

[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

$$\begin{array}{c} R' & C & H \\ R' & OH \end{array} \xrightarrow{R'} C & H \\ R' & OH \end{array} \xrightarrow{R'} C & H \\ SET & R' & O \\ \hline ref 4-5 \\ \hline radical reaction \end{array} \xrightarrow{R'} C & H \\ (1)$$

N-hydroxy propargylamines with nucleophiles to form 3substituted amino-2-en-1-ones.³ In our recent findings,^{4,5} Cucatalyzed 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/O₂ or O₂ 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 O₂, the yield of isoxazolidin-5-ol 3a increased to 80%, whereas undesired diazene oxide 4 was significantly decreased to 8% yield; O₂ 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 = 1,3bis(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. CuCl₂ had no effect, but CuCl, CuBr, and CuBr₂ gave moderate

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Table 1. Reactions over Various Cu Salts^a

HC N 1a ^c) + N=O N Ph Ph 2a (1.2 equ	catalyst (5 mol %) oxidant t, toluene, 25 °C		Ph Ph + N=	0- 	
				yield	yield ^{b} (%)	
entry	additives	oxidant	time (min)	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**; CuCl₂ was better than the other three catalysts for the oxidation of amines. The efficiency of IPrCuCl and CuCl₂ 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



(7) R² = CO₂Et (**3h**, 25 min, 91%) (9) R² = Me (**3j**, 25 min, 78%) (11) R² = CI (**3l**, 20 min, 70%)
 (8) R² = NO₂ (**3i**, 30 min, 82%) (10) R² = OMe (**3k**, 30min, 68%) (12) R² = CO₂Et (**3m**, 15 min, 70%)

^aIPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene. ^bProduct yields are reported after purification from a neutral alumina column. ^c1a = 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 O₂ (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, electrondeficient anilines (X = Cl and Br) are better than their electronrich 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 allenvlamine substrates $1f(R^1 =$ Et) that reacted with nitrosoarenes ($R^2 = Cl, CO_2Et$) to yield products 31-3m with 70% yields (entries 11-12). We have attempted the reactions between tert-butyl-substituted Nhydroxyallenyl 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/O₂ (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



^{*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.

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



of *m*-chloronitrosobenzene **2c** with species **2b** gave 6- and 4chloro 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 antiinflammatory and analgesic drug (IC₅₀ 4.9 μ M, K_i 2511 nM at CB₁).^{8a} The reaction sequence employs one of our products, **5a** (eq 4), with prior amide protection (**5a** \rightarrow **6**), followed by treatment with MeOC₆H₄MgBr (1.2 equiv); the overall yield was 77% (**5a** \rightarrow pravadoline). Likewise our method also provides a short synthesis of two drug molecules¹⁵ WIN53365 (7b) and JWH015 (7c) that act as cannabinoid agonists;^{8b,c} their synthetic protocols are provided in Scheme 1.

The key annulation $(1 \rightarrow 3)$ 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 O₂ afforded compound **8** in 79% yield (eq 8). The treatment of *N*-hydroxy allenylamines **1a** alone with O₂ 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).





In the IPrCuCl/O₂ 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



co-workers;^{7a-d} O₂ has a similar effect.^{6c} The postulated cyclization $(A \rightarrow C)$ 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 reaction¹³ 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-2,3dihydroisoxazole 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 O₂, 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 $(3a \rightarrow 5a)$ 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.

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/O₂ functions as a radical initiator to generate key nitroxyl radicals.¹⁷ In the presence of DBU, these isoxazolidin-5ols 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 nitrosoene reactions and ketenimine intermediates. Finally, we demonstrate the utility of this indole synthesis¹⁸ with the short synthesis of three commercial drug molecules based on the derivatives of pravadolines.¹⁵

ASSOCIATED CONTENT

Supporting Information

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Experimental details and spectral data of all compounds (PDF)

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The authors declare no competing financial interest.

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REFERENCES

 (1) For reviews for N-CH oxidation, see: (a) Girard, S. A.; Knauber, T.; Li, C.-J. Angew. Chem., Int. Ed. 2014, 53, 74. (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. Angew. Chem., Int. Ed. 2011, 50, 11062.
 (c) Klussmann, M.; Sureshkumar, D. Synthesis 2011, 2011, 353. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. Chem. Rev. 2011, 111, 1780. (e) Zhang, C.; Tang, C.; Jiao, N. Chem. Soc. Rev. 2012, 41, 3464.

(2) (a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. Chem. Rev. 2011, 111, 3076. (b) Toure, B. B.; Hall, D. G. Chem. Rev. 2009, 109, 4439. (c) Hwu, J. R.; Tsay, S.-C.; Chen, B.-L.; Patel, H. V.; Chou, C.-T. J. Chem. Soc., Chem. Commun. 1994, 1427. (d) Lebeuf, R.; Nardello-Rataj, V.; Aubry, J.-M. Chem. Commun. 2014, 50, 866. (e) Gribble, G. W.; Barden, T. C. J. Org. Chem. 1985, 50, 5900. (f) Sakurai, T.; Uematsu, Y.; Tanaka, O.; Inoue, H. J. Chem. Soc., Perkin Trans. 2 1992, 2163.

(3) Kawade, R. K.; Tseng, C.-C.; Liu, R.-S. Chem. - Eur. J. 2014, 20, 13927.

(4) Sharma, P.; Liu, R.-S. Chem. - Eur. J. 2015, 21, 4590.

(5) Ghorpade, S.; Liu, R.-S. Angew. Chem., Int. Ed. 2014, 53, 12885.
(6) For reviews, see: (a) Sheldon, R. A.; Arends, I. W. C. E. Adv. Synth. Catal. 2004, 346, 1051. (b) Cao, Q.; Dornan, L. M.; Rogan, L.; Hughes, N. L.; Muldoon, M. L. Chem. Commun. 2014, 50, 4524. (c) Ryland, B. L.; Stahl, S. S. Angew. Chem., Int. Ed. 2014, 53, 8824. (d) Tebben, L.; Studer, A. Angew. Chem., Int. Ed. 2011, 50, 5034.

(7) (a) Ryland, B. L.; McCann, S. D.; Brunold, T. C.; Stahl, S. S. J. Am. Chem. Soc. 2014, 136, 12166. (b) Steves, J. E.; Stahl, S. S. J. Am. Chem. Soc. 2013, 135, 15742. (c) Rafiee, M.; Miles, K. C.; Stahl, S. S. J. Am. Chem. Soc. 2015, 137, 14751. (d) Kim, J.; Stahl, S. S. ACS Catal. 2013, 3, 1652. (e) Hamada, S.; Furuta, T.; Wada, Y.; Kawabata, T. Angew. Chem., Int. Ed. 2013, 52, 8093. (f) Allen, A. D.; Porter, J.; Tahmassebi, D.; Tidwell, T. T. J. Org. Chem. 2001, 66, 7420. (g) Babiarz, J. E.; Cunkle, G. T.; DeBellis, A. D.; Eveland, D.; Pastor, S. D.; Shum, S. P. J. Org. Chem. 2002, 67, 6831. (h) Lu, Q.; Liu, Z.; Luo, Y.; Zhang, G.; Huang, Z.; Wang, H.; Liu, C.; Miller, J. T.; Lei, A. Org. Lett. 2015, 17, 3402. (i) Schmidt, V. A.; Alexanian, E. J. J. Am. Chem. Soc. 2011, 133, 11402. (j) Studer, A. Angew. Chem., Int. Ed. 2000, 39, 1108. (k) Schmidt, V. A.; Alexanian, E. J. Angew. Chem., Int. Ed. 2010, 49, 4491. (l) Schmidt, V. A.; Alexanian, E. J. Chem. Sci. 2012, 3, 1672.

(8) (a) Ross, R. A.; Brockie, H. C.; Stevenson, L. A.; Murphy, V. L.; Templeton, F.; Makriyannis, A.; Pertwee, R. G. *Br. J. Pharmacol.* **1999**, *126*, 665. (b) Dutta, A. K.; Ryan, W.; Thomas, B. F.; Singer, M.; Compton, D. R.; Martin, B. R.; Razdan, R. K. *Bioorg. Med. Chem.* **1997**, *5*, 1591. (c) Murataeva, N.; Mackie, K.; Straiker, A. *Pharmacol. Res.* **2012**, 66, 437. (d) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620. (e) Arisawa, M.; Kasaya, Y.; Obata, T.; Sasaki, T.; Nakamura, T.; Araki, T.; Yamamoto, K.; Sasaki, A.; Yamano, A.; Ito, M.; Abe, H.; Ito, Y.; Shuto, S. *J. Med. Chem.* **2012**, *55*, 8152. (f) Leneva, I. A.; Russell, R. J.; Boriskin, Y. S.; Hay, A. J. *Antiviral Res.* **2009**, *81*, 132. (g) Biswal, S.; Sahoo, U.; Sethy, S.; Kumar, H. K. S.; Banerjee, M. *Asian J. Pharm. Clin. Res.* **2012**, *5*, 1.

(9) (a) Zeng, Q.; Zhang, L.; Yang, J.; Xu, B.; Xiao, Y.; Zhang, J. Chem. Commun. 2014, 50, 4203. (b) Winter, C.; Krause, N. Angew. Chem., Int. Ed. 2009, 48, 6339. (c) Lalonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. Angew. Chem., Int. Ed. 2010, 49, 598.

(10) Lutz, R. E.; Lytton, M. R. J. Org. Chem. 1937, 2, 68.

(11) Kang, J. Y.; Bugarin, A.; Connell, B. T. Chem. Commun. 2008, 3522.

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

(13) Adam, W.; Krebs, O. Chem. Rev. 2003, 103, 4131.

(14) Fisher, D. J.; Burnett, L. G.; Velasco, R.; de Alaniz, J. R. J. Am. Chem. Soc. **2015**, 137, 11614.

(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).

(16) (a) Kawade, R. K.; Huang, P.-H.; Karad, S. N.; Liu, R.-S. Org. Biomol. Chem. 2014, 12, 737. (b) Wang, Y.; Ye, L.; Zhang, L. Chem. Commun. 2011, 47, 7815.

(17) Under IPrCuCl/O₂, 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).

(18) For indole synthesis see: (a) Porcheddu, A.; Mura, M. G.; De Luca, L.; Pizzetti, M.; Taddei, M. Org. Lett. **2012**, *14*, 6112. (b) Larock, R. C.; Yum, E. K. J. Am. Chem. Soc. **1991**, *113*, 6689. (c) Bartoli, G.; Palmieri, G. Tetrahedron Lett. **1989**, 30, 2129. (d) Allen, G. R.; Pidacks, C., Jr.; Weiss, M. J. J. Am. Chem. Soc. **1966**, 88, 2536. (e) Chen, Y.; Xie, X.; Ma, D. J. Org. Chem. **2007**, *72*, 9329.