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A novel reductive ring-opening reaction of isoxazolidine to form functionalized 1,3-amino-alcohol

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Abstract

Reductive cleavage of the N–O bond of isoxazolidine ring with catalytic hydrogenation over Raney nickel was described. Bicyclic isoxazolidines could be effectively converted into the corresponding 1,3-amino-alcohol possessing a sultone or sultam moiety with high conversion and yield when the hydrogenation was catalyzed by freshly prepared Raney nickel under a pressure of 40 psi in the presence of triethylamine.

Keywords: Isoxazolidine; Hydrogenation; Raney nickel; 1,3-Amino-alcohol

Isoxazolidines are synthetic useful class of heterocycles. The labile N–O bond present in isoxazolidines may undergo reductive bond cleavage to give 1,3-amino-alcohol [1]. In the literature, isoxazolidines have been extensively demonstrated to be useful intermediates for the preparation of substituted amines and a variety of alkaloids [2]. Moreover, the stereochemistry of isoxazolidines can be maintained intact during the reductive transformation into the open-chain compounds. Thus, chiral isoxazolidines are versatile precursors for the synthesis of natural products and multifunctional chiral materials [3,4]. Furthermore, some of the cycloadducts obtain optically active form while the other adducts were incorporated with strong fluorescent moieties such as pyrenyl group [5]. On the other hand, chemical transformation of the isoxazolidines, obtained via 1,3-dipolar cycloaddition reaction, could lead to chiral 1,3-amino-alcohols and bicyclic sultams. Chiral 1,3-amino-alcohols can be developed as viable chiral ligands in promoting asymmetric synthesis, and the potential uses of chiral sultams as chiral auxiliaries have been well demonstrated [6].

Bicyclic isoxazolidines **1** can be effectively prepared from the 1,3-dipolar cycloaddition reaction between nitrones and propene sultone or propene sultam [7]. To further explore the synthetic applications of the cycloadducts, the reductive N–O bond cleavage of bicyclic isoxazolidines **1** was investigated. Optimal reduction conditions were sought to transform the bicyclic isoxazolidines into multifunctional synthetic intermediates.

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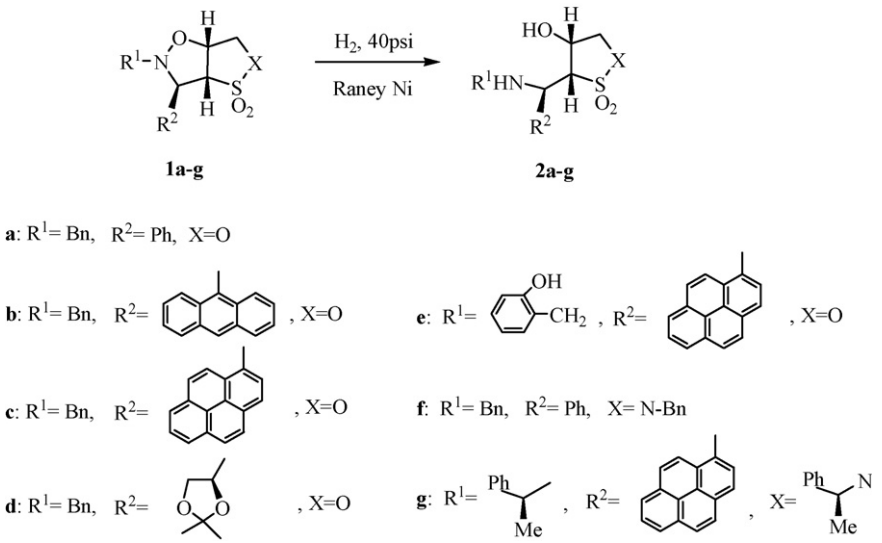

Scheme 1.

Over the years, many methods for the reduction of isoxazolines derived from cycloaddition of nitrile oxides and alkenes have been developed [8]. However, only number of examples concerning the reduction of isoxazolidines were reported in the literature. Isoxazolidines can be reduced by Zn/acetic acid [9], and catalytic hydrogenation with palladium on charcoal [10], or palladium hydroxide [11] as the catalyst.

In the context of synthesizing multifunctional compounds from the cycloadducts, we investigated their reduction under a wide variety of conditions. It was reported that isoxazolidines could be converted into 1,3-amino-alcohols by hydrogenation using palladium on charcoal as the catalyst [10]. However, the hydrogenation experiments revealed that bicyclic isoxazolidine **1** cannot be reduced to form the desired 1,3-amino-alcohol. The analysis of the reduction product showed that a complicated mixture was produced when the hydrogenation was carried out under 20 psi hydrogen over Pd/C catalyst at room temperature for 12 h. Attempts to cleave the N–O bond of isoxazolidine **1** by other reductive means such as Zn/acetic acid [9], SmI_2 [12] and lithium aluminum hydride [11b], or sodium borohydride were all unsuccessful. Presumably, the presence of the sultone or sultam moiety in the bicyclic compounds may cause the complication of the reduction reaction. Among other possible reducing agents, Raney nickel seems to be a promising option for our purpose. We are aware of the fact that Raney nickel has been often employed as an effective catalyst to hydrogenate isoxazolines. In contrast, catalytic hydrogenation of isoxazolidines over Raney nickel has not been fully explored. After some experimentation, freshly prepared Raney nickel was found to be an active reagent in achieving clean N–O bond cleavage of **1**. For instance, when **1a** was chosen as a model compound for in-depth study, it was hydrogenated at room temperature for 12 h under atmospheric pressure with Raney nickel as the catalyst, affording the corresponding 1,3-amino-alcohol **2a** in about 80% yield. More efficient transformation with 90% yield and 100% conversion was achieved in 6 h when the hydrogenation was carried out

Table 1
Catalytic hydrogenation of bicyclic isoxazolidines[a]

Entry	Isoxazolidine	Product	Reaction temperature (°C)	Reaction time (h)	Yield (%)
1	**1a**	**2a**	23	6	90
2	**1b**	**2b**	60	12	60
3	**1c**	**2c**	60	12	58
4	**1d**	**2d**	23	12	92
5	**1e**	**2e**	60	12	62
6	**1f**	**2f**	23	6	91
7	**1g**	**2g**	60	12	55

[a] H_2/Ni, 40 psi, 1,4-dioxane/methanol (1/4, v/v).