COMMUNICATION

Brønsted Acid Catalyzed Cyclization of β-Amino-1,4-enols to Oxazol-2(3*H*)-ones and 5-Alkenyloxazolidin-2-ones

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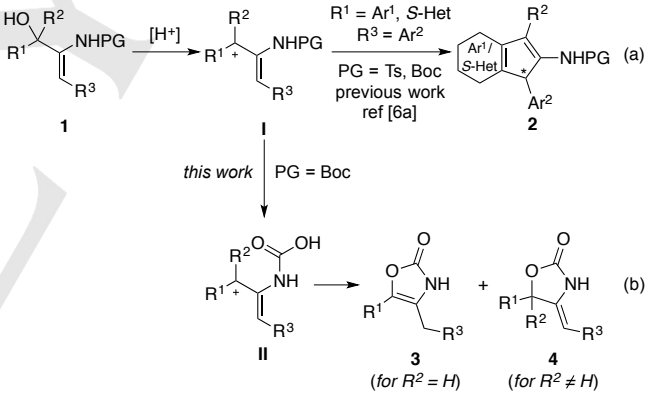
Abstract: A synthetic method to prepare oxazol-2(3*H*)-ones and 5-alkenyloxazolidin-2-ones efficiently that relies on Brønsted acid-catalyzed cyclization of the respective secondary and tertiary β-amino-1,4-enols in ethanol under reaction conditions that did not require the exclusion of air or moisture is described.

Oxazolidin-2-ones represent an immensely important member of the heterocyclic compound family due to their prevalence in many biologically and materials significant compounds.[1] The *O*,*N*-containing five-membered ring motif is also a versatile building block and ligand in organic synthesis.[2] For this reason, the development of catalytic methods for their facile assembly with selective control of substitution patterns continues to be actively pursued.[1–3]

In recent years, an increasing number of studies have demonstrated the versatility of π-rich alcohols as substrates in Brønsted acid-catalyzed carbon-carbon bond formation methods.[4–6] This has included efforts by us and others to shepherd the putative carbocationic species generated under such reaction conditions to participate in cyclization pathways to afford cyclic products of potential synthetic value.[5,6] For example, we recently described an enantioselective synthetic route to 1*H*-indenes and 4*H*-cyclopenta[*b*]thiophenes involving the chiral *N*-triflyl phosphoramide ([H$^+$])-mediated asymmetric dehydrative Nazarov-type electrocyclization (DNE) of electron-rich aryl and 2-thienyl vinyl β-amino alcohols (Scheme 1a).[6a] Building on this initial work, we queried whether the posited allylic cation species **I** formed in this manner could be intercepted by a tethered *t*-butyl carbamate (*N*-Boc) motif instead of the DNE reaction (Scheme 1b). By fine-tuning the reaction conditions, it was envisioned that this could be achieved by promoting the concurrent decomposition of the *N*-protecting group in these substrates to give the posited *in situ* formed carbamic acid species **II**. Its subsequent participation in a cyclization pathway involving addition of the carbonyl oxygen center to the allylic carbocationic



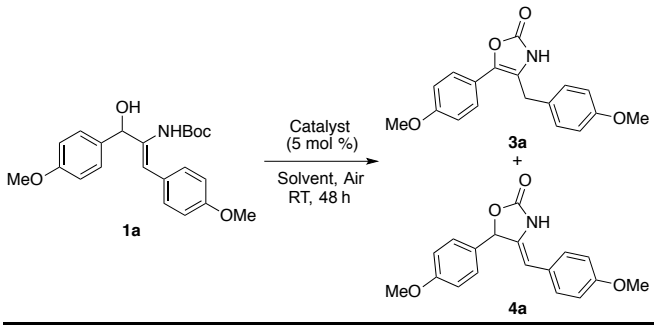
Scheme 1. Brønsted acid-catalyzed reactivities of β-amino-1,4-enols.

motif would then be anticipated to provide either the oxazolidin-2-one derivatives **3** or **4**. Herein, we describe the details of this chemistry that offers a facile synthetic route to these two members of the *O*,*N*-heterocyclic family of compounds from electron-rich secondary and tertiary aryl vinyl β-amino alcohols under mild atmospheric reaction conditions.

We commenced our investigations by examining the Brønsted acid-catalyzed reactions of the *N*-Boc-protected electron-rich aryl vinyl β-amino alcohol **1a** to establish the optimum reaction conditions (Table 1). This initially revealed treating the substrate to 5 mol % of TfOH in ethanol under atmospheric conditions at room temperature for 48 h furnished the oxazol-2(3*H*)-one **3a** in 60% yield (entry 1). The structure of the *O*,*N*-heterocycle was unambiguously determined by NMR measurements and X-ray crystallographic analysis of two closely related analogues (*vide infra*).[7] A separable mixture of the product and its regioisomer **4a** in respective yields of 12–59 and 9–39% were obtained on

repeating the reaction in dichloromethane, 1,2-dichloroethane, diethyl ether, ethyl acetate, acetone or THF in place of ethanol as the solvent (entries 3–8). Our studies subsequently found that the analogous control experiment mediated by TfOH in ethanol under atmospheric conditions at reflux temperature for 1 h gave the best result, giving **3a** as the only product in 59% yield (entry 2). In a final set of control reactions, either the recovery of the substrate or a mixture of the two *O*,*N*-heterocycles in 13 and 21% yield was found when TfOH was replaced with *p*-TSA, TFA or benzoic acid as the catalyst (entries 9–11).

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	Yield [%][b]	
			3a	**4a**
1	TfOH	EtOH	60[c]	-
2[d]	TfOH	EtOH	59[c]	-
3	TfOH	EtOAc	35	22
4	TfOH	$(CH_3)_2CO$	27	30
5	TfOH	THF	38[c]	39[c]
6	TfOH	Et_2O	12	33
7	TfOH	CH_2Cl_2	59	12
8	TfOH	$(CH_2Cl)_2$	46	9
9	*p*-TSA	EtOH	13	21
10	TFA	EtOH	-[e]	-
11	$PhCO_2H$	EtOH	-[e]	-

[a] Unless otherwise stated, all reactions were performed at the 0.1 mmol scale with 5 mol % of catalyst, in 1 mL of solvent under atmospheric conditions at room temperature for 48 h. [b] ^{1}H NMR product yield with CH_2Br_2 as the internal standard. [c] Isolated product yield. [d] Reaction conducted at reflux temperature for 1 h. [e] No reaction based on TLC analysis and ^{1}H NMR measurements.

To evaluate the generality of the present procedure, we first turned our attention to the reactions of a series of secondary β-amino-1,4-enols (Figure 1). Overall, experiments with starting materials **1b**–**f** and **1i**–**n** demonstrated the Brønsted acid-mediated reaction conditions to be broad, producing a variety of oxazol-2(3*H*)-ones in 42–99% yield. The cyclization of diaryl-substituted substrates containing a combination of either an electron-donating or withdrawing group or both at the *para*-position of the aromatic rings (**1b**–**d** and **1f**) were found to be well-tolerated and furnished **3b**–**d** and **3f** in 60–99% yield. The transformation of *O*,*N*-heterocycle **3b** to its *N*-tosyl protected analogue ***N*-Ts–3b** additionally allowed the structure of the five-membered ring system to be determined by X-ray crystallographic analysis.[7,8] Likewise, replacing the aryl group at the enamine carbon center with an alkyl (**1i**,**j**) or cyclohexyl (**1k**) motif was found to give the corresponding five membered ring adducts **3i**–**k** in 86–97% yield. A similar outcome was obtained for starting materials containing a *p*-tolyl and benzyl (**1l**) or phenyl and benzyl (**1m**) or cyclohexyl (**1n**) substitution pattern at the respective carbinol and enamine carbon centers. In these reactions, the corresponding oxazol-2(3*H*)-ones **3l**–**m** were afforded in 42–65% yield with **3l** also furnished as an inseparable mixture of positional isomers in a ratio of 10:1. Intriguingly, the analogous experiments of *p*-anisyl-substituted substrates with a pendant *p*-bromophenyl (**1e**), 2-furanyl (**1g**) or 2-benzofuranyl (**1h**) motif at the enamine carbon center were found to be the exceptions. For the cyclization of **1e**, a separable mixture of both the oxazol-2(3*H*)-one **3e** and oxazolidin-2-one **4e** was obtained in respective yields of 26 and 21%. In the case of the latter two substrates, the oxazolidin-2-ones **4g** and **4h** were the only products afforded in 51 and 68% yield, respectively.

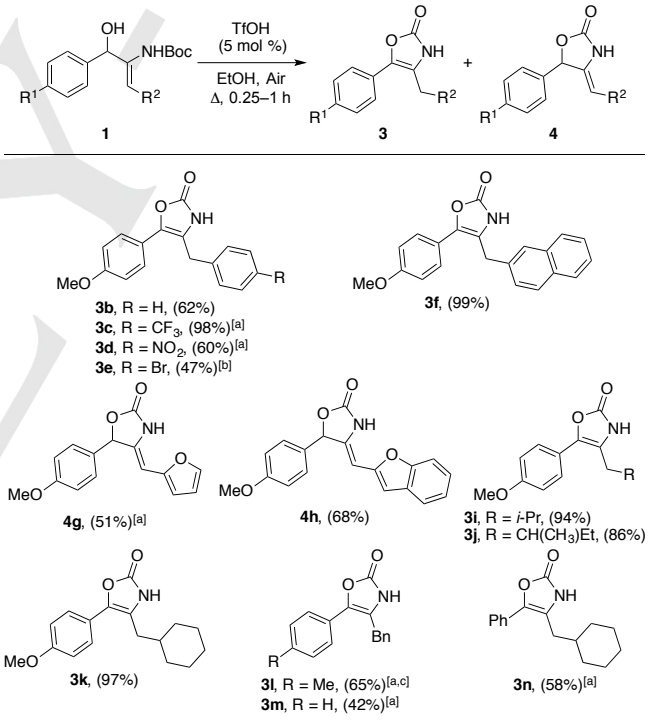


Figure 1. Cyclization of β-amino-1,4-enols **1b**–**n** catalyzed by TfOH. Unless otherwise stated, all reactions were performed at the 0.1 mmol scale with 5 mol % of TfOH, in EtOH (1 mL) under atmospheric conditions at reflux temperature for 0.25–1 h. [a] Reaction conducted in 1,2-dichloroethane as the solvent. [b] Product was obtained as a separable mixture of **3e** and **4e** in an overall yield of 68% and a ratio = 2.2:1 with compound **4e** isolated in 21% yield. [c] Product was obtained as an inseparable mixture of positional isomers in a ratio = 10:1.

To further gauge the scope of the present Brønsted acid-catalyzed cyclization protocol, the reactions of a variety of tertiary β-amino-1,4-enols were next examined, and the results are summarized in Figure 2. This revealed substrates containing a di-*p*-anisyl group at the carbinol carbon and a *p*-

(trifluoromethyl)phenyl (**1o**) or cycloalkyl (**1p**,**q**) group gave the corresponding oxazolidin-2-ones **4o**–**q** in 40–99% yield. Under the TfOH-mediated standard reaction conditions, the cyclization of **1r** containing geminal diphenyl and cyclohexyl motifs at the respective carbinol and enamine carbon centers was also found to give the corresponding *O*,*N*-heterocyclic adduct **4r** in 87% yield. The structure of the five-membered ring adduct was also confirmed by X- ray crystallography.[7] Similarly, starting materials containing a geminal dimethyl group and phenyl (**1s**), 2-furanyl (**1t**) or 2-benzofuranyl (**1u**) substitution pattern at the respective carbinol and enamine carbon centers were found to furnish the corresponding cyclic adducts **4s**–**u** were afforded in 47–91% yield.

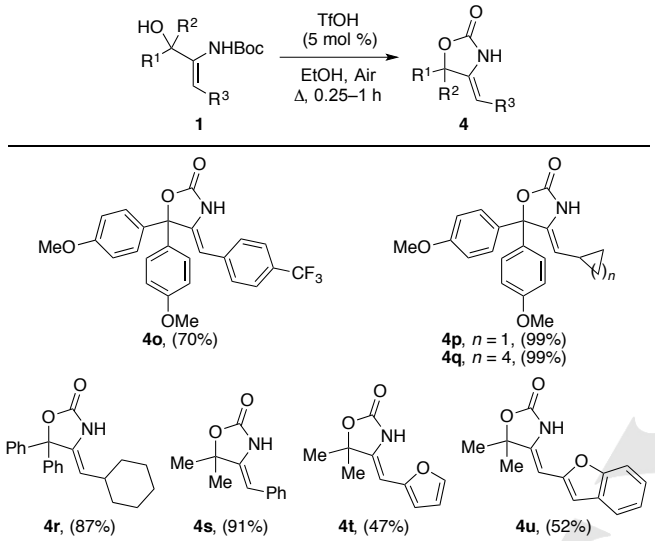
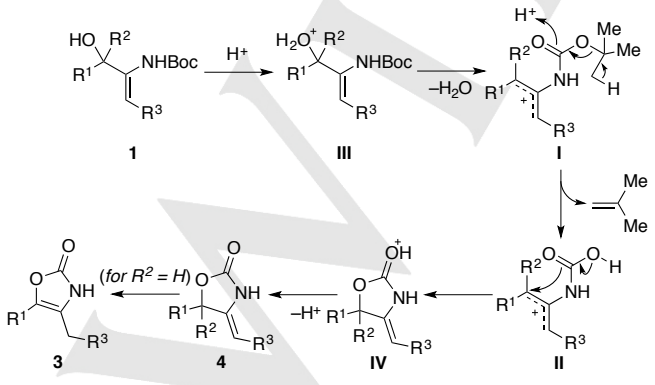


Figure 2. Cyclization of *β*-amino-1,4-enols **1o**–**u** catalyzed by TfOH. Unless otherwise stated, all reactions were performed at the 0.1 mmol scale with 5 mol % of TfOH, in EtOH (1 mL) under atmospheric conditions at reflux temperature for 0.25–1 h.

On the basis of the above results and previous work, a tentative mechanism for the present Brønsted acid-catalyzed cyclization reaction is presented in Scheme 2.[6a] This might initially involve protonation of the carbinol oxygen center of the 1,2-amino alcohol **1** by the Brønsted acid. This leads to the protonated analogue **III** to undergo dehydration followed by protonation of the *t*-butyl



Scheme 2. Proposed mechanism for the cyclization of *β*-amino-1,4-enols mediated by TfOH.

carbamate motif in the ensuing putative carbocationic species **I**. As a consequence, the *t*-butyl group is eliminated as isoprene to give the carbamic acid species **II**, which subsequently undergoes cyclization involving addition of the carbonyl oxygen center to the allylic carbocationic group. Deprotonation of the resulting oxonium adduct **IV** would then deliver the oxazolidin-2-one **4** that can isomerize to the more stable oxazol-2(3*H*)-one **3** for reactions involving substrates containing a secondary alcohol function group. While the reason for the formation of both **3e** and **4e** remains unclear, the preferential generation of **4g** and **4h** could be due to possibility of H-bonding between the oxygen center of the heterocycle and amino group in these adducts preventing isomerization to the anticipated compounds **3g** and **3h**.

In summary, we have developed a Brønsted acid-catalyzed method for the cyclization of secondary and tertiary *β*-amino-1,4-enols as an efficient approach to oxazol-2(3*H*)-ones and 5-alkenyloxazolidin-2-ones. Achieved by under reaction conditions that did not require the exclusion of air and moisture, the method was shown to be applicable to a variety of substrates that compliments the transition metal-mediated versions to these two members of the *O*,*N*-heterocyclic compound family.

Experimental Section

To a 2 mL round-bottomed flask was added the *β*-amino enol **1** (0.1 mmol) and a 1 mL solution of TfOH in EtOH (0.005 mmol/mL) in one portion. The reaction mixture was brought to reflux and allowed to stir for 0.25–1 h whilst the progress of the reaction was followed by TLC analysis. Upon completion, the reaction mixture was quenched with water (20 mL/mmol) and the product extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with saturated brine (100 mL/mmol), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (15% EtOAc/*n*-hexane) to afford the oxazol-2(3*H*)-one **3** or oxazolidin-2-one **4**.

Acknowledgements

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Keywords: alcohols • Brønsted acids • cyclizations • heterocyclic synthesis • synthetic methods

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[7] CCDC 1901829 (***N*-Ts–3b**) and CCDC 1901829 (**4r**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[8] See the Supporting Information for details.

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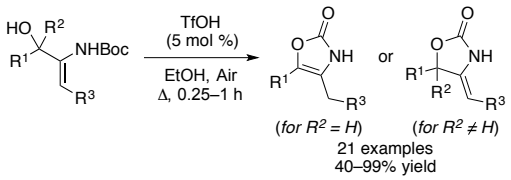

A Brønsted acid-catalyzed cyclization method for the efficient synthesis of oxazol-2(3*H*)-one and 5-alkenyloxazolidin-2-one derivatives from the respective secondary and tertiary β-amino-1,4-enols in ethanol under atmospheric reaction conditions is disclosed.