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Cu-catalyzed Intramolecular Aryl-etherification Reactions of Alkoxyl Alkynes with Diaryliodonium Salts via Cleavage of a stable C-O Bond

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A novel Cu-catalyzed intramolecular aryl-etherification reactions of alkoxyl alkynes with diaryliodonium salts is realized. The reactions proceed smoothly to produce valuable oxo-heterocycles with readily available linear starting materials via cleavage of a stable C-O bond.

Electrophiles initiated intramolecular etherification reactions of alkynes and alkenes are versatile synthetic transformations with wide applications to prepare various oxygen containing heterocycles,¹ which are ubiquitous backbones in organic materials², natural products³ and medicinal molecules⁴. In these intramolecular etherification reactions, electrophiles play significant roles and are generally applied with halogen or chalcogen onium sources, i.e. halo-etherification or chalko-etherification reactions. The analogous carbo-etherification with the formation of C-C bonds rather than C-X bonds is relatively unusual. However, this reaction is a powerful and convergent tool for oxo-heterocycle synthesis, and can allow access to a variety of analogs from readily accessible linear starting materials. Surprisingly, nearly all of the carboetherifications that have been reported, to date, are catalyzed by Pd-a novel metal complexes.⁵ In this context, we would like to report a Cu-catalyzed intramolecular aryl-etherification reactions of alkoxyl alkynes with diaryliodonium salts.⁶ The reactions proceed smoothly with readily available linear starting materials via the cleavage of a stable C-O bond (Scheme 1).



Scheme 1. Cu-catalyzed intramolecular aryl-etherification reactions of alkoxyl alkynes with diaryliodonium salts.

of synthesizing heterocycles During the study with diaryliodonium salts,⁷⁻⁸ we attempted to realize the cyclization reaction of methoxyl alkyne 2a with diphenyliodonium salt 1a. Interestingly, under a simple Cu(OTf)₂-catalyzed condition, an aryletherification product **3aa** was observed,⁹ apparently via selective cleavage of a stable C-O bond.¹⁰ After various attempts, the yield of 3aa was increased from <10% to 92% (NMR yield) under the conditions shown as entry 2 in Table 1. When other copper salt was tested as catalyst, 3aa was formed in very low yield (entry 4-9). Expectedly, no desired product was obtained without copper catalyst (entry 10). Similarly as many reactions with diaryliodonium salts, this reaction proceeded best in dichloroethane (DCE) among common solvents (entry 11-14). The protecting group **R** on oxygen atom is essential. When methoxyl group in 2a was replaced by -OH group, only 50% of **3aa** was observed with OH-arylated product contaminated;¹¹ when methyl group was replaced by other alkyl groups, the reaction also worked well, but in lower yields. It should be noted that when diaryliodonium hexafluorophosphates 1a were replaced by the corresponding triflates, product 3aa was only generated in small amount (ca 30%).

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Encouraged by the successful realization of the first Cu-catalyzed intramolecular aryl-etherification reactions of alkoxyl alkynes, next, the scope of diaryliodonium salts was examined, and the results were summarized in Scheme 2. Under the optimal conditions, a variety of symmetric and unsymmetric diaryliodonium hexafluorophosphates 1 with 2a. were reacted Symmetric diaryliodonium hexafluorophosphates with methyl and halogen substituents (1b-1g) reacted smoothly with 2a producing the corresponding products 3ba-3ga, all in excellent yields except 3da probably due to the steric hindrance. Unsymmetric diaryliodonium salts, ArI+Mes were also suitable for the reaction to give desired products (3ba, 3ja, 3ka) with high chemo-selectivity. It was also pleasant to find that diaryliodonium salts could accommodate trifluoromethyl group (an electron withdrawing group) at the meta or para positions of phenyl

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rings to conduct the transformation to give trifluoromethylated compounds (**3ha** and **3ja**).

 Table 1. Conditions screened for the aryl-etherification of alkoxyl alkyne 2a.

Ph ₂ IPF ₆ .	+	O-R <u>Cu</u> DC	u(OTf) ₂ 10% CE, 60 ℃	
1a	2	a : R = Me		3aa
R =	н	Et V		Br
yield of 3	Baa : 50%	71% 81%	6	85%
entry	Solvent	Cat. (10%.)	Temp. (°	C) Yield ^a
1	DCE	Cu(OTf) ₂	40	<10%
2	DCE	Cu(OTf) ₂	60	92% (65% ^b)
3	DCE	Cu(OTf) ₂	80	34%
4	DCE	Cu(OAc) ₂	60	0
5	DCE	CuCl	60	10%
6	DCE	CuBr	60	20%
7	DCE	CuI	60	<10%
8	DCE	Cu ₂ O	60	0
9	DCE	(CuOTf) ₂ C ₆ H ₆	60	<10%
10	DCE		60	0
11	DCM	Cu(OTf) ₂	60	11%
12	THF	Cu(OTf) ₂	60	0
13	Tol	Cu(OTf) ₂	60	21%
14	Dioxane	Cu(OTf) ₂	60	0

^aNMR yields with trichloroethylene (TCE) as internal standard; ^bisolated yield.

Inspired by the above results, the scope of this novel intramolecular etherification was further explored by varying the alkynes 2 (Scheme 3). It was delightful to find that alkyne 2a could also allow various substituents on the phenyl ring to conduct the transformation to give expected products **3ab-3af**. The structure of **3af** was unequivocally confirmed with X-ray diffraction (Figure 1, CCDC number: 1019497).¹² When substituted 4-methoxyl-1-phenyl-1-butyne derivatives (**4a-4c**) were used as the substrates, furan derivatives (**5aa-5ac**) were obtained in synthetically useful yields.



Scheme 2. The scope investigation of diaryliodonium salts: the yields were evaluated by ¹H NMR with TCE as standard and isolated yields were shown in parentheses. The products with * labeled were obtained with corresponding ArI⁺Mes salts.



Figure 1. ORTEP drawing of 3af with 35% probability ellipsoids.

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Scheme 3 The scope investigation of alkynes: the yields were evaluated by ¹H NMR with TCE as standard and isolated yields were shown in parentheses.

After the facile construction of oxo-heterocycles with linear alkoxyl alkynes and diaryliodonium salts, we made further attempt to benzo-fused heterocycles. For this goal, 2'-methoxyl tolane **4d** was synthesized¹³ and subjected to react with a few diaryliodonium salts (scheme 4). Regretfully, the desired benzofuran products could only isolated in modest yields while the starting materials were all consumed. This may be attributed to the lower nucleophility of oxygen atom conjugated with a phenyl ring in **4d**. The usage of TMS-protected 2'-hydroxyl tolane didn't increase the yield neither (see ESI).



5ad: 37%5bd: 40%5fd: 27%5hd: 23%Scheme 4. The isolated yields of 1,2-diaryl benzofuran derivativesthrough Cu-catalyzed intramolecular aryl-etherification reaction.

It's already accepted that the diaryliodonium salts could generate highly electrophilic Ar-Cu(III) species in situ in the presence of copper salt and the Ar-Cu(III) I species could be easily attacked by alkynes to produce vinyl-copper(III) species II (Scheme 5), resembling a vinyl-cation III.¹⁴ Rationally, when the alkoxyl alkynes were used as the substrates, the copper centre (followed by elimination of Cu(I)X) or vinyl cation centre was easily attacked by oxygen atom to give an oxonium intermediate IV. The substitution of **R** group on the electrophilic oxonium intermediate **IV** with counteranion would produce final product 3. To seek some clues of this pathway, alkyne 2x with 3-(4-bromophenyl)-propyl group-a larger substituent was prepared and treated with $Ph_2I^+PF_6$ under the standard condition. Interestingly, besides the product 3aa formed in 85% yield, 3-(4-bromophenyl)-propyl fluoride and 4-allyl-phenyl bromide (or its isomer) were also observed by GC-MS in significant amount (see ESI) and this was an evidence for the presence of oxonium intermediate IV during the reaction.

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Scheme 5. Plausible mechanism for the Cu-catalyzed intramolecular aryl-etherification reaction.

To explore the further application of this Cu-catalyzed intramolecular aryl-etherification reaction, the newly formed oxoheterocycle **3aa** was applied to a photo-cyclization reaction¹⁵ to produce phenanthrene derivative **6** and a hydrogenation reaction¹⁶ to give pyran **7** in high yields. Moreover, when **3aa** was treated with PhMgBr in the presence of Ni-catalyst,¹⁷ coupling product **8**-a useful intermediate for medicinal compounds¹⁸ was formed.



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Conclusions

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In summary, we reported a novel Cu-catalyzed intramolecular aryl-etherification reaction of alkoxyl alkynes with diaryliodonium salts. The reactions proceed smoothly to give useful oxo-heterocycles with readily available linear starting materials via cleavage of a stable C-O bond.

Notes and references

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^b Key Laboratory of Systems Bioengineering, Ministry of Education, Department of Pharmaceutical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China. † This work was supported by National Natural Science Foundation of China (21102080, 21372138) and Tsinghua University Initiative Scientific Research Program (2011Z02150). Electronic supplementary Information (ESI) available: Full experimental details, including ¹H and ¹³C NMR data of new compounds For ESI and crystallographic data in CIF (CCDC 1019497) of **3af** see DOI: 10.1039/c000000x/

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