Organic LETTERS

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Cu-Catalyzed Ring Opening Reaction of 2*H*-Azirines with Terminal Alkynes: An Easy Access to 3-Alkynylated Pyrroles

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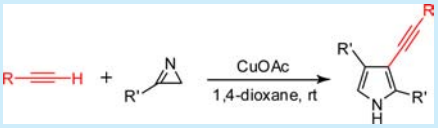
Supporting Information

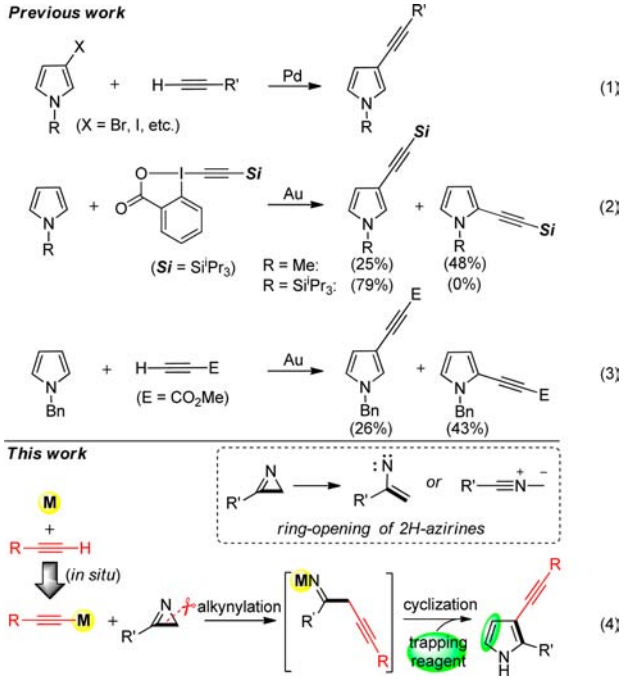
ABSTRACT: A highly efficient Cu-catalyzed ring expansion reaction of 2*H*-azirines with terminal alkynes has been developed. This transformation provides a powerful method for the synthesis of 3-alkynyl polysubstituted pyrroles under mild conditions in good yields. The direct transformation process, specific selectivity, and good tolerance to a variety of substituents make it an alternative approach to the reported protocols.



Pyrroles are not only key structures in numerous natural products and pharmaceuticals but also important building blocks in material sciences.[1] Consequently, the synthesis and functionalization of pyrroles have attracted much attention.[2] Owing to the rigidity property and convenient transformation of the triple bond, the introduction of an alkynyl group into pyrroles for constructing alkynylated pyrroles will bring about different physical, chemical, and pharmacological properties.[3] To date, many elegant catalytic methods have been developed for the synthesis of alkynylated pyrroles. However, most of these methods focused on the construction of a 2-alkynylated product due to the higher reactivity at the C2-position of pyrroles.[4] In constrast, only limited examples on the synthesis of 3-alkynylated pyrroles have been described. The cross-coupling reaction between pyrrole halides and terminal alkynes is one of the most widely used methods for constructing 3-alkynylated pyrroles, but it requires the premodification of the starting materials (Scheme 1, eq 1).[5] Recently, the direct alkynylation of pyrroles has emerged as a more efficient tool for the introduction of alkynyl groups. Waser reported a gold(I)-catalyzed alkynylation of pyrroles with a hypervalent iodine reagent via a formal inverse Sonogashira reaction,[6] and the regioselectivity largely depends on the *N*-substitution of pyrroles (Scheme 1, eq 2). Subsequently, Nevado documented a gold(I)-catalyzed oxidative cross-coupling of *N*-benzyl pyrrole and electron-deficient terminal alkynes, with mixtures of 2- and 3-alkynylated pyrroles as the products (Scheme 1, eq 3).[7] Despite these advances, most of these methods have some limitations with respect to the regioselectivity and substrate scope. Therefore, the development of an efficient strategy for the regioselective synthesis of 3-alkynylated pyrroles is still highly desirable yet a great challenge.

Strain-driven ring expansion is regarded as an effective method for the construction of carbo- and heterocyclic structures.[8] 2*H*-Azirines are highly strained three-membered heterocyclic compounds and have been exploited as useful precursors for reactive intermediates such as vinyl nitrenes and nitrile ylides.[9] Therefore, 2*H*-azirines have been employed in the synthesis of various N-containing heterocycles, such as pyrroles,[10] indoles,[11] pyridines,[12] isoquinolines,[13] and piperidines.[14] Among these

Scheme 1. Synthesis of Alkynylated Pyrroles



transformations, the C−N single bond of 2*H*-azirine is easily cleaved in the presence of heat, metal catalysts, nucleophilic reagents, or light irradiation. In this context, and following our ongoing interest in the synthesis of pyrroles,[15] we envisioned the possibility of transferring the alkynyl group to 2*H*-azirine through cleavage of the C−N single bond (Scheme 1, eq 4). In such a process, the nucleophilic addition of in situ generated metal acetylide species to 2*H*-azirine would produce an α-alkynylated imine species, which would be further captured by alkynes, alkenes, or azirines to construct 3-alkynylated pyrroles. Herein, we report a Cu-catalyzed ring expansion reaction of 2*H*-

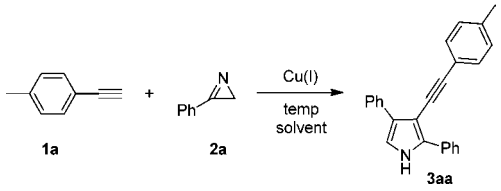
Received: July 31, 2014
Published: September 3, 2014

dx.doi.org/10.1021/ol502282j | *Org. Lett.* 2014, 16, 4806−4809

azirines to construct 3-alkynylated pyrroles in which the N-atom is unprotected.

Initially, we attempted to synthesize the target compound via a three-component reaction of 2*H*-azirine, terminal alkyne, and another molecule of alkyne or alkene but failed. Fortunately, without adding any additional trapping reagent, the reaction between 2*H*-azirine and terminal alkyne could provide the desired product. Therefore, 4-ethynyltoluene **1a** and 2*H*-azirine **2a** were selected as substrates for the optimization of reaction conditions (Table 1). To our delight, the desired 3-alkynylated

Table 1. Optimization of the Reaction Conditions[a]



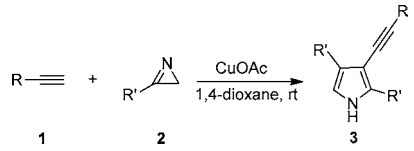
entry	Cu(I)	solvent	temp	**1a**/**2a**	yield (%)[b]
1	CuI	THF	50 °C	1:2.5	14
2	CuCN	THF	50 °C	1:2.5	21
3	CuOTf	THF	50 °C	1:2.5	15
4	CuOAc	THF	50 °C	1:2.5	52
5	CuOAc	toluene	50 °C	1:2.5	36
6	CuOAc	DCE	50 °C	1:2.5	52
7	CuOAc	1,4-dioxane	50 °C	1:2.5	77
8	CuOAc	1,4-dioxane	rt	1:2.5	83
9	CuOAc	1,4-dioxane	rt	1:2	56
10	CuOAc	1,4-dioxane	rt	1:3	89 (86)[c]
11	CuOAc	1,4-dioxane	rt	1:4	78

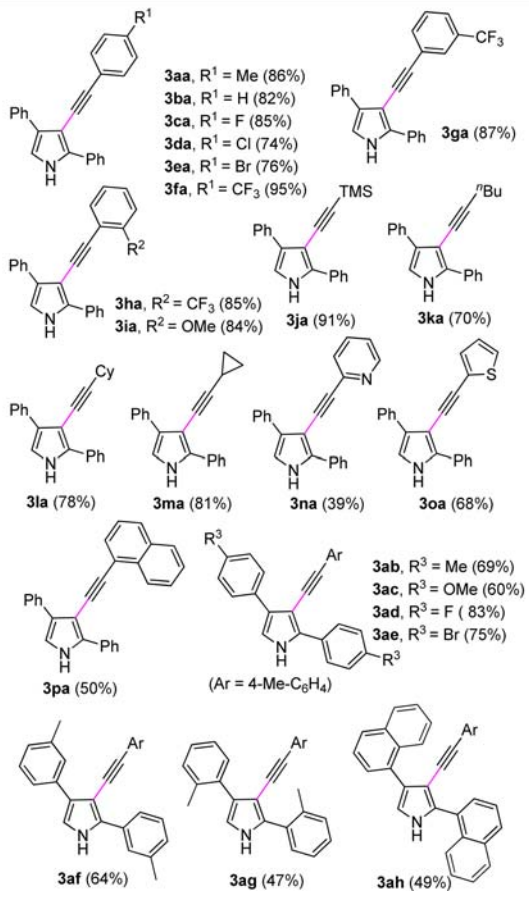
[a]Reaction conditions: alkyne **1a** (0.2 mmol), 2*H*-azirine **2a**, Cu(I) (10 mol %), solvent (2 mL), 20 h. [b]Determined by HPLC using biphenyl as an internal standard. [c]Isolated yield.

pyrrole **3aa** was obtained in 14% yield (Table 1, entry 1) when using CuI as a catalyst. A screening of Cu(I) catalysts showed that CuOAc was the most effective catalyst (Table 1, entries 1−4). Subsequently, examination of different solvents revealed that the reaction proceeded well in 1,4-dioxane and afforded the best result (Table 1, entries 4−7). Intriguingly, when decreasing the temperature to rt, the catalyst system was somewhat more effective (Table 1, entry 8). Increasing the ratio of **2a** to **1a** resulted in a slight improvement in the yield and afforded the desired product in 89% yield (Table 1, entry 10). However, decreasing or further increasing the ratio all jeopardized the yield (Table 1, entries 9 and 11). Therefore, the optimal conditions were established as follows: 10 mol % of CuOAc as the catalyst, with 3 equiv of **2a** in 1,4-dioxane at rt.

With the optimal conditions in hand, we examined the substrate scope of the reaction (Table 2). First, various aryl substituted terminal alkynes were investigated in this reaction with 2*H*-azirine **2a**. Both electron-withdrawing (**3ca**−**3ha**) and electron-donating (**3aa**, **3ia**) groups were compatible on the aryl alkynes, generating the functionalized products in good yields. Aryl alkynes with the CF_3 group at the *ortho*-, *meta*-, and *para*-positions were all well tolerated (**3fa**−**3ha**). Notably, the trimethylsilylacetylene afforded 3-alkynylated pyrrole **3ja**[16] in excellent yield, which could be easily converted into a free acetylene product or used as a precursor for further functionalization. Fortunately, not only aryl alkynes but also aliphatic alkynes could be transformed into corresponding

Table 2. Substrate Scope[a,b]





[a]Alkyne **1** (0.4 mmol) and 2*H*-azirine **2** (1.2 mmol) with CuOAc (10 mol %) in 1,4-dioxane (4 mL) at rt. [b] Isolated yields.

pyrroles (**3ka**−**3ma**). Both cyclohexylacetylene **1l** and cyclopropylacetylene **1m** reacted well with **2a** to afford the corresponding pyrroles **3la** (78%) and **3ma** (81%), respectively. The heterocyclic alkynes also reacted but with a lower yield, which may be attributed to the decreased activity of the catalyst caused by heteroatoms (**3na**, **3oa**). In addition, the reaction of sterically hindered 1-naphthylacetylene (**1p**) afforded the product with a slightly lower yield (**3pa**).

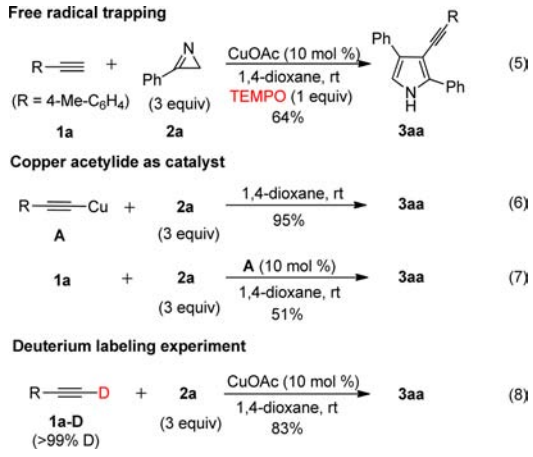
Subsequently, we turned our attention to evaluate various 2*H*-azirines with alkyne **1a**. Generally, most reactions proceeded smoothly to give 3-alkynylated pyrroles in moderate yields (**3ab**−**3af**). Reactions with both electron-rich and -deficient aryl groups gave the corresponding products in moderate to good yields (**3ab**−**3ae**). 2*H*-Azirines with a *meta*- and *ortho*-methyl group on the phenyl ring afforded the corresponding 3-alkynylated pyrroles **3af** and **3ag** in 64% and 47% yield, respectively. The steric effect may be the main reason for the low yield of **3ag**. A similar result was also observed in the reaction of **1a** with **2h** which bears a sterically demanding naphthyl group, leading to the formation of **3ah** in 49% yield.

To clarify the reaction mechanism, a series of control experiments were conducted under standard conditions. In the

dx.doi.org/10.1021/ol502282j | *Org. Lett.* 2014, 16, 4806−4809

presence of a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the reaction provided pyrrole **3aa** in 64% yield (Scheme 2, eq 5, versus 86% yield in Table 1, entry 10). This

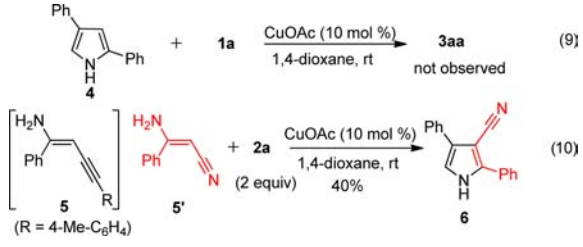
Scheme 2. Control Experiments



observation indicated that the reaction could not be triggered through a radical pathway. It is noteworthy that copper acetylide **A** was precipitated during the reaction process when terminal alkyne **1a** was added into the solution of CuOAc in 1,4-dioxane. Therefore, copper acetylide **A** was isolated and then subjected into the reaction system. Without the addition of alkyne **1a**, the reaction of 2*H*-azirine **2a** and a stoichiometric amount of **A** generated pyrrole **3aa** in 95% yield (Scheme 2, eq 6). Moreover, the reaction of alkyne **1a** and 2*H*-azirine **2a** in the presence of 10 mol % of **A** afforded the desired product in 51% yield. These experiments suggested that copper acetylide **A** attacked 2*H*-azirine at the beginning and acted as a real catalyst (Scheme 2, eq 7). Notably, the reaction of **2a** with deuterated terminal alkyne **1a-D** afforded **3aa** in 83% yield without accompanying any deuterated product (Scheme 2, eq 8). The production of ammonia (NH_3) was expectedly detected by a gas mass spectrometer after reaction completion,[17] demonstrating that ammonia was removed as a byproduct in the reaction.

Furthermore, the exposure of the C3-unsubstituted pyrrole **4** and alkyne **1a** to the standard reaction conditions failed to deliver any 3-alkynylated pyrrole **3aa** (Scheme 3, eq 9), revealing that

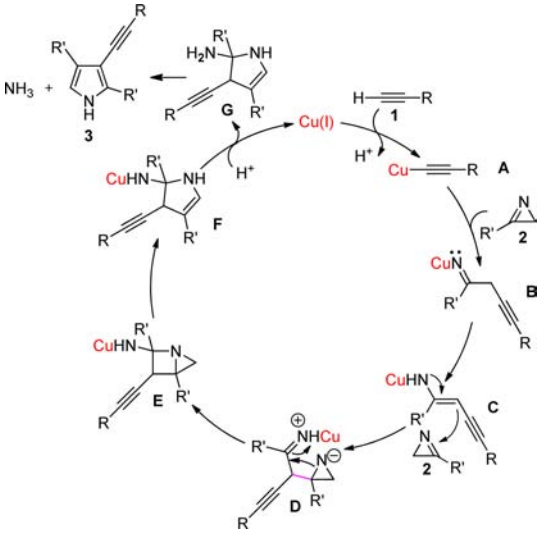
Scheme 3. Intermediate Simulation Experiment



the alkynyl moiety was not introduced into the pyrrole ring via the Cu-catalyzed cross-coupling between **4** and **1a**. In contrast, the alkynyl moiety might be performed in the C3-position of the pyrrole ring before its formation. Accordingly, we envisioned that an α-alkynylated imine species (Scheme 1, eq 4) might be involved. However, attempts to synthesize yne-enamine intermediate **5** did not succeed. Fortunately, a structure similar to that of (*Z*)-3-amino-3-phenylacrylonitrile **5′** was synthesized[18] to test the reaction. The reaction of **5′** and 2*H*-azirine **2a** provided pyrrole **6** in 40% yield (Scheme 3, eq 10), which was analogous to **3aa**. This discovery indicated that the reaction maybe go through the yne-enamine intermediate.

On the basis of these experimental data, a plausible mechanism was proposed (Scheme 4). Initially, copper acetylide **A** is formed

Scheme 4. Possible Reaction Pathway



from terminal alkyne in the presence of Cu(I) salt. The reaction of copper acetylide **A** with 2*H*-azirine leads to cleavage of the C−N single bond of 2*H*-azirine and generates copper-imine species **B**, which readily isomerizes to afford copper-enamine species **C**. Intermediate **C** then attacks another molecule of 2*H*-azirine on the imine carbon to generate species **D**. Subsequently, an intramolecular cyclization reaction occurs to give intermediate **E**, which is quickly transformed into the pyrroline intermediate **F** driven by ring strain.[19] Further protonation of **F** regenerates Cu(I) into the catalytic cycle and provides intermediate **G**. Finally, elimination of one molecule of ammonia from **G** affords 3-alkynylated pyrrole product **3**. It is noteworthy that the C≡C triple bond of alkyne remains unchanged in this pathway.

In conclusion, we have developed a powerful strategy for the synthesis of 3-alkynylated pyrroles from 2*H*-azirines and terminal alkynes at rt. In the presence of the CuOAc catalyst, this approach provides a straightforward access to the 3-alkynyl polysubstituted pyrroles with complete regiocontrol. A possible mechanism involving the yne-enamine intermediate is proposed to satisfactorily elucidate the generation of 3-alkynylated pyrroles. In view of the direct transformation process, specific selectivity, mild reaction conditions, and good functional group tolerance, we believe that this protocol would be potentially utilized in synthetic chemistry. Further exploration of a detailed mechanism and other reactions involving 2*H*-azirines is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, X-ray structure, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol502282j | *Org. Lett.* 2014, 16, 4806−4809

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (21372219, 21172218).

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(16) CCDC 993260 contains the supplementary crystallographic data for **3ja** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ddcd.cam.ac.uk/data_request/cif.

(17) See Figure 1 in the Supporting Information.

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