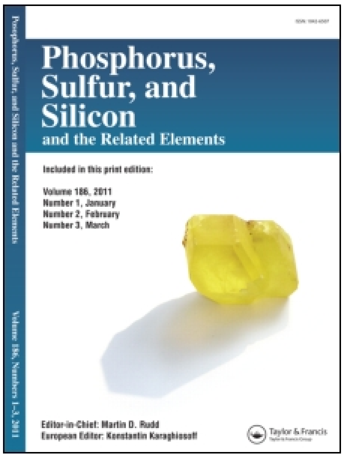

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Hassan Valizadeh[a]; F. Mahmoodi Kordi[b]; Hamid Gholipur[a]; Mohammad Amiri[a]
[a] Department of Chemistry, Faculty of Sciences, Azarbaijan University of Tarbiat Moallem, Tabriz, Iran [b] Department of Biology, Faculty of Sciences, Azarbaijan University of Tarbiat Moallem, Tabriz, Iran

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Hassan Valizadeh,[1] F. Mahmoodi Kordi,[2]
Hamid Gholipur,[1] and Mohammad Amiri[1]
[1]Department of Chemistry, Faculty of Sciences, Azarbaijan University of Tarbiat Moallem, Tabriz, Iran
[2]Department of Biology, Faculty of Sciences, Azarbaijan University of Tarbiat Moallem, Tabriz, Iran

Phosphoric acid imidazolium dihydrogenphosphate was found to work well as a catalyst and excellent reaction medium in the Pechmann condensation of substituted phenols or α-naphthol with ethyl acetoacetate to give 4-methyl coumarins under microwave irradiation. This method is simple, cost effective, requires short reaction times, and gives very good to excellent yields.

Keywords Coumarin; microwave-assisted; Pechmann reaction; phosphoric acid imidazolium dihydrogenphosphate

INTRODUCTION

The coumarins are heterocyclic organic compounds, also known as benzo-2-pyrone derivatives, and constitute an important group of natural products having varied activities. Among the various coumarin derivatives, 7-substituted coumarins are an important group of derivatives showing various biological applications such as anthelmintic and hypnotic properties.[1] They are widely used as additives in food, perfumes, agrochemicals, cosmetics, and pharmaceuticals,[2] and in the preparation of insecticides, optical brightening agents, dispersed fluorescent, and tunable dye lasers.[3] They have varied bioactivities, such as the inhibition of platelet aggregation,[4,5] antibacterial,[6] anticancer,[7]

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Address correspondence to Hassan Valizadeh, Department of Chemistry, Faculty of Science, Azerbaijan University of Tarbiat-Moallem, P. O. Box 53714-161, Tabriz, Iran. E-mail: h-valizadeh@azaruniv.edu

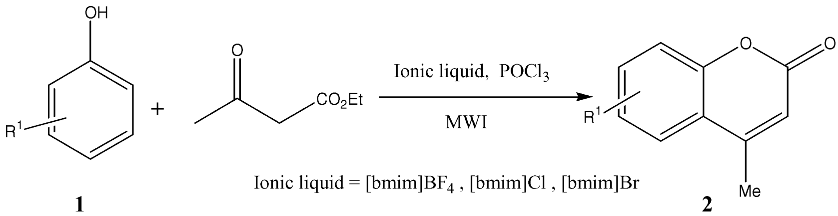
and inhibition of steroid 5α-reductase[8] and HIV-1 protease[9] activities. Coumarins also act as intermediates for the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols.[10,11]

Coumarins can be synthesized by various methods such as Pechmann,[12] Perkin,[13,14] Knoevenagel,[15,16] Reformatsky,[17] and Witting[18] reactions. Pechmann condensation is one of the most common procedures for the preparation of coumarin and its derivatives.

Conventionally, the Pechmann reaction is carried out in the presence of a concentrated sulfuric acid catalyst,[19] phosphorous pentaoxide,[20] trifluoroacetic acid,[21] or aluminum chloride.[22] These acids are corrosive and required in excess. For example, nearly one liter of concentrated H_2SO_4 is required to synthesize 1 mol of 7-hydroxy-4-methylcoumarin[23]; the reaction also requires 12–24 h of reaction time[24] and may also result in the formation of undesired side products.[25]

With the increasing public concern over environmental degradation and future resources, it is of great importance for chemists to come up with new approaches that are less hazardous to human health and environment. Being employed in large amounts and usually volatile in nature, the solvents used in organic synthesis are high on the list of environmental pollutants. For overcoming these problems, one approach is to use water as a green medium;[26] another approach is to develop new processes involving solvent-free conditions. In recent years, ionic liquids have been emerged as a powerful alternative to conventional molecular organic solvents due to their particular properties, such as undetectable vapor pressure and wide liquid range, as well as ease of recovery and reuse, and making them a greener alternative to volatile organic solvents. Ionic liquids (IL), as new generation solvents, have proven their utility in various reactions of synthetic importance.[27–29] Apart from the tunable physical and chemical properties of ionic liquids, their immiscibility with various organic solvents enables the biphasic separation of the desired products.

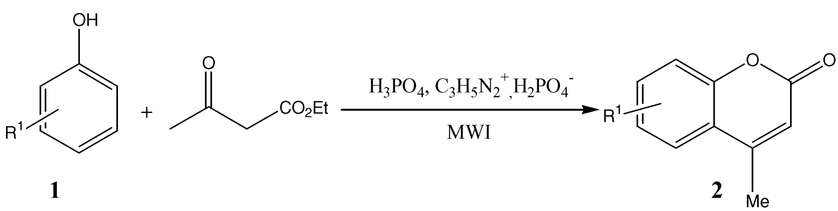
Potdar et al. have reported coumarin synthesis via the Pechmann condensation in Lewis acidic chloroaluminate ionic liquid.[30] However, there are some disadvantages associated with the use of chloroaluminate ionic liquids: they are moisture sensitive and cannot be recycled after the reaction. In the present study, we have studied the possibility of Pechmann condensation employing neutral ionic liquids. We have carried out Pechmann condensation of phenols and ethylacetoacetate catalyzed by using phosphorus oxychloride in 1-butyl-3-methylimidazolium chloride ([bmim]Cl), 1-butyl-3-methylimidazolium bromide ([bmim]Br), and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) ionic liquids (Scheme 1). The reaction of phenols bearing electron-donating groups afforded high yields of coumarins



SCHEME 1

under microwave irradiation. The results are recorded in I. Evidently, [bmim]BF_4 was found to be superior in terms of yield (up to 88%) and reaction time (15 min) as compared with other ILs.

To study the extent of present conversion, we thought of using phosphoric acid imidazolium dihydrogenphosphate as a catalyst and reaction medium for Pechmann condensation. Potdar et al. have used 1-methylimidazolium p-toluenesulfonic acid ([Hmim]Tsa) and 1-methylimidazolium trifluoroacetic acid ([Hmim]Tfa) ionic liquids for this reaction, and they have observed that neither of the ionic liquids mentioned above gave the required conversion at room temperature as well as at high temperature.[34] We extended the microwave synthesis of coumarins via the Pechmann condensation employing phosphoric acid imidazolium dihydrogenphosphate to establish cleaner synthetic methodologies (Scheme 2).



SCHEME 2

Herein, we report that the substituted phenols and ethyl acetoacetate undergo condensation in the presence of phosphoric acid imidazolium dihydrogenphosphate catalyst under microwave irradiation to produce the coumarins in excellent yields (Table II). We have carried out these reactions with a series of monohydric and polyhydric phenols with ethyl acetoacetate to obtain the corresponding coumarins. Substrates having electron-donating groups in the para position to the site of electrophilic substitution gave maximum yields under reaction conditions in short periods of time. The present catalyst can be prepared according to the procedure reported in the literature.[35] From Table II,

TABLE I Phosphorus Oxychloride–Catalyzed Pechmann Condensation in Neutral Ionic Liquids ([bmim]Br, bmim]Cl, bmim]BF_4)

Phenolic substrate **1**	Coumarin derivative **2**	Product [mp (°C)]		Yield[a] of product (%)		
		Found	Reported	[bmim]Br	[bmim]Cl	bmim]BF_4
Phenol	4-Methyl-	181–183	185[31]	66	68	82
Resorcinol	4-Methyl-7-hydroxy-	183–187	182–184[32]	65	68	84
A-naphthol	4-Methyl-[h]-benzo-	152–155	154[32]	63	65	81
Phloroglucinol	5,7-Dihydroxy-4-methyl-	280–282	280[32]	70	72	87
Pyrogallol	7,8-Dihydroxy-4-methyl-	240–243	242[32]	75	72	88
Para-nitrophenol	Not obtained	—	—	—	—	—
Ortho-nitrophenol	Not obtained	—	—	—	—	—
Meta-cresol	4,5-Dimethyl-	128–131	129[32]	74	72	81
2-methylresorcinol	7-Hydroxy-4,8-dimethyl-	260–264	263–265[33]	72	74	87

[a]Isolated yield after recrystallization.

TABLE II Coumarin Synthesis via Pechmann Condensation in Phosphoric Acid Imidazolium Dihydrogenphosphate

Phenolic substrate **1**	Product **2**	Time (min)	(Mp) (°C)	Yield[a] (%)
Phenol	4-Methyl-	35	181–183	83
Resorcinol	4-Methyl-7-hydroxy-	25	183–187	85
A-naphthol	4-Methyl-[h]-benzo-	30	152–155	87
2-Methylresorcinol	7-Hydroxy-4,8-dimethyl-	35	260–264	81
Phloroglucinol	5,7-Dihydroxy-4-methyl-	25	280–282	78
Pyrogallol	7,8-Dihydroxy-4-methyl-	25	240–243	79
Salicylic acid	Not obtained	–	–	–
Meta-cresol	4,5-Dimethyl-	30	128–131	–
Para-nitrophenol	Not obtained	–	–	78
Ortho-nitrophenol	Not obtained	–	–	–

[a]Isolated yield after recrystallization.

it is observed that the reactions proceeded faster than the conventional methods, and the yields are comparable. All the products were fully characterized by mp, IR, and ^{1}H NMR, and the values were in agreement with those reported in literature.

In conclusion, we have demonstrated the use of phosphoric acid imidazolium dihydrogenphosphate for Pechmann condensation to synthesis of coumarins. We believe our procedure is environmentally benign and will find important applications in the synthesis of coumarins.

EXPERIMENTAL

All of the melting points are uncorrected and were determined with a Stuart scientific apparatus. Infrared spectra were recorded in KBr and were determined on a Perkin-Elmer FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal standard. All solvents and chemicals were of research grade and were used as obtained from Merck. Microwave experiments were conducted in an unmodified oven. Melting points and spectra were compared to those reported in the literature.

GENERAL PROCEDURE

The phenol derivative or naphthol (2.00 mmol) and ethyl acetoacetate (2.20 mmol) were taken in a mortar, and to it phosphoric acid imidazolium dihydrogenphosphate (0.45 mmol) was added and the components were mixed thoroughly. Then the reaction mixture was transferred to a 30 mL beaker and was covered with a watch glass and subjected to microwave irradiation (140 W) for various time intervals. The progress of the reaction was monitored by TLC using (EtOAc:petroleum, 1:8) as an eluent. After completion of the reaction, it was allowed to cool and crushed ice was added into it. The beaker was scratched to obtain a solid, which was filtered, dried, and recrystallized from ethanol to obtain coumarins in good yield and high purity.

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