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A one-pot [Bmim]OH-mediated synthesis of 3-benzamidocoumarins

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ABSTRACT

The first example of an ionic liquid-promoted one-pot synthesis of 3-benzamidocoumarins from salicylaldehydes and 2-pheny-1,3-oxazolan-5-one via Knoevenagel condensation-ring transformation cascades has been reported. No by-product formation, operational simplicity, ambient temperature and high yield (85–97%) are the salient features of the present synthetic protocol. After isolation of the product, the ionic liquid, [Bmim]OH can be easily recycled for further use without any loss of efficiency.

To design a catalyst with high activity and selectivity, which is benign to the environment and easily recovered, is an interesting and rapidly growing area of synthetic chemistry. Owing to their green credentials, ionic liquids (ILs) have attracted considerable interest as environmentally benign reaction media,[1–4] catalysts[4–6] and reagents.[7] They are also easy to recycle.[7] Although ILs are still significantly greener than volatile organic solvents, there are environmental issues with their biodegradability and toxicity, hence recently, considerable attention has been paid in this regard.[8]

Coumarins (2*H*-1-benzopyran-2-ones) are an elite class of compounds present in natural and non-natural products and have found applications in technological[9] and therapeutic[10] fields. 3-(N-substituted)aminocoumarins are of special interest as their derivatives have been found to possess many biological activities such as antibacterial,[11] antiallergic,[12] insect-growth regulatory,[13] and CNS depressant.[14] Also, they show the potential for use as anticancer drugs.[15] Novobiocin (Fig. 1), a 3-benzamidocoumarin derivative, is the only coumarin antibiotic which has been licensed for the treatment of human infections and its efficiency has been confirmed in several clinical trials.[16] Novobiocin also inhibits a well-validated drug target (DNA gyrase)[17] and is an exciting new target in the cancer drug discovery.[18]

Moreover, 3-(N-substituted)aminocoumarins have found applications as fluorescent markers and are also known to exhibit photochemical properties.[19] From a chemical viewpoint, 3-aminocoumarins are effective as starting materials for the synthesis of different molecules of high biological and medicinal interest, such as 1,2,3,4-tetrahydropyrido[2,3-*c*]coumarins,[20] tetrahydro-6*H*-benzo[*c*]chromene-6-ones,[21] pyrrolocoumarins,[22] and pyrano[3,2-*f*]benzothiophenes,[23] thus, increasing the synthetic utility of this biologically and pharmaceutically important ring system. These unique properties have triggered a renewed interest in developing new synthetic methods which enable rapid access to 3-amidocoumarins. Naturally, there has been a continuous effort to develop new, convenient and versatile syntheses of coumarins,[24] though the literature records limited routes to 3-(N-substituted)aminocoumarins.[25] The most common method is the multistep reduction of 3-nitrocoumarins followed by N-functionalization.[18b,26] Recently, a Buchwald–Hartwig coupling protocol has been reported for the synthesis of 3-(N-substituted)aminocoumarins starting from 3-halocoumarins with defined structural features.[25a] Although this method is a good addition to this area, the yields were not consistently good and the reactions were performed at higher temperatures using bulky ligands and bases as catalysts. This method does not cater a direct process for the synthesis of 3-amidocoumarins.

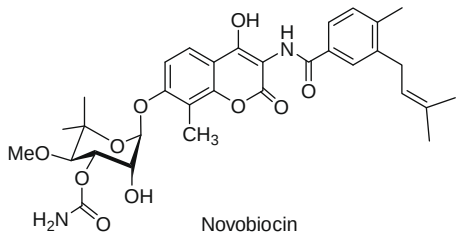

Figure 1. Natural antibiotic containing a 3-benzamidocoumarin motif.

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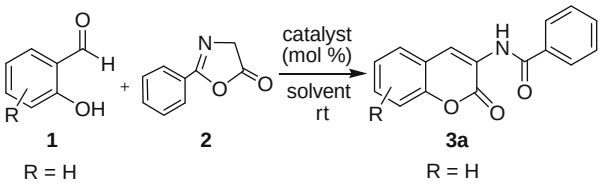
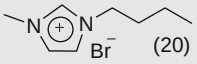
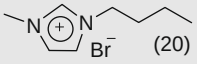
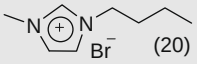
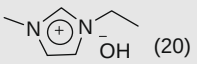
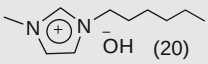
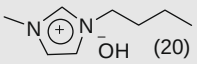
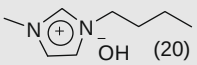
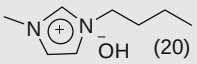
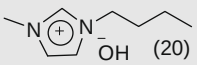
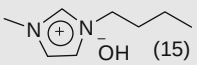
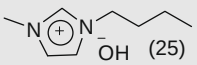
In this Letter, we report a new one-pot method for the preparation of 3-benzamidocoumarins **3** in a single step using ionic liquid [Bmim]OH as a green reaction promoter. The method is highly atom efficient as there is no by-product formation. This one-pot synthetic protocol involves the novel utilization of masked amino acid, 2-phenyl-1,3-oxazolan-5-one **2** with salicylaldehyde **1**, a bifunctional building block whose application in coumarins chemistry[24] as well as in the construction of various fused oxygen heterocycles of chemical and biological interest is well documented,[27] and is the cornerstone of the present investigation (Scheme 1). Furthermore, the present synthesis of 3-(N-substituted) amino functionalized coumarins is an outcome of our quest for developing new heterocyclic frameworks using green protocols,[28] especially ionic liquids.[28a,b]

In our preliminary experiments, we investigated the optimization of reaction conditions regarding both the catalyst and solvent. For this purpose, salicylaldehyde **1** (R = H) and 2-phenyl-1,3-oxathiolan-5-one **2** were chosen as model substrates for the synthesis of representative compound **3a** (Table 1). First, we performed the reaction using [Bmim]Br as a catalyst and MeOH as a solvent for Knoevenagel condensation-ring transformation cascades. The reaction did take place, but the yield of the target compound **3a** was not good (Table 1, entry 1). With the hope of increasing the yield, we tried the reaction in other solvents such as CH_2Cl_2 and CH_3CN. Although among MeOH, CH_2Cl_2 and CH_3CN, CH_3CN was found to be the best solvent, there was no satisfactory increase in the yield (Table 1, entries 1–3). This indicates that [Bmim]Br is not an efficient catalyst for the present reaction.

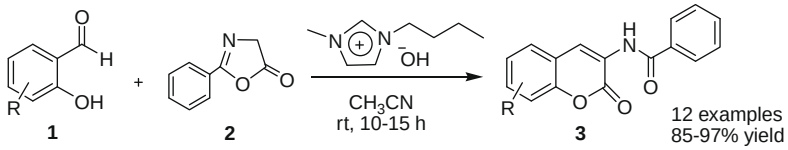
Then, we began to harness the basic IL [Bmim]OH as a catalyst, which evidenced its catalytic efficacy in the reaction affording **3a** in excellent yields (Table 1, entry 6). This is in conformity with the earlier report on [Bmim]OH-catalyzed Knoevenagel condensation reactions.[24f] In addition, several imidazolium-based ILs were tested by varying their alkyl substituents and [Bmim]OH was found to be the most effective catalyst (Table 1, entries 4–6). The optimum catalyst loading for [Bmim]OH was found to be 20 mol %. When the amount of the catalyst decreased to 15 mol % from 20 mol % relative to the substrates, the yield of product **3a** was reduced and more time was required to complete the reaction (Table 1, entries 6 and 10). However, the use of 25 mol % of the catalyst showed the same yield and the same time was required (Table 1, entries 6 and 11). However, the reaction did not occur without using a catalyst (Table 1, entry 12). Optimization of the solvent for the synthesis of **3a** using [Bmim]OH was also undertaken and it was found that amongst THF, CH_2Cl_2, MeOH and CH_3CN (Table 1, entries 6–9), the best solvent in terms of yield and reaction time was CH_3CN (Table 1, entry 6). It was noted that a higher reaction temperature, for example, in a refluxing solvent instead of at rt, had no any appreciable effect on the yield. Next, in order to investigate the substrate scope for the general validity of the present investigation, a variety of substituted salicylaldehydes **1** were used employing the present optimized reaction conditions and different 3-benzamidocoumarins **3** were synthesized.[29] The yields were consistently good (Table 2) and the highest yield was 97% (Table 2, entry 6). The [Bmim]OH was prepared employing the known method.[30]

Table 1
Optimization of reaction conditions for the formation of representative compound **3a**[a]



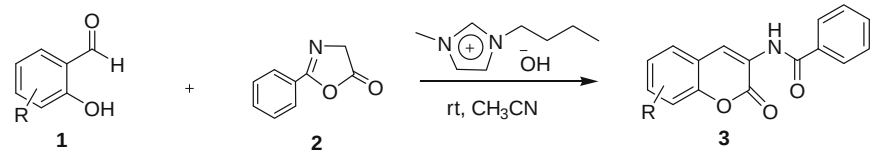
Entry	Catalyst (mol %)	Solvent	Time[b] (h)	Yield[c] (%)
1	 (20)	MeOH	15	42
2	 (20)	CH_2Cl_2	15	39
3	 (20)	CH_3CN	15	48
4	 (20)	CH_3CN	18	72
5	 (20)	CH_3CN	12	89
6	 (20)	CH_3CN	12	91
7	 (20)	THF	15	80
8	 (20)	CH_2Cl_2	14	78
9	 (20)	MeOH	14	83
10	 (15)	CH_3CN	15	85
11	 (25)	CH_3CN	12	91
12	—	CH_3CN	12	—

[a] For the experimental procedure, see Ref. 29.
[b] Time required for completion of the reaction as monitored by TLC.
[c] Yield of isolated and purified products.



Scheme 1. Direct synthesis of 3-benzamidocoumarins **3**.

Table 2
One-pot synthesis of 3-benzamidocoumarins **3**[a]



1 + **2** → **3**

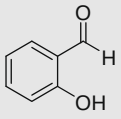
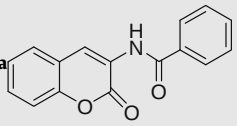
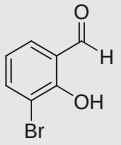
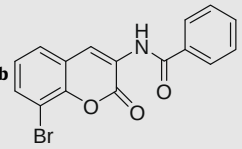
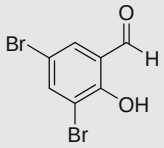
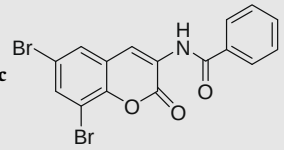
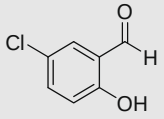
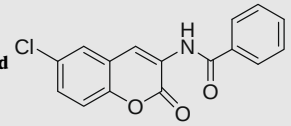
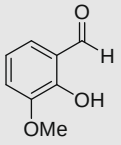
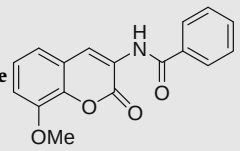
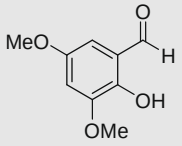
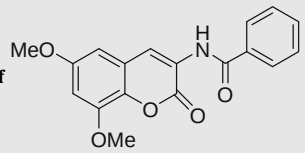
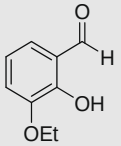
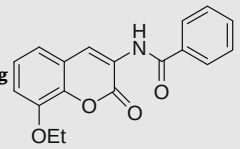
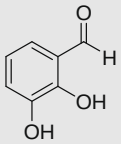
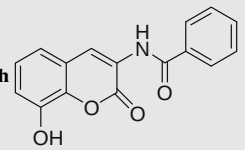
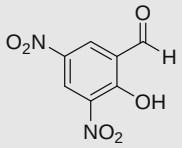
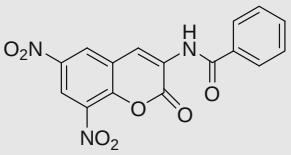
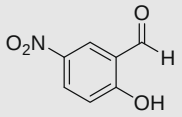
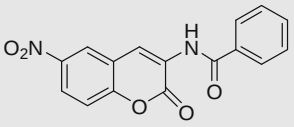
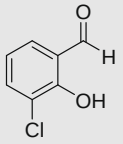
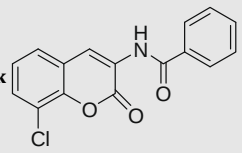
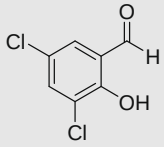
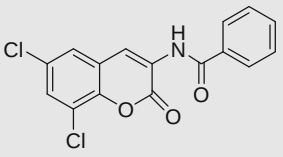
Entry	Salicylaldehyde **1**	Reaction time[b] (h)	3-Aminocoumarin **3**	Yield[c,d] (%)
1		12	**3a** 	91
2		13	**3b** 	94
3		10	**3c** 	95
4		12	**3d** 	89
5		12	**3e** 	94
6		15	**3f** 	97
7		13	**3g** 	96
8		14	**3h** 	92

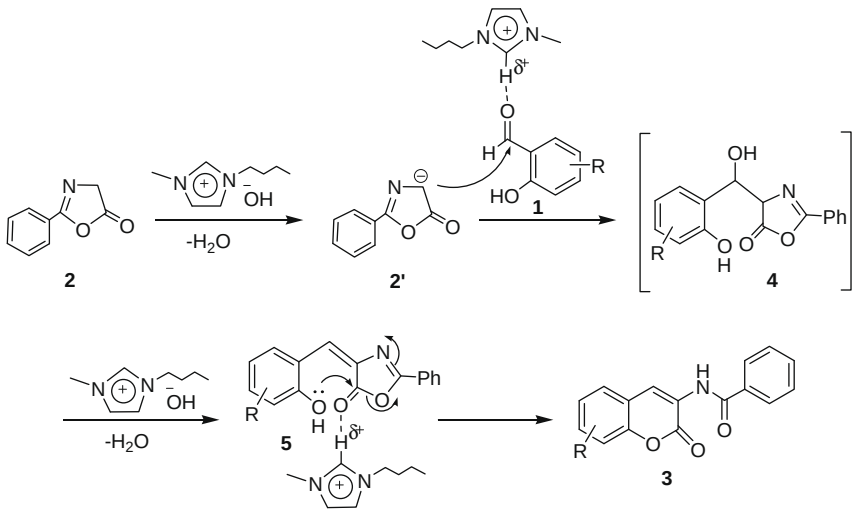
Table 2 (*continued*)

Entry	Salicylaldehyde **1**	Reaction time[b] (h)	3-Aminocoumarin **3**	Yield[c,d] (%)
9		11	**3i** 	85
10		12	**3j** 	89
11		12	**3k** 	90
12		10	**3l** 	93

[a] For the experimental procedure, see Ref. 29.
[b] Time required for completion of the reaction as monitored by TLC.
[c] Yield of isolated and purified products.
[d] All compounds gave C, H and N analyses ±0.39% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EI-MS) data.

The formation of **3** is rationalized by the nucleophilic attack of the active methylene carbon (C-4) of **2** to the carbonyl carbon of salicylaldehyde **1** followed by dehydration of **4** leading to the isolable intermediate **5**. The driving force for the dehydration process is the presence of a high degree of conjugation of the C=C bond formed in intermediate **5** and also assisted by [Bmim]OH. The adduct **5** undergoes the intramolecular nucleophilic attack of the oxygen atom of the OH group on the carbonyl carbon (C-5) of the oxazolan-5-one nucleus to yield target compounds **3** (Scheme 2). This conclusion is based on the observation that the representative intermediate compound **5a** (R = H) could be isolated in 49% yield and that it could be converted into the corresponding coumarin **3a** in quantitative yield (Scheme 2).[31] It is noteworthy that in all these cases the intermediate **4** was never isolated.

Here, [Bmim]OH not only acts as a base to generate a carbanion at the methylene carbon in **1** but it also catalyzes the reaction probably through a hydrogen bond formation with the carbonyl oxygen of salicylaldehyde **1**, thereby increasing the electrophilic character of its carbonyl carbon. Moreover, it also helps in the dehydration by producing an anion at C-4 of the oxazolan-5-one ring, and ring transformation step probably through hydrogen bonding with the C=O group of intermediate **5** as depicted in



Scheme 2. Plausible mechanism for the formation of 3-benzamidocoumarins **3** and the role of [Bmim]OH.

Scheme 2. Thus, [Bmim]OH promotes all the steps, that is, Knoevenagel condensation and dehydration steps by acting as a strong base and the ring transformation step owing to the acidic character of C-2 proton of the imidazolium cation (Scheme 2). The Knoevenagel condensation has also been previously studied for its 'greenness',[32] The reactions were clean and all the synthesized products were characterized by their ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data.

In summary, we have documented a one-pot high yielding synthetic protocol for 3-benzamidocoumarins using the environmentally benign catalyst [Bmim]OH. In the present investigation there is no by-product formation and also the ionic liquid [Bmim]OH used could be easily recycled for further use without any loss of efficiency. Thus, this simple methodology would be a practical alternative to the existing procedures for the production of this kind of fine chemical to cater to the need of academic institutions as well as of industries.

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29. *General procedure for the synthesis of 3-benzamidocoumarins* **3**: A mixture of 2-phenyl-1,3-oxazol-5-one **2** (2.0 mmol), salicylaldehyde **1** (2.0 mmol) and [Bmim]OH (0.4 mmol) in 10 mL of CH_3CN was stirred at room temperature for 10–15 h. After completion of the reaction as indicated by TLC, 20 mL of water was added and the product was extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and were evaporated under reduced pressure to afford the crude product, which was recrystallized from ethanol to afford an analytically pure sample of **3** (Table 2). After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (10 mL) to remove any organic impurity, dried under vacuum at 90 °C to afford [Bmim]OH, which was used in subsequent runs without further purification. Physical data of the representative compound **3d**: Yellowish solid, yield 89%, mp 171–173 °C. IR (KBr) ν_{max} 3348, 3033, 1746, 1659, 1599, 1581, 1457 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$/TMS) δ 6.91 (s, 1H, 4-H, 7.03–7.65 (m, 6H$_{arom}$), 7.81–8.08 (m, 2H$_{arom}$), 8.66 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ 118.5, 121.3, 124.2, 125.3, 126.0, 127.5, 130.1, 131.2, 132.8, 133.5, 134.1, 151.9, 168.9, 176.7. EIMS (*m/z*): 299, 301 (M, M+2). Anal. Calcd for $C_{16}H_{10}ClNO_3$: C, 64.12; H, 3.36; N, 4.67. Found: C, 63.73; H, 3.61; N, 4.39.
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31. *Isolation of the intermediate compound* **5a** *and its ring transformation into the corresponding compound* **3a**: The procedure followed was the same as described above for the synthesis of **3** (Ref. 29) except that the time of stirring in this case was 8 h instead of 12 h for **3a**. The adduct **5a** was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to obtain an analytically pure sample of **5a** in 49% yield. A mixture of the intermediate compound **5a** (2.0 mmol) and [Bmim]OH (0.4 mmol) in 10 mL of CH_3CN was stirred at rt for 4 h to give the corresponding product **3a** quantitatively and was isolated and purified in the same way as described above for **3a**. The ionic liquid [Bmim]OH was also recovered by following the same procedure as described in Ref. 29. Physical data of isolated intermediate compound **5a**: Yellowish solid, yield 49%, mp 157–159 °C. IR (KBr) ν_{max} 3389, 3051, 1745, 1605, 1579, 1451 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$/TMS) δ 6.27 (br s, 1H, OH, exchangeable with D_2O), 6.89–7.85 (m, 10H$_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ 114.3, 117.4, 119.2, 125.5, 127.5, 129.9, 130.2, 131.1, 132.3, 133.0, 135.5, 156.5, 161.5, 172.7. EIMS (*m/z*): 265 (M^+). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.14; H, 3.95; N, 5.57.
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