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Copper-Catalyzed Aerobic Cyclization of β,γ-Unsaturated Hydrazones with Concomitant C═C Bond Cleavage

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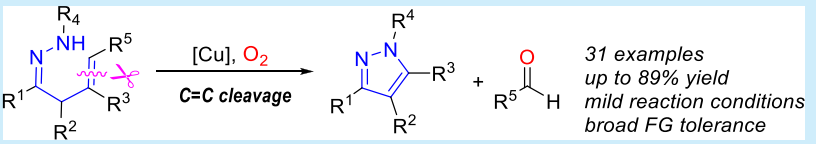
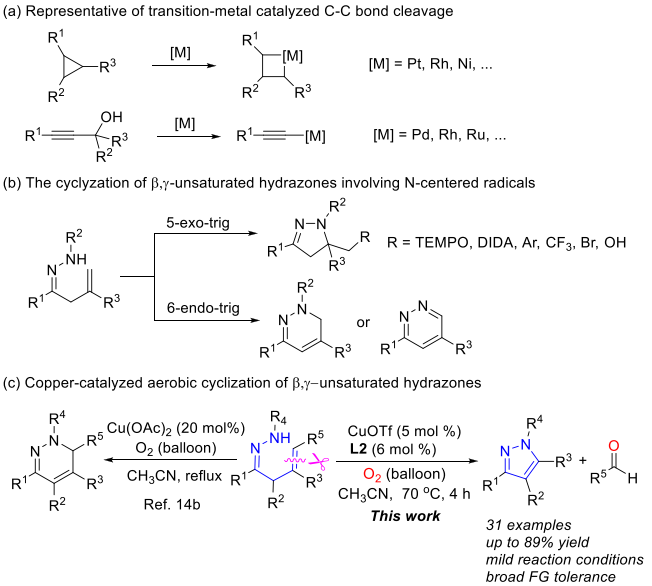


ABSTRACT: A Cu-catalyzed aerobic oxidative cyclization of β,γ-unsaturated hydrazones for the preparation of pyrazole derivatives has been developed. The hydrazonyl radical promoted the cyclization, along with a concomitant C═C bond cleavage of β,γ-unsaturated hydrazones. This process has been verified via several control experiments, including a radical-trapping study, an ^{18}O-labeling method, and the identification of the possible byproducts. The advantages of this reaction include operational simplicity, a broad reaction scope, and a mild selective reaction process.

The C−C bonds in organic molecules are ubiquitous, strong, and surrounded by C−H bonds. The C−C bond cleavage thus represents a grand challenge, because of their relative inertness, thermodynamic, and kinetic stability.[1] The prevalent strategies of C−C bond cleavage by transition-metal catalysis rely on the reaction of small rings[2] or a substrate with latent coupling fragments such as tertiary alcohol,[3] whereas these strategies usually suffer from harsh reaction conditions, together with limited functional group tolerance (Scheme 1a).

Scheme 1. Cyclization of β,γ-Unsaturated Hydrazones with Concomitant C = C Bond Cleavage



The advent of readily accessible radical species under milder conditions has fueled a reinvigoration into radical chemistry, resulting in the discovery of novel transformations of radical C−C bond cleavage for the production of functional molecules that complement conventional ionic processes.[4] In this context, nitrogen-centered radicals (NCRs) are of eminent importance in chemical synthesis, which can be further leveraged to enable radical addition/cyclization transformations.[5] In recent years, the chemistry of NCRs has witnessed remarkable advances, as illustrated by the flourishing field of NCR-mediated transformations.[6]

From the standpoint of sustainable chemistry, the development of an efficient and selective approach for the transformation of NCRs involving C−C bond cleavage is promising, which provided an appealing synthetic platform for the creation of a wide array of nitrogen-containing heterocyclic molecules.

The pyrazole moiety is widely present in the field of natural products, biologically/pharmacologically active molecules, agrochemicals, and synthetic ligands. Therefore, the efficient synthesis of functionalized pyrazoles has attracted substantial attention from both academia and industry (see Figure 1).[7] Hydrazones constitute a class of structurally versatile reagents, because of their broad modularity and ready accessibility.[8] However, the conventional cyclization of hydrazones for the preparation of pyrazole derivatives usually suffered from the

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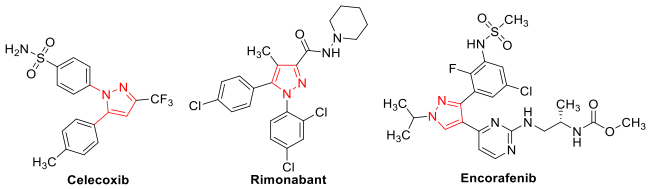


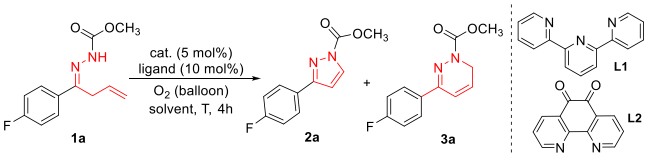
Figure 1. Selected examples of biologically active drug molecules with a phenylpyrazole framework.

employment of a stoichiometric promoter, precious metal catalysts, harsh reaction conditions, and restricted functional group tolerance.[9] The straightforward cyclization of hydrazonyl radicals has recently been developed to be a new powerful synthetic strategy to construct pyrazole scaffolds. In this context, enormous progress has been achieved in the employment of *β,γ*-unsaturated hydrazones as fascinating and unconventional approaches toward enabling a range of structurally diverse synthetic transformations.[10] Nevertheless, most of the reported approaches rely on the catalytic 5-exo-trig or 6-endo-trig ring closure in the realm of *β,γ*-unsaturated hydrazone chemistry (see Scheme 1b).[11] The catalyst-controlled aerobic radical cyclization of hydrazones for the synthesis of pyrazoles via the cleavage of the C=C double bond has rarely been exploited so far.[12,13] Therefore, the fabrication of pyrazoles with readily accessible starting materials in a controllable manner would be greatly desirable.

Recently, we report one Cu-catalyzed oxidative 6-endo-trig annulation of *β,γ*-unsaturated hydrazones for the pyridazines, and 1,6-dihydropyridazines synthesis with a different reaction solvent.[14] In this paper, we disclose a Cu-catalyzed oxidative cyclization of *β,γ*-unsaturated hydrazones for the synthesis of pyrazole with the concomitant cleavage C=C bond (Scheme 1c). In this approach, O_2 served as the terminal oxidant and low-cost Cu(I) salt was employed as the catalyst. The features of operational simplicity and mild reaction conditions, in combination with a more general functional group tolerance, made this Cu-catalyzed aerobic oxidative transformation particularly synthetically advantageous, practical, and green.

Initially, *β,γ*-unsaturated hydrazine **1a** was chosen as a model compound and catalytic $Cu(OAc)_2$ was evaluated under a balloon pressure of O_2 atmosphere (see Table 1). Pleasingly, the reaction does indeed occur in CH_3CN at 80 °C, thus giving the desired pyrazole product **2a** in a 25% yield (Table 1, entry 1). It is noteworthy that an undesired side-product was formed during the screening reactions. Further cautious analytical characterization confirmed that it was a six-endo-trig cyclization product **3a**. Screening of the reaction solvent could not afford better results, and **3a** was obtained exclusively with toluene or dioxane as the reaction medium (Table 1, entries 2 and 3). Different copper(I) salts, such as CuOAc, CuBr, $Cu(acac)_2$, CuOTf, and $Cu(OTf)_2$, were explored (Table 1, entries 4−8); among these salts, CuOTf provided the best result. We then determined that **2a** could be generated as the sole product by decreasing the reaction temperature (Table 1, entries 9 and 10). Subsequently, various types of ligands were tested with the expectation to stabilize the catalytic metal center and increase the reaction outcome (Table 1, entries 11−14). Delightedly, the optimal reaction yield was achieved (76%) when 1,10-phenanthroline-5,6-dione **L2** (10 mol %) was added. Lowering the ligand loading to 6 mol % only led to a slight decrease in the reactivity (Table 1, entry 15). Further exploration of alternative solvents (Table 1, entries 16−18) led to inferior results, whereas lowering the reaction temperature resulted in a obviously slower reaction rate and decreased substrate conversion (Table 1, entries 19 and 20). The reaction delivered no product when oxygen or copper catalyst was removed from the reaction conditions (Table 1, entries 21 and 22). Finally, the best result was eventually achieved with CuOTf (5 mol %) and 1,10-phenanthroline-5,6-dione (6 mol %), under an atmosphere of O_2 (Table 1, entry 15).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	ligand	temp, *T* (°C)	Yield[b] (%) 2a	3a
1	$Cu(OAc)_2$	CH_3CN	–	80	25	50
2	$Cu(OAc)_2$	toluene	–	80	nd	50
3	$Cu(OAc)_2$	dioxane	–	80	nd	20
4	CuOAc	CH_3CN	–	80	30	25
5	CuBr	CH_3CN	–	80	37	trace
6	$Cu(acac)_2$	CH_3CN	–	80	38	trace
7	CuOTf	CH_3CN	–	80	53	nd
8	$Cu(OTf)_2$	CH_3CN	–	80	trace	trace
9	CuOTf	CH_3CN	–	70	67	nd
10	CuOTf	CH_3CN	–	60	61	nd
11	CuOTf	CH_3CN	2,2′-bpy	60	25	nd
12	CuOTf	CH_3CN	phen	60	43	nd
13	CuOTf	CH_3CN	**L1**	60	nd	nd
14	CuOTf	CH_3CN	**L2**	70	76	nd
15	CuOTf	CH_3CN	**L2**[c]	70	75	nd
16	CuOTf	THF	**L2**[c]	70	25	nd
17	CuOTf	DMF	**L2**[c]	70	40	nd
18	CuOTf	CH_3OH	**L2**[c]	70	nd	nd
19	CuOTf	CH_3CN	**L2**[c]	50	42	nd
20	CuOTf	CH_3CN	**L2**[c]	40	trace	nd
21[d]	CuOTf	CH_3CN	**L2**[c]	70	nd	nd
22		CH_3CN	**L2**[c]	70	nd	nd

[a]Reaction conditions: **1a** (0.1 mmol), catalyst (5 mol %), ligand (6 mol %), O_2 (balloon), solvent (2.0 mL), 4 h. [b]Isolated yield. [c]6 mol % of ligand was used. [d]The reaction was conducted under N_2.

A study on the substrate scope demonstrates that this approach offers great potential and utility in the streamlined and divergent assembly of pyrazole derivatives. It was shown that hydrazone derivatives with a wide range of substituents at the aromatic moiety worked well to afford pyrazole derivatives **2** with CuOTf as the catalyst (see Scheme 2). The optimized reaction conditions showed high functional group tolerance, and the steric and electronic properties of the substitute only impart a slight impact on the reaction. *β,γ*-Unsaturated hydrazones bearing either electron-donating (e.g., alkyl and aryl group) or electron-withdrawing groups (e.g., Cl, Br, CN, CO_2CH_3) at the *para*-position of the phenyl rings were compatible with the transformation to afford the pyrazoles **2b**−**2j** in good to high yields (55%−81%). Notably, CF_3O-substituted hydrazone also smoothly afforded the desired product **2k**. The molecular structure of **2h** was elucidated by an X-ray crystallography study. Moreover, substrates containing substitutes at the *meta*-position of the phenyl moiety

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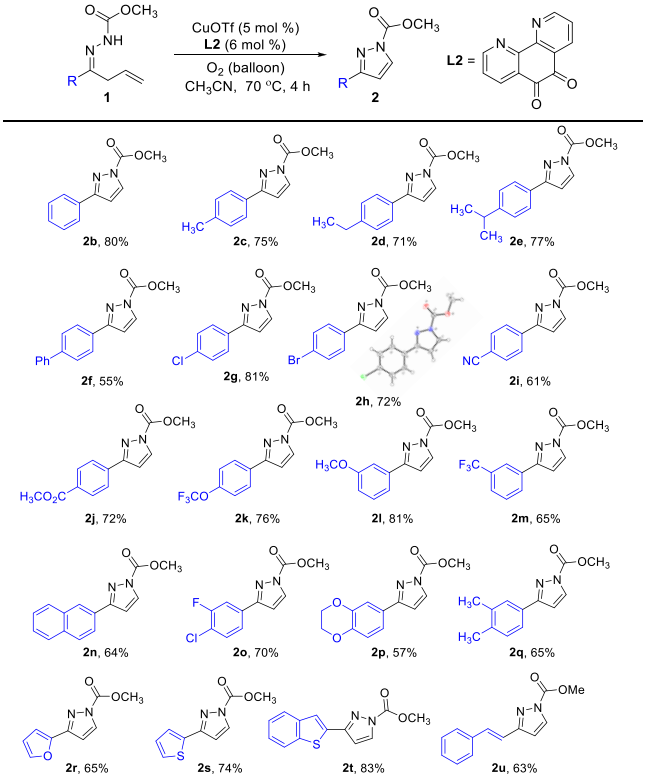
Scheme 2. Scope of Copper-Catalyzed Oxidative Cyclization for the Synthesis of Pyrazole Derivatives[a]

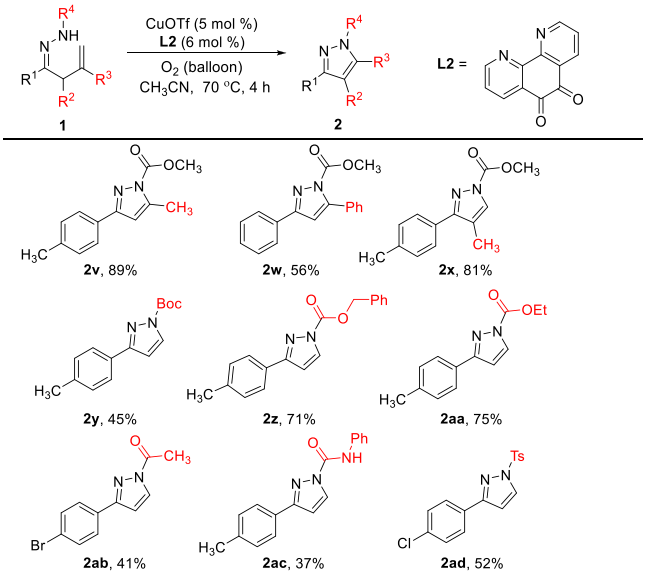


[a]Reaction conditions: **1** (0.1 mmol), CuOTf (5 mol %), ligand 1,10-phenanthroline-5,6-dione (6 mol %), O_2 (balloon) in CH_3CN (1.0 mL) at 70 °C for 4 h.

proves to be compatible with the CuOTf (**2l** and **2m**). When a naphthalene ring-substituted hydrazone was prepared and subjected to the Cu-catalyzed reaction conditions, pyrazole **2n** was delivered in a 64% yield. We then observed that the current catalytic system was suitable for substrates derived from 3,4-*bis*-substituted phenyl ketones, affording the corresponding products in moderate to high yields (**2o**−**2q**). Remarkably, a substrate containing heteroaryl frameworks could also be applied with this oxidative cyclization reaction, which delivered the target product in an overall good yield (**2r**−**2t**). Finally, we are pleased to find that an olefinic substituent could be used instead of an aryl group, leading to the generation of the cyclization pyrazole product in 63% yield (**2u**).

The structural diversity of hydrazone was further examined by varying the substitute of the olefin moiety (see Scheme 3). To our delight, hydrazone with a methyl or phenyl group at the terminal olefin moiety was well-transferred to the corresponding pyrazole products (**2v** and **2w**) in good to high yields. Note that the substrate scope could also be extended to hydrazone with an alkyl group at the *α*-position (**2x**). Furthermore, the N-protecting group of **1** was investigated. N-Boc-, N-CO_2Bn-, and N-CO_2Et-substituted hydrazones also underwent the reaction to deliver **2y**−**2aa** with a promising outcome, whereas the use of N-Ac- or N-CONHPh-based **1** resulted in a low yield (**2ab** and **2ac**). In addition, the reaction exhibited great tolerance with *N*-arylsulfonyl-substituted hydrazone, generating **2ad** in 52% yield.

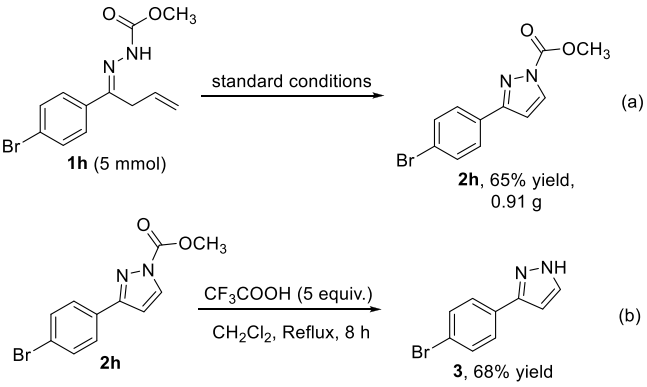
Scheme 3. Cyclization of Various Hydrazones for the Synthesis of Pyrazole Derivatives[a]



[a]Reaction conditions: **1** (0.1 mmol), CuOTf (5 mol %), ligand 1,10-phenanthroline-5,6-dione (6 mol %), O_2 (balloon), CH_3CN (1.0 mL) at 70 °C for 4 h.

To assess the synthetic practicality of the current procedure, the gram-scale preparation of **1h** was performed and the reaction worked well with the production of the cyclization product **2h** in 65% yield (Scheme 4). To further showcase the

Scheme 4. Gram-Scale Reaction and Synthetic Derivatization



utility of the present approach, the deprotection of the N-protecting group was performed using product **2h**, and the derivatization proceeded smoothly to deliver the N−H pyrazole derivative **3**.[15]

To gain preliminary insight into the model reaction, we performed additional control experiments to elucidate the underlying mechanism (see Scheme 5). Upon addition of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the established conditions, a significantly lower production yield of the target reaction was observed (Scheme 5a). Notably, TEMPO-trapped adduct **4** was isolated in 20% yield, which is indicative of the carbon-centered radical engaged in the process. Subsequently, hydrazone **5** was added under the standard conditions to afford an 81% yield of **6**, which directly confirmed the cleavage of the C═C bond

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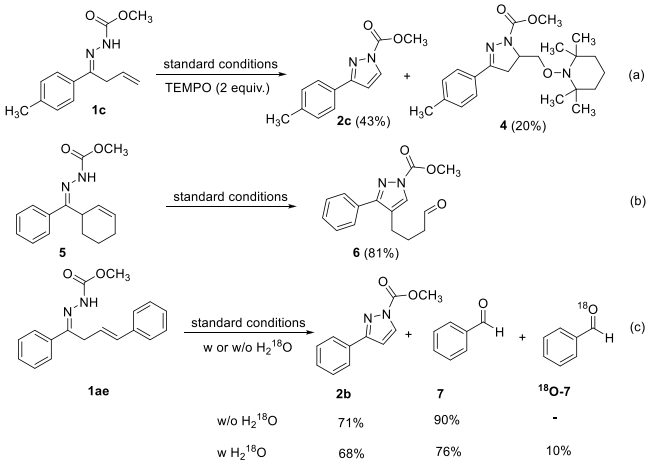
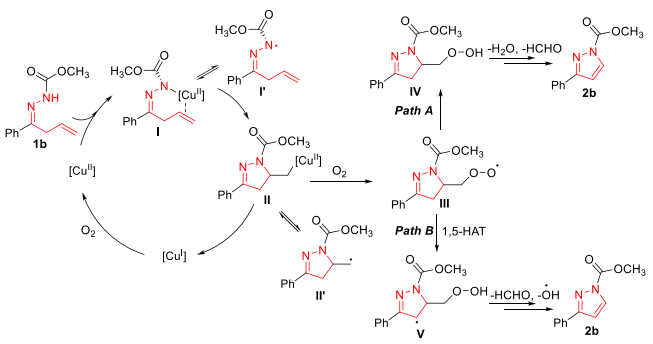
Scheme 5. Mechanism Study



during the reaction process (Scheme 5b). Furthermore, when hydrazine **1ae** with a phenyl group attached to the olefin moiety was used as the substrate (Scheme 5c), the aldehyde byproduct **7** was furnished in 90% yield, along with the isolation of the cyclization product **2b**. To verify the origin of oxygen in the reaction process, we performed the isotopic labeling experiments with the addition of 5 equiv of ^{18}O-enriched water. The observation of the 76% yield of ^{18}O-unlabeled products suggested that the aldehyde O atoms mainly originated from the atmospheric oxygen. Although the specific reaction pathway is still not clear, the 10% yield of the ^{18}O-labeled product indicates the partial origin of oxygen from water, which has seldom been reported previously.[16] Consistent with the result from the optimization studies that no product was afforded in the absence of O_2 (Table 1, entry 16), it is reasonable to speculate that the activation of O_2 must be one of the key steps in the catalytic process.

The mechanistic rationale based on the literature[17] and additional control experiments is proposed in Scheme 6. The

Scheme 6. Proposed Reaction Pathway



reaction is initiated by the interaction of Cu catalyst with substrate **1b** to generate intermediate **I**, which underwent reversible homolysis of the N−[Cu(II)] bond to give N-centered hydrazonyl radical **I′**.[18] The intramolecular amino-cupration of Cu(II)-activated substrate **1b** occurs to provide the alkyl-copper complex **II**. Homocleavage of intermediate **II** would give the carbon-centered radical intermediates **II′**, which could be readily trapped by molecular oxygen to generate the radical intermediate **III**. The finding of TEMPO-trapping adduct **4** is consistent with the generation of carbon-centered radical **II′**. Following pathway A in Scheme 6, alkylhydroperoxide **IV** is afforded via a hydrogen abstraction, and product **2b** is formed through the elimination of aldehyde and H_2O from intermediate **IV**. Alternatively, a 1,5-hydrogen atom transfer (HAT)[19] may first deliver the alkyl radical **V**, and subsequent C−C bond cleavage would finally lead to the oxidative cyclization product **2b**.

In conclusion, a facile one-pot, copper-catalyzed aerobic cyclization has been successively developed for the synthesis of the pyrazoles using *β,γ*-unsaturated hydrazones as the readily accessible substrates. The radical cyclization, along with the cleavage of the C=C bond of *β,γ*-unsaturated hydrazones occurred, and this process has been verified by several control experiments, including a radical-trapping study, an ^{18}O-labeling method, and isolation of the possible byproduct. This Cu-catalyzed aerobic oxidative cyclization features operational simplicity, commercially available catalysts, broad substrate scope, and amenability to scale-up without precautions to avoid air or moisture. More-detailed mechanistic studies and synthetic applications of the hydrazonyl-radical-promoted reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02911.

Detailed experimental procedure; ^{1}H, ^{13}C, ^{19}F NMR and HPLC spectra; X-ray data information (PDF)

Accession Codes

CCDC 2023937 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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