Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Gold-catalyzed sequential cyclization/rearrangement reaction of *O*-allyl hydroxamates: atom economical synthesis of 3-hydroxyisoxazoles

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ARTICLE INFO

Article history:
Received 6 February 2016
Revised 7 March 2016
Accepted 10 March 2016
Available online xxxx

Keywords:
3-Hydroxyisoxazole
Gold catalysis
Cyclization
Rearrangement
Atom economy

ABSTRACT

A gold-catalyzed sequential reaction of *O*-allyl hydroxamates bearing an alkyne moiety has been developed for the preparation of 3-hydroxyisoxazoles and isoxazole-3-ones. Notably, this domino reaction involving cyclization and rearrangement provided facile access to the desired compounds in a highly atom-economical manner.

Isoxazoles are important structural components that can be found in numerous natural products,[1] biologically active compounds,[2] and functional materials.[3] Among the many isoxazole groups reported in the literature, 3-hydroxyisoxazoles have attracted considerable interest because of their potent activity toward central nervous system targets, such as their 5-HT_2 receptor agonist,[4] GABA uptake inhibitory,[5] and GABA receptor agonist and antagonist[6] activities.

The most common strategy for the synthesis of 3-hydroxyisoxazoles involves the cyclization of β-keto esters with hydroxylamine.[7] However, this method generally suffers from a lack of regioselectivity, resulting from the competitive formation of the undesired oxime as an intermediate instead of the desired hydroxamic acid. The development of practical and straightforward methods for the synthesis of 3-hydroxyisoxazoles is therefore highly desired. With this in mind, we envisaged that the transition-metal-catalyzed cyclization of *N*-allyloxypropiolamide **1** would provide access to the corresponding 4-allyl-3-hydroxyisoxazole **3** via the migration of the allyl group (Scheme 1). The transition-metal-catalyzed annulation of hydroxamates bearing an alkyne moiety via C—N bond formation have already been developed, where the nitrogen atom acts as a nucleophile.[8] In contrast, there have been no reports in the literature to date pertaining to the C—O bond-forming version of this reaction as a strategy for the formation of 3-hydroxyisoxazoles. As a part of our ongoing work toward the development of novel synthetic methods based on substrates bearing an N—O bond,[9] we report herein the gold-catalyzed synthesis of 4,5-disubstituted 3-hydroxyisoxazole through a domino process involving sequential cyclization and rearrangement reactions.

The *O*-allyl hydroxamate **1a**, which was prepared by the condensation of phenylpropiolic acid with *O*-allylhydroxylamine, was initially employed as a model substrate in this study for the optimization of the reaction conditions. A series of alkynophilic catalysts were screened in term of their ability to catalyze the synthesis of 3-hydroxyisoxazole (Table 1). When **1a** was treated with AuCl in $(CH_2Cl)_2$ at reflux, the desired 4-allyl-3-hydroxyisoxazole (**3a**) was obtained, albeit in a low yield with 44% of recovered **1a** (Table 1, entry 1). The use of $AuCl_3$ led to an increase in the yield to 74%, whereas the use of $CuCl_2$ or $PtCl_2$ failed to afford any of the desired product (Table 1, entries 2–4). Pleasingly, the use of $PicAuCl_2$ (Pic = 2-picolinate)[10] as a catalyst gave **3a** in 86% yield together with a small amount of the corresponding *N*-allylisoxazolone **4a** (Table 1, entry 6). This catalyst was therefore determined to be the optimum catalyst for this transformation.

With the optimized conditions in hand, we proceeded to investigate the scope of this reaction by varying the nature of the substituent at alkyne terminus (Table 2). Substrates bearing a *p*-methoxyphenyl or *p*-fluorophenyl group were well tolerated, affording the corresponding 3-hydroxyisoxazoles in good yields.

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http://dx.doi.org/10.1016/j.tetlet.2016.03.032
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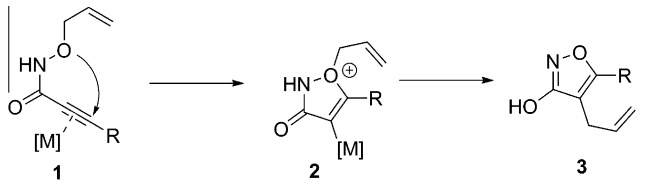
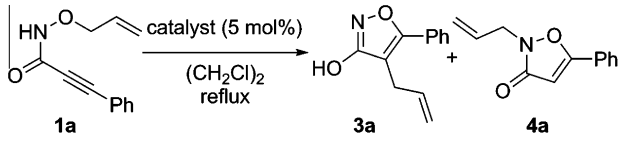


Scheme 1. Transition-metal-catalyzed cyclization–rearrangement of *O*-allyl hydroxamate **1**.

Table 1
Optimization of cyclization–rearrangement reaction



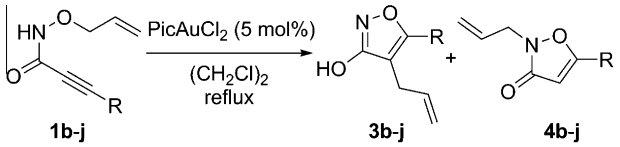
Entry	Catalyst	Time (h)	Yield[a] (%)	
			3a	**4a**
1	AuCl	10	36 (44)	–
2	$CuCl_2$	24	N.R.[b]	
3	$PtCl_2$	11	N.R.	
4	$AuCl_3$	2	74 (8)	8
5	$AuBr_3$	6	64	–
6	$PicAuCl_2$[c]	2	86	8

[a] Yields in parentheses are those of the recovered starting material.
[b] N.R.: no reaction.
[c] Pic = 2-picolinate.

However, substrate **1c** bearing a *p*-trifluoromethylphenyl group required an extended reaction time to achieve complete conversion to the corresponding isoxazole **3c** (Table 1, entries 1–3). Although various aliphatic substituents were well tolerated at the terminal position of the alkyne under these conditions, substrate **1h** bearing a *t*-butyl group gave **3h** in a low yield because of steric repulsion. It is noteworthy that substrates **1e** and **1i** bearing a methyl or cyclopropyl group at the terminal position of their alkyne gave the corresponding 3-hydroxyisoxazoles **3e** and **3i** exclusively, whereas **1h** also afforded the *N*-allylisoxazolone **4h** in 15% yield. These results therefore suggest that the formation of *N*-allylisoxazolone **4** may be influenced by the bulkiness of the substrate.

A plausible mechanism for this reaction is shown in Scheme 2. The initial intramolecular addition of the oxygen atom of the hydroxamate to the Au(III)-activated alkyne moiety would occur in a 5-*endo*-*dig* fashion to give oxonium intermediate **B-1**. The subsequent [3,3]-sigmatropic rearrangement of the allyl group to the C-4 carbon would proceed via conformation **B-2** to give intermediate **C**, which would undergo an aromatization process to give the 3-hydroxyisoxazole **3**. In contrast, the rearrangement via conformation **B-3** would lead to the formation of intermediate **D**, which would undergo an aromatization reaction to give the undesired *N*-allylisoxazolone **4**.[11] Substrates bearing a bulky substituent at the terminal position of their alkyne (e.g., **1h**) would experience severe steric repulsion in conformation **B-2** between the bulky R substituent and the allyl moiety. This steric repulsion explains the decrease observed in the yield of **3h** compared with **3i**, with the reaction being forced to proceed via conformation **B-3** to give *N*-allylated product **4h**.

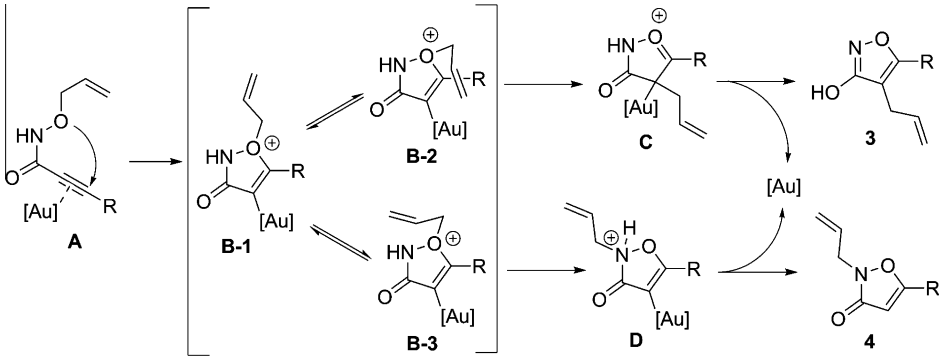
Table 2
Substituent effect at alkyne terminus



Entry	Substrate	R	Time (h)	Yield (%)	
				3b–j	**4b–j**
1	**1b**	4-$MeOC_6H_4$	2	78	9
2	**1c**	4-$CF_3C_6H_4$	4	75	5
3	**1d**	4-FC_6H_4	2	88	6
4	**1e**	Me	2	65	–
5	**1f**	*n*-Bu	2	74	11
6	**1g**	*c*-Hexyl	2	75	11
7	**1h**	*t*-Bu	4	52	15
8	**1i**	*c*-Propyl	2	72	–
9	**1j**	1-Cyclohexenyl	2	90	3

The proposed reaction pathway was partially supported by the results of a crossover experiment (Scheme 3). Treatment of an equimolar mixture of **1k** and **1g** with 5 mol % of $PicAuCl_2$ gave **3k**, **3g**, **4k**, and **4g** in 62%, 59%, 8%, and 8% yields, respectively, without any crossover products. This result indicates that the transfer of the allyl moiety proceeds in an intramolecular manner.

We then studied the effect of different substituents on the allyl moiety (Scheme 4). The introduction of a methyl group at the C2 position was well tolerated, with *O*-2-methylallyl hydroxamate **1k** reacting smoothly under the optimized conditions to give 4-(2-methylallyl)-3-hydroxyisoxazole **3k** in high yield (Eq. 1). In marked contrast, the introduction of substituents at the C1 and C3 positions had an adverse impact on the rearrangement process. For example, the reaction of *O*-3-cyclohexenyl hydroxamate **1l** with $PicAuCl_2$ under the optimized conditions led to the formation of *N*-(3-cyclohexenyl)-3-isoxazolone **4l** as the major product (Eq. 2). Furthermore, the reaction of *O*-crotyl hydroxamate **1m** gave



Scheme 2. Plausible reaction pathway.