

Selective Transformation of *N*-(Propargylic)hydroxylamines into 4-Isloxazolines and Acylaziridines Promoted by Metal Salts

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Cyclization of *N*-(propargylic)hydroxylamines catalyzed by AgBF₄ afforded the corresponding 4-isloxazolines in good yields. Copper salts were found to promote the further transformation to acylaziridines. The combined use of AgBF₄ and CuCl realized direct transformation of *N*-(propargylic)-hydroxylamines into *cis*-acylaziridines.

Compounds bearing a 4-isloxazoline ring have biological activities and are versatile synthetic intermediates for nitrogen-containing chemicals.¹ 1,3-Dipolar cycloaddition of nitrones to acetylenes is one of the most attractive approaches to the synthesis of 4-isloxazolines, however, the method often suffers from poor regioselectivity.¹ Conjugate addition of hydroxylamines to α,β -unsaturated carbonyl compounds followed by dehydration is an alternative way.¹ 4-Isloxazolines could be also prepared via ring-closure of *N*-(propargylic)hydroxylamines catalyzed by zinc, palladium, or gold salt in the presence of an amine.² Furthermore, direct ring-closure of zinc salts of *N*-(propargylic)hydroxylamines, generated in situ by addition of alkynylzinc reagents to nitrones with an ester or amide group, has been reported.³ Recently, we have reported a one-pot reaction consisting of an enantioselective nucleophilic addition of alkynylzinc reagents to nitrones and a subsequent cyclization to give the corresponding (*S*)-4-isloxazolines with excellent enantioselectivity.⁴ However, the cyclization step was quite slow even when excess amounts of dimethylzinc were added for the promotion. In order to prepare 4-isloxazolines more efficiently, the cyclization of *N*-(propargylic)hydroxylamines to 4-isloxazolines was investigated in the presence of a metal salt. Herein, we wish to describe our finding that AgBF₄ was an efficient catalyst for the cyclization and further addition of a copper salt could rearrange the 4-isloxazolines to the corresponding acylaziridines. Direct stereoselective generation of *cis*-acylaziridines from *N*-(propargylic)hydroxylamines was also achieved with a AgBF₄–CuCl combined system.

First, the cyclization of *N*-benzyl-*N*-(1,3-diphenylprop-2-ynyl)hydroxylamine (**1a**) was examined in the presence of a catalytic amount of metal salt without an amine in CH₂Cl₂ at rt as shown in Table 1. It was reported that ZnI₂ and PdCl₂ promoted the cyclization in the presence of an amine base.^{2a,2b} Although ZnI₂ was not a suitable catalyst for the cyclization in the absence of the base (Entry 1), PdCl₂ promoted the cyclization to give the corresponding 4-isloxazoline in 86% yield after 17 h (Entry 2). PtCl₂ was not as effective as PdCl₂ (Entry 3). It was found that silver salts also promoted the cyclization (Entries 4–6). Cationic silver salts were more effective and the cyclization was completed within 4 h by using AgBF₄, rather faster than PdCl₂, to give 4-isloxazoline **2a** in 89% yield (Entry 6). Activity of AuCl₃ for the cyclization was high, but unknown by-products

Table 1. Cyclization of **1** in the presence of a metal salt

Entry	R ¹	R ²	1	MX _m	t/h	Yield/%
1	Ph	Ph	a	ZnI ₂	23	39
2				PdCl ₂	17	86
3				PtCl ₂	42	— ^a
4				AgNO ₃	40	57
5				AgOTf	21	84
6				AgBF ₄	4	89
7				AuCl ₃	0.3	61
8				AuCl ₃	22	74
9	Ph	<i>n</i> -Hex	b	AgBF ₄	8	73
10	Ph	<i>t</i> -Bu	c	AgBF ₄	22	82
11	<i>n</i> -Pr	Ph	d	AgBF ₄	8	53 ^b
12				AgBF ₄ ^c	8	64
13	<i>c</i> -Hex	Ph	e	AgBF ₄	6	85
14	Me	<i>n</i> -Hex	f	AgBF ₄	8	70

^aMost of the hydroxylamine **1a** was recovered. ^bThe hydroxylamine **1d** was recovered in 14% yield. ^cThe amount of AgBF₄ was 0.2 equiv.

were produced lowering the chemical yield of **2a** (Entries 7 and 8). Thus we chose readily available AgBF₄ (0.1 equiv) as the catalyst for the cyclization of several other *N*-(propargylic)-hydroxylamines **1b–1f** and the corresponding 4-isloxazolines **2b–2f** were obtained in good to high chemical yields (Entries 9–14). In the case of **1d**, the use of 0.2 equiv of AgBF₄ improved the chemical yield (Entry 12).

During the survey of metal salts for the cyclization of **1a**, it was found that not only 4-isloxazoline **2a** but also a *cis*-acylaziridine **3a**^{5f,6} was produced with complete diastereoselectivity when CuCl was used (Table 2, Entry 1). Although the transformation of 4-isloxazolines to acylaziridines had been reported,^{1,5} the conditions were drastic and the diastereoselectivity was not always good.

Next, direct transformation of **1a** to acylaziridine **3a** was intensively investigated (Table 2). By the use of cationic copper salts, the *cis*-acylaziridine **3a** was obtained as a major product (Entries 4–7). However, the reaction was messy and chemical yield was not satisfactory. In order to accelerate the cyclization step, a catalytic amount of AgBF₄ was added. Among copper salts examined, CuCl was most effective in the presence of AgBF₄ as a co-catalyst (Entries 9 and 13–16). By the use of 0.2 equiv of AgBF₄ and 1.0 equiv of CuCl, **3a** was finally obtained in 88% yield (Entry 10). When the amount of CuCl was

Table 2. Direct transformation of **1** to **3**

Entry	R ¹	R ²	1 / equiv	CuX _m / equiv	n ¹ / equiv	n ² / equiv	t /h	2 /%	3 /%
1	Ph	Ph	a	0	CuCl	1.0	41	16	2 ^a
2				0	CuCl ₂	1.0	44	—	—
3				0	CuI	1.0	44	—	— ^b
4				0	CuOTf ^c	1.0	17	23	58
5				0	Cu(OTf) ₂	1.0	48	—	45
6				0	CuBF ₄ ^d	1.0	7	—	45
7				0	Cu(BF ₄) ₂	1.0	25	—	48
8				0.1	CuCl	1.0	8	32	61
9				0.2	CuCl	1.0	8	13	84
10				0.2	CuCl	1.0	20	4	88
11				0.2	CuCl	0.2	8	10	58
12				0.2	CuCl	0.2	23	—	82
13				0.2	CuOTf ^c	1.0	7	—	35
14				0.2	Cu(OTf) ₂	1.0	8	—	13
15				0.2	CuBF ₄ ^d	1.0	8	—	42
16				0.2	Cu(BF ₄) ₂	1.0	8	10	42
17	Ph	<i>n</i> -Hex	b	0.2	CuCl	1.0	27	—	63
18	Ph	<i>t</i> -Bu	c	0.2	CuCl	1.0	24	—	72 ^c
19	<i>n</i> -Pr	Ph	d	0.2	CuCl	1.0	41	—	49 ^{e,f}
20	<i>c</i> -Hex	Ph	e	0.2	CuCl	1.0	25	14	64
21				0.3	CuCl	1.0	24	7	76
22	Me	<i>n</i> -Hex	f	0.2	CuCl	1.0	23	—	58

^aThe hydroxylamine **1a** was recovered in 69% yield. ^bMost of the hydroxylamine **1a** was recovered. ^cCuOTf(C₆H₅)_{0.5}. ^dCuBF₄(CH₃CN)₄. ^eThe corresponding *trans*-isomer of **3** was obtained in 6% (Entry 18) and in 10% (Entry 19) yields, respectively. ^fAn imine, *N*-(1-phenylhex-1-yn-3-ylidene)-benzylamine (**4d**), was obtained in 28% yield.

decreased to 0.2 equiv, the transformation proceeded a little sluggishly to afford **3a** still in high yield (Entries 11 and 12). The one-pot cyclization-isomerization was applied to several other *N*-(propargylic)hydroxylamines **1b–1f** in the presence of AgBF₄ (0.2 equiv) and CuCl (1.0 equiv) to afford the corresponding *cis*-acylaziridines **3b–3f** (Entries 17–22).⁶ In the case of *cis*-pivaloylaziridine **3c**, a small amount of *trans*-isomer was formed (Entry 18). Transformation from **1d** was not so clean and formation of the corresponding *trans*-isomer and a dehydrated imine **4d** was also observed (Entry 19). In the case of **1e**, increase of the amount of AgBF₄ could improve the chemical yields (Entries 20 and 21).

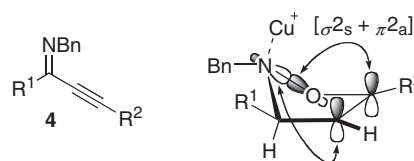
To confirm that copper salt promotes transformation of the 4-isoxazoline into the acylaziridine, 4-isoxazoline **2a** was treated with copper salts (Table 3). Although the reaction was rather sluggish when CuCl was used (Entry 1), CuOTf(C₆H₅)_{0.5} realized high chemical yield (Entry 2).

Finally, when the optically active **1a** (99% ee) was subjected to the present reactions under the same conditions as those of Entry 6 in Table 1 and Entry 10 in Table 2, the optically active **2a** (92%, 98% ee) and **3a** (87%, 98% ee) were obtained without loss of optical purities, respectively.

Table 3. Transformation of **2a** to **3a** promoted by a copper salt

Entry	CuX _m	t/h	Yield/%
1	CuCl	41	23 ^a
2	CuOTf(C ₆ H ₅) _{0.5}	4	81
3	Cu(OTf) ₂	41	3
4	CuBF ₄ (CH ₃ CN) ₄	22	71
5	Cu(BF ₄) ₂	41	45

^aThe 4-isoxazoline **2a** was recovered in 68% yield.

**Figure 1.**

Although the precise reaction mechanism is not yet clear, a radical mechanism might be ruled out, since addition of galvinoxyl free radical in the reaction of **1a** to **2a** (according to Entry 6 in Table 1) or **2a** to **3a** (according to Entry 2 in Table 3) as a radical inhibitor did not affect the reaction.^{7–9}

In the transformation of 4-isoxazoline to acylaziridine, [1,3]-sigmatropic rearrangement is a possible pathway to afford the *cis*-aziridine (Figure 1).^{5c–5e} Copper salt might activate the reaction via coordination by nitrogen resulting in lowering the LUMO energy of the N–O bond.

As described above, a convenient one-pot transformation of *N*-(propargylic)hydroxylamines into the corresponding 4-isoxazolines and aziridines, which are useful synthons for the synthesis of nitrogen-containing biologically active compounds, has been developed.^{1,10} Further studies on this reaction are in progress in our laboratory.

The present work was financially supported in part by a Grant-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science (JSPS).

References and Notes

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- 6 The *cis*-stereochemistry of **3a–3f** was confirmed by the coupling constant J_{2-3} (6.4–7.4 Hz) between the methine protons in aziridine rings.⁵
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- 8 When **2a** was treated with 1.0 equiv of CuOTf(C₆H₆)_{0.5} in ClCH₂CH₂Cl at 80 °C for 0.5 h, **3a** was obtained in 80% yield and diastereoselectivity was still high (**3a**/*trans*-isomer = 20/1, determined by ¹H NMR spectrum of the crude products) different from the result of the similar reaction promoted by Co₂(CO)₈ (0.5 equiv), in which *cis*/*trans* isomers' ratio was 2.8/1.^{5f} This fact might suggest that the present reaction does not proceed through a radical pathway via the metal enolate–aza radical intermediate as proposed in ref. 5f.
- 9 When the direct transformation of **1a** to **3a** according to Entry 10 in Table 2 was performed in the presence of galvinoxyl free radical (1.2 equiv), the reaction proceeded sluggishly to give **3a** in 10% yield accompanied by the production of an imine, *N*-(1,3-diphenylprop-2-ylidene)-benzylamine (**4a**) (34%). Galvinoxyl free radical might oxidize CuCl to give more Lewis acidic Cu(II) species, which promoted the dehydration of **1a**.
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