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Copper-Catalyzed Aerobic Cascade Cycloamination and Acyloxylation: A Direct Approach to 4-Acyloxy-1*H*-pyrazoles

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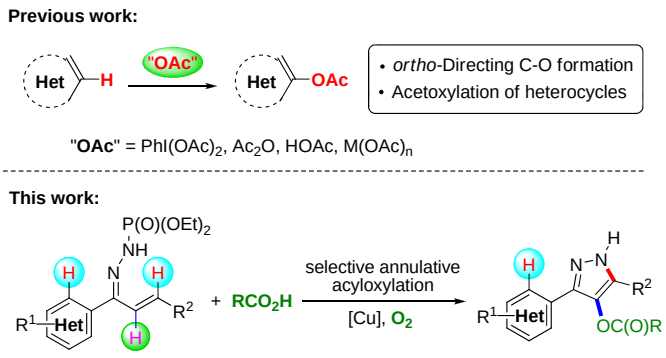
A novel direct transformation of hydrazones to acyloxylated pyrazoles by copper-catalyzed regioselective olefinic C(sp^2)–H bond cycloamination and acyloxylation was developed under mild conditions, which combines the formation of the pyrazole skeleton and installation of an acyloxyl group in a single step, using facile carboxylic acids as the acyloxylation reagents.

Transition-metal-catalyzed regioselective C–O bond formation via C–H functionalization of arenes has been developed as an efficient approach for the acyloxylation and hydroxylation of C(sp^2)–H bonds.[1-3] In contrast to *ortho* C–H bond oxidation of benzene rings, the regioselectivity of C–O bond formation of heterocycles is mainly controlled by their inherent reactivity and, consequently, no *ortho*-directing groups are necessary. However, there are only a few reports on direct acyloxylation of heterocycles in which the scope of substrates is mainly limited to electron-rich pyrroles and indoles,[4] and most of these transformations have been restricted to acetoxylation employing $PhI(OAc)_2$ as a terminal oxidant under the catalysis of $Pd(OAc)_2$ (Scheme 1).[4] Furthermore, carboxylic acids are seldom applied in these reactions as the coupling source probably due to their rapid formation of complex with metals.[2a,2g,5] In this event, an alternative efficient approach to acyloxyl heterocycles would be to combine the heterocyclic ring construction and acyloxylation in one step and ideally, employing simple carboxylic acids as the acyloxylation reagents under the catalysis of non-noble metals, which would be particularly attractive in terms of synthetic efficiency (Scheme 1).

Pyrazole derivatives represent a major class of nitrogen-containing heterocycles with a wide range of biological and pharmacological activities[6] including analgesic,[7] antibacterial,[8] antidepressant,[9] anti-inflammatory,[10] antiviral,[11] anticancer,[12] and antihypertensive properties.[13] They have appeared as the core structures in a large variety of commercial leading drugs and pesticides, such as Celebrex,[14] Cyenopyrafen,[15] and Fenpyroximate,[16] as well as utilized as useful ligands for some cross-coupling reactions.[17] Generally, classical approaches to substituted pyrazoles involved the condensation reaction between 1,3-dicarbonyl compounds or their equivalents with diazoacetates[18a] or hydrazines,[18b,18c] and the 1,3-dipolar cycloaddition of diazo compounds or other N=N bond containing dipoles with alkynes[19] or alkenes.[20] In particular, 4-acyloxy-pyrazole nucleus is exemplified as a unique structure in many potentially biologically active compounds,[21] which are generally prepared by direct acylation of the corresponding 4-hydroxy-pyrazoles, however multi-steps are required for the synthesis of the latter in turn.[22] For example, 4-acyloxy-1*H*-pyrazoles have been synthesized in three steps from 1,3-diketones by sequential halogenation, substitution and condensation reaction with hydrazine.[23] While these methods allow the construction of 4-acyloxypyrazoles, development of a novel and more efficient synthetic methodology to this valuable structural unit is highly desirable.



Scheme 1 Acyloxylation through C–H bond functionalization.

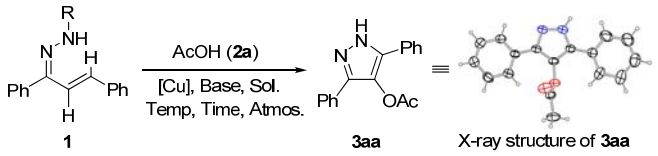
In the context of our research program aimed at efficient construction of heterocycles through C–H amination reaction,[24] herein, we report a novel direct transformation of hydrazones to acyloxylated pyrazoles by copper-catalyzed regioselective olefinic C(sp^2)–H bond cycloamination and acyloxylation, whereby in sequence the C–N/C–O bonds are formed followed by one N–P bond cleavage of unique *N*-diethoxy-phosphoryl hydrazones under mild conditions (Scheme 1). To our knowledge, the given approach represents the first transformation of hydrazones to 4-acyloxy-1*H*-pyrazoles which combines the formation of the pyrazole skeleton and installation of an acyloxyl

group in a single step, using facile carboxylic acids as the acyloxylation reagents.

We started our study by exploring the reaction of diethyl (2-((*E*)-1,3-diphenylallylidene)hydrazinyl)phosphonate (**1a**) in the presence of $CuCl_2$ (10 mol%) and AcOH (1.2 equiv) in DMSO under oxygen atmosphere. However, no acetoxylated product **3aa** was obtained in the absence of a base (entry 1, Table 1). Intriguingly, the addition of Na_2CO_3 to the reaction led to the isolation of **3aa**[25] in 52% yield together with the direct cyclized byproduct 3,5-diphenyl-1*H*-pyrazole (**4**) in 23% yield (entry 1).[26] An extensive screening of the bases (entries 3–4), the amounts of AcOH and base (entries 5–6), and solvents (entries 7–10) revealed that the use of K_2CO_3 as a base in DMSO with 1.2 equivalents of acetic acid turned out to be the best choice and resulted in the desired product **3aa** in a 63% yield (entry 3). Furthermore, it was observed that the existence of water played a subtle role for this transformation, and the isolated yield could improve to 69% in a mixed solvent of DMSO and H_2O (*v*/*v* = 30:1) with the yield of byproduct **4** suppressed to 15% (entry 11). Lowering or elevating the reaction temperature led to lower yields (entries 12–13). Slightly decreased yield was obtained when the reaction was conducted under air atmosphere (entry 14), while no apparent product could be detected under nitrogen atmosphere (entry 15), which suggested that molecular oxygen was crucial to this reaction. Switching of $CuCl_2$ to other copper sources afforded similar results (entries 16–17). Next, the effect of leaving group in the substrate **1** was investigated. When $P(O)(OEt)_2$ was replaced by $P(O)(O\textit{i}\text{-Pr})_2$ or $P(O)(OMe)_2$, the yield of **3aa** was reduced to 44% and 36%, respectively (entries 18–19). No product was observed when leaving groups such as Ts or Ac were used instead (entries 20–21), indicating the vital role of $P(O)(OR)_2$ for such a transformation. Finally, copper salt proved to be indispensable as no desired product was detected in the absence of copper salt (entry 22).

With the optimized reaction conditions in hand, we then extended the reaction to a range of readily available phosphoryl hydrazones as shown in Table 2. Substrates bearing both electron-donating and electron-withdrawing groups proceeded efficiently to give the desired products (**3ba**–**3ga**) selectively with moderate to good yields. This protocol was not limited to simple benzene-containing hydrazones, substrates bearing a naphthyl group also gave the desired products (**3ha** and **3ia**) smoothly. Pyrazoles containing different heterocycles (**3ja** and **3ka**) were also obtained in moderate yields. Gratifyingly, product containing a double bond (**3la**), which could be reserved for further functionalization, was also prepared by this method and the C=C double bond remained intact during the reactions. Furthermore, the reactions show very good selectivity as no indazoles were observed significantly in all cases which could be formed through the aromatic $C(sp^2)$–H bond functionalization other than the olefinic $C(sp^2)$–H amination. However, try to expand the aryl substitution to aliphatic substituents failed, no designed acetoxylated products obtained. Notablely, the absolute spectroscopic analysis for products is convoluted, due to their dynamic tautomeric forms that NH-pyrazoles can adopt.

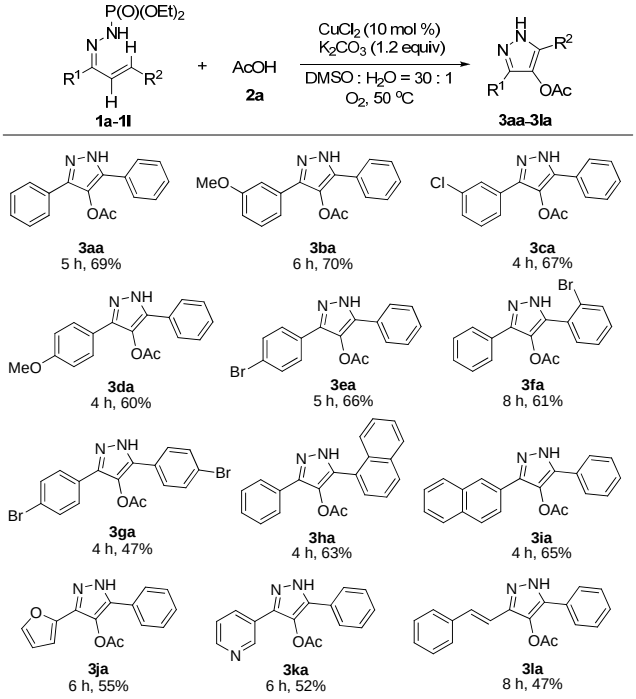
Table 1 Optimization of the Reaction Conditions.[a]



Entry	R	Cu salt	Base	Solvent	Yield[b] [%]
1	$P(O)(OEt)_2$	$CuCl_2$	-	DMSO	ND
2	$P(O)(OEt)_2$	$CuCl_2$	Na_2CO_3	DMSO	52 (23)
3	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DMSO	63 (20)
4	$P(O)(OEt)_2$	$CuCl_2$	Et_3N	DMSO	ND
5	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DMSO	56[c]
6	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DMSO	58[d] (21)
7	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DMF	45 (14)
8	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	Toluene	ND
9	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	CH_3CN	ND
10	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DCE	ND
11	**$P(O)(OEt)_2$**	**$CuCl_2$**	**K_2CO_3**	**DMSO/H_2O**	**69 (15)**
12	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DMSO/H_2O	47[e]
13	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DMSO/H_2O	54[f] (26)
14	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DMSO/H_2O	57[g]
15	$P(O)(OEt)_2$	$CuCl_2$	K_2CO_3	DMSO/H_2O	ND[h]
16	$P(O)(OEt)_2$	$Cu(OAc)_2$	K_2CO_3	DMSO/H_2O	66[i]
17	$P(O)(OEt)_2$	CuCl	K_2CO_3	DMSO/H_2O	63
18	$P(O)(O\textit{i}\text{-Pr})_2$	$CuCl_2$	K_2CO_3	DMSO/H_2O	44[j] (21)
19	$P(O)(OMe)_2$	$CuCl_2$	K_2CO_3	DMSO/H_2O	36 (33)
20	Ts	$CuCl_2$	K_2CO_3	DMSO/H_2O	ND
21	Ac	$CuCl_2$	K_2CO_3	DMSO/H_2O	ND
22	$P(O)(OEt)_2$	-	K_2CO_3	DMSO/H_2O	ND

[a] Reaction conditions: **1a** (0.3 mmol), AcOH (0.36 mmol), copper catalyst (10 mol%), base (0.36 mmol) in solvent (1.5 mL), 50 °C, O_2, 6 h. Ac = Acetyl, Ts = 4-Toluenesulfonyl, ND = Not detected. DMSO/H_2O refers to a mixed solvent with DMSO/H_2O = 30:1 (*v*/*v*). [b] Isolated yield. The value in parentheses is the isolated yield of byproduct 3,5-diphenyl-1*H*-pyrazole (**4**). [c] AcOH (0.3 mmol), K_2CO_3 (0.3 mmol). [d] AcOH (0.45 mmol), K_2CO_3 (0.45 mmol). [e] At 40 °C. [f] At 60 °C. [g] Under air. [h] Under N_2. [i] Reacted for 28 h. [j] Reacted for 16 h.

Table 2 Hydrazone scope in the synthesis of pyrazoles.[a,b]

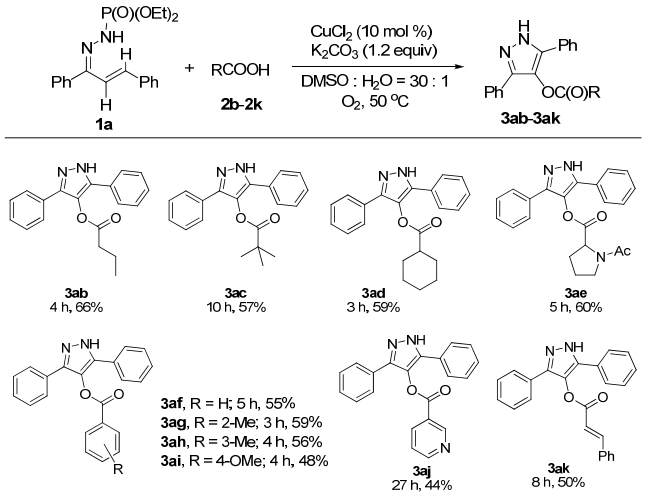


[a] Reaction conditions: **1a**–**1l** (0.3 mmol), **2a** (0.36 mmol), $CuCl_2$ (10 mol %), K_2CO_3 (0.36 mmol) in DMSO/H_2O (1.5 mL, *v*/*v* = 30:1), O_2, 50 °C. [b] Isolated yield.

In order to further explore the generality and scope of this method, various carboxylic acids were investigated, and the results are summarized in Table 3. Both acyclic and cyclic aliphatic carboxylic acids could all give corresponding pyrazoles expectedly (**3ab**–**3ad**) with good yields under the optimized conditions, even for

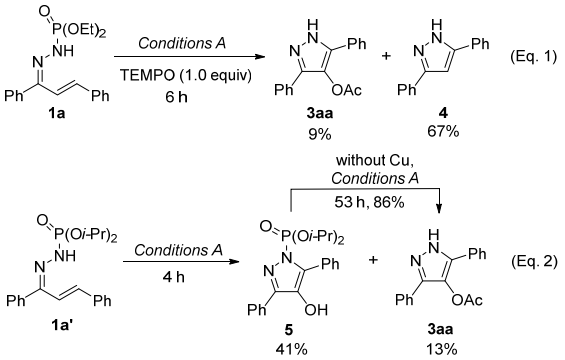
a substrate with highly sterically hindered substitution (**3ac**). Substrate with *N*-acetyl proline could also be employed in this transformation to give the desired product **3ae** in 60% yield. In addition, benzoic acid and its derivatives also worked well and afforded the corresponding products in moderate yields, regardless of their different electronic and steric properties (**3af**–**3ai**). To our delight, this approach also permitted the tolerance of heterocyclic and alkenyl carboxylic acids and afforded the desired products smoothly (**3aj** and **3ak**).

Table 3 Carboxylic acid scope in the synthesis of pyrazoles.[a,b]



[a] Reaction Conditions: **1a** (0.3 mmol), **2b**–**2k** (0.36 mmol), $CuCl_2$ (10 mol %), K_2CO_3 (0.36 mmol) in DMSO/H_2O (1.5 mL, *v*/*v* = 30:1), O_2, 50 °C. Yields shown are of the isolated products. [b] Isolated yield.

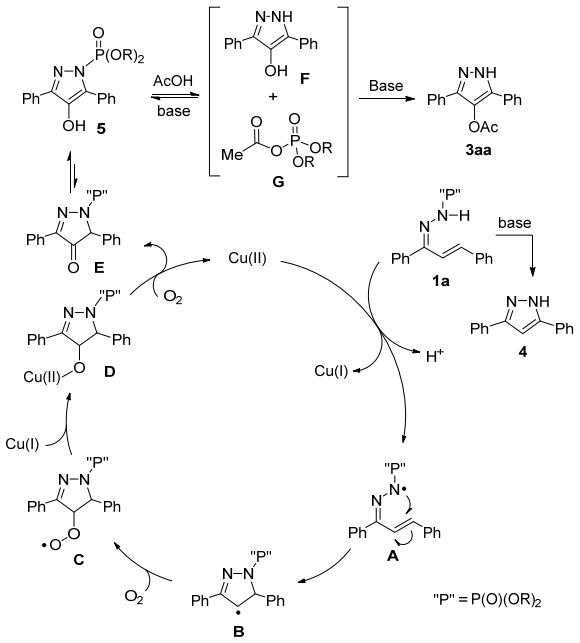
To gain insight into the reaction mechanism, several control reactions were performed under the optimized reaction conditions, as shown in Scheme 2. We firstly conducted the reaction by adding 1.0 equivalent of a radical scavenger 2,2,6,6-tetramethyl-piperidine-1-oxy (TEMPO) to the reaction of **1a** (Eq. 1). To our surprise, the targeted product **3aa** was obtained in only 9% yield and the direct cyclization byproduct **4** could be isolated in 67% yield, which implied that the formation of acyloxylated product **3aa** mainly involved a radical process and the competitive byproduct **4** preferred to form in a non-radical pathway. Try to convert **4** to **3aa** and its deacylated product **F** (Scheme 3) under optimized conditions failed, indicating the formation of **3aa** and **4** through independent pathways. In order to isolate the possible key intermediates, a less active substrate analogue of **1a** with isopropyl substitution, diisopropyl-(2-



Scheme 2 Mechanistic studies. Conditions A: $CuCl_2$ (10 mol%), HOAc (1.2 equiv), K_2CO_3 (1.2 equiv), in DMSO/H_2O (*v*/*v* = 30:1), O_2, 50 °C.

((*E*)-1,3-diphenylallylidene)hydrazinyl) phosphornate (**1a'**), was employed under the standard conditions. To our delight, a phosphonate-containing intermediate **5** could be isolated in 41% yield along with 13% yield of **3aa** after reacted for 4 h. Treatment of **5** under the standard condition in the absence of copper salt further afforded the desired 4-acyloxy-1*H*-pyrazole **3aa** in 86% yield (Eq. 2), which strongly indicated that **5** might be the key intermediate for this transformation and the copper salt is not necessary during this step.

Although a detailed reaction pathway remains to be clarified, a tentative mechanism for this cascade reaction was proposed on the basis of above investigations (Scheme 3). The reaction initially proceeded via a one-electron transfer and deprotonation process from substrate **1a** in the presence of $CuCl_2$ to give a radical species **A**. The generated radical intermediate **A** was subsequently trapped by the intramolecular C=C double bond to produce corresponding alkyl radical **B** through the formation of C–N bond.[27] Radical **B** would react with molecular oxygen to afford a superoxo radical **C**, which would deliver Cu(II) alkoxide **D** by the Fenton-type fragmentation.[28] β-Elimination of **D** will generate intermediate **E** which could be isomerized to the isolable intermediate **5** (R = *i*-Pr). Treatment of intermediate **5** with acetic acid gave **F** and acyl phosphate **G** due to the strong affinity between oxygen and phosphine atoms, which finally afforded the desired pyrazole product **3aa**.[29] On the other hand, the formation of the direct cyclization byproduct **4** will undergo through an intramolecular ionic pathway in the presence of a base.[30,31]



Scheme 3 Proposed mechanism (ligands are omitted for clarity).

In summary, we have developed a novel protocol for the copper-catalyzed regioselective synthesis of multisubstituted 4-acyloxy-1*H*-pyrazoles in a single step from hydrazones and carboxylic acids under mild conditions. Highly selective olefinic C(sp^2)–H functionalization was realized through N–P bond cleavage of unique *N*-diethoxy-phosphoryl hydrazones. The characteristics of wide substrate scope, good functionality tolerance and synthesis modularity will provide the described reaction a broad utility in organic synthesis. Currently, we are engaged in further insight into the mechanism, reaction scope, and the synthetic applications for other bioactive compounds.

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Notes and references

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† Electronic Supplementary Information (ESI) available: General experimental procedures, characterization data and copies of the ^{1}H, ^{13}C and ^{19}F NMR spectra for all compounds. CCDC 1032969 (compound **3aa**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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