Organic LETTERS

Letter

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Mild Cu(I)-Catalyzed Cascade Reaction of Cyclic Diaryliodoniums, Sodium Azide, and Alkynes: Efficient Synthesis of Triazolophenanthridines

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Supporting Information

ABSTRACT: Linear iodoniums are widely used as arylating reagents. However, cyclic diaryl idodoniums are ignored despite their potential to initiate dual arylations, atom and step economically. In our current work, a three-component cascade reaction of cyclic diaryliodoniums, sodium azide, and alkynes has been successfully achieved under mild conditions, catalyzed by cheap copper species. The regioselectivity associated with unsymmetrical iodoniums was enhanced by installing two methyls ortho and para to the I^{III} center. The reaction enables a rapid access to a variety of complex molecules, triazolophenanthridine derivatives.

Transition-metal mediated cascade reactions constitute one of the most active research fields in modern organic synthesis.[1] These reactions are often performed in a catalytic manner with respect to the metal. The efficiency of such processes can be evaluated by the number of new bonds made, the turnover frequency of the catalyst, and the complexity of the final products. To date, copper has been widely used in such organic reactions, including copper-catalyzed azide−alkyne cycloaddition reactions (CuAAC),[2] Ullmann-type coupling reactions,[3] and Sonogashira coupling reactions.[4]

Linear diaryliodonium salts have found numerous applications as electrophilic arylating reagents in both transition-metal catalyzed and metal-free reactions with carbon and heteroatom nucleophiles.[5] In the arylation of the involved nucleophiles with linear diaryliodoniums, an iodoarene was produced along with the desired products and inevitably discarded as waste. Cyclic diaryliodoniums can avoid this problem because the generated iodoarene becomes a part of the arylated products (Scheme S1, Supporting Information).[6] Moreover, a cascade reaction could be set up if the incorporated iodoarene continues further transformations. However, to our best knowledge, the synthetic application of cyclic iodoniums is still less developed compared to linear iodoniums.[7]

We are interested in the development of synthetic methodology to conveniently construct libraries of complex molecules that can provide novel scaffolds in modern drug development. Recently, our group has prepared a series of cyclic diaryliodonium salts as NAD(P)H oxidase inhibitors.[8] To utilize these cyclic iodoniums for further transformation to complex molecules, we have successfully performed two types of reactions: an amine insertion for the construction of carbazoles[6a,b] and a multicomponent reaction with boronic acids and alkynes to prepare fluorenes.[6c]

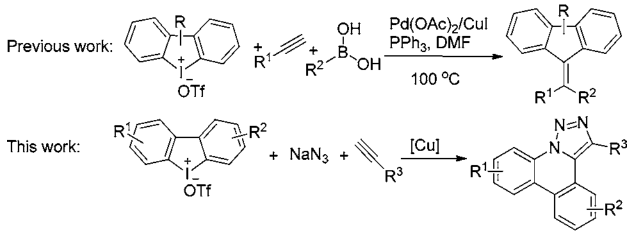
1,2,3-Triazoles have received much attention due to their unique properties in the material, chemical, and biological sciences.[9] Especially, they were reported to possess diverse biological activity including anti-HIV[10] and antiallergic properties.[11] They can be accessible from azides and alkynes via CuAAC under mild conditions. Phenanthridines are another important heterocycle, found in bioactive natural alkaloids and medicinally relevant compounds[12] that show antibacterial and antitumor activities.[13]

As aforementioned, our previous work reported a three-component reaction with cyclic iodoniums, alkynes, and boronic acids, catalyzed by the Pd/Cu system (Scheme 1). The reaction was initiated by alkynylation of the iodoniums, followed by aryl insertion to the intramolecular triple bond and Suzuki coupling. Recently, the reactions of linear diaryliodoniums and sodium azide were reported to afford aryl azides conveniently.[14] It was in our interest to investigate whether the paired reactions could be coupled and tuned in a cascade manner while three components, cyclic iodoniums, sodium azide, and alkynes, are reactive to each other. Herein, we demonstrate a well organized multicomponent cascade reaction with cyclic iodoniums, sodium azide, and alkynes to set up fused tetracycles, namely [1,2,3]triazolo[1,5-

Received: September 7, 2014
Published: October 22, 2014

dx.doi.org/10.1021/ol502654a | *Org. Lett.* 2014, 16, 5600−5603

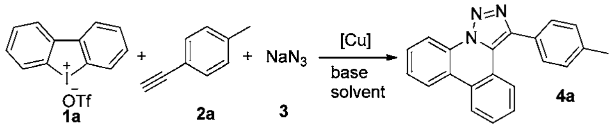
Scheme 1. Multicomponent Reactions with Cyclic Iodoniums



f]phenanthridines, catalyzed by cheap copper species under mild conditions.

To test our hypothesis, we initially carried out a one-pot reaction with cyclic iodonium **1a**, *p*-tolylacetylene **2a**, and sodium azide **3** in the presence of 1 equiv of CuI in anhydrous DMF at 50 °C for 5 h. As shown in Table 1, the desired product **4a** was obtained regardless of the presence of K_2CO_3 (entries 1–2). However, it seemed that an additional base favored the reaction. Then, other copper species including CuCl, $Cu(OAc)_2$, $CuBr_2$, $Cu(OTf)_2$, and $Cu(acac)_2$ were screened (entries 3–7). $CuBr_2$ and $Cu(acac)_2$ provided low yields while other copper catalysts gave modest yields, still inferior to CuI. A screening of bases was also carried out, and the results indicated that bases had a great influence on the reactions (entries 8–13). No desired product was obtained with KOH, and Cs_2CO_3 gave an unexpected low yield. $NaHCO_3$ was finally selected for further condition optimization, as it gave the best yield of the product (entry 13).

Table 1. Reaction Condition Optimization[a]



entry	catalyst	base	temp (°C)	solvent	time (h)	yield[b] (%)
1	CuI	K_2CO_3	50	DMF	5	54
2	CuI	–	50	DMF	5	38
3	CuCl	K_2CO_3	50	DMF	5	50
4	$Cu(OAc)_2$	K_2CO_3	50	DMF	5	51
5	$CuBr_2$	K_2CO_3	50	DMF	5	16
6	$Cu(OTf)_2$	K_2CO_3	50	DMF	5	47
7	$Cu(acac)_2$	K_2CO_3	50	DMF	5	20
8	CuI	KOH	50	DMF	5	ND
9	CuI	KO*t*-Bu	50	DMF	5	42
10	CuI	Cs_2CO_3	50	DMF	5	19
11	CuI	Na_2CO_3	50	DMF	5	55
12	CuI	K_3PO_4	50	DMF	5	60
13	CuI	$NaHCO_3$	50	DMF	5	63
14	CuI	$NaHCO_3$	50	DMSO	5	73
15	CuI	$NaHCO_3$	50	DCE	5	7.2
16	CuI	$NaHCO_3$	50	*i*-PrOH	5	6.6
17	CuI	$NaHCO_3$	50	dioxane	5	12
18	CuI[c]	$NaHCO_3$	50	DMSO	5	89
19	CuI[c]	$NaHCO_3$	40	DMSO	5	23
20	CuI[c]	$NaHCO_3$	60	DMSO	5	83
21	CuI[c]	$NaHCO_3$	70	DMSO	5	30
22	CuI[c]	$NaHCO_3$	rt	DMSO	5	ND
23	CuI[c]	$NaHCO_3$	50	DMSO	8	90
24	CuI[c]	$NaHCO_3$	50	DMSO	24	89

[a] Reaction conditions: **1a** (70.1 μmol), **2a** (1.5 equiv), **3** (1.5 equiv), catalyst (1 equiv), base (5 equiv) in anhydrous solvents (2 mL), under Ar. [b] HPLC yield. [c] Catalyst (0.1 equiv). Note: acac, pentane-2,4-dione; ND, not detected; DCE, 1,2-dichloroethane.

While investigating the effect of solvents, DMSO and DMF gave high yields compared to dichloromethane, isopropanol, and dioxane (entries 13–17). In the following studies, DMSO was employed as solvent. To our satisfaction, the yield still remained high while the amount of CuI was decreased to 10 mol % (entry 18). Our further studies indicated that heating at 50–60 °C gave the best yield while the reactions did not proceed at room temperature (entries 18–22). Finally, a reaction time longer than 5 h did not improve the yield obviously (entries 23–24). Thus, our final optimal reaction conditions used 10 mol % CuI and 5 equiv of $NaHCO_3$ in anhydrous DMSO at 50 °C for 8 h.

With the optimal reaction conditions in hand, we first explored the scope of alkynes with cyclic iodoniums **1a** and sodium azide **3** (Figure 1). It was found that the electron density of aryl alkynes played a role in the reactions. Both strong electron-donating groups (**4i**) and strong electron-withdrawing groups (**4j**) in the aryl alkynes provided low yields. Other aryl alkynes provided the products at good to excellent yields, in a range of 70% to 95% (**4a**–**4h**). In our method, halogens such as F and Cl were well

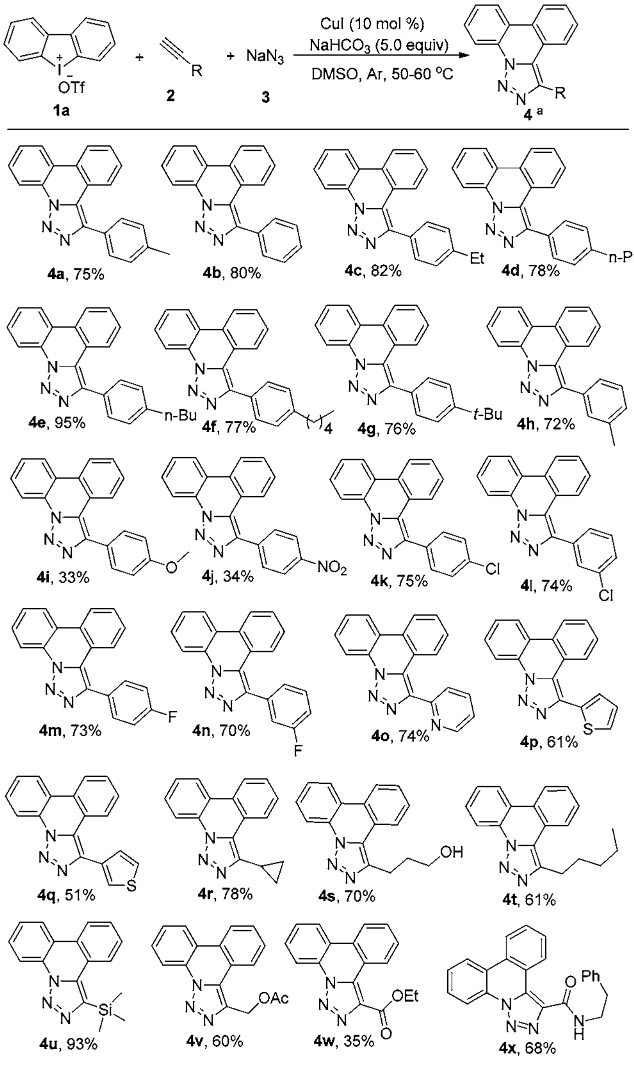


Figure 1. Scope of alkynes. [a] Isolated yields.

tolerated (**4k**–**4n**). Furthermore, the scope of heterocyles and alkyl alkynes was also exploited for the reaction. To our satisfaction, 2-pyridine and 2- or 3-thiozole tethered acetylenes also provided the expected triazolophenanthridines in good yields (**4o**–**4q**). Except for ethyl propiolate, alkyl alkynes provided the products in good yields (**4r**–**4x**). It is worth mentioning that these vulnerable functional groups including cyclopropyl (**4r**), hydroxyl (**4s**), trimethylsilyl (**4u**), and propargyl acetate (**4v**) were well tolerated. These functional groups provide opportunities for further transformation if needed.

The scope of cyclic symmetrical and unsymmetrical diaryliodoniums was also investigated (Figure 2). Under the reaction conditions, all the cyclic diaryliodoniums provided the expected products at modest to good yields. While an unsymmetrical diaryliodonium was exploited, our previous and current results indicated that electronic properties and weak steric effects did not solve the regioselectivity problem well (**5d**).[6c] It was recently reported that methyl substitutents ortho to the I^{III} center offered a modest acceleration in elimination rates under metal-free conditions.[15] In these reports, the arylation favored the ortho methyl substituted aryl side due to the ortho effect. Meanwhile, the Gaunt[16] and Sanford[17] groups have observed that the large steric substituents in unsymmetrical linear iodoniums forced the arylation to occur on the less hindered aryl side under transition-metal catalyzed systems. Thus, incorporation of steric groups orth and para to the I^{III} center of cyclic unsymmetrical iodoniums would therefore offer an opportunity to enhance the arylation regioselectivity although the precedent reports gave the opposite arylation preference. Accordingly, a series of unsymmetrical cyclic iodoniums with two methyl groups attached were prepared. Subsequently, the reactions were carried out. The regioselectivity turned out to be better while steric hindrance was more obvious (**5e**–**5g**). It seemed that the regioselectivity was still modest while the other side of the unsymmetrical iodoniums had no substituent (**5e**) or weak (methyl, **5f**) or strong electron-donating substituents (methoxyl, **5g**). However, to our satisfaction, almost one single isomer was obtained while an electron-withdrawing group was introduced to the other side to the iodoniums (**5h**–**5j**). Further experiments are still ongoing to investigate the influences of other factors on the regioselectivity.

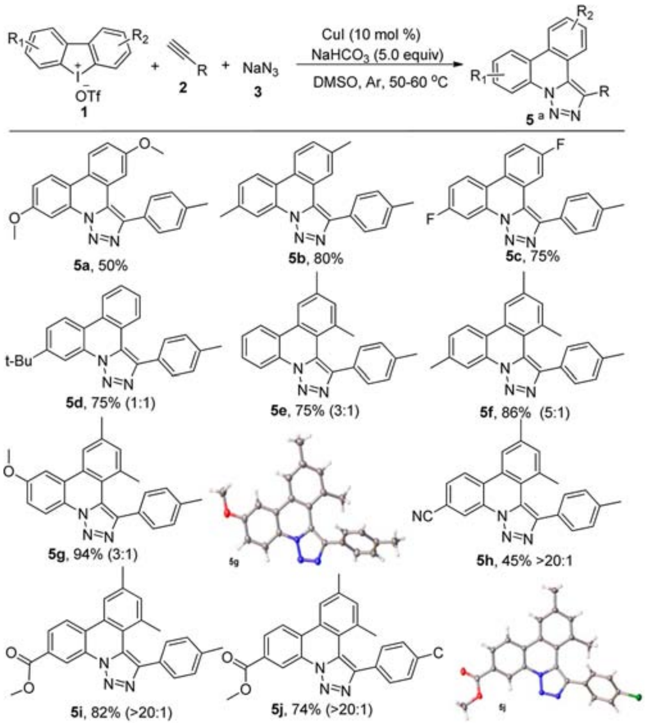
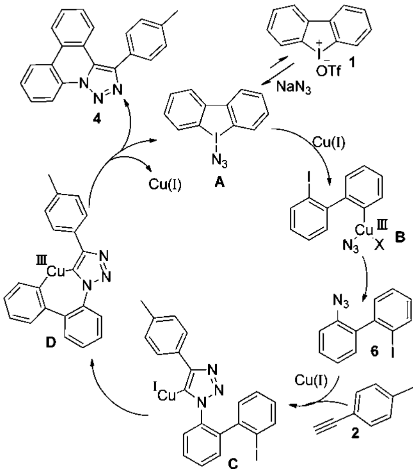


Figure 2. Scope of cyclic iodoniums. [a] Isolated yields. The structures of **5d**, **5g**, and **5j** were determined by crystal X-ray diffraction; see the Supporting Information.

It was known that three components, iodoniums, sodium azide, and alkyne, are reactive to each other. However, it seemed that our current reaction acted in a well organized way under the optimal conditions. To gain more insight into the mechanism, a number of reactions were carried out (Figure S1, Supporting Information). First, the iodonium **1a** and sodium azide were charged under the optimal conditions, and 2′-iodobiphenyl-2-azide **6** was obtained in a high yield (85%). It is noteworthy that the azidation did not take place in the absence of Cu species although arylation of linear diaryliodonims with some nucleophiles can be realized in the transition-metal-free systems.[18] The azide **6** was then able to react with *p*-tolylacetylene **2a** to provide the expected triazolophenanthridine **4a** in a high yield (95%). In another study, a mixture of **1a** and **2a** was stirred under our conditions for 8 h. Thin layer chromatography (TLC) indicated that the two starting materials remained unreactive. While sodium azide was then added to the mixture, the desired product **4a** was observed in 78% yield. Finally, it was of interest to investigate whether a triazole could react with iodonium **1a**, catalyzed by CuI. In practice, 4-(*p*-tolyl)-1*H*-1,2,3-triazole **8** was prepared beforehand and then stirred with **1a** under the optimal conditions. The TLC showed that no **4a** was generated. The only obtained product **9** was confirmed to link two species **8** and **1a** by a newly formed C–N bond via an Ullmann coupling reaction, without further cyclization. Based on our results, a plausible mechanism was proposed (Scheme 2). First, the iodoniums **1** and sodium azide interchanged an anion,[19] followed by an oxidative addition, and then a subsequent reductive elimination gave rise to **6**. A CuAAC reaction proceeded between intermediate **6** and alkynes to produce copper intermediate **C**. After another oxidative addition and reductive elimination cycle, triazolophenanthridine **4** was finally formed from **C**, and copper(I) species was regenerated for the next reaction cycle.

Scheme 2. Proposed Mechanism



In summary, we have successfully achieved a three-component cascade reaction by tuning and merging azidation of cyclic diaryliodonium, CuAAC, and Ullmann coupling reactions, catalyzed by cheap CuI. Four new bonds, including three C−N bonds and a C−C bond, and two new fused rings were created in one single operation. In addition, regioselectivity was enhanced for the reactions involving cyclic unsymmetrical iodoniums by installing two methyl substituents ortho and para to the I^{III} center. Our current work offers an efficient synthetic method to construct complex molecules, [1,2,3]triazolo[1,5-*f*]phenanthridines which might be biologically useful. The biological evaluation of these compounds is underway.

■ ASSOCIATED CONTENT

Supporting Information

The experiment procedure and characterization of the novel compounds. 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.

■ ACKNOWLEDGMENTS

The work was supported by the Doctoral Program of Higher Education of China (Grant 20110171120098), the National Basic Research Program of China (973 Program Grant 2012CB967004), and Guangdong Provincial International Cooperation Project of Science & Technology (2013B051000034).

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