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Mild, Efficient, One-Pot Synthesis of Imidazolones Promoted by *N*,*O*-Bistrimethylsilylacetamide (BSA)

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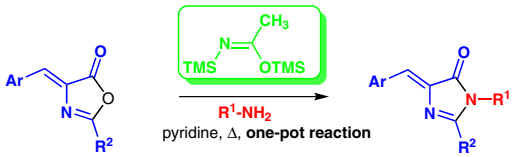

synthesis of 4,4-dialkyl and 4-arylidene imidazolones:
R^1 = alkyl, aryl ; R^2 = **H**, alkyl, aryl, alkenyl
24 examples
yields 45–99%

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Abstract The formation of imidazolones by means of dehydrative cyclization was developed, using bistrimethylsilylacetamide. This highly versatile, friendly, safe, and cost-effective reagent exhibited a very large scope of starting materials, since it can promote the formation of 4-benzylidene imidazolones, 4,4-dialkyl-imidazolones, bearing alkyl, aryl, or even no substituent at C2, the latter being unavailable by classical methods. This reagent also afforded clean and high-yielding one-pot reactions in the presence of amine or imine reagents.

Key words imidazolone, oxazolone, amide dehydration, bistrimethylsilyl acetamide, silylating agent

Imidazolones are compounds of very high importance in many research areas, in particular as fluorescent probes derived from naturally occuring fluorescent proteins. Our recent investigations[2a] in the field of CH arylation of 2*H*-imidazolones prompted us to find reliable sources of the latter. In the literature, several routes towards imidazolones are described, each one having its own scope and limitations. Besides the classical Erlenmeyer synthesis,[2b] more recent advances in this field have emerged. The reaction of glycine imidate with imines[3] is also widely used, however, its main limitation concerns the availability of the imidate, restricting the choice of substituents at C2. Other syntheses published recently include copper-catalyzed coupling of amidines[4a] or addition of amidines to acetylenic compounds.[4b]

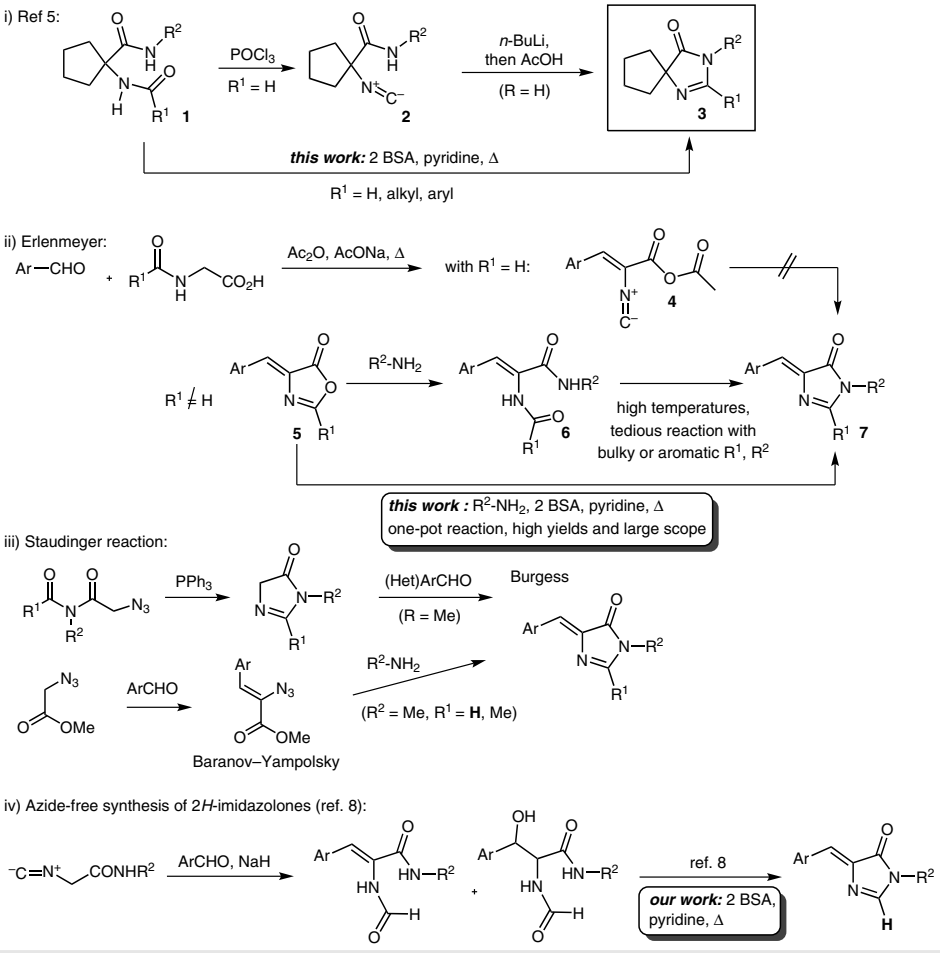
Despite these recent achievements and already abundant literature in this field (Scheme 1), a general method compatible with all families of imidazolones is still required and this prompted us to develop a mild and versatile procedure to access these compounds. Unconjugated imidazolones, especially 4,4-dialkylated compounds, are readily available following the methodology described by Marcaccini et al.[5]; the isonitrile **2** being a useful precursor of 2*H*-imidazolones. The authors developed a *n*-BuLi-promoted addition of the amide anion onto the vicinal isonitrile, followed by AcOH protonation at low temperature. In our hands, this procedure worked smoothly with 4,4-dimethyl and 4,4-cycloalkyl isonitriles, but proved unsuccessful in the case of 4-benzylidene imidazolones, since the latter are more stabilized by conjugation with the aromatic ring. Furthermore, although high yields were obtained, the compatibility of functional groups with $POCl_3$ or *n*-BuLi would become a major issue in this strategy, leading us to prepare these compounds using *N*,*O*-bistrimethylsilylacetamide (BSA), a mild reagent with a large tolerance for usual functional groups.

Concerning conjugated, 4-arylidene imidazolones, the Erlenmeyer condensation[2b] remains, to date, the most widely used synthesis. In such process, the N-acylated amino acid is first condensed with an aldehyde in the presence of acetic anhydride and sodium acetate, to yield the Erlenmeyer oxazolone or azlactone **5**. In this compound, the carbonyl group is sufficiently activated to allow further amidification with primary amines such as methylamine or benzylamine, giving the diamide **6**. Ring closure leading the imidazolone **7** through extrusion of a water molecule has been obtained by various methods, the most widespread being to reflux in ethanol. Unfortunately, two major issues rapidly appeared when we tried to use this procedure for the preparation of our target compounds. First, the yields of the ring-closing step were generally very low when the amine component of the reaction was other than methylamine, the reaction being highly sensitive to steric hindrance. On the other hand, when we attempted this procedure with *N*-formyl glycine, the formation of the Erlenmeyer azlactone proved unsuccessful, since the formamide had a high propensity for dehydration in the presence of acetic anhydride, leading to the isonitrile **4**. In contrast with

4,4′-dialkyl analogues, a similar isonitrile bearing a carboxamide at C1 gave no ring closure upon deprotonation and led only to degradation products.

At this stage, we faced the requirement for mild conditions that would allow the activation of *N*-formyl-2-amino acid amides with a sufficiently poor leaving group to avoid the formation of the isonitrile. In addition, we became interested in a method that would allow the synthesis of both 4,4-dialkyl and 4-benzylidene imidazolones and would be versatile enough to furnish 2*H*- or 2-substituted imidazolones. Therefore, we wished to develop a robust and versatile protocol for the formation of both families of imidazolones, avoiding substrate dependence and restrictions due to other functional groups.

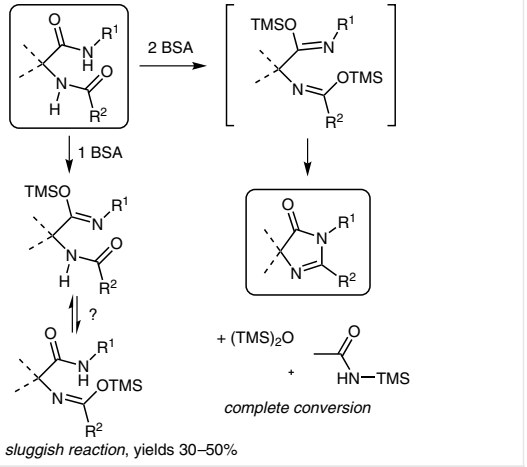
Initially, we tested the literature conditions in the case of cycloleucine derivative **1**, obtained in one step by Ugi condensation from cyclopentanone and benzyl isonitrile. As described,[5] deprotonation of the *N*-benzylamide with *n*-BuLi at –60 °C resulted in a rapid attack on the isonitrile, the imidazolone carbanion being subsequently reprotonated with acetic acid to yield the 2H compound. However, this synthetic route first requires the preparation of the isonitrile **2** by $POCl_3$-mediated dehydration of the formamide, meaning a two-step synthesis with prior isolation of the isonitrile. Although this reaction proceeded smoothly, we were attracted by the possibility of carrying out direct dehydrative ring formation through formamide activation with a leaving group of moderate electron-withdrawing character. Thus, the OTMS group was chosen. We focused our attention towards *N*,*O*-bistrimethylsilylacetamide or BSA as a mild and easy-to-handle silylating agent.[6] Since the original report mostly concentrated on silylation of amides, enols, and phenols,[6b] many other uses have been reported for this reagent; such as transient protection of carboxylic acids,[6c] with simultaneous N-silylation to enhance amine nucleophilicity in the case of amino acids,[6d] or selective acid protection of *N*-Boc peptides to minimize use of TMSI used for *N*-Boc cleavage.[6e] Besides its silylating properties, this reagent was also recently employed as a building block in oxazole synthesis.[6f] This reagent has several advantages. Firstly, it does not require any additional base, as is needed with TMSCl or TMSOTf which both release a strong



Scheme 1 Use of BSA in the synthesis of 4,4′-dialkyl, 4-arylidene, 2*H*-, 2-alkyl, 2-aryl imidazolones

acid. On the other hand, its moderate reactivity makes it compatible with a wide range of functional groups. For instance, we observed a selectivity of the amide towards the *tert*-butyl carbamate group (vide supra). In addition, BSA is less expensive and more stable over prolonged storage than bis(trimethylsilyl) trifluoroacetamide or BSTFA. Finally, one of the most important reasons for selecting this reagent over TMSCl or HMDS lies in the formation of inert byproducts, avoiding both the nucleophilic character of ammonia released from HMDS, or the acid arising from TMSCl or TMSOTf.

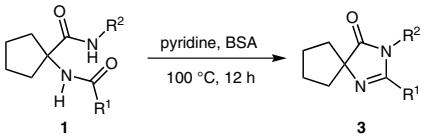
Mechanistic considerations led us to consider both sites of silylation. As depicted in Scheme 2, a monosilylation of the diamide may require selectivity to lead to cyclization, or be reversible and afford the imidazolone upon equilibrium shift. However, we observed that the use of one single equivalent of BSA never resulted in a complete conversion, while quantitative cyclizations were obtained with two equivalents of BSA. This result suggests that a disilylated intermediate is required, affording both electrophilic character at C2 and a nucleophilic nitrogen at N1. Obviously, only one TMS group is transferred from each BSA molecule, since the NMR spectra of the crude materials exhibit the signals expected for *N*-TMS acetamide.[7]



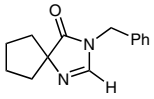
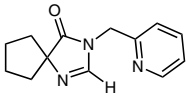
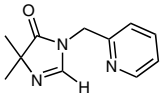
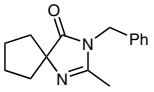
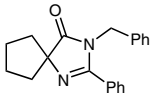
Scheme 2 Proposed mechanism

As listed in Table 1, the synthesis of 2*H*-imidazolones **3a**,**b** starting from *N*-formyl-cycloleucine derivatives occurred with good yields with no formation of the isonitrile (Table 1, entries 1 and 2). Dimethylglycine, a substrate profiting from the Thorpe–Ingold effect gave an 83% isolated yield of imidazolone (Table 1, entry 3). Although the BSA reactivity is moderate, we were interested to determine whether it exhibited a sufficient O-silylating ability for the cyclization of amides with alkyl or aryl groups instead of more reactive formamides. For this purpose, *N*-propionyl and *N*-benzoyl cycloleucines were prepared from propionic anhydride and benzoyl chloride, respectively, the acid moiety being coupled with benzylamine.

Table 1 Synthesis of Cycloleucine-Derived Imidazolones



1 **3**

Entry	Imidazolone **3**		Yield (%)
1	**3a**		74
2	**3b**		77
3	**3c**		83
4	**3d**		80
5	**3e**		63

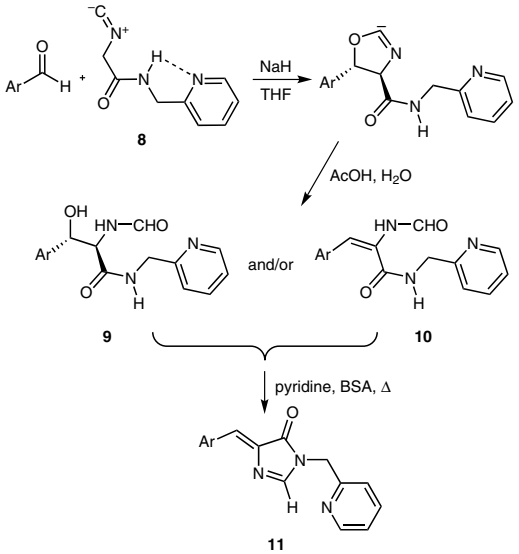
Both diamides were tested under the same dehydrative conditions (2 equiv of BSA in pyridine, 0.5 M substrate concentration), with heating at 100 °C for 12 h. Pleasingly, 80% and 63% yields were obtained respectively (Table 1, entries 4 and 5), demonstrating that BSA was suitable for more hindered, less reactive substrates.

These promising results prompted us to examine whether the method could be applied to conjugated (4-arylidene) imidazolones, since the latter are important in the field of fluorescent molecules with biological and material applications.

Our starting point was the synthesis of 2*H*-4-benzylidene imidazolones that were required as substrates for CH arylation and vinylation at C2.[8] The literature concerning this particular class of compounds is sparse, presumably due to ring closure of formamides not occurring under the Erlenmeyer conditions. We believed that any harsh dehydrating reagent would lead to the isonitrile, since the acetate itself can be eliminated from the *O*-acetylformamide before the nucleophilic attack of the nitrogen atom of the neighboring amide. Moreover, by analogy with cycloleucine analogues, there is a specific route using the Staudinger reaction, for the preparation of imidazolones having no sub-

stituent at C2 (R^1 = H), and the latter may be considered as a particular class of compounds with a completely different reactivity.

Indeed, as presented in Scheme 3,*N*-formyl-dehydroaminoamides and their 'aldol' analogues can be obtained in high yields via a [3+2] cycloaddition[9] of aldehydes or ketones with deprotonated isocyano acetamides such as compound **8**; the latter being prepared by simple amidification of commercially available methyl isocyanoacetate. Cycloaddition followed by acidic hydrolysis with aqueous acetic acid led to 2-formamido-3-hydroxyamides **9**. Interestingly, when we applied this reaction, with a slight modification of the published protocol, starting from picolylamine derivatives, good diastereomeric ratios (ca. 95:5) were obtained, whereas *N*-benzyl amides resulted in approximately 60:40 dr. As our target was the dehydrated form, we did not investigate the stereochemical outcome of the reaction further. Depending on the substituent on the aromatic ring, carrying out the reaction under the same conditions can lead either to the hydroxylated form **9**, or the dehydroamidoamide **10**, or even mixtures of both compounds. Nevertheless, both products, either pure or as a mixture, can be cleanly dehydrated upon heating with BSA in pyridine, leading to 2*H*-imidazolones **11**. In our preliminary work,[8] we exclusively focused on 2*H*-imidazolones, and we initially believed that BSA was only suitable for *N*-formyl amino amides, since the latter are the less-hindered and most reactive in this series. It is worth noting that these conditions are still compatible with formamides, although acetic anhydride only led to the corresponding isonitrile. Furthermore, the isonitrile-bearing amide cannot lead to base-promoted ring closure as with cycloleucine, since the conjugation of the isonitrile with the aromatic ring precludes imidazolone formation.



Scheme 3 Synthesis of 2*H*-imidazolones

To the best of our knowledge, our cyclization method with BSA is the first example of formation of 2*H*-imidazolones through a dehydration process. In the literature, besides the isonitrile/amide ring closure, the Staudinger reaction has been described[10] and extensively used by Burgess[11] as a versatile source of fluorescent imidazolones by means of a further Knovenagel condensation. The group of Baranov and Yampolsky also used the Staudinger reaction,[10c] enabling the synthesis of 2*H*-imidazolones for the first time although with a moderate yields. Following our strategy, we could prepare imidazolones on a multigram scale, in a very short sequence, avoiding the use of potentially explosive azides.

In this study, we wished to examine the reactivity of a wide range of diamides, obtained through a one-pot procedure starting from oxazolones, under similar conditions. For over a hundred years, the Erlenmeyer procedure[2b] for the preparation of imidazolones has been extensively used. This consists of a preliminary condensation of *N*-acyl amino acids with the appropriate aldehyde, heating in acetic anhydride in the presence of anhydrous sodium acetate. The formation of the oxazolones generally proceeds efficiently; however, the isolated yields depend strongly on the ability of the oxazolone to precipitate from water during workup, while avoiding hydrolysis. In addition, the use of strictly anhydrous sodium acetate is preferred; generally the use of freshly fused sodium acetate is recommended.[12]

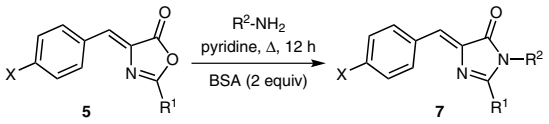
The following transformation involves the reaction with an amine; the formation of the diamide proceeding readily due to the strongly electrophilic character of the oxazolone. The subsequent ring closure is the most limiting step, except when methylamine has been used, and generally proceeds by heating in ethanol in the presence of K_2CO_3.[13] In the case of other amines the ring closing is sluggish in most cases. Thus, other methods have been explored, such as heating at 220 °C,[14a] fusing a mixture of the oxazolone and the amine in the presence of freshly fused sodium acetate at 160 °C[14b] or heating in DMF with Cs_2CO_3 as a base.[15] In the case of imidazolones, however, silylation has seldom been used as a dehydration technique. To our knowledge, only TMSCl in DMF at 90–125 °C[16a] and HMDS in refluxing DMF have described previously.[16b,c] As for the above-mentioned 4,4′-cycloalkyl imidazolones, BSA is likely to behave as a more versatile reagent, allowing both syntheses starting from either the oxazolone in the presence of an amine, or dehydration of a preformed diamide, and would moreover be compatible with acid-sensitive substrates and electrophile-sensitive formamides.

Amongst recent, interesting reports dealing with the synthesis of imidazolones, Kao and Chien et al.[17] have extensively studied the synthesis of imidazolones by ring closure of previously isolated diamides obtained by the Erlenmeyer procedure. They first examined this dehydration under Mitsunobu conditions with an excess of reagent, therefore leading to concomitant formation of substantial

amounts of byproducts. They also reported very poor yields of dehydration of the diamides under classical conditions (K_2CO_3, EtOH, reflux), which led them to improve the process by heating in dry pyridine. Good yields were generally obtained, though necessitating long reaction times, up to five days, and the reaction became even more sluggish with arylamines. This work is, to our knowledge, the most complete report concerning the formation of imidazolones with substituents other than methyl, but we decided to investigate the condensation in the presence of BSA of the more challenging substrates.

Furthermore, in order to shorten the synthetic route, we used the oxazolones as starting material, instead of isolated diamides. Hence, when the oxazolone was allowed to react in the presence of an amine in pyridine, the formation of the diamide occured within a few minutes at room temperature, except with less reactive aniline which required heating at 50 °C for the amidification to reach completion. As the oxazolone opening is presumably facilitated by pyridine, there was no need for the isolation of the diamide. Thus, upon completion of the reaction between the amine and oxazolone, BSA was added, and the resulting solution heated at 100 °C during 12 hours; although the reaction was usually complete within a few hours with less-hindered amines (Table 2).

Table 2 One-Pot Synthesis of 4-Benzylidene Imidazolones



Entry	X	R^1	R^2	7	Yield (%)
1	OMe	Me	Me	**7a**	98
2	OMe	Me	Bn	**7b**	91
3	OMe	Ph	Me	**7c**	99
4	OMe	4-NCC_6H_4	Bn	**7d**	82
5	OMe	Ph	Bn	**7e**	90
6	OMe	Ph	Ph	**7f**	58
7	OMe	Ph	$(CH_2)_3NHBoc$	**7g**	84
8	OMe	Ph	CH_2CO_2t-Bu	**7h**	45
9	OMe	styryl	Me	**7i**	85
10	OMe	styryl	Bn	**7j**	84
11	OMe	styryl	Ph	**7k**	52
12	NMe_2	Me	Me	**7l**	98
13	NMe_2	Me	Bn	**7m**	92
14	NMe_2	Ph	Me	**7n**	89
15	NMe_2	Ph	Bn	**7o**	96
16	NMe_2	Ph	Ph	**7p**	82
17	H	Me	CH_2-2-furyl	**7q**	94
18	H	Ph	CH_2-2-furyl	**7r**	84

In an initial study, heating diamide **6e** (Ar = 4-$MeOC_6H_4$; R^1 = Ph, R^2 = Bn) in pyridine in the presence of BSA resulted in complete conversion (92% isolated yield) into the expected imidazolone **7e**. As a result, we immediately focused on the same reaction being run in a one-pot process starting from the oxazolone **5** instead of isolated diamide **6**.[21]

As expected, less-hindered substrates derived from methylamine (R^2 = Me) led to high isolated yields (Table 2, entries 1, 3, 9, 12, 14). Furthermore, the more challenging substrate derived from benzylamine also led to good to very good yields (82–96%, Table 2, entries 2, 4, 5, 10, 13, 15).

Most fluorescent imidazolones bear an aromatic substituent at C2 and pleasingly, substrates derived from hippuric acid (R^2 = Ph) also gave good yields despite the presence of the more bulky group at R^2 (84–96%, Table 2, entries 4, 5, 15, 18). Not surprisingly, poorly nucleophilic aniline gave moderate yields (Table 2, entries 6 and 11), although entry 16 shows that this amine can also afford a good yield of imidazolone when the arylidene group possesses a 4-dimethylamino substituent.

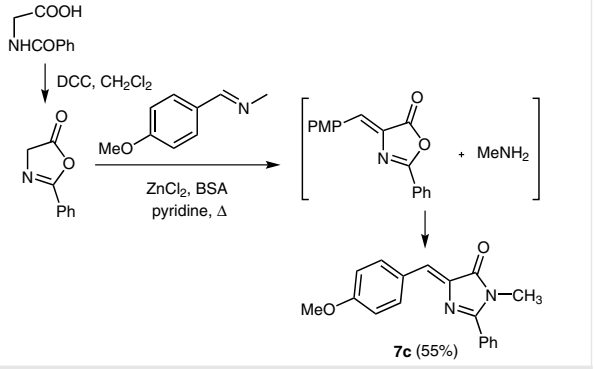
In comparison, under similar conditions without BSA, compound **7e** was obtained with a 15% yield after two days refluxing in pyridine,[17] or 74% yield when reacting under Mitsunobu conditions (2 equiv of Ph_3P and DIAD), in the presence of DBU (2 equiv) and catalytic DMAP, but requiring time-consuming purification in order to remove large amounts of Mitsunobu byproducts. Similarly, after three days refluxing in pyridine, **7o** was obtained in 42%; whereas under conditions developed in this work, not only the yields were satisfactory, but also the purification was straightforward. Likewise, the synthesis of compound **7p** has been reported[18] by refluxing the oxazolone in the presence of four molar equivalents of aniline, in glacial acetic acid with anhydrous sodium acetate for seven hours, with a 45% yield. Finally, we prepared compounds derived from 2-furylamine, in order to compare our method to another procedure published in the literature utilizing microwave irradiation.[19]

For further applications, we needed to assess the compatibility of this method with *tert*-butyl protective groups such as Boc or *tert*-butyl esters. Thus *N*-Boc-propanediamine and glycine *tert*-butyl ester were used as the amine component of the reaction, giving 84% and 45% yields, respectively, the modest yield obtained with glycine ester being due to some degradation of the amino ester itself during its extraction in the free amine form. This paves the way for further applications towards fluorophores bearing a linker for protein labeling. Noteworthy, in the field of fluorescent imidazolones, extended conjugation at C2 gives rise to red-shift and better quantum yields. This prompted us to examine the reaction of *N*-cinnamoyl glycine, and we were pleased to observe similar yields (Table 2, entries 9 and 10), without any noticeable degradation. With a good electron-

donating groups such as 4-dimethylamino, widely used in fluorescent molecules, we obtained even better yields than with 4-methoxy-bearing compounds (Table 2, entries 12–16).

The scope of this reaction shows the excellent versatility of the one-pot synthesis under BSA activation for the dehydration process, and the functional-group tolerance with *tert*-butyl ester, *N*-Boc, and conjugated alkenes.

To extend this one-pot strategy, we investigated the reaction of an imine with the oxazolone derived from hippuric acid as depicted in Scheme 4. In this case, freshly fused zinc chloride was added to activate the imine and allow the condensation. However, the methylamine released could attack either the starting oxazolone, or the oxazolone resulting from condensation with the imine. Only the latter will lead to imidazolone formation, and a 55% yield was obtained in this case. This yield must be compared to that obtained when reacting the precondensed oxazolone with methylamine and BSA in pyridine (99%, Table 2, entry 3), making the previous methodology much more efficient. For this reason, we did not examine the scope of this reaction further.



Scheme 4 One-pot reaction of imine with oxazolone

In summary, this study has demonstrated the efficiency and versatility of BSA as a cyclocondensation reagent, for the formation of a range of imidazolones.[21] The compatibility with *tert*-butyl groups, activated double bonds, and formamides and promoting cyclization of poorly reactive substrates such as *N*-arylamides makes BSA a reagent of choice for the preparation of these compounds.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562524.

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(21) To a solution of (*Z*)-4-(4-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (**5b**, 280 mg, 1 mmol) in pyridine (2 mL) was added methylamine (1 mL of a 1 M solution in THF). The reaction mixture was stirred for 30 min at room temperature, then BSA (407 mg, 2 mmol) was added and the reaction heated to 110 °C overnight. It was cooled, diluted with EtOAc, washed with 1 M citric acid, water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography using PE and EtOAc provided pure (*Z*)-4-(4-methoxybenzylidene)-1-methyl-2-phenyl-1*H*-imidazol-5(4*H*)-one (**7c**) as a yellow solid (290 mg, 99%); mp 176 °C. ^{1}H NMR (300 MHz, DMSO): δ = 8.29 (d, *J* = 8.9 Hz, 2 H), 7.93 (dd, *J* = 7.8, 1.7 Hz, 2 H), 7.66–7.55 (m, 3 H), 7.16 (s, 1 H), 7.05 (d, *J* = 8.9 Hz, 2 H), 3.82 (s, 3 H), 3.27 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.80, 161.59, 161.30, 137.26, 134.64, 131.40, 129.55, 129.09, 128.89, 128.70, 127.39, 114.41, 55.46, 29.14. HRMS (CI): *m/z* calcd for $C_{18}H_{17}N_2O_2$ $[M + H]^+$: 293.1285; found: 293.1290. IR (ATR): 3154, 2947, 1734, 1694, 1574, 1421, 1094 cm^{-1}. Ideally, these reactions are run in a sealed tube. When carried out in a round-bottomed flask equipped with a reflux condenser, it is necessary to add a further molar equivalent of BSA to achieve completion of the reaction, since some BSA can be lost through evaporation.