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Nitrogen−Iodine Exchange of Diaryliodonium Salts: Access to Acridine and Carbazole

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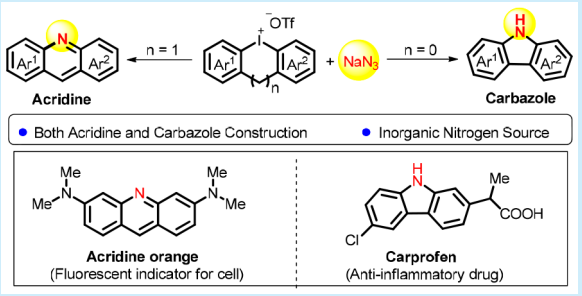
Supporting Information

ABSTRACT: A nitrogen−iodine exchange protocol of diaryliodonium salts with sodium azide salt is developed for general construction of significant functional acridines and carbazoles, in which introduction of nitrogen at a late stage was successfully established avoiding heteroatom incompatibility. Inorganic sodium azide served as the sole nitrogen atom source in this transformation. The diversiform functional acridines and carbazoles were comprehensively achieved through annulated diaryliodonium salts, respectively. Notably, Acridine orange (a fluorescent indicator for cell lysosomal dye) and Carprofen (a nonsteroidal anti-inflammatory drug) were efficiently established through this protocol.



Acridine and carbazole, as two types of the most significant nitrogen-containing heteroaromatic molecules, have attracted considerable interest due to their extensive applications in pharmaceuticals and organic light-emitting materials.[1] For example, Acridine-containing Quinacrine has been found to be an exclusive antimalarial drug, which was first synthesized by Bayer.[2] Amsacrine has been applied for acute lymphoblastic leukemia.[3] Acridine orange has been widely used as a fluorescent indicator for cell lysosomal dye (Figure 1A).[4] Carbazole-containing Carazolol and Carvedilol are commonly applied as antihypertensive drugs.[5] Carprofen is a nonsteroidal anti-inflammatory pharmaceutical treatment for various joint pain as well as postoperative pain.[6] Since acridine and carbazole are common structural motifs in pharmaceutical and material science, many fantastic contributions for their synthesis have been pursued. Typical Brenthsen reaction was achieved via coupling of a diphenylamine and a carboxylic acid with the assistance of zinc chloride at 200−270 °C, which is one of the earliest syntheses of acridines.[7] Other methods for the preparation of acridines include the bilateral cyclization of benzaldehydes with aromatic azides[8] and aryl nitroso compounds[9] under Rh(III)-catalyzed conditions (Figure 1B-1). Stoichiometric trifluoroborane realized intramolecular Friedel−Crafts reaction of aryne with aryl amide to afford acridines as well.[10] On the other hand, the famous Fischer−Borsche and Graebe−Ullmann synthesis,[11] the intramolecular coupling of 2-aminobiphenyl through C−N bond formation,[12] and the intramolecular coupling of diarylamines through C−C bond formation[13] have been commonly used for the preparation of carbazoles (Figure 1B-2). Especially, the nitrogenation of 2-iodobiphenyls with sodium azide for the synthesis of carbazoles has been developed.[12g] The synthesis of *N*-arylated carbazoles was described through an amination of iodonium salts with aniline.[12j,k] Although these elegant methods have been established for

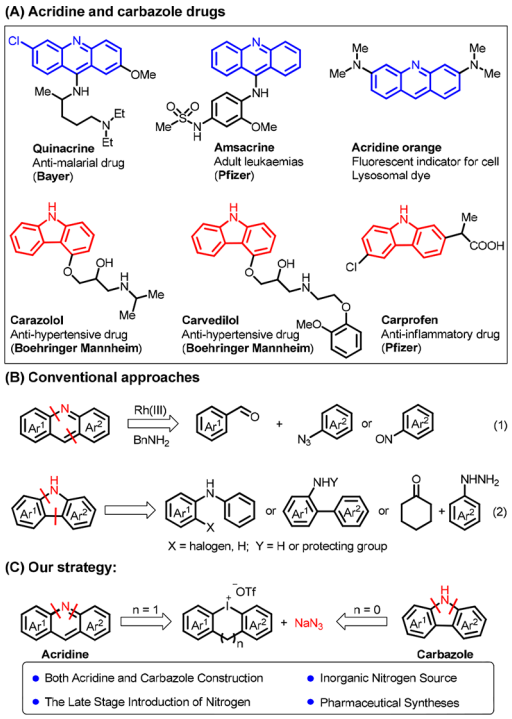


Figure 1. Significant functional acridines and carbazoles.

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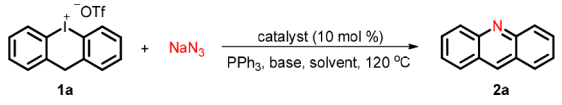
acridines or carbazoles synthesis in an early stage, it is still highly desirable for fast drug discovery with a general and compatible strategy for both modified heteroaromatic molecules through direct nitrogen atom introduction at a late stage. Diaryliodonium salt as a stable and commercially available reagent is one of the most efficient arylation reagents in organic synthesis.[14] Recently, the controllable and divergent synthesis strategies were developed by our group for construction of nitrogen-containing alkaloids.[15] Herein, we disclose a copper-catalyzed direct nitrogen−iodine exchange of diaryliodonium salts for acridines and carbazoles synthesis (Figure 1C).

Table 1. Condition Optimization[a]



1a 2a

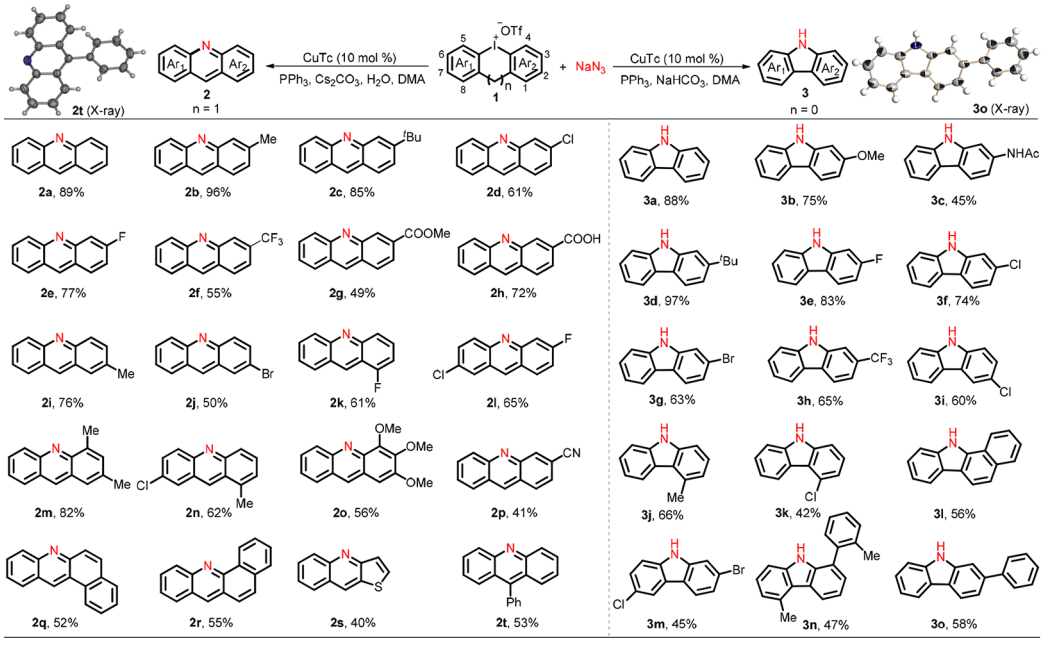
entry	catalyst	base	solvent	yield[b]
1	$Pd(OAc)_2$	–	DMSO	ND
2	$Fe(acac)_2$	–	DMSO	ND
3	$Cu(OTf)_2$	–	DMSO	35
4	CuI	–	DMSO	20
5	CuTc	–	DMSO	45
6	CuTc	K_2CO_3	DMSO	58
7	CuTc	Cs_2CO_3	DMSO	68
8	CuTc	DBU	DMSO	35
9	CuTc	KO^{t}Bu	DMSO	40
10	CuTc	Cs_2CO_3	NMP	10
11	CuTc	Cs_2CO_3	DMA	73
12	CuTc	Cs_2CO_3	DMF	44
13[c]	***CuTc***	***Cs_2CO_3***	***DMA***	***89***
14[d]	CuTc	Cs_2CO_3	DMA	48

[a]Reaction conditions: **1a** (0.1 mmol), NaN_3 (0.12 mmol), catalyst (0.01 mmol), PPh_3 (0.15 mmol), base (0.2 mmol), solvent (1 mL), 48 h. [b]Isolated yield of **2a**. [c]50 μL H_2O (2.8 mmol) was added. [d]Performed under a N_2 atmosphere.

We commenced the exchange between sodium azide as the nitrogen source and diaryliodonium salt **1a**. In order to reduce the azide, a stoichiometric amount of triphenylphosphine was employed. No desired acridine product **2a** was detected when palladium acetate or Iron(II) acetylacetonate was used (Table 1, entries 1−2). Compound **2a** could be afforded in 35% yield when copper trifluoromethanesulfonate was served as the catalyst (Table 1, entry 3). Copper(I) thiophene-2-carboxylate displayed a better result in 45% yield (Table 1, entries 4−5). The additional bases afforded positive results, and cesium carbonate was the best choice affording **2a** in 68% yield (Table 1, entries 6−8). Stronger base potassium *tert*-butoxide was adverse to the transformation (Table 1, entry 9). Dimethylacetamide was found to be the best solvent (Table 1, entries 10−12). **2a** could be formed in 89% yield when water was added to help solubility (Table 1, entry 13). The efficiency of the reaction was dramatically decreased when conducted under a N_2 atmosphere, indicating that an air oxidative process was included in this transformation (Table 1, entry 14).

The nitrogen−iodine exchange, exhibiting powerful synthesis of functionalized acridine, is shown in Scheme 1. A broad range of diaryliodonium salts with electron-rich (**2b** and **2c**) and -deficient (**2d**−**2g**) groups at position 3 were readily achieved. Remarkably, a substrate containing active hydrogen, such as carboxyl acid, could be tolerated (**2h**). The substituents on position 2 (**2i** and **2j**) and position 1 (**2k**) with different electronic properties were well tolerated. Diaryliodonium salts with two different substituents at different positions were all effective candidates, regardless of electron-donating or -with-drawing (**2l**−**2n**). Diaryliodonium salt, bearing naturally frequently existing 2,3,4-trimethoxyl, afforded the acridine alkaloid analogue **2o**. The cyano group was compatible in this transformation to give the desired product **2p**. Fused rings proved to be entirely compatible affording the corresponding conjugated products **2q** and **2r**. Replacing the phenyl substituent of diaryliodonium salt with heteroaryl (**2s**) was well tolerated in

Scheme 1. Nitrogen−Iodine Exchange[a]



[a]Reaction conditions: **1** (0.1 mmol), NaN_3 (0.12 mmol), PPh_3 (0.15 mmol), CuTc (0.01 mmol), DMA (1 mL), isolated yields. n = 1: Cs_2CO_3 (0.2 mmol), H_2O (50 μL), 120 °C. n = 0: $NaHCO_3$ (0.2 mmol), 100 °C.

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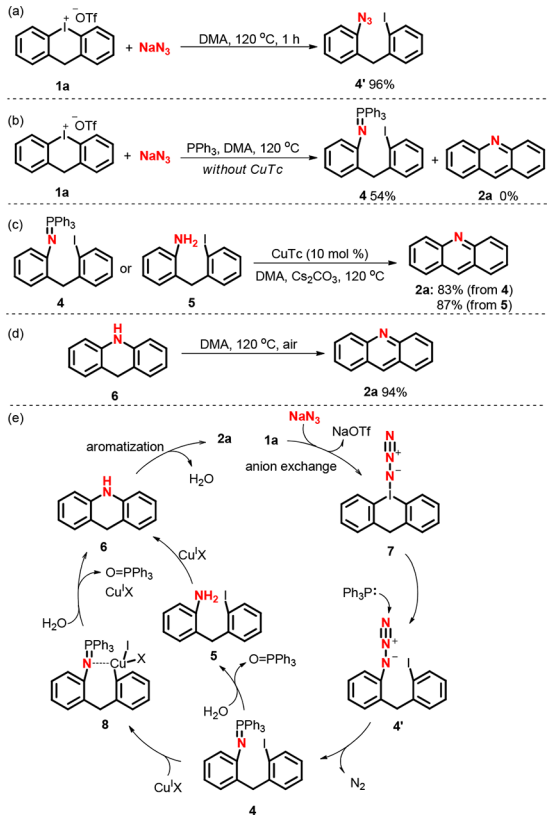
this exchange process. 9-Phenylacridine (**2t**) was efficiently furnished in good yield when the substituent is on the methylene position of six-membered diaryliodonium salt, and the structure was further confirmed via X-ray diffraction analysis (CCDC 1577512).[16]

Following the success of six-membered diaryliodonium salt for the construction of acridine, five-membered diaryliodonium salts were further studied (see Supporting Information for conditions optimization), which exhibited collective synthesis of carbazoles through the current methodology (Scheme 1). Five-membered carbazoles bearing electron-donating (**3b**−**3d**) and electron-withdrawing (**3e**−**3h**) substituents at position 3 were efficiently achieved in good to excellent yields. The substituents on positions 2 (**3i**) and 1 (**3j**−**3k**) with different electronic properties were perfectly tolerated as well. The fused rings (**3l**), which are beneficial for enhancing carrier mobility in semiconductor materials, proved to be entirely compatible. Diaryliodonium salts bearing halogen moieties, which may provide further derivatization via cross-couplings, were successfully accommodated affording the corresponding products (**3m**). A multisubstituted substrate such as at position 3 with a 2-methylphenyl group and position 8 with a methyl group was also tolerated and smoothly afforded the corresponding adduct **3n**. Conjugated phenyl groups could be efficiently transformed into product **3o** (CCDC 1577511).[16]

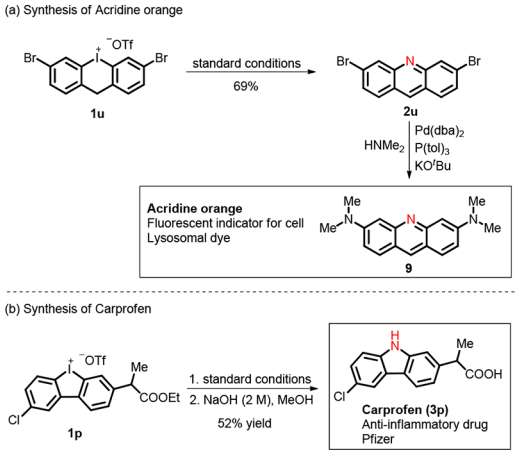
In order to figure out the mechanism of the nitrogen−iodine exchange reaction, diaryliodonium salt **1a** and NaN_3 were reacted without PPh_3 and catalyst, and aryl azide **4′** was afforded in 96% yield (Scheme 2a). With only the absence of CuTc catalyst in the reaction, no desired product **2a** was detected and triphenylphosphoranylidene **4** was found in 54% yield (Scheme 2b). Intermediate **4** and aryl amine **5** could afford the desired product **2a** in 83% and 87% yield, respectively, under the standard conditions, and 9,10-dihydroacridine **6** could give **2a** in 94% yield under the help of an air atmosphere (Scheme 2c and 2d). These results indicated that **4**, **5**, and **6** are the possible intermediates during the nitrogen−iodine exchange process. Thus, a postulated reaction pathway is depicted in Scheme 2e. The azide anion exchanged with the anion of diaryliodonium salt **1a** to give intermediate **7**. Aryl azide **4′** was formed from the reductive elimination of intermediate **7**. Subsequently, addition of aryl azide **4′** with triphenylphosphine formed intermediate **4**, which included a process similar to that of the Staudinger reaction. Oxidative addition of intermediate **4** with Cu(I) provided Cu(III) aryl species **8** as an Ullman type intermediate, in which a hydrolytic process assisted generating intermediate **5** and regenerated the Cu(I) catalyst. It is also possible that intermediate **4** was hydrolyzed to aryl amine **5**, which underwent an intramolecular coupling to generate **6**. The aromatization of **6** gave the desired product **2a** under an air atmosphere.

To further reveal the practicability of the exchange protocol, the syntheses of pharmaceutical molecules were conducted. Acridine orange **9**, as a fluorescent indicator for cell lysosomal dye, could be afforded in a good yield from diaryliodonium salts **1u** through this nitrogen−iodine exchange approach (Scheme 3a).

Scheme 2. Mechanistic Study



Scheme 3. Synthesis of Acridine Orange and Carprofen



Nonsteroidal anti-inflammatory pharmaceutical Carprofen **3p** was efficiently synthesized from diaryliodonium salt **1p**, followed by one step of hydrolysis (Scheme 3b), which provided a new synthetic route for Carprofen and analogues.[17]

In summary, a novel synthetic pathway to access the acridine and carbazole alkaloid analogue was developed through nitrogen−iodine exchange of diaryliodonium salts. This effective transformation employs sodium azide salt as the nitrogen source to realize the exchange strategy. Mechanistic studies demonstrated that the Staudinger intermediate involves the coupling step in the exchange transformation. Divergent functionalized acridines and carbazoles libraries were efficiently established through this method. Furthermore, new pathways for the syntheses of Acridine orange and nonsteroidal anti-inflammatory drug Carprofen demonstrated the great potential of this protocol. Further explorations of drug discovery with an atom exchange strategy are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures; NMR spectral, X-ray and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1577511−1577512 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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