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SHORT COMMUNICATION

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An Easy Route to *N*,*N*-Diarylhydrazines by Cu-Catalyzed Arylation of Pyridine-2-carbaldehyde Hydrazones with Aryl Halides

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Keywords: Synthetic methods / Arylation / Hydrazines / Cross-coupling / Copper / Halides

A copper-catalyzed C–N coupling reaction is described for the preparation of pyridine-2-carbaldehyde *N*,*N*-diarylhydrazones by the arylation of *N*-mono- or -non-substituted hydrazones with aryl bromides/iodides, and the subsequent conversion of the hydrazones into *N*,*N*-diarylhydrazines by a transimination process with an aqueous solution of H_2NNH_2. The reaction features the use of CuI as the catalyst without the need for external ligands. This methodology provides a convenient alternative to the synthesis of structurally diverse *N*,*N*-diarylhydrazines from simple, easily accessible precursors.

Introduction

N,*N*-Disubstituted hydrazines, particularly *N*,*N*-diarylhydrazines, are highly valuable molecules due to their bioactivity[1] and intermediacy in the synthesis of pharmaceutically important *N*-arylindoles[2] (by the Fischer indole synthesis[3]) and important organic photoelectrical materials.[4] Typically, *N*,*N*-disubstituted hydrazines are prepared by the reduction of the corresponding *N*-nitrosamine precursors, which are, in turn, obtained by the treatment of secondary anilines with HNO_2.[5] The classical method suffers from harsh reaction conditions, limited functional group tolerance, complicated work-up, and low yields. Over the past decade, transition-metal-catalyzed cross-coupling reactions of aryl halides with hydrazine-type nucleophiles have attracted intense interest and become a useful alternative to the synthesis of aryl-substituted hydrazines,[6–10] of which successful examples related to *N*,*N*-diarylhydrazine synthesis include the Pd-catalyzed cross-coupling of benzophenone hydrazone with aryl bromides,[8] Cu-mediated diarylation of *N*-acylhydrazines,[10a] Cu-mediated arylation of Boc-protected hydrazines with bismuthane,[10b,10c] Cu-catalyzed coupling of *N*-acyl-*N*′-arylhydrazines with aryl iodides/bromides,[10d] and the CuI/PPAPM-promoted *N*-arylation of phenylhydrazine with activated aryl bromides/iodides.[10e]

Our motivation to develop a new copper-catalyzed strategy for the synthesis of *N*,*N*-diarylhydrazines arose from a chance finding: We observed that in some copper-catalyzed cross-coupling reactions using pyridine-2-carbaldehyde *N*-arylhydrazone as a ligand, the hydrazone readily underwent an *N*-arylation reaction with arylating agents. This prompted us to carry out a detailed investigation into the copper-catalyzed cross-coupling reactions of hydrazone substrates.

Results and Discussion

Pyridine-2-carbaldehyde (*E*)-*N*-phenylhydrazone (**1a**) and *p*-bromoanisole were selected as model substrates to determine the optimal reaction conditions for the catalytic C–N coupling reaction (Table 1). We first surveyed the role of copper in the reaction. As can be seen in Table 1, no reaction occurred in the absence of copper catalysts (entry 2). Various Cu salts, whether mono- or divalent, were effective to a certain degree (entries 1 and 3–6), with CuI giving the best result with an almost quantitative conversion and high isolated yield of the desired product (entry 1). However, the use of copper metal powder substantially slowed the reaction rate, likely due to heterogeneous catalysis (entry 7). The nature of the base is also important for this reaction. Moderately strong K_3PO_4 (entry 1), K_2CO_3 (entry 10), and Cs_2CO_3 (entry 11) seemed to be suitable bases, whereas weaker bases like Na_2CO_3 (entry 9) or stronger bases such as KOH (entry 12) and *t*BuOK (entry 13) were almost ineffective. Of the solvents, 1,4-dioxane (entry 1) proved to be far superior to other solvents such as toluene (entry 14), DMF (entry 15), acetonitrile (entry 16), and ethanol (entry 17). Attempts to reduce the reaction temperature led to a significantly lower yield (entry 8 vs.

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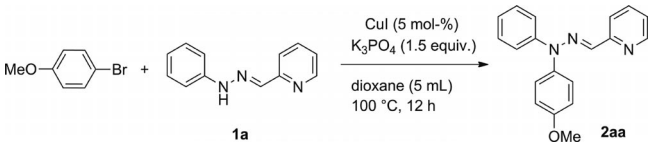
entry 1). It was also found that *p*-iodoanisole is more favorable for the reaction (entry 18), but that *p*-chloroanisole was unreactive under the conditions (entry 19).

Table 1. Optimization of the copper-catalyzed coupling reaction of pyridine-2-carbaldehyde *N*-phenylhydrazone (**1a**) with *p*-bromoanisole.[a]



1a 2aa

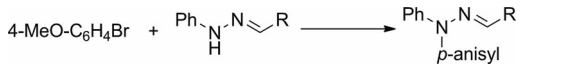
Entry	Variation from standard conditions	Yield [%][b]
1	none	83
2	no [Cu]	0
3	CuBr instead of CuI	71
4	CuCl instead of CuI	73
5	$CuBr_2$ instead of CuI	70
6	$Cu(OAc)_2$ instead of CuI	72
7	Cu powder instead of CuI	33
8	80 °C instead of 100 °C	67
9	Na_2CO_3 instead of K_3PO_4	6
10	K_2CO_3 instead of K_3PO_4	69
11	Cs_2CO_3 instead of K_3PO_4	79
12	KOH instead of K_3PO_4	trace
13	*t*BuOK instead of K_3PO_4	<5
14	toluene instead of 1,4-dixoane	58
15	DMF instead of 1,4-dixoane	–
16	MeCN instead of 1,4-dixoane, sealed tube	23
17	EtOH instead of 1,4-dixoane, sealed tube	33
18	*p*-iodoanisole instead of *p*-bromoanisole, 6 h	90
19	*p*-chloroanisole instead of *p*-bromoanisole	0

[a] Normal reagents and conditions: hydrazone (1 mmol), *p*-bromoanisole (1.5 mmol), CuI (0.05 mmol), base (1.5 mmol), solvent (5 mL), 100 °C, 12 h. [b] Isolated yield.

This reaction does not need an external ligand, which is unusual in homogenous copper-catalyzed C–N coupling reactions performed under relatively mild reaction conditions, particularly with aryl bromides as electrophilic coupling partners.[9,10d,10e,11] We speculated that the catalytic efficiency of copper salts is related to the presence of the 2-pyridyl group in the hydrazone substrate. To confirm this, a number of phenylhydrazones were prepared[12] and subjected to the coupling reaction with *p*-bromoanisole under the same conditions (Table 2). It can be observed from the results in Table 2 that the electronic effects of the R group did not affect the reaction of benzaldehyde hydrazones (entries 2–4, 8, and 9) and that the reactions of phenylhydrazones with a 3-pyridyl group (entry 5) or five-membered heterocyclic groups (entries 6 and 7) failed. Thus, only the 2-pyridyl group demonstrates the ability to activate CuI in this reaction.

The scope of the electrophilic coupling partners in the reaction was then examined under the optimized conditions (Table 3). In general, the reaction was insensitive to the electronic effects of aryl bromides but sensitive to their steric effects. For example, both *p*-electron-donating (**2aa** and

Table 2. Effect of R groups at the hydrazone end on the reaction.[a]



Entry	R	Yield [%]
1	2-pyridyl	83
2	phenyl	0
3	4-nitrophenyl	0
4	2-hydroxyphenyl	0
5	3-pyridyl	0
6	2-thienyl	0
7	2-furyl	0
8	4-(*N*,*N*-dimethyl)phenyl	0
9	4-(trifluromethyl)phenyl	0

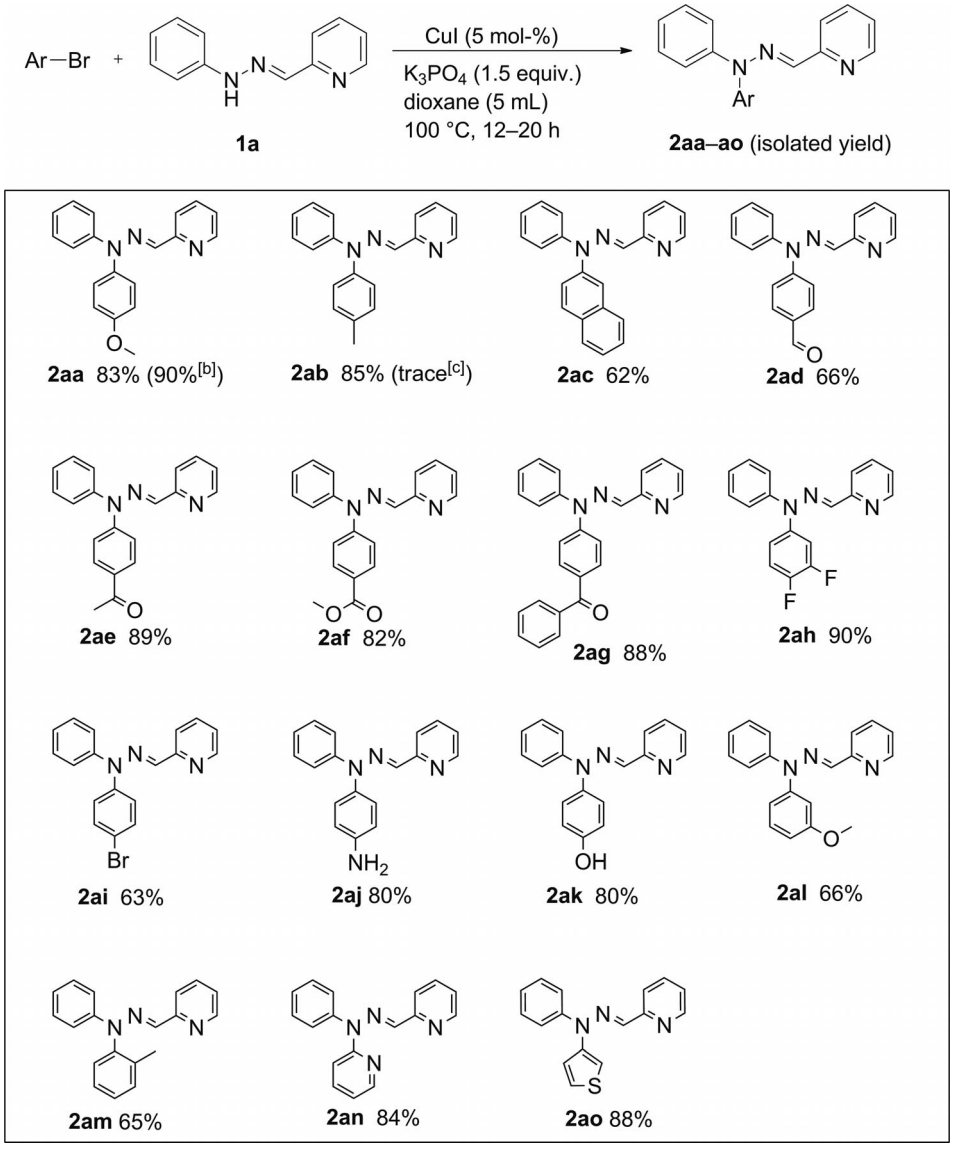
[a] Reagents and conditions: hydrazone (1 mmol), *p*-bromoanisole (1.5 mmol), CuI (0.05 mmol), K_3PO_4 (1.5 mmol), dioxane (5 mL), 100 °C, 12 h.

2ab) and -withdrawing (**2ad**, **2af**, **2ag**, and **2ah**) aryl bromides gave excellent yields except in the case of 4-formylphenyl bromide (**2ad**; the reason is unclear at present), but bromides with steric hindrance (**2ac**, **2al**, and **2am**) slowed the reaction, providing moderate yields with appreciable amounts of the starting material **1a** remaining. Free amino and hydroxy groups in the bromide substrates generally produced no adverse effect on the coupling reaction (**2aj** and **2ak**). Furthermore, heteroaryl bromides readily coupled to **1a** in high yields (**2an** and **2ao**). Again, it should be noted that iodides (**2aa**) perform better than the corresponding bromides, but that chlorides are not suitable substrates for the reaction (**2ab**).

Next, we explored the effect on the reaction of the aryl group at the amine end of pyridine-2-carbaldehyde hydrazones. Several *N*-aryl-substituted pyridine-2-carbaldehyde hydrazones were prepared[12] and treated with aryl bromides under the optimal conditions described above (Table 4). The coupling reactions with electron-neutral and -deficient aryl groups proceeded readily in most cases (**2ba**–**2bc** and **2ca**–**2cd**), whereas the yields of the reactions with heteroaryl bromides were not very satisfactory but acceptable (**2bd**, **2be**, **2cd**, and **2ce**). On the other hand, electron-rich aryl groups generally retarded the reaction (**2da**–**2de**); the yields were particularly poor when the electrophilic substrates were also electron-rich (**2da**) or sterically hindered (**2dc**).

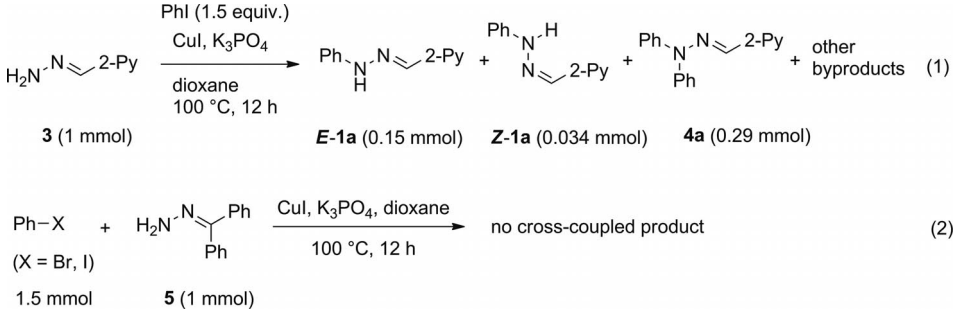
Aqueous H_2NNH_2 is a readily available, convenient hydrazine source from which nonsubstituted pyridine-2-carbaldehyde hydrazone (**3**) was readily prepared.[12] We wanted to utilize hydrazone **3** as a starting material for the synthesis of aryl-substituted hydrazones by a CuI-catalyzed process similar to that described above. Initially, a 1:1 molar ratio of bromobenzene/hydrazone **3** was used to obtain an *N*-monoarylated product. Unfortunately, hydrazone **3** failed to be arylated with bromobenzene; rather, cyclization of pyridine-2-carbaldehyde hydrazone took place to give a 1,2,3-triazolo heterocycle as a byproduct in a high yield of over 70%.[13] When bromobenzene was replaced with iodo-

Table 3. CuI-catalyzed arylation of pyridine-2-carbaldehyde *N*-phenylhydrazone with aryl bromides.[a]



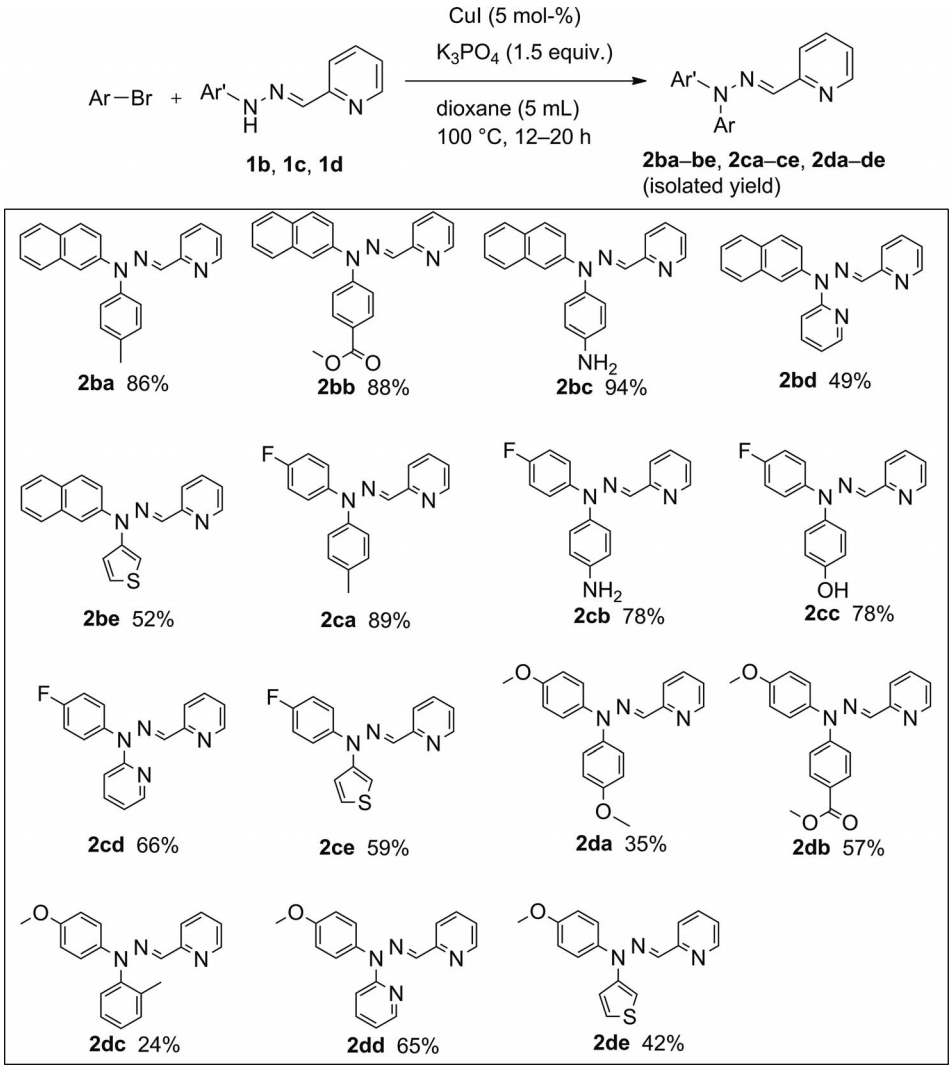
[a] Reagents and conditions: hydrazone (1 mmol), aryl bromide (1.5 mmol), CuI (0.05 mmol), K_3PO_4 (1.5 mmol), dioxane (5 mL), 100 °C, 12–20 h. [b] The iodide used. [c] The chloride used.

benzene, the coupling reaction occurred but afforded a complex distribution of products. The product mixture included mono- (both *E* and *Z* forms)[14] and diarylated products as well as other byproducts [Scheme 1, Eq. (1)]. Interestingly, diarylhydrazone **4a** was the predominant product. For comparison, benzophenone hydrazone **5**, a precursor



Scheme 1.

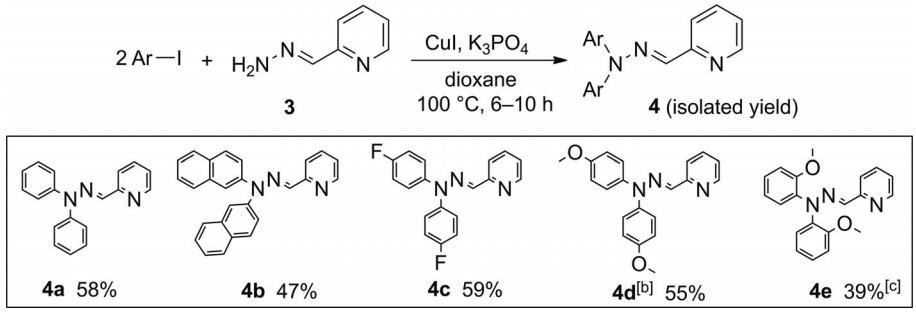
Table 4. CuI-catalyzed coupling reactions of pyridine-2-carbaldehyde *N*-arylhydrazones with aryl bromines.[a]



[a] Reagents and conditions: hydrazone (1 mmol), aryl bromines (1.5 mmol), CuI (0.05 mmol), K_3PO_4 (1.5 mmol), dioxane (5 mL), 100 °C, 12–20 h.

in the palladium-catalyzed arylhydrazine synthesis,[6,8] was also tested. In this case, no cross-coupled product was detected with either the bromide or iodide as the coupling partner [Scheme 1, Eq. (2)], which indicates once again that the 2-pyridyl group of the hydrazone substrate plays a special role in the CuI-catalyzed *N*-arylation reaction.

Table 5. CuI-catalyzed diarylation of pyridine-2-carbaldehyde hydrazone (**3**).[a]

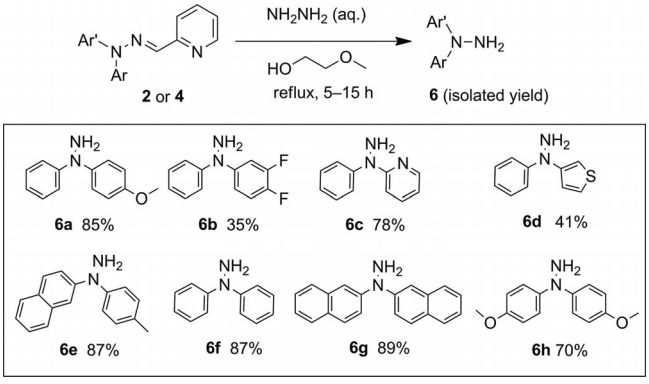


[a] Reagents and conditions: hydrazone (1 mmol), aryl iodide (2 mmol), CuI (0.05 mmol), K_3PO_4 (3.0 mmol), dioxane (5 mL), 100 °C, 6–10 h. Isolated yields are provided. [b] **4d** = **2da**. [c] Aryl iodide (3 mmol); significant amounts of the monoarylated product were obtained: 22% of (*E*)-**1e** and 15% of (*Z*)-**1e**.[14]

In view of the fact that the second arylation of pyridine-2-carbaldehyde hydrazone (**3**) proceeds more rapidly than the first, we attempted to transform hydrazone **3** directly into *N*,*N*-diarylhydrazones by using a 2:1 molar ratio of aryl iodide/hydrazone **3** in the coupling reaction (Table 5); several aryl iodides were chosen as arylating agents. We found that the diarylation reaction did not provide high yields of the desired products **4a**–**d**, mainly because there exists a competing ring-closing side-reaction of the starting hydrazone **3**.[13] In the case of *o*-iodoanisole (**4e**), steric factors further lower the yield of the diarylated product with appreciable amounts of the monoarylated product formed.

We then turned our attention to the cleavage of the protecting group in pyridine-2-carbaldehyde *N*,*N*-diarylhydrazones to release the corresponding *N*,*N*-diarylhydrazines. For this, acidic hydrolysis of the aldehyde/ketone hydrazones is the most commonly employed procedure. Unfortunately, we found that even strong acids such as hydrochloric acid or p-toluenesulfonic acid failed to hydrolyze pyridine-2-carbaldehyde *N*,*N*-diarylhydrazones to release the corresponding diarylhydrazines. However, *N*,*N*-diarylhydrazines can readily be freed by transimination of the hydrazones with H_2NNH_2 (Table 6). Several pyridine-2-carbaldehyde *N*,*N*-diarylhydrazones were treated with an aqueous solution of H_2NNH_2 with complete conversion (Table 6).

Table 6. Release of *N*,*N*-diaryhydrazines from pyridine-2-carbaldehyde diarylhydrazones.[a]



[a] Reaction conditions: diarylhydrazone (1 mmol), aqueous hydrazine (85%, 2 mL), 2-methoxyethanol (3 mL), reflux, 5–15 h.

Conclusions

We have presented an easy route to *N*,*N*-diarylhydrazines by the CuI-catalyzed arylation of pyridine-2-carbaldehyde hydrazones followed by a hydrazine exchange reaction. Our protocol offers several advantages over previously used methods: The simple copper salt works efficiently without the need for additional ligands, the catalyst is cheaper, lower loadings are required, and mild bases and relatively mild reaction temperatures are employed. It is worth noting that the 2-pyridylmethylene moiety in the hydrazone substrates serves not only as a "blocking group" for regioselectivity, but also as a "promoter", activating the copper precatalyst. This provides a useful example of the selection of protecting groups of substrates in metal-catalyzed coupling reactions, which can be exploited in future studies. The mechanism of the reaction is under investigation and the results will be reported in due course.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for all compounds prepared.

Acknowledgments

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[14] The *E* and *Z* isomers of the compound can be isolated and purified by chromatography.

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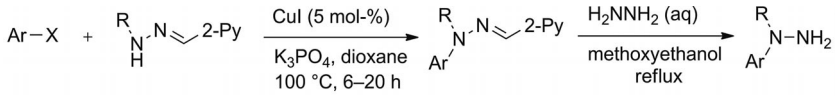

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