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Expeditious Approach to Coumarins via Pechmann Reaction Catalyzed by Molecular Iodine or AgOTf

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Abstract: An efficient and facile route for the synthesis of coumarins via the Pechmann reaction catalyzed by molecular iodine or AgOTf was described.

Keywords: AgOTf, coumarin, iodine, Pechmann reaction

The prominence of coumarin in natural products and biologically active molecules has encouraged considerable efforts to synthesize it. As a privileged scaffold, substituted coumarin shows interesting biological properties, especially for anti-HIV and antibiotic activities.[1] Our continued interest to build a coumarin-based combinatorial library led us to develop efficient methods for the synthesis of diversified coumarin molecules.[2]

Coumarins have been synthesized by several routes, including Pechmann,[3] Perkin,[4] Knoevenagel,[5] Reformatsky,[6] and Wittig reactions[7] and by flash vacuum pyrolysis.[8] Among these, the Pechmann reaction is the most widely used method, because the reaction involves the use of simple starting materials, that is, phenols and β-keto esters, in the presence of acidic condensing agents. Various acids have been used to carry out this reaction.[9] However, many of these procedures suffered from harsh reaction conditions, difficulties in workup, and the use of stoichiometric and/or toxic, relatively expensive reagents. Because coumarin derivatives are increasingly useful and important in pharmaceuticals and industry, the development of simple, environmentally benign, low-cost protocols is still desirable.

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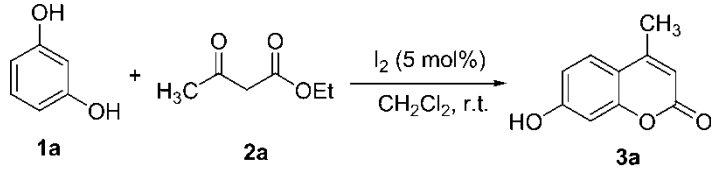
Recently, the use of molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations, which affords the corresponding products in excellent yields with high selectivity.[10] The mild Lewis acidity associated with iodine expanded its use in organic synthesis to several organic transformations, using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this ecofriendly element, iodine has been explored as a powerful catalyst for various organic transformations.[10] Recently, we found that it was also efficient as a catalyst in the synthesis of coumarins via the Pechmann reaction, which is disclosed herein.

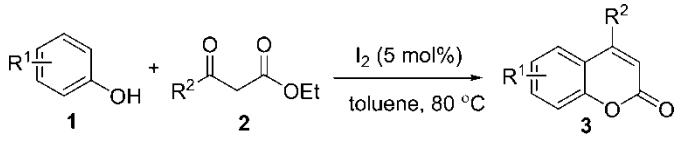
An initial study was performed by treatment of resorcinol **1a** with ethyl acetoacetate **2a** in CH_2Cl_2 in the presence of a catalytic amount of I_2 (5 mol%) at room temperature. To our delight, we observed the formation of 7-hydroxy-4-methyl-coumarin **3a** after 24 h (76% yield). When the reaction temperature was elevated to 40°C, complete conversion and 80% isolated yield was obtained after 16 h (Scheme 1).

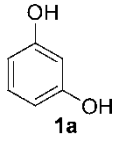
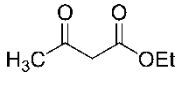
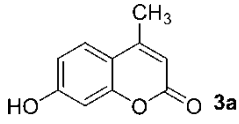
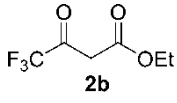
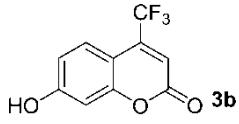
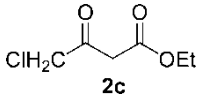
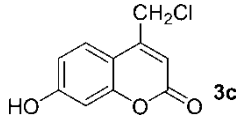
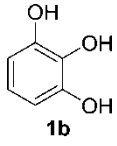
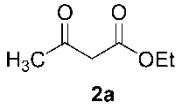
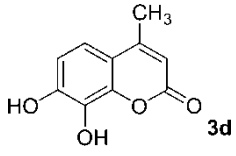
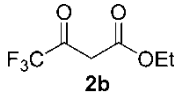
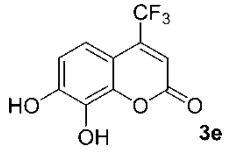
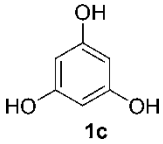
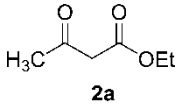
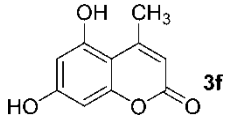
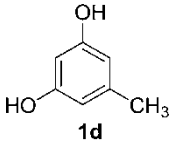
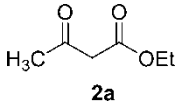
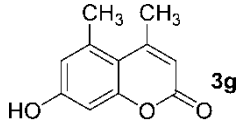
Further studies established that 1 mol% of catalyst was also efficient in this reaction, although prolonged reaction time was needed (48 h, 81% yield). Moreover, it is noteworthy that this reaction could be run in air without loss of efficiency. Among the solvents screened, (THF, MeCN, MeOH, toluene) toluene was demonstrated as the best. Further study for temperature showed that the reaction worked most efficiently at 80°C, and it went to completion in 3 h in toluene (with 85% isolated yield). To demonstrate the generality of this method, we next investigated the scope of this reaction under the optimized conditions (toluene, 5 mol% of iodine, 80°C), and the results are summarized in Table 1. As shown in Table 1, this method is equally effective for both phenols and β-keto esters. Various substituted phenols **1** reacted smoothly with β-keto esters **2** to produce a range of coumarin derivatives. Generally, reactions were performed at 80°C for 3–12 h irrespective of various range of substitutions. Complete conversion and good to excellent isolated yields were observed for all substrates employed. And in some cases, high catalyst loading had to be employed to obtain respective yields. For example, 50 mol% of iodine had to be utilized when resorcinol **1a** or benzene-1,2,3-triol **1b** reacted with ethyl trifluoroacetoacetate **2b**. On the other hand, because of



Scheme 1. Reaction of phenol **1a** with β-ketoester **2a** catalyzed by molecular iodine.

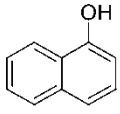
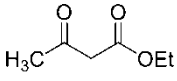
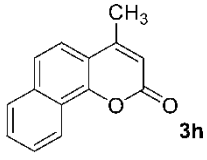
Table 1. Reaction of phenol **1** with β-ketoester **2** catalyzed by molecular iodine



Entry	Substrate 1	Substrate 2	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	85
2[b]		 **2b**	 **3b**	99
3		 **2c**	 **3c**	51
4	 **1b**	 **2a**	 **3d**	89
5[b]		 **2b**	 **3e**	82
6	 **1c**	 **2a**	 **3f**	70
7	 **1d**	 **2a**	 **3g**	88

(*continued*)

Table 1. Continued

Entry	Substrate 1	Substrate 2	Product	Yield (%)[a]
8	 **1e**	 **2a**	 **3h**	76

[a]Isolated yield based on phenol.
[b]50 mol% of I_2 was employed.

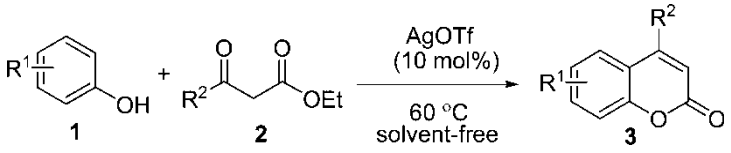
the growing concern about the influence of the organic solvent on the environment as well as on the human body, organic reactions without use of conventional organic solvents have attracted the attention of synthetic organic chemists.[11,12] We found that under solvent-free conditions, the reaction of resorcinol **1a** with ethyl acetoacetate **2a** also proceeded smoothly to afford the corresponding product **3a** at 60°C in 4 h, although the yield is slightly lower (80%).

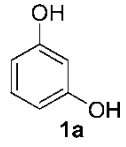
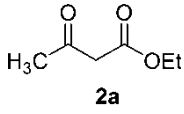
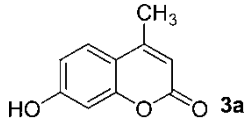
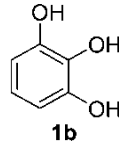
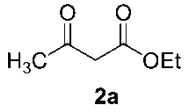
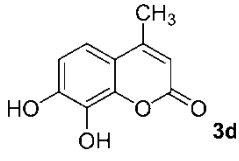
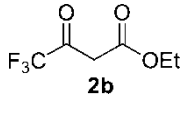
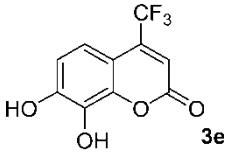
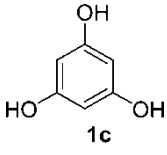
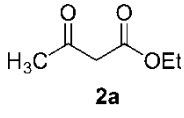
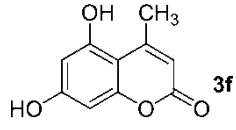
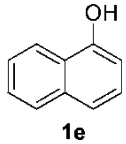
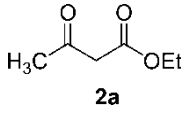
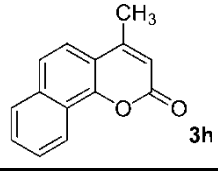
We also screened a series of metal salts, which are easily available for the reaction shown in Scheme 1 under solvent-free conditions at 60°C. Among the various metal salts studied for this transformation, AgOTf was found also effective for the reaction. The scope and generality of this process is illustrated with respect to various phenols **1** and β-keto esters **2**, and the results are summarized in the Table 2. Similar yields were obtained using 10 mol% of AgOTf at 60°C (3–10 h).

In a typical experimental procedure, the catalyst (method **A:** iodine, 5 mol%; method **B:** AgOTf, 10 mol%) was added to a mixture of resorcinol **1a** (0.50 mmol) and ethyl acetoacetate **2a** (0.60 mmol, 1.2 equiv.) under an air atmosphere (method **A:** toluene, 80°C; method **B:** solvent free, 60°C), and the mixture was stirred for a period of time (3–12 h). Following completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction mixture was cooled, diluted with ethyl acetate (10 mL), washed with water (5.0 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography to give the corresponding products **3a**.

In conclusion, we describe an efficient route for the synthesis of coumarins utilizing molecular iodine or silver triflate as a novel catalyst via the Pechmann reaction. This method not only provides a good complement to coumarin synthesis via the Pechmann reaction but also avoids the use of hazardous acids and harsh reaction conditions. The advantages of this method include the use of inexpensive reagents and catalyst under mild conditions and operational ease.

Table 2. Reaction of phenol **1** with β-ketoester **2** catalyzed by AgOTf



Entry	Substrate 1	Substrate 2	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	85
2	 **1b**	 **2a**	 **3d**	60
3		 **2b**	 **3e**	65
4	 **1c**	 **2a**	 **3f**	95
5	 **1e**	 **2a**	 **3h**	68

[a]Isolated yield based on phenol.

EXPERIMENTAL

All reactions were performed in test tubes under air atmosphere at room temperature. Flash column chromatography was performed as described by Still et al.[13] using silica gel (60-Å pore size, 32–63 μm, standard grade, Sorbent Technologies). Analytical TLC was performed using glass plates precoated with 0.25-mm, 230–400 mesh silica gel impregnated with a

fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~20 Torr (house vacuum) at 25–35°C. Commercial reagents and solvents were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with Varian 400 Inova spectrometers and are recorded in parts per million (PPM) from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$: δ 7.27, DMSO-*d*6: δ 2.50). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constant(s) in Hertz, integration, assignment].

General Procedure

Catalyst (method **A**: iodine, 5 mol%; method **B**: AgOTf, 10 mol%) was added into a mixture of phenol **1** (0.50 mmol) and β-keto esters **2** (0.60 mmol, 1.2 equiv.) under an air atmosphere (method **A**: toluene, 80°C; method **B**: solvent free, 60°C), and the mixture was stirred for a period of time (3–12 h). Following completion of the reaction as monitored by TLC, the reaction mixture was cooled, diluted with ethyl acetate (10 mL), washed with water (5.0 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography to give the corresponding products **3**. (All the products are known compounds. The characterizations of these compounds are identical with the literature reports.[9])

Data

7-Hydroxy-4-methyl-2H-chromen-2-one **3a**:[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 6.15 (s, 1H), 6.86 (d, J = 8.0 Hz, 1H), 7.00 (s, 1H), 7.05 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H).

7-Hydroxy-4-(trifluoromethyl)-2H-chromen-2-one **3b**:[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.70 (s, 1H), 6.78 (s, 1H), 6.87 (s, 1H), 7.08 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H).

4-(Chloromethyl)-7-hydroxy-2H-chromen-2-one **3c**:[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.00 (s, 2H), 6.41 (s, 1H), 6.75 (s, 1H), 6.85 (s, 1H), 7.66 (d, J = 8.8 Hz, 1H), 10.66 (s, 1H).

7,8-Dihydroxy-4-methyl-2H-chromen-2-one **3d**:[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 3H), 6.10 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 9.30 (br, 1H), 10.04 (br, 1H).

7,8-Dihydroxy-4-(trifluoromethyl)-2H-chromen-2-one **3e**:[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.70 (s, 1H), 6.92 (d, $J = 8.8$ Hz, 1H), 7.04 (s, 1H), 9.40–10.50 (br, 2H).

5,7-Dihydroxy-4-methyl-2H-chromen-2-one **3f**:[9a] ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.44 (s, 3H), 3.90–4.30 (br, s, 2H), 5.90 (s, 1H), 6.25 (d, $J = 1.8$ Hz, 1H), 6.35 (d, $J = 1.8$ Hz, 1H).

7-Hydroxy-4,5-dimethyl-2H-chromen-2-one **3 g**:[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.24 (s, 3H), 2.50 (s, 3H), 3.34 (s, 1H), 6.00 (s, 1H), 6.54 (s, 1H), 6.57 (s, 1H).

4-Methyl-2H-benzo[h]chromen-2-one **3 h**:[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.49 (s, 3H), 6.47 (s, 1H), 7.67–7.82 (m, 4H), 7.95–8.15 (m, 1H), 8.32–8.35 (m, 1H).

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