Indole Oxygenation

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Internal Oxidant-Triggered Aerobic Oxygenation and Cyclization of Indoles under Copper Catalysis

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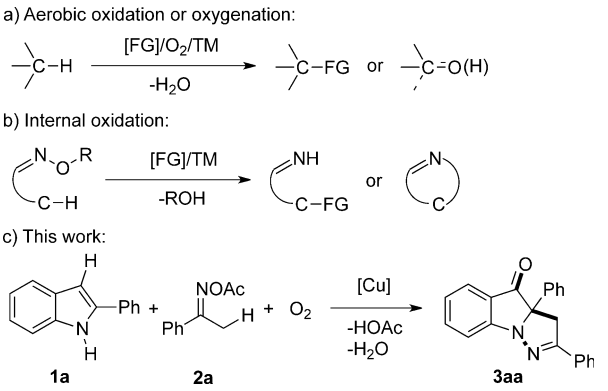
Abstract: *A concise synthesis of pyrazolo[1,5-a]indole derivatives by copper-catalyzed aerobic oxygenation and cyclization of indoles with oxime acetates is described. This protocol represents an elegant example of N-1, C-2, and C-3 trifunctionalization of indoles in one-pot. Mechanistic studies indicate the reaction proceeds through a radical procedure. Oximes as an internal oxidant have been demonstrated to be a driver to initiate aerobic oxidation, which provides a new oxidative pattern for C-H functionalization even with high atom- and step-economy.*

Indole is a privileged structure among pharmacological compounds and natural products.[1] Consequently, the functionalization of indoles to introduce chemical functional groups around the indole ring is still an active field of research in synthetic chemistry.[2] Numerous catalytic systems dedicated to N-1, C-2, or C-3 mono-functionalization of indoles have been developed to prepare a broad range of functionalized indoles.[3] Di-functionalization of indoles, including indole-involved cycloaddition, was frequently performed at the C-2 and C-3 positions, which gave convenient access to significant indole-fused heterocycles or other di-functionalized indoles.[4] N-1 and C-3 di-functionalization of indoles were also discovered.[5] To our knowledge, however, examples of N-1, C-2, and C-3 tri-functionalization of indoles in one pot are rather rare.[6] The key challenge may be attributed to the fact that chemoselectivity can be difficult to control in a one pot reaction. You and co-workers described a Ru/TsOH co-catalyzed allylic dearomatization/cyclization/allylic amination cascade reaction of indoles, enabling N-1, C-2, and C-3 tri-functionalization of indoles in one pot.[6a] The asymmetric synthesis was realized later under an iridium-based catalytic system.[6b] This multi-functionalization strategy is of great significance for providing facile access to highly functionalized indoles with step-economy, and thereby improved overall efficiency.

Molecular oxygen is well feted as an ideal oxidant and oxygenating reagent in organic synthesis. Direct C–H functionalization by aerobic oxidation with molecular oxygen is a fascinating topic of research (Scheme 1 a), however the challenge of elusive oxygen activation remains an issue. In this field, copper catalysts are powerful reagents to engage molecular oxygen in organic synthesis owing to their abundant valence states and the affinity with oxygen.[7] As a result, a large number of facile copper-based catalytic systems have been developed for aerobic synthesis.[8] In recent years, oximes as an internal oxidant were found to be versatile building blocks (Scheme 1 b),[9] especially in copper-catalyzed systems.[10] While in most cases, single-electron transfer (SET) is a basic process in copper-based aerobic oxidation,[7d] we set out to design oxime-based aerobic transformations under copper catalysis, in which the radical intermediate derived from the internal oxidant oximes would trigger external aerobic oxidation of the desired reactant. The strategy of internal/external co-oxidation with oxygen would provide a specific paradigm for oxidative C–H functionalization even with high activity and high atom-economy, and moreover this synergistic effect may achieve high levels of chemo- and regio-selectivity. Based on this conception, a range of simple organic chemicals have been treated with oxime acetates in copper/oxygen-based system in our initial attempts. Herein, we describe an internal oxidant-triggered aerobic oxygenation and cyclization of indoles with oximes (Scheme 1 c), which enables N1, C2, and C3 tri-functionalization of indoles in a one-pot manner and, more importantly, provides a concise route to pharmacologically significant pyrazolo[1,5-a]indole derivatives.[11]



Scheme 1. C–H functionalization by internal or/and aerobic oxidation. TM = transition metal catalyst.

With our continuing interest in the functionalization of indoles,[12] 2-phenyl-1H-indole **1a** and acetophenone oxime acetate **2a** were chosen as the model system to explore the reaction conditions (Supporting Information, Table S1–S4).[13] The final optimized reaction conditions include indole and oxime (1.2 equiv) with 15 mol% of $CuCl_2$ in 1,4-dioxane

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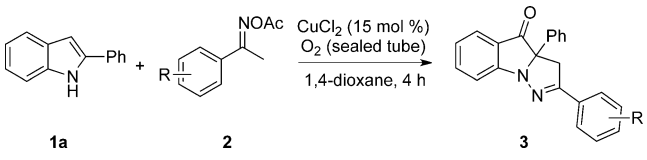
(0.2 M) under 1 atm O_2 at 80 °C for 4 h, affording **3aa** in 77 % isolated yield. With these optimized conditions in hand, the scope and generality of the aerobic oxygenation and cyclization were next probed. Firstly, various substituted acetophenone oxime acetates were subjected to the copper-catalyzed aerobic system (Table 1). Generally, the aromatic methyloximes screened reacted smoothly to give the corresponding pyrazolo[1,5-a]indoles (**3aa–3as**) in moderate to good yields (Table 1, entries 1–19), regardless of the functional groups at the *para*-, *meta*-, or *ortho*-positions. A large range of functional groups on the benzene ring, such as alkyl (**2b–d**), methoxyl (**2e** and **2l**), fluoro (**2f**), and trifluoromethyl (**2p**) were all tolerated well. Both the steric and electronic effects of the substituents are not apparent, however, the oximes with iodo- and nitro-groups afforded relatively low yield (entries 9–10). While naphthyl oxime **2t** furnished the corresponding product **3at** in 37 % yield (entry 20), heteroaromatic oximes **2u** and **2v** produced furyl and thienyl pyrazolo[1,5-a]indoles (**3au–3av**) in good yields (62 % and 85 %, respectively; entries 21–22). Vinyl oxime **2w** also worked, albeit in a moderate yield (entry 23). Finally, we found either aliphatic oxime **2x** or non-methyl oximes **2y–z** could transfer into the desired products on the basis of GC-MS analysis with very low yield (entries 24–26), however, no purified products could be obtained after column chromatography.

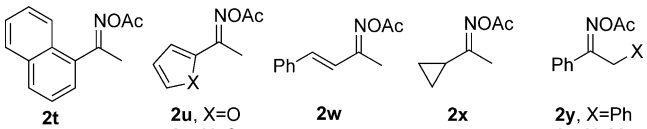
Subsequently, a range of indoles were subjected to this copper/O_2-based system (Scheme 2). 2-Phenyl-substituted indoles bearing alkyl, halogen, methoxyl, and trifluoromethyl at the benzene rings are all readily accommodated, affording the corresponding products in moderate to good yields (Scheme 2, **3be–3me**). Analogously, there seems to be no steric effect among the benzene substituents (Scheme 2, **3he–3me**), which, in connection to the previous observation,

Table 1: Oxime scope for the cyclization.[a]



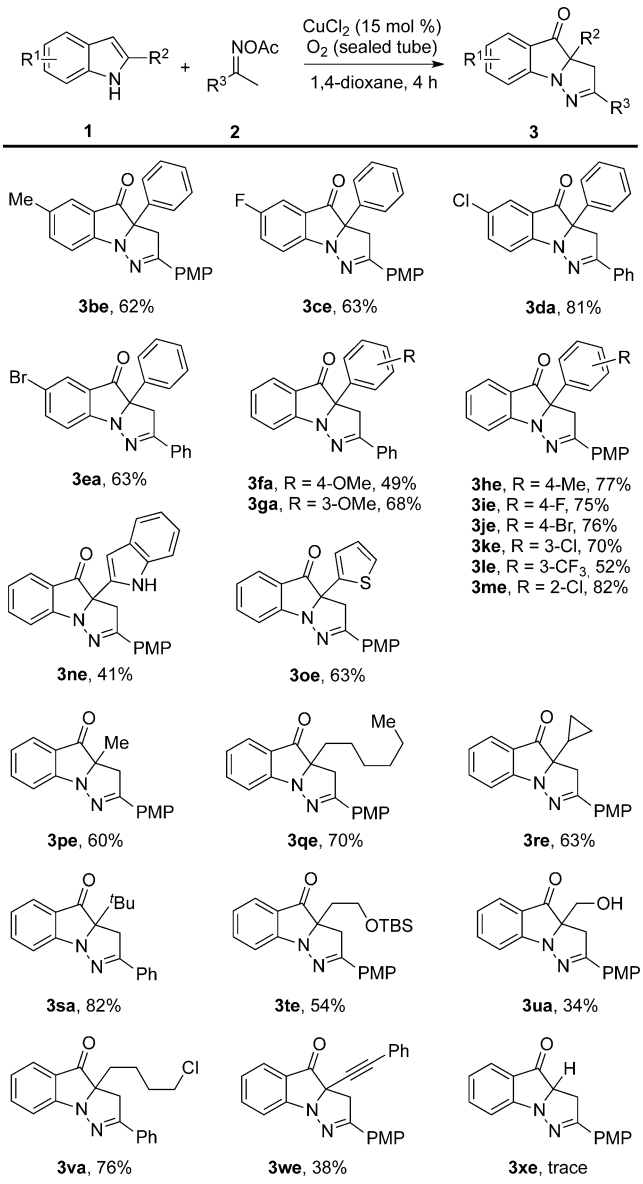
1a **2** **3**

Entry	Oximes (**2**)	Product (**3**)	Yield [%][b]
1	**2a** (R = H)	**3aa**	77
2	**2b** (R = 4-Me)	**3ab**	74
3	**2c** (R = 4-*t*Bu)	**3ac**	83
4	**2d** (R = 4-*i*Bu)	**3ad**	71
5	**2e** (R = 4-OMe)	**3ae**	86
6	**2f** (R = 4-F)	**3af**	67
7	**2g** (R = 4-Cl)	**3ag**	73
8	**2h** (R = 4-Br)	**3ah**	80
9	**2i** (R = 4-I)	**3ai**	54
10	**2j** (R = 4-NO_2)	**3aj**	43
11	**2k** (R = 4-Ph)	**3ak**	73
12	**2l** (R = 3-OMe)	**3al**	72
13	**2m** (R = 3-Cl)	**3am**	81
14	**2n** (R = 3-Br)	**3an**	67
15	**2o** (R = 3-NO_2)	**3ao**	58
16	**2p** (R = 3-CF_3)	**3ap**	74
17	**2q** (R = 2-Cl)	**3aq**	66
18	**2r** (R = 2-NO_2)	**3ar**	76
19	**2s** (R = 3,4-Cl_2)	**3as**	84
20	**2t**	**3at**	37
21	**2u**	**3au**	62
22	**2v**	**3av**	85
23	**2w**	**3aw**	41
24	**2x**	**3ax**	15[c]
25	**2y**	**3ay**	6[c]
26	**2z**	**3az**	18[c]



2t **2u**, X=O **2v**, X=S **2w** **2x** **2y**, X=Ph **2z**, X=Me

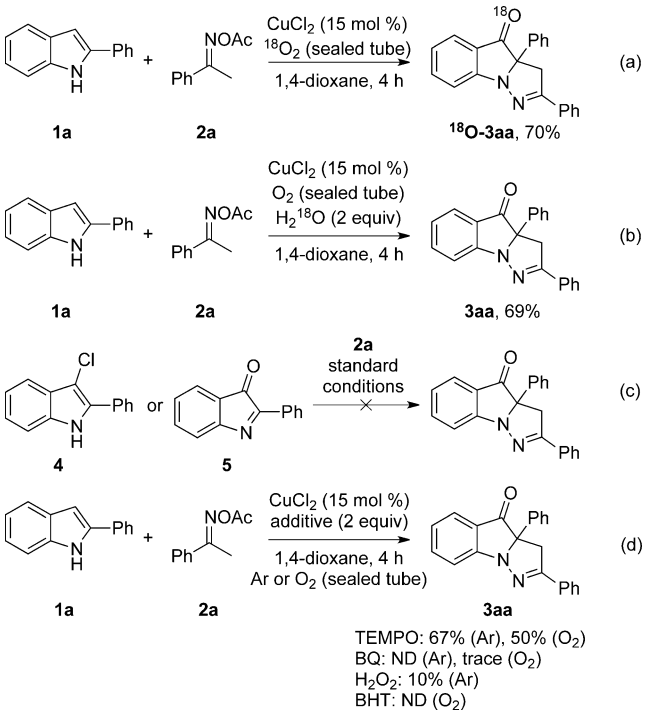
[a] Reactions were conducted on a 0.2 mmol scale relative to **1**. [b] Isolated yields are given. [c] GC analysis using dodecane as the internal standard.



Scheme 2. Indole scope for the cyclization. PMP = *para*-MeO-C_6H_4.

indicates the copper complex may not be involved in the formation of the quaternary carbon at the indole C-2 position. 2-Heteroaryl-substituted indoles, such as 2,2′-biindole and 2-thienyl-indole, reacted smoothly, albeit in moderate yields (Scheme 2, **3ne**–**3oe**). An unexpected result was observed when using 2,2′-biindole as the reactant, which has two reaction sites, but only coupled with one molecule of reaction partner even with excessive oxime acetate. When treated with 2-alkyl indoles, including 2-*t*Bu-indole, the reactions afforded the target products in good yields (Scheme 2, **3pe**–**3re** and **3sa**). While the indole with TBS-protected hydroxy group gave a moderate yield of product **3te**, free hydroxy group decreased the yield to 34% (**3ua**). Notably, indoles with alkyl chloro and alkyne functional groups were well tolerated in the present system, delivering the corresponding pyrazolo[1,5-a]indoles in 76% (**3va**) and 38% (**3we**) yield, respectively. Unforunately, all of the 2-non-substituted or 2,3-disubstituted indoles tested did not work in this system.

For the mechanistic studies of this transformation, a series of control experiments were conducted (Supporting Information, Schemes S1, S2 and Table S5).[13] The reactions with ^{18}O-labeling molecular oxygen and water reveal that oxygen would be involved in the indole dehydrogenation and oxygenation (Scheme 3a, b). Furthermore, indole derivatives **4**

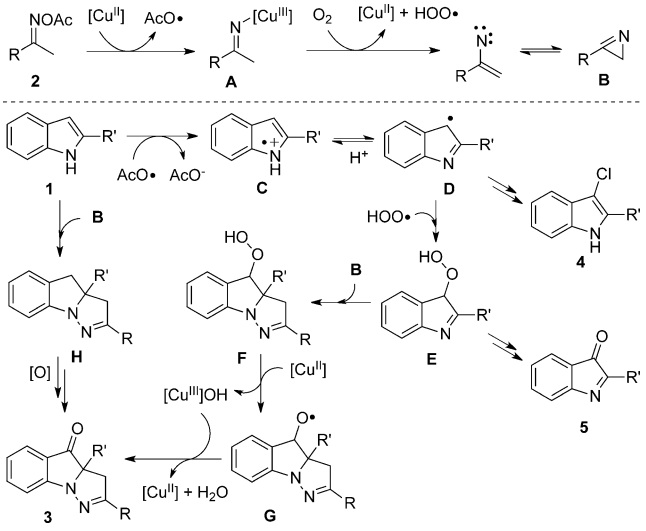


Scheme 3. Mechanistic experiments. ND = not detected.

and **5** were often detected in the system. The two products, however, could not produce the desired products under the standard reaction conditions (Scheme 3c). We also performed the reactions under a range of external oxidants in the absence of O_2. While TEMPO, which can generally serve as an oxygenating reagent through a radical process, was found to be effective for the reaction and H_2O_2 gave a low yield, other oxidants such as pyridine-*N*-oxide, 1,4-benzoquinone (BQ), and *tert*-butylhydroperoxide (TBHP) did not enable this transformation. Finally, the addition of a radical scavenger, such as *tert*-butylhydroxytoluene (BHT) and BQ, under the standard conditions prevented the desired transformation completely (Scheme 3d). These observations indicate the oxygenation of indole probably proceeds via a radical intermediate.

To gain more information about the mechanism of this reaction, electroparamagnetic resonance (EPR) experiments were performed with the addition of the free radical spin-trapping agent 5,5-dimethyl-1-pyrroline N-oxide (DMPO; Supporting Information, Figures S1–S5).[13] Despite reports of copper(I)-triggered nitrogen radical formation from oximes,[10j] we detected no signals of nitrogen radicals, but we did observe signals corresponding to acetoxyl radical under the present copper(II) system without **1a** under Ar atmosphere (Supporting Information, Figure S1). Moreover, in an O_2 system, other signals appeared, albeit at low intensity, which potentially correspond to superoxide radical (Supporting Information, Figure S2). Some signals of organic radicals were readily observed in the reaction system, which are classical 6 peaks corresponding to an alkoxyl radical (Supporting Information, Figure S3), and these signals did not disappear with the addition of superoxide dismutase (SOD; Supporting Information, Figure S4). These results imply that some unknown radicals, such as an alkoxyl radical, probably exist during the reaction, and that superoxide radical may not be involved.

On the basis of the results from the mechanistic studies,[13] a plausible reaction mechanism was proposed (Scheme 4). An imine-[Cu^{III}] species **A** forms in situ by [Cu^{II}]-mediated reduction of ketonoximes **2**, simultaneously releasing an acetoxyl radical. Then, under an oxygen system, **A** would be oxidized and converted to vinyl nitrene or an azirine intermediate **B**[14] while generating peroxyl radical. On the other hand, acetoxyl radical would seize an electron from the electron-rich indole **1** to form intermediate **C**. Subsequently, intermediate **C** affords indolyl radical **D** by isomerization and



Scheme 4. Possible reaction mechanism.

proton elimination. Also, indolyl radical **D** could be directly formed by the copper/O_2 treatment, which are suspected to convert to 3-Cl-indole **4** in the absence of oxime, as well as one of observed byproducts in the conditions optimization. Then **D** traps peroxyl radical to form peroxyl intermediate **E**, which could be delivered to the byproduct **5**. For the fact that **5** could not transfer into our desired product under the optimal conditions, intermediate **E** is supposed to participate in the cycloaddition with azirine **B**.[15] The intermediate product **F** would afford the final product, probably, through an alkoxyl radical **G** and with the assistance of the copper catalyst. Notably, azirine **B** could directly react with indole to form 4H-pyrazolo[1,5-a]indole **H**, which subsequently transfers into pyrazolo[1,5-a]indolone by a radical oxidation. However, such a pathway was found to be unfavorable because only a trace amount of the desired product was detected when directly using azirine instead of oxime (Supporting Information, Scheme S2 d).[13] This also indicates that the radical formed in situ from the oxime had activated the indole.

In summary, a concise copper-catalyzed oxygenation and cyclization of 2-substituted indoles with oximes has been developed, providing a rapid access to complex and pharmacologically significant pyrazolo[1,5-a]indole derivatives. The advantages of the present protocol include low-cost catalyst, green oxidant, facile conditions, easy handling, and high atom-economy. This is an elegant example of indole trifunctionalization in which the obvious feature resides in the internal oxidant-triggered aerobic oxygenation and annulations through a radical-mediated pathway. The present cooxidative transformation represents a new pattern for dehydrogenative coupling with high efficiency, excellent chemo- and regio-selectivities, and robust synthetic flexibility. Detailed mechanistic studies and further applications of this methodology are currently under way in our laboratory.

Experimental Section

Indole **1a** (0.2 mmol, 1.0 equiv), oxime acetate **2a** (0.24 mmol, 1.2 equiv), and $CuCl_2$ (0.03 mmol, 15 mol%) were charged in a septum capped vial (10 mL). The vial was placed under vacuum for 10 min and then oxygen was pumped into it (approximately 10 mL, 0.4 mmol). The solvent 1,4-dioxane (1 mL, 0.2 M) was added into the vial by syringe. The reaction mixture was stirred at 80 °C for 4 h. The mixture was then allowed to cool down to room temperature and flushed through a short column of silica gel with ethyl acetate, and, after rotary evaporation, the residue was separated by column chromatography (petroleum ether/EtOAc 15:1) to give the pure product **3aa** as a yellow solid in 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) $\delta = 7.77$–7.55 (m, 7H), 7.39–7.23 (m, 6H), 7.14 (t, $J =$ 7.2 Hz, 1H), 3.94 (d, $J = 17.6$ Hz, 1H), 3.51 (d, $J = 17.6$ Hz, 1H). ^{13}C NMR: (100 MHz, $CDCl_3$, ppm) $\delta = 202.7$, 162.0, 158.3, 139.9, 137.2, 131.2, 130.3, 128.8, 128.6, 128.1, 126.7, 125.6, 125.2, 124.6, 124.5, 118.5, 78.4, 44.3.

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