield. Therefore using of solvent in large scales is necessary. Using organic solvents is preferred. Because reactants can solved in them completely, that increase reaction yield by increasing the collision between reactant molecules.

Recently, environmental laws force chemical companies to reduce use of organic solvents. In this situation, water is preferred solvent. If we can use water as reaction media, we can reduce environmental pollution. As previously mentioned we did Wittig reaction in water with acceptable yields. Using of water cause formation of emulsion that can prevent from heat built-up in reaction mixture.

In summary, we have introduced a new alternative method for the synthesis of functionalized coumarins by the triphenylphosphine-mediated Wittig reaction. Obviously, improvement of yields in short reaction times under solvent free conditions has been reported.

CONCLUSIONS

In conclusion, we have synthesized functionalized 2-*oxo*-2*H*-coumarin derivatives with high yields and short reaction times. The reaction could be carried out

Table 1: Synthesis of coumarins via Wittig reaction under classical heating conditions in solvent or solvent-free medium.

Entry	Product	Solvent			M.P. (°C) Found (reported)
		EtOAc[a]	H_2O[a]	SF[a]	
1	4a	78(150)	58(189)	82(90)	68-69 (69)[b]
2	4b	82(90)	62(180)	86(100)	120-123 (119-120)[c]
3	4c	62(240)	48(240)	74(100)	184-185 (185-187)[d]
4	4d	65(240)	54(240)	75(120)	240-242 (241-242)[d]
5	5	73(120)	51(210)	79(60)	140-143 (139-142)[c]

in solvent free condition or water as a solvent. These reaction conditions are environmentally friendly which makes proposed pathway a green synthetic method.

Acknowledgement

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University.

Received : Oct. 10, 2009 ; Accepted : Feb. 7, 2011

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