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An alternative approach to differentially substituted 2-oxazoline chalcogen derivatives

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ABSTRACT

In this study we present an alternative method to obtain several substituted mono or bis-2-oxazolines containing a chalcogen atom as a tether element. Alkylation of 2-tosyloximethylene-2-oxazoline with an appropriate sodium, lithium or potassium alkoxide yielded the corresponding ether. Introduction of sulfur or selenium was easily accomplished using the corresponding sodium salts. The ^{77}Se NMR for alkyl or aryl 2-methylene-2-oxazoline selenides shows good correlation with the electronegativity pattern of substituents. Most products containing oxazolinyl-chalcogen were stable under the usual experimental conditions. However, the tellurium derivatives showed unusual sensitivity to light and oxygen, decomposing through a very complex mechanistic pathway. As a result of this oxidative process, 4,4-dimethyl-2-oxazoline-2-carbaldehyde could be isolated and fully characterized for the first time, in 17% yield.

1. Introduction

2-oxazolines are important heterocyclic compounds [1] that occur in nature as iron chelators [2], cytotoxic peptides [3], and neuroprotective agents [4], to cite a few. They are also important in biological systems, since they are involved in the complexation of metallic ions such as Cu^{2+} and Zn^{2+} [5]. Moreover, 2-oxazolines have several well-known applications in organic synthesis as protective groups [6], synthetic intermediates [7], and chiral ligands [8].

The most common approach to synthesize 2-oxazolines involves the condensation of a 1,2-amino alcohol with a carboxylic acid or its ester derivatives [9]. Several other masked carboxylic acid functional groups can be used, including nitriles [10], imidate hydrochlorides [11], orthoesters [12], and iminoether hydrochlorides [13]. A variety of reagents have been employed to accomplish the cyclodehydration step, such as PPh_3/DDQ [14], diethylaminosulfur trifluoride (DAST) [15], bis-(2-methoxyethyl)-aminosulfur trifluoride (Deoxo-Fluor) [16], and PPh_3/DEAD [17]. CaO has been utilized to promote dehydration from boron esters of *N*-(2-hydroxyethyl) amides [18]. Recently, the synthesis of 2-pyridyl-2-oxazolines was reported using $Zn(OAc)_2$ as catalyst under microwave heating [19].

2-oxazoline-inspired ligands (Fig. 1) such as BOX, PYBOX (**1a-d**), and INDABOX **2**, to name a few, were developed and applied to metal catalysis involving copper, palladium, rhenium, rhodium, or ruthenium [20]. Most of the existing methods used to obtain these BOX-type ligands are restricted to structures with a C_2-symmetry chiral axis [21–23].

Although the *ortho*-lithiation of 2-aryl-2-oxazolines has been widely used for the regioselective functionalization of arenes and heteroarenes [24], the anion derived from 2-methyl-2-oxazoline is the most frequently explored species. It has been employed in the synthesis of carboxylic acid homologues [25], lactones [26], and zinc [27] or copper [28] organometallic reagents, among others [29].

A clever way to use 2-methyl-2-oxazolines is by placing a leaving group at the 2-position. One example is 2-chloromethylene-2-oxazoline, which can be obtained using a classic condensation method by reacting chloromethyl imidate hydrochloride and an aminoalcohol [30]. Unfortunately, this

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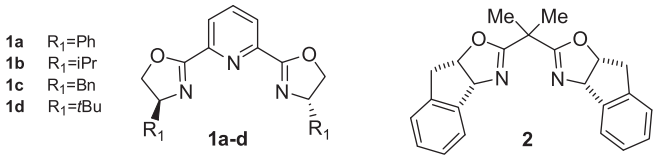
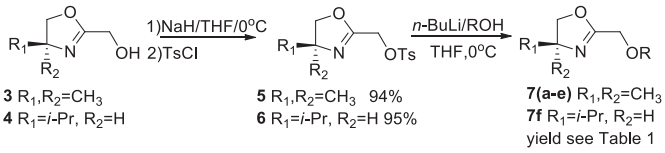


Fig. 1. Examples of BOX type ligands found in the literature.



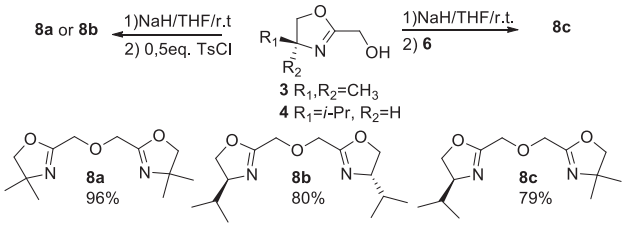
Scheme 1. General route for the synthesis of 2-oxazolinyl ethers.

method is very inefficient when 2-amino-2-methyl-1-propanol is used [31]. To overcome this limitation, an alternative chlorination method using *t*-butylhypochlorite in carbon tetrachloride was developed by Langlois [31] and well explored by Florio [32] in several studies. However, due to environmental restrictions, the use of carbon tetrachloride has been banned in many countries, including Brazil.

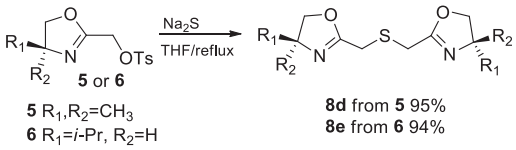
In order to extend the studies with 2-oxazoline chemistry, we report the development of an alternative building block that can be used in place of 2-chloromethylene-4,4-dimethyl-2-oxazoline. It was used for the synthesis of 2-oxazolines with more diverse structural features, avoiding the use of environmentally aggressive reagents. During the synthesis of tellurium-oxazoline compounds, an unusual photo oxidation process was observed that is similar to the decomposition of allylic or benzylic tellurides.

2. Results and discussion

2-hydroxy-methylene-2-oxazolines **3** and **4** were prepared in multi-gram scale [33] and easily converted into the corresponding tosylates **5** or **6,** in 94 and 95% yields, respectively, through reaction with tosyl chloride in THF at 0 °C (Scheme 1).



Scheme 2. Synthesis of compounds **8a**, **8b** and **8c**.

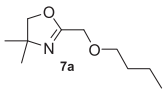
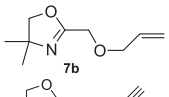
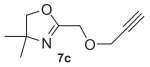
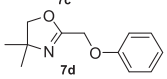
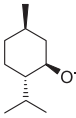
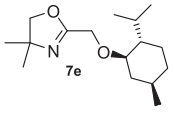
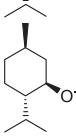
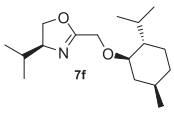


Scheme 3. Synthesis of sulfide **8d** and chiral sulfide **8e**.

The dropwise addition of an appropriate alkoxide solution in THF at room temperature into a solution of **5** or **6,** also dissolved in THF, followed by 2 h of reflux, afforded the desired products in good to excellent yields (Table 1). As observed, the reaction worked very well with several alkoxides such as alkyl (**7a**) (80%), allylic (**7b**) (72%), propargylic (**7c**) (75%) or aromatic (**7d**) (85%). Reactions were very clean and the products could be easily purified by column chromatography. Lower yields were observed only when isolating the more volatile products (**7b, 7c).** This method also preserves the stereochemistry of the substrate, as can be seen for products **7e** and **7f** (Table 1, entries 5 and 6).

During the initial studies for preparation of compound **5**, a small amount of the BOX-like, bis-(2-methyl-2-oxazolinyl) ether (**8a**) was formed as a byproduct, which prompted us to conduct further investigations. By fine-tuning the reaction conditions, either compound **5** or **8a** could be obtained with high selectivity and excellent yield. The symmetrical and chiral ether **8b** was achieved by using similar conditions (Scheme 2). Additionally, the differentially substituted ether **8c** was obtained in 79% isolated yield by reacting the sodium alkoxide from **3** with chiral tosylate **6**. Thus, this

Table 1
Synthesis of 2-oxazolinyl ethers.

Entry	Tosylate	Alkoxide	Product	Yield[a]
1	**5**			80%
2	**5**			72%
3	**5**			75%
4	**5**			85%[b]
5	**5**			85%
6	**6**			90%

[a] Isolated yield.
[b] Obtained using K_2CO_3/acetone.