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Bismuth(III) nitrate pentahydrate—a mild and inexpensive reagent for synthesis of coumarins under mild conditions

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This work is dedicated to the late Dr. B. M. Khadilkar

Abstract—Bismuth(III) nitrate pentahydrate is found to be an efficient catalyst for the Pechmann condensation reaction of phenols and β-ketoesters under solvent-free conditions. The reaction protocol is simple and is followed by aqueous work-up leading to the formation of the corresponding coumarin derivatives in good yield and high purity.

Coumarins and their derivatives form an elite class of compounds, occupying an important place in the realm of natural products and synthetic organic chemistry. Their applications range from additives in food, perfumes, cosmetics, pharmaceuticals and in the preparation of insecticides,[1] optical brighteners[2] and dispersed fluorescent and tunable laser dyes.[3] Also, coumarins have varied bioactivities, for example, inhibition of platelet aggregation,[4] anticancer[5] and inhibition of steroid 5α-reductase.[6] These properties have made coumarins into interesting targets for organic chemists. The last decade witnessed a series of publications on the development of synthetic protocols for this important heterocyclic scaffold. Thus, it is clearly evident that the need for the development of new and flexible protocols is required, especially when they accommodate important functionalities and are broad in scope.

Coumarins have been synthesized by several routes including Pechmann,[7] Perkin,[8] Knoevenagel,[9] Reformatsky[10] and Wittig reactions[11] and by flash vacuum pyrolysis.[12] Among these, the Pechmann reaction is the most widely used method, as the reaction involves the use of simple starting materials, that is, phenols and β-ketoesters, in the presence of acidic condensing agents. The use of various reagents such as H_2SO_4, P_2O_5, $FeCl_3$, $ZnCl_2$, $POCl_3$, $AlCl_3$, PPA, HCl, phosphoric acid, trifluoroacetic acid, montmorillonite and other clays are all well documented in the literature.[13] Most of these methods suffer from severe drawbacks including the use of a large amount of catalysts, sometimes long reaction times and very often temperatures to the extent of 150 °C. Some of the recent achievements in the efficient construction of this nucleus include the development of cation exchange resins,[14] several solid acid catalysts[15a–c] and metal nitrates,[15d] supported polyaniline catalysts,[16] the use of microwave irradiation[17] and very recently, the use of ionic liquids as efficient catalysts.[18]

The use of bismuth(III) derivatives as catalysts in organic synthesis has increased considerably over the years. This new interest in bismuth is easily justified by its favourable ecological behaviour.[19]

Bismuth(III) nitrate pentahydrate, $Bi(NO_3)_3{\cdot}5H_2O$ is one such addition to the list of compounds exploited under this class. It is relatively nontoxic, inexpensive, insensitive to air and requires no special care during its handling. The potential of this reagent for aromatic nitration,[20a] oxidation of alcohols,[20b] deprotection of oximes,[20c] conversion of thiocarbonyls to the corresponding carbonyl compounds,[20d] aromatic iodination[20e] and Michael reactions[20f] has been recently explored. The versatility of this reagent encouraged us to study its utility for the Pechmann condensation. We

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Keywords: Coumarins; Pechmann condensation; $Bi(NO_3)_3{\cdot}5H_2O$; Solvent free.

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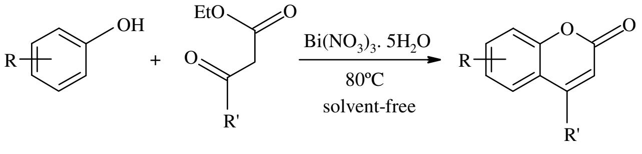
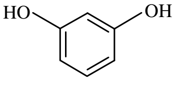
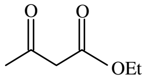
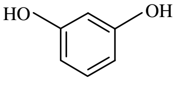
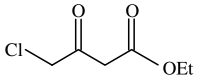
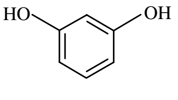
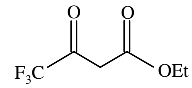
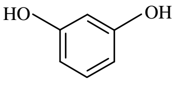
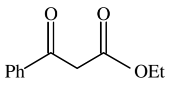
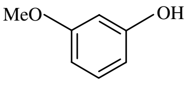
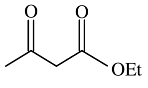
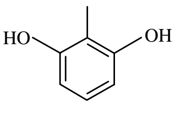
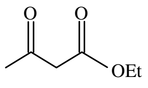
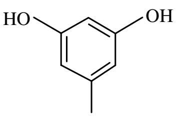
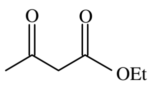
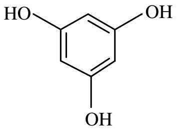
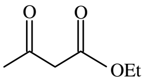
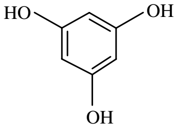
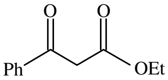
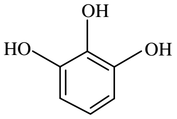
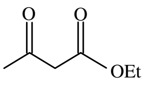
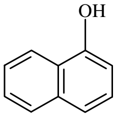
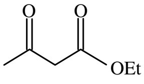
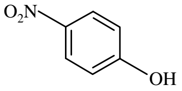
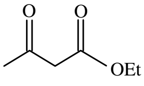
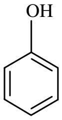
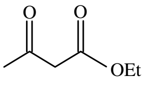
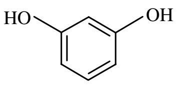
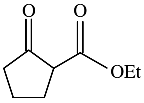
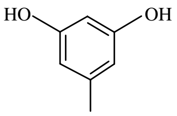
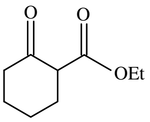


Scheme 1. Synthesis of coumarins using $Bi(NO_3)_3{\cdot}5H_2O$, under solvent-free conditions.

herein disclose for the first time the catalytic activity of bismuth(III) nitrate pentahydrate, for the efficient synthesis of coumarins, under solvent-free conditions (Scheme 1).[21]

To study the feasibility of the $Bi(NO_3)_3{\cdot}5H_2O$ catalyzed Pechmann condensation, the reaction of resorcinol with ethyl acetoacetate was selected as a model. Our initial experiments focused on the optimization of the amount of $Bi(NO_3)_3{\cdot}5H_2O$. We observed that only 5 mol % of $Bi(NO_3)_3{\cdot}5H_2O$ could effectively catalyze the reaction at a comparatively mild reaction temperature of 80 °C. An increase in the catalyst to 10 mol % showed no substantial improvement in the yield, though a slight improvement in the reaction time was observed. In view of the current interest in environmentally benign catalytic processes, a protocol involving a lower amount of $Bi(NO_3)_3{\cdot}5H_2O$ would be more appreciable, therefore we decided to extend the scope of the reaction using only 5 mol % of the catalyst. Thus, to generalize the solvent-free protocol, we subjected a series of monohydric and polyhydric phenols to react with a variety of β-ketoesters to obtain the corresponding substituted coumarins (Table 1).

Table 1. Synthesis of coumarins from phenols and β-ketoesters using $Bi(NO_3)_3{\cdot}5H_2O$[a]

Entry	Phenol	β-Ketoester	Time (min)	Yield[b] (%)
1			15	94
2			20	93
3			30	84
4			30	88
5			20	91
6			30	86
7			20	90
8			20	92
9			30	78
10			30	80
11[c]			120	72
12[c]			120	76
13[c,d]			300	47
14			30	84
15			20	77

[a] Phenol (10 mmol); β-ketoester (10 mmol); $Bi(NO_3)_3{\cdot}5H_2O$ (5 mol %); oil-bath temperature (80 °C); solvent free.

[b] Yields refer to isolated yields of pure products.

[c] The reaction was performed using 10 mol % $Bi(NO_3)_3{\cdot}5H_2O$.

[d] The reaction was carried out at 130 °C.

A wide range of structurally varied phenols reacted smoothly to give the corresponding coumarins in good yield and purity. The remarkable feature of this improved protocol is the wide stability of a variety of functional groups, such as ether, hydroxy, nitro, etc., 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, showed better reactivity giving moderate to excellent yields, under these reaction conditions.

Another important feature is that no detectable demethylation was observed in the case of 3-methoxy phenol (entry 5). In the case of 1-naphthol (entry 11) and *p*-nitrophenol (entry 12), a slightly larger amount of the catalyst (10 mol %) was required, to obtain the corresponding coumarin derivative. The reaction of phenol (entry 13) with ethyl acetoacetate was found to be the most sluggish, requiring a longer reaction time and also a higher reaction temperature (130 °C). To generalize the protocol, we also attempted the condensation reaction using a further variety of β-ketoesters such as 4-chloroethyl acetoacetate, ω,ω,ω-trifluoroethyl acetoacetate, benzoyl acetoacetate, 2-carbethoxy cyclopentanone and also 2-carbethoxy cylcohexanone. In all these cases, good yields of the corresponding coumarin derivatives were obtained. Thus, several pharmacologically relevant substituent patterns could be introduced with high efficiency under the present conditions. However, the reaction of resacetophenone and *m*-cresol with ethyl acetoacetate failed to give the coumarin derivative under the present conditions.

In conclusion, we have successfully demonstrated the catalytic activity of $Bi(NO_3)_3 \cdot 5H_2O$ for the synthesis of a variety of coumarins under solvent-free conditions. This practical and simple method led to good yields of the coumarin derivatives under mild conditions and within short times. This protocol could serve as a valuable alternative to known reaction systems.

Acknowledgements

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21. Typical experimental procedure: To the phenol (10 mmol) and β-ketoester (10 mmol), the bismuth nitrate pentahydrate (5–10 mol %) was added and the contents were stirred in a pre-heated oil-bath at 80 °C. After completion of the reaction, after the time indicated in Table 1, the reaction mixture was cooled to room temperature and the contents were poured into ice-cold water. The products were collected by filtration, washed with ice-cold water, and then recrystallized from hot ethanol to afford the coumarin derivative. All the coumarin derivatives are well-known in literature and were identified by comparison of their physical and spectral data.