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Practical Synthesis of Pyrazoles via Copper-Catalyzed Relay Oxidation Strategy

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Various 1,3- and 1,3,4-substituted pyrazoles are smoothly formed via copper-catalyzed cascade reactions of oxime acetates, amines and aldehydes. This relay oxidative process involves copper-promoted N-O bond cleavage and C-C/C-10 N/N-N bond formations to furnish pyrazolines, and sequential

- Cu/O_2 system-involved oxidative dehydrogenation of pyrazolines to afford pyrazoles. This transformation provides a novel and versatile approach for the synthesis of pyrazoles, with inexpensive copper catalyst and green oxidants. It is of
- 15 atom- and step-economy, good functional group tolerance, as well as operational simplicity.

Oxidation reactions are an important component of organic chemistry to construct C-C and C-hetero bonds.¹ There is no doubt that molecular oxygen (O₂), comparing with other ²⁰ commonly used oxidants such as BQ, hypervalent iodonium salts and heavy metal salts, is an ideal oxidant which is inexpensive,

atom economical and environmentally friendly.² However, O_2 is a relatively weak oxidant which is often used in oxidative dehydrogenation process. Thus, using O_2 as the sole oxidant to

- ²⁵ realize oxidative formation of several chemical bonds is challenging. Recently, the N-O bond containing compounds were frequently used as the internal oxidant and substrates for transition-metal catalyzed C-H activation and cross couplings.^{3, 4} We proposed that a relay oxidation process combining O₂ with
- ³⁰ the green internal oxidant might be able to construct several bonds in one pot.

Pyrazole is an important motif which is widely used in agricultural and pharmaceutical area and also as classical ligands.⁵ Selected pharmaceutical examples include Zometapine,

- ³⁵ Tebufenpyrad, Celebrex and Viagra.⁶ Owing to their good synthetic utility, numerous approaches have been developed in past decades, such as the reactions of hydrazine with 1,3-diketones or their analogues,⁷ dipolar [3 + 2] cycloadditions,⁸ and hydrohydrazination of alkynes.⁹ However, the most methods for
- ⁴⁰ the synthesis of pyrazoles limit to construct 5-subsituted pyrazoles and need to the employment of N-N bond containing substrates, that is hydrazines. In the past several years, oxime esters have become a powerful synthon for N-heterocycles such as pyridines,¹⁰ pyrroles,¹¹ and imidazo[1,2- a]pyridines¹² in the
- ⁴⁵ presence of copper catalyst. Based on our continuous interest in oxime esters (Figure 1a, 1b), ^{11a,12,13} herein, we present a copper-catalyzed synthesis of 1,3- and 1,3,4-substituted pyrazoles from

oxime acetates, anilines and paraformaldehyde (Figure 1c). It is noteworthy that many oxidative C-C and C-hetero bond ⁵⁰ formations can be achieved using various of transition metal catalysts.¹ However, there is scarce examples about the oxidative N-N bond formation.¹⁴ One seminal work was reported by Glorius et al., who had developed a novel strategy for pyrazoles from enamines and excess nitriles via oxidative N-N bond ⁵⁵ formation under the treatment of copper catalyst.^{14a,b} Our process involves copper-catalyzed N-O bond cleavage, C-C/C-N/N-N bond formation and oxidative dehydrogenation process which is a relay oxidation process and the oxidants are oxime acetates and O₂.

Figure 1 Our previous work and this work



In our initial studies, we took acetophenone oxime acetate (1a), ⁶⁵ aniline (2a) and paraformaldehyde (3a) as our model reaction to investigate different copper salts, bases and solvents under air atmosphere (Table 1). Fortunately, the expected transformation occurred when we used CuCl (10 mol %) as catalyst and Cs₂CO₃ (20 mol %) as base in DMSO. The desired product 4aaa was ⁷⁰ formed in 57% GC yield (entry 1). The screening of other copper salts indicated that copper(I) salts were better than copper(II) salts for this conversion. More satisfying isolated yield (83%) was obtained by utilizing 10 mol % copper bromide as the catalyst and 20 mol % of Cs₂CO₃ as the base (entries 2-5). ⁷⁵ However, when 50 mol % or 100 mol % Cs₂CO₃ was used, the yields of product were trace and acetophenone oxime acetate was decomposed into acetophenone oxime and acetophenone (entries 6-7). The examination of different bases such as K₂CO₃, Li₂CO₃, Na₂SO₃, NaHSO₃, DBU, and NEt₃ revealed that the base was crucial to this reaction (entries 8-13). Cs₂CO₃ was proved to be ⁵ the best choice and only trace amount of desired product was obtained without base (entry 14). No product was obtained in the absence of copper salt (entry 15). Different solvents such as xylene and DMF were also investigated, and DMSO was found to be the optimal solvent (entries 16-17). A gram scale preparation ¹⁰ was performed and the isolated yield was 71% (entry 18).

Table 1	Screening	for	ontimal	reaction	conditions "
Table L.	Screening	101	opumai	reaction	conuntions.

N	OAc			N Ph
Ph	+ PhNH ₂	+ (CH ₂ O) _n	[Cu], base	Ph→
1a	2a	3a ^s	solvent, 120 °C	4aaa
Entry	[Cu]	Base	Solvent	Yield (%)
1	CuCl	Cs ₂ CO	3 DMSO	57
2	CuI	Cs ₂ CO	3 DMSO	79
3	CuBr	Cs ₂ CO	3 DMSO	87 (83)
4	CuBr ₂	Cs ₂ CO	3 DMSO	41
5	CuCl ₂	Cs ₂ CO	3 DMSO	15
6^b	CuBr	Cs ₂ CO	3 DMSO	trace
7^c	CuBr	Cs ₂ CO	3 DMSO	trace
8	CuBr	K ₂ CO	B DMSO	65
9	CuBr	Li ₂ CO	3 DMSO	71
10	CuBr	Na ₂ SO	3 DMSO	22
11	CuBr	NaHSC	D ₃ DMSO	24
12	CuBr	DBU	DMSO	68
13	CuBr	NEt ₃	DMSO	37
14	CuBr		DMSO	trace
15		Cs ₂ CO	3 DMSO	n.r.
16	CuBr	Cs ₂ CO	3 xylene	45
17	CuBr	Cs ₂ CO	3 DMF	74
18^{d}	CuBr	Cs ₂ CO	3 DMSO	75 (71)

^a Reaction conditions: unless otherwise noted, all reactions were performed with 1a (0.5 mmol), 2a (0.5 mmol), 3a (0.5 mmol), [Cu] (10 mol %), base (20 mol %) and DMSO (3.0 mL) at 120 °C under air for 12 h. GC yield. Number in parentheses is isolated yield. ^b 50 mol % Cs₂CO₃ was used. ^c 100 mol % Cs₂CO₃ was used. ^d A gram scale preparation were performed with 1a (7 mmol), 2a (7 mmol), 3a (7 mmol), CuBr (10 mol %), Cs₂CO₃ (20 mol %) and DMSO (15 mL) at 120 °C under air for 20 12 h.

Based on the optimization study, we studied the scope of oxime acetates and the results are summarized in Table 2. Different substituents on the aromatic ring of acetophenone oxime acetate such as methyl, methoxyl, fluoro, chloro, bromo ²⁵ were well tolerated and the corresponding products could be formed in good to excellent yields (**4aaa-4jaa**). Interestingly, electron-donating groups exhibited positive effect on this transformation. 3,4-Methylenedioxyacetophenone oxime acetate could also be transformed into the corresponding pyrazole in 87% a yield (**4kaa**). Moreover, oxime acetates derived from other

- ³⁰ yield (**4kaa**). Moreover, oxime acetates derived from other aromatic ketones such as α -aetonaphthone, β -aetonaphthone could be accessed through this route to generate the annulation products (**4laa-4maa**) in good yields. To our delight, the heteroarene containing oxime acetates were compatible in this
- ³⁵ transformation (4naa-4oaa). It is worth noting that aliphatic ketone was also applicable under these reaction conditions and afforded product 4paa in 65% yield. More importantly, the

strategy was also available for the construction of 1,3,4-substituted pyrazole derivatives in good yields (**4qaa-4raa**).

40 Table 2 Substrate scope of various oxime acetates.⁴



^{*a*} Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), Cs_2CO_3 (20 mol %), CuBr (10 mol %), DMSO (3.0 mL), under air, 120 °C for 12 h. Isolated yields.

The reaction scope with respect to the anilines was next examined (Table 3). A variety of monosubstituted anilines reacted smoothly to generate the corresponding pyrazoles in good to excellent yields (**4aba-4aka**). Generally, electron-withdrawing groups on the anilines slightly increased the yield of product. We ⁵⁰ were excited that polysubstitutd anilines were also suitable starting materials and the desired products were formed in 80% and 82% yields, respectively (**4ala** and **4ama**). Unfortunately, aliphatic amines such as n-propylamine and benzylamine were not able to give the pyrazole products. Except paraformaldehyde, ⁵⁵ other aldehydes such as benzaldehyde and n-butylaldehyde were failed to transfer into the corresponding products. The reason may be their electrophilicity was lower than that of paraformaldehyde.

Table 3 Substrate scope of various anilines.^a



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^{*a*} Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), **3a** (0.5 mmol), Cs_2CO_3 (20 mol %), CuBr (10 mol %), DMSO (3.0 mL), under air, 120 °C for 12 h. Isolated yields.

- ⁵ To gain more insight into the mechanism of the process, we conducted several control experiments. When we coupled compound **9** with paraformaldehyde **3a** in the standard conditions, we could not obtain product **8** [Eq. (1)]. This result revealed that **9** was not an intermediate in the transformation.¹⁵ Moreover, ¹⁰ when we took our standard reaction under N₂, **7** was formed in
- ¹⁰ when we took our standard reaction under N₂, 7 was formed in 70% GC yield,¹⁶ and the yield of **8** was low [Eq. (2)]. When increasing the amount of Cs₂CO₃, the yield of product **8** was trace.¹⁷ However, when we made the standard reaction continue under air after 1 h, pyrazoline 7 was completely transformed into ¹⁵ product **8**, which indicated that **8** should come from **7** by
- oxydehydrogenation under the Cu/O_2 system.¹⁸

- ²⁰ On the basis of these experiments and previous reports,¹⁰⁻¹⁴ a plausible mechanism is illustrated in Scheme 1. Firstly, acetophenone oxime acetate **1** was smoothly transferred to copper enamide intermediate **2** with copper catalyst and produced another Cu^{II} species.¹⁰⁻¹³ Subsequently, imine intermediate **3** was
- ²⁵ formed via nucleophilic addition of **2** to paraformaldehyde.^{10b} Imine intermediate **3** was coupled with aniline, followed by the coordination with copper catalyst to give intermediate **4**. Then, intermediate **5** was formed by losing one molecule of H_2O .^{14a,b} With the release of H⁺, intermediate **5** was converted to
- ³⁰ intermediate **6**,^{14a,b} which underwent reductive elimination to afford pyrazoline **7** and copper(0).¹⁴ Finally, copper(0) was oxidized by copper(II) to form copper(I) and product **8** was obtained by oxidative dehydrogenation process under the Cu/O₂ system.¹⁸



Scheme 1 Possible reaction mechanism.

35

In summary, various 1,3- and 1,3,4-substituted pyrazoles were efficiently synthesized via copper-catalyzed assembly of 40 oxime acetates, aniline and paraformaldehyde. This process involved copper-catalyzed N-O bond cleavage, C-C/C-N/N-N bond formations and oxidative dehydrogenation. In addition, this protocol utilized the oxime acetate as the internal oxidant to initiate the reaction and the green oxygen to end up the 45 transformation. Detailed mechanistic studies showed that this transformation went through two processes, which included the formation of pyrazoline ring and oxidative dehydrogenation under the Cu/O₂ system. The oxidant of the first process was oxime acetate and the following was O₂, which could be called 50 oxidation relay. Further study on this topic is currently undergoing in our laboratory.

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ¹H and ¹³C NMR 65 spectra for selected compounds. See DOI: 10.1039/b000000x/

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