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CuI-Mediated Cross-Coupling of Aryl Halides with Oximes: A Direct Access to *O*-Aryloximes

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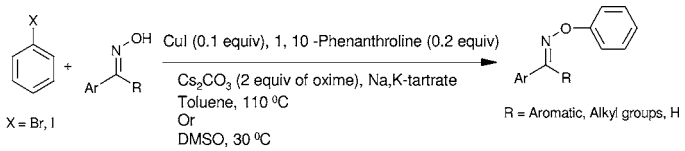
ABSTRACT



The first Cu-catalyzed cross-coupling of aromatic oximes and haloarenes is reported. This one-step formation of the ═N–O–Ar linkage gives access to a range of oxime ethers in good to moderate yields.

O-Aryloxime ethers are attractive synthetic targets because of their considerable application potential in medicinal and bioorganic chemistry. For example, some benzisoxazole derivatives have been reported as inhibitors of protein chaperone Hsp 90[1a] and monoamine oxidase.[1b] Some others show good cytokinin-like[1c] and neuroleptic[1d] activities. 1,2-Oxazines are NO-prodrugs[2a] and show anticholinesterase activity,[2b] and molecules like 6-aryl-3,6-dihydro-1,2-oxazines are mGluR1 receptor antagonists.[2c] Recently, some bisaryl-oxime ethers were found to be potent inhibitors of trans-thyratin amyloid fibril formation.[3] Despite their potential applications, the synthesis of *O*-aryloxime ethers remains a challenge. As a result, there is a need to develop a general synthetic method for *O*-aryloxime ethers.

Available literature approaches for the preparation of *O*-aryl oxime ethers essentially deal with the reaction of the sodium salt of an oxime with fluorobenzene derivatives,[4a] reaction of aldehydes/ketones with *O*-phenylhydroxylamine,[3] or reaction of oximes with aryl nitrates[4b]/diazonium salts.[4c]

However, these procedures lack generality and cannot be used with other haloarenes such as iodo- and bromobenzenes. A serendipitous intramolecular coupling of 2-iodo-2′,5-dichlorobenzophenone oxime (**1**) to yield the corresponding benzisooxazole derivative (**1a**) under standard Sonogashira conditions was reported in the literature.[5] This formed the basis for our exploratory work to develop a simple and general method for the synthesis of *O*-aryloxime ethers.

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(1) (a) Mailliet, P.; Ruxer, J. M.; Thompson, F.; Luc, C. C. New 3-aryl-1,2-benzisoxazole derivatives, compositions containing them and their use for treating cancer. French Patent FR 288236, August 25, 2006. (b) Yoshimi, K.; Kozuka, M.; Sakai, J.; Lizawa, T.; Shimizu, Y.; Kaniko, I.; Kojima, K.; Iwata, N. *Jpn. J. Pharmacol.* **2002**, *88*, 174. (c) Ricci, A.; Carra, A.; Torelli, A.; Maggiali, C. A.; Vicini, P.; Zani, F.; Branca, C. *Plant Growth Regul.* **2001**, *34*, 167. (d) Strupczewski, J. T.; Allen, R. C.; Gardner, B. A.; Schmid, B. L.; Stache, U.; Glamkowski, E. J.; Jones, M. C.; Ellis, D. B.; Huger, F. P.; Dunn, R. W. *J. Med. Chem.* **1985**, *28*, 761.

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(3) (a) Johnson, S. M.; Petrassi, H. M.; Palaninathan, S. K.; Mohamed-mohaideen, N. N.; Purkey, H. E.; Nichols, C.; Chiang, K. P.; Walkup, T.; Sacchettini, J. C.; Sharpless, K. B. and Kelly, J. W. *J. Med. Chem.* **2005**, *48*, 1576. (b) Blake, J. A.; Pratt, D. A; Lin, S.; Walton, J. C.; Mulder, P.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 3112.

(4) (a) Mooradian, A.; Dupont, P. E. *J. Heterocycl. Chem.* **1967**, *4*, 441. (b) Jacob, B. B. *Synthesis* **1975**, 782. (c) Nesynov, E. P. *Zh. Org. Khim.* **1976**, *12*, 1955.

(5) Coffen, D. L.; Schaer, B.; Bizzarro, F. T.; Chung, J. B. *J. Org. Chem.* **1984**, *49*, 296. Reaction conditions: $(PPh_3)_2PdCl_2$−CuI/Et_3N−CH_2Cl_2.

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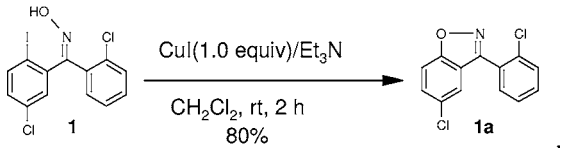
We repeated the same experiment with the reported reaction conditions,[5] and to our surprise, both Pd(II) and Pd(0) furnished product **1a** in 80% yield after column chromatography. This led us to investigate the role of Pd and CuI. The oxime remained unchanged in control experiments [either $(PPh_3)_2PdCl_2$ or $(PPh_3)_4Pd$)] in the absence of CuI. Interestingly, when only CuI (with no Pd) was used product **1a** was formed in 80% isolated yield (Scheme 1).

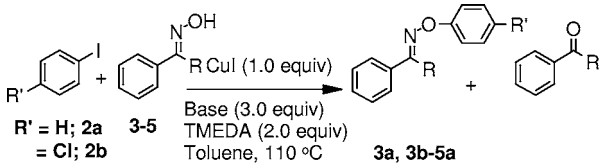
Scheme 1. CuI-Catalyzed Intramolecular Cyclization of 2-Iodo-2′,5-dichlorobenzophenone Oxime



These experimental results clearly suggested that the use of Pd is not necessary, and we proceeded with Cu(I) for the intermolecular version of this reaction.

Iodobenzene (**2a**) and acetophenone oxime (**3**) were subsequently used as model substrates to find conditions for intermolecular coupling. Interestingly, no reaction took place under the same conditions, and replacing the solvent by toluene and heating to reflux was not beneficial. However, upon replacing Et_3N by K_2CO_3 or Cs_2CO_3, **3** was found to furnish *O*-phenylacetophenone oxime (**3a**) in the presence of CuI (1.0 equiv) at 110 °C (Table 1). 4-Chloroiodobenzene

Table 1. CuI-Catalyzed Intermolecular Cross-Coupling of Oximes **3**−**5** with Iodoarenes



3; acetophenone oxime, **4**; benzophenone oxime, **5**; fluorenone oxime

entry	oxime	Ar−I	base/ ligand	time (h)	product[a] (yield, %)
1	**3**	**2a**	K_2CO_3	2	**3a** (20)
2	**3**	**2a**	Cs_2CO_3	2	**3a** (40)
3	**3**	**2a**	K_2CO_3/TMEDA	2	**3a** (30)
4	**3**	**2a**	Cs_2CO_3/TMEDA	2	**3a** (56)
5	**3**	**2b**	Cs_2CO_3	2	**3b** (15)
6	**4**	**2a**	Cs_2CO_3/TMEDA	2	**4a** (50)
7	**5**	**2a**	Cs_2CO_3/TMEDA	2	**5a** (10)

[a] Deoximation was observed in all cases.

(**2b**) also reacted with **3** in the presence of CuI and Cs_2CO_3 in toluene to furnish oxime ether **3b** (15%).

Although Cs_2CO_3 seemed to give a cleaner reaction, considerable deoximation was observed in almost all cases. With *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)[6] as the ligand for CuI, the yields improved (Table 1).

Under the reaction condition involving Cs_2CO_3 and TMEDA, benzophenone oxime (**4**) and fluorenone oxime (**5**) produced the corresponding oxime ethers **4a** and **5a** in 50% and 10% yields, respectively. But in both cases, along with the oxime ether, the ketones formed by deoximation were isolated. While the decomposition of oxime ethers by the cleavage of the N−O bond[3] to form phenol and aryl nitriles is known, the mechanism of formation of the carbonyl compound is not clear.

We subsequently explored the feasibility of this cross-coupling reaction using a catalytic amount of CuI with 1,10-phenanthroline as the ligand.[7] Under these conditions, compounds **3, 4**, as well as 1-tetralone oxime (**7**), 4-methoxyacetophenone oxime (**9**), and 4-chloroacetophenone oxime (**10**) produced the corresponding oxime ethers when reacted with iodobenzene (**2a**) in good yields (Table 2). Compound **5**, however, furnished **5a** in only 15% yield, and a ketoxime bearing α-benzylic hydrogens such as deoxybenzoin oxime (**8**) furnished the corresponding oxime ethers (**8a**) in poor yields. Under these conditions, **3** produced **3b** and *O*-(4-nitrophenyl)acetophenone oxime (**3d**) in moderate yields when reacted with **2b** and 4-nitroiodobenzene (**2d**). The structure of **3d** was unambiguously proved using single-crystal X-ray diffraction (Figure 1), which also suggest the

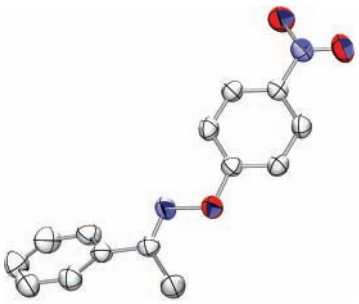


Figure 1. ORTEP diagram of the single-crysytal X-ray structure of *O*-(4-nitrophenyl)acetophenone oxime **3d**.

geometrical purity of the oxime ether obtained under our experimental conditions.

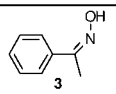
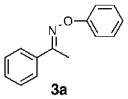
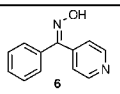
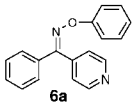
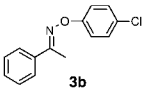
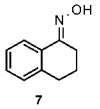
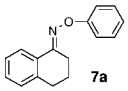
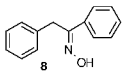
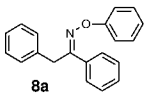
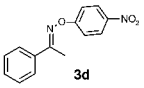
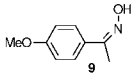
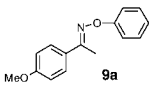
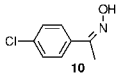
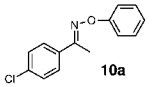
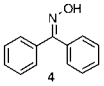
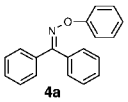
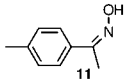
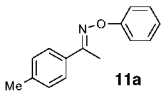
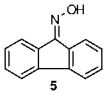
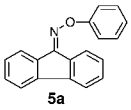
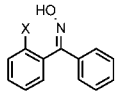
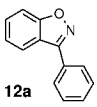
Since deoximation continued to occur, we speculated that possibly Cu(II),[8] generated during the course of the reaction, was responsible for facile deoximation, and hence, Na,K-tartrate (2.0 equiv with respect to CuI) was used as a chelating agent for Cu(II). This led to an increment in the yield of **5a** (45%). Cross-coupling of **3** with various iodobenzenes (**2b**−**d**) showed that iodobenzenes with electron-

(6) Carril, M.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2006**, *8*, 1467.

(7) (a) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. (b) Kunz, K.; Scholz, U.; Gazner, D. *Synlett* **2003**, 2428.

(8) When water was chosen as solvent, **1** produced **1a** in comparable yields (80%) and the aqueous extract showed a blue color, indicating the formation of Cu(II).

Table 2. Cross-Coupling of Ketoximes with Haloarenes with Catalytic CuI in Refluxing Toluene

entry	oxime	Ar-X	product	time (h)[a] [yield (%)]	entry	oxime	Ar-X	product	time (h)[a] [yield (%)]
1	 3	 2a	 3a	2 [67] 2 [65][a]	8	 6	2a	 6a	2 [40]
2	3	 2b	 3b	1.5 [76] 2 [46][a]	9	 7	2a	 7a	0.6 [80] 1 [49][a]
3	3	 2c	-	1	10	 8	2a	 8a	1.5 [45] 1.5 [15][a]
4	3	 2d	 3d	1.5 [75] 1.5 [48][a]	11	 9	2a	 9a	1.5 [52] 2 [48][a]
5	3	 2e	3a	1 [30]	12	 10	2a	 10a	1.5 [49] 1.5 [46][a]
6	 4	2a	 4a	1 [67] 2 [65][a]	13	 11	2a	 11a	1.5 [47]
7	 5	2a	 5a	1 [45] 1 [15][a]	14	 12; X = I, 13; X =Br	-	 12a	0.25 [80][b] 0.75 [90][c]

[a] Refers to the time/[yield] in the absence of tartrate. [b] Refers to the time/[yield] for **12**. [c] Refers to the time/[yield] for **13**.

withdrawing groups (**2b**, **2d**; entries 2 and 4, Table 2) reacted to give good yields. But, 4-methoxyiodobenzene (**2c**) did not react at all. Bromobenzene (**2e**) did couple with **3** to furnish **3a**, but in low yield (30%).

In order to investigate the role of Na,K-tartrate and the source of ketone formed during the course of our reaction conditions, a number of control experiments were done. It is known in the literature that Cu(II) chelates with oximes and subsequently results in deoximation.[9] When a mixture of acetophenone oxime **3** and $CuSO_4 \cdot 5H_2O$ (10 mol %) was stirred in toluene at reflux, complete degradation of the oxime into acetophenone was observed after 24 h. On the other hand, when the oxime was added to a premixed $CuSO_4 \cdot 5H_2O$ (10 mol %) and Na,K-tartrate (20 mol %)[10] in toluene and stirred at reflux, it remained unchanged after 24 h. When similar experiments were carried out using acetophenone oxime ether **3a** instead of oxime, it remained unchanged under both experimental conditions. It thus provides two important pieces of information: (i) it is the oxime which is undergoing cleavage and (ii) Na,K-tartrate forms a complex with Cu(II) and prevents it from chelating to the oxime.

The need for a base and a catalytic amount of CuI suggested a possible $S_{RN}Ar$ mechanistic pathway for this reaction. The formation of **3b** (from **2b**) rules out the possibility for an addition−elimination pathway for this reaction, and in addition, the lack of a reaction between **2c** and **3** supports the formation of an *electrophilic* aryl radical followed by the facile coupling with the oximate anion.[11]

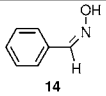
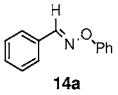
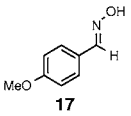
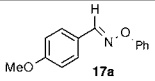
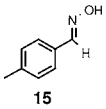
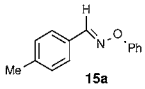
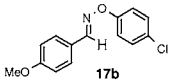
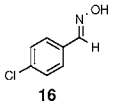
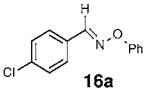
A competition experiment carried out with **3** and an equimolar mixture of **2a** and **2b** in the presence of Cs_2CO_3, CuI (10 mol %), and 1,10-phenanthroline (20 mol %) led to

(9) (a) Kaminskaia, N. V.; Kostić, N. M. *J. Chem. Soc., Dalton Trans.* **2001**, 1083. (b) Attanasi, O.; Gasperoni, S.; Carletti, C.; *J. Prakt. Chem.* **1980**, 1063. (c) Onindo, C. O.; Sliva, Y, T.; Jankowska, T. K.; Fritsky, I. O.; Buglyo, P.; Pettit, L. D.; Kozlowski, H.; Kiss, T. *J. Chem. Soc., Dalton Trans.* **1995**, 3911.

(10) (a) Sing, E. J.; Dey, A. K. *Z. Analyt. Chem.* **1959**, *165*, 81. (b) Baffi, F.; Dadone, A.; Frache, R. *Chromatographia* **1976**, *9*, 280. These references clearly suggest that Cu(II) forms a stable complex above 2.0 equiv of tartrate.

(11) A control experiment was carried out by flushing the reaction vessel with oxygen. The reaction was then carried out with the standard reaction conditions under oxygen atmosphere, resulting in deoximation (up to 80%). No oxime ether formation was observed.

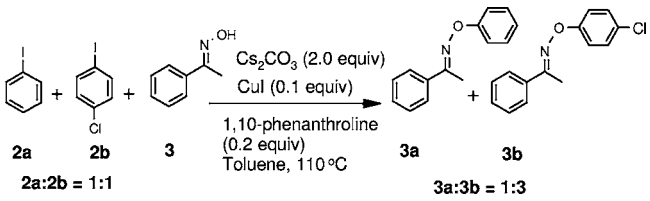
Table 3. Cross-Coupling of Aldoximes with Haloarenes with Catalytic CuI in DMSO at 30 °C

entry	oxime	Ar-X	product	time (h)[a] [yield(%)]	entry	oxime	Ar-X	product	time (h)[a] [yield (%)]
1	 **14**	**2a**	 **14a**	2 [45]	4	 **17**	**2a**	 **17a**	1 [48]
2	 **15**	**2a**	 **15a**	1.5 [67] 3 [50][a]	5	**17**	**2b**	 **17b**	2 [40]
3	 **16**	**2a**	 **16a**	1.5 [25] 1 [5][a]					

[a] Refers to the time/[yield] in the absence of tartrate.

the formation of **3a** and **3b** in a 1:3 ratio (Scheme 2). This result supports the suggested mechanism.

Scheme 2. Cross-Coupling of Acetophenone Oxime (**3**) with a Mixture of **2a** and **2b**



The cross-coupling of aldoximes with haloarenes did not work at all under the conditions used for ketoximes, and rapid deoximation was observed. However, upon reaction of **14** with **2a** at 30 °C in DMSO in the presence of Cs_2CO_3, catalytic CuI, 1,10-phenanthroline, and Na,K-tartrate, **14a** was isolated in 45% yield. Under identical conditions, 4-methylbenzaldoxime (**15**), 4-chlorobenzaldoxime (**16**), as well as 4-anisaldoxime (**17**) produced corresponding oxime ethers with **2a** (Table 3).

Moreover, the DMSO conditions were also found to be compatible with ketoximes. For example, **4** produced **4a** (62%, 1 h) and **7** produced **7a** (56%, 1.5 h).

In conclusion, the cross-coupling of haloarenes with aromatic ketoximes and aldoximes has been successfully accomplished using a catalytic amount of CuI in toluene or in DMSO and Cs_2CO_3 as the base. The inter- as well as intramolecular reactions are rapid, and *O*-aryloxime ethers are produced in good to acceptable yields. The application of this methodology on substrates having other functional groups is being actively investigated in our laboratory, and the results will be reported in due course.

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Supporting Information Available: Representative experimental procedures and ^1H NMR, ^{13}C NMR, and HRMS characterization data for all new compounds; X-ray data for compound **3d** (CCDC No. CCDC 647523) (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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