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Synthesis of 2-oxazolines and related N-containing heterocycles using $[Et_2NSF_2]BF_4$ as a cyclodehydration agent

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ABSTRACT

The preparation of 2-oxazolines and related N-containing heterocycles from the corresponding hydroxyamides using XtalFluor-E ($[Et_2NSF_2]BF_4$) as a cyclodehydration agent is described. A wide range of heterocycles are obtained under mild conditions in good to excellent yields.

2-Oxazolines are important members of the N-containing five-membered ring family. This heterocyclic structure is used, for example, in pharmaceutical sciences,[1] in catalysis,[2] in synthetic organic chemistry,[3] and in material sciences.[4] Likewise, related heterocycles such as 2-thiazolines or 2-benzoxazoles have also attracted their share of attention in similar fields.[5,6] Illustrative examples of bioactive heterocycles are shown in Figure 1.

Consequently, numerous methods have been published for the preparation of these heterocycles.[3,5,7] Among the number of methods available to synthesize them, the cyclodehydration reaction of β-hydroxyamides and related derivatives is the most encountered and this transformation can be promoted by various reagents (Fig. 2).[3] Notably, the use of DAST and DeoxoFluor®, reagents originally developed for deoxofluorination, has been reported.[7e,8]

Recently, diethylaminodifluorosulfinium tetrafluoroborate ($[Et_2NSF_2]BF_4$), XtalFluor-E,[9] has been described as a valuable alternative to DAST and DeoxoFluor® in deoxofluorination reaction due to its crystallinity and enhanced thermal stability.[10] We recently reported that this reagent could be used as a cyclodehydration agent for the preparation of 1,3,4-oxadiazoles from 1,2-diacylhydrazines.[11] Herein, we demonstrate that XtalFluor-E can also be used for the preparation of 2-oxazolines and related N-containing heterocycles from the corresponding hydroxyamides.

Optimization was performed with β-hydroxyamide **1a**[12] and initial results are reported in Table 1. Exposure of **1a** to 2 equiv of XtalFluor-E in CH_2Cl_2 at −78 °C followed by stirring at rt for 18 h resulted in 73% yield (entry 1). Addition of the reagent at 0 °C gave a similar result (entry 2) while simply running the whole reaction at rt resulted in a slightly increased yield (entry 3). Heating at 45 °C provided an improved 84% yield. Finally, changing the solvent to 1,2-dichloroethane (DCE) allowed the reaction to be performed at higher temperature. Thus, running the reaction at 90 °C yielded 95% of the desired oxazoline **2a**. Using less XtalFluor-E (1.5 equiv) resulted in a reduced yield of 83%. In all cases,

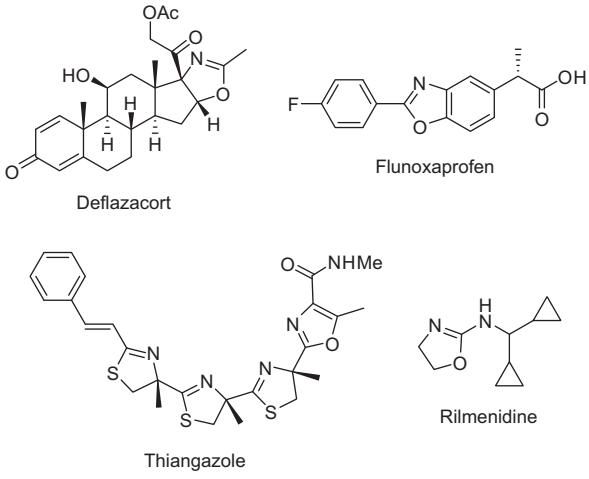

Figure 1. Bioactive 2-oxazolines and related N-containing heterocycles.

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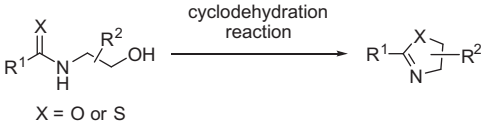
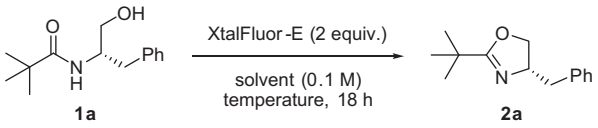


Figure 2. Cyclodehydration reaction of β-hydroxyamides and related derivatives.

Table 1
Initial results and optimization



Entry	Solvent	Temperature (°C)	Yield[a] (%)
1	CH_2Cl_2	−78 to rt	73
2	CH_2Cl_2	0 to rt	71
3	CH_2Cl_2	rt	79
4	CH_2Cl_2	45	84
5	DCE	90	95

[a] Isolated yield.

examination of the crude mixtures by NMR provided no evidence of potentially competitive fluorination.[13]

The optimized conditions (Table 1, entry 5) were then used to examine the scope of this reaction (Table 2). A wide range of oxazolines bearing various substituents at the 2 position (*tert*-butyl, cyclohexyl, substituted phenyl rings, cinnamyl group) could be prepared in good to excellent yields (entries 1–5). An ester functional group is also well tolerated (entry 6) although slight erosion of the enantiomeric purity was observed (85% ee).[14] Finally, cyclization of the threonine derived hydroxyamide **1h** lead to oxazoline **2h** as a single diastereomer in 82% yield (entry 8). Mechanistically, this last result is interesting (Scheme 1). Indeed, the isolation of a single diastereomer of **2h**, which was confirmed by ^{1}H NMR,[15] supports a mechanism where **1h** upon reaction with XtalFluor-E, would produce an activated alcohol **3**[16] which undergoes cyclization via an intramolecular S_N2 reaction leading to the observed diastereomer of **2h**, therefore providing an explanation for the inversion of configuration at this carbon.

Finally, we explored the possibility of using XtalFluor-E as cyclodehydration agent for the preparation of other N-containing heterocycles of interest (Table 3). Thus, cyclization of β-hydroxythioamide **4a**[17] furnished 2-thiazoline **5a** in 76% yield (entry 1). Likely, 2-benzoxazole **5b**[18] could be obtained in good yield from the corresponding 2-amidophenol **4b** (entry 2). Moreover, 2-oxazoline derivatives with larger ring sizes, 2-dihydro-1,3-oxazine (entry 3),[7k,19] and a 2-tetrahydro-1,3-oxazepine (entry 4),[7k] could also be prepared from the corresponding γ- and δ-hydroxyamides respectively. Notably, the 55% yield for compound **5d** represents a neat improvement over the 11% yield previously reported from **4d**.[7k] In all cases, the desired N-containing heterocycles were isolated in moderate to excellent yields.

In conclusion, we have demonstrated that 2-oxazolines and related N-heterocycles could be obtained, in good to excellent yields, from their hydroxyamide precursors using XtalFluor-E as a cyclodehydration agent. These conditions should find use in the synthesis of these important N-containing heterocycles.

Acknowledgments

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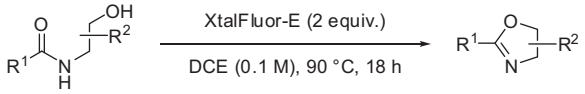
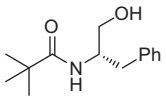
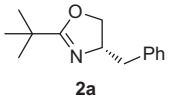
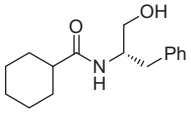
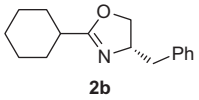
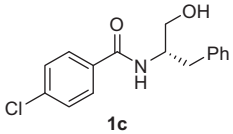
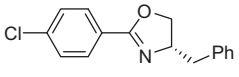
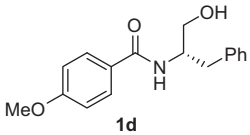
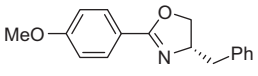
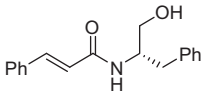
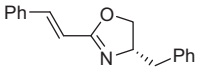
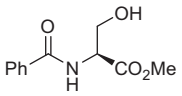
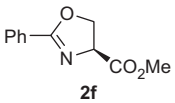
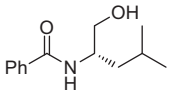
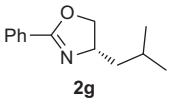
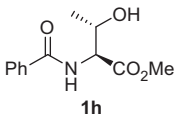
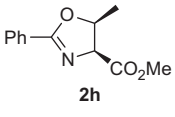
Table 2
Preparation of 2-oxazolines

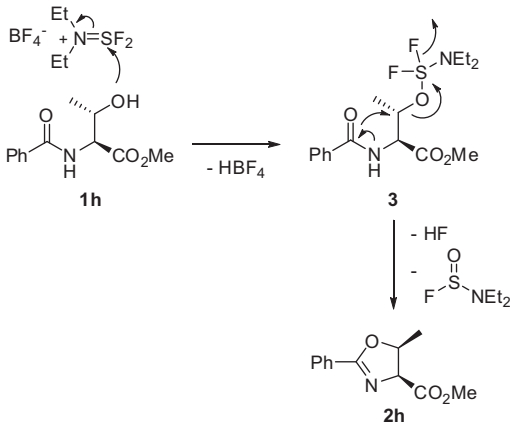


Entry	Substrate	Product	Yield[a] (%)
1	 1a	 2a	95
2	 1b	 2b	73
3	 1c	 2c	81
4	 1d	 2d	92
5	 1e	 2e	83
6	 1f	 2f	84
7	 1g	 2g	80
8	 1h	 2h	82

[a] Isolated yield.

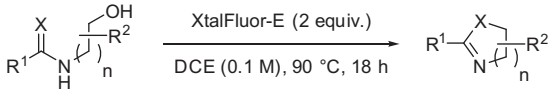
Supplementary data

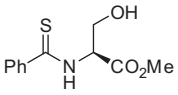
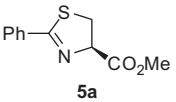
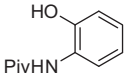
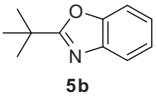
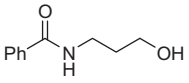
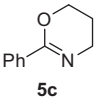
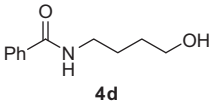
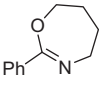
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.130.



Scheme 1. Mechanistic proposal for the cyclodehydration reaction.

Table 3
Preparation of N-containing heterocycles



Entry	Substrate	Product	Yield[a] (%)
1	 **4a**	 **5a**	76
2	 **4b**	 **5b**	70
3	 **4c**	 **5c**	81
4	 **4d**	 **5d**	55

[a] Isolated yield.

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14. Compound **2f** is prone to epimerization, see for example: Kuwano, R.; Kameyama, N.; Ikeda, R. *J. Am. Chem. Soc.* **2011**, *133*, 7312–7315.
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