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Communication

Mild and efficient one-pot synthesis of chiral β-chalcogen amides via 2-oxazoline ring-opening reaction mediated by indium metal

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ABSTRACT

A simple and efficient procedure for the synthesis of β-seleno and β-thio amides via the ring-opening reaction of chiral 2-oxazolines in the presence of indium metal has been developed. Features of this method include the following: (i) easily and accessible starting materials; (ii) indium metal is more stable and less expensive then its respective salts; (iii) useful to excellent yields of β-chalcogen amides derivatives.

1. Introduction

Organoselenium and sulfur compounds have been employed as very useful reagents in organic synthesis [1]. They allow the chemo-, regio- and stereoselective introduction of new functional groups into complex organic substrates under mild experimental conditions. In addition, these compounds are gaining contemporary interest due to their applications as powerful ligands in asymmetric catalysis [2] as well as for the design, synthesis and investigation of new molecular materials, especially for conducting or superconducting materials and for liquid crystals [3].

Besides, the biological and medicinal role of selenium and organoselenium compounds has also become increasingly esteemed, mainly due to their antioxidant, anti-tumor, antimicrobial, and antiviral properties [4]. Therefore, the development of new methods for the introduction of selenium-containing groups into organic molecules [5], particularly in a stereocontrolled manner, remains a significant challenge.

It is well known that the selenium anions are generated *in situ* via chemical Se–Se bonds cleavage to avoid handling unstable reagents such as selenols. Reduction of Se–Se bonds, especially cleavage of diaryl diselenides were performed with reducing agents such as $NaBH_4$, Na/NH_3, Bu_3SnH and $LiAlH_4$ [6]. In recent years, some protocols with indium(I) iodide-mediating cleavage of diorganoyl diselenides have been developed to prepare vinylic selenides [7], selenoesters [8], β-hydroxyl selenides [9], selenocysteine derivatives [10] with special attention given to unsymmetrical diorganyl selenydes [11].

In this context, we recently reported an indium(I) protocol for the preparation a wide range of useful chiral β-seleno amides and selenocysteine derivatives via 2-oxazolines ring-opening reaction promoted by *in situ* generated bis(organoseleno)iodoindium(III) [12]. This method provided a practical and concise synthesis of a structurally diverse organochalcogen compounds in a straightforward and flexible strategy in the absence of a Lewis acid [13]. Attempting to disclose further extension of these previous reports, we describe herein a simple experimental procedure which uses metallic indium it is easy to handle, less expensive when compared to indium(I) protocols and active enough to promote the heterocycle ring-opening reaction (Scheme 1). The study resulted in an efficient synthesis of β-chalcogen amides 2 under mild and neutral conditions.

2. Results and discussion

Aiming to determine the optimum conditions, we performed studies about effects that can influence this reaction, such as: (i) loading and structure of organoyl halide; (ii) loading of indium metal; (iii) temperature and; (iv) solvent. We first investigated the present reaction under the following conditions: oxazoline **1a**, PhSeSePh, indium powder in refluxing 1,4-dioxane on varying the halide R^3-X (Table 1). When a *tert*-alkyl, benzylic or allylic halide were employed under the above conditions, **2a** was obtained in

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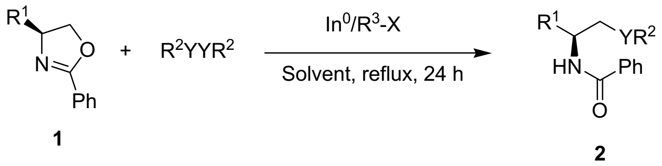
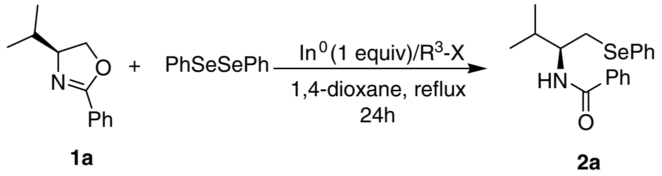


Scheme 1. General procedure for the synthesis of β-chalcogen amides mediated by indium metal.

Table 1

Ring-opening reaction of 2-oxazoline **1a** in the presence of structurally diverse R^3-X



Entry	R^3-X	In^0 (equiv)	Yield (%)[a]
1	*t*-BuCl	1.0	70
2	BnCl	1.0	45
3	BnBr	1.0	90
4	AllylBr	1.0	62
5	*p*-$ClPhCH_2Cl$	1.0	98
6	MeI	1.0	_
7	PhBr	1.0	_
8	*p*-$ClPhCH_2Cl$	0	_
9	*p*-$ClPhCH_2Cl$	0.5	46
10[b]	*p*-$ClPhCH_2Cl$	1.0	15
11[c]	*p*-$ClPhCH_2Cl$	1.0	76

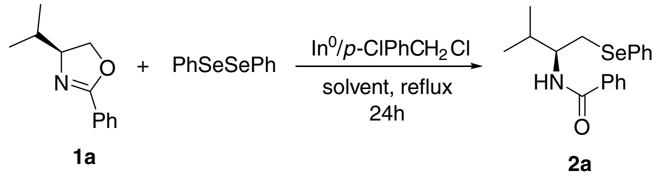
[a] Yields refer to those pure isolated products characterized by spectroscopic methods.

[b] Reaction was carried out at room temperature.

[c] 0.8 equiv. of *p*-$ClPhCH_2Cl$ was used.

Table 2

Ring-opening reaction of 2-oxazoline **1a** in the presence of different solvents



Entry	Solvent	Yield (%)[a]
1	1,4-Dioxane	98
2	DCM	15
3	THF	78
4	Acetonitrile	93
5	DMF	48
6	EtOH	34
7	Toluene	86
8[b]	1,4-Dioxane/H_2O	23

[a] Yields refer to those pure isolated products characterized by spectroscopic methods.

[b] 1,4-Dioxane/H_2O = 2:1.

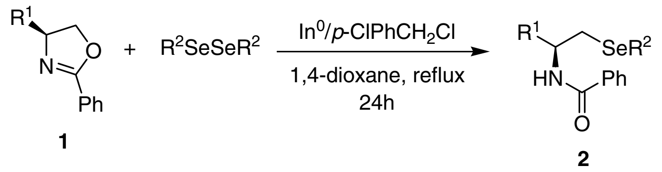
yields ranging from 45% to 98% (Table 1, entries 1–5) and the most efficient ring-opening process was achieved when *p*-chloro benzyl chloride was used in the ring-opening process (Table 1, entry 5). On the other hand, no product was observed when the reaction was performed in the presence of a primary alkyl or an aryl halide (Table 1, entries 6–7). These results are consistent with respect to the stability and reactivity under radical reaction conditions, readily generated from organoyl halides and indium metal [14].

When the reaction was carried out in the absence or in a lower amount of indium metal, the formation of the product was not observed or it was obtained in lower yields (Table 1, entries 8 and 9). The influence of reaction temperature and loading of the corresponding halide were also investigated in the present ring-opening reaction. We could observe a drastic decrease in the yield of the product when the reaction was performed at room temperature, probably due to a decreasing in the efficiency of the ring-opening step in a less energetic system (Table 1, entry 10). The reaction was also evaluated in the presence of 0.8 equivalent of *p*-$ClPhCH_2Cl$. However, a significant decrease in the product yield was observed (Table 1, entry 11).

With these results in hand, the efficiency of the solvent to promote the present process was examined (Table 2). When the reaction was carried out in dichloromethane, quite disappointing results were observed (Table 2, entry 2). By increasing the polarity

Table 3

Ring-opening reaction of 2-oxazolines

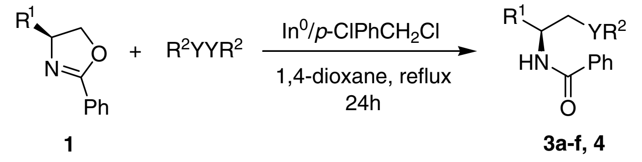


Entry	Oxazoline	R^1	R^2	**2**, Yield (%)[a]
1	**1a**	*i*Pr	Ph	**2a**, 98
2	**1b**	Bn	Ph	**2b**, 94
3	**1c**	Ph	Ph	**2c**, 86
4	**1d**	*i*Bu	Ph	**2d**, 81
5	**1a**	*i*Pr	*p*-ClPh	**2e**, 97
6	**1a**	*i*Pr	*p*-MeOPh	**2f**, 94
7	**1a**	*i*Pr	*o*-MePh	**2g**, 83
8	**1a**	*i*Pr	Bn	**2h**, 88
9	**1a**	*i*Pr	*n*Bu	**2i**, 44
10	**1a**	*i*Pr	Et	**2j**, 58

[a] Yields refer to those pure isolated products characterized by spectroscopic methods.

Table 4

Ring-opening reaction of 2-oxazolines in the presence of sulfur and tellurium nucleophiles



Entry	Oxazoline	R^1	R^2	Y	Product, yield (%)[a]
1	**1a**	*i*Pr	Ph	S	**3a**, 79
2	**1b**	Bn	Ph	S	**3b**, 71
3	**1a**	*i*Pr	*p*-ClPh	S	**3c**, 92
4	**1a**	*i*Pr	*p*-MeOPh	S	**3d**, 94
5	**1a**	*i*Pr	Bn	S	**3e**, 50
6	**1a**	*i*Pr	Et	S	**3f**, 40
7	**1a**	*i*Pr	Ph	Te	**4**, 12

[a] Yields refer to those pure isolated products characterized by spectroscopic methods.