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[3 + 2]-Annulations of *N*-Hydroxy Allenylamines with Nitrosoarenes: One-Pot Synthesis of Substituted Indole Products

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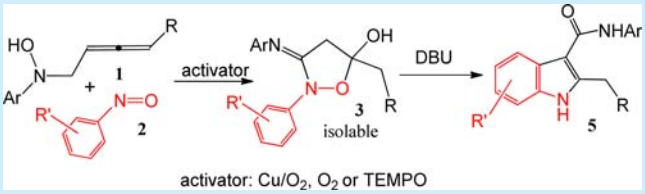
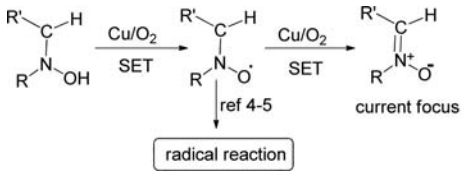
Supporting Information

ABSTRACT: In the presence of O_2 and an IPrCuCl additive (5 mol %), [3 + 2]-annulation reactions of *N*-hydroxyaniline with nitrosobenzenes in cold toluene form isoxazolidin-5-ol derivatives. Heating the same reaction mixture with DBU in toluene affords highly functionalized indole products efficiently. This method provides short synthesis of several bioactive molecules including WIN 48098, WIN 53365, and JWH 015.

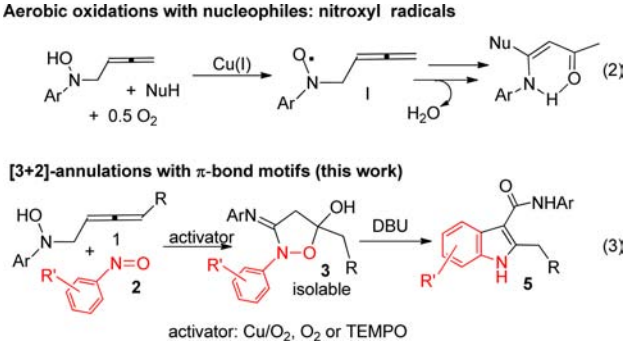


Metal-catalyzed aerobic oxidations of N−CH groups to form iminium ions are appealing surrogates for Mannich reactions.[1] Few examples obviate this iminium route over various oxidants and catalysts. In the context of *N*-hydroxy alkylamines, current catalytic aerobic oxidations focus on the formation of nitrones (eq 1),[2,3] including Cu-catalyzed aerobic oxidations of



(1)

N-hydroxy propargylamines with nucleophiles to form 3-substituted amino-2-en-1-ones.[3] In our recent findings,[4,5] Cu-catalyzed aerobic oxidations of *N*-hydroxy allylamines and allenylamines surprisingly generated nitroxyl radicals (**I**), which directed the subsequent N−CH oxidations with nucleophiles via non-nitrone routes (eq 2). Accordingly, the generation of



nitroxyl radicals is no longer restricted to those *N*-hydroxyamines bearing no N−CH moieties.[6,7] We seek new synthetic utility of nitroxyl radicals (**I**) with π-bond motifs as the reaction partner. Herein, we report [3 + 2]-annulations of *N*-hydroxy allenylamines (**1**) with nitrosoarenes (**2**) to form isolable isoxazolidin-5-ol species **3** (eq 3). Herein, the Cu/O_2 or O_2 additive resembles TEMPO (*vide infra*) to serve as a radical initiator, rather than as an oxidant. With DBU as a promoter, we develop a one-pot synthesis of useful 2,3-disubstituted indole derivatives (**5**) from the same reactants, greatly manifesting their synthetic value. Indole compounds (**5**) are often encountered as structural cores of many bioactive molecules;[8] selected examples are provided in Figure S1 (see Supporting Information, SI); this new indole synthesis is applicable to the short synthesis of several drug molecules including pravadoline derivatives (WIN 48098) and others (WIN 53365 and JWH-015).[8a−c]

N-Hydroxy allenylamines have been widely used in various Au- and Pt-catalyzed cyclizations to access *N*- and *O*-containing heterocycles.[9] The easy oxidation of these allenylamines (eq 2) stimulated us to explore their intermolecular redox reactions with nitrosoarenes that have low reduction potentials (0.5−0.6 eV).[10]

As shown in Table 1, the treatment of *N*-hydroxy allenylamine **1a** with nitrosobenzene **2a** (1.2 equiv) alone in toluene and argon (25 °C, 20 min) afforded annulation product **3a** in 62% yield, together with diazene oxide **4** in 14% yield (entry 1). This observation is not surprising because nitrosoarenes readily form nitroxyl radicals even with mild reductants such as styrene.[11] Under O_2, the yield of isoxazolidin-5-ol **3a** increased to 80%, whereas undesired diazene oxide **4** was significantly decreased to 8% yield; O_2 was known to be an activator for generation of the nitroxyl radical (entry 2).[6c]

Among various Cu additives in O_2, only IPrCuCl (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) was efficient to increase the yield of desired **3a** to 92% respectively, whereas diazene oxide **4** was obtained in only 4% yield. Herein, acidic CuOTf and $Cu(OTf)_2$ completely inhibited the annulation reactions (entries 6−7), probably due to their coordination with *N*-hydroxy allenylamine (**1a**) to retard the amine oxidation. $CuCl_2$ had no effect, but CuCl, CuBr, and $CuBr_2$ gave moderate

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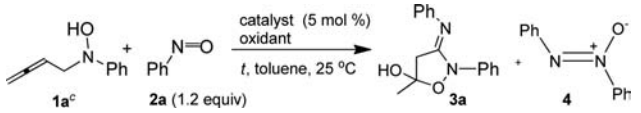
Table 1. Reactions over Various Cu Salts[a]

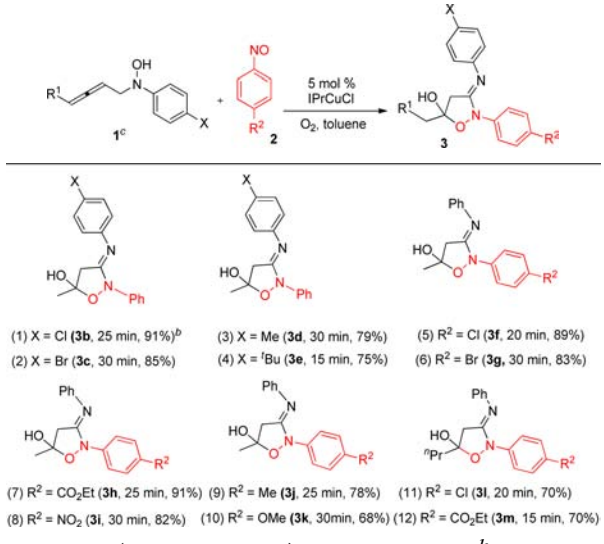


entry	additives	oxidant	time (min)	yield[b] (%) 3a	4
1	–	Ar[d]	20	62	14
2	–	O_2	20	80	8
3	CuCl	O_2	30	40	30
4	$CuCl_2$	O_2	30	80	10
5	IPrCuCl	O_2	20	92	4
6	$Cu(OTf)_2$	O_2	60	–	50
7	$CuOTf{\cdot}C_6H_6$	O_2	60	–	50
8	CuBr	O_2	20	56	22
9	$CuBr_2$	O_2	20	50	25
10	IPrCuCl	Ar	20	83	9
11	$CuCl_2$	Ar	20	70	15

[a]IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene. [b]Product yields are reported after purification from a neutral alumina column. [c]**1a** = 0.20 M. [d]Ar = Argon gas.

yields (40–56%) of desired **3a**; $CuCl_2$ was better than the other three catalysts for the oxidation of amines. The efficiency of IPrCuCl and $CuCl_2$ was affected by argon to afford product **3a** in decreased yields, ca. 83% and 70% (entries 10–11). The molecular structure of compound **3a** was inferred from X-ray diffraction of its relative **3h** (Table 2, entry 7).[12]

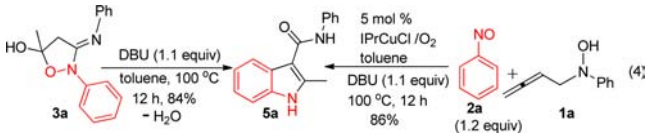
Table 2. Scope of [3 + 2]-Annulation Reaction[a]



[a]IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene. [b]Product yields are reported after purification from a neutral alumina column. [c]**1a** = 0.20 M, nitroso **2** = 1.2 equiv.

Table 2 assesses the generality of this [3 + 2]-annulation reaction with various *N*-hydroxy allenylamines and nitrosoarenes. The reactions were run with IPrCuCl (5 mol %) under O_2 (1 atm) in toluene (25 °C, 0.20 M). Entries 1–4 show the compatibility of this catalytic reaction with *N*-hydroxy allenylamines species **1b–1e** bearing various anilines, giving isoxazolidin-5-ols **3b–3e** in 75–91% yields. Herein, electron-deficient anilines (X = Cl and Br) are better than their electron-rich analogues (X = Me, *t*-Bu) for the product yields, as the latter tend to undergo a subsequent SET (single electron transfer) to give nitrones. We tested also the annulation of model allenylamine **1a** with various nitrosoarenes comprising various C(4)-substituents (R^2 = Cl, Br, CO_2Et, NO_2, Me, OMe), which all proceeded well to afford desired product **3f–3k** with 68–91% yields (entries 5–10). Again, electron-deficient nitrosoarenes (R^2 = Cl, Br, CO_2Et, NO_2) were compatible with this annulation (product yields >82%), as such substituents increased the reduction tendency of nitroso species. The molecular structure of **3h** was confirmed by X-ray diffraction (entry 7).[12] The scope of this [3 + 2]-annulation was further expanded by its applicability to 4-alkyl substituted *N*-hydroxy allenylamine substrates **1f** (R^1 = Et) that reacted with nitrosoarenes (R^2 = Cl, CO_2Et) to yield products **3l–3m** with 70% yields (entries 11–12). We have attempted the reactions between *tert*-butyl-substituted *N*-hydroxyallenyl amine and nitrosobenzene, but the reactions were unsuccessful.

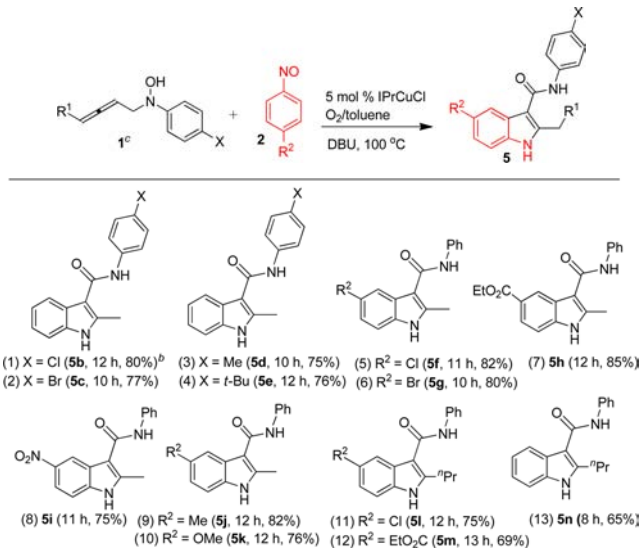
Notably, isoxazolidin-5-ol **3a** undergoes a DBU-mediated skeletal rearrangement to form indole product **5a** efficiently (84% yield, eq 4). More importantly, such a useful product is



directly accessible by heating a mixture of nitrosobenzene **2a** (1.2 equiv) and *N*-hydroxy allenylamine **1a** with IPrCuCl/O_2 (5 mol %) and DBU (1.1 equiv) in hot toluene; the yield of resulting indole **5a** is up to 86%. This one-pot reaction meets atom economy, as water is only the byproduct.

The viability of this one-pot reaction is manifested in Table 3; the procedure followed exactly that for indole compound **5a** (eq 4). This indole synthesis was applicable to various allenylamines **1b–1e** bearing various aniline functionalities (X = Cl, Br, Me, *t*-Bu), giving desired indole species **5b–5e** in satisfactory yields (76–80%). The molecular structure of compound **5e** was confirmed by X-ray diffraction.[12] The scope of this synthetic

Table 3. Scope of Substituted Indole Products[a]



[a]IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene. [b]Product yields are reported after purification from a silica gel column. [c]**1a** = 0.20 M, nitroso 1.2 equiv, DBU 1.1 equiv.

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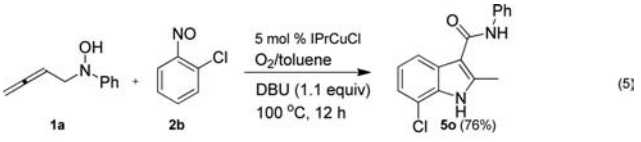
method was expanded with its compatibility with various substituted nitrosoarenes **2b**−**2g** (R^2 = Cl, Br, CO_2Et, NO_2, Me, OMe) to deliver 5-substituted indole derivatives **5f**−**5g** with yields exceeding 75% (entries 5−10); herein, the tolerance of functional groups such as nitro, ester, and methoxy is ascertained. This reaction also proved to be effective for sensitive functional nitrosobenzene (R^2 = NO_2, CO_2Et) providing 5-substituted indole product **5h**−**5i** with 75−85% yield (entries 7−8). This method was successfully applicable to C(4)-ethyl substituted allenylamine **1f** with various nitrosoarenes (R^2 = H, Cl and CO_2Et), giving desired indole derivatives **5l**−**5n** in 65−75% yield (entries 11−13). Notably, the isoxazolidin-5-ol precursor of indole **5n** was unstable toward chromatographic purification, but its indole synthesis was operable (entry 13).

Access to indole derivatives substituted with varied phenyl positions highlights the utility of this one-pot reaction. The same reaction sequence of *N*-hydroxy allenylamine **1a** with *o*-chloronitrosobenzene **2b** (1.2 equiv) delivered 7-chloro substituted indole product **5o** in 76% yield (eq 5). The reaction



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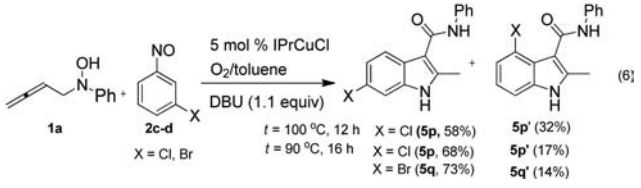


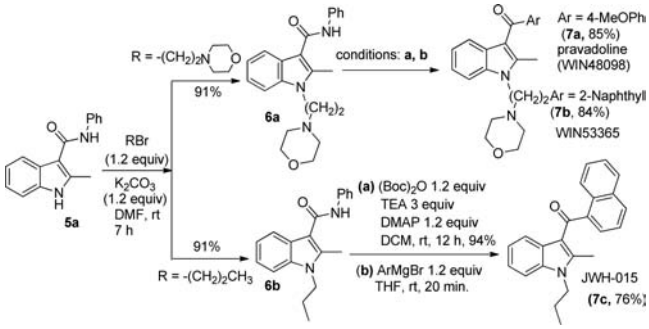
(6)

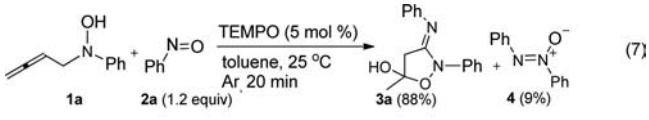
of *m*-chloronitrosobenzene **2c** with species **2b** gave 6- and 4-chloro substituted indoles **5p**/**5p**′ with isolated 58% and 32% yield respectively (eq 6). Interestingly, the regioselectivity of **5p**/**5p**′ was greatly improved at 90 °C with isolated 68% and 17% yields, respectively. Under these conditions, the reaction of *m*-bromonitrosobenzene **2d** with species **1a** gave 6- and 4-bromo substituted indole **5q**/**5q**′ with isolated yields of 73% and 14% respectively.

This new synthetic method provides a short synthesis of pravadoline **7a** (WIN 48098) that acts as a potent anti-inflammatory and analgesic drug (IC_{50} 4.9 μM, K_i 2511 nM at CB_1).[8a] The reaction sequence employs one of our products, **5a** (eq 4), with prior amide protection (**5a** → **6**), followed by treatment with $MeOC_6H_4MgBr$ (1.2 equiv); the overall yield was 77% (**5a**→ pravadoline). Likewise our method also provides a short synthesis of two drug molecules[15] WIN53365 (**7b**) and JWH015 (**7c**) that act as cannabinoid agonists;[8b,c] their synthetic protocols are provided in Scheme 1.

The key annulation (**1** → **3**) likely involves the intermediacy of nitroxyl radicals. We thus tested the reaction efficiency with TEMPO (5 mol %) alone in toluene under Ar; the reaction was complete in 20 min to yield isoxazolidin-5-ol **3a** and diazene oxide **4**, respectively in 88% and 9% yield (eq 7). TEMPO (5 mol %), indeed, enhanced the reaction efficiency via generation of nitroxyl radicals. The reaction of species **1a** with TEMPO (2 equiv) under O_2 afforded compound **8** in 79% yield (eq 8). The treatment of *N*-hydroxy allenylamines **1a** alone with O_2 led to the formation of β-oxoamide **9** with 30% isolated yield.[4] Formation of compounds **8** and **9** has been described in our previous work;[4] their mechanisms involve intermediate **C** (see Scheme 3).

Scheme 1. Short Synthesis of Drug Molecules





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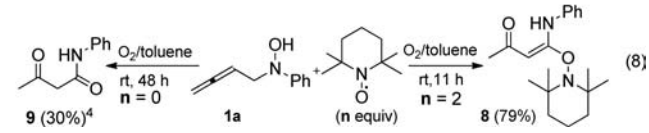

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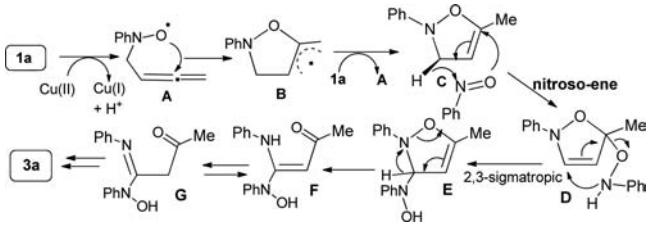
In the IPrCuCl/O_2 system, Cu(II) species is likely to exist in small proportion, which reacts with initial **1a** to form nitroxyl radical **A** (Scheme 2) according to the recent reports of Stahl and

Scheme 2. Postulated Mechanisms for [3 + 2]-Annulations



co-workers;[7a−d] O_2 has a similar effect.[6c] The postulated cyclization (**A** → **C**) reveals the catalytic role of nitroxyl radical (A) that suffices in this radical chain reaction even in small proportion. Particularly notable is our proposed nitroso-ene reaction[13] on 2,3-dihydroisoxazole species **C**, enabling its intermolecular redox reaction with nitrosobenzene. A subsequent 2,3-sigmatropic shift of species **D** forms 3-amino-2,3-dihydroisoxazole **E** that subsequently undergoes a Pinacol-like 1,2-hydrogen shift to yield the precursor of final product **3a**. In the absence of IPrCuCl and O_2, the generation of nitroxyl radical **A** is achievable with nitrosobenzene alone (see Table 1, entry 1), but the efficiency is inferior to that in the IPrCuCl/O_2 system. Although the carbon-radical can react with nitrosobenzene to form a C−N bond,[14] the addition of nitrosobenzene to allyl radical **B** is challenging in deducing a rational route to afford desired **3a**.

The DBU-mediated indole synthesis (**3a** → **5a**) is mechanistically interesting because the reaction involves a noteworthy structural rearrangement. A postulated mechanism, shown in Scheme 3, assesses the key role of ketenimine intermediates. DBU can assist the ring opening of initial ketal **3a** to form species H, further catalyzing its rearrangement to its *O*-linkage isomer **J** via reversible formation of ketenimine species **I**.

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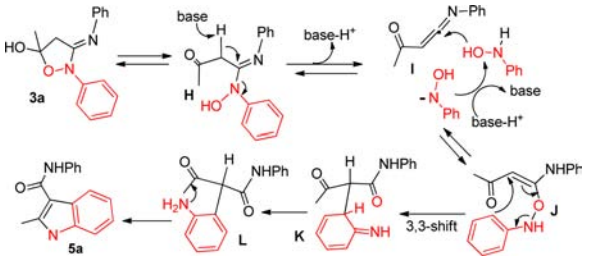
Scheme 3. DBU-Catalyzed Skeletal Rearrangement



Unlike its *N*-linkage isomer **H**, species **J** is chemically reactive to undergo a 3,3-sigmatropic shift,[16] yielding 3-oxo-2-arylamides **K** and **L** and ultimately providing desired product **5a**.

[3 + 2]-Annulation reactions of *N*-hydroxy allenylamines with nitrosoarenes to form isoxazolidin-5-ols are described; herein, IPrCuCl/O_2 functions as a radical initiator to generate key nitroxyl radicals.[17] In the presence of DBU, these isoxazolidin-5-ols undergo skeletal rearrangement to form indole products. A direct synthesis of such useful indole derivatives is developed to manifest the practicality. The structural rearrangement of isoxazolidin-5-ols (**3**) and indoles (**5**) can be satisfactorily assessed, as their mechanisms are postulated to comprise nitroso-ene reactions and ketenimine intermediates. Finally, we demonstrate the utility of this indole synthesis[18] with the short synthesis of three commercial drug molecules based on the derivatives of pravadolines.[15]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03447.

Experimental details and spectral data of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Crystallographic data for compounds **3h** and **5e** were deposited at Cambridge Crystallographic Center (**3h**, CCDC 1418733; **5e**, CCDC 1423186).

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(15) Pravadoline **7a** (WIN 48098) is commercially sold at Abmole Bioscience Inc., Adooq Biosciences, and Axon Medchem (>USD 170/50 mg). Compound **7c** (JWH-015) is currently available at Enzo Life Science and Sigma (>USD 328/25 mg).

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(17) Under IPrCuCl/O_2, the reaction of *N*-hydroxy allylamine with nitrosoarene gave [3 + 2]-annulation products through vinyl nitrone intermediates; one example is provided in the SI (see Scheme s1).

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Org. Lett. 2016, 18, 412−415