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Copper-Catalyzed Synthesis of Substituted 4-Acylpyrazole Derivatives through a Cascade Transformation from *N*-Propargylic Sulfonylhydrazones and Diaryliodonium Salts

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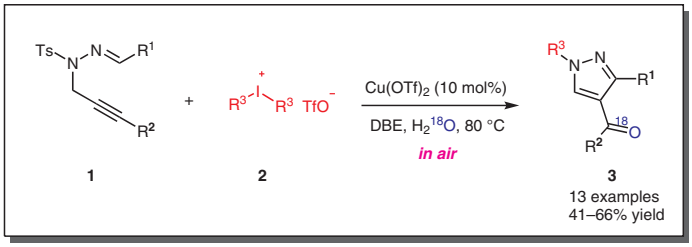

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Abstract A concise strategy for the synthesis of substituted 4-acylpyrazole derivatives from *N*-propargylic sulfonylhydrazones and diaryliodonium salts has been developed. The pyrazole derivatives are formed through a five-step cascade sequence that includes intramolecular cyclization, hydroxylation, elimination, copper-catalyzed aerobic oxidation, and intramolecular rearrangement.

Key words propargylic sulfonylhydrazones, diaryliodonium salts, cascade transformation, acylpyrazoles

Pyrazole derivatives are commonplace heterocyclic skeletons that exhibit important bioactivities in a variety of natural products and other molecules.[1] Among these, substituted 4-acylpyrazoles are useful building blocks in heterocyclic chemistry, and there are dozens of reports in the patent literature on the use of pyrazolyl ketones as pharmaceutical intermediates.[2] Because of the importance of 4-acylpyrazoles, various methods for the construction these scaffolds have been developed. Although these reported protocols are generally reliable, some still suffer from such limitations as difficulties in obtaining the substrates,[3,4] poor regioselectivity,[5] or harsh reaction conditions.[6] Recently, Fan and co-workers reported a novel and efficient one-pot synthesis of diversely substituted 4-acylpyrazole derivatives through multiple aliphatic C–H bond functionalization and C–C bond cleavage.[7] However, in consideration of the potential important applications of 4-acylpyrazoles, it is still essential to develop an efficient and simple method for the construction of 4-acylpyrazoles.

N-Propargylic hydrazones represent a novel group of synthons for a variety of pyrazoles. In 2008, Chung et al. reported a simple and efficient procedure for the $AgSbF_6$-catalyzed formation of pyrazoles from *N*-propargyl sulfonylhydrazones (Scheme 1, Equation 1).[8] Subsequently, we developed diverse routes to various kinds of valuable highly substituted pyrazoles through the intramolecular cyclization of *N*-propargylic hydrazones (Scheme 1, Equations 2–4).[9–11]

As part of our ongoing efforts to expand the synthetic utility of *N*-propargylic hydrazones, we conjectured that if an electrophilic reagent could be introduced onto the nitrogen atom of the *N*-propargylic hydrazone, it might promote attack by the triple bond on the imine carbon atom, leading to a novel cyclized product. Diaryliodonium salts have been extensively used as efficient electrophilic reagents with low toxicities and excellent selectivities.[12] We chose diaryliodonium salts **2** as electrophilic reagents to react with the *N*-propargylic sulfonylhydrazones **1** to produce the 4-acylpyrazoles **3** in moderate yields (Scheme 1, Equation 5). This process involves a cascade sequence consisting of intramolecular cyclization, hydroxylation, elimination, copper-catalyzed aerobic oxidation, and intramolecular rearrangement.

To identify the most suitable condition for this reaction, we screened a series of catalysts and solvents (Table 1). We began by screening various metal catalysts and protonic acid catalysts in DCE at 80 °C. The *N*-propargyl sulfonylhydrazone **1a** and the diaryliodonium salt **2a** were treated

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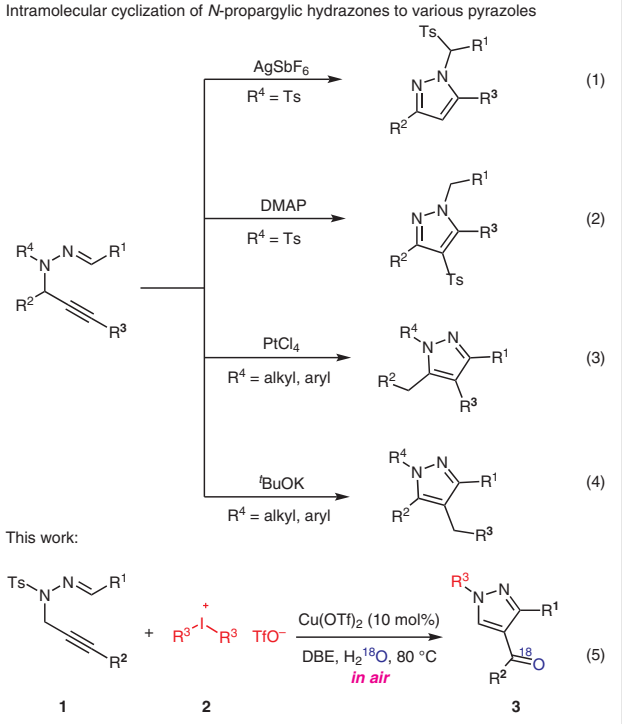
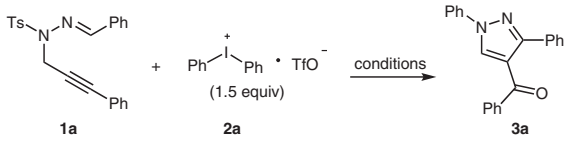


Scheme 1 Synthesis of various pyrazoles from *N*-propargylic hydrazones

with 10 mol% of $FeCl_3$, $Cu(OTf)_2$, AgOTf, $In(OTf)_3$, or TFA in DCE at 80 °C for two hours (Table 1, entries 1-5). Only $Cu(OTf)_2$ gave the desired 4-acylpyrazole **3a** in 48% yield (entry 2). This result suggested that a copper catalyst could promote the reaction and, with this in mind, we then tested a range of other copper catalysts: CuI, CuCl, $Cu(OAc)_2$, $CuBr{\cdot}SMe_2$, and $Cu(acac)_2$ (entries 6–10). However, no improvement was detected with any of these catalysts. Further optimization was directed toward the solvent. A variety of solvents [toluene, 1,4-dioxane, *p*-xylene, chlorobenzene, DMSO, THF, and 1,2-dibromoethane (DBE)] were screened (entries 11–17), and the reaction was found to proceed most effectively in DBE as solvent, which gave product **3a** in 57% yield (entry 17). Changing the reaction temperature did not give satisfactory results (entries 18 and 19). Finally, when water (0.5 mL) was added to the reaction system, the yield decreased (entry 20), indicating that excess water might inhibit the activity of the reaction. After full screening, the optimal reaction conditions were determined to be 10 mol% of $Cu(OTf)_2$ as the catalyst in DBE contains trace amounts of water as solvent, and a reaction temperature of 80 °C (entry 17).

With the optimized conditions in hand, we examined the reactions of range of substrates, and the results are summarized in Scheme 2. We first investigated the effect of the aryl group of the diaryliodonium salts **2**, and we found that one containing an electron-withdrawing group (Ar = 4-ClC_6H_4) and one containing an electron-donating groups (Ar = 4-Tol) both participated readily in this reaction, affording the corresponding product **3b** and **3c** in moderate yields of 49% and 44%, respectively. Next, we examined the effects of various R^1 groups in the propargylic hydrazone. We were delighted to find that when R^1 was a substituted phenyl group (4-BrC_6H_4, 4-Tol, 4-ClC_6H_4, or 3-BrC_6H_4), the reaction proceeded well to afford the corresponding pyrazoles **3d–g** in moderate yields of 47–65%. It is worth mentioning that the hydrazone bearing a sterically large 1-naphthyl group also reacted well and without an obvious decrease in the yield, giving **3h** in 50% yield. Unfortunately, when R^1 was a 2-thienyl or alkyl group, the reaction gave a complex mixture of products, and the starting materials could not be recovered. We then investigated the effects of various R^2

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent[b]	Yield[c] (%)
1	$FeCl_3$	DCE	0
2	$Cu(OTf)_2$	DCE	48
3	AgOTf	DCE	0
4	$In(OTf)_3$	DCE	trace
5	TFA	DCE	0
6	CuI	DCE	36
7	CuCl	DCE	trace
8	$Cu(OAc)_2$	DCE	27
9	$CuBr{\cdot}SMe_2$	DCE	trace
10	$Cu(acac)_2$	DCE	34
11	$Cu(OTf)_2$	toluene	50
12	$Cu(OTf)_2$	1,4-dioxane	trace
13	$Cu(OTf)_2$	*p*-xylene	52
14	$Cu(OTf)_2$	PhCl	trace
15	$Cu(OTf)_2$	DMSO	0
16	$Cu(OTf)_2$	THF	trace
17	**$Cu(OTf)_2$**	**DBE**	**57**
18[d]	$Cu(OTf)_2$	DBE	trace
19[e]	$Cu(OTf)_2$	DBE	43
20[f]	$Cu(OTf)_2$	DBE	42

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), solvent (5 mL), catalyst (10 mol %), 2 h, 80 °C, in air.
[b] All solvents were used without drying.
[c] Isolated yield.
[d] 50 °C.
[e] Reflux.
[f] Water (0.5 mL) was added.

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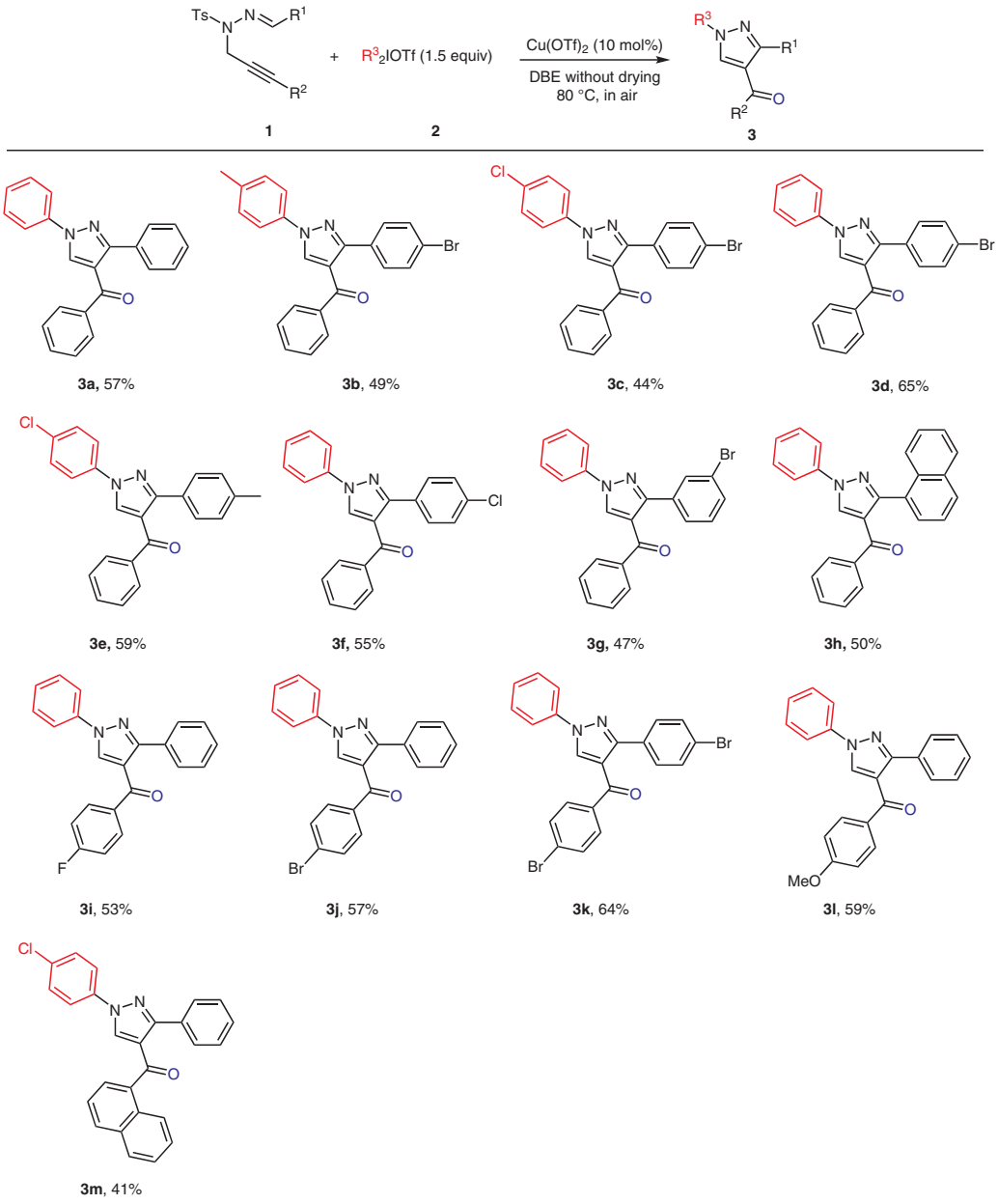

Scheme 2 Synthesis of polysubstituted pyrazoles. *Reaction conditions*: **1** (0.5 mmol), **2** (0.75 mmol), $Cu(OTf)_2$ (10 mol%), DBE (5 mL, without drying), 80 °C, 2 h, in air. Isolated yields are reported.

group in the hydrazone, and we obtained satisfactory results when R^2 was phenyl substituted with an electron-withdrawing or electron-donating group or when R^2 was a 1-naphthyl group (**3i–m**; 41–64% yield).

Finally, when we investigated the reaction of a nonsymmetric diaryliodonium salt, we found that it gave a mixture of products **3b** and **3c** (Scheme 3).

To gain insight into the mechanism of the reaction, we carried out a control experiment under anhydrous conditions in the presence of O_2 (Scheme 4, Equation 1). The desired product **3e** was detected but its yield was low (< 5%), indicating that the oxygen in the product does not originate from O_2 and that trace amounts of water in the DBE solvent are essential. We then carried out this reaction in the presence of [^{18}O]water (Scheme 4, Equation 2) and we obtained the ^{18}O-labelled product **3e**-[^{18}O], indicating that the oxygen of the product originated from H_2O. When we carried out the reaction in the absence of a diaryliodonium salt (Scheme 4, Equation 3), it gave a complex mixture in which no pyrazole product was detected, confirming that the diaryliodonium salt plays an important role in the reaction.

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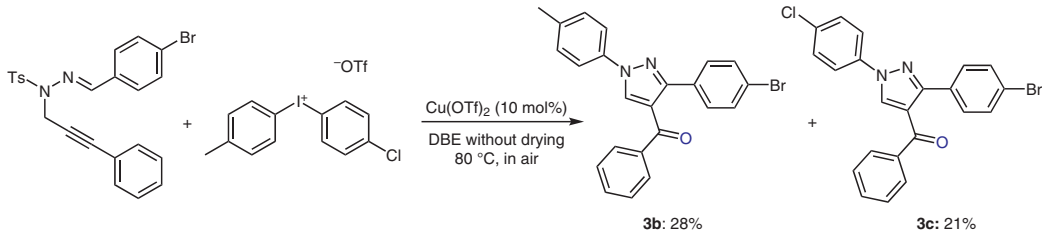
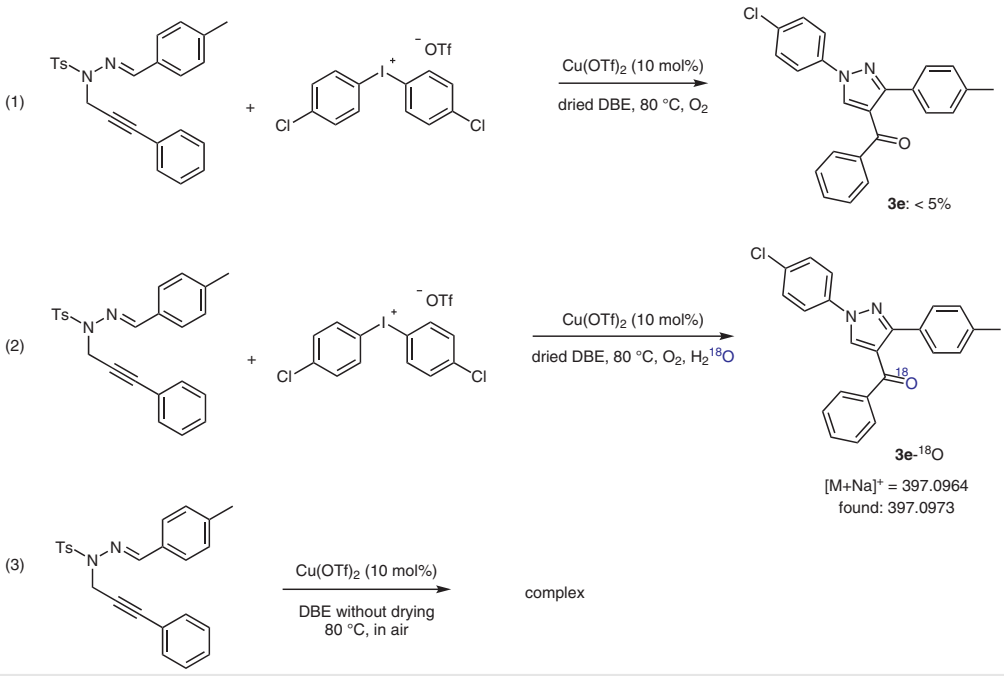
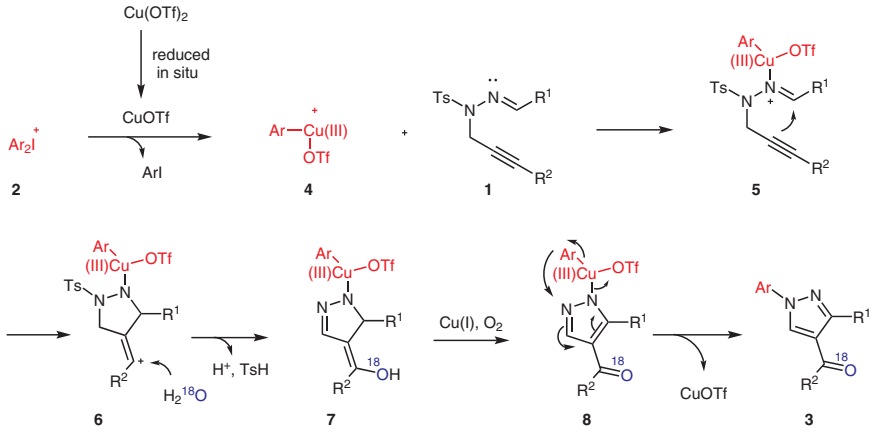


Scheme 3 Reaction of a nonsymmetric diaryliodonium salts with an *N*-propargyl sulfonylhydrazone



Scheme 4 Mechanistic studies



Scheme 5 Proposed mechanism

As a working hypothesis, we proposed the following plausible mechanism (Scheme 5). First, the diaryliodonium salts **2** reacts with the copper catalyst to generate the aryl cation **4**,[13] which undergoes electrophilic addition onto the

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nitrogen atom of the imine to afford intermediate **5**. Intermediate **5** is attacked by the alkynyl group to give the five-membered ring **6**. The imine carbocation is then captured by H_2O and eliminates a molecule of TsH to give intermediate **7**, which is oxidized under the aerobic conditions with copper catalysis to give intermediate **8**. Finally, intramolecular electron rearrangement and migration of the aryl group give the 4-acylpyrazole **3**.

In summary, we have developed a concise strategy for the synthesis of polysubstituted 4-acylpyrazole derivatives from *N*-propargylic sulfonylhydrazones.[14] The pyrazole derivatives are formed through a five-step cascade sequence that includes intramolecular cyclization, hydroxylation, elimination, copper-catalyzed aerobic oxidation, and intramolecular rearrangement.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610271.

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(14) **Pyrazoles 3a–m; General Procedure**

A 10 mL round-bottomed flask was charged with the appropriate *N*-propargylic sulfonylhydrazone **1** (0.5 mmol), diaryliodonium salt **2** (0.75 mmol), and $Cu(OTf)_2$ (18.1 mg, 0.05 mmol). Undried DBE (5 mL) was added, and the mixture was stirred at 80 °C in air until the reaction was complete (TLC). The solvent was removed under vacuum, and the crude residue was purified by column chromatography (silica gel, eluent: petroleum ether/EtOAc = 30/1).

(1,3-Diphenyl-1*H*-pyrazol-4-yl)(phenyl)methanone (3a)

White solid; yield: 92 mg (57%); mp 117–119 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.37 (m, 2 H), 7.43 (t, *J* = 7.7 Hz, 2 H), 7.50–7.56 (m, 4 H), 7.74–7.77 (m, 2 H), 7.80–7.88 (m, 5 H), 8.31 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 119.6, 121.2, 127.5, 128.1, 128.3, 128.6, 128.9, 129.4, 129.6, 132.1, 132.2, 132.6, 138.9, 139.2, 154.0, 190.0. HRMS (ESI): *m/z* [M + Na] calcd for $C_{22}H_{16}N_2NaO$: 347.1155; found: 347.1160.

[3-(4-Bromophenyl)-1-(4-tolyl)-1*H*-pyrazol-4-yl](phenyl)-methanone (3b)

White solid; yield: 102 mg (49%); mp 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.44–7.52 (m, 4 H), 7.58 (t, *J* = 7.3 Hz, 1 H), 7.64–7.72 (m, 4 H), 7.86 (d, *J* = 7.7 Hz, 2 H), 8.23 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 119.5, 120.8, 122.8, 128.4, 129.4, 130.1, 130.5, 131.1, 131.2, 132.5, 132.6, 136.8, 137.7, 138.9, 152.6, 189.7. HRMS (ESI): *m/z* [M + Na] calcd for $C_{23}H_{17}BrN_2NaO$: 439.0416 and 441.0396; found: 439.0419 and 441.0399.

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