

Pentafluorophenylammonium triflate (PFPAT): An efficient, metal-free and reusable catalyst for the von Pechmann reaction

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ABSTRACT

Pentafluorophenylammonium triflate (PFPAT) is used as an efficient catalyst in the von Pechmann condensation of phenols with β -ketoesters leading to the formation of coumarin derivatives. Short reaction times, easy and quick isolation of the products, excellent chemoselectivity, excellent yields and ease of catalyst recovery with consistent activity makes this protocol efficient and environmentally benign.

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1. Introduction

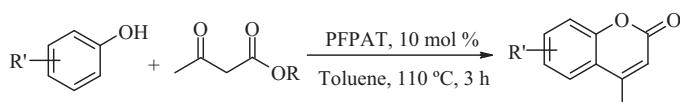
The ubiquitous coumarins have attracted more and more attention in both industrial and academic fields for decades. This interest arises from the fact that a variety of natural and synthetic compounds which contain the coumarin substructure exhibit significant biological activities such as inhibitory of platelet aggregation [1], antibacterial [2], anticancer [3], inhibitory of steroid 5 α -reductase [4] and inhibitory of HIV-1 protease [5]. For instance, 7-hydroxy 4-methyl coumarin (β -methylumbelliferon) is used as fluorescent brightener, efficient laser dye, standard for fluorometric determination of enzymatic activity and as a starting material for the preparation of insecticide and furano coumarins [6–8]. Moreover, coumarins act also as intermediates on the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols [9]. Owing to their important applications, various synthetic methodologies for coumarin derivatives have been developed. The von Pechmann reaction is a venerable reaction and it 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 [10]. Several acid catalysts have been used in the von Pechmann reaction including sulfuric acid [11], aluminium chloride [12], phosphorus pentoxide [13], trifluoroacetic acid [14] and other acids [15]. However, in many of these methods an excess amount of acid is needed to complete the reaction; for instance, reactions conducted in sulfuric acid [11] and trifluoroacetic acid [14] required 10–12 and 3–4 equivalent amount of acid respectively. Disposal of the acidic waste in these procedures also causes environmental pollution. Several other acid catalysts, including Lewis acids, are known to affect this condensation [16]. However, moisture sensitivity of the majority of Lewis acids to the water produced in the Pechmann reaction renders them unsuitable for use in large scale applications. Ionic liquids [17] and microwave irradiation [18] have been applied to the Pechmann reaction, but these methods also generated strongly acidic wastes and they utilize highly expensive and non-recyclable reagents. To improve the above mentioned problems, a number of heterogeneous alternatives such as Amberlyst ion-exchange resins [19], zeolites [20,21], montmorillonite K-10 [22], polyaniline sulfate salt [23,24], heteropoly acids [25], nafion resin/silica nanocomposites [26], nano-crystalline sulfated-zirconia [27] and sulfonic acid functionalized SBA-15 silica [28] have been employed for this purpose in

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Scheme 1.

the Pechmann condensation. Although these methods are effective, but some of them suffer from either a tedious synthetic methodology [23,24], or requirement of a large amount of catalyst to complete the reaction. For example, zeolites [20,21] and Amberlyst [19] are required in almost stoichiometric amount

Table 1

Pechman reaction of different substituted phenols with ethyl-acetoacetate employing PFPAT.

Entry	Phenol	Product	Yield [Ref.]
1			90 [28]
2			95 [33]
3			95 [28]
4			90 [28]
5			90 [28]
6			90 [33]
7			85 [28]
8			90 [28]
9			80 [28]
10			60 [33]
11			60 [33]
12			70 [28]

(phenol to catalyst weight ratio = 1); nafton resin/silica nanocomposites [26] and Amberlyst ion-exchange resins [19] are required in phenol to catalyst weight ratio of 2, for giving 80–96% yield of 7-hydroxy-derivative. Therefore, the search continues for a better catalyst for the synthesis of coumarins in terms of operational simplicity, reusability, economic viability, and greater selectivity. Organocatalysis has greatly gained importance in organic synthesis as it provides a high selectivity with fewer by-products, thus making it an environmentally benign alternative to chemical transformations [29]. Recently, Tanabe et al. reported the application of pentafluorophenylammonium triflate ($C_6F_5N^+H_3\cdot OTf^-$; PFPAT) as a novel organocatalyst in organic transformation such as esterification of carboxylic acids with alcohols [30], C-acylations of enol silyl ethers or ketene silyl (thio)acetals with acid chlorides [31] and Mukaiyama aldol and Mannich reactions using ketene silyl acetals with ketones and oxime ethers [32]. However, there are no any reports about the application in catalysis as a Brønsted acidic organocatalyst in the von Pechmann condensation. Herein, we report the first example of the PFPAT-catalyzed one-pot synthesis of coumarins in toluene at 110 °C (Scheme 1).

2. Results and discussion

To initiate our study, the reaction of ethyl acetoacetate with resorcinol was chosen as a model reaction in the presence of PFPAT (10 mol%) in toluene at room temperature, but no reaction was occurred. Much to our surprise, when we carried out the reaction in toluene at 110 °C, the corresponding coumarin derivative (Table 1, entry 1) was obtained in high yield (90%) after 3 h. A wide range of structurally varied phenols reacted smoothly and quickly to give the corresponding coumarins in high yield and purity as listed in Table 1.

The remarkable feature of this improved protocol is the wide stability of a variety of functional groups, such as ether, hydroxy, nitro, alkyl and amino group under the present reaction conditions. It is worth mentioning that substrates like phenol, nitrophenols and cresols which failed to react in many of the protocols reported in the literature [17a,33], showed better reactivity giving moderate to excellent yields. Substrates (entries 1–8) having electron-donating groups in the *para* position to the site of electrophilic substitution gave higher yields of the corresponding coumarins. Phenols, without having electron-donating groups (entry 10) or with an electron withdrawing group (entry 11) gave lower yield of the products. In the case of *m*-aminophenol (entry 12) a chemoselective reaction was occurred and 7-amino-4-methyl coumarin was formed in good yield.

The PFPAT catalyst was easily separated from the reaction mixture after work-up and recrystallized from hot hexane to give a pure PFPAT for subsequent use. For example, the reaction of ethyl acetoacetate with resorcinol afforded the corresponding coumarin in 90, 90 and 88% isolated yield over three cycles.

3. Conclusions

In conclusion, we have successfully demonstrated the catalytic activity of PFPAT in the von Pechmann condensation of phenols with β -ketoesters leading to the formation of coumarin derivatives. In addition to its simplicity and mild reaction conditions, this method has the ability to tolerate a wide variety of substitutions in both components, which can afford different substituted coumarins in high yields. The present practical method is a new candidate for synthetic chemists to apply for the von Pechmann reaction.

4. Experimental

4.1. Typical experimental procedure

A mixture of resorcinol (1 mmol), ethyl acetoacetate or methyl acetoacetate (1.1 mmol) dissolved in 3 ml toluene, and PFPAT (10 mol%) was refluxed with stirring for 3 h. The reaction mixture, after being cooled to room temperature was poured onto crushed ice and stirred for 5–10 min. The crystalline product was collected by filtration under suction (water aspirator), washed with ice-cold water (40 ml) and then recrystallized from hot ethanol to afford pure 7-hydroxy-4-methylcoumarin as colorless prisms (90%), mp 185–187 °C. The filtrate was concentrated under reduced pressure and then recrystallized from hot hexane to recover the PFPAT for subsequent use. This procedure was followed for the preparation of all the 4-substituted coumarins listed in Table 1. All the compounds were identified by comparison of analytical data (IR, ¹H NMR, and ¹³C NMR) and mp with those reported [28].

Spectroscopic data for selected examples follow:

7-Hydroxy-4-methyl-chromen-2-one (Entry 1): Colorless solid, mp 185–186 °C (lit. 184–185 °C); ¹H NMR (400 MHz; DMSO-*d*₆): δ = 2.31 (s, 3H), 6.1 (brs, 1H), 6.66 (s, 1H), 6.74 (d, *J* = 9 Hz, 1H), 7.53 (d, *J* = 9 Hz, 1H), 10.61 (brs, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 18.48, 102.6, 110.6, 111.1, 113.2, 127.1, 153.2, 155.2, 161.1, 162.5.

7,8-Dihydroxy-4-methyl-chromen-2-one (Entry 2): White solid, mp 242–243 °C (lit. 241–243 °C); ¹H NMR (400 MHz; DMSO-*d*₆): δ = 2.32 (s, 3H), 6.04 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 9.5 (brs, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 18.6, 110.5, 112.5, 113.2, 115.8, 132.6, 143.7, 149.8, 154.3, 160.6.

5,7-Dihydroxy-4-methyl-chromen-2-one (Entry 3): Colorless solid, mp 282–283 °C (lit. 281–283 °C); ¹H NMR (400 MHz; DMSO-*d*₆): δ = 2.12 (s, 3H), 5.70 (s, 1H), 6.14–6.34 (m, 2H), 10.26 (brs, 1H), 10.51 (brs, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 23.8, 94.3, 99.5, 102.5, 109.2, 155.4, 156.9, 158.4, 160.5, 161.4.

7-Methoxy-4-methyl-chromen-2-one (Entry 4): Colorless solid, mp 155–157 °C (lit. 156–158 °C); ¹H NMR (400 MHz; DMSO-*d*₆): δ = 2.38 (s, 3H), 3.83 (s, 3H), 6.2 (s, 1H), 6.92–7.66 (m, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 18.5, 56.3, 101.1, 111.6, 112.5, 113.5, 127.1, 153.9, 155.2, 160.6, 162.8.

7-Hydroxy-4,8-dimethyl-chromen-2-one (Entry 6): Colorless solid, mp 264–265 °C (lit. 263–265 °C); ¹H NMR (400 MHz; DMSO-*d*₆): δ = 2.11 (s, 3H), 2.31 (s, 3H), 6.11 (s, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 10.3 (brs, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 11.2, 18.6, 110.3, 111.1, 112.1, 113.1, 122.4, 152.2, 154.1, 159.1, 159.5, 161.2.

4-Methyl-benzo[*h*]chromen-2-one (Entry 9): Colorless solid, mp 154–155 °C (lit. 153–155 °C); ¹H NMR (400 MHz; DMSO-*d*₆): δ = 2.51 (s, 3H), 6.50 (s, 1H), 7.65–7.81 (m, 4H), 8.00–8.02 (m, 1H), 8.32–8.35 (m, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 19.1, 114.3, 115.5, 121.7, 122.1, 122.6, 124.4, 127.8, 129.1, 128.4, 134.7, 154.6, 160.1.

7-Amino-4-methyl-chromen-2-one (Entry 12): Colorless solid, mp 221–223 °C (lit. 223–225 °C); ¹H NMR (400 MHz; DMSO-*d*₆): δ = 2.28 (s, 3H), 5.87 (s, 1H), 6.06 (brs, 2H), 6.37–6.52 (m, 2H), 7.35–7.39 (m, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 18.4, 98.9, 107.9, 109.3, 111.6, 126.6, 153.5, 154.2, 155.9, 161.1.

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