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COMMUNICATION

Multiple-Functionalizations of Terminal Alkynes with Sodium Sulfinates and *tert*-Butyl Nitrite: Facile Synthesis of 2*H*-Azirines

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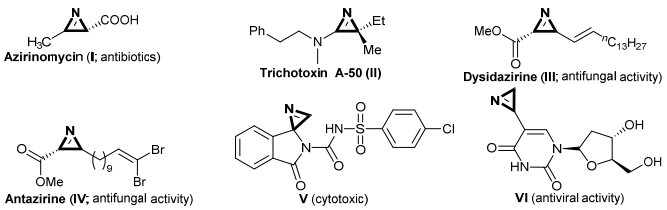
Xingyi He,[a] Xin Yue,[a] Lei Zhang,[a] Shuang Wu,[a] Ming Hu*,[a] and Jin-Heng Li*[abc]

A new, catalyst-free tandem annulation access to 2,2-disulfonyl-2*H*-azirines *via* multiple-functionalizations of terminal alkynes with sodium sulfinates and *tert*-butyl nitrite is described. The use of sodium sulfinates and *tert*-butyl nitrite enables the formation of sulfonyl and NO radicals to selectively initiate and terminate the tandem annulation protocol, constituting a straightforward, conceptually different method to existing 2*H*-azirine synthesis techniques that are currently required multiple steps by prior activation of the common starting materials.

2*H*-Azirines represent important *N*-heterocyclic compounds that are ubiquitously encountered in natural products, pharmaceuticals, agrochemicals and organic materials (Scheme 1).[1] In addition, 2*H*-azirines have proved to be versatile precursors of nitrenes, electrophiles, dienophiles, and dipolarophiles that are widely utilized to synthesize complex nitrogen-containing non-cyclic molecules and various azacyclic compounds, such as pyrroles, indoles, pyrazolo[1,5-a]pyridines, oxazoles, isoxazoles and piperidines.[2] Inspired by their broad utility, many practical methods have been established, such as the Neber reaction of imine substrates (Scheme 2a),[3] thermal/photochemical rearrangement of vinyl azides (Scheme 2b),[4] ring contraction of isoxazole/oxazaphosphole derivatives (Scheme 2c)[5] and elimination/oxidation of aziridines (Scheme 2d).[6] Such precedents remain a challenge of the requirement of pre-functionalized starting materials that are generated from the reaction of common chemicals (e.g., alkynes, alkenes, carbonyls) with the nitrogen source reagents, thereby offering limited functional 2*H*-azirine frameworks. Therefore, development of general strategies that utilize common, especially commercial available starting materials directly in a single reaction toward these structures is strongly appealing.



Scheme 1. Important examples of biologically active 2*H*-azirines.

Recently, annulation of common starting materials (e.g., alkynes) for the construction of the aziridine skeletons in one pot was proven to be particularly attractive.[7] Yet, examples of such available transformations are rare, and the ability to effectively control the simultaneous incorporation of a new external nitrogen fragment and the other functional reagents across a simple alkyne in a single reaction remains an elusive goal in synthetic endeavors. In 2015, Liu and co-workers[7a] developed a room temperature, one-pot access to CF_3-containing azirines in two steps by copper-catalyzed trifluoromethylazidation with simple there-component starting materials (terminal alkynes, Togni's reagent and $TMSN_3$) followed by a photocatalyzed rearrangement. Meanwhile, Liang and co-workers have reported a similar copper catalysis which enables the formation of CF_3-containing azirines in a single reaction promoted by NaOAc base under heating (80 °C).[7b] The Liang group[7c] and Yu/Han group[7d] have independently extended this copper catalysis to annulation cascades of enynes with Togni's reagent and $TMSN_3$ for producing complex functionalized aziridines in one step with the aid of heating (60 to 90 °C).

Herein, we report a new annulation reaction of terminal alkynes with sodium sulfinates using *tert*-butyl nitrite as nitrogen source[8] for the synthesis of functionalized 2*H*-azirines (Scheme 2e). This method is distinguished by its success achieved through the use of common, most commercial available starting materials under mild, catalyst-free conditions, as well as by its exquisite chemo- and site-selectivity, thus allowing the formation of 2,2-disulfonyl-2*H*-azirines via multiple-functionalizations of terminal alkynes.

Our investigations began by assessing three-component tandem annulation of 1-bromo-4-ethynylbenzene (**1a**) with sodium

[a] Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China
[b] State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China
[c] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China
E-mail: huming0731@163.com and jhli@hnu.edu.cn

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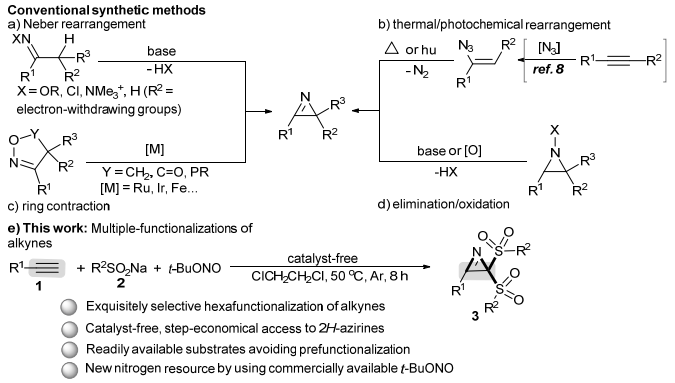
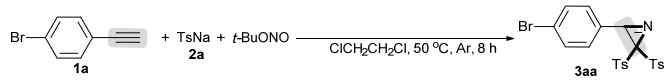


Scheme 2. Synthesis of 2*H*-azirines.

optimization of the reaction conditions, the reaction in $ClCH_2CH_2Cl$ at 50 °C for 8 h afforded the desired azirine **3aa** in 75% yield along with trace of 1,2,5-oxadiazole 2-oxide **4aa** (entry 1).[9] Other solvents, namely, THF, toluene, $HCONMe_2$ and $MeCONMe_2$ also exhibited reactivity, but they were less effective than $ClCH_2CH_2Cl$ (entries 2-5). A higher amount of TsNa (4 equiv) had no improvement of the yield of **3aa** (entry 6), and a lower amount of TsNa (2.2 equiv) had a negative effect (entry 7). Brief screening of the amounts of *t*-BuONO indicated that 3 equiv was preferred (entries 1, 8 and 9). Lowering (entry 10) or raising (entry 11) reaction temperatures led to diminishing yields of **3aa**. The diminishing yields in entry 10 & 11 was a result of incomplete conversion in lower temperatures and a possibility of product **3aa** instability under higher temperatures. The reaction still proceeds efficiently at 1 mmol loading of alkyne **1a**, affording **3aa** in high yield (entry 12).

Table 1 Screening of optimal reaction conditions[a]

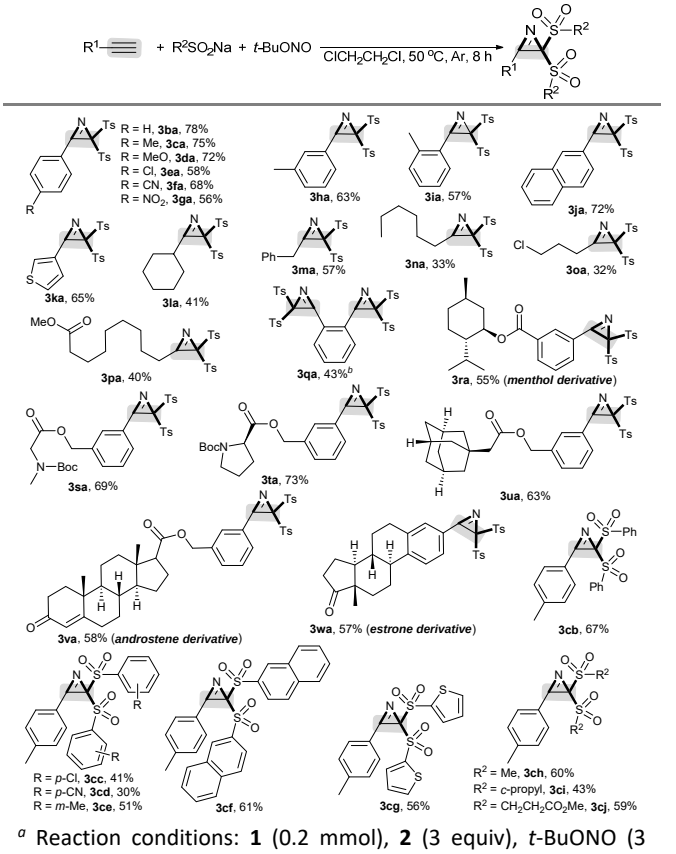


Entry	Variation from the standard conditions	Isolated yield (%)
1	none	75
2	THF instead of $ClCH_2CH_2Cl$	8
3	toluene instead of $ClCH_2CH_2Cl$	12
4	$HCONMe_2$ instead of $ClCH_2CH_2Cl$	15
5	$MeCONMe_2$ instead of $ClCH_2CH_2Cl$	23
6	TsNa (4 equiv)	76
7	TsNa (2.2 equiv)	63
8	*t*-BuONO (4 equiv)	74
9	*t*-BuONO (2 equiv)	53
10[b]	at 40 °C	39
11	at 70 °C	43
12[c]	none	70

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (3 equiv), *t*-BuONO (3 equiv), $ClCH_2CH_2Cl$ (2 mL), 50 °C, argon and 8 h. [b] > 40% of **1a** was recovered. [c] **1a** (1 mmol) and 16 h.

With the optimal reaction conditions in hand, we set out to investigate the generality of the catalyst-free tandem annulation protocol with terminal alkynes **1** and sodium sulfinates **2** using *t*-BuONO as the nitrogen source for the synthesis of 2,2-disulfonyl-2*H*-azirines (Table 2). In the presence of sulfinate **2a** and *t*-BuONO, a wide range of aryl alkynes **1b-k, 1q-w** and alkyl analogues **1l-p** could be utilized as substrates, giving the targeted 2*H*-azirine **3ba-wa** in moderate to good yields. For common arylalkynes, an array of substituents, including Me, MeO, Cl, CN, and NO_2, on the aryl ring were tolerated well, and both the electronic nature and position affected the reactivity (**3ba-ia**). Alkynes **1b-d**, possessing electron-rich C_6H_5, *p*-MeC_6H_4 and *p*-$MeOC_6H_4$ groups, respectively, were converted efficiently into **3ba-da** in 72-78% yields. Whereas alkynes **1f-g** with an electron-deficient group (e.g., *p*-CNC_6H_4 and *p*-$NO_2C_6H_4$) delivered **3fa-ga** in diminishing yields. The reactivity of Me-substituted arylalkynes **1c, 1h-i** decreased from *para* (**3ca**) to *meta* (**3ha**) to *ortho* substitution (**3ia**) in terms of yields. Both 1-ethynylnaphthalene **1j** and 3-ethynylthiophene **1k** were viable substrates (**3ja-ka**). Using ethynylcyclohexane **1l** allowed the formation of **3la** smoothly. Other alkylalkynes **1m-p**, even bearing a functional group (e.g., phenyl, Cl, ester), could all be accommodated perfectly, albeit with lower yields (**3ma-pa**). Interestingly, two 2*H*-azirine rings could be incorporated in the resulting product **3qa** when using 1,3-diethynylbenzene **1q**. Notably, the synthetic utility of the annulation protocol in modified bioactive molecules and drug derivatives were examined. Ethynylarenes built on the backbones of menthol, glycine, D-proline, adamantine, 3-oxo-androstene and estrone[10] underwent the annulation efficiently, affording the valuable products **3ra-wa** in 55-73% yields. However,

Table 2. Synthesis of 2*H*-azirines (**3**).

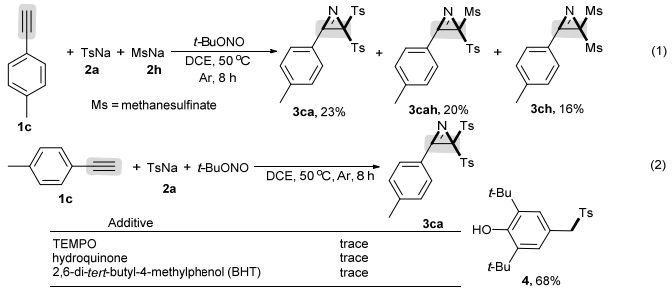


[a] Reaction conditions: **1** (0.2 mmol), **2** (3 equiv), *t*-BuONO (3 equiv), $ClCH_2CH_2Cl$ (2 mL), 50 °C, argon and 8 h. [b] **1a** (1 mmol) and 16 h. [b] **2a** (6 equiv), *t*-BuONO (6 equiv) and DCE (4 mL).

ethyl propiolate (**1x**) had no reactivity for the reaction.

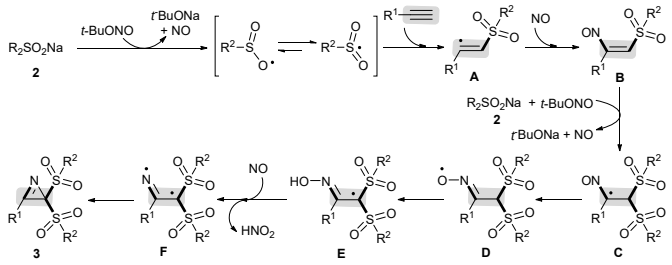
This annulation technology was applicable a host of sodium sulfinates (**3cb-cj**), including arylsulfinates and alkylsulfinates. In the presence of alkyne **1c** and *t*-BuONO, the reaction could be performed efficiently with sodium arylsulfinates containing various aryl groups, such as C_6H_5 (**3cb**), *p*-ClC_6H_4 (**3cc**), *p*-CNC_6H_4 (**3cd**), *m*-MeC_6H_4 (**3ce**), naphthalen-2-yl (**3cf**) and thiophen-2-yl (**3cg**). Alkysulfinates, possessing a methyl, a cyclopropyl or a 3-methoxy-3-oxopropyl group, were also competent reaction partners to access the corresponding products **3ch-cj**.

As shown in Scheme 3, control reaction of alkyne **1c** with a mixture of TsNa **2a** and sodium methanesulfinate (MsNa) **2h** in the presence of *t*-BuONO afforded three products, **3ca**, **3ch** and a cross product **3cah** (eqn (1)). The chemoselectivity supports addition of sulfonyl radical twice during the annulation process. Notably, the reaction of alkyne **1c** with TsNa **2a** and *t*-BuONO was inhibited completely by a radical inhibitor [e.g., TEMPO, 2,6-di-*tert*-butyl-4-methylphenol (BHT) and hydroquinone], and 2,6-di-*tert*-butyl-4-(tosylmethyl)phenol **4** was formed by the reaction between BHT and TsNa (eqn (2)). These results suggest that the reaction is initiated by sulfonyl radical.



Scheme 3. Control experiments.

The possible mechanisms for the tandem annulation protocol are proposed in Scheme 4 on the basis of the previous reported results[7,8] and the current results. Initially, the reaction of sodium sulfinate **2** with *t*-BuONO affords the sulfonyl radical, the NO radical and *t*-BuONa.[8] Subsequently, selective addition of the sulfonyl radical across the C≡C bond of alkyne **1** forms the sulfonyl-containing vinyl radical **A**, followed by radical coupling with NO to produce the intermediate **B**. The second radical addition of the sulfonyl radical across the C=C bond of the intermediate **B** gives the C(sp^3)-centred radical intermediate **C**, which would sequentially undergo isomerization to generate the other C(sp^3)-centred radical intermediate **E**. The reaction between the intermediate **E** and the NO radical leads to the formation of the two radical-containing intermediate **F** and HNO_2. Finally, intramolecular radical coupling



Scheme 4. Possible reaction mechanism.

occurs and delivers the desired 2,2-disulfonyl-2*H*-azirine **3**.

In summary, we have developed a mild, catalyst-free, chemo- and site-selective tandem annulation of various terminal alkynes with sodium sulfinates and *t*-BuONO for producing 2,2-disulfonyl-2*H*-azirines. This reaction allows the formation of four new chemical bonds, two C(sp^3)-S bonds, one C(sp^3)-N bond and one C=N bond, via radical-mediated multiple-functionalizations of terminal alkynes, and represents a new, straightforward technology for the construction of the 2*H*-azirine frameworks using *tert*-butyl nitrite as the nitrogen source where avoids use of acid, base and transition-metal catalysts. Moreover, additional highlights involves derivatization of the bioactive structural systems by incorporation of a 2,2-disulfonyl-2*H*-azirine unit.

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9 CCDC 1871132 (**3aa**) 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.

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