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An Green and Efficient One-Pot Synthesis of Coumarin Derivatives Catalyzed by Cerium(IV) triflate at Room Temperature

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Abstract
Cerium(IV) triflate [$Ce(OTf)_4$] was employed as a catalyst for facile preparation of coumarin derivatives via the one-pot Pechmann condensation of phenol derivatives with a β-ketoester. Various phenol derivatives with β-ketoesters were utilized in the reaction. At all experiments, the desired products were synthesized successfully. The described novel synthesis method proposes several advantages of safety, mild condition, short reaction times, high yields, simplicity and easy workup compared to the traditional method of synthesis.

Keywords: $Ce(OTf)_4$, Coumarin, Pechmann condensation, β-ketoester.

1. Introduction

The synthesis of coumarin derivatives has attracted considerable notice of many organic and medicinal chemists for several years. This interest arises from the fact that a variety of natural and synthetic compounds which contain the coumarin substructure, exhibit significant biological activities such as cytotoxicity, enzyme inhibitory activities [1-3],urease inhibitory [4-7],anti-HIV, antithrombotic, anticancer, antifungal, anticoagulant, antioxidant and antimicrobial [8-12].Moreover, coumarins act as intermediates on the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols [13].

Various synthetic methodologies for coumarin derivatives have been developed such as Wittig [14], Knoevenagel [15], Reformatsky [16], Pechmann [17], and Perkin [18] reactions. In addition, their optical and fluorescence emission properties have already been studied [19-21]. The Pechmann reaction is a venerable reaction which is one of the most simple and straightforward methods used to produce coumarins. Classically, the process consists of the condensation of phenols with β-ketoesters in the presence of a variety of reagents to give good yields of 4-substituted coumarins [22]. Nowdays, synthesis of category of heterocyclic compounds under mild conditions have been reported in the presence of promoters, such as, polyaniline sulfate salt [23,24], heteropoly acids [25], zeolites [26,27], amberlyst 15 [28], montmorillonite clay [29], Nafion-H [30], and other solid acids [26]. Large amounts of solid supports result in the generation of a large amount of toxic waste. Pechmann reactions have also been conducted in chloroaluminate ionic liquids [31-35].

However, some of these reported methods have one or more disadvantages such as moisture sensitive, or highly toxic in environment, unpleasant experimental procedure and also reagents which are expensive. A mild and an efficient catalyst for the synthesis of coumarins is very desirable. Performing organic reactions in aqueous media has attracted much attention because of wonderful water properties. It would be significantly safe, cheap, non-toxic and environmentally friendly compared to organic solvents [36]. Additionally, the catalyst system can be recycled using the water soluble catalyst and the insoluble products can be separated by simple filtration. In continuation of our investigations on the development of new synthetic methodology [37,38], we herein report

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an innovative, convenient, mild and efficient procedure for the synthesis of coumarins. One-pot condensation of phenol derivatives with *β*-ketoesterswas utilized for synthesizing of coumarins, respectively. The experiments carried out using the cerium(IV) triflate [$Ce(OTf)_4$] under ambient temperature.

2. Material and methods

NMR spectra were determined on a Fourier-transform (FT)-NMR Bruker AV-400 spectrometer in dimethyl sulfoxideDMSO-d_6 and are expressed in δ values relative to tetramethylsilane; coupling constants (J) are measured in Hz. Melting points were determined on a ELECTR THERMAL9100. Infrared spectra were recorded on a RAYLEIGH WQF-510 Fourier transform instrument. Commercially available reagents were used throughout without further purification.

2.1. General procedure for the synthesis of coumarin derivatives

A mixture of phenol derivatives (1.0 mmol), *β*-ketoester (1.0 mmol) and $Ce(OTf)_4$ as a catalyst (1 mol%) in water (2 mL) was stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC (n-hexan/ethyl acetate 5:2). After completion of the reaction, the resulting solid (crude product) was filtered and then recrystallized with ethanol–water to obtain pure product. The physical data (mp, NMR, IR) of these known compounds were found to be identical with those reported in the literature.

2.2. Spectral data for the synthesis of coumarin derivatives

7-hydroxy-4-methyl-coumarin (Table 3 ,entry 3b): Yield 92%; m.p. 184-186 ^oC (lit. [47] 185 ^oC); IR (KBr): υ 3267–3085, 2985, 1670, 1257, 958 cm^{-1};^1H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H), 3.27 (br s, 1H), 6.05 (s, 1H), 6.8 (s, 1H), 6.83 (d, 1H, J = 7.9 Hz), 7.45 (d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.3, 102.5, 110.3, 111.1, 112.7, 125.2, 152.7, 154.7, 160.9, 161.3.

7-methoxy-4-methyl-coumarin (Table 3, entry 3d): Yield 91%; m.p. 162-164 ^oC (lit. [48] 161-163 ^oC); IR (KBr): υ 3260–3080, 2995, 1677, 1265, 967 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 3.87 (s, 3H), 6.13 (s, 1H), 6.47 (s, 1H), 6.85 (d, 1H, J = 9.8 Hz), 7.47 (d, 1H, J = 9.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.7, 55.5, 100.8, 111.6, 112.3, 113.45, 125.5, 153.1, 155.0, 161.9, 162. 6.

5,7-dihydroxy-4-methyl-coumarin (Table 3, entry 3j): Yield 94%; m.p. 286-288 ^oC (lit. [47] 285 ^oC); IR (KBr): υ 3473-3297, 2995, 1665, 1617, 1535, 1414, 1260, 875 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.87 (brs, 1H), 9.74 (brs, 1H), 6.21 (d, 1H, J = 7.3 Hz), 6.18 (d, 1H, J = 7.2 Hz), 5.71 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.7, 94.1, 99.3, 102.5, 109.4, 155.34, 157.1, 158.2, 160.3, 161.5. *Ethyl-2-oxo-2H-chromene-3-carboxylate (Table 3, entry 4c)*: Yield 93%; m.p. 92-94 ^oC (lit. [53] 90-91 ^oC); IR (KBr): υ 3375-3295, 2985, 1676, 1591, 1243, 1201 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.376 (t, J = 7.3 Hz, 3H), 4.35 (q, J = 7.4 Hz, 2H), 7.25-7.67 (m, 3H), 8.47 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1, 156.8, 155.2, 148.8, 134.7, 129.4, 124.6, 118.3, 117.8, 116.7, 62.1, 14.2.

3. Results and discussion

Herein, we report an efficient method for the preparation of coumarin derivatives using thecerium(IV) triflate [$Ce(OTf)_4$]as a catalyst in the Pechmann reaction. According to Scheme 1, the synthesis was done through a mixture of phenol derivatives with a *β*-ketoester in water solvent under ambient temperature.The effect of solvent on the yield of coumarin (3, 4) is given in Table 1. The reaction of resorcinol (1) with ethyl acetoacetate (2) in the synthesis of coumarin was chosen as a model reaction to investigate the effect of solvent. The experiment results depicted that water was the most effective solvent.

Table 1. Solvent effect on the reaction between resorcinol with ethyl acetoacetate in the synthesis of coumarin[a]

Entry	Solvent	Reaction time/min	Yield[c]/%
1	H_2O	15	92
2	C_2H_5OH	16	92
3	$CHCl_3$	30	85
4	THF	38	82
5	CH_3CN	20	92
6	$CH_3CO_2C_2H_5$	26	88

Reaction condition: [a] resorcinol (1 mmol), ethyl acetoacetate (1 mmol), $Ce(OTf)_4$ (1 mol%), solvent (2 mL); [c] Isolated yield.

In order to show the merit of ILs in comparison with the other catalysts used for the similar reaction, some of the results are tabulated in Table 2. According to Table 2, the required ratio for the most catalysts used for this purpose is >1 mol%. The required reaction yields are also much lower and times are much longer. After finding the optimized reaction conditions, further experiments were preceded by performing the reaction between a series of phenol derivatives with *β*-ketoester. To show the general applicability of this method, various monohydric and polyhydric phenols were efficiently reacted with one equivalents of *β*-ketoester in the same conditions. These results encouraged us to investigate the scope and the generality of this new protocol for various phenol derivatives under optimized conditions. As shown in Table 3, a series of phenol derivatives underwent electrophilic substitution reaction with *β*-ketoester to afford a wide range of substituted coumarin derivatives in good to excellent yields without any side products.

Table 2. Reaction of resorcinol with ethyl acetoacetate (synthesis of coumarin-entries 1-5) in the presence of different catalysts

Entry	Catalyst/mol%	Solvent/Temperature	Time/min	Yield/%	Ref.
1	$Ce(OTf)_4$/1	H_2O/r.t.	15	92	This work
2	PFPAT/10	Toluene/110 ºC	180	90	[42]
3	MFRH/0.05 gr	Solvent free/80 ºC	50	65	[43]
4	Oxalic acid/10	Solvent free/80 ºC	30	95	[44]
5	Nanoreactors/7	Solvent free/130 ºC	60	30	[45]

Table 3. Synthesis of coumarin derivatives employing of 1 mol% catalyst (IL)

Entry	phenol derivatives	R’	M.p (ºC)	Time (min)	Yield (%) [Ref.]
3a	phenol	Me	82-84	25	91 [43]
3b	resorcinol	Me	184-186	15	92 [47]
3c	hydroquinone	Me	185-187	15	92 [43]
3d	3- methoxyphenol	Me	162-164	19	91 [48]
3e	4-methoxyphenol	Me	165-167	16	92 [43]
3f	3-methylphenol	Me	133-135	18	92 [49]
3g	2-nitrophenol	Me	185-187	13	92 [47]
3h	4-nitrophenol	Me	151-153	9	97 [47]
3i	benzene-1,2,3-triol	Me	237-239	20	92 [50]
3j	benzene-1,3,5-triol	Me	286-288	19	94 [47]
3k	2-methylbenzene-1,3-diol	Me	138-140	23	92 [51]
3l	5-methylbenzene-1,3-diol	Me	259-261	21	93 [47]
3m	4-methoxybenzene-1,3-diol	Me	163-165	25	94 [51]
3n	resorcinol	Ph	256-258	13	93 [52]
3o	2-methylbenzene-1,3-diol	Ph	285-287	19	94 [52]
3p	benzene-1,2,3-triol	Ph	195-197	19	94 [52]
3q	benzene-1,3,5-triol	Ph	241-243	17	95 [52]
4a	2-hydroxybenzaldehyde	OMe	118-120	19	93 [53]
4b	2-hydroxy-4-methoxybenzaldehyde	OMe	200-202	17	94 [53]
4c	2-hydroxybenzaldehyde	OEt	92-94	16	93 [53]
4d	2-hydroxy-4-methoxybenzaldehyde	OEt	125-127	13	95 [53]

The nature and electronic properties of the substituents on the aromatic ring effect the conversion rate, and aromatic phenols having electron-withdrawing groups on the aromatic ring (Table 3, entries 3g, 3h) react faster than electron-donating groups (Table 3, entries 3b, 3c, 3e, 3f). Though meta and para- substituted aromatic Phenols gave good results and ortho-substituted aromatic phenols (such as 2-nitrobenzadehyde) gave lower yields because of the steric effects. As well, the work-up of present method was easy. It includes the pouring of reaction mixture on ethanol to precipitate the solid, which could be collected by filtration to give the corresponding coumarin product with better yield.

The reusability of the catalysts was checked using the reaction of resorcinol with ethyl acetoacetate as a model substrate. At the end of the reaction, CH_2Cl_2 was added to the mixture. The aqueous layer was separated and used without further purification. In this media, as shown in Figure 1, the recovered catalyst can be reused at least six additional times in subsequent reactions without appreciable loss in the catalytic activity.

4. Conclusions

The objective of this paper is to describe green, simple and efficient $C(OTf)_4$ to catalyze one-pot method for the synthesis of coumarin derivatives. The experimental procedure for this reaction is remarkably facile and requires no toxic organic solvents. The catalyst offers several advantages including mild reaction conditions, cleaner reactions, shorter reaction times, high yield of the products, lower catalytic loading as well as simple experimental and isolation procedures. In addition, the catalyst was able to be reused easily for six-time experiments with a small decrease in the catalytic activity of the recovered catalyst.

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سنتز تک مرحله اي و سبز مشتقات کومارين کاتاليز شده بوسيله سريم (4) تريفلات در دماي اتاق

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چکيده

سريم (4) تريفلات $[Ce(OTf)_4]$ به عنوان يک کاتاليزگر براي تهيه آسان مشتقات کومارين از طرق تراکم پچمن تک مرحله اي مشتقات فنول و β- کتو استر بکار گرفته شد. مشتقات مختلف فنول و β- کتو استرها در واکنش استفاده شد. در همه آزمايشات، محصولات مورد انتظار با موفقيت سنتز شدند. روش سنتزي جديد توصيف شده از مزاياي متعددي از جمله سالم بودن، شرايط ملايم، زمان هاي کوتاه واکنش، بهره بالا، ساده بودن و آساني جداسازي در مقايسه با روش هاي قبلي سنتزي برخوردار است.

کلمات کليدي: $[Ce(OTf)_4]$، کومارين، تراکم پچمن، β-کتو استر

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