SHORT COMMUNICATION

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Cesium Carbonate Promoted Direct Arylation of Hydroxylamines and Oximes with Diaryliodonium Salts

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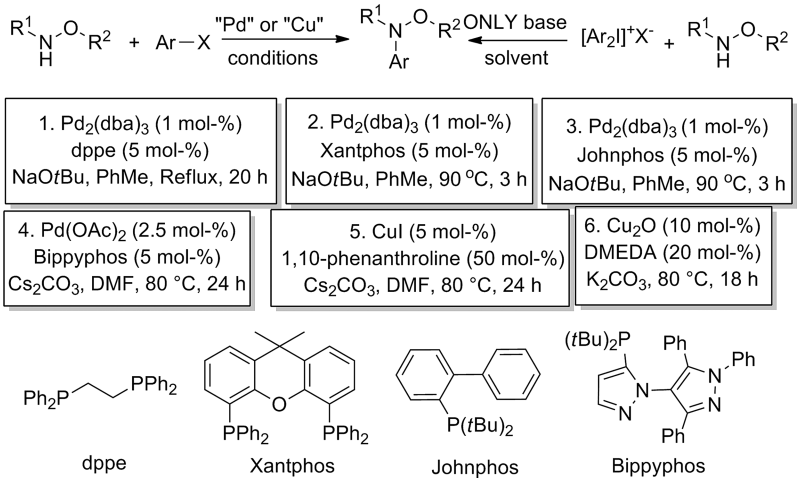
A transition-metal-free approach for the arylation of hydroxylamines and oximes with diaryliodonium salts was developed. The reaction proceeded smoothly at room temperature in the presence of cesium carbonate. As a result, a wide range of *N*- and *O*-arylated hydroxylamines were synthesized in good to excellent yields (45–98 %).

Introduction

Introduction of new carbon–heteroatom bonds by direct arylation of hydroxylamine derivatives has received particular interest owing to the potential preparation of useful intermediates and valuable chemicals containing nitrogen–oxygen bonds.[1] Notably, *N*-arylhydroxylamines can be converted into protected 2-hydroxylanilines by either a Bamberger rearrangement or a disproportionation process depending on the reaction conditions employed.[2] Another representative sample is *N*-benzoyl-*N*-phenylhydroxylamine, which is often used as metal chelator in the photometric determination and even separation of tantalum, vanadium, niobium, and other metal ions.[3]



Scheme 1. Reaction conditions for the arylation of hydroxylamines. dba = dibenzylideneacetone, DMEDA = *N*,*N*′-dimethylethylenediamine.

Reported approaches for the arylation of hydroxylamines essentially deal with transition-metal-catalyzed coupling reactions of hydroxylamines with aryl halides.[4] Several catalytic systems involving copper and palladium in combination with various ligands were developed over the past decade (Scheme 1). However, the drawbacks of transition-metal catalysis, such as high economic cost, toxicity, and a major problem regarding purification, have received much consideration recently. As such, the development of methods for the metal-free arylation has become a rapidly growing area of extensive research.[5] Amongst these methods,

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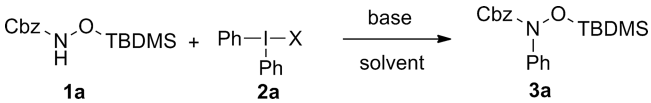
the arylation of nucleophiles by using diaryliodonium salts without transition-metal catalysts was achieved in an oxidative activation strategy.[6,7] The successful protocols included the *C*-arylation of electron-rich aromatic compounds,[7b–7d] *N*-heteroarenes,[7e,7f] and naphthalene;[7g] *O*-arylation of phenols, alcohols, and carboxylic acids;[7h–7l] *N*-arylation of anilines[7m] and aqueous ammonia;[7n] *S*-arylation of arylsulfinic acid salts;[7o] and even the dearomatizating arylation of phenols[7p] and indole derivatives.[7q] The arylation of *N*-hydroxylcarbamates with diphenyliodonium bromide was briefly reported in 1980, and in the case of *N*-hydroxyl-*N*-methylcarbamate, the subsequent [3,3] sigmatropic rearrangement was also found to afford 2-aminophenols.[8] As part of our ongoing research program directed towards the exploitation of *N*-arylations, we previously reported the metal-free *N*-arylation of carbazoles and the *C*-arylation of tetrahydrocarbazoles with diaryliodonium salts mediated by KO*t*Bu.[9] Within this paper, we present our results on the efficient arylation of hydroxylamines by using diaryliodonium(III) salts under transition-metal-free conditions at room temperature.

Table 1. Screening of the reaction conditions for the metal-free arylation of hydroxylamines.[a]



1a 2a 3a

Entry	X	Base	Solvent	Yield[b] [%]
1	OTf	KO*t*Bu	toluene	91
2	OTf	Cs_2CO_3	toluene	97
3	OTf	K_2CO_3	toluene	46
4	OTf	KOH	toluene	94
5	OTf	LiOH	toluene	15
6	OTf	NaH	toluene	51
7	OTf	Et_3N	toluene	trace
8	OTf	Cs_2CO_3	DCE[c]	78
9	OTf	Cs_2CO_3	THF	61
10	OTf	Cs_2CO_3	DMF	trace
11	OTf	Cs_2CO_3	CH_3CN	50
12	OTs	Cs_2CO_3	toluene	81
13	BF_4	Cs_2CO_3	toluene	93
14	Br	Cs_2CO_3	toluene	82

[a] Reaction conditions: **1a** (0.25 mmol), diphenyliodonium salt (0.3 mmol, 1.2 equiv.), base (0.375 mmol, 1.5 equiv.), solvent (1.0 mL), r.t., 6 h. [b] Yield of isolated product. [c] DCE = 1,2-dichloroethane.

Results and Discussion

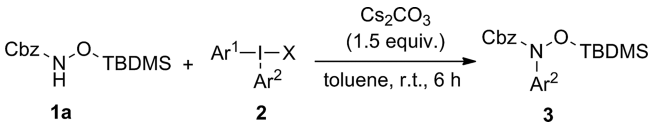
In preliminary studies, we investigated the reaction of *N*-Cbz-*O*-TBDMS-hydroxylamine (**1a**; Cbz = benzyloxycarbonyl, TBDMS = *tert*-butyldimethylsilyl) with diphenyliodonium triflate (Ph_2IOTf, **2a**) in the presence of KO*t*Bu as the base. To our delight, this reaction took place without any metal catalyst or ligand, and 91% yield of desired *N*-phenylhydroxylamine (**3a**) was achieved in toluene at room temperature (Table 1, entry 1). As shown in Table 1, after examining a series of bases and solvents, the best results were obtained with cesium carbonate as the base, and the reaction proceeded smoothly in toluene to give the product in an excellent yield of 97% (Table 1, entries 2–11). Polar aprotic solvents such as *N*,*N*-dimethylformamide (DMF) only gave a trace amount of the desired product. Evaluation of different diphenyliodonium anions showed that the nature of the counteranion did not have a significant influence on the yield of the desired products; diphenyliodonium salts with different anions worked efficiently, although TfO^- as the counteranion gave a better yield than BF_4^-, TsO^- (tosylate), and Br^- (Table 1, entries 12–14).

Subsequently, with the optimal conditions in hand, we examined the structural diversity of the various iodonium salts as the coupling partners; notably, a wide variety of functionalities regardless of the electronic nature of the substituents, for example, chloro and bromo and electron-donating groups such as methoxy and alkyl and electron-withdrawing groups including a nitro substituent on the aromatic ring, were well tolerated in the arylation of the hydroxylamines (Table 2, entries 1–7). The transfer of a *p*-methoxyphenyl group to give product **3g** was achieved in moderate yield of 61% owing to byproduct formation (Table 2, entry 6).[10] Interestingly, steric bulk of the iodonium salts did not affect the reactivity, and 86% yield of the product was achieved with bis(2,4,6-trimethylphenyl)-iodonium triflate as the arylating reagent (Table 2, entry 8). Notably, unsymmetrical salt **2k** ([(Ph)I(mesityl)]BF_4) preferentially transferred the bulky mesityl group to the desired product in a yield of 83% with a Ph/mesityl ratio of 24:59 (Table 2, entry 10). In connection with the influence of the electronic properties on the reactivity, 4-methoxy-4′-nitrodiphenyliodonium salt was allowed to react with **1a** under the standard conditions; selective transfer of the *p*-nitrophenyl group to the corresponding product in 58% yield was observed, which is in contrast to the result obtained for the arylation reaction performed with metal catalysts.[11] Upon using [(Ph)I(2-thienyl)]OTf under the standard conditions, **3a** was formed exclusively. Unfortunately, almost no reaction took place with [(2-thienyl)$_2$I]OTs as the coupling partner.

To further probe the scope of this reaction, a range of hydroxylamine derivatives were *N*-phenylated under the established conditions with diphenyliodonium triflate. Generally, the conditions proved to be effective for a variety of hydroxylamines bearing both nitrogen protecting groups [*tert*-butoxycarbonyl (Boc), Cbz] and oxygen substituents, including TBDMS, *tert*-butyldiphenylsilyl (TBDPS), benzyl (Bn), and methyl groups (Table 3, entries 1–7). The reactions gave the arylated products in excellent yields of 85–98%. Coupling of *N*-PhCO-*O*-Me-hydroxylamine with diphenyliodonium triflate resulted in corresponding product **4a** in a moderate yield of 45% even at a higher temperature of 60 °C (Table 3, entry 8).

Intrigued by the properties of *O*-arylated hydroxylamines, which could undergo cleavage of the N–O bonds and sequential rearrangement to interesting compounds, we treated BocNHOH with diphenyliodonium triflate by using

Table 2. Scope of diverse iodonium salts in the arylation reaction.[a]

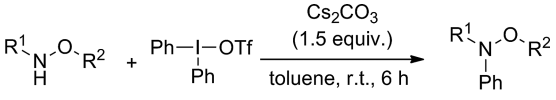


1a 2 3

Entry	Ar^1	Ar^2	X	2	Product	Yield[b] [%]
1	4-MeC_6H_4	4-MeC_6H_4	OTf	**2b**	**3b**	90
2	4-FC_6H_4	4-FC_6H_4	OTf	**2c**	**3c**	68
3	4-ClC_6H_4	4-ClC_6H_4	OTf	**2d**	**3d**	81
4	4-BrC_6H_4	4-BrC_6H_4	OTf	**2e**	**3e**	70
5	4-*t*BuC_6H_4	4-*t*BuC_6H_4	OTf	**2f**	**3f**	88
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	OTf	**2g**	**3g**	61
7	3-$O_2NC_6H_4$	3-$O_2NC_6H_4$	Br	**2h**	**3h**	45
8	mesityl	mesityl	OTf	**2i**	**3i**	86
9	2,5-$Me_2C_6H_3$	2,5-$Me_2C_6H_3$	OTf	**2j**	**3j**	81
10	Ph	mesityl	BF_4	**2k**	**3a/3i**	24:59
11	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	OTs	**2l**	**3k**	58
12	Ph	2-thienyl	OTf	**2m**	**3a**	80
13	2-thienyl	2-thienyl	OTs	**2n**	**3l**	trace

[a] Reaction conditions: **1a** (0.25 mmol), iodonium salt (0.3 mmol, 1.2 equiv.), Cs_2CO_3 (0.375 mmol, 1.5 equiv.), toluene (1.0 mL), r.t., 6 h. [b] Yield of isolated product.

Table 3. Scope of hydroxylamines in arylation.[a]



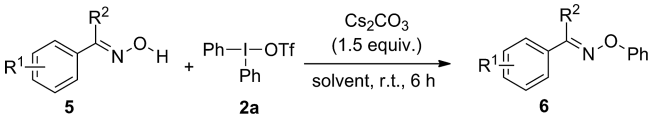
1 2a 4

Entry	R^1	R^2	Product	Yield[b] [%]
1	Cbz	TBDPS	**4a**	98
2	Cbz	Bn	**4b**	96
3	Cbz	Me	**4c**	85
4	Boc	TBDMS	**4d**	95
5	Boc	TBDPS	**4e**	90
6	Boc	Me	**4f**	85
7	Boc	Bn	**4g**	95
8[c]	PhCO	Me	**4h**	45

[a] Reaction conditions (unless otherwise specified): **1** (0.25 mmol), diphenyliodonium triflate (0.3 mmol, 1.2 equiv.), Cs_2CO_3 (0.375 mmol, 1.5 equiv.), toluene (1.0 mL), r.t., 6 h. [b] Yield of isolated product. [c] Reaction temperature was 60 °C.

cesium carbonate as the base; however, LC–MS spectrometry experiments showed that a complex mixture was obtained with the possibility of occurred rearrangements.[8] Then, our attention was turned to the *O*-arylation of oximes and then reduction of the resulting oximes to *N*-alkyl-*O*-aryl-hydroxylamines.[12,13] It was pleasing to find that *O*-phenyloxime ether **6a** was furnished in 46% yield under the same conditions developed. To our surprise, the yield could be improved to 95% upon simply replacing toluene by acetonitrile as the solvent. As shown in Table 4, the reaction scope was expanded and the desired *O*-aryloximes were prepared in excellent yields. However, in our efforts to reduce oximes **6a**–**e** for the preparation of *N*-alkyl-*O*-aryl-substituted hydroxylamines, reducing reagents such as $LiAlH_4$ and $NaBH(OAc)_3$ were unsuccessful. $LiAlH_4$ provided complex mixtures, and $NaBH(OAc)_3$ gave no reaction at all. An extensive survey of the literature found that reports concerning the reduction of *N*-alkyl-*O*-aryl-substituted oximes to their *O*-substituted hydroxylamines was a challenging task because of the instability of the corresponding products.[14] Overall, the results proved that this protocol for the synthesis of *O*-aryloximes is robust and an efficient alternative to metal-catalyzed methods.[15]

Table 4. Scope of the *O*-arylation of oximes **5** with diaryliodonium salts.[a]



5 2a 6

Entry	R^1	R^2	Solvent	Product	Yield[b] [%]
1	4-Me	H	toluene	**6a**	46
2	4-Me	H	MeCN	**6a**	95
3	H	C_6H_5	MeCN	**6b**	90
4	H	Me	MeCN	**6c**	91
5	H	H	MeCN	**6d**	85
6	4-MeO	Me	MeCN	**6e**	90

[a] Reaction conditions: **5** (0.25 mmol), diphenyliodonium triflate (0.3 mmol, 1.2 equiv.), Cs_2CO_3 (0.375 mmol, 1.5 equiv.), acetonitrile (1.0 mL), r.t., 6 h. [b] Yield of isolated product.

Conclusions

In summary, a method for the direct *N*-arylation of hydroxylamines and *O*-arylation of oximes with diaryliodonium salts mediated by cesium carbonate was developed. The method is very efficient and tolerant of a variety of substituents. More importantly, with this protocol, both *N*-arylated hydroxylamine products and *O*-arylated oxime products can be obtained easily. The advantages of the present reaction system are that it is metal free, mild conditions are used, and the reagents are easily handled. The application of this method to the preparation of relevant compounds bearing N–O bonds for further transformations is being actively explored in our laboratory; therefore, it is anticipated that some valuable chemicals could be produced by using this method in the future.

Experimental Section

General Procedure: A solution of cesium carbonate (0.375 mmol) and the hydroxylamine (0.25 mmol) in dry toluene (1.0 mL) was stirred for 5 min at room temperature. Then, diaryliodonium salt **2** (0.3 mmol) was added in one portion at room temperature, and the mixture was stirred for 6 h at room temperature. The solvent was evaporated in vacuo. Then, the crude product was directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) to afford the desired product.

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

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[13] During the preparation of this manuscript, two independent papers concerning the arylation of oximes with diaryliodonium salts appeared, see: a) H. Gao, Q. Xu, C. Keene, L. Kürti, *Chem. Eur. J.* **2014**, *20*, 8883–8887; b) R. Ghosh, E. Stridfeldt, B. Olofsson, *Chem. Eur. J.* **2014**, *20*, 8888–8892.

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