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Diverse Tandem Cyclization Reactions of *o*-Cyanoanilines and Diaryliodonium Salts with Copper Catalyst for the Construction of Quinazolinimine and Acridine Scaffolds

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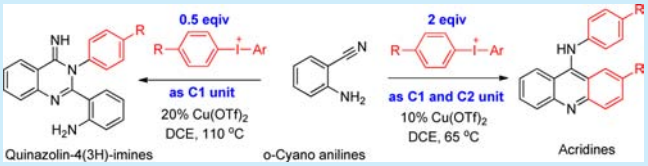
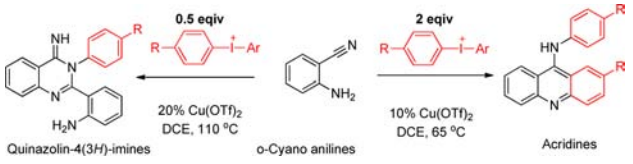
Supporting Information

ABSTRACT: Two cyclization modes are realized to produce different nitrogen-containing heterocycles, i.e., quinazolin-4(3*H*)-imines and acridines by assembling *o*-cyanoanilines and diaryliodonium salts via tandem reaction pathways.



Naturally occurring or synthetically produced nitrogen-containing heterocycles are ubiquitous backbones for many organic materials, pharmaceutic agents, and important ligands in catalysis. Consequently, the development of quick, efficient, and versatile methods for the synthesis of nitrogen-containing heterocycles are highly desired.[1] In this context, assembling small molecules via a tandem reaction[2] to synthesize nitrogen-containing heterocycles has received intensive attention. Herein, we report that two cyclization modes are realized to produce different nitrogen-containing heterocycles, i.e., quinazolin-4(3*H*)-imines and acridines, by assembling *o*-cyanoanilines and diaryliodonium salts[3] via tandem reaction pathways (Scheme 1).

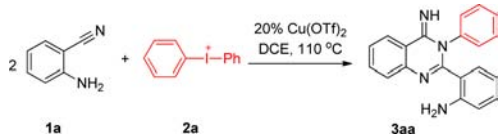
Scheme 1. Two Cyclization Modes To Produce Quinazolin-4(3*H*)-imines or Aridines by Assembling *o*-Cyanoanilines and Diaryliodonium Salts via Tandem Reaction Pathways



As an important subclass of quinazoline,[4] quinazolin-4(3*H*)-imine, is a featured structural motif in biologically active compounds that behave as cholinesterase inhibitors, cMETkinase inhibitors, or modulators of chemokine CCR3 activity or exhibit antiproliferative or cardiotonic activities.[5] Recent methods for the preparation of quinazolin-4(3*H*)-imines include the palladium-catalyzed reaction of carbodiimide, isocyanide, and a nucleophile, the synthesis of 3-aryl-4(3*H*)-quinazoliniminium halides from heteroenyne−allenes in three steps, the reaction of anthranilonitrile with triethyl orthoformate, the single-step synthesis from 2-azido-5-nitrobenzonitrile via condensation reaction, and a tandem cyclization of α-amino ketones and 2-(dichloroisocyanido) benzonitrile.[6] However, some of the reported methods required long reaction time or high temperature. The development of efficient and versatile methods to construct quinazolin-4(3*H*)-imines with readily available starting materials and catalyst is still in high demand.

During the study of synthesizing nitrogen-containing heterocycles with diaryliodonium salts,[7] we found an interesting tandem reaction of *o*-cyano aniline **1a** and diphenyliodonium salt **2a** to produce quinazolin-4(3*H*)-imine derivative **3aa** (see Table 1). Excited by the finding, we executed a series of

Table 1. Conditions Screened for the Formation of 3aa



1a **2a** **3aa**

entry	solvent	cat. (20%)	temp (°C)	yield[a] (%)
1	DCE	$Cu(OTf)_2$	70	29
2	DCE	$Cu(OTf)_2$	90	55
3	**DCE**	**$Cu(OTf)_2$**	**110**	**96 (95[b])**
4	DCE	$Cu(OTf)_2$	120	74
5	DCE	CuCl	110	33
6	DCE	CuBr	110	41
7	DCE	CuI	110	27
8	Tol	$Cu(OTf)_2$	110	82
9	DCM	$Cu(OTf)_2$	110	77
10	CH_3CN	$Cu(OTf)_2$	110	66
11	DMSO	$Cu(OTf)_2$	110	84
12	DCE	$Cu(OTf)_2$	110	71[c]

[a]NMR yields with trichloroethylene (TCE) as internal standard. [b]Isolated yield. [c]1.5 equiv of **1a** was used.

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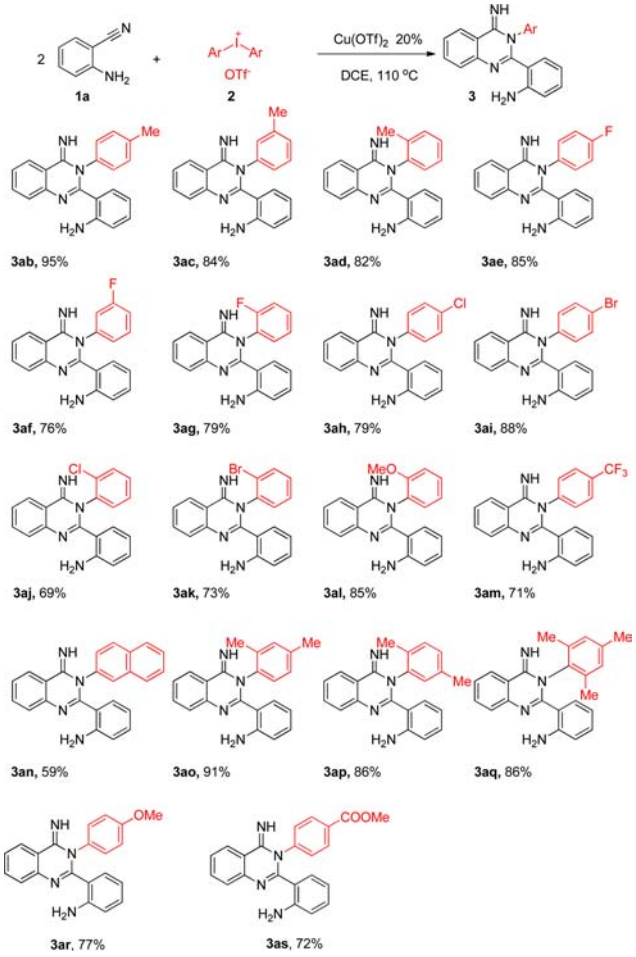
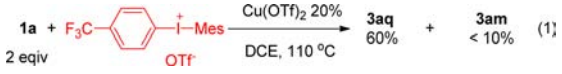
optimized reactions to improve the efficiency. Actually, when 2 equiv of **1a** was reacted with **2a** in DCE at 70 °C for 6 h in the presence of 20% $Cu(OTf)_2$, product **3aa** was formed in only 29% yield monitored by NMR. After various attempts, we found that the best yield of **3aa** was obtained when the reaction was performed at 110 °C. When other copper salts were examined as catalyst, **3aa** was formed in lower yields (entries 5−7). Similar to many reactions using diaryliodonium salts, the reaction proceeded best in dichloroethane (DCE) among common solvents (entries 9−11). Apparently, 2 equiv of **1a** was required in this tandem cyclization, and when the loading was decreased to 1.5 equiv, product **3aa** was formed in 71% yield (entry 12). Thus, the optimal conditions for this reaction are shown as entry 3 in Table 1, and under these conditions **3aa** was isolated in 95% yield.

After realizing the cyclization of *o*-cyanoaniline **1a** and diphenyliodonium salt **2a**, the reaction was next extended to other diaryliodonium triflates (Scheme 2). Under the optimal

Scheme 2. Formation of *N*-Arylquinazolin-4(3*H*)-imines 3 from Various Diaryliodonium Salts 2



conditions, *o*-, *m*-, or *p*-ditolyliodoniums (**2b−d**) reacted smoothly with **1a** producing the corresponding quinazolin-4(3*H*)-imines **3ab−ad**, all in good yields. Diaryliodonium salts bearing a single halogen (F-, Cl-, or Br-) atom were suitable for the reaction to give the expected products **3ae−ak**. It was also pleasant to find that diaryliodonium salts could accommodate a trifluoromethylgroup (an electron-withdrawing group), methoxyl group (an electron-donating group), or poly substituents (**2n−s**) in this reaction to give corresponding products **3al−as**. It should be noted that when an unsymmetric diaryliodonium salt such as *p*-CF_3Ph-I^+-Mes was used to react with **1a**, the mesityl group was transferred to give product **3aq** rather than **3am** (eq 1).The structure of **3ai** was unequivocally confirmed with X-ray diffraction (Figure 1).[8]



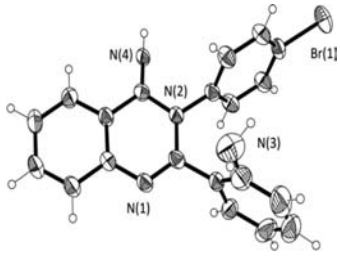
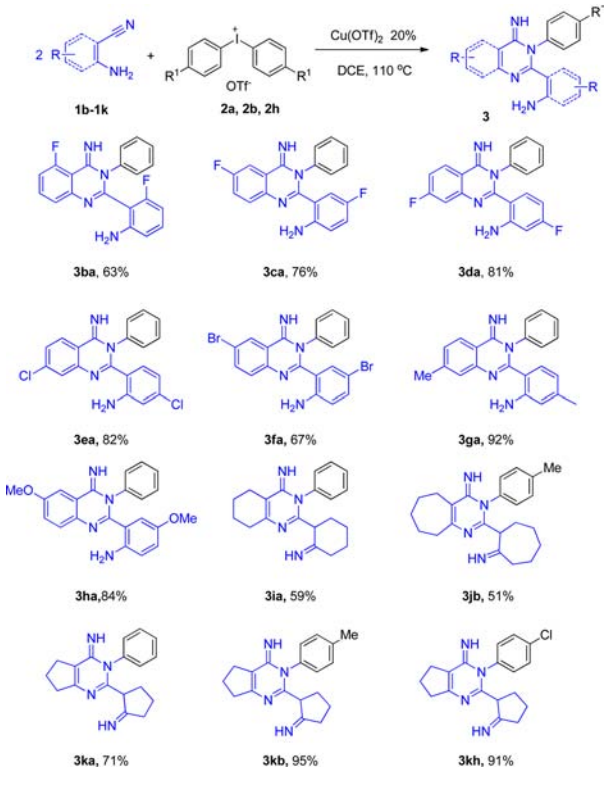


Figure 1. ORTEP drawing of **3ai**($C_{20}H_{15}BrN_4$) with 35% probability ellipsoids.

The above results were achieved demonstrating the generality of diaryliodonium salts for the synthesis of 3-arylquinazolin-4(3*H*)-imine derivatives. Next, we turned to prepare functional quinazolin-4(3*H*)-imine derivatives by varying the *o*-cyanoaniline derivatives. As shown in Scheme 3, *o*-cyanoanilines**1b−f** bearing a single halogen (F-, Cl-, or Br-) atom were also suitable for the reaction with **2a** to give expected products **3ba−fa**. The use of 5-methyl-2-cyanoaniline **1g** or 4-methoxyl-2-cyanoaniline **1h** gave the corresponding products **3ga** and

Scheme 3. Formation of Quinazolin-4(3*H*)-imines 3 from Various *o*-Cyanoanilines 1 and Analogues



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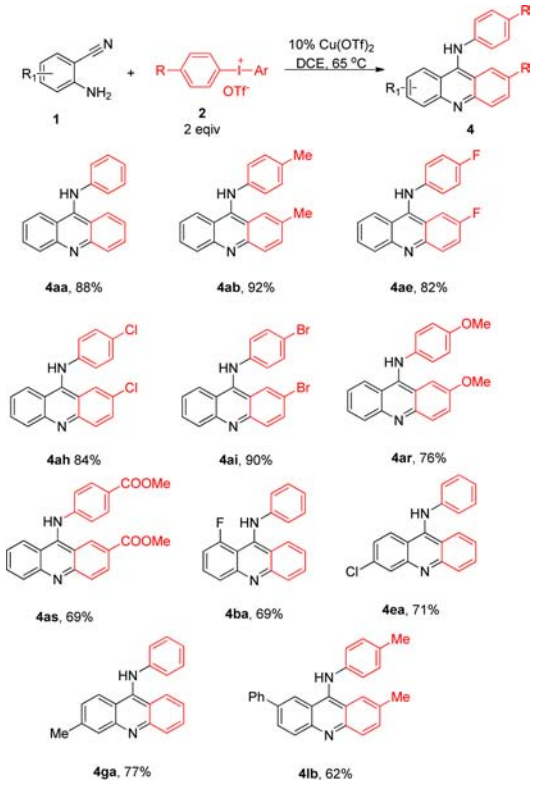
3ha in excellent yields. Excitingly, the reaction is applicable to 1-cyano-2-aminocyclohexene **1i**, i.e., a hydrogenated analogue of **1a**.[9] When 2 equiv of **1i** was reacted with **2a** under the standard conditions, tetrahydroquinazolin-4(3*H*)-imine (or more accurately, pyrimidine) derivative **3ia** was obtained in 59% yield. The analogous 1-cyano-2-aminocyclopentene **1j** and 1-cyano-2-aminocyclohexene **1k** were also suitable for this reaction to supply pyrimidine derivatives (**3jb**−**kh**). This is a unique approach to construct the pyrimidine backbone.

During the study, we found that a ratio of 2:1 for two substrates (*o*-cyanoanilines and diaryiodonium salts) was crucial for the formation of quinazolin-4(3*H*)-imine **3**. In fact, when the ratio of **1a** to **2a** was adjusted to 1:2, dramatically, the reaction could proceed well at 65 °C but produced acridine **4aa** in 90% yield instead. Since the acridine skeleton is featured in many dyes, drugs, and organic materials,[10] the scope of the reaction is worth extending. As shown in Scheme 4, a range of

Scheme 4. Formation of Acridines 4 from Various *o*-Cyanoanilines 1 and 2 Equiv of Diaryliodonium Salts 2



para-substituted diphenyliodonium salts reacted with *o*-cyanoaniline to produce **4aa**−**ai** in excellent yields. Diaryliodonium salts with a methoxyl group (an electron-donating group) or ester group (an electron-withdrawing group) also worked well to give products **4ar**−**as**. Moreover, various functionalized *o*-cyanoanilines were suitable for this reaction to give products **4ba**,**ea**,**ga**,**lb** in good yields. The product **4aa** was reported in the literature, and its structure was further confirmed by X-ray diffraction (Figure 2).[11,12]

Interestingly, di(*m*-tolyl)iodonium **2c** reacted with **1a** in a regioselective way to produce 3-methylacridine **4ac** without another isomer observed (eq 2).

According to others' and our work, both the cyano group and amino group can be arylated with diaryliodonium salts.[7,13] Apparently, on the basis of the findings in this paper, since the

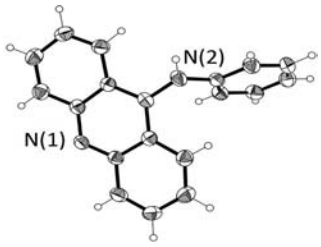
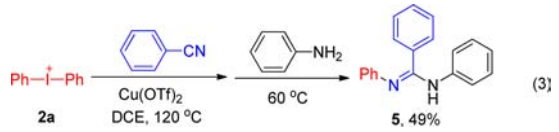


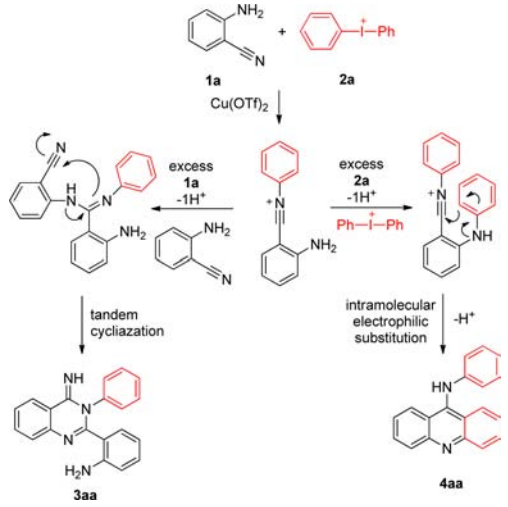
Figure 2. ORTEP drawing of **4aa**($C_{19}H_{14}N_2$) with 35% probability ellipsoids.

aryl group of diaryliodonium salt **2** was always attached to the nitrogen atom derived from the cyano group of **1**, the cyano group is considered to be more favorable for arylation than the amino group in *o*-cyanoaniline **1**. Actually, as shown in eq 3, the



reaction of diphenyliodonium **1a**, benzonitrile, and aniline in one pot could give compound **5**,[14] which contains the main backbone in quinazolin-4(3*H*)-imines **3**. As exemplified in Scheme 5, the reaction of **1a** with **2a** could produce *N*-

Scheme 5. Plausible Tandem Pathway for the Formation of Quinazolin-4(3*H*)-imines and Acridines by Assembling *o*-Cyanoanilines and Diaryliodonium Salts



phenylnitrilium intermediate **I** in the presence of $Cu(OTf)_2$.[7] When there is an excess amount of **1a** in the reaction mixture, intermediate **I** would be attacked by **1a** followed by tandem cyclization via intermediate **II** to give product **3aa**. On the other hand, if there is an excess amount of **2a** in the reaction mixture, the amino group in intermediate **I** would be further arylated by **2a** to give **III**, which could undergo intramolecular

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electrophilic substitution to produce **4aa**. Delightfully, these two pathways proceeded at different temperatures.

With the rapid growth of demand from pharmaceutics and the organic photoelectric industry for a large variety of nitrogen-containing heterocycles, the development of new synthetic approaches toward heterocycles with greater levels of molecular complexity from readily accessible starting materials is still one of the major research endeavors in modern organic synthesis. With two kinds of readily available starting materials (*o*-cyanoanilines and diaryliodonium salts), we realized two pathways to produce a range of quinazolin-4(3*H*)-imines and acridines via tandem cyclization modes. Assembly of other small molecules with this strategy to synthesize valuable heterocycles is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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