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Assembly of *N*,*N*-Disubstituted Hydrazines and 1-Aryl-1*H*-indazoles via Copper-Catalyzed Coupling Reactions

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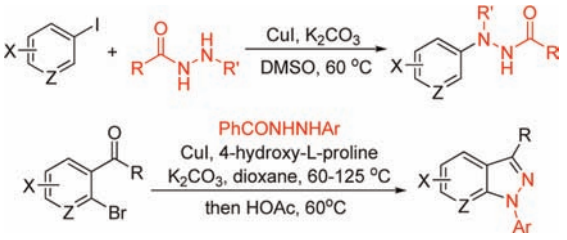
ABSTRACT



CuI-catalyzed coupling of *N*-acyl-*N*′-substituted hydrazines with aryl iodides takes place at 60−90 °C to afford *N*-acyl-*N*′,*N*′-disubstituted hydrazines regioselectively and thereby gives a facile method for assembling *N*,*N*-diaryl hydrazines. *N*-Acyl-*N*′-substituted hydrazines can also react with 2-bromoarylcarbonylic compounds at 60−125 °C under the catalysis of CuI/4-hydroxy-L-proline to provide 1-aryl-1*H*-indazoles.

In the past decades, a considerable number of bioactive *N*,*N*-disubstituted hydrazines have been discovered, which include sensory neuron inhibitors,[1] cell harm inhibitors,[2] α-adrenoceptor antagonists,[3] potential agents for the treatment of thrombolic disease,[4] PGI2 agonists,[5] papilloma virus inhibitors,[6] and D_1 dopamine receptor antagonists.[7] Additionally, *N*,*N*-disubstituted hydrazines are versatile intermediates for assembling azo heterocycles, such as indazoles,[8] indoles,[9] and 1,2,4-benzotriazines.[10]

Conventional methods for preparing *N*,*N*-diaryl hydrazines involve oxidation of diaryl amines and subsequent reduction of the resulting aryl diazoniums.[11] This approach normally suffers from multistep synthesis, harsh reaction conditions, and low yields. This drawback has stimulated some investigations on assembly of *N*,*N*-diaryl hydrazines via metal-catalyzed or metal-mediated reactions. Successful examples include Cu-catalyzed diarylation of *N*-acyl hydrazines,[12] Pd-catalyzed cross-coupling of benzophenone hydrazine with aryl halides,[13] Cu-catalyzed

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(2) Kuratani, K.; Nakahama, K.; Morita, I.; Murota, S. Phenylhydrazine derivative and cytotoxic preventive. JP 09110815, April 28, 1997.

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(5) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Shigeoka, S.; Hamada, S.; Kato, H.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1087.

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(7) Sasikumar, T.; Burnett, D.; Zhang, H.; Smith-Torhan, A.; Fawzi, A.; Lachowicz, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4543.

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(10) (a) Blatter, H.; Lukaszewskl. *Tetrahedron Lett.* **1968**, *22*, 2701. (b) Waldrep, T.; Rieder, B.; Thibault, T.; Canada, E. *J. Agric. Food Chem.* **1991**, *39*, 392. (c) Elliott, A. *J. Org. Chem.* **1980**, *45*, 3677.

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(12) Suzuki, H.; Yamamoto, A. *J. Chem. Res., Synop.* **1992**, 280.

(13) (a) Wagaw, S.; Yang, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2090.

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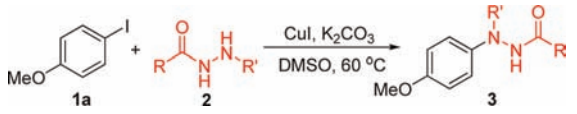
Table 1. CuI-Catalyzed Coupling of 4-Iodoanisole with *N*-Acyl-*N*′-substituted Hydrazines[a]



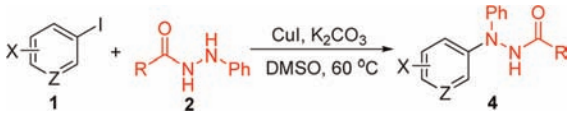
entry	R	R′	product	yield (%)[b]
1	Ph	Ph	**3a**	94[c]
2	Ph	Ph	**3a**	98
3	Me	Ph	**3b**	95
4	Bn	Ph	**3c**	70
5	2-furanyl	Ph	**3d**	98
6[d]	*t*-BuO	Ph	**3e**	76
7[d]	CF_3	Ph	**3f**	85
8	Ph	4-$MeOC_6H_4$	**3g**	94
9	Ph	4-$NO_2C_6H_4$	**3h**	97
10	Ph	3-ClC_6H_4	**3i**	96
11[e]	Ph	2-MeC_6H_4	**3j**	15
12[d]	Ph	*n*-Pr	**3k**	53
13[d]	Ph	Bn	**3l**	32

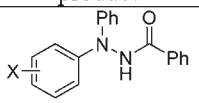
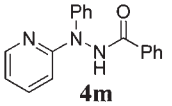
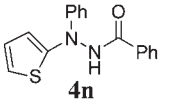
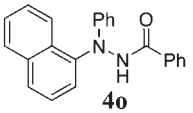
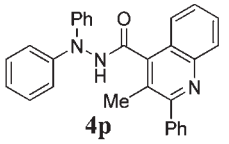
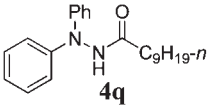
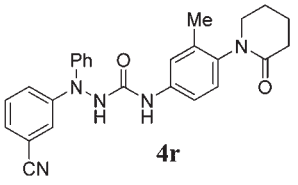
[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.6 mmol), CuI (0.04 mmol), K_2CO_3 (0.8 mmol), DMSO (1 mL), 60 °C, 20−30 h. [b] Isolated yield. [c] The reaction was carried out at 30 °C in the presence of 4-hydroxy-L-proline (0.08 mmol). [d] Stirred at 90 °C. [e] Stirred at 130 °C.

N-arylation of hydrazines with bismuthanes,[14] and addition of organometallic nucleophiles to symmetrical and unsymmetrical azo compounds.[15] During the studies on exploring the scope of Cu-catalyzed arylation by using unusual nucleophiles,[16,17] we revealed that *N*-acyl-*N*′-substituted hydrazines were excellent coupling partners, which could regioselectively react with aryl iodides and 2-bromoarylcarbonylic compounds under mild conditions. This advantage offers a facile method for synthesizing *N*,*N*-disubstituted hydrazines and 1-aryl-1*H*-indazoles. Herein, we wish to disclose our results.

As indicated in Table 1, we initially attempted the coupling of *N*′-phenylbenzohydrazide with 4-iodoanisole. This reaction worked well under the catalysis of 10 mol % CuI and 20 mol % 4-hydroxy-L-proline in DMSO at 30 °C to afford **3a** in 94% yield (entry 1). Further attempts revealed that ligand was not necessary if the reaction was carried out at 60 °C (entry 2). Under these conditions a series of *N*-acyl-*N*′-substituted hydrazines were examined. We were pleased that other *N*-acyl-*N*′-phenylhydrazines gave the corresponding coupling products with good yields (entries 3−7) and thereby allowing assembly of *N*,*N*-diaryl hydrazines with different protecting groups. The *N*-aryl

Table 2. CuI-Catalyzed Coupling of Aryl Iodides with *N*-Phenyl Hydrazides[a]



entry	product	yield (%)[b]
1	 **4a**: X = 4-Br	96
2	**4b**: X = 4-Ph	89
3[c]	**4c**: X = 4-COMe	95
4[c]	**4d**: X = 4-CO_2Me	96
5	**4e**: X = 3-OMe	97
6	**4f**: X = 3-CN	95
7[c]	**4g**: X = 3-NO_2	93
8	**4h**: X = 2-OMe	95
9	**4i**: X = 2-NHCOPh	98
10	**4j**: X = 2-CO_2Me	97
11	**4k**: X = 2-OH	82
12	**4l**: X = 2-NH_2	97
13	**4t**: X = 2-Me, 4-OMe	93
14	 **4m**	95
15	 **4n**	94
16	 **4o**	96
17	 **4p**	45
18	 **4q**	96
19	 **4r**	73

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol), CuI (0.04 mmol), K_2CO_3 (0.8 mmol), DMSO (1 mL), 60 °C, 20−30 h. [b] Isolated yield. [c] Stirred at 90 °C.

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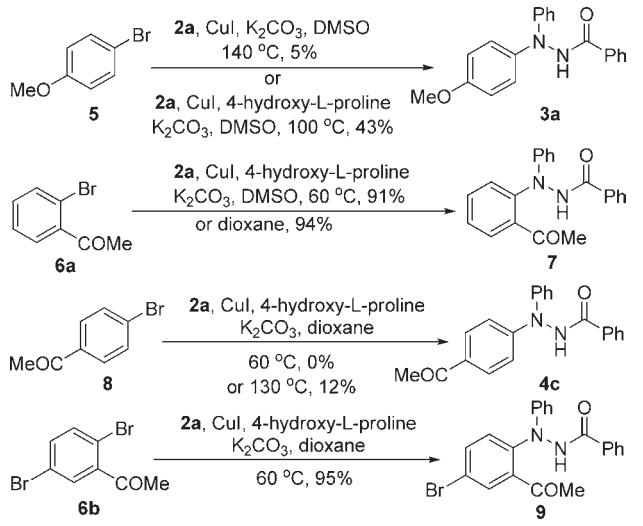
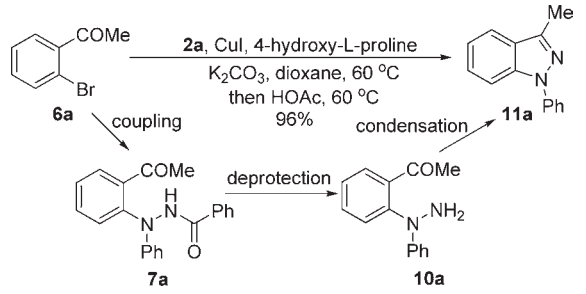
(17) For related studies from other groups, see: (a) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803. (b) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 348. (c) Cortes, M.; Nguyen, B.; Cuevas, J.; Pennypacker, K.; Antilla, J. C. *Org. Lett.* **2010**, *12*, 1316. (d) Racine, E.; Monnier, F.; Vors, J.; Taillefer, M. *Org. Lett.* **2011**, *13*, 2818.

Scheme 1



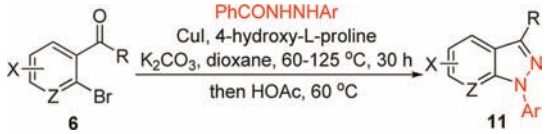
Scheme 2

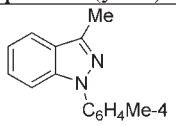
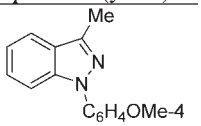
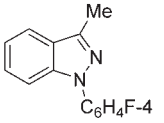
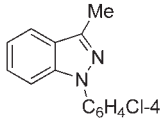
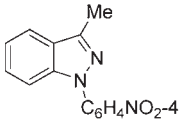
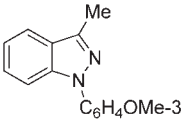
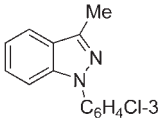
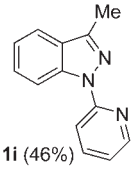
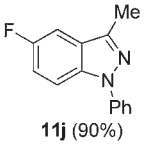
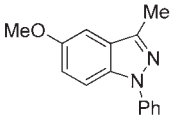
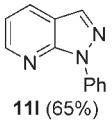
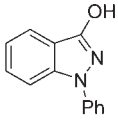
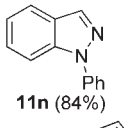
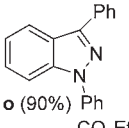
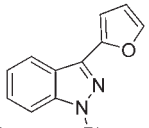
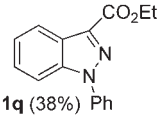


hydrazides with electron-donating as well as electron-withdrawing substituents at the *meta*- or *para*-positions also proceeded well (entries 8−10). However, a low yield was obtained when an *ortho*-substituted *N*-aryl hydrazide was used (entry 11), indicating that the steric hindrance of aryl hydrazides plays a key role in the coupling reaction. Additionally, preparation of *N*-aryl-*N*-alkyl hydrazides was proven possible from *N*-alkyl hydrazides (entries 12 and 13). In these cases the yields were not satisfactory due to incomplete conversion, which illustrated that subtle change in electronic nature of substituted hydrazides could alter the reaction process.

In another set of experiments, we explored the reaction scope via coupling *N*-phenyl hydrazides with various aryl iodides, and the results were summarized in Table 2. To our delight, both electron-rich and electron-deficient aryl iodides were compatible with these conditions, providing the corresponding *N*,*N*-diaryl hydrazides in 80−98% yields (entries 1−12). Interestingly, six *ortho*-substituted aryl iodides worked well (entries 8−13), indicating that steric hindrance of aryl iodides has little influence on coupling reaction. This phenomenon is in contrast with that observed with sterically hindered hydrazides.

Table 3. One-pot Reaction Process for Assembly of 1-Aryl-1*H*-indazoles[a]



entry	product (yield)[b]	entry	product (yield)[b]
1	 **11b** (92%)	2	 **11c** (94%)
3	 **11d** (93%)	4	 **11e** (90%)
5[c]	 **11f** (57%)	6	 **11g** (85%)
7	 **11h** (89%)	8[c]	 **11i** (46%)
9	 **11j** (90%)	10	 **11k** (92%)
11	 **11l** (65%)	12[c,d]	 **11m** (83%)
13	 **11n** (84%)	14[c]	 **11o** (90%)
15[c]	 **11p** (49%)	16	 **11q** (38%)

[a] Reaction conditions: **6** (0.5 mmol), ArNHNHCOPh (0.6 mmol), CuI (0.05 mmol), 4-hydroxy-L-proline (0.1 mmol), K_2CO_3 (1.0 mmol), dioxane (1 mL), 60 °C, 30 h; then HOAc (2 mL), 60 °C. [b] Isolated yield. [c] The coupling reaction was carried out at 125 °C. [d] Methyl 2-bromobenzoate was used as the starting material.

Two heterocycle-embodied *N*,*N*-diaryl hydrazides **4m** and **4n** (entries 14 and 15) were successively obtained from 2-iodopyridine and 2-iodothiophene, respectively. Another notable feature is that a wide range of functional groups, including hydroxy, amino, ketone, ester, amide, nitro, and

bromo, were well tolerated to these conditions. These characters would allow diversity synthesis of *N*,*N*-diaryl hydrazides. Indeed, by employing some functionalized *N*-phenyl hydrazides, neurokinin receptor antagonist **4p** (entry 17),[1] cell harm inhibitor **4q** (entry 18),[2] and compound **4r** (entry 19), that is useful for the treatment of thrombolic disease,[4] were effectively prepared.

When 4-bromoanisole was utilized as coupling partner, poor conversion was observed even at 140 °C (Scheme 1). Using 4-hydroxy-L-proline as a promoter could help the coupling, but the reaction yield was still poor. However, CuI/4-hydroxy-L-proline catalyzed coupling of 2-bromophenyl-acetone **6a** with **2a** could complete at 60 °C to afford N-aryl hydrazide **7** with a good yield in either DMSO or dioxane. This result implied that there is an *ortho*-substituent effect[18] directed by an acyl group in this case. This hypothesis was further supported by poor conversion of 4-bromophenylacetone **8** to **4c** even at 130 °C and exclusive formation of *N*-aryl hydrazide **9** from dibromide **6b**.

The easy coupling of 2-bromoarylcarbonylic compounds caused by their *ortho*-acyl groups prompted us to design a one-pot reaction process for preparing 1-aryl-1*H*-indazoles, a class of biologically important heterocycles.[19,20] As outlined in Scheme 2, we believed that the coupling products could undergo deprotection and subsequent intramolecular condensation to afford 1-aryl-1*H*-indazoles. After some attempts, we found that formation of 3-methyl-1-phenyl-1*H*-indazole **11a** from **6a** could be achieved by adding HOAc after coupling reaction was completed.

This one-pot reaction process was then checked by varying aryl bromides and *N*-aryl hydrazides. As summarized in Table 3, a number of *N*-aryl hydrazides bearing either electron-donating or electron-withdrawing groups could be used for obtaining the corresponding 1-substituted 3-methylindazoles (entries 1−7). The yields are generally excellent except for a nitro-substituted product, which might probably result from the poor nucleophility of the corresponding *N*-aryl hydrazide. The similar problem was observed when a pyridine-embodied substrate was utilized (entry 8). It seemed that electronic nature of aryl bromides has little influence to this process, as evident from the **11j** and **11k** that were obtained in similar yields (entries 9 and 10). Further investigations indicated that the method was amenable to 1-(2-bromopyridin-3-yl)ethanone (entry 11) and 2-bromophenylacetone with different α-substituents (entries 12−16), although in some cases the yields were not so satisfactory.

In conclusion, we have discovered a convenient method for assembling *N*,*N*-disubstituted hydrazines, which relies on a CuI-catalyzed coupling of aryl iodides with *N*-acyl-*N*′-substituted hydrazines. We also revealed that CuI/4-hydroxy-L-proline catalyzed coupling of aryl hydrazides with 2-bromoarylcarbonylic compounds worked under mild conditions, thereby providing a facile method for preparing 1-aryl-1*H*-indazoles. Various functional groups were found to tolerate these reaction conditions, and therefore these methods may find applications in organic synthesis.

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Supporting Information Available. Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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