## **Green Chemistry**

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# K<sub>2</sub>CO<sub>3</sub> promoted direct sulfenylation of indoles: a facile approach towards 3-sulfenylindoles†

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Accepted 2nd June 2013 DOI: 10.1039/c3gc40724a www.rsc.org/greenchem Peng Sang,<sup>a</sup> Zhengkai Chen,<sup>a</sup> Jianwei Zou<sup>a,b</sup> and Yuhong Zhang\*<sup>a,c</sup>

An efficient and convenient method was developed for the preparation of 3-sulfenylindoles *via* a  $K_2CO_3$  promoted direct sulfenylation of indoles with disulfides. The method is applicable to a wide range of indoles containing different functional groups furnishing good to excellent yields. This synthetic strategy features environmental friendliness, easy operation, and mild reaction conditions.

### Introduction

3-Sulfenylindoles represent pharmaceutically and biologically important structures with their therapeutic value in the treatment of heart disease,<sup>1</sup> allergies,<sup>2</sup> cancer,<sup>3</sup> HIV<sup>4</sup> and obesity.<sup>5</sup> They are also used as potent inhibitors of tubulin polymerization.<sup>6</sup> The fascinating biological profiles of this group of compounds stimulated researchers to explore efficient methods for the synthesis of 3-sulfenylindoles and their structural analogues. In the past few decades, a number of significant synthetic methods for the construction of 3-sulfenylindoles have been developed. Among these approaches, the direct sulfenylation of the indole ring by various sulfenylating agents such as sulfenyl halides,<sup>7</sup> N-thioimides,<sup>8</sup> sulfonium salts,<sup>9</sup> thiols,<sup>10</sup> disulfides,<sup>11</sup> quinone mono-O,S-acetals,<sup>12</sup> arylsulfonyl chlorides<sup>13</sup> and sulfonyl hydrazides14 is the most common. However, in many of these transformations, harsh reaction conditions (such as a stoichiometric strong base), toxic reagents and oxygen-free techniques are required. An alternative method is the annulation of 2-(1-alkynyl)-benzenamines with sulfenylating agents such as disulfides and arylsulfenyl chlorides, which is performed with the aid of transition-metal catalysts<sup>15</sup> or a stoichiometric amount of *n*-Bu<sub>4</sub>NI.<sup>16</sup> But these methods need preparation steps of the starting materials and often suffer

from limitations, such as low yield or low functional group tolerance. It is desirable to develop new methods for the synthesis of 3-sulfenylindoles from simple and readily available precursors under mild reaction conditions with regard to green chemistry and synthetic practice.

As part of our continuing effort to construct bioactive molecules by developing cheap, green and sustainable methods,<sup>17</sup> our group took an interest in the 3-sulfenylindoles. Herein, we wish to report the cheap  $K_2CO_3$  promoted direct C(3)–H sulfenylation of free (N–H) indoles with disulfides. The protocol here has a broad substrate scope, simple reaction conditions, and excellent yields. Notably, in this transformation, no noble metal salts, ligands or additives were added and without exclusion of air and moisture.

### **Results and discussion**

The development of economical and environmentally benign strategies for the construction of useful molecular skeletons is an important goal in contemporary organic synthesis. Our initial attempts started with the reaction of simple and readily available 1H-indole 1a and 1,2-diphenyldisulfane 2a (0.5 equiv.) in the presence of K<sub>2</sub>CO<sub>3</sub> (1 equiv.) at 100 °C under air (Table 1, entry 1). To our delight, the sulfenylation product 3a was obtained in 84% yield. Increasing the amount of 1,2diphenyldisulfane (2a) improved the yield of the product (entries 6 and 7). Screening of the solvents (Table 1, entries 1-5) revealed that DMSO was optimal. A relatively lower yield was obtained when the reaction was carried out by the use of DMF as the solvent (Table 1, entry 2). The use of NMP delivered the product with moderate yield (Table 1, entry 3), and the reaction was sluggish in toluene and 1,4-dioxane (Table 1, entries 4 and 5). The effect of bases was also investigated, and the commonly used inorganic bases such as K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub> and KOH all gave excellent results (Table 1, entries 7-10). KOAc gave a moderate yield (Table 1, entry 11). No reaction was observed in the absence of base. We also examined organic bases such as Et<sub>3</sub>N and DBU, but no product was

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Table 1 Optimization of reaction conditions<sup>a</sup>



| untry | 2a (equiv.) | Base (equiv.)     | bolvent     | 11010 (70)            |
|-------|-------------|-------------------|-------------|-----------------------|
| 1     | 0.5         | $K_2CO_2(1)$      | DMSO        | 84                    |
| 2     | 0.5         | $K_{2}CO_{3}(1)$  | DMF         | 80                    |
| 3     | 0.5         | $K_{2}CO_{3}(1)$  | NMP         | 63                    |
| 1     | 0.5         | $K_2CO_3(1)$      | Toluene     | nr                    |
| 5     | 0.5         | $K_2CO_3(1)$      | 1,4-Dioxane | nr                    |
| 5     | 0.75        | $K_2CO_3(1)$      | DMSO        | 96                    |
| 7     | 1           | $K_2 CO_3 (1)$    | DMSO        | 99                    |
| 3     | 1           | $Cs_2CO_3(1)$     | DMSO        | 99                    |
| Ð     | 1           | $K_3PO_4(1)$      | DMSO        | 99                    |
| 10    | 1           | KOH (1)           | DMSO        | 99                    |
| 11    | 1           | KOAc (1)          | DMSO        | 68                    |
| 12    | 1           | $Et_3N(1)$        | DMSO        | nr                    |
| 13    | 1           | DBU(1)            | DMSO        | nd                    |
| 14    | 1           | $K_2CO_3$ (0.8)   | DMSO        | 99                    |
| 15    | 1           | $K_2 CO_3 (0.5)$  | DMSO        | 99 (78 <sup>°</sup> ) |
| 16    | 1           | $K_2 CO_3 (0.4)$  | DMSO        | 95                    |
| 17    | 1           | $K_2 CO_3 (0.3)$  | DMSO        | 95                    |
| 18    | 1           | $K_2 CO_3 (0.2)$  | DMSO        | 89                    |
| 19    | 1           | $K_2 CO_3 (0.1)$  | DMSO        | 81                    |
| 20    | 1           | $K_2 CO_3 (0.05)$ | DMSO        | 77                    |
| 21    | 1           | $K_2 CO_3 (0.5)$  | DMSO        | $76^d$                |
| 22    | 1           | $K_2 CO_3 (0.5)$  | DMSO        | $54^e$                |
|       |             |                   |             |                       |

<sup>*a*</sup> Reaction conditions: 1*H*-indole (0.5 mmol), 1,2-diphenyldisulfane (0.5–1 equiv.), base (0.05–1 equiv.), solvent (2 mL) under air. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Under a nitrogen atmosphere (exclusion of air). <sup>*d*</sup> The reaction was carried out at 90 °C. <sup>*e*</sup> The reaction was carried out at 80 °C.

detected (Table 1, entries 12 and 13). Considering the cost and corrosivity,  $K_2CO_3$  was selected for further studies. In addition, the amount of  $K_2CO_3$  was examined (entries 14–20) and we found that a small amount of  $K_2CO_3$  also afforded the target product (**3a**) in higher yields. It is important to note that a 77% yield of **3a** could be obtained even if 0.05 equiv. of  $K_2CO_3$  was employed (Table 1, entry 20). When the reaction was subjected to a nitrogen atmosphere, a relatively lower yield was obtained (Table 1, entry 15). The reaction afforded the highest yield when performed at 100 °C. A temperature lower than that was deleterious to the reaction (Table 1, entries 21 and 22). Therefore, the standard reaction conditions for the synthesis of 3-sulfenylindoles were obtained: 1,2-diphenyldisulfane **2a** (1.0 equiv.),  $K_2CO_3$  (0.5 equiv.) under air in DMSO (2 mL) at 100 °C for 9 h.

The observation of the direct C(3)–H sulfenylation product 3a in the absence of any added metal catalyst concerned us, and our initial thoughts were whether the transformation was being induced by metal impurities in the  $K_2CO_3$ . To explore this possibility, we examined the  $K_2CO_3$ . Indeed, 10 ppb–10 ppm of Cu, Pd, Fe and other metal species were contained in the  $K_2CO_3$ . Therefore, we subjected 10–1000 times these amounts of various metal salts to the reaction system and we found that the addition of these metal salts decreased the efficiency of this reaction (Table 2, entries 3–7). This result reveals that transition metals may play a minor role in this

Table 2 The effect of transition-metal salts<sup>a</sup>

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|-------|---|-----------|---------|--------------------------------|--|--|
| Entry | TM salt   | Base      | Solvent | $\operatorname{Yield}^{b}(\%)$ |  |  |
| 1     | None  | $K_2CO_3$ | DMSO    | 77                             |  |  |
| 2     | None  | $K_2CO_3$ | DMSO    | 77 <sup>c</sup>                |  |  |
| 3     | CuI   | $K_2CO_3$ | DMSO    | Trace                          |  |  |
| 4     | $Pd(OAc)_2$   | $K_2CO_3$ | DMSO    | 19                             |  |  |
| 5     | $NiCl_2(PCy_3)_2$   | $K_2CO_3$ | DMSO    | nr                             |  |  |
| 6     | Fe(acac) <sub>3</sub>   | $K_2CO_3$ | DMSO    | nr                             |  |  |
| 7     | [Cp*RhCl <sub>2</sub> ] <sub>2</sub>  | $K_2CO_3$ | DMSO    | Trace                          |  |  |

 $^a$  Reaction conditions: 1*H*-indole (0.5 mmol), 1,2-diphenyldisulfane (1.0 mmol), K<sub>2</sub>CO<sub>3</sub> (0.025 mmol), DMSO (2 mL) under air.  $^b$  Isolated yield.  $^c$  K<sub>2</sub>CO<sub>3</sub> with 99.997% purity was from Alfa Aesar Co.

sulfenylation reaction. Furthermore, we purchased  $K_2CO_3$  with 99.997% purity from Alfa Aesar Co. and used new glassware and a new magnetic stirring bar to avoid the involvement of other metals in the reaction. The result shows that the reaction outcome was not affected (Table 2, entry 2), indicating that the reaction might not be related to transition metals and  $K_2CO_3$  determines the rate of the reaction.

With our optimal reaction conditions in hand, the substrate scope of the free (N-H) indoles was investigated as shown in Table 3. The indoles containing both electron-donating substituents (Me and OMe) and electron-withdrawing substituents (NO<sub>2</sub>, CN, F, Cl and Br) in the benzene ring tolerated the reaction conditions well to give 3-arylthioindoles in good to excellent yields (Table 3, 3b-3k). The electronic properties of the substituents in the benzene ring exerted a very limited influence on the reactivity. As for substitution patterns, 6-substituted and 7-substituted indoles delivered a relatively low yield compared with their 3- or 4-analogues (Table 3, 3b-3e). Encouraged by this successful C(3)-H sulfenylation of indoles with substituents in the benzene ring, we next examined various indoles with C-2 functional groups. It was found that the desired products were also obtained in good to excellent yields (Table 3, 3l-3p). We were delighted to find that C-2 naphthyl- and heteroaryl-substituted indoles were also tolerated in this process to provide the corresponding 2-(naphthalen-2-yl)-3-(phenylthio)-1H-indole 30 and 2-(furan-2-yl)-3-(phenylthio)-1H-indole 3p. Notably, 1H-pyrrolo[2,3-b]pyridine participated in the reaction easily with 1,2-diphenyldisulfane to afford the 3-(phenylthio)-1H-pyrrolo[2,3-b]pyridine derivative 3q in excellent yield (Table 3).

We next examined the scope of variously substituted disulfides (Table 4, **3r-3v**). All of the substrates provided good to excellent yields, showing good functional group tolerance. A variety of substituted aromatic disulfides participated in the reaction smoothly to give the desired products, including electron-withdrawing fluoro and chloro, as well as electron-donating methyl and benzamido groups. But disulfides with strong electron-withdrawing-substituted groups such as a nitro group

### Table 3 Scope of free (N–H) indoles<sup>a</sup>





<sup>*a*</sup> Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), K<sub>3</sub>CO<sub>3</sub> (0.25 mmol), DMSO (2 mL) under air. <sup>*b*</sup> Isolated yield.

failed to give the 3-arylthioindole product. It is noteworthy that the introduction of functional groups, such as F, Cl, Br and CN, adds flexibility to further elaborate the 3-arylthio-indole products that are formed.

To demonstrate the synthetic utility of the new method, the reaction was carried out on a gram scale (Scheme 1; 10.0 mmol of 1*H*-indole (1a) in the presence of 10.0 mmol of 1,2-diphenyldisulfane (2a) and 5 mmol of  $K_2CO_3$  in 40 mL of DMSO). The reaction could afford 2.07 g of 3a in 92% yield. Therefore, this protocol could be used as a practical method to synthesize the precursors of some important bioactive molecules.

The reaction mechanism was also investigated. In Table 1, entries 2 and 3 indicate that DMSO (as an oxidant) is not required by the reaction; entry 15 demonstrates that oxygen is not required but could facilitate the reaction; entries 15–20 suggest that  $K_2CO_3$  could work under catalytic loading. We 
 Table 4
 Scope of disulfides<sup>a</sup>



 $^a$  Reaction conditions: 1 (0.5 mmol), 2 (0.5 mmol), K<sub>2</sub>CO<sub>3</sub> (0.25 mmol), DMSO (2 mL) under air.  $^b$  Isolated yield.



have also tried the reaction of 0.5 mmol of indole with 0.25 mmol of disulfide (Table 1, entry 1). Only the sulfenylation product **3a**, indole and disulfide were detected by GC-MS. These results reveal that the possible thiolate by-product might be reoxidized by air to generate disulfide *in situ*. Further studies to elucidate the detailed reaction mechanism are ongoing in our laboratory.

In conclusion, we have demonstrated an easy and efficient  $K_2CO_3$ -promoted C(3)–H sulfenylation of free (N–H) indoles. In the presence of  $K_2CO_3$ , the reactions performed well under mild conditions without exclusion of air and moisture, and the corresponding 3-sulfenylindoles were obtained in good to excellent yields. This novel method provides a complementary, environment-friendly, and easy operation approach to accessing 3-sulfenylindole derivatives.

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