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MeOTf-Induced Carboannulation of Isothiocyanates and Aryl Alkynes with C═S Bond Cleavage: Access to Indenones

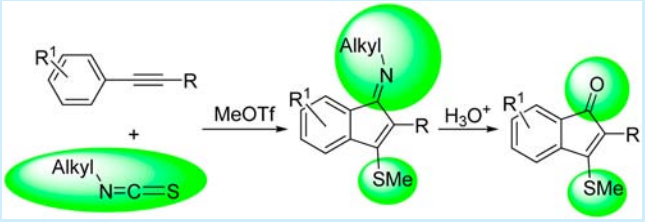
Peng Zhao,[†] Yu Liu,[†] and Chanjuan Xi*[,†,‡]

[†]Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

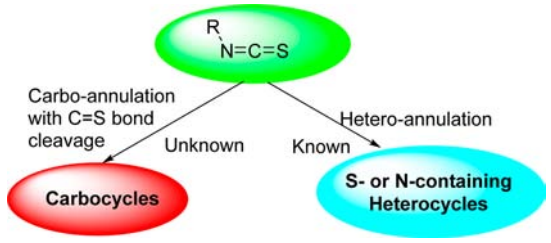
Supporting Information

ABSTRACT: MeOTf-induced carboannulation of alkyl isothiocyanates and aryl alkynes for the synthesis of indenones in good yields under metal-free conditions with C═S bond cleavage is described. The thioalkoxy group at the 3-position of the indenone can also be converted into other functional groups, such as phenyl, methylsulfonyl, amino, and ethoxy groups.



Isothiocyanates possess the chemical group −N═C═S, which represents versatile reactivity in the synthesis of nitrogen- or sulfur-containing heterocycles,[1] including thiohydantoins, thiopyrimidones, thioquinazolones, mercaptoimidazoles, benzoimidazolethiols, benzothiazolamines, and benzothiazines, which are valuable skeletons in synthetic chemistry, biology, and materials.[2] Nevertheless, to the best of our knowledge there has been no report of exhaustive cleavage of the C═S bond of isothiocyanates for the construction of carbocyclic compounds (Scheme 1).

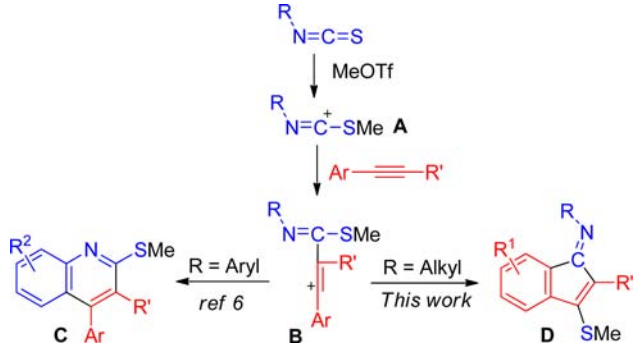
Scheme 1. Annulation of Isothiocyanates



Indenones are important carbocycles that are ubiquitous in pharmaceutical and material sciences.[3] A variety of methodologies for their synthesis have been reported.[4,5] Among these methods, transition-metal-catalyzed annulation of functionalized arenes with alkynes has been widely achieved for the construction of indenones.[5] Nonetheless, annulation of functionalized arenes with alkynes under metal-free conditions has rarely been reported.[6a] Herein we describe the methyl triflate (MeOTf)-induced intermolecular carboannulation of alkyl isothiocyanates and aryl alkynes with C═S bond cleavage to provide access to indenones.

We recently reported MeOTf-triggered annulation of aryl isothiocyanates and alkynes leading to multiply substituted quinolines.[7] In this process, MeOTf as an electrophile reacts with the aryl isothiocyanate to form methylthio-substituted carbenium ion **A**, which is followed by the reaction with the alkyne to form intermediate **B** and subsequent electrophilic annulation to give the quinoline **C** (Scheme 2). During the course of our studies of the MeOTf-triggered annulation,[6,7] we found a new reaction of alkyl isothiocyanates, alkynes, and MeOTf with C═S bond cleavage to form ketamine **D**, which affords an indenone after workup (Scheme 2).

Scheme 2. MeOTf-Induced Reactions of Isothiocyanates and Alkynes



On the basis of our former research work on triflate-triggered annulation,[6,7] we initially explored the reaction of ethyl isothiocyanate (**1a**), MeOTf (**2a**), and diphenylacetylene (**3a**) in a 1.5:3:1 ratio in dichloroethane (DCE) at different temperatures for 1.5 h (Table 1, entries 1−5), and 100 °C was found to be the best temperature for this reaction, with an isolated yield of 75% (entry 4). Then different solvents were screened, such as CH_3CN, dimethylformamide (DMF),

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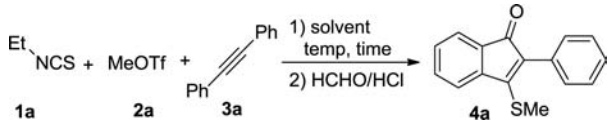
Table 1. Optimization of the Reaction Conditions for the Formation of 4a[a]



entry	T/°C	t/h	solvent	yield/%[b]
1	rt	1.5	DCE	NR
2	60	1.5	DCE	42
3	80	1.5	DCE	65
4	100	1.5	DCE	75
5	120	1.5	DCE	69
6	100	1.5	CH_3CN	NR
7	100	1.5	DMF	NR
8	100	1.5	CH_2Cl_2	55
9	100	1.5	$CHCl_3$	45
10	100	1.5	CCl_4	28
11	100	0.2	DCE	32
12	100	0.5	DCE	56
13	100	1	DCE	63
14	100	2	DCE	69
15	100	6	DCE	58

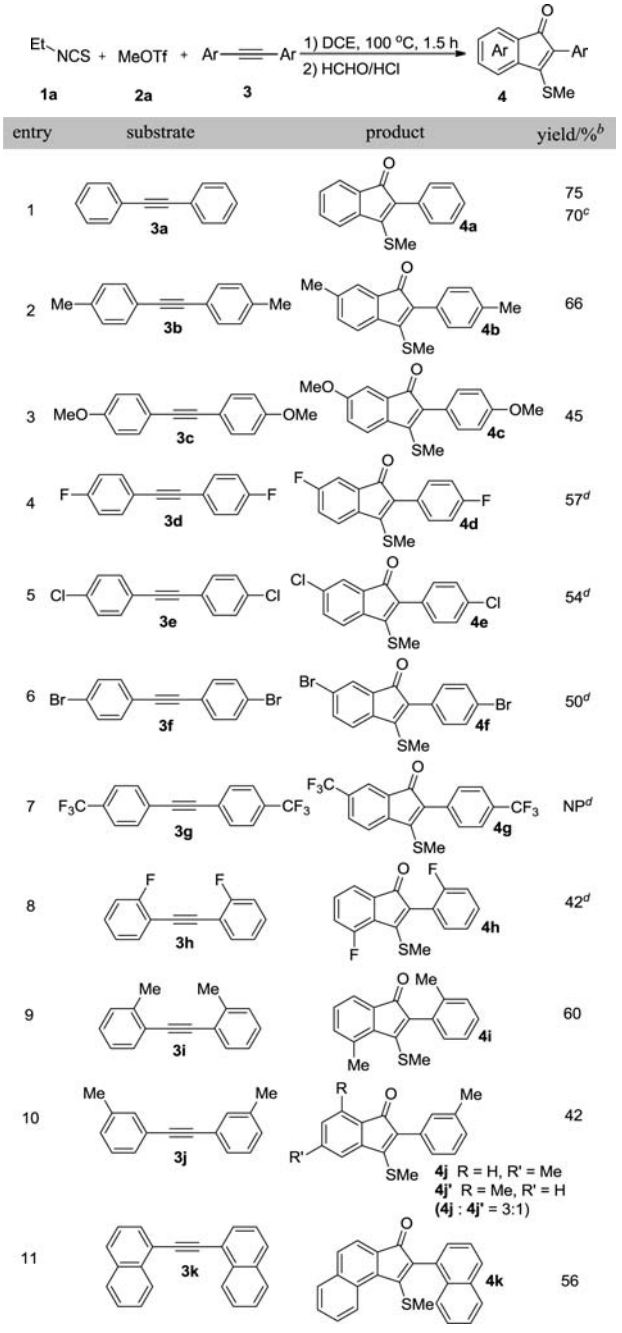
[a]Reaction conditions: 0.5 mmol of **3a**, 0.75 mmol of **1a**, and 1.5 mmol of MeOTf in 2 mL of solvent in a sealed tube under nitrogen. [b]Isolated yields.

dichlomethane (CH_2Cl_2), chloroform ($CHCl_3$), and tetrachloromethane (CCl_4) (entries 6−10). DCE was found to be the superior solvent for this reaction (entry 4). Furthermore, the effect of the reaction time was also examined (entries 4 and 11−15), and the best time for improving the yield was 1.5 h (entry 4). On the basis of the above results, the optimal conditions are shown in entry 4.

Having identified the optimized reaction conditions, we first tested various symmetrical diarylacetylenes (Table 2). Diarylacetylenes having various electron-donating and electron-withdrawing groups at the *para* positions of the benzene rings reacted without incident to give indenone derivatives in good yields (entries 1−6), except for *p*-trifluoromethyl-substituted diphenylacetylene **3g**, wherein the strong electron-withdrawing group largely inhibited the reaction (entry 7). Other functional groups such as methyl and halides, including fluoro, chloro, and bromo groups, were tolerated (entries 2 and 4−6). When 1,2-bis(4-methoxyphenyl)ethyne (**3c**) was used, the product **4c** was formed in modest yield (entry 3), which may be due to the interaction of MeOTf and the methoxy group. To our delight, the structure of **4b** was confirmed by single-crystal X-ray diffraction (see the Supporting Information). The reactions of *o*-fluoro- and *o*-methyl-substituted diphenylacetylenes gave the desired products in moderate yields (entries 8 and 9, respectively). The reaction of *m*-methyl-substituted diarylacetylene **3j** gave a mixture of two regioisomers in a 3:1 ratio. A substrate with a naphthalene nucleus, 1,2-bis(naphthalen-1-yl)acetylene (**3k**), afforded the corresponding indenone **4k** in 56% yield. Crystals of **4k** suitable for X-ray analysis were obtained (see the Supporting Information), and this result further confirmed the formation of indenone with the C═S bond cleavage.

Next, we tried a range of unsymmetrical diaryl alkynes with **1a** and MeOTf (Table 3). When asymmetric diaryl alkynes such as (4-methoxyphenyl)phenylacetylene (**3l**) or (4-trifluoromethylphenyl)phenylacetylene (**3m**) was used as the

Table 2. Synthesis of Indenones from Various Symmetrical Diarylacetylenes[a]



[a]Reaction conditions: 0.5 mmol of alkyne, 0.75 mmol of **1a**, and 1.5 mmol of MeOTf in 2 mL of DCE at 100 °C for 1.5 h. [b]Isolated yields. [c]Yield for gram scale. [d]At 120 °C for 12 h.

substrate, a single regioisomer was obtained in modest yield (entries 1 and 2). The annulation occurred selectively in the electron-rich benzene ring. This may occur because the electron-rich benzene ring is more stable for formation of intermediate **B**. When 1-(phenylethynyl)naphthalene (**3n**) was employed, a single product **4n** was obtained in 60% yield, with the annulation occurring in the naphthalenyl group. To our delight, the reaction could also proceed with aryl alkyl alkynes. The reactions of 1-phenyl-1-propyne (**3o**), 1-phenyl-1-butyne (**3p**), and 1-phenyl-1-hexyne (**3q**) afforded indenones **4o**, **4p**, and **4q** in 57%, 50%, and 55% yield, respectively,

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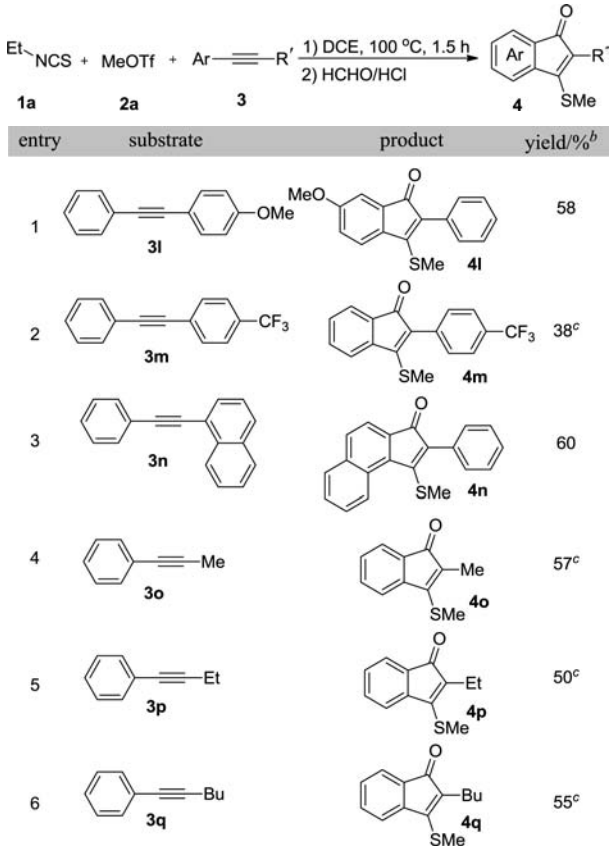
Table 3. Synthesis of Indenones from Various Unsymmetrical Alkynes[a]



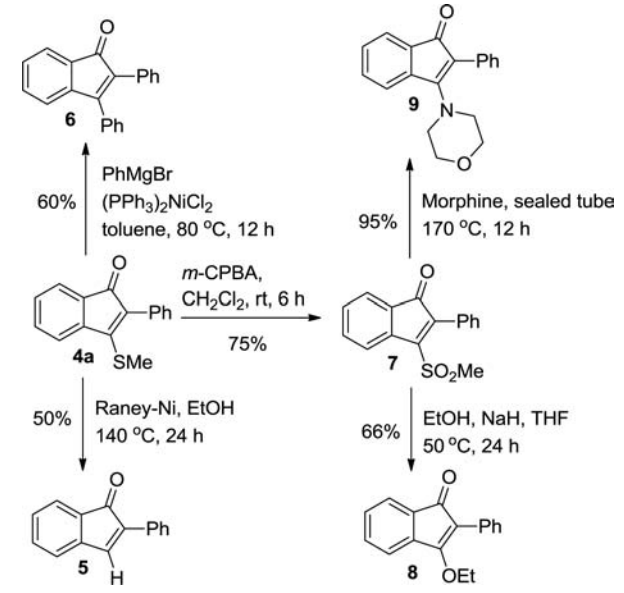
[a]Reaction conditions: 0.5 mmol of alkyne, 0.75 mmol of **1a**, and 1.5 mmol of MeOTf in 2 mL of DCE at 100 °C for 1.5 h. [b]Isolated yields. [c]At 120 °C for 12 h.

with the alkyl group at the 2-position. 1-Phenylacetylene failed to undergo the desired reaction. When trimethylsilyl- or bromo-substituted phenylacetylene was employed, the reaction did not proceed.

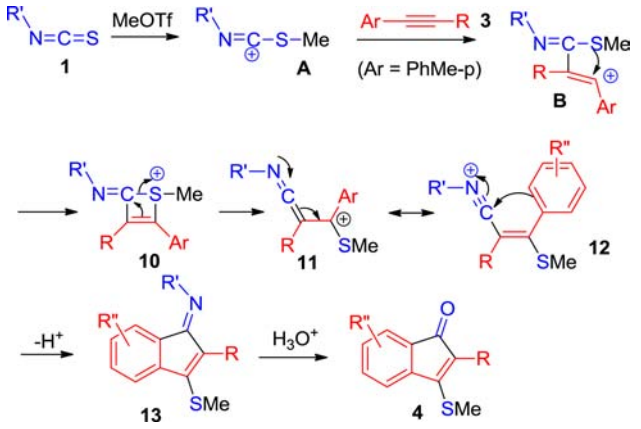
It is noteworthy that there is a methylthio group at the 3-position of the indenone, and it could be transformed into other functional groups.[8,9] As illustrated in Scheme 3, 3-methylthio-2-phenyl-1*H*-inden-1-one (**4a**) could be transformed into indenone **5** by treatment with Raney Ni in refluxing ethanol. The 3-methylthio group could also be converted into a phenyl group to give 3-phenylindenone **6** in 60% yield upon treatment with phenylmagnesium bromide using $Ni(PPh_3)_2Cl_2$ as a catalyst. The oxidation of **4a** with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded 3-methylsulfonyl-2-phenylindenone (**7**) in 75% yield. The 3-methylsulfonyl group on the indenone ring could be easily replaced not only by ethanol to generate 3-ethoxyindenone **8** in 66% yield but also by morpholine to produce 3-aminoindenone **9** in 95% yield.

On the basis of the above results and related precedents, a plausible mechanism is proposed as follows (Scheme 4): First, methylation of the isothiocyanate by MeOTf affords carbenium ion **A**.[7,10] Then the alkyne attacks the carbon atom of **A** to afford intermediate **B**.[11] Next, the strongly nucleophilic sulfur atom attacks the carbenium in **B** to form four-membered thiete **10**,[12] which is followed by ring opening with C−S bond cleavage to form carbenium **12** via

Scheme 3. Transformations of 4a into Other Substituted Indenones



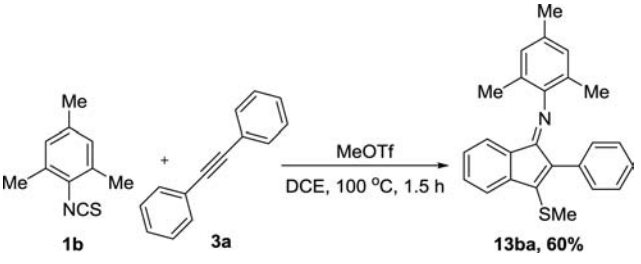
Scheme 4. Plausible Reaction Mechanism



intermediate **11**. Finally, intramolecular Friedel−Crafts reaction of **12** affords indenone imine **13**, which undergoes hydrolysis to form indenone **4**.

To probe the reaction mechanism, mesityl isothiocyanate (**1b**) instead of **1a** was employed under the same reaction conditions (Scheme 5). Indenone **4a** was not obtained, but instead indenone imine **13ba** was isolated in 60% yield, which indicates indenone imine **13** as the intermediate before hydrolysis.

Scheme 5. Reaction of Mesityl Isothiocyanate with Alkyne 3a



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In conclusion, we have developed a MeOTf-induced carboannulation between alkyl isothiocyanates and aryl alkynes. This annulation represents the first example of cleavage of the isothiocyanate C═S bond for construction of the carbocyclic compound. This reaction provides access to a range of synthetically useful indenone derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02201.

Experimental procedures, full characterization including ^{1}H and ^{13}C NMR data and spectra for all new compounds, and X-ray structures of products **4b** and **4k** (PDF)

Crystallographic data for **4b** (CIF)

Crystallographic data for **4k** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cjxi@tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

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