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Copper-Promoted Coupling of Propiophenones and Arylhydrazines for the Synthesis of 1,3-Diarylpyrazoles

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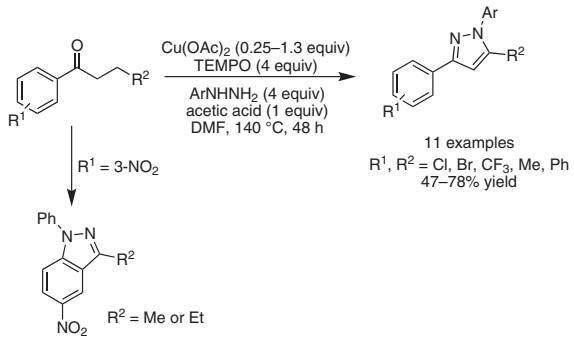

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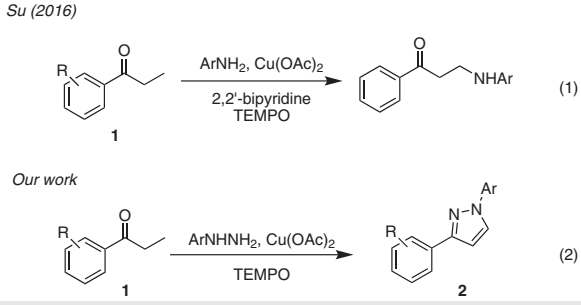
Abstract Synthesis of 1,3-diarylpyrazoles from commercial substrates and/or simple transformations is still underrated. In this report, we have developed a method for copper-promoted coupling of propiophenones and arylhydrazines. The reactions afforded substituted pyrazoles in the presence of TEMPO oxidant, acetic acid additive, and DMF solvent. A number of functionalities were compatible with reaction conditions, including halogens, methoxy, trifluoromethyl, and nitro groups. An indazole could be obtained if an electron-poor propiophenone was used.

Key words copper, 1,3-diarylpyrazoles, TEMPO, oxidative, dehydrogenation



Scheme 1 Dehydrogenative coupling of propiophenones with amine nucleophiles

Dehydrogenation of aliphatic ketones and isosteres is a growing methodology that allows for the synthesis of hitherto demanding molecules.[1] Perhaps the Saegusa–Ito oxidation is the earliest method for yielding enones from silyl enol ethers.[1a,b] Since then, developments of methods that do not require the use of hygroscopic silyl halides have been attempted. Palladium-, platinum-, and rhodium-catalyzed desaturation of cyclic and acyclic carbonyl compounds is known.[1c–f] Notably, only a few first-row metals are used to facilitate the transformation. Ueno and Kuwano firstly reported a method for nickel-catalyzed dehydrogenative amination of ethyl ketones.[1g] Su later presented a coupling of propiophenones **1** with many nucleophiles including sulfonamides, amides, amines, and phenols.[1h] The transformation was promoted by a combination of copper catalyst and TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) oxidant (Scheme 1, eq 1). Multiple dehydrogenation of aliphatic carbonyls and alcohols is also precedented.[1i] Notably, metal-free oxidation of allylic sp^3 C–H bonds has been reported.[1j] To our surprise, there have not been any examples that leverage the advantages of the available methods for the synthesis of valuable heterocycles.

Pyrazoles are prevalent in many natural products,[2a] useful chemicals,[2b–d] and functional materials.[2e–g] Scorpionate ligands comprising sterically hindered pyrazoles play a prominent role in stabilizing metal complexes used in catalysis.[2h–k] Synthesis of densely 1,3-diarylated pyrazoles **2** is notoriously challenging and has attracted substantial attention of synthetic chemists. Conventional cycloaddition of 1,3-dicarbonyl compounds and arylhydrazines often suffers from the formation of regioisomeric products.[3] Consequently, well-tailored starting materials are required to obtain the selectivities.[4] Beller has reported a condensation of butoxypropenones, *in situ* formed via a Heck coupling of aryl bromides and vinyl butyl ether, with phenylhydrazines to afford moderate yields of 1,3-diarylpyrazoles.[4a] The group of Panda has developed an iron-catalyzed reaction of diarylhydrazones and vicinal diols.[4b] Oxime acetates of propiophenones could be used to couple with aromatic amines and paraformaldehyde under copper catalysis to yield disubstituted pyrazoles.[4c] Coupling N–H bonds in 3-substituted pyrazoles, which are commercially limited, with aryl iodides or boronic acids is also possible.[5] It would be much more beneficial if commercial substrates are di-

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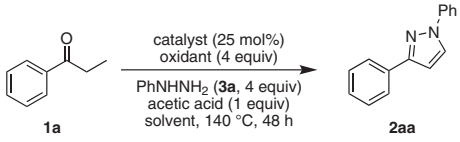
rectly used, thus shortening synthetic schemes. Our hypothesis was that a copper-catalyzed dehydrogenative coupling of propiophenones **1** and arylhydrazines could afford 1,3-disubstituted pyrazoles **2** (Scheme 1, eq 2), since copper(II) complexes are known to facilitate desaturation of phenyl alkyl ketones[1i] and β-amination of carbonyl compounds.[1h] If successful, our method would offer a rapid route for the synthesis of 1,3-diarylpyrazoles. It should be noted that such a method has not been reported in the literature.

On the basis of previous results,[1h,i] we decided to use $Cu(OAc)_2$ in combination with TEMPO for the synthesis of **2aa** from the corresponding starting materials. The reaction optimization was carried out with regard to solvent, catalyst, and oxidant (Table 1). Alcoholic solvents such as glycerol and ethylene glycol were inferior to DMF (entries 1–3). In contrast to other copper-catalyzed dehydrogenation of carbonyl compounds,[1h,i] 1,2-dichlorbenzene only afforded a trace amount of product **2aa** (entry 4). Copper(II) acetate was more active than copper(II) bromide and copper(I) iodide (entries 5 and 6). Only TEMPO and the hydroxy derivative were competent oxidants (entry 7), while running the reaction under air as the sole oxidant gave an indole (entry 8). The byproduct was of the competitive Fischer process. A moderate yield of **2aa** was obtained if acetic acid was omitted (entry 9). The presence of copper(II) acetate was crucial to achieve a substantial conversion of propiophenone **1a** (entry 10). Using a stoichiometric amount of copper(II) acetate gave 81% isolated yield of product **2aa** (entry 11). It should be noted that α-amination of C–H bonds in propiophenone **1a** did not occur under these reaction conditions.[6]

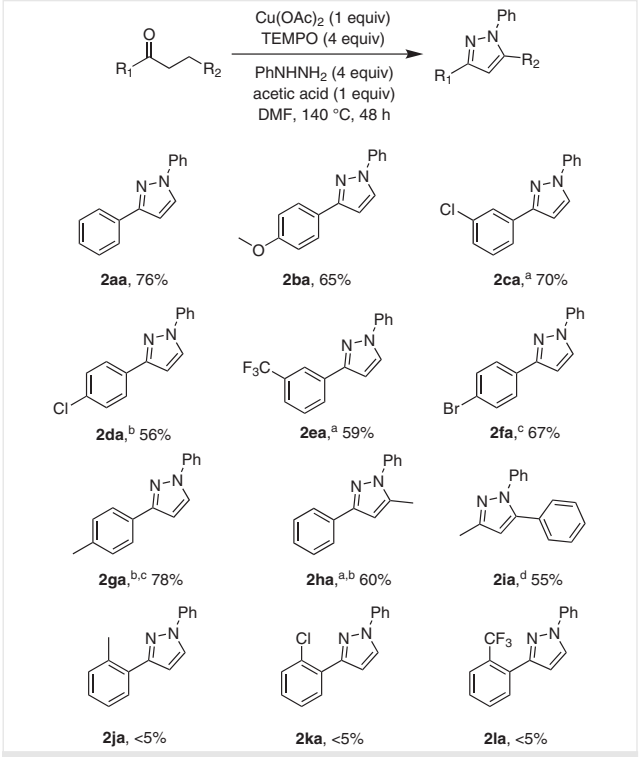
Scope of the transformation was next studied and is presented in Scheme 2. Positions of the substituents somewhat affected the yields of 1,3-diarylpyrazoles. If a catalytic amount of $Cu(OAc)_2$ was used, *para*-substituted substrates such as 4′-methoxy, 4′-chloro, 4′-bromo, and 4′-methyl propiophenones coupled with phenylhydrazine to give the sluggish crude reaction mixtures (**2ba**, **2da**, **2fa**, and **2ga**). Some intermediates such as enones or dihydropyrazoles were detected (by GC–MS). In those entries, excess $Cu(OAc)_2$ was often required. Meanwhile, the reactions of *meta*-substituted propiophenones were far easier and only needed a catalytic amount of $Cu(OAc)_2$ (**2ca** and **2ea**).[7] Other aliphatic ketones were also investigated. Condensation of butyrophenone and phenylhydrazine afforded a 1,3,5-trisubstituted pyrazole **2ha** in 60% yield. Benzylic sp^3 C–H bonds were active, yielding a highly dense diaryl pyrazole

Table 1 Optimization Results[a]



Entry	Solvent	Catalyst	Oxidant	Yield of **2aa** (%)
1	glycerol	$Cu(OAc)_2$	TEMPO	60
2	ethylene glycol	$Cu(OAc)_2$	TEMPO	41
3	DMF	$Cu(OAc)_2$	TEMPO	70
4	1,2-dichlorobenzene	$Cu(OAc)_2$	TEMPO	<5
5	DMF	$CuBr_2$	TEMPO	60
6	DMF	CuI	TEMPO	12
7	DMF	$Cu(OAc)_2$	4-OH-TEMPO[b]	65
8[c,d]	DMF	$Cu(OAc)_2$	none	<5
9[e]	DMF	$Cu(OAc)_2$	TEMPO	31
10	DMF	none	TEMPO	<5
11[f]	DMF	$Cu(OAc)_2$	TEMPO	81

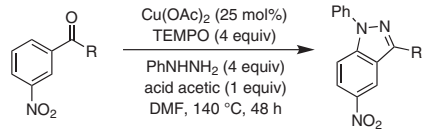
[a] Reaction conditions: Acetophenone (**1a**, 0.2 mmol), phenylhydrazine (**3a**, 0.8 mmol), catalyst (0.05 mol), oxidant (0.8 mmol), acetic acid (0.2 mmol), solvent (1 mL), 140 °C, 48 h. Yields of **2aa** are GC yields using diphenyl ether internal standard.
[b] 4-OH-TEMPO = 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxy.
[c] Air is the sole oxidant.
[d] Major product is 3-methyl-2-phenyl-1*H*-indole.
[e] No acetic acid.
[f] $Cu(OAc)_2$ (0.2 mmol) was used, yield is isolated yield.



Scheme 2 Reaction scope with respect to propiophenones. *Reagents and conditions*: Phenyl ketone (1 mmol), phenylhydrazine (4 mmol), $Cu(OAc)_2$ (1 mmol), TEMPO (4 mmol), acetic acid (0.2 mmol), DMF (5 mL), 140 °C, 48 h. Isolated yields are given. [a] $Cu(OAc)_2$ (0.25 mmol) was used. [b] Average yields of two independent runs. [c] $Cu(OAc)_2$ (1.3 mmol) was used. [d] $CuBr_2$ (0.25 mmol) instead of $Cu(OAc)_2$.

2ia in 55% yield. At this moment, our conditions were limited to sterically hindered *ortho*-substituted propiophenones.[8]

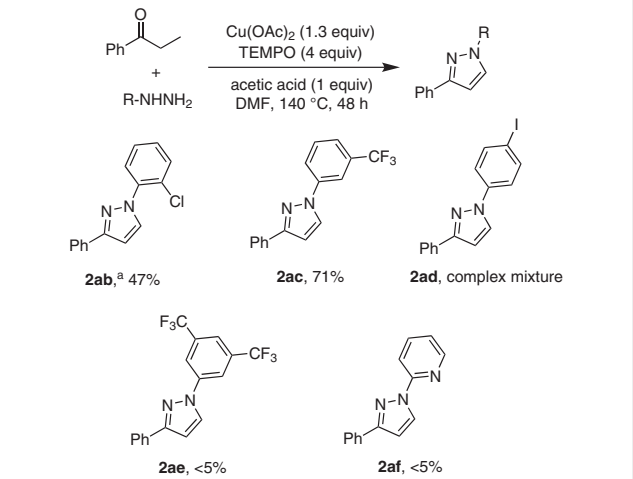
Notably, if 3′-nitropropiophenone coupled with phenylhydrazine under the reaction conditions, indazole **4a** was isolated in a moderate yield (Scheme 3). Similarly, 3′-nitroacetophenone was also a competent substrate, affording the corresponding indazole **4b** in 57% yield. Synthesis of such biorelated indazoles is rare and often requires the prefunctionalization of carbonyl compounds.[9] One should be noted that Chang and co-workers have reported a relevant iodine-mediated cyclization of hydrazones to afford fully substituted indazoles.[9c] However, the scope was limited to those not containing α-C–H bonds. It was envisaged that under our reaction conditions, the nitro group plays a role as a directing group for intramolecular amination,[10] after the formation of imine intermediate, to afford the product.



Scheme 3 Synthesis of indazoles. *Reagents and conditions*: 3′-Nitropropiophenone or 3′-nitroacetophenone (1 mmol), phenylhydrazine (4 mmol), $Cu(OAc)_2$ (0.25 mmol), TEMPO (4 mmol), acetic acid (1 mmol), DMF (5 mL), 140 °C, 48 h. Isolated yields are given.

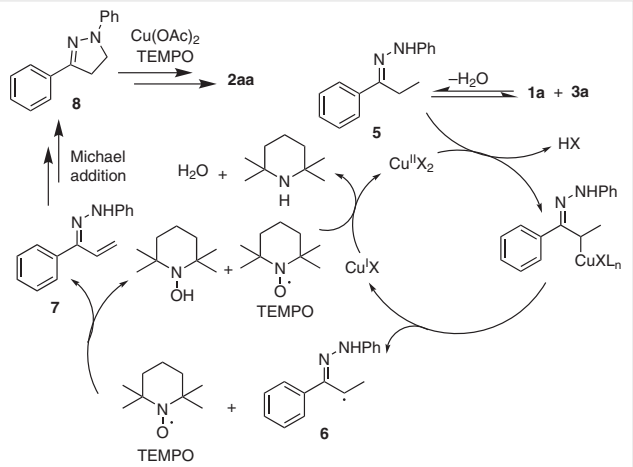
We next studied the scope of arylhydrazines. The result is shown in Scheme 4. A hindered *ortho*-chloro phenylhydrazine coupled with propiophenone to furnish 47% yield of the pyrazole **2ab**. A 71% yield of the pyrazole (**2ac**) containing trifluoromethyl group was obtained. It should be noted that the reaction of 4-iodophenylhydrazine gave the desired product **2ad**, albeit in an inseparably complex mixture. Neither a very electron-poor phenylhydrazine (**2ae**) nor a substrate derived from heterocycle (**2af**) was active under our conditions. Attempts to expand the scope with respect to arylhydrazine are ongoing.

A brief mechanism was proposed based on a relevant result reported by Su and co-workers.[1h] Given that indazole **4** was obtained if a very electron-poor propiophenone was used, the coupling of aryl ethyl ketones and arylhydrazines possibly proceeds via the formation of hydrazones, such as **5**, in the presence of acetic acid (Scheme 5). Copper(II)-promoted activation of α-C–H bonds[6] in **5** followed by a single-electron transfer between **6** and TEMPO would afford the enone **7**. Running the 'homocoupling' of propiophenone **1a** (in the absence of phenylhydrazine **3a**) yielded a dimer, somewhat showing the involvement of intermediate **6** in the mechanism. The oxidation of C–C bond (**5** → **6**) is likely the rate-limiting step, via the formation of **4**, and strongly affected by electronic properties of the substituents. An intramolecular Michael addition would give the dihydropyrazole **8**, followed by another copper/TEMPO co-promoted oxidation of C–C bond to furnish the pyrazole **2aa**. For some entries, such ene–imine[11] and dihydropyrazole intermediates were detected by GC–MS.[12]



Scheme 4 Scope of arylhydrazines. *Reagents and conditions*: 3′-Nitropropiophenone (1 mmol), arylhydrazine (4 mmol), $Cu(OAc)_2$ (1.3 mmol), TEMPO (4 mmol), acetic acid (1 mmol), DMF (5 mL), 140 °C, 48 h. Isolated yields are given. [a] Hydrochloride salt was used.

In conclusion, we report a method for the synthesis of 1,3-diarylpyrazoles from propiophenones and arylhydrazines. Reactions proceeded in the presence of copper(II) acetate TEMPO oxidant, acetic acid promoter, and DMF solvent. Functionalities such as halogens, methoxy, and trifluoromethyl groups were compatible with reaction conditions. An indazole was isolated if 3-nitropropiophenone was used. The method is a promising candidate for the synthesis of densely substituted pyrazoles from commercial, simple substrates.



Scheme 5 Plausible mechanism

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690835.

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(7) **3-(3-Chlorophenyl)-1-phenyl-1*H*-pyrazole (2ca) – Typical Procedure**

To a 16 mL vial was added 3′-chloropropiophenone (169 mg, 1 mmol), phenylhydrazine (432 mg, 4 mmol), $Cu(OAc)_2$ (46 mg, 0.25 mmol), TEMPO (624 mg, 4 mmol), acetic acid (60 mg, 1 mmol), and DMF (5 mL). The vial was placed into a preheated oil bath (140 °C) and vigorously stirred for 48 h. The reaction mixture was cooled to room temperature, quenched with brine (10 mL), then extracted with EtOAc (3 × 15 mL). Combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Crude product was purified by flash column chromatography (hexanes/EtOAc, 10:1) to obtain 179 mg (70%) of a white solid. This compound is known.[4c]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 2.5 Hz, 1 H), 7.86 (t, *J* = 1.9 Hz, 1 H), 7.71 (tt, *J* = 7.6, 1.2 Hz, 3 H), 7.45–7.37 (m, 2 H), 7.29 (t, *J* = 7.8 Hz, 1 H), 7.27–7.21 (m, 2 H), 7.19 (s, 1 H), 6.70 (d, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.6, 135.0, 134.7, 129.9, 129.5, 128.2, 128.0, 126.6, 125.9, 123.9, 119.2, 105.2 ppm. One carbon signal could not be located.

(8) Small amounts of dehydrogenation products were observed by GC–MS analysis.

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(10) One reviewer recommended the use of 4′-nitropropiophenone; however, only the starting material was recovered. For NO_2-directed intermolecular amination, see selected example: Kumar, S.; Rathore, V.; Verma, A.; Prasad, C. D.; Kumar, A.; Yadav, A.; Jana, S.; Sattar, M.; Meenakshi; Kumar, S. *Org. Lett.* **2015**, *17*, 82.

(11) For selected example of intermolecular ene–imine cycloaddition, see: Li, Z.; Hu, B.; Wu, Y.; Fei, C.; Deng, L. *Proc. Natl. Acad. Sci. U.S.A.* **2018**, *115*, 1730.

(12) Attempts to isolate possible intermediates are ongoing.

