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Synthesis of 2-oxazolines via boron esters of *N*-(2-hydroxyethyl) amides

Baris Ilkgul, Deniz Gunes, Okan Sirkecioglu *, Niyazi Bicak *

Istanbul Technical University, Department of Chemistry, Maslak, Istanbul 34469, Turkey

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ABSTRACT

A new, convenient, one-pot process is presented for the synthesis of 2-oxazolines in high yields (75–94%) via boron esters of *N*-(2-hydroxyethyl) amides. The procedure involves thermolysis of the boron esters at 240–260 °C, in the presence of solid CaO as an acid scavenger and allows the preparation of oxazolines from hydroxyethyl amides of aliphatic and aromatic monocarboxylic acids.

1. Introduction

The presence of oxazolines in marine organisms has stimulated syntheses of these compounds via different methods.[1] 2-Oxazolines are valuable intermediates in various organic transformations.[2,3] These compounds are known to be resistant to base hydrolysis and are useful reagents as protecting groups for carboxylic acids.[4] Metal complexes of bis-oxazolines derived from chiral amines are efficient catalysts in asymmetric syntheses.[5,6] They have also found extensive use in polymer chemistry due to their ability to undergo ring-opening polymerization that allows the preparation of various macromolecular architectures. Hydrolysis of their polymers offers an easy pathway to linear polyethylene imines, which are not attainable by other means.[7]

Various procedures have been developed for the synthesis of 2-oxazolines from carboxylic acids,[8] esters,[9] nitriles,[10,11] and *N*-(2-hydroxyethyl) amides.[12–16] Among these, the procedures based on dehydrative cyclization of *N*-(2-hydroxyethyl) amides are preferred due to their easy access from ethanolamine and carboxylic acid derivatives.

Li and Xu reported the direct synthesis of 2-oxazolines from 2-hydroxyethyl amides using a mixture of triphenylphosphine (PPh_3) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as the dehydrating agent. This procedure gave mono-oxazolines in high yields at room temperature.[12] In a similar study, Williams et al. described a one-pot procedure using diethylaminosulfur trifluoride (DAST) or bis-(2-methoxyethyl) aminosulfur trifluoride (Deoxo-Fluor) as the cyclodehydrating agent for the conversion of 2-hydroxyethyl amides into oxazolines at low temperature.[13] Bandgar and Pandit reported the syntheses of 2-oxazolines from 2-acyloxy-4,6-dimethoxy-1,3,5-triazines with 2-amino-2-methyl-1-propanol at room temperature.[14] In addition, Moyano's group described the syntheses of alkynyl-substituted chiral oxazolines using PPh_3-diethyl azodicarboxylate (DEAD) in boiling dichloromethane.[15]

More recently, Kangani and Day reported the use of an indium catalyst together with cyanuric acid chloride for the cyclocondensation of carboxylic acids with ethanolamines to prepare 2-oxazolines.[16]

Most of these procedures involve tedious work-ups, multistep reactions, and the use of specialized dehydrating agents or catalysts. The critical issue while dehydrating 2-hydroxy ethyl amides is to avoid decomposition of the 2-oxazolines already formed in the reaction.

Herein, we describe a new and simple protocol to provide 2-oxazolines in high yields and high purities. This protocol is based on the thermolysis of boron esters of *N*-(2-hydroxyethyl) amides at 240–260 °C. The precursor, *N*-(2-hydroxyethyl) amides were prepared either by aminolysis of the appropriate carboxylic acid esters or by dehydration of 2-hydroxyethyl ammonium carboxylates at 180–200 °C. A series of 2-hydroxyethyl amides possessing alkyl and aromatic groups were prepared and esterified with boric acid according to the general procedure described in the literature.[17,18] The eliminated water was continuously removed using a Dean–Stark trap over 3–4 h. Except for the cases of hydroxyethyl amides of 4-nitrobenzoic acid and stearic acid, the resulting boron esters were liquids or low melting solids.

Differential scanning calorimetry (DSC) traces of the boron esters derived from hydroxyethyl amides of stearic acid, acetic acid, and 4-nitrobenzoic acid showed sharp endotherms at 240, 255, and 245 °C, respectively. This implies fast decomposition of the boron esters in the temperature range 240–260 °C to give 2-oxazolines. The overall process involves formation of boron esters of *N*-(2-hydroxyethyl) amides and subsequent thermolysis in the presence of CaO as an acid scavenger (Fig. 1).

The experiments revealed that, without CaO, the oxazoline yield was extremely low (15%) and charred residues were obtained (Table 1). It is thought that the solid residue is a polymeric by-product formed by the action of boric acid on the oxazoline. This was ascribed to the high susceptibility of oxazolines to acids yielding polymeric products while decomposing the boron ester. The polymerization of 2-oxazolines promoted by boric acid at elevated

* Corresponding authors. Tel.: +90 212 2953280; fax: +90 212 2856386 (O.S.).
E-mail address: sirkeci@itu.edu.tr (O. Sirkecioglu).

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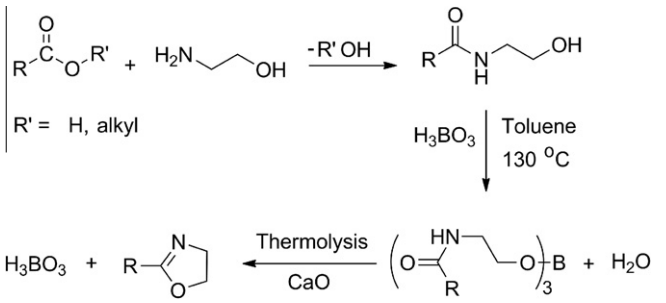
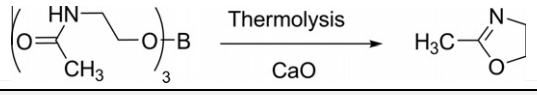


Figure 1. Synthesis of 2-oxazolines in three steps starting from ethanolamine and carboxylic acids or their esters.

temperatures was proved by a separate experiment in which 2-methyloxazoline (2 mL) was heated at 115 °C together with 0.05 g of H_3BO_3 for 3 h. The resulting dark residue was diluted with a small amount of water (~5 mL) and precipitated from acetone. The ^1H NMR spectrum of the product in $CDCl_3$ revealed a poly(*N*-acetyl ethyleneimine) structure.

This result seems to contradict early reports describing the synthesis of 2-oxazolines by acid-catalyzed cyclodehydration of *N*-(2-hydroxyethyl) amides. Reasonable yields in those reports might be due to low reaction temperatures.

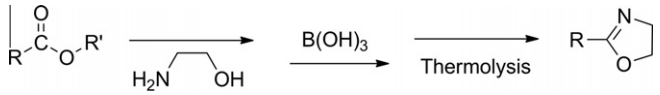
Table 1
Effects of boric acid scavengers on the yield of 2-methyl 2-oxazoline

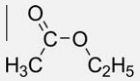
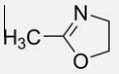
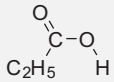
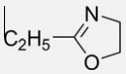
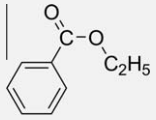
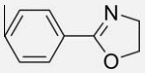
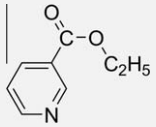
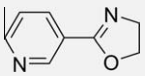
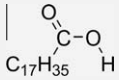
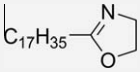
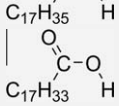
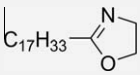
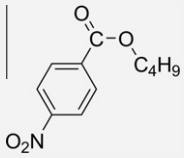
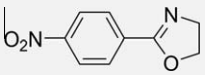
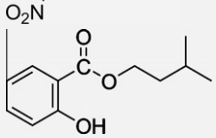
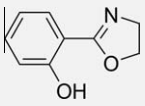


Entry	Base	Time (h)	Yield (%)	Remarks
1	None	1.5	15	Charred residue
2	Pyridine	2	34	Viscous residue
3	Trioctylamine	2	39	Viscous residue
4	CaO (solid)	2	84	None

These experiments showed that the use of an acid scavenger such as solid CaO is essential to avoid side reactions including polymerization and other thermal decompositions. Indeed, higher yields of oxazoline were obtained in the presence of CaO. We also studied pyridine and trioctylamine as bases for trapping the boric acid. The yields of the 2-methyl-2-oxazoline in both cases were higher in comparison to the yield of the reaction performed without base under the same conditions. The highest yield of oxazoline (84%) in the presence of solid CaO must be due to the formation of insoluble calcium borate by the reaction with boric acid as it forms. Therefore, CaO acts as trapping agent for the boric acid and suppresses side reactions at elevated temperatures. Removal of the

Table 2
Synthesis of oxazolines from *N*-(2-hydroxyethyl) amides via boron esters



Entry	Precursor	Product	Yield[a,b] (%)	Bp[c]/Mp[d] (°C)	Reference
1			99[a] (94[b])	110–112[c]	21
2			99[a] (92[b])	128–130[c]	21
3			91[a] (86[b])	75–77[c] (0.1 Torr)	21
4			90[a] (82[b])	80–85[c] (0.2 Torr)	21
5			89[a] (79[b])	51–52[d]	21
6			86[a] (75[b])	165–171[c] (0.4 Torr)	21
7			90[a] (85[b])	96–97[d]	22
8			22[a] (17[b])	Oil[d]	22

[a] Conversion estimated by ^1H NMR spectroscopy.
[b] Yield of isolated product.
[c] Boiling point of isolated product.
[d] Melting point of isolated product.

boric acid from the liquid phase in this way results in considerable rises in the oxazoline yields.

The ^{1}H NMR spectrum of the product obtained by thermolysis of the boron ester of *N*-(2-hydroxyethyl) acetamide indicated the 2-methyl-2-oxazoline structure. A methyl group signal was observed as a singlet at 1.58 ppm. The protons of the methylene group adjacent to an oxygen atom occurred as a triplet at 3.90 ppm. The other methylene group of the oxazoline was present as a triplet at 3.46 ppm.

It is important to note that Barton et al. described a related procedure based on direct heating of a carboxylic acid and 2-ethanolamine mixture in the presence of boric acid as the catalyst.[19] Using 3 equiv of ethanolamine and 0.66 equiv of boric acid, this group was able to attain high yields of 2-oxazolines, but after very long reaction times (65–72 h). Apparently, the use of excess ethanolamine in this procedure deactivates the boric acid and prevents polymerization. However, this procedure was reported to be unsuccessful for preparing oxazolines derived from aromatic carboxylic acids, though why this procedure fails in these cases is not clear.

In a similar study, Wipf and Wang described the use of 3-nitrophenylboronic acid as a catalyst for dehydration of hydroxamides and mercaptoamides for preparing oxazolines and thiazolines in moderate to excellent yields.[20] However, the yields of oxazoline from phenyl hydroxethyl benzamides were reported to be low (33–41%) even after 30–45 h reaction times.

By contrast, the procedure presented herein is also applicable for the synthesis of 2-oxazolines derived from aromatic carboxylic acids. Thermolysis of the boron esters of hydroxyamides derived from monocarboxylic acids proceeded without significant colorization and the crude thermolysis products were highly pure as inferred from their ^{1}H NMR spectra showing only the presence of water as an impurity. Drying and redistillation yielded pure oxazolines in very good to excellent yields (Table 2).

The hydroxyethyl amide of salicylic acid was an exception; the oxazoline yield in this case did not exceed 17% using the same reaction conditions. An attempt to increase the oxazoline yield by using K_2CO_3 instead of CaO was not successful, but we did not study this reaction any further.

This procedure also failed in preparing bis-oxazolines from the corresponding bis-hydroxamides. The yields of bis-oxazoline from dihydroxyethyl amides derived from malonic, terephthalic acids, and pyridine 2,5-dicarboxylic acid were extremely low (8–12%) under the same reaction conditions. This must be due to the formation of polymeric boron esters by reaction of the trivalent boric acid with the bis-hydroxyamides. Owing to the heterogeneity of the reaction medium in this case, the heat transfer was lowered and CaO was unable to trap the boric acid formed in the polymer matrix. To overcome this drawback, the reaction was performed in silicon oil and liquid paraffin. Despite the difficulties in isolation of the products from the reaction medium, no significant improvements in the bis-oxazoline yields were observed.

In conclusion, the present procedure based on the thermolysis of boron esters of hydroxyamides represents a useful synthetic pathway to 2-oxazolines possessing aromatic and aliphatic groups. In contrast to the boric acid-catalyzed procedure reported by Barton et al., the present method is also applicable for preparing 2-oxazolines with aromatic moieties. The easy access to the starting materials and no requirement for a special catalyst make this procedure attractive as an alternative protocol for mono-oxazolines.

2. General procedure for the preparation of 2-oxazolines

All the oxazolines were prepared by a one-pot, three-step process. Thus, 2-hydroxyethyl amides were formed either by aminolysis of carboxylic acid esters with ethanolamine or by dehydration of the carboxylic acid salt of ethanolamine in the first step. These were then heated with 0.33 equiv of boric acid to generate the corresponding boron esters at 130 °C in the second step. The water was removed in 3–4 h by azeotropic removal with toluene (50 mL per 0.1 mol) and collected in a Dean–Stark trap. In the final step, solid CaO (0.3 mmol) was added to the flask and the temperature of the oil-bath was adjusted to 280 °C and thermolysis was conducted for 3 h.

The oxazolines (Table 2, entries 1–4) were isolated by distillation under vacuum (see Table 1) and redistillation gave pure products. Isolation of higher oxazolines (Table 2, entries 5–8) was carried out by extraction with CH_2Cl_2 (3×10 mL). The organic solution was washed with aqueous Na_2CO_3 solution (50 mL, 5%) and treated with activated charcoal (1 g per 50 mL). The filtered solutions were dried over anhydrous Na_2SO_4 and the CH_2Cl_2 was removed by evaporation. The products were recrystallized from EtOH.

Supplementary data

Supplementary data (materials, instrumentation and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.167.

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