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Microwave assisted metal-/oxidant-free cascade electrophilic sulfenylation/5-*endo-dig* cyclization of 2-alkynylanilines to generate diversified 3-sulfenylindoles

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ABSTRACT

A metal-/oxidant-free sustainable protocol for the synthesis of 3-sulfenylindoles based on electrophilic cyclization of 2-alkynylanilines has been developed under microwave irradiation. Herein, catalytic amount of iodine and stoichiometric amount of sulfonyl hydrazides were employed as catalyst and electrophiles respectively to induce the 5-*endo-dig* cyclization of 2-alkynylanilines. This strategy allows a wide substrate scope, demonstrates good functional group tolerance, utilizes easily available reagents and overcome multistep synthesis.

Cascade reactions are emerging as powerful chemical tool to construct molecular complexity from simple precursors.[1] A sequential activation of C–C multiple bonds using electrophilic sulphur sources to generate thiiranium ion intermediate, following by its opening using various nucleophiles is an elegant cascade strategy for accessing 1,2-difunctionalized products [Eq. (1)].[2] Interestingly, the cascade strategy employed on the substrates having nucleophilic partner tethered to the C–C multiple bond would furnish bioactive 3-thiolated indoles and benzofurans [Eq. (2)]. The methodology has distinct advantages over the conventional synthetic routes for 3-functionalized indoles and benzofurans, such as (i) cross-coupling of vinyl/ aryl halides with thiolating agents such as thiols, disulfides etc,[3] (ii) coupling of aryl- and alkyl lithium or Grignard reagents with sulfenylating agents,[4] and (iii) direct sulfenylation of C–H bond using various sulfurating agents[5] that required pre-functionalized starting materials, harsher reaction conditions, and noxious and unstable sulphur sources. The most extensively used electrophilic sulphur sources for the activation of C–C multiple bond are the arylsulfenyl chlorides[6] and diaryl disulfides.[7] However, these methods required use of either expensive and air sensitive metal catalysts and/or oxidants, and obnoxious, toxic and unstable sulfur reagents. Hence, a direct and concise method based on stable and environmentally friendly reagents would be highly desirable to generate these organo-sulfur compounds. Recently, sulfonyl hydrazides have emerged as cleaner, odourless and stable source of sulfenylating agents to afford organo-sulfur compounds.[8]

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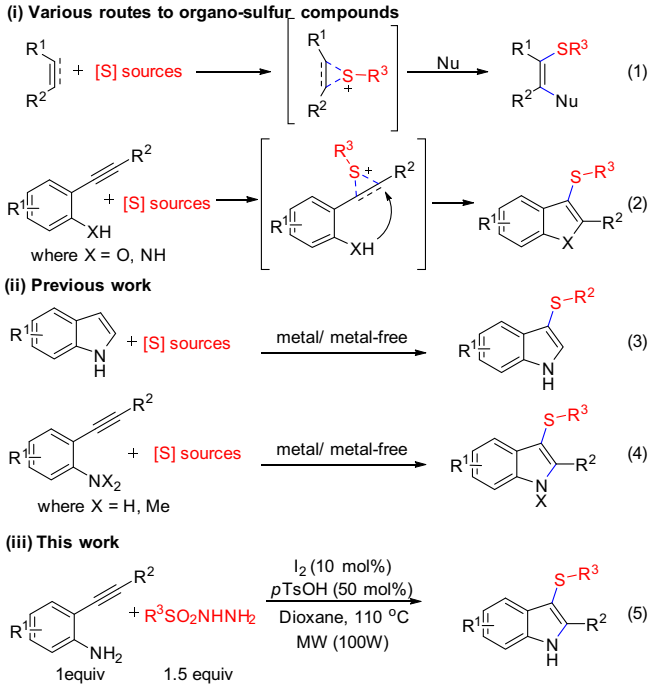
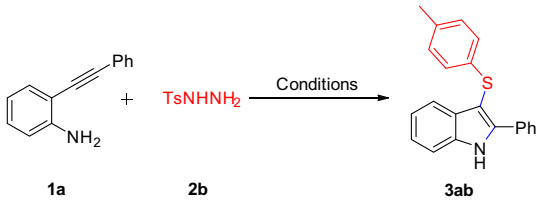


The indole is a privileged heterocycle found in a spectrum of natural products and pharmacologically active compounds.[9] Of these, 3-sulfenylindoles are important class of compounds that possess pharmacological activity against various diseases such as HIV,[10] neuroleptic,[11] allergies,[12] cardiovascular,[13] obesity[14] and cancer.[15] In general, 3-sulfenylindoles are synthesized by direct sulfenylation of indoles[16] [Eq (3)] or *via* transition-metal catalysed (or oxidant mediated) annulation of 2-(1-alkynyl)aniline[6,7] [Eq. (4)] using various sulfenylating agents. Recently, the effective synthetic strategies have been developed to access these 3-sulfenylindoles using sulfonyl hydrazides as sulfenylating agents.[17] Since electrophilic aryl sulfenyl intermediate is generated *in situ* from the reaction of iodine and sulfonyl hydrazides, therefore this strategy could be elegantly applied for the cascade electrophilic sulfenylation/ 5-*endo-dig* cyclization to furnish 3-sulfenylindoles. Very recently, Kahukarn et al.[18] reported synthesis of the *N*-alkyl-3-sulfonylindoles and *N*-alkyl-3-sulfanylindoles by cascade annulation of 2-alkynyl-*N*,*N*-dialkylaniline using excess of sulfonyl hydrazides as sulphur source. But this strategy was limited to 2-alkynyl-*N*,*N*-dialkylaniline, with the requirement of stoichiometric amount of iodine. In continuation of our interest in generating bioactive heterocycles,[19] we report herein metal or oxidant free cascade electrophilic sulfenylation/5-*endo-dig* cyclization of 2-alkynylanilines under microwave irradiation using catalytic amount of molecular iodine [Eq. (5)]. The combination of cascade strategy with microwave assisted organic synthesis (MAOS),[20] is considered as a sustainable synthetic approach because of shorten reaction time and minimal side products.

Initially, our investigation began by reacting 2-alkynylaniline **1a** with *p*-tolylsulfonyl hydrazines **2b** (2.0 equiv) and iodine (10 mol %) in ethanol at 70 °C as reported by Tian et al.[17a] However, no conversion occurred at this temperature and **1a** was recovered as such (entry 1, table 1). Fortunately, increasing the temperature of the reaction mixture to 110 °C and use of *p*-TsOH[21] resolved this problem (entry 2) and furnished the desired 3-sulfenylindoles **3ab** in 45% isolated yield in 24 h. Next, a series of solvents were explored (entries 3–7) and 1,4-dioxane showed a better result compared to ethanol. Consequently, it was observed that microwave irradiation could rapidly facilitate this transformation with minimal reaction time and maximal product yield (entry 8). Explorations with different Brønsted and Lewis acids revealed that a Ca $(OTf)_2$ afforded maximum yield up to 74% (entries 9–17), but *p*-TsOH was the best choice. Lowering of reaction temperature prolonged the reaction time with reduced yield (entry 18). However, increasing the temperature had detrimental effect on the outcome of reaction (entry 19). Finally the effect of catalyst loading and equivalence of **2b** were investigated. The best result was observed when 1 equiv of **2b** was reacted with **1a** (1.5 equiv) using 10 mol% of iodine and 0.5 equiv of *p*-TsOH in 1,4-dioxane at 110 °C under microwave irradiations for 15 min furnishing **3ab** in 85% isolated yield.

With the optimized reaction conditions in hand, the generality and substrate scope of sulfonyl hydrazides were investigated and the results are shown in Scheme 1. Both electron withdrawing and electron donating substituents bearing aryl sulfonyl hydrazides underwent sulfenylation to afford the corresponding indole thioethers (**3ab**-**3aj**) in moderate to good yields. Even benzylsulfonylhydrazide worked efficiently (**3ak**). However, aliphatic sulfonyl hydrazides such as camphor and octylsulfonyl hydrazide

Table 1
Optimisation of reaction conditions.



1a **2b** **3ab**

Entry	I_2 (mol%)	Additive (50 mol%)	t (h)	T (°C)	Solvent	Isolated Yield (%)
1.	10	–	24	70	EtOH	–
2.	10	*p*-TsOH	24	110	EtOH	45
3.	10	*p*-TsOH	24	110	H_2O	10
4.	10	*p*-TsOH	24	110	DCE	48
5.	10	*p*-TsOH	24	120	Toluene	64
6.	10	*p*-TsOH	24	120	DMF	–
7.	10	*p*-TsOH	4	110	1,4-Dioxane	82
8.	10	*p*-TsOH	0.25	110	1,4-Dioxane	85[a]
9.	10	AcOH	0.25	110	1,4-Dioxane	–[a]
10.	10	CF_3CO_2H	0.25	110	1,4-Dioxane	–[a]
11.	10	TfOH	0.25	110	1,4-Dioxane	23[a]
12.	10	$PhCO_2H$	0.25	110	1,4-Dioxane	42[a]
13.	10	$(COOH)_2$	0.25	110	1,4-Dioxane	39[a]
14.	10	PhH_2PO_2	0.25	110	1,4-Dioxane	–[a]
15.	10	$Ca(OTf)_2$	0.25	110	1,4-Dioxane	74[a]
16.	10	$Sc(OTf)_2$	0.25	110	1,4-Dioxane	69[a]
17.	10	$In(OTf)_2$	0.25	110	1,4-Dioxane	62[a]
18.	10	*p*-TsOH	0.50	80	1,4-Dioxane	43[a]
19.	10	*p*-TsOH	0.25	140	1,4-Dioxane	31[a]
20.	5	*p*-TsOH	0.25	110	1,4-Dioxane	70[a]
21.	1	*p*-TsOH	0.25	110	1,4-Dioxane	traces[a]
22.	10	*p*-TsOH	0.25	110	1,4-Dioxane	72[a,d]
23.	10	*p*-TsOH	0.25	110	1,4-Dioxane	50[a,e]
24.	10	*p*-TsOH	0.25	110	1,4-Dioxane	64[a,b]
25.	10	*p*-TsOH	0.25	110	1,4-Dioxane	86[a,c]
26.	10	*p*-TsOH	0.25	110	1,4-Dioxane	61[f,h]
27.	10	*p*-TsOH	0.25	110	1,4-Dioxane	48[g,i]

Reaction condition: **1a** (1.0 mmol), **2b** (1.5 mmol), additive (50 mol%), solvent (1 mL).
[a] MW (100 W).
[b] 1.0 mmol of **2b**.
[c] 2.0 mmol of **2b**.
[d] 30 mol% of *p*TsOH.
[e] 10 mol% of *p*TsOH was employed.
[f] MW (80 W).
[g] MW (150 W).
[h] 30% Starting material recovered.
[i] multiple spots observed.