Radical Reactions

DOI: 10.1002/ange.201303347

Direct Vicinal Disubstitution of Diaryliodonium Salts by Pyridine *N*-oxides and *N*-amidates by a 1,3-Radical Rearrangement**

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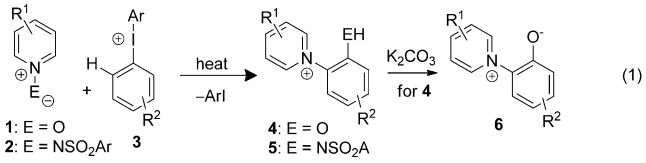
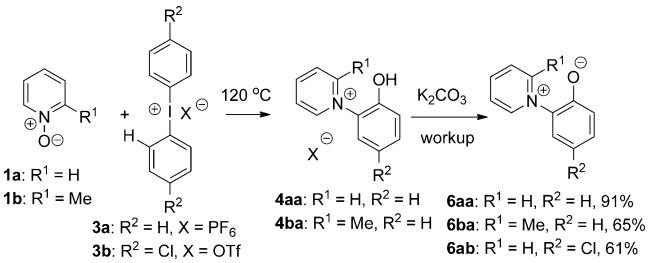
Diaryliodonium salts, $Ar_2I^+X^-$, are an important and appealing class of aromatic iodine(III) derivatives, and recently have received considerable attention because of their powerful arylation of a wide range of nucleophiles to synthesize valuable aromatic compounds.[1] They can be directly substituted by various nucleophiles under ecological and mild reaction conditions.[1,2] In the presence of transition metals, diaryliodonium salts are often applied in cross-coupling reactions and even substituted by weak nucleophiles such as alkenes, alkynes, arenes.[1b,3–5] The generation and trapping of the benzyne intermediates from *ortho*-silyl diaryliodonium salts exhibits an efficient way to produce aromatic compounds having a unique substitution manner.[6] Since there exists a vast and long-term demand for the synthesis of arenes with various substitutents, the development of new strategic substitution modes of diaryliodonium salts to produce valuable aromatic compounds will be of great importance. Recently, we reported a three-component reaction of diaryliodonium salts, nitriles, and alkynes to synthesize quinolines, where *ipso* and *ortho* positions of the arene in the diaryliodonium salts were substituted consecutively in the annulation.[7] As a result of our ongoing project, we herein report a novel vicinal disubstituion of diaryliodonium salts by the pyridine *N*-oxides **1** and *N*-amidates **2** by an interesting 1,3-radical rearrangement [Eq. (1)]. The direct vicinal disubstitution reaction of diaryliodonium salt produces a series of pyridinium phenols (**4**) and anilines (**5**), which are important synthetic intermediates, valuable optical materials, and components of natural products.[8–10]



(1)

The study commenced using a mixture of pyridine *N*-oxide (**1a**) and diphenyliodonium hexafluorophosphate (**3a**; 1.0 equiv), which in solution gave an unstable complex assumed to be the diphenyliodonium pyridine *N*-oxide λ^3 complex (Scheme 1).[11] When the mixture was heated to



Scheme 1. Tf = trifluoromethanesulfonyl.

120 °C, a new product, 2-pyridinium phenol hexafluorophosphate (**4aa**), was obtained in 17% yield after column chromatography on silica gel. The reaction of 2-picoline *N*-oxide (**1b**) with **3a** gave the analogue **4ba** (8% yield), whose molecular structure was confirmed by X-ray diffraction studies. The crystal structure clearly shows the N–O bond has been broken with insertion of a phenylene group from the fragmentation of diphenyliodinium salt (Figure 1; for details

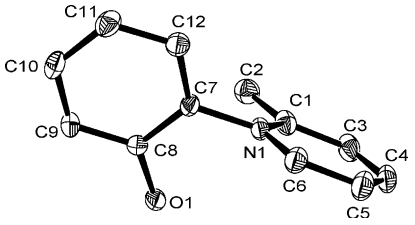


Figure 1. X-ray Crystal structure of **4ba.** Hydrogen atoms and PF_6^- are omitted for clarity. For ORTEP drawing the thermal ellipsoids shown at 35% probability.[20]

see the Supporting Information). Considering the low solubility of **4aa** and **4ba** in nonpolar solvents, K_2CO_3 (1.0 equiv) was added after the reaction was stopped. Thus, after work-up the betaine **6aa** was isolated in 91% yield and **6ba** in 65% yield (for reaction optimization and details, see the Supporting Information). To determine the exact substitution position on the phenyl ring, di(4-chlorophenyl)iodonium triflate (**3b**)

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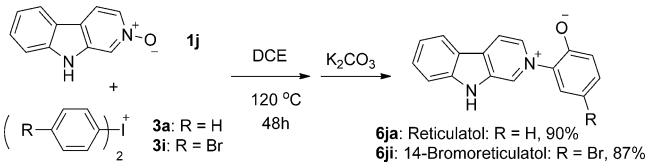
[**] This work was supported by the National Natural Science Foundation of China (21102080 and 21290194), the Tsinghua University Initiative Scientific Research Program (2011Z02150), and the Chinese Academy of Sciences.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201303347.

was chosen to react with **1a** under the same reaction conditions, and **6ab** was isolated in 61% yield (Scheme 1). Further investigation of **6ab** by two-dimensional NMR spectroscopy has proved that the *ipso*-carbon atom of **3a** is linked to an oxygen atom and the *ortho*-carbon atom linked to the nitrogen atom.

The products, *o*-pyridinium phenolates, have already been investigated as an important class of optical materials[9] and have also been found in naturally occuring pyridine alkaloids.[10] However, present approaches to pyridinium phenolates are of low generality and only suitable for specific backbones.[9b,12] Encouraged by the above finding, we attempted to synthesize more fuctionalized *o*-pyridinium phenols by the vicinal disubstitution of diaryliodonium salts. Reactions of various pyridine *N*-oxides and diaryliodinium salts have been performed and representative results are shown in Table 1. Gratifyingly, various methyl pyridine N oxides, as well as fluoro pyridine, 2,6-lutidine, cyano pyridine, and benzoisoquinoline N oxides all reacted with **3a** to give the expected products (entry 1–7). Most reactions gave the products in good yields except the 2,6-lutidine *N*-oxide, probably because of the steric bulk. The iodonium salts bearing methyl, fluoro, and *tert*-butyl groups on the phenyl ring (entry 7–9, 11, and 12) worked well and the iodonium salts with substituents at the *ortho* position (entry 10 and 13) gave the desired products, albeit in relatively low yields. The products were isolated in the betaine form except **4ha** (sensitive to base). The vincinal substitution took place on the less hindered ring of unsymmetric iodonium salts (**3g**).[3,13] The diaryl iodonium salt **3h** having a CF_3 group, a strong electron-withdrawing group, did not work. In some cases, we observed pyridine as the by-product (e.g. 2-benzyl-pyridine in 15% yield; entry 8).

The scope of this reaction was further demonstrated by its application to the synthesis of two β-carboline natural products, reticulatol and 14-bromoreticulatol (Scheme 2),

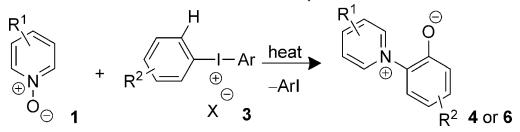


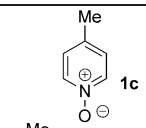
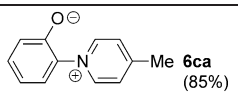
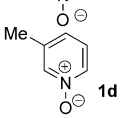
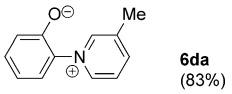
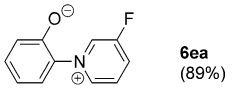
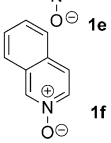
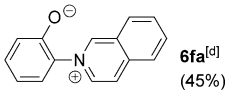
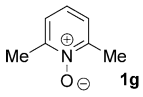
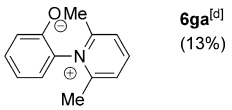
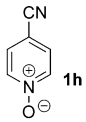
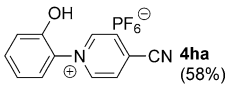
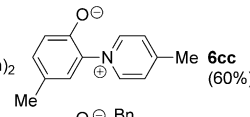
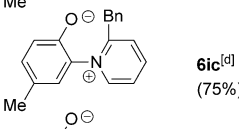
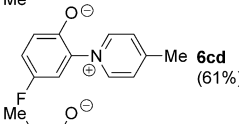
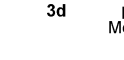
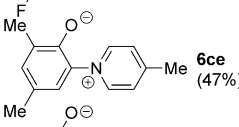
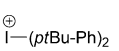
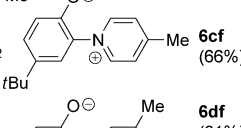
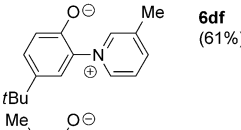
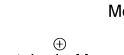
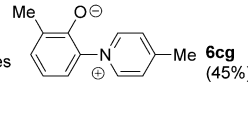
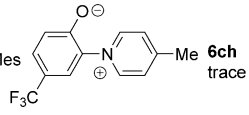
Scheme 2. The synthesis of reticulatol and 14-bromoreticulatol.

which were isolated (3 mg) as new fascaplysin derivatives and reported to show significant bioactivity for human leukemia.[10] For this goal, the β-carboline *N*-oxide **1j** was readily prepared by a known method.[12] A 1:1 mixture of **1j** (1 mmol) and **3a** (1 mmol) was heated at 120 °C for 48 hours and purified to give the betaine form of reticulatol (**6ja**) in 90% yield upon isolation. Analogously, the betaine form of 14-bromoreticulatol (**6ji**) was obtained in 87% yield.

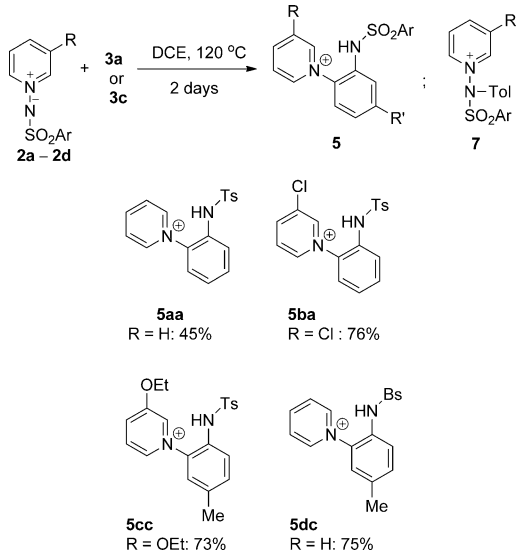
Inspired by the successful vicinal disubstitution of diaryliodonium salts by pyridine oxides, the scope was extended to the pyridine amidates[14] **2** as substrates. To our delight, the disubstitution was also realized and the desired products, the

Table 1: The vicinal disubstitution of diaryliodonium salts with **1**.[a,b,c]



1		**1c**	**3a**		**6ca** (85%)
2		**1d**	**3a**		**6da** (83%)
3		**1e**	**3a**		**6ea** (89%)
4		**1f**	**3a**		**6fa**[d] (45%)
5		**1g**	**3a**		**6ga**[d] (13%)
6		**1h**	**3a**		**4ha** (58%)
7	**1c**		**3c**		**6cc** (60%)
8		**1i**	**3c**		**6ic**[d] (75%)
9	**1c**		 **3d**		**6cd** (61%)
10	**1c**		 **3e**		**6ce** (47%)
11	**1c**		 **3f**		**6cf** (66%)
12	**1d**		**3f**		**6df** (61%)
13	**1c**		 **3g**		**6cg** (45%)
14	**1c**		**3h**		**6ch** trace

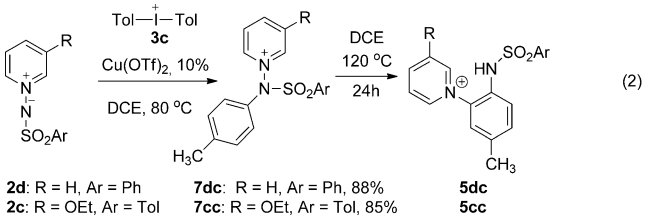
[a] The reaction of **1** (1.0 mmol) and **3** (1.0 mmol) was carried out in 1,2-dichloroethane at 120 °C for 2 days. [b] The anion of **3c–h** is triflate. [c] Yields are those of isolated products. [d] The reduced pyridines were observed. For example, 2-benzyl pyridine was isolated in 15% yield (entry 8). Mes = 2,4,6-trimethylphenyl.



Scheme 3. The vicinal disubstitution of diaryliodonium salts with **2**.

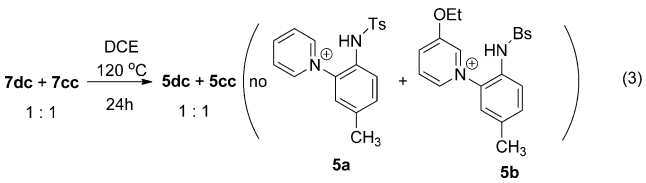
o-pyridinium anilines **5**, were formed in good yields (Scheme 3; Ts = 4-toluenesulfonyl, Bs = benzenesulfonyl).

During the synthesis of **5**, we observed the by-product **7** in trace amounts. To identify whether **7** was the intermediate of the reaction, we prepared **7** separately. Excitingly, when **2d** was heated with **3c** at 80 °C for 12 h in the presence of $Cu(OTf)_2$ (10 mol %), **7dc** was obtained in 88 % yield [Eq. (2)]. Analogously, **7cc** was obtained in 85 % yield.

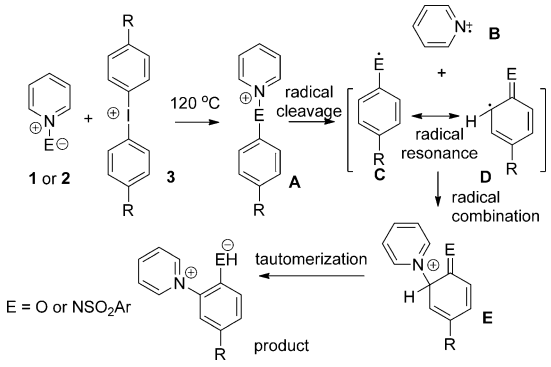


Interestingly, upon heating **7dc** and **7cc** at 120 °C for 24 hours, complete conversion into **5dc** and **5cc**, respectively, were observed.

Additionally, a 1:1 mixture of **7dc** and **7cc** was heated and only a mixture of **5dc** and **5cc** was observed without any formation of **5a** or **5b** [Eq. (3)]. This suggested the rearrangement of **7** to **5** was an intramolecular process.



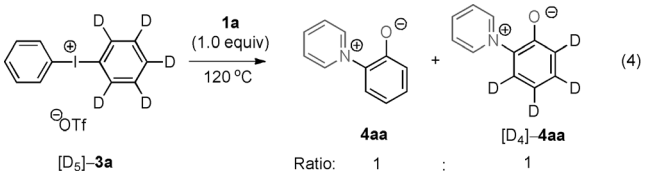
Based on the above-mentioned results, we propose a mechanism for the reaction as depicted in Scheme 4 (for clarity, the substituents are omitted except the *para*-group on phenyl ring): 1) the pyridine *N*-oxide **1** or *N*-amidate **2** was arylated by diaryliodonium salts to give the intermediate **A** [isolated as **7dc** and **7cc**; Eq. (2)]; 2) the N–O or N–N single



Scheme 4. Proposed mechanism of the vicinal disubstitution of diaryliodoniums with the pyridine *N*-oxides **1** and *N*-amidates **2**.

bond in **A** was homolytically cleaved upon heating to give a radical pair comprising the pyridine cationic radical **B**[15] and the heteroatom aryl radical **C** (phenoxyl radical[16] and anilino radical[17]); 3) conceivably, the radical on the heteroatom of **C** is easily rearranged to the carbon atom at the *ortho* or *para*- position of the phenyl ring (**D**); 4) solvent-cage radical recombination favored the bond formation between **B** and the *ortho* position of **D** to give **E**; 5) the tautomerization of **E** resulted in the final product.

In the kinetic isotope effect experiment, [D_5]-**3a** was synthesized and subjected to the reaction with **1a**. The phenolate **4aa** and [D_4]-**4aa** were both observed with a ratio of 1:1 [Eq. (4)].



To shed more light on the reaction mechanism at the molecular level, density functional theory (DFT) calculations were conducted. As shown in Figure 2, our computations

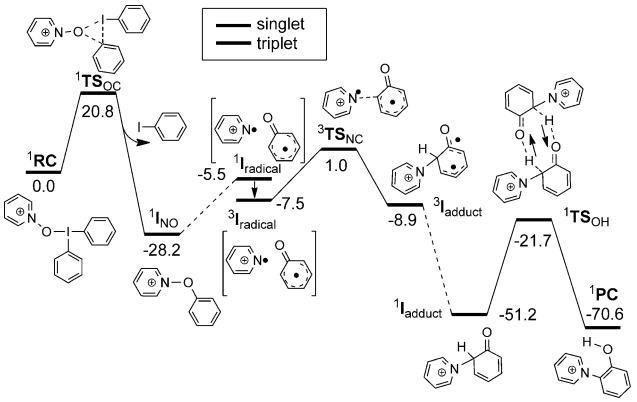


Figure 2. DFT calculated pathway of prototype reaction of pyridine *N*-oxides with diaryliodonium salts to generate 2-pyridinium phenols. The calculated relative energies labeled for each species in kcal mol^{-1} and include zero-point energy (ZPE) corrections. The superscript before the label represents spin multiplicity.

suggest that the reaction is initiated from the diphenyliodonium pyridine *N*-oxide λ^3 complex ^{1}**RC** by arylation of the pyridine *N*-oxide through a reductive elimination via transition-state $^1\mathbf{TS}_{OC}$ having a barrier of 20.8 kcal mol^{-1}. Then, through thermolysis, the in situ formed *N*-aryloxy pyridinium cation intermediate $\mathbf{I}_{NO}$ generates the radical pair intermediate $\mathbf{I}_{radical}$ comprising the pyridine cationic radical and phenoxyl radical. The triplet-state radical pair $^3\mathbf{I}_{radical}$ is slightly lower in energy than the singlet $^1\mathbf{I}_{radical}$, thus it is likely that radical pair will convert from the singlet state into the triplet state by spin flipping. From $^3\mathbf{I}_{radical}$, subsequent attack of the pyridine cationic radical on the *ortho* position of the phenoxyl radical occurs with only a small barrier of 8.5 kcal mol^{-1} via the transition-state $^3\mathbf{TS}_{NC}$, whereby the radical pair recombines to reach the triplet adduct $^3\mathbf{I}_{adduct}$ first and then the more stable singlet adduct $^1\mathbf{I}_{adduct}$. Finally two molecules of the singlet adduct exchange their protons to reach the final product, 2-pyridinium phenol or aniline. The intramolecular H shift from $^1\mathbf{I}_{adduct}$ to ^{1}**PC** is not preferred because of very high calculated reaction barrier of 55 kcal mol^{-1}.

Considering the irreversibility of first step in the reaction pathway (Figure 2), it is obvious that this arylation of pyridine N oxide, without direct involvement of the H on the aryl group, will determine the aryl ring selectivity from the diaryliodonium salt. This theoretical result explains the experimental observation shown in Equation (4). Upon inspection of the entire reaction profile, the thermolysis of the $^1\mathbf{I}_{NO}$ and subsequent product-oriented radical pair combination should be the most difficult step, and would have an effective activation energy of about 30 kcal mol^{-1} from $^1\mathbf{I}_{NO}$. Once the radical pair adduct $^1\mathbf{I}_{adduct}$ is formed, it is very unlikely to go back to $^1\mathbf{I}_{NO}$ as a result of the large barrier of the reverse reaction. Thus transition to the final product from $^1\mathbf{I}_{adduct}$ is not the key step. Concerning the solvent-caged radical pair, we also calculated the dissociation energy of $^3\mathbf{I}_{radical}$ needed to separate this radical pair, and the value of 10.4 kcal mol^{-1}, which exceeds the 8.5 kcal mol^{-1} barrier for radical combination, is in line with the intramolecular character of the reaction [Eq. (3)].

In conclusion, the direct vicinal disubstitution of the diaryliodonium salts **3** by pyridine *N*-oxides **1** and *N*-amidates **2** has been realized. This reaction has revealed an efficient and new strategic way to access *ortho*-disubstituted benzene derivatives from readily available starting materials in one step.[18] The reaction proceeds thermally by an arylation and 1,3-radical rearrangement sequence. Remarkably, the combined experimental and computational mechanistic studies identified the key step to be homolytic cleavage to give the radical pair, from which a solvent-cage radical recombination ensures high regioselectivity.

Experimental Section

Diaryliodonium salts (**3**) were easily synthesized according to literature procedure[19] except for the commercially available **3a** and **3f**. 1,2-Dichloroethane (DCE) was dried over 4 Å M.S. before use.

3 mL of DCE were added to a mixture of the pyridine *N*-oxide **1** (1.0 mmol) and diaryliodonium salt **3** (1.0 mmol) under a nitrogen atmosphere in a Schlenk tube with screw-cap. Then the mixture was sealed and stirred at 120 °C for 48 h. The mixture was cooled to room temperature. Then 1 mmol of K_2CO_3, 2 mL of methanol, and silica gel (ca. 1 g) were added to the reaction mixture. All the volatiles were removed by rotatory evaporation and the product **6** was obtained by column chromatography (elution: CH_2Cl_2/petroleum ether/methanol = 10:5:3) as a highly hygroscopic solid. The details of DFT computations are given in the Supporting Information.

Received: April 20, 2013
Published online: June 12, 2013

Keywords: arenes · iodonium · radicals · rearrangement · synthetic methods

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[20] CCDC 934290 (**4ba**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

