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무 용매 조건에서 potassium dihydrogen phosphate를 촉매로 사용하는 쿠마린의 마이크로파-유도 단일 용기 내 합성

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Microwave-induced one-pot Synthesis of Coumarins Using Potassium Dihydrogen Phosphate as a Catalyst Under Solvent-free Condition

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요 약. Potassium dihydrogen phosphate는 마이크로파 조사조건에서 용매 없이 페놀과 아세토아세트산 에틸의 Pechmann 축합반응에 의하여 쿠마린을 합성하는 효과적인 촉매로 밝혀졌다. 이 방법은 쿠마린 합성에 있어서 소량의 촉매를 필요로 하며 수율이 높고, 반응이 깨끗할 뿐만 아니라 반응 시간이 짧은 장점들을 가지고 있다.

주제어: Pechmann 축합, 쿠마린, Potassium dihydrogen phosphate,무 용매, 마이크로파

ABSTRACT. Potassium dihydrogen phosphate was found to be an efficient catalyst for the Pechmann condensation of phenols with ethyl acetoacetate, leading to the formation of coumarins under microwave-irradiation and solvent-free condition. This procedure offers several advantages, including the low loading of catalysts, high yields, clean reactions, short reaction time for the synthesis of coumarins.

Keywords: Pechmann condensation, Coumarins, Potassium dihydrogen phosphate, Solvent-free, Microwave

INTRODUCTION

Coumarins, the most important classes of fluorescent molecules, constitute important structural features present in a number of bioactive natural products. The heterocycles derived from these intermediates have also been tested for their potential as anti-HIV,[1] anti-inflammatory,[2] anticonvulsant,[3] anti-viral,[4] anti-coagulant,[5] antioxidant,[6] antibacterial,[7] antifungal,[8] anti-carcinogenic material[9] and antihistamine.[10]

Coumarins are an important group of organic compounds and can be used for the preparation of coumarino-α-pyrones, coumarino-g-pyrones, furocoumarins, chromenes, coumarones and 2-acylresorcinols. 7-Hydroxy-4-methylcoumarin acts as a starting material for the preparation of the insecticide Hymecromone. 6-Bromocoumarins are useful synthetic intermediates for various pharmaceuticals and active compounds.[11-13]

Coumarins have been synthesized by several routes including Pechmann,[14] Perkin,[15] Knoevenagel,[16] Reformatsky[17] and Wittig[18] reactions.

The Pechmann reaction is simple and straight forward employing β-keto esters and substituted phenols together with an acid catalyst. In the past, strong acids like H_2SO_4,[14] P_2O_5,[19] $AlCl_3$, ZnC_{l2},[20] TFA,[21] ionic liquids,[22] sulfated zircon,[23] indium halides,[24] $CuPy_2Cl_2$,[25] palladium[26] and ammonium metavanadate[27] have been used. However, many of these methodologies suffer from the drawback of green chemistry and have been associated with several short comings such as long reaction times, expensive reagents, low product yields and difficulty in recovery and reusability of the catalysts. These shortcomings certainly demand the search for a safe, more convenient and efficient method.

Now a day, it is shown that the use of solid acidic catalysts has gained importance in organic synthesis due to several advantages such as, operational simplicity, no toxicity and ease of isolation after completion of the reaction. In the current study, the commercially available catalyst potassium dihydrogen phosphate having pH 4.2-4.7 is used as a catalyst but its scope has not been fully explored.

Potassium dihydrogen phosphate can be used as buffer, neutralizing agent, sequestrate, yeast food and also as an efficient heterogeneous acid catalyst.[28] Recently, Gill & his co-workers have reported the synthesis of á-hydroxyphosphonates using potassium dihydrogen phosphate[29] under solvent-free condition. Owing to the numerous advantages associated with this cheap and non hazardous catalyst, we have considered Potassium dihydrogen phosphate to be an ideal heterogeneous acid catalyst for the synthesis of coumarins. Herein, we would like to report the facile and eco-friendly methodology for the synthesis of coumarins under solvent-free condition and microwave-irradiation.

Organic synthesis in dry media, eventually under microwave (MW) irradiation is presently under extensive examination. The relatively low cost of modern domestic microwave ovens makes them readily available to academic and industrial chemists and the use of such non-conventional reaction conditions reveals several features such as: a short reaction time compared to conventional heating, reduction of the usual thermal degradation and better selectivity.[30] Furthermore, microwave-assisted reactions under solvent-free conditions provide access to work with open vessels and to scale up reactions.[31]

In this communication, we report for the first time a facile and efficient synthetic strategy for preparing coumarins in very short reaction time with excellent yield using potassium dihydrogen phosphate as a catalyst under solvent-free condition and microwave-irradiation.

EXPERIMENTAL

All starting materials and reagents were commercially available and used without further purification. All the melting points were taken in an open capillary and are uncorrected. The progress of the reactions was monitored by thin layer chromatography (TLC). IR spectra were recorded on Perkin-Elmer FT-IR spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on mercury plus Varian spectrometer at 400 MHz in DMSO-d_6 as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

General procedure

Synthesis of compounds (3a-j): A mixture of substituted phenol (1 mmol), ethyl acetoacetate (1 mmol) and potassium dihydrogen phosphate (KH_2PO_4) (10 mol%) were placed in a beaker. The mixture was irradiated under microwave-irradiation, the progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into ice cold water (50 mL) and extracted with ethyl acetate (25 × 2 mL), which was then dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the pure coumarins (*Table* 3). The products 3(a-j) were confirmed by comparisons with authentic samples, IR, ^{1}H NMR, mass spectra and melting point. Spectral data of principal compounds.[27]

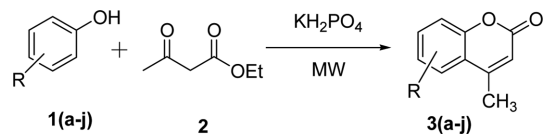
RESULTS AND DISCUSSION

As a part of our ongoing research devoted to the development of useful synthetic methodologies,[32-34] using solid acid catalyst and microwave irradiation techniques, herein we report an efficient and practical method for the synthesis of coumarins using potassium dihydrogen phosphate which makes use of mild catalyst under solvent-free condition and microwave-irradiation (*Scheme* 1).

In the first examination, we have performed the different reaction conditions on model reaction. The result revealed that, when the reaction was carried out at stirring and heating condition it gave lower yield of product even after prolonged reaction time. But at the same time when the reaction was carried out under microwave-irradiation we got the excellent yields of product in short span (*Table* 1).

We have also carried out the model reaction in microwave at different powers, it was found that if reaction carried out without microwave irradiation it takes more reaction time (30 min) with negligible yield (20%). As increase in the power (100, 200, 300, 400 W), there is increase in yield with decrease in reaction time still at 400 W, but future that there is no significant change observed at 600 W. Hence, we satisfied over 400W and done all derivatization at 400 W.

After optimizing the various powers of microwave, the



***Scheme* 1.**

***Table* 1.** Optimization of model reaction **3a** at different reaction condition[a]

Entry	Reaction condition	Time	Yield (%)[b]
1	Stirring	12 (h)	40
2	Heating	8 (h)	65
3	Microwave	3 (min)	95

[a]Reaction condition: **1** (1 mmol), **2** (1 mmol) and KH_2PO_4 (10 mol%). [b]Isolated yields

***Table* 2.** Effect of microwave-irradiation powers for the synthesis of coumarins[a]

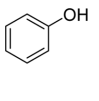
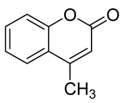
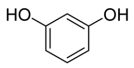
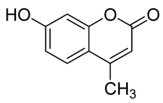
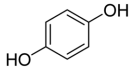
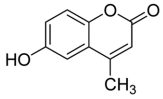
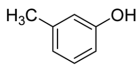
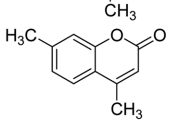
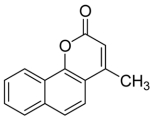
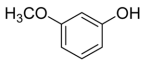
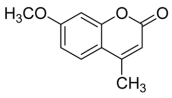
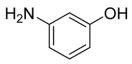
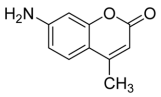
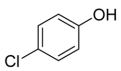
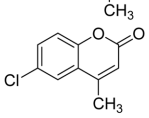
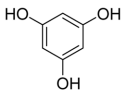
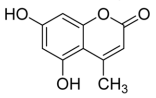
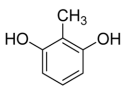
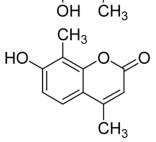
Entry	MW (Watts)	Time(min.)	Yield(%)[b]
1	-	30	20
2	100	30	42
3	200	30	55
4	300	30	60
5	400	3	95
6	600	3	95

[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol) and KH_2PO_4 (10 mol%). [b]Isolated yields

generality of this method was examined by the reaction of substituted phenols and ethyl acetoacetate using potassium dihydrogen phosphate as a catalyst under microwave-irradiation, the results are shown in *Table* 3. Here, we have found that many phenols, such as resorcinol, 4-hydrxy phenol, 3-methoxy phenol, 3-aminophenol could be converted to corresponding coumarins in good yields (entries 3a-3c & 3f-3j). The reactivities of 3-methylphenol and 1-naphthol seem to be inferior as compared with that of the former (entries 3d, 3e), only 82% and 85% of the yields were obtained, respectively.

The synthesized compounds were compared (MS, NMR, and IR) with compounds that were prepared by using the literature method.[27] This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds. The developed methodology is simple with good to excellent yields.

***Table* 3.** Synthesis of coumarins catalyzed by potassium dihydrogen phosphate under microwave-irradiation[a]

Entry	Reactant	Product	Time(min)	Yield(%)	M.P(°C)
3a			3	95	78-80
3b			3	94	180-182
3c			5	92	241-243
3d			10	82	129-131
3e			12	85	153-155
3f			7	89	160-162
3g			5	90	220-222
3h			5	89	180-183
3i			7	91	281-283
3j			8	88	137-138

[a]Reaction conditions: **1** (1 mmol), **2 (a-j)**(1 mmol), catalyst (10 mol%). bIsolated yield. All the compounds characterised by their spectroscopy method ^{1}H NMR, Mass, IR and melting point and compare to their authentic sample

Spectral Data for representative compounds:

4-methyl-2H-chromen-2-one(3a): IR (KBr) 1056, 1240, 1547, 1720, 3015 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.30 (s, 1H), 7.22-7.44 (m, 3H), 7.46 (d, J = 6.0 Hz, 1H); MS: m/z 160.9 (M+1).

4-methyl-2H-benzo[h]chromen-2-one (3e): IR (KBr) 1044, 1230, 1565, 1715, 3010 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 2.40 (s, 3H), 6.37 (s, 1H), 7.30-7.65 (m, 4H), 8.2 (d, J = 9.0 Hz, 1H), 8.50 (d, J = 9.0Hz, 1H); MS: m/z 211.1 (M+1).

7-methoxy-4-methyl-2H-chromen-2-one(3f): IR (KBr) 1080, 1223, 1542, 1710, 3055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.70 (s, 3H), 6.22 (s, 1H), 6.79 (s, 2H), 7.65 (d, J = 8.7 Hz, 1H); MS: m/z 191.1 (M+1).

7-hydroxy-4,8-dimethyl-2H-chromen-2-one(3j): IR (KBr) 1465, 1609, 1682, 3146, 3464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.36 (d, J = 1.2 Hz, 3H), 6.15 (d, J = 1.2 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H),7.45 (d, J = 8.5 Hz, 1H), 10.2 (s, 1H); MS: m/z 191.0 (M+1).

CONCLUSION

In conclusion, the present method is very simple, mild and efficient for the synthesis of coumarin. This method offers several advantages, including the low loading of catalysts, high yields, clean reactions, short reaction time for the synthesis of coumarins. We believed that, microwave-assisted synthesis of coumarins using potassium dihydrogen phosphate as a catalyst promoted methodology will be a valuable contribution in the field of chemistry as compare to the existing processes.

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