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Zinc Mediated Direct Transformation of Propargyl *N*-hydroxylamines to α,β -Unsaturated Ketones and Mechanistic Insight

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Abstract

A Lewis acid catalyzed direct transformation of propargyl *N*-hydroxylamines to α,β -unsaturated ketones in the presence of aqueous Zn(II)-salts has been described. This investigation also provides a novel observation for the stoichiometric role of Zn-halides over what is known to date for catalytic processes. A thorough mechanistic study has been established based on the experiment using ¹⁸O-labeled water in optimized reaction conditions; the incorporation of ¹⁸O in the desired product was also substantiated by HRMS. This methodology is also a mild, inexpensive, and an efficient approach for this unusual conversion.

Graphical abstract

Keywords

Zinc; Propargyl hydroxylamines; α,β Unsaturated ketones; Mechanistic insight

Since the first discovery in 1911¹ and further development in various nucleophilic additions to nitrones,² propargyl hydroxyl amines have been understood to be a key milestone in organic synthesis.³ The C-C triple bond adjacent to *N*-hydroxylamine facilitated its versatile modes of action (e.g. oxidative cleavage,⁴ reduction,⁵ hydrogenation,⁶ hydroboration, and cyclization⁷) to a wide number of synthetically useful building blocks including amino acids, isoxazolines, amines, keto-amines, and lactams. These versatility natures of propargyl

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Supplementary Material

Supplementary data (compound data including ¹H NMR, ¹³C NMR, IR, HRMS and X-ray) associated with this article can be found, in the online version, at

hydroxylamines have also stimulated great interest in discovering its new chemical transformation. In this direction, Zn(II) based catalysts have been exploited significantly to promote a broad range of organic transformations due to its mild reactivity, abundance, affordability, and environmental friendliness. Most interestingly, Carreira et al. have demonstrated the catalytic role of Zn(II)-salts for the transformation of propargyl hydroxyl amines to the corresponding isoxazolines.⁷

In earlier report, the *N*-methyl-4-isoxazolinium, a quaternized salt of neutral isoxazolines are known to undergo a base mediated transformation to its enamino ketones and enones through a deprotonation of 5-CH₂ and *N*-methyl respectively.⁸ Later a related observation by Hermecz et al⁹ described that a tertiary propargylamine *N*-oxide undergoes a facile thermal concerted [2,3] sigmatropic¹⁰ transformation in aprotic media (CCl₄, THF, and CH₂Cl₂) to an intermediate *O*-propadienyl hydroxylamine which subsequently underwent a facile^{1,5} hydrogen shift to furnish the *N*-benzylidenemethylamine and propenal. According to this report, even after heating with ¹⁸O-labeled water, no incorporation of ¹⁸O-isotope was observed in the desired products. As several mechanistic pathways have been proposed thus far, a comprehensive mechanistic understanding is highly warranted.

We herein report a novel and mild behavior of zinc salts for the aforesaid transformation. It is also important to note that this is an inexpensive, alternative, and an efficient approach for this unusual conversion. To the best of our knowledge, other than what is known in Scheme 1, a similar transformation of either propargyl hydroxylamine or its isoxazoline intermediate remains unexplored due to the prevalence in developing a catalytic method over stoichiometric one. However, we believe that this finding as well as mechanistic insight would be the guiding factor for understanding the unusual nature of Zn(II)-salt in the presence of water and would allow the synthetic access to construct useful building blocks as well.

It is important to highlight that continuing our ongoing spiroisoxazoline work,¹¹ we were synthesizing isoxazolines following one of the Carreira's methods,⁷ using commercial grade hydrated ZnI₂ in stoichiometric amount, we realized an out of the ordinary reaction rather than the desired one. Further investigation of this reaction, led us to report this communication accentuating the unprecedented behavior of Zn(II)/H₂O for the transformation of propargyl hydroxylamine to the corresponding α,β -unsaturated ketone. It is worth mentioning that according to Carreira's recent work, Zn(II)-catalyzed transformation of propargyl hydroxylamine to the corresponding 2,3-dihydroisoxazoles required inert reaction conditions, and even after a prolonged reaction time, there was no report of product other than the formation of 2,3-dihydroisoxazoles. Based upon the preliminary observation, we focused our interests on optimizing the reaction conditions (ZnI₂, CH₂Cl₂/H₂O, and reflux). In the context of our investigation, we first examined the reactivity of various Zn(II)-salts that can promote this sort of transformation. When **1** was treated with stoichiometric amount of various Zn(II)-salts in the presence of water and under reflux conditions, we realized the formation of desired product **2**. However, we also observed the formation of a cyclic isoxazoline **3** (minor product, up to 50% yield) in some cases along with the major unsaturated ketone **2** (Table 1) We also observed a polar compound in TLC which was later characterized as benzyl hydroxylamine.

The ratio (**2**:**3**) was determined by NMR spectroscopy from the crude reaction mixture. The ratio between integrated signals at δ 6.7 ppm for α,β -unsaturated ketone **2** and δ 5.5 ppm for isoxazoline **3** enabled us to determine the optimized reaction conditions. As depicted in entries **1–3**, Table 1, it is apparent that transformation over zinc halides have a higher propensity to manifest this unusual other zinc salts. Based on the NMR ratio between major/minor products and the corresponding isolated yields, it is also obvious that ZnI_2 is better than other halides (ZnCl_2 and ZnBr_2). Further reaction of **1** with $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ and $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ produced the required compound **2** as the major product in 27% and 20% yields respectively after 24h of reflux (entries **4** and **9**, Table 1). In case of $\text{Zn}(\text{OH})_2$, $\text{Zn}(\text{SO}_4)_2 \cdot 7\text{H}_2\text{O}$, and ZnO , we isolated compound **2** along with compound **3** in a 1:1 ratio from trace to 50% yields, and we also recovered the starting material in most of the cases. Particularly, when $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was employed as a catalyst, no trace of compound **2** or **3** was isolated, instead, decomposition of the starting material was observed. Based on the data from Table 1, ZnI_2 (entry 3) was found to be the superior Lewis acid promoter for the formation of **2**.

In order to further optimize other experimental parameters (e.g. solvent, equiv, and reaction time), and to find optimal reaction conditions, we chose a range of solvents such as CH_2Cl_2 , toluene, CH_3CN , and THF (Table 2). Of the aforementioned solvents, CH_2Cl_2 was found to be the best solvent. The time dependent experiment showed that the usual reaction time is 2–4 hours for the maximum transformation. However, the extended period of reaction time has no significant improvement on yield. To understand the stoichiometric and catalytic behaviors of ZnI_2 , we performed the reaction under various loading (from 10 to 100 mol%). We also realized that catalytic loading (10 mol%, entry 7, Table 2) dawdled down the reaction time to the completion and respectively the yield of the desired product **2**. However, in the presence of stoichiometric amount of ZnI_2 (1 equiv), both the reaction time and the isolated yields were affected significantly. In order to fine tune and determine the optimal amount of ZnI_2 , we further reduced the loading of ZnI_2 to 0.5 equiv; the reaction was monitored by frequently checking the TLC. In this setting, the reaction usually takes 2–4 h to reach its completion.

Under optimized reaction conditions, the substrate scope was also explored in order to understand reaction compatibility and efficacy (Table 3). Subsequently, a plethora of tri-substituted propargyl hydroxylamines were generated from diethyl zinc-mediated nucleophilic addition of several substituted alkynes to disubstituted nitrones (aliphatic or aromatic substituted) following a reported procedure.¹² Having in hand a variety of tri-substituted propargyl hydroxylamines, we then performed the aforementioned reaction by following our optimized reaction conditions (ZnI_2 0.5 equiv, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, reflux 2–12 h). As shown in Table 3, it is clearly evident that a wide range of alkynes are compatible with this reaction environment, and the desired products were isolated in good yields.

We also investigated the effect of functional group tolerance by incorporating –OTBS, – CO_2Et , –Ph, or methyl groups on the terminal alkyne. It is worth mentioning that bulky substituents (e.g. –TMS or – CO_2^tBu) based alkynes have a negative effect on the reaction and no trace of desired product has been isolated. This is due to the fact that the proposed

nucleophilic oxidative addition of H₂O might be hindered in the presence of bulky substituent.

Based on literature precedence,^{8,9} we at this point speculated that the formation of α,β -unsaturated ketone could be facilitated by N-O bond cleavage of a cyclic isoxazoline intermediate followed by an elimination of benzyl amine. It is worth noting that the N-O bond cleavage will provide the unsaturated ketone where the ¹⁶O-atom comes from hydroxylamine. Regardless, the formation of isoxazolines, the stoichiometric zinc salt could also facilitate the elimination of the hydroxylamine *via* a proposed nucleophilic attack by H₂O to the terminal alkyne might result an allenol formation which could further tautomerize to give the desired product where the O-atom in the product comes from water. In order to understand the role of water and to establish a plausible mechanistic pathway, we next envisioned running a couple of reactions shown in Scheme 2 using ¹⁸O-labeled water. This modification was also executed separately for propargyl hydroxylamine and its corresponding cyclic isoxazolines (obtained by Carreira's method)⁷ as well. In both cases, we observed the ¹⁸O isotope incorporation in the product which was further corroborated by HRMS. This observation not only enlightens our understanding, it also enabled us to propose novel pathways for this type of unusual transformation.

As depicted in Scheme 3, where propargyl amine is the starting material, we propose that ZnI₂ first coordinates to the triple bond **b** followed by a nucleophilic oxidative addition of H₂O to furnish intermediate **d** in the presence of excess ZnI₂. The intermediate **d** then undergoes a reductive elimination and protonation to form the allenol **e** with further rearrangement to α,β -unsaturated ketone **f** (Scheme 3). It is important to note that this plausible elimination resembles the reported process where an elimination of an imine has been shown from a propargyl secondary amine through an allene intermediate.⁹

On the other hand, in the case of isoxazoline **g**, ZnI₂ might be playing the role as a Lewis acid and coordinated with N- and O- atoms where the *O*-vinyl center becomes electrophilic as shown in intermediate **h** in Scheme 4. As a result, facilitating a similar oxidative addition of H₂O, followed by a migration of double bond and elimination of hydroxylamine provided the desired unsaturated system **j** (Scheme 4).

In conclusion, we documented the Zn(II)/H₂O-mediated mild and efficient reaction condition for a smooth transformation of the propargyl hydroxylamine to unusual α,β -unsaturated ketone. This reaction can be performed for a wide range of substrates with few limitations as explained in the text. We believe that this observation not only grasps reader's attention due to its novel mechanistic pathway, it also facilitates the accumulation of many important building blocks of synthetic and medicinal interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Direct Transformation of Propargyl *N*-hydroxylamines to unsaturated ketones
- Zn(II)/H₂O-mediated mild and efficient reaction condition
- This reaction can be performed for a wide range of substrates with few limitations

Previous strategies: *Heterocycles* 1993, 36, 585-600 *J. Org. Chem.* 2001, 66, 7219-7222**This work:** **Scheme 1.**Unusual transformation of propargyl *N*-hydroxylamines to α,β -unsaturated ketones.

Scheme 2.

Unusual transformation of propargyl *N*-hydroxylamines to α,β -unsaturated ketones.

^aGeneral procedure: 10 mol % of ZnI_2 and 10 mol% of DMAP were added to a solution of propargylic *N*-hydroxylamine in CH_2Cl_2 at 23 °C. After 4h at rt, usual workup and purification provided the desired product.

Scheme 3.

Plausible mechanism for the decomposition of propargyl hydroxylamine.

Scheme 4.

Plausible mechanism for the decomposition of isoxazoline.

Table 1Product ratios and isolated yields for Zn(II) promoted decomposition of propargyl hydroxylamines (**1**).^a

Entry	Zn-Salts	ratio[2:3] ^b	2, Yield[%] ^c
1	ZnBr ₂	1:0.05	88
2	ZnCl ₂	1:0.05	78
3	ZnI ₂	1:0.0	91
4	Zn(OAc) ₂ ·2H ₂ O	1:0.5	27
5	Zn(OH) ₂	1:1	12
6	Zn(SO ₄) ₂ ·7H ₂ O	1:1	30
7 ^d	Zn(ClO ₄) ₂ ·6H ₂ O	-----	-----
8	ZnO	1:1	50
9	Zn(NO ₃) ₂ ·6H ₂ O	1:0.1	20

^a General procedure: **1** (0.122 mmol), Zn(II)-salt (1 equiv), H₂O (1eq), CH₂Cl₂ (2 mL), under reflux.^b NMR ratios of crude **2** and **3**.^c Isolated yield of **2**.^d No purification was attempted due to the lack of characteristic TLC indications for **2** or **3**.

Table 2

Optimization of other parameters for ZnI_2 mediated decomposition of propargyl hydroxylamine (**1**).^a

Entry	ZnI_2 (equiv.)	Solvent	Temp. (°C)	Time (h)	2. Yield (%) ^b
1	1.0	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	50	24	92
2	1.0	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	50	24	90
3	0.5	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	50	24	91
4	0.5	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	50	24	92
5	0.5	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	rt	24	85
6 ^c	0.5	$\text{CH}_2\text{Cl}_2/\text{-----}$	50	24	20
7	0.1	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	50	24	65
8	0.5	toluene/ H_2O	70	24	80
9	0.5	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	70	24	70
10	0.5	THF/ H_2O	70	24	50

^a General procedure: **1** (0.122 mmol), $\text{Zn}(\text{II})$ -salt (0.1–1 equiv), H_2O (1 equiv), CH_2Cl_2 (2 mL) for the given temperature and time.

^b Isolated yield of **2**.

^c In absence of water.

Table 3

Substrate scope for the decomposition of propargyl hydroxylamine.

$ \begin{array}{c} R_1-N^+-O^- \\ \\ R_2-CH \\ \\ \equiv R_3 \end{array} \xrightarrow[24\text{ h, toluene}]{Et_2Zn} \begin{array}{c} R_1-N-OH \\ \\ R_2-CH \\ \\ \equiv R_3 \end{array} \xrightarrow[reflux, 2\text{ h}]{CH_2Cl_2, H_2O, ZnI_2 (0.5\text{ equiv.})} \begin{array}{c} O \\ \\ R_2-CH=CH-R_3 \end{array} $	
Nitrone	Propargyl hydroxylamine ^a α,β -unsaturated ketone ^b
Yield %	Time (h), Yield (%)
$R_1=Me$ $R_2=Ph$ 4 , 80%	2 (2h, 85%)
$R_1=Bn$ $R_2=Ph$ 5 , 81%	14 (6h, 78%)
$R_1=Bn$ $R_2=Ph$ 6 , 88%	15 (2h, 82%)
$R_1=Bn$ $R_2=Ph$ 7 , 80%	16 (2h, 85%)
$R_1=Bn$ $R_2=Ph$ 8 , 85%	17 (4h, 79%)
$R_1=Me$ $R_2=Ph$ 9 , 70%	16 (2h, 70%)
$R_1=Bn$ $R_2=Ph$ 10 , 98%	18 (2h, 90%)
$R_1=Me$ $R_2=Ph$ 11 , 82%	18 (2h, 88%)
$R_1=Bn$ $R_2=Ph$ 12 , 92%	19 (2h, 92%)
$R_1=Bn$ $R_2=Ph$ 13 , 95%	20 (2h, 95%)

^aGeneral procedure: alkyne (1 mmol), nitrone (1.1 mmol), toluene (4 mL), diethylzinc (1M in hexane, 0.2 mmol), under N₂ atmosphere at rt provided isolated yield.

^bGeneral procedure: propargyl hydroxylamine (1 equiv), ZnI₂ (0.5 equiv), H₂O (1equiv.), CH₂Cl₂ (2 mL), under reflux condition provided isolated yield.