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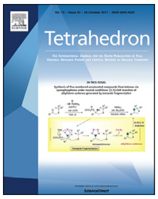

# C–S and C–N bond formation via Mn-promoted oxidative cascade reaction: Synthesis of C3-sulfenated indoles

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## ABSTRACT

Thioethers are of synthetic value in pharmaceutical molecules and nature products, herein, we report an oxidative cascade reaction that delivers multiple substituted indole thioethers with great efficiency. This transformation utilized *ortho*-azido aromatic alkynes as the substrates, and sulfonyl hydrazides as the sulfenation reagent promoted by Mn(III) catalyst. Notably, great functional group tolerance, in combination with nitrogen and water as the byproducts, highlighted the sustainable chemistry of this protocol.

## 1. Introduction

To control the synthesis of architecturally complex molecules through catalysis is a key aspect in modern drug discovery.[1] Cascade reaction provides an efficient platform for the rapidly increase the molecular complexity of simple substrates via quick construction of multiple chemical bonds that delivers valuable molecules.[2,3] In this context, radical addition to unsaturated C–C bonds initiated cascade reactions[4] have received much attention due to their synthetic application in complex molecules. These transformations hold the advantages as follows: 1) multiple chemical bonds were formed in one-pot manner; 2) regio- and stereoselectivity were observed to highlight the synthetic potential for the rapid access to complex molecules, thus these concepts are accordance with requirements of green chemistry in modern organic chemistry.

The construction of C–S bond with great efficiency has been a long-standing endeavor of chemical community,[5] since thioether and their derived functionalities are of enormous utility in material science and drug discovery.[6] For instance, several drug candidates listed in Scheme 1 contained thioether key moiety. For example, pergolide,[7] which has been showed activity against at the postsynaptic dopamine receptor and served as medicine to treat of Parkinson's disease, contained indole-derived thioether key structural moiety.

Despite the synthetic power of C–S bond in organic synthesis, due to the strong coordination ability of sulfur to metal center, the choice of metal catalysts in combination of sulfenation reagents is crucial to realize catalytic C–S bond formation.[8] C3-sulfenated indoles hold great synthetic utility in various areas across pharmaceutical, material area and serve as versatile building block in organic synthesis. Towards this goal, much efforts have been exploited in this research field toward expedient access to their derivatives. General methods[8] to afford these molecules include: 1) nucleophilic substitution of halogen derived indoles with aryl thiophenol derivatives; 2) transition-metal catalyzed cross-couplings as well as C–H bond functionalization of indoles with various sulfenation reagents.

Considering the overall efficiency and sustainable chemistry of the transformations, great advancements have been achieved by using various types of sulfenation reagents,[9] such as aryl thiol, disulfide, 1-(thio)-1*H*-pyrrole-2,5-dione derivatives, sulfinic acid and its sodium salt, sulfonyl hydrazides, et al. In combination of different types of radical acceptor, chemists have realized various structurally diverse sulfur-containing complex molecules.

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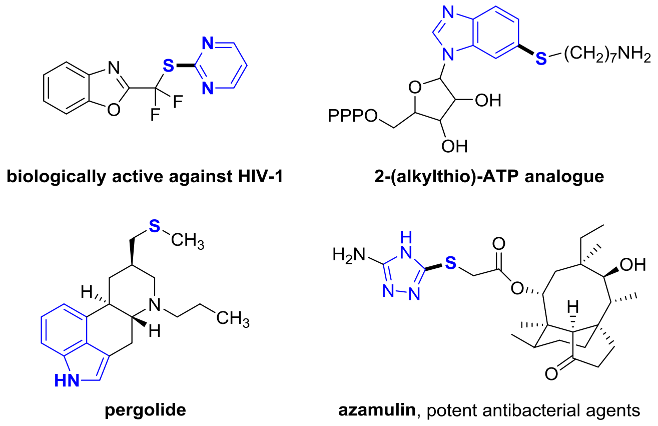


**Scheme 1.** Thioether-containing bioactive molecules.

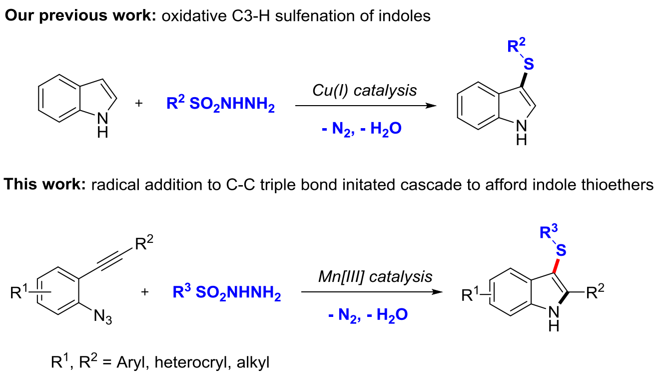
Recently, we have achieved copper-catalyzed direct oxidative functionalization of indoles with aryl sulfonyl hydrazines as the sulfenation reagent.[8e] In this reaction, cheap metal catalyst in combination with molecular oxygen as the green oxidant made this protocol applicable in direct synthesis as well as late-stage modification of sulfur-containing pharmaceuticals (Scheme 2).

Nevertheless, the scope of thioether substrates was usually limited and the reaction conditions were relatively harsh. Therefore, the development of versatile and efficient methods for constructing different useful skeletons bearing thioether group under mild conditions is highly desirable. On our continuous research interest in the development of aerobic oxidative transformations[10] that enable quick access to valuable molecules, herein, we report a radical addition to C—C multiple bond initiated cascade reaction, delivering C3-sulfenated indole derivatives. Compared to our previous results, this oxidative difunctionalizations of alkynes[11] deliver highly substituted indole-substituted thioethers, and afford structurally divergent products from easily accessible starting materials. More significantly, this methodology builds fundament for the further research on intermolecular aminosulfenation of alkynes, of which, the obtained products are of great value as synthetic intermediates (Scheme 2).

## 2. Results and discussion

### 2.1. Reactions design

Considering the synthetic utilities of highly substituted sulfonated indoles, as well as the limited methods toward these molecules, efficient methodologies are highly desirable. Since *Ortho*-azido aromatic alkynes and alkenes serve as important synthetic intermediates for constructing important bioactive small molecules.[4b,12] We speculated that employing Ortho-azido aromatic alkynes to a catalytic system than enable the radical addition initiated the cascade reaction, the desired sulfenated indole products could be obtained under relative mild conditions.

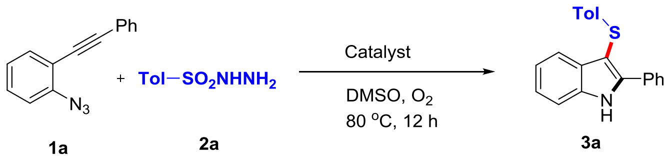


**Scheme 2.** Synthesis of C3-thioether with sulfonyl hydrazide via transition metal catalysis.

To commence our research, we selected 1-azido-2-(phenylethynyl)benzene (**1a**, 0.2 mmol) as the substrate, and 4-methylbenzenesulfonohydrazide **2a** as the sulfenation reagent under oxidation conditions. Previous work has demonstrated that azides might both act as precursors of metal carbenoids and nitrogen centered radical,[13] thus, the choice of metal catalyst might be crucial for these transformations. Moreover, due to the rich chemistry of C—C triple bond, et al. while difunctionalization of alkynes with nucleophiles and electrophiles have been developed as state-of-art,[14] radical addition of C—C triple bonds initiated cascade reaction remained a hot topic arena for the rapid construction of multiple functionalized molecules.

Quick solvent screening revealed that only solvents DMF or DMSO led to a noticeable conversion. As shown in Table 1, various metal catalysts were tested, $Mn(OAc)_3$ was identified to be the most efficient catalyst for the C3-sulfenation reaction, furnishing the desired C3-thioether indole **3a** in 44% yield. Other metal catalysts such as Ag(I), Fe(III), or Cu(II) complexes, which could work as one-electron oxidants,[15] were not viable for this transformation, the deleterious side reaction is indole product without sulfenation reaction. Further investigations of the reaction parameters indicated that both additive and solvent play critical roles in this transformation. Addition of base additive, such as $K_2CO_3$ was beneficial for this transformation, while LiBr additive led to practical yield,

**Table 1**
Optimization of reaction conditions.[a]



| Entry | Catalyst | Additive | Ligand | Yield[b] (%) |
|---|---|---|---|---|
| 1 | CuI | – | – | 20 |
| 2 | $Cu(OAc)_2$ | – | – | 11 |
| 2 | $FeCl_3$ | – | – | 26 |
| 3 | $FeCl_2$ | – | – | 15 |
| 4 | $Rh_2(OAc)_4$ | – | – | n.d. |
| 5 | $Pd(OAc)_2$ | – | – | n.d. |
| 6 | $AgNO_3$ | – | – | n.d. |
| 7 | $Mn(OAc)_3$ | – | – | 44 |
| 8 | $Mn(OAc)_3$ | $K_2CO_3$ | – | 49 |
| 9 | $Mn(OAc)_3$ | LiBr | – | 57 |
| 10 | $Mn(OAc)_3$ | $K_3PO_4$ | – | 52 |
| 11 | $Mn(OAc)_3$ | TBAF | – | 31 |
| 12 | $Mn(OAc)_3$ | LiBr | – | 64 |
| 13 | $Mn(OAc)_3$ | LiBr | DABCO | 72 |
| 14 | $Mn(OAc)_3$ | LiBr | 1,10-phen | 87 (85) |
| 15 | $Mn(OAc)_3$ | LiBr | Bpy | 68 |
| 16 | $Mn(OAc)_3$ | LiBr | DBU | 67 |
| 17[c] | $Mn(OAc)_3$ | LiBr | 1,10-phen | trace |
| 18[d] | $Mn(OAc)_3$ | LiBr | 1,10-phen | 35 |

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (10 mol%), additive (10 mol%), ligand (10 mol%) were stirred at 80 °C under oxygen atmosphere for 12 h.
[b] GC yield with biphenyl as the internal standard. Yield in the parenthesis was determined after flash column chromatography.
[c] HOAc as the solvent.
[d] DMF as the solvent.