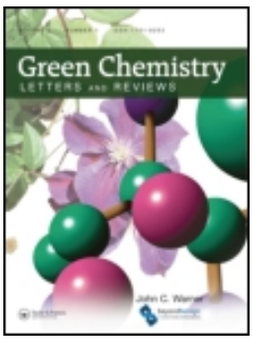

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RESEARCH LETTER

Modified Pechmann condensation using grinding technique under solvent-free condition at room temperature

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A simple and efficient condition for Pechmann condensation for the synthesis of coumarins involving grinding of different phenols and β-ketoesters in the presence of *p*-toluenesulfonic acid at room temperature under solvent-free conditions has been described. A faster reaction and higher yields compared to the conventional methods are the advantages of present protocol.

Keywords: coumarins; Pechmann reaction; phenols; β-ketoesters; grinding technique

Introduction

Coumarins are the important class of naturally occurring oxygen heterocyclic compounds having a distinct and important place in the realm of natural and synthetic organic chemistry as these compounds display useful and diverse biological properties, viz. antibacterial, antiviral, anticancer, anti-HIV (*1*–3), and have been reported to exhibit activity against several types of animal tumors (*4*), prostate cancer, and metastatic renal cell carcinoma (*5*), and also have been used as additives in food, cosmetics (*6*), optical brighteners (*7*), dispersed fluorescent, and laser dyes (*8*).

Due to importance of the coumarins, continuous efforts have been made to achieve the simple and efficient procedures for the synthesis of these compounds. Many routes are available for the synthesis of coumarins which include use of Pechmann (*9*), Perkin (*10*), Knovengal (*11*), Reformatsky (*12*), and Wittig (*13*) reactions. Among these, Pechmann reaction is considered to be one of the most important one as it requires simple starting materials and a large number of condensing agents, such as strong acids H_2SO_4, HCl, H_3PO_4, F_3CCOOH, solid super acid (*9*, *14–16*), Lewis acids such as $ZnCl_2$, $FeCl_3$, $AlCl_3$, $BF_3{\cdot}2H_2O$, $ZnCl_2/Al_2O_3$, and $ZrCl_4$ (*14–18*), and ion exchange resins (*19*). Recently, the use of microwaves (*20*), ionic liquid (*21*) as Lewis acid, Zn/I_2 (*22*), $Yb(OTf)_3$ (*23*), LiBr (*24*), I_2 (*25*), and $CoPy_2Cl_2$ (*26*) has also been reported.

Some of the above mentioned conditions possess shortcomings, such as use of harsh or hazardous chemicals, expensive and large amount of reactants, longer reaction time, elevated temperature, and formation of side products. The shortcomings led us to develop a safe, environmentally benign, and more efficient method for Pechmann reaction.

In continuation of our work to develop simple procedures for the synthesis of organic compounds (*27*), herein, we wish to report a highly efficient procedure for the synthesis of coumarins via Pechmann condensation under solvent-free conditions using grinding technique.

Results and discussion

A mixture of resorcinol and ethylacetoacetate was ground in the presence of *p*-toulenesulfonic acid (*p*-TSA) in a mortar by a pestle (Scheme 1). The progress of the reaction was checked by thin layer chromatography (TLC) when the reactants were found to have reacted almost completely in 10 minutes but it had to be kept at room temperature for another 20 minutes for the completion of the reaction. Optimum conditions of the reaction was achieved by using varying amounts of *p*-TSA and best yields could be obtained by using 2 equivalents of *p*-TSA to the substituted phenols. During grinding, the reaction mixture absorbed moisture which was found sufficient to make the reaction mixture homogeneous. The product could be isolated by just diluting the reaction mixture with ice-cold water.

In summary, it can be stated that the present protocol for the Pechmann condensation is highly efficient as it avoids the use of organic solvents at any stage of the reaction.

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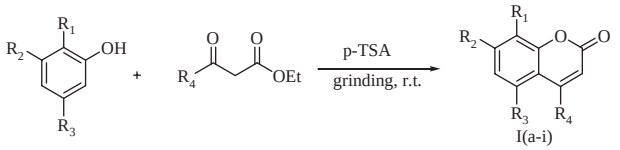

Scheme 1. Synthesis of 4-substituted coumarins using *p*-TSA.

The scope of the method was further studied by reacting differently substituted phenols with ethylacetoacetate, 1-chloro ethylacetoacetate, and benzoyl acetoacetate. The identity of the products (Table 1) obtained was confirmed by their IR, ^{1}H-NMR spectral data, and comparison with authentic samples.

Experimental

All the chemicals were purchased from Aldrich and Fluka. Melting points (MPs) were determined in open capillary tubes. All the compounds were characterized from their spectral data (IR and ^{1}H-NMR). A mortar and pestle of porcelain was used for all the experiments.

General procedure

Synthesis of coumarins

A mixture of substituted phenol (1 mmol) and β-ketoester (1 mmol) was ground with dry *p*-TSA (2 mmol) in a mortar by pestle for 10 minutes when a color change of the reaction mixture took place. The reaction mixture was kept at room temperature for about 20–80 minutes. The completion of the reaction was checked by TLC (silica gel using solvent petroleum ether (60–80°):acetone, 2:1). The reaction mixture was diluted with ice-cold water. The solid that separated out was filtered at vacuum, washed with water, and recrystallized from ethanol to give pure coumarin in high yield.

7,8-Dihydroxy-4-methyl-chromen-2-one

IR (KBr): 3415, 3230, 1645, and 1585; ^{1}H-NMR (DMSO-d_6,200 MHz): δ 10.12 (s, 1H, OH), 9.53 (s, 1H, OH), 7.37 (d, 1H, $J = 8.5$ Hz, ArH), 6.86 (d, 1H, $J = 8.5$ Hz, ArH), 6.17 (s, 1H, C-3H), and 2.20 (s, 3H, CH_3) (Table 1, Entry **Ic**).

4-Chloromethyl-5,7-dihydroxy-chromen-2-one

IR (KBr): 3420, 3375, 1728, and 1562; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 10.25 (s, 1H, OH), 10.02 (s, 1H, OH), 7.40 (s, 1H, ArH), 6.93 (s, 1H, ArH), 6.30 (s, 1H, C-3H), and 4.05 (s, 2H, CH_2Cl) (Table 1, Entry **Ie**).

7-Hydroxy-4-phenyl-chromen-2-one

IR (KBr): 3398, 1720, and 1547; ^{1}H-NMR (DMSO-d_6, 200 MHz): △ 10.30 (s, 1H, OH), 7.16–7.40 (m, 5H, ArH), 6.97 (d, 2H, $J = 8.8$ Hz, ArH), 6.85 (s, 1H, ArH), and 6.32 (s, 1H, C-3H) (Table 1, Entry **Ig**).

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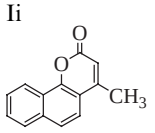
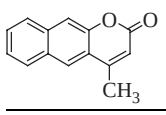
Table 1. Synthesis of coumarins by Pechmann reaction.

Entry	R_1	R_2	R_3	R_4	Time (min), a + b	% Yield	MP (°C)	Lit. MP (°C)
Ia	H	OH	H	CH_3	10 + 20	95	184–186	185 (*26*)
Ib	H	OH	OH	CH_3	10 + 20	92	276–278	280 (*26*)
Ic	OH	OH	H	CH_3	10 + 50	90	240	242 (*26*)
Id	H	OH	H	CH_2Cl	10 + 50	90	175–178	180 (*26*)
Ie	H	OH	OH	CH_2Cl	10 + 50	87	185	187 (*26*)
If	OH	OH	H	CH_2Cl	10 + 50	85	195	196–198 (*25*)
Ig	H	OH	H	Ph	10 + 80	90	255	257 (*26*)
Ih	H	OH	OH	Ph	10 + 80	85	243–246	244–246 (*24*)
Ii	OH	OH	H	Ph	10 + 80	82	195	196–198 (*24*)
					10 + 80	92	153–155	154–155 (*25*)
					10 + 80	90	180	183–184 (*25*)

Note: a – grinding time; b – time for which the reaction mixture was kept at room temperature.

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