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Copper-Catalyzed Aerobic Oxidations of 3-*N*-Hydoxyaminoprop-1-ynes to Form 3-Substituted 3-Amino-2-en-1-ones: Oxidative Mannich Reactions with a Skeletal Rearrangement

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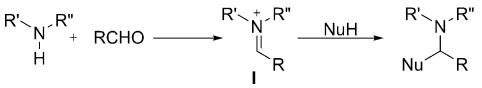
Abstract: Cu-catalyzed aerobic oxidations of readily available 3-*N*-hydroxyaminopro-1-ynes with water, alcohols, or thiols to form diverse 3-substituted 3-amino-2-en-1-ones are described. The utility of this catalysis is manifested by a wide scope of applicable *N*-hydroxyl propargylamines and nucleophiles, thus enabling the design of one-pot cascade or two-step sequential reactions. Besides synthetic significances, such oxidative Mannich reactions are mechanistically interesting because structurally reorganized products were obtained. Our mechanistic studies reveal that the aerobic oxidations involve initial formation of nitrone intermediates, followed by the attack of nucleophiles. Herein, water and MeOH implement the conversion of nitrone intermediates to reaction products in two distinct pathways.

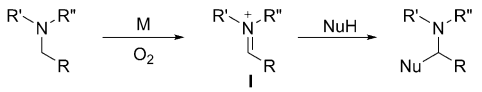
Iminium ions (**I**) are versatile reagents that react with nucleophiles to form new C–X bonds (X = C, N, O and S), as manifested by the Mannich reaction [Eq. (1)].[1] The formation of iminium ions by chemical oxidations of a N–CH functionality is an appealing surrogate for the Mannich reaction because tertiary amines are readily available reagents.[2] Numerous examples were reported for such C–H functionalizations with nucleophiles using Cu,[3] Fe,[4] Ru,[5] Rh,[6] and V[7a] catalysts, combined with *tert*-butyl hydroperoxide, di-*tert*-butylperoxide, or H_2O_2 as oxidants. Dioxygen is free and environmentally benign; aerobic oxidations of tertiary amines with nucleophiles (oxidative Mannich reactions) were achieved with Cu,[8] Ru,[9] Mo[10] V,[7b] and Fe[11] catalysts or with dual metal/photo-oxidations[12] [Eq. (2)]. We sought new aerobic oxidations of tertiary amines with nucleophiles beyond the present scope.[8f,13] We report here the Cu-catalyzed oxidations of 3-*N*-hydoxyaminoprop-1-ynes to form 3-substituted 3-amino-2-en-1-ones **2**–**4** that are useful building blocks in organic syntheses [Eq. (3)]. Among these products, highly functionalized 2-en-1-ones **3** and **4** were prepared from uncommon and sophisticated reagents including β-oxothioxo esters,[14a] α-oxoketene *S*,*S*-ketals,[14b] aryl isothiocyanate,[14c] 3,5-disubstituted isoxazole,[14d] and β-ketothioamides.[14e] In this oxidative skeletal rearrangement, nitrone intermediates **II** were generated initially and attacked by nucleophiles before proceeding to the products. When water and MeOH were utilized as nucleophiles, the routes to reaction products proceeded through distinct pathways.

Mannich reactions



(1)

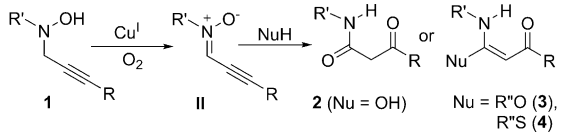
Oxidative Mannich reactions



(2)

M = Cu, Ru, Mo, V, and Fe

Oxidative Mannich reactions with skeletal rearrangemnt



(3)

Table 1 shows the oxidative rearrangement of *N*-hydoxypropargylamine **1a** with various metal catalysts by using O_2 (1 atm.) as the oxidant. We tested first CuCl (3 mol%) in hot THF (40 °C), which gave β-oxoamide **2a** in 88% yield (Table 1, entry 1); this yield was maintained even for 1 mol% Cu catalyst (entry 2). ^{1}H NMR spectra in $CDCl_3$ revealed that major species **2a** equilibrated with its enol form **2a′** with **2a**/**2a′** = 7.0. [CuCl(IPr)] (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) was nearly as effective as CuCl yielding **2a** in 87% yield (entry 3), whereas CuBr and CuOTf were less effective yielding species **2a** in 79 and 69% yields, respectively (entries 4 and 5). The use of Cu^{II} salts, such as $CuCl_2$ and $Cu(OTf)_2$, gave product yields (58–61%, entries 6 and 7), smaller than their Cu^{I} salts. Dioxygen is the required oxidant because no reaction occurred when starting with **1a** under N_2 (entry 8). CuCl maintained good efficiency in 1,4-dioxane and toluene at 40 °C, giving the desired product **2a** in 77 and 86% yields, respectively (entries 9 and 10). We also examined the oxidations with $FeCl_3$ and $RuCl_3$, which gave poor yields (23–42%) of compound **2a**

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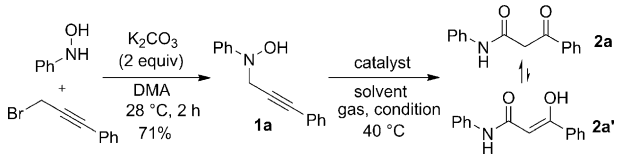
Table 1. Catalytic oxidations with various catalysts.



Entry	Cat.[a] ([mol%])	Solvent	Gas	t [h]	Yields [%][b,c] 1a	2a/2a′
1	CuCl (3)	THF	O_2	7	–	88
2	CuCl (1)	THF	O_2	8	–	88
3	[CuCl(IPr)] (1)	THF	O_2	14	–	87
4	CuBr (1)	THF	O_2	5	–	79
5	CuOTf (1)	THF	O_2	14	–	69
6	$CuCl_2$ (1)	THF	O_2	24	–	58
7	$Cu(OTf)_2$ (1)	THF	O_2	8	–	61
8	CuCl (1)	THF	N_2	12	78	trace
9	CuCl (1)	1,4-dioxane	O_2	10	–	77
10	CuCl (1)	toluene	O_2	8	–	86
11	$FeCl_3$ (1)	THF	O_2	2	–	23
12	$RuCl_3$ (1)	THF	O_2	7	–	42
13	–	THF	O_2	24	59	18
14	–	toluene	O_2	24	63	16

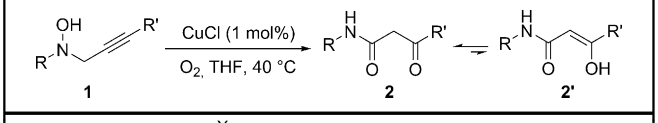
[a] [**1a**] = 0.22 M, O_2 (1 atm.). [b] Product yields (**2a**/**2a**′) are reported after purification from a silica column. [c] Keto/enol (**2a**/**2a**′) = 7.

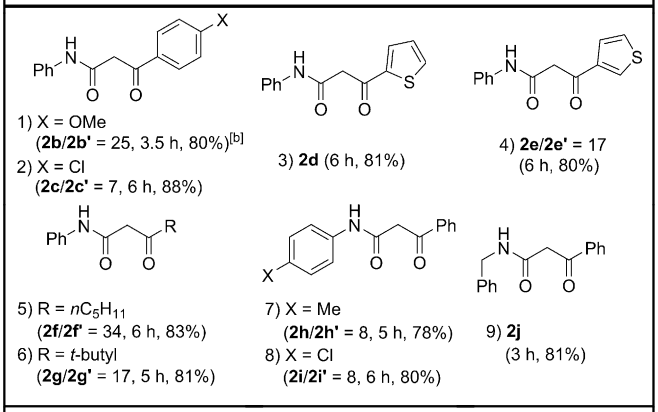
under O_2 (entries 11 and 12). In the absence of a metal catalyst, 3-*N*-hydoxyaminoprop-1-yne **1a** still afforded β-oxoamide **2a** in 18 and 16% yields in THF and toluene, respectively, under O_2 (entries 13 and 14). The NMR spectroscopic data of compound **2a** are identical to those of an authentic sample.[15]

We assess the scope of such an oxidative rearrangement with various *N*-hydoxypropargylamines bearing distinct R and R^1 substituents. β-Oxoamides **2** were formed as major (or sole) species that equilibrated with minor enol forms **2**′. Table 2, entries 1–4, show the applicability of this Cu-catalyzed oxidation to substrates **1b**–**c** and **1d**–**e** bearing varied phenyl (R′ = 4-XC_6H_4, X = OMe, Cl) and heteroaryl substituents (R′ = 3-thienyl and 2-thienyl), affording β-oxoamides **2b**–**e** in good yields (80–88%, entries 1–4). The same oxidations were amenable to substrates **1f**–**g** bearing aliphatic substituents (R′ = *n*-pentyl and *tert*-butyl), affording desired **2f**–**g** in 81–83% yields (entries 5 and 6). For substrates **1h**–**j** bearing various *N*-hydroxamino groups with R = 4-XC_6H_4 (X = Me and Cl) and benzyl, their corresponding oxidations gave compounds **2h**–**j** in 78–81% yields (entries 7–9). Although β-oxo amides can be readily prepared from β-oxo carboxylic acids and suitable amines,[16] our new method is equally convenient using cheap reagents sources.

We envisage that the preceding reactions likely occur by an attack of H_2O at the nitrone intermediates **II** [Eq. (3)]. To verify this hypothesis, we performed the reactions in hot THF containing various alcohols and thiols (5 equiv, 40 °C), yielding *E*-configured 3-substituted 3-amino-2-en-1-ones **3a**–**m** and **4a**–**b** (Table 3); these products were isolated as 2-en-1-one forms as sole (or major) species that equilibrated with minor tautomers **3**′–**4**′. As Table 3, entries 1–5 show, the Cu-catalyzed oxi-

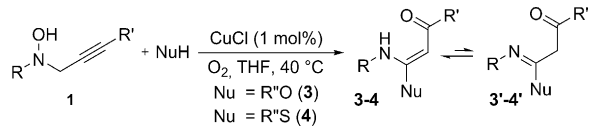
Table 2. Catalytic oxidations with water.[a]

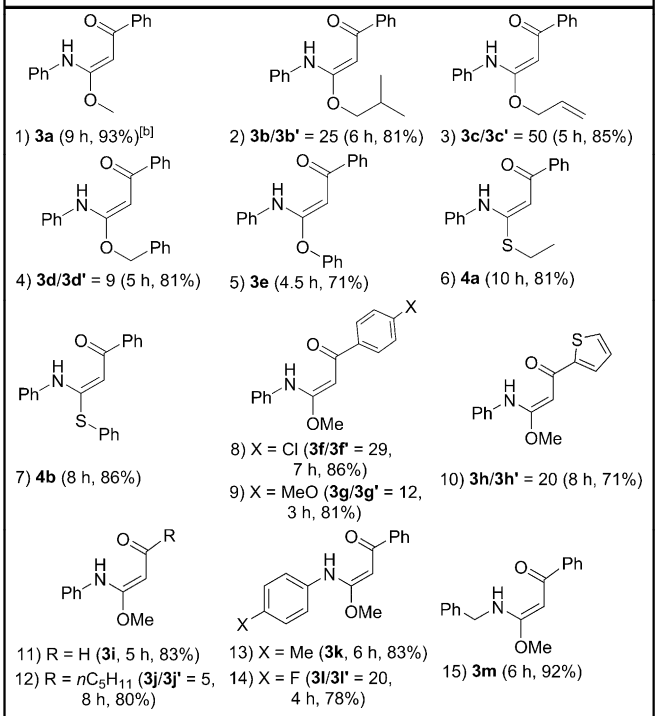




[a] [**1**] = 0.22 M, O_2 (1 atm.), The ratio of keto/enol (**2**/**2**′) was determined by ^{1}H NMR spectroscopy by using $CDCl_3$ as the solvent. [b] Product yields of the keto/enol (**2**/**2**′) mixture are reported after purification from a silica column.

Table 3. Catalytic oxidations with alcohols and thiols.[a]





[a] [**1**] = 0.22 M, NuH = (5 equiv), O_2 (1 atm.), The ratio of **3**/**3**′ was determined by ^{1}H NMR spectroscopy by using $CDCl_3$ as the solvent. [b] Product yields are reported after purification from a silica column.

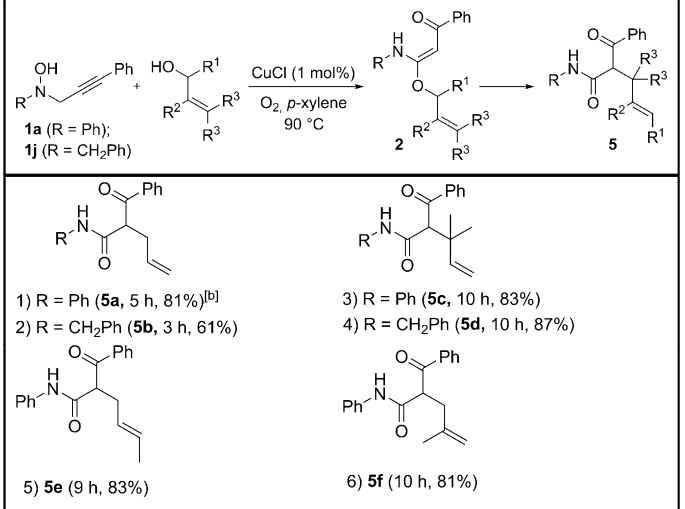
dations of *N*-hydroxypropargylamine derivative **1a** occurred with various ROH groups (R = methyl, isobutyl, allyl, benzyl, phenyl) to afford 3-alkoxy-3-amino-2-en-1-ones **3a**–**e** in good yields (71–93%). The reactions of species **1a** with thiols (RSH, R = Et and Ph) afforded thio-substituted analogues **4a** and **4b** in 81 and 86% yields, respectively, (entries 6 and 7). For varied *N*-hydroxypropargylamines bearing R′ = 4-XC_6H_4 (X = Cl and OMe) and R′ = 2-thienyl, their aerobic oxidations with MeOH yielded the desired products **3f**–**g** and **3h** in 71–86% yields (entries 8–10). We tested the reactions also on additional *N*-hydroxypropargylamines bearing R′ = H and *n*-pentyl, delivering 2-en-1-al **3i** and 2-en-1-one **3j** in 83 and 80% yields, respectively (entries 11–12). These aerobic oxidations were extendible to substrates bearing various *N*-hydroxamino groups with R = 4-XC_6H_4 (X = Me and F) and benzyl, yielding the expected 2-en-1-ones **3k**–**m** in 78–92% yields, respectively (entries 13–15). The molecular structures of compounds **3g** and **3l** were confirmed by X-ray diffraction.[17]

The facile introduction of alloxy groups into products **2** enables a cascade Claisen rearrangement,[18] as depicted in Table 4. The reactions were catalyzed with CuCl (1 mol%) and O_2 in hot *p*-xylene (90 °C, 3–10 h), giving 2-allyl-3-oxoamides **5a**–**f** efficiently. Table 4, entries 1 and 2 show the reactions of allylic alcohol with *N*-hydroxypropargylamines **1a** and **1j**, yielding the desired products **5a** and **5b** in 81 and 61% yields, respectively (entries 1 and 2). The catalytic oxidations of these substrates with 3,3-dimethyl-2-en-ol gave the corresponding products **5c** and **5d** in 83–87% yields (entries 3 and 4). For 1- or 2-methyl-2-en-1-ol, their reactions with propargylamine **1a** afforded the desired **5e** and **5f** in 83 and 81% yields, respectively (entries 5 and 6). Although products like **5a**–**b**, **5e**, and **5f** can also be prepared from the direct allylation of β-oxo-amide **2a**/**2a**′, our method is also convenient using different cheap reagents.

Table 5 manifests new synthetic utility using alkynols and allenols in two-step reactions. With 2,3-butadien-1-ol and 3-phenyl-2-propyn-1-ol, their corresponding Cu-catalyzed aerobic oxidations produced 3-substituted 3-amino-2-en-1-ones **6a** and **6b** in 78 and 79% yields, respectively (entries 1 and 2). Heating compounds **6a** and **6b** in *p*-xylene and toluene yielded dienones **7a** and **7b** by a Claisen-type rearrangement. We also prepared similar 2-en-1-ones **6c** and **6d**, respectively, from 3,4-pentadien-1-ol and 4-phenyl-3-butyn-3-ol; their subsequent treatment with [P(*t*Bu)$_2$(*o*-biphenyl)AuSbF$_6$] in hot DCE (50–60 °C) afforded six- and seven-membered oxacyclic products **7c** and **7d** in 83 and 68% yields, respectively. The diene geometry of compound **7b** was determined by ^{1}H NOE spectroscopy.

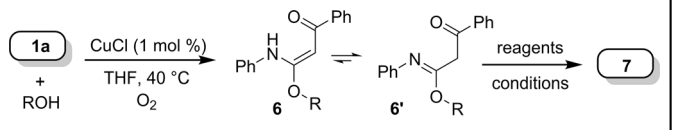
The preceding Cu-catalyzed aerobic oxidations are mechanistically interesting because the resulting products **2**–**4** involve an oxidative skeletal rearrangement. The treatment of species **1a** with H_2O* (2 equiv O* = 98% ^{18}O), O_2, and CuCl (1 mol%) in hot toluene (40 °C), at a 20% conversion level, afforded ^{18}O-**2a** bearing one ^{18}O atom (ca. 86% ^{18}O content) at the amide oxygen [Eq. (4)]. Notably, there was no ^{18}O content for the resulting β-oxoamide **2a** when $^{18}O_2$ was the oxidant [Eq. (4)]. To generate nitrones **II** in-situ, *N*-hydroxyaniline and alkynylaldehyde in equimolar proportions was treated with CuCl (1 mol%) and MeOH (2 equiv) in toluene (28 °C) under N_2, yielding the desired product **3a** in 72% yield [Eq. (5)].

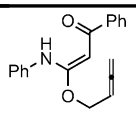
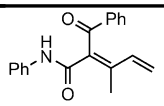
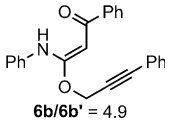
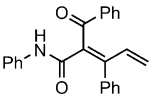
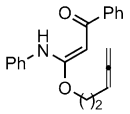
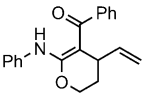
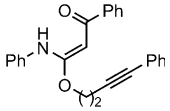
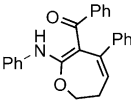
Table 4. Oxidations/Claisen rearrangement cascades.[a]



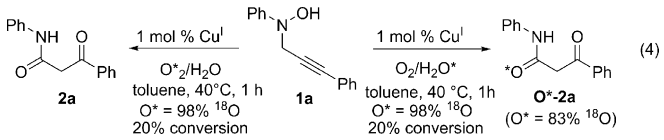
[a] [**1**] = 0.22 M, allylic alcohols (5 equiv), O_2 (1 atm). [b] Product yields are reported after purification from a silica column.

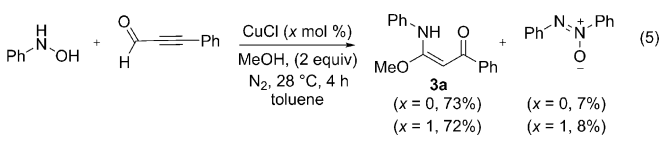
Table 5. Synthetic utility with two-step reactions.[a]



Entry	Step 1 **6** (*t*, yields)[b,c]	Reagents	Step 2 conditions	**7** (yields)[b]
1	 **6a** (5 h, 78%)	–	*p*-xylene, 90 °C, 5 h	 **7a** (71%, *E*/*Z* = 10:1)
2	 **6b/6b'** = 4.9 (6 h, 79%)	–	toluene, 110 °C, 24 h	 **7b** (81%)
3[d]	 **6c/6c'** = 20 (5 h, 80%)	5 mol%, [AuCl(L)]/ $AgSbF_6$	DCE, 60 °C, 10 h	 **7c** (83%)
4[d]	 **6d/6d'** = 14.6 (8 h, 72%)	5 mol%, [AuCl(L)]/ $AgSbF_6$	toluene, 50 °C, 12 h	 **7d** (68%)

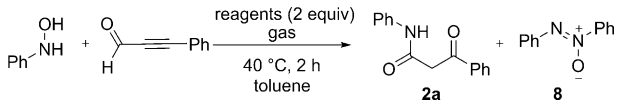
[a] [**1a**] = 0.22 M, ROH (5 equiv), O_2 (1 atm.); the ratio of **6**/**6**′ was determined by ^{1}H NMR spectroscopy by using $CDCl_3$ as the solvent. [b] Product yields are reported after purification from a silica column. [c] [**6**/**6**′] = 0.17 M. [d] L = P(*t*Bu)$_2$(*o*-biphenyl).





Compound **3a** was obtained in the same yield even though CuCl was absent. In contrast, β-oxoamide **2a** was produced in only 4% yield when water was used as the nucleophile (Table 6, entry 1) in THF (40 °C, 2 h) under N_2; herein, diazene

Table 6. Effects of oxidants on water as a nucleophile.

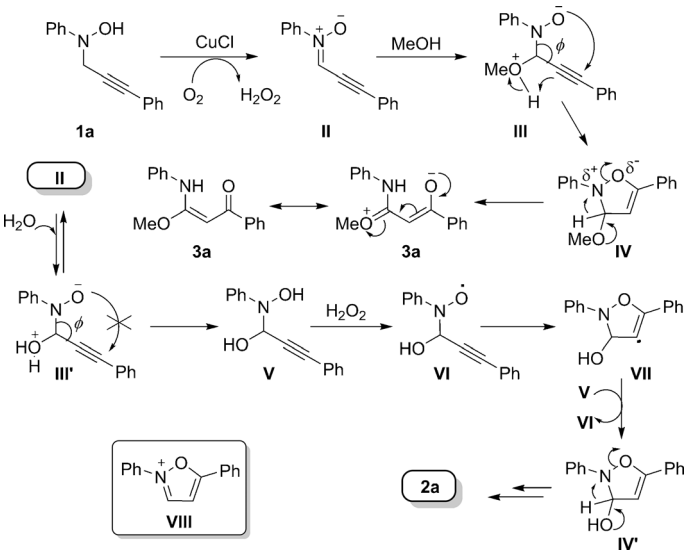


Entry	Reagent/gas	Yield [%][a] 2a	8
1	H_2O/N_2	4	23
2	H_2O/O_2	14	20
3	30% H_2O_2/O_2	51	8
4	30% $tBuO_2H/N_2$	11	22
5	30% $tBuO_2H/N_2$	33	14

[a] Product yields are reported after purification from a silica column.

oxide was obtained in 23% from the decomposition of *N*-hydroxyaniline. Under O_2, the yield of β-oxoamide **2a** was increased to 14% (entry 2). Surprisingly, the use of H_2O_2 (2 equiv, 30% in water) greatly improved the reactions to afford β-oxoamide **2a** in 51% yield (entry 3). As aqueous *tert*-butyl hydroperoxide was used under N_2, the yield of **2a** was decreased to 11% (entry 4). Di-*tert*-butylperoxide was active to provide the desired **2a** in 33% yield (entry 5). Accordingly, the mechanisms of the Cu-catalyzed aerobic oxidations with MeOH and water evidently differed.

The control experiments in [Eq. (5)] and Table 6 reveal that Cu-catalyzed oxidation of *N*-hydroxypropargylamine **1a** with O_2 generates nitrone **II** and H_2O_2 as an initiate step,[19,20] as depicted in Scheme 1. We exclude the involvement of isoxazolium salts (**VIII**) that could give desired **2a** and **3a** upon treatment with strongly basic NaOH or NaOMe.[21] In contrast, a prior attack of MeOH at nitrone species **II** is expected to form oxonium species **III** bearing an acidic proton; this Brønsted acid increases the electrophilicity of the alkyne to react facilely with the tethered oxygen anion, as depicted by the **III**→**IV** conversion. We postulate a novel 1,2-hydride shift of species **IV** to induce a ring cleavage, ultimately yielding the observed product **3a**; this 1,2-hydride shift is facilitated by the methoxy group as well as by the weak and charge polarity of the N–O bond in species **IV**. In Table 6, β-oxoamide **2a** was produced from nitrone more efficiently with aqueous H_2O_2 than with H_2O



Scheme 1. Proposed mechanisms for MeOH versus H_2O.

(entries 1 and 3). For H_2O, its corresponding intermediate **III′** is expected to have a ϕ larger than that of species **III** derived from MeOH (Thorpe–Ingold effect); accordingly species **III′** tends to form species **V** without a cyclization. H_2O_2 is weaker than water in nucleophilicity; the reaction of nitrone **II** with aqueous H_2O_2 still generates species **V** as well. Some *N*-hydroxyamines were reported to undergo metal-free aerobic oxidations to form *N*-amidoxyl radicals;[21] accordingly, we postulate that species **V** may be oxidized by H_2O_2 to form new *N*-amidoxyl radicals **VI** that are very active in a cyclization to producing species **VII**. With *N*-hydroxyamine **V** as a possible hydrogen donor, this alkenyl radical forms the desired intermediate **IV′**, ultimately yielding β-oxoamide **2a** by a 1,2-hydride shift. This mechanism rationalizes well the ^{18}O-labeling experiment [Eq. (4)].

In summary, we report Cu-catalyzed aerobic oxidations of 3-*N*-hydoxyaminoprop-1-ynes with water, alcohols, and thiols to form β-oxo amides and 3-substituted 3-amino-2-en-1-ones. The utility of this catalysis is manifested by a wide scope of applicable *N*-hydroxyl propargylamines and nucleophiles. With allylic alcohols, alkynols, and allenols, we develop cascade or sequential reactions to involve a Claisen rearrangement or gold-catalyzed cyclizations, providing new products with molecular complexity. Notably, these oxidations involve structural reorganization of products; the mechanisms have been elucidated with ^{18}O-labeling and control experiments. The aerobic oxidations are postulated to involve initial formation of nitrone species followed by attack of nucleophiles before proceeding to products. Among these nucleophiles, the production of β-oxoamides **2** with water is facilitated by H_2O_2, whereas MeOH alone implements effectively the conversion of nitrone to analogous products.

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Keywords: aminoenones · aerobic oxidations · copper catalysis · hydroxypropargylamines · skeletal rearrangement

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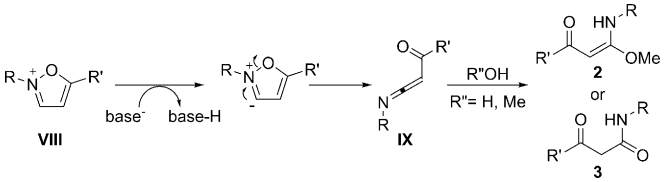
[21] Under basic conditions, isoxazolium salts **VIII** could react with stronly basic NaCN, NaOH, NaOMe, or NaOAc to give similar products including β-oxoamides **2** or 3-amino-2-en-1-one **3**; the mechanism was postulated to proceed with α-ketonketenimine intermediates **IX**. This pathway was unlikely to occur under our neutral conditions. See: R. B. Woodward, R. A. Olofson, *Tetrahedron* **1966**, *22*, 415 – 440 and reference therein.



VIII IX 2 3

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Organic Synthesis

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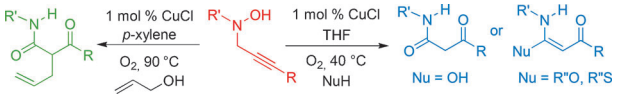
Copper-Catalyzed Aerobic Oxidations of 3-*N*-Hydoxyaminoprop-1-ynes to Form 3-Substituted 3-Amino-2-en-1-ones: Oxidative Mannich Reactions with a Skeletal Rearrangement



Go Mannich! We report Cu-catalyzed aerobic oxidations of 3-*N*-hydroxyaminopro-1-ynes with water, alcohols, or thiols to form diverse 3-substituted 3-amino-2-en-1-ones (see scheme). Such oxidative Mannich reactions are mechanistically interesting because structurally reorganized products were obtained.