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Metal-free synthesis of 3-chalcogen benzo[*b*]furans via an iodine-mediated electrophilic cyclisation of 2-alkynylanisoles

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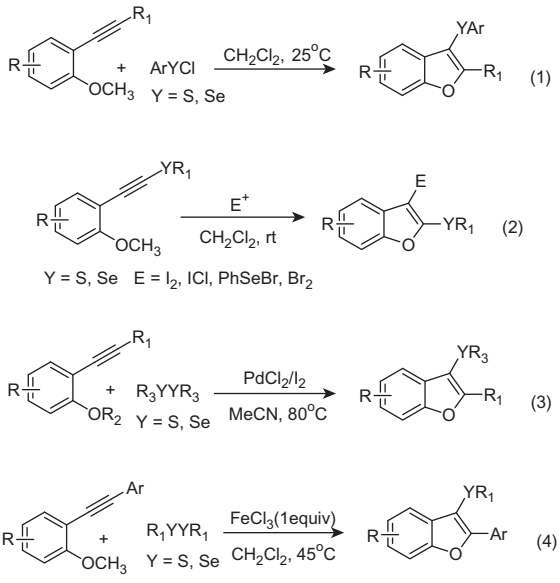
ABSTRACT

An efficient and metal-free method was developed to synthesize 3-chalcogen benzo[*b*]furans via the iodine-mediated electrophilic cyclisation of 2-alkynylanisoles with disulfides or diselenides. In the presence of I_2, various 3-sulfenylbenzofurans or 3-selenenylbenzofurans were obtained in moderate to high yields.

Introduction

Benzofurans are an important class of heterocycles that are present in many natural products and pharmaceutical intermediates.[1] Many benzo[*b*]furans are found to exhibit a broad range of biological activities, including anticancer,[2] antimicrobial,[3] anti-inflammatory,[4] antiviral[5] and antifungal activities.[6] Because of their potential utility, growing interest has recently centred on efficiently constructing the benzo[*b*]furans scaffold.[7] However, to the best of our knowledge, there is little information available in the literature about the synthesis of 3-chalcogen benzo[*b*]furans, such as sulfenylbenzo[*b*]furans and selenenylbenzo[*b*]furans.[8] For example, in 2005, Larock and co-workers reported the synthesis of a limited number of 3-chalcogen benzo[*b*]furans through the electrophilic cyclisation of 2-(phenylethynyl)anisole with 4-$NO_2C_6H_4SCl$ or PhSeCl (Eq. 1, Scheme 1).[9] In 2009, Zeni and co-workers prepared 2-chalcogen benzo[*b*]furans via the electrophilic cyclisation of 2-chalcogen-alkynylanisoles (Eq. 2, Scheme 1) using I_2, ICl, Br_2 or PhSeBr as the electrophilic sources.[10] Nevertheless, these two methods are limited to the use of toxic and unstable sulfenyl halides as the reaction partners. To avoid using unstable sulfenyl halides, Li[11] and Zeni[12] synthesized chalcogen benzo[*b*]furans via palladium-promoted annulation reactions of 2-alkynylphenol derivatives (Eq. 3, Scheme 1) and $FeCl_3$-promoted cyclisations of 2-alkynylanisoles (Eq. 4, Scheme 1) with disulfides or diselenides, respectively. However, transition-metal-based protocols usually have several inherent limitations, including moisture sensitivity, costly metal catalysts and environmental toxicity. Therefore, there is still a need for developing a direct and metal-free method to synthesize chalcogen benzo[*b*]furans. While studying the reaction of 2-(phenylethynyl) alkynylanisole (**1a**) with 1,2-diphenyl disulfide (**2a**), we serendipitously discovered that the annulation reaction



Scheme 1. Synthesis of chalcogen benzo[*b*]furans through different methods.

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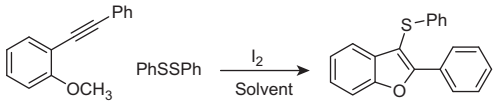
Table 1
Screening optimal conditions[a]



1a 2a 3

Entry	I_2 (equiv)	**2a** (equiv)	Solvent	Temp (°C)	Conversion [a] (%)
1	0.5	0.5	CH_2Cl_2	45	23
2	1.0	0.5	CH_2Cl_2	45	30
3	1.0	1.0	CH_2Cl_2	45	43
4	1.0	1.0	CH_3OH	45	12
5	1.0	1.0	CH_3CN	45	13
6	1.0	1.0	DMSO	45	—
7	1.0	1.0	*m*-Xylene	45	68
8	1.0	1.0	Toluene	45	76
9	1.0	1.0	Toluene	80	82
10	1.0	1.0	Toluene	110	93

[a] The conversion of **1a** by GC–MS analysis.

can be accomplished in the presence of I_2 alone without using transition-metals, with competitive yields as compared to its metal-catalysed counterparts.[9–12] In this Letter, we describe our results in detail.

Results and discussion

As mentioned above, we chose to study the reaction of 2-(phenylethynyl) alkynylanisole (**1a**) with 1,2-diphenyl disulfide (**2a**) as a model system to determine the optimal reaction conditions (Table 1). The amounts of **2a** and I_2 were first explored using CH_2Cl_2 as solvent at 45 °C. It can be seen that the conversion of **1a** was increased to 43% by increasing the associated amounts of **2a** and I_2 to 1 equiv each (entries 1–3). However, more than 50% **1a** was found to be transformed into the by-product 3-iodo-2-phenylbenzofuran, as shown by GC–MS analysis (entries 1–3). To enhance the yield of the target product **3**, different solvents, including CH_3OH, CH_3CN, DMSO, *m*-xylene and toluene were investigated. Of these choices, toluene was proved to be the most effective solvent, leading to a 76% conversion of **1a** to **3** (entries 4–8). When the reaction temperature was elevated to 80 °C or 110 °C in toluene, the conversion of **1a** was improved, and it reached 93% when the reaction was carried out at 110 °C (entries 9 and 10). These results indicated that the solvent and temperature played important roles in the formation of **3**.

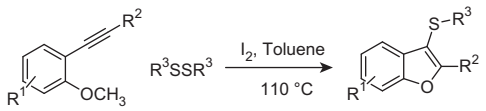
The application of the above-modified conditions to other 2-alkynylanisoles and disulfides was studied, and the results are summarised in Table 2. Initially, a set of disulfides, **2b–k**, were examined by their reaction with 2-(phenylethynyl) alkynylanisole (**1a**) (entries 1–10). The results showed that the reaction seemed to be sensitive to the electronic effects of the substituents in the aromatic ring of the disulfide. For example, disulfides with Cl and F moieties gave lower yields than their methyl and methoxy equivalents (entries 1–5). Moreover, no desired product but only the by-product, 3-iodo-2-phenylbenzofuran, was obtained in a 45% yield when the disulfide substituent was NO_2, a strong electron-withdrawing group (entry 6). Gratifyingly, diaryl disulfides, such as diethyl or dicyclohexyl disulfide, were suitable for the reaction and gave the desired products in 50% and 55% yields, respectively (entries 9 and 10). However, the reactions of 1,2-di(pyridin-2-yl) disulfide (**2h**) or 1,2-dibenzyl disulfide (**2i**) with anisole **1a** were unsuccessful, and the by-product 3-iodo-2-phenylbenzofurans were obtained in 83% and 58%, respectively (entries 7 and 8).

With the optimal reaction conditions, we investigated the scope of this process with respect to the 2-alkynylanisoles **1b–g** (Table 2, entries 11–20). We found that the optimal conditions were compatible with substrates that had aromatic groups at the terminal of the 1-ethynyl-2-methoxybenzene but inconsistent with alkyl groups. For example, treatment of substrate **1b** bearing an *m*-Cl group on the anisole moiety with disulfide **2a, 2b** or **2c** afforded the corresponding products, **11, 12** and **13**, in 61%, 78% and 63% yields, respectively (entries 11–13). However, substrate bearing an alkyl group, such as 1-methoxy-2-(oct-1-ynyl)benzene or 1-methoxy-2-(*t*-Bu-1-ethynyl)benzene, gave no desired but the by-products in 87% or 80% yields (entries 14 and 15). To our delight, substrate with a 4-MeC_6H_4 or a 3-ClC_6H_4 group at the terminal of 1-ethynyl-2-methoxybenzene was well tolerated (entries 17–20). Unfortunately, the annulation of 1-methoxy-2-(4-nitrophenylethynyl)benzene (**1g**) to the target product failed under the same conditions, and 90% by-product-3-iodo-2-phenylbenzofuran was obtained (entry 20).

Subsequently, we studied the reactions of diselenides **2** with 2-alkynylanisoles **1** under our previous optimal conditions, and we found that the reactions could proceed successfully to give the desired 3-selenenylbenzo[*b*]furans in moderate yields (Table 3). Substrate **1a** reacted smoothly with diaryl diselenide **2l** or dialkyl diselenide **2m** in the presence of I_2 to give the target products **18** and **19** in 67% and 59% yields, respectively (entries 1 and 2). Similarly, the substrate **1b**, bearing the electron-withdrawing Cl atom, smoothly underwent the reaction with satisfactory yields (entry 3). The treatment of substrates **1e** or **1f** with 1,2-diphenyldiselenide **2l** also afforded the corresponding products in moderate yields (entries 4 and 5).

To explain the formation of the desired product and the by-product, we hypothesise that the mixture of RSSR, I_2 and 2-alkynylanisole results in a competition between the electrophilic cyclisation of anisole via I_2 and RSI. This proposed mechanism is shown in Scheme 2. According to path a, the reaction of disulfide with I_2 would yield RSI (**A**) in situ. Then, the electrophilic addition of RSI (**A**) with 2-alkynylanisoles would afford intermediate **B**. Annulation of intermediate **B** gives intermediate **C**, and then the CH_3 group can be removed from intermediate **C** with the aid of I^- to afford the target product. However, the direct electrophilic addition of 2-alkynylanisoles can occur instead with I_2 to give intermediate **E**. After annulation and the removal of the CH_3 group from **E**, the by-product of 3-iodo-2-phenylbenzofuran can be produced (path

Table 2
Iodine-mediated electrophilic cyclisation of 2-alkynylanisoles (**1**) with disulfides (**2**)[a]



1a-1g 2

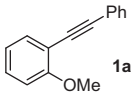
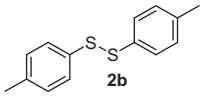
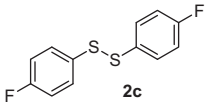
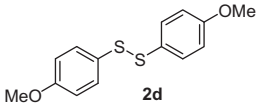
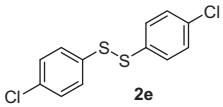
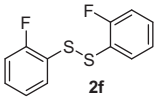
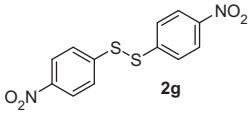
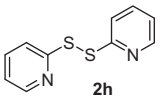
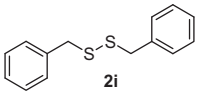
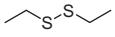
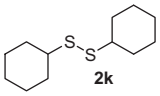
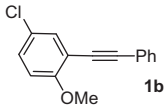
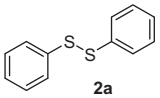
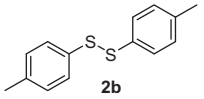
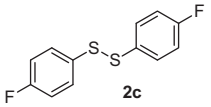
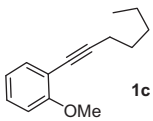
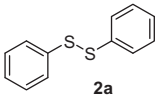
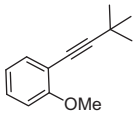
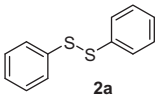
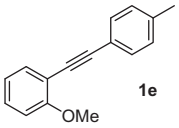
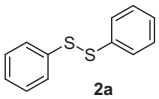
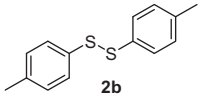
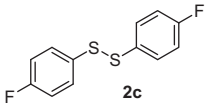
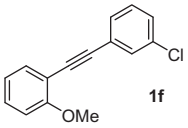
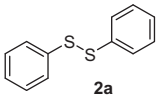
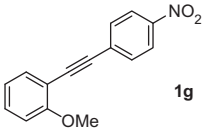
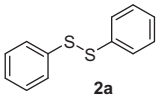
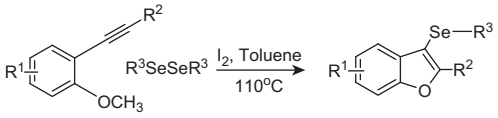
Entry	Alkynylanisole	R^3SSR^3	Product (yield%)[b]
1	 **1a**	 **2b**	**4** (96)
2	**1a**	 **2c**	**5** (80)
3	**1a**	 **2d**	**6** (87)
4	**1a**	 **2e**	**7** (59)
5	**1a**	 **2f**	**8** (46)
6	**1a**	 **2g**	45[c]
7	**1a**	 **2h**	83[c]
8	**1a**	 **2i**	58[c]
9	**1a**	 **2j**	**9** (50)
10	**1a**	 **2k**	**10** (55)
11	 **1b**	 **2a**	**11** (61)
12	**1b**	 **2b**	**12** (78)
13	**1b**	 **2c**	**13** (63)
14	 **1c**	 **2a**	87[c]
15	 **1d**	 **2a**	80[c]

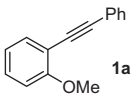
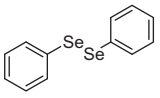
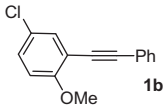
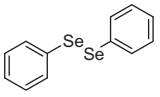
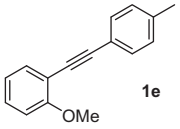
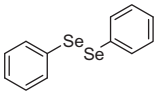
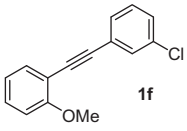
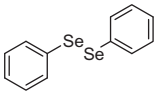
Table 2 (*continued*)

Entry	Alkynylanisole	R^3SSR^3	Product (yield%)[b]
16	 **1e**	 **2a**	**14** (90)
17	**1e**	 **2b**	**15** (91)
18	**1e**	 **2c**	**16** (76)
19	 **1f**	 **2a**	**17** (35)
20	 **1g**	 **2a**	90[c]

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), I_2 (0.2 mmol), and toluene (2 mL) at 110 °C for 10 h.
[b] Yield of isolated products.
[c] The isolated yield of by-product 3-iodo-2-phenylbenzofuran.

Table 3
Cyclisation reactions of 2-alkynylanisoles (**1**) with diselenides (**2**)[a]

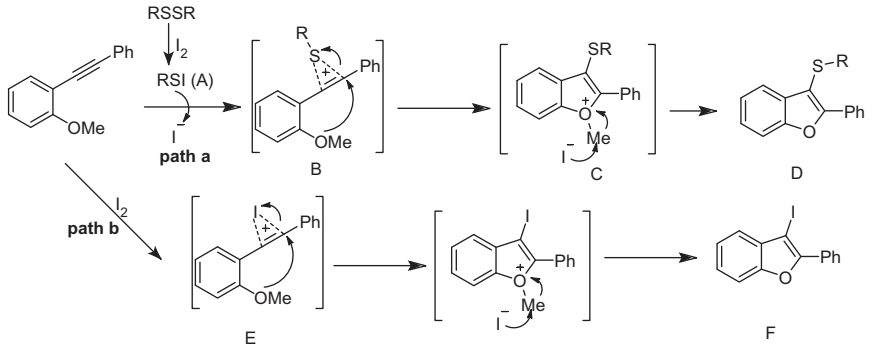


Entry	Alkynylanisole	Diselenides	Product (yield%)[b]
1	 **1a**	 **2l**	**18** (67)
2	**1a**	 **2m**	**19** (59)
3	 **1b**	 **2l**	**20** (54)
4	 **1e**	 **2l**	**21** (80)
5	 **1f**	 **2l**	**22** (43)

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), I_2 (0.2 mmol), and toluene (2 mL) at 110 °C for 10 h.
[b] Yield of isolated products.

b). Path a and b appear to be competitive processes. When path a dominated, target product **D** was obtained as the main product. Conversely, when path b dominated, the main product was the undesired by-product **F**.

In conclusion, we have developed a convenient and metal -free protocol for the construction of 3-chalcogen benzo[*b*]furans via the iodine-mediated annulation of 2-alkynylanisoles and disulfides or diselenides. In the presence of I_2, a variety of



Scheme 2. Proposed mechanism.

3-sulfenylbenzo[*b*]furans or 3-selenenylbenzo[*b*]furans were synthesized from the reaction of 2-alkynylanisoles derivatives with different disulfides or diselenides in moderate to good yields.

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References and notes

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