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Palladium-Catalyzed Annulation of 2-(1-Alkynyl)benzenamines with Disulfides: Synthesis of 3-Sulfenylindoles

Yan-Jin Guo,[a] Ri-Yuan Tang,[a] Jin-Heng Li,[a,b,]* Ping Zhong,[a]
and Xing-Guo Zhang[a,]*

[a] College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, People's Republic of China
Fax: (+86)-577-8836-8607; phone: (+86)-577-8836-8607; e-mail: jhli@hunnu.edu.cn or xgzhang99@yahoo.com.cn
[b] Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research (Ministry of Education), Hunan Normal University, Changsha 410081, People's Republic of China

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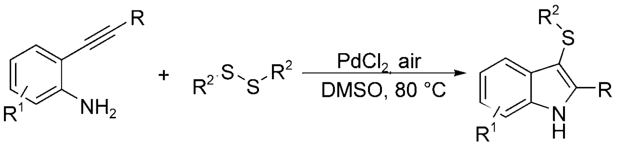
Abstract: 3-Sulfenylindoles can be efficiently prepared in moderate to good yields from 2-(1-alkynyl)benzenamines and disulfides using the palladium/air catalytic systems. The study also provides a useful route to the synthesis of fipronil analogues.

Keywords: 2-(1-alkynyl)benzenamines; annulation; disulfides; palladium; 3-sulfenylindoles

The indole moiety is a basic component of many pharmacophores, natural products, and synthetic building blocks.[1] 3-Sulfenylindoles, important topical indoles, were identified for their potential in many major therapeutic areas, such as oncology, HIV, and heart disease.[2] Therefore, many efficient methods have been developed for their preparation.[3–9] The vast majority of these transformations are the direct sulfenylation of indoles with thiols,[2a,3] disulfides,[4] quinone mono-*O,S*-acetals,[5] *N*-thioalkyl(aryl)-phthalimides,[6] and ammonium thiocyanates.[7] Thus, the development of some novel alternative strategies for synthesizing 3-sulfenylindoles remains a challenging area. During our preparation of this paper, Larock and co-workers described a novel synthetic route to 3-sulfenylindoles by $(n\text{-Bu})_4$NI-induced electrophilic cyclization of *N,N*-dialkyl 2-(1-alkynyl)benzenamines with arylsulfenyl chlorides.[8] Here, we report another new route to the synthesis of 3-sulfenylindoles by palladium-catalyzed annulation of 2-(1-alkynyl)benzenamines with disulfides in the presence of air (Scheme 1).[10]

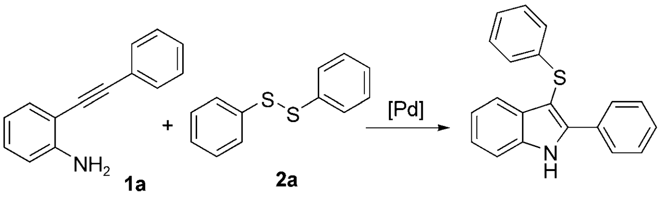
As shown in Table 1, the reaction between 2-(2-phenylethynyl)benzenamine (**1a**) and 1,2-diphenyl disulfide (**2a**) was screened to optimize the reaction conditions. Our investigation began with an attempted annulation of substrate **1a** with disulfide **2a** in the absence of Pd catalysts, but no reaction was observed (entry 1). After a series of trials, we found that the reaction could be conducted successfully to afford an 88% yield of the target product **3** in the presence of 10 mol% of $PdCl_2$ (entry 2), and a satisfactory yield was still achieved at 5 mol% of $PdCl_2$ (entry 3). Other Pd catalysts, $PdCl_2/PPh_3$, $Pd(OAc)_2$ and $Pd(PPh_3)_4$, were also tested, and they were less effective than $PdCl_2$ (entries 4–6). The results indicated that the increased amount of 1,2-diphenyl disulfide (**2a**) has no effect on the reaction (entry 7). Among the solvents and reaction temperatures examined, DMSO combined with 80 °C gave the best results (entries 3 and 8–12). Finally, the role of oxidation reagents was evaluated. The results revealed that the addition of $CuCl_2$ affected the reaction slightly (entry 13). One equivalent of $CuCl_2$ instead of air provided the same results under air or argon atmosphere (entries 14 and 16). However, without $CuCl_2$ the reaction under argon atmosphere gave the target product **3** in a low yield together with another product **4**, 2-phenyl-1*H*-indole, in 50% yield (entry 15). These results suggested that air played a crucial role in the reaction.

With the optimal reaction in hand, we decided to explore the scope of 2-(1-alkynyl)benzenamines first. As listed in Table 2, a variety of 2-(1-alkynyl)benzen-



Scheme 1. Palladium-catalyzed annulation of 2-(1-alkynyl)-benzenamines with disulfides.

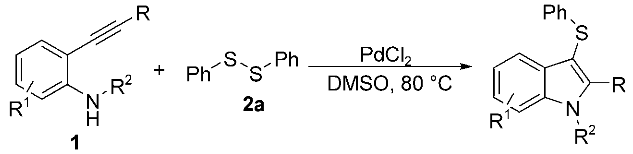
Table 1. Screening conditions for the synthesis of 3-sulfenylindoles.[a]

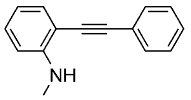
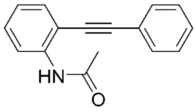
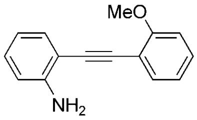
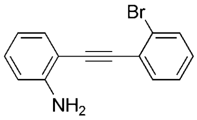
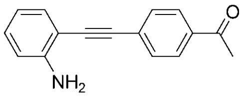
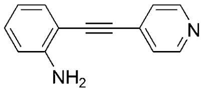
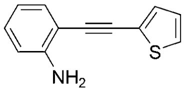
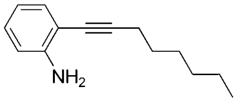
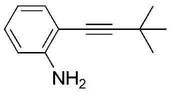
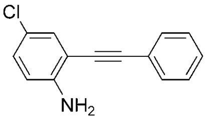
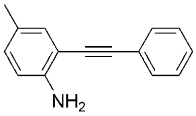


Entry	[Pd] (mol%)	Solvent	Temp. [°C]	Isolated Yield [%] (Product)
1	–	DMSO	80	0 (**3**)
2	$PdCl_2$ (10)	DMSO	80	88 (**3**)
3	$PdCl_2$ (5)	DMSO	80	76 (**3**)
4[b]	$PdCl_2$ (10)	DMSO	80	65 (**3**)
5	$Pd(OAc)_2$ (10)	DMSO	80	18 (**3**)
6[c]	$Pd(PPh_3)_4$ (10)	DMSO	80	trace (**3**)
7[d]	$PdCl_2$ (10)	DMSO	80	89 (**3**)
8	$PdCl_2$ (10)	DMF	80	25 (**3**)
9	$PdCl_2$ (10)	MeCN	80	72 (**3**)
10	$PdCl_2$ (10)	NMP	80	29 (**3**)
11[c]	$PdCl_2$ (5)	DMSO	25	trace (**3**)
12	$PdCl_2$ (5)	DMSO	100	52 (**3**)
13[e]	$PdCl_2$ (5)	DMSO	80	92 (**3**)
14[f]	$PdCl_2$ (5)	DMSO	80	86 (**3**)
15[g]	$PdCl_2$ (5)	DMSO	80	25 (**3**)
16[f,g]	$PdCl_2$ (5)	DMSO	80	85 (**3**)

[a] *Reaction conditions:* **1** (0.2 mmol), **2a** (0.1 mmol), [Pd] and solvent (2 mL) for 24 h under air atmosphere.
[b] PPh_3 (20 mol%) was added.
[c] >95% of **1a** was recovered.
[d] **2a** (0.2 mmol) was added.
[e] $CuCl_2$ (20 mol%) was added.
[f] $CuCl_2$ (100 mol%) was added under argon atmosphere.
[g] Under an argon atmosphere. 2-phenyl-1*H*-indole (**4**) was obtained in 50% yield.

Table 2. $PdCl_2$-catalyzed annulation of 2-(2-ethynyl)benzenamines (**1**) with 1,2-diphenyldisulfane (**2a**).[a]

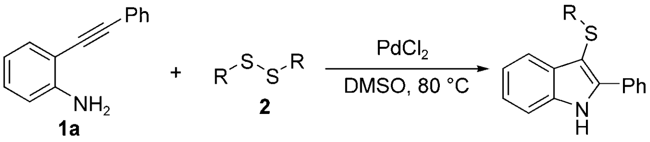


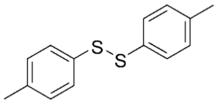
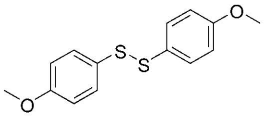
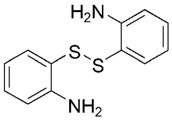
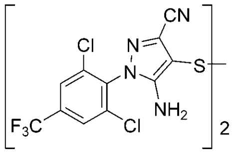
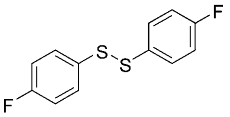
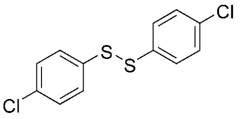
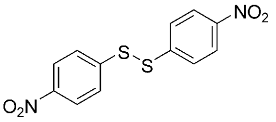
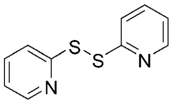
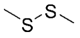
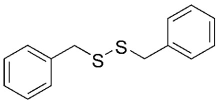
Entry		Substrate **1**	Time [h]	Isolated yield [%] (Product)
1	**1b**		24	65 (**5**)
2[b]	**1c**		24	trace (**6**)
3	**1d**		24	35 (**7**)
4	**1e**		30	59 (**8**)
5	**1f**		24	19 (**9**)
6[c]	**1g**		96	trace (**10**)
7	**1h**		24	82 (**11**)
8	**1i**		24	56 (**12**)
9	**1j**		24	83 (**13**)
10	**1k**		24	95 (**14**)
11	**1l**		24	61 (**15**)

[a] *Reaction conditions:* **1a** (0.2 mmol), **2** (0.1 mmol), $PdCl_2$ (10 mol%) and DMSO (2 mL) at 80 °C under air atmosphere.
[b] Some unidentified products were observed by GC-MS analysis.
[c] >95% of **1g** was recovered.

amines **1b–1l** were tested by treating with 1,2-diphenyl disulfide (**2a**), $PdCl_2$ and air. We were pleased to disclose that satisfactory results were still obtained from the analogous amine with the hydrogen group replaced by a methyl group in the presence $PdCl_2$ and air (entry 1), but replacement by an acetyl group gave only a trace amount of the target product **6** (entry 2). Subsequently, substituents at the terminal alkyne moiety of 2-(1-alkynyl)benzenamine were evaluated, and the results demonstrated that both electronic and steric effects of substituents affected the reaction to some extent (entries 3–9). We found that 2-bromophenyl, thiophen-2-yl and alkyl groups favored the reactions providing moderate to good yields (entries 4 and 7–9), but 2-methoxyphenyl, pyridin-4-yl and 4-acetylphenyl groups gave low yields (entries 3, 5 and 6). To our delight, substrates **1k** and **1l**, having a chloro or a methyl group on the corresponding aromatic ring of benzenamine, also underwent the annulation reaction with disulfide **2a**, $PdCl_2$, and air smoothly in 95% and 61% yields, respectively (entries 10 and 11).

Table 3. $PdCl_2$-catalyzed annulation of 2-(2-phenylethynyl)-benzenamine (**1a**) with disulfides (**2**).[a]



Entry		Disulfide **2**	Time [h]	Isolated yield [%] (Product)
1	**2b**		25	58 (**16**)
2	**2c**		24	70 (**17**)
3	**2d**		48	27 (**18**)
4	**2e**		24	95 (**19**)
5	**2f**		24	89 (**20**)
6	**2g**		24	92 (**21**)
7	**2h**		24	96 (**22**)
8	**2i**		24	74 (**23**)
9	**2j**		24	78 (**24**)
10[b]	**2k**		24	trace (**25**)

[a] *Reaction conditions:* **1a** (0.2 mmol), **2** (0.1 mmol), $PdCl_2$ (10 mol%) and DMSO (2 mL) at 80 °C under air atmosphere.

[b] >95% of **1a** was recovered.

Next, a set of disulfides **2b–2k** were examined under the standard conditions, and the results are summarized in Table 3. The results indicated that diaryl disulfides **2b–2i** or dimethyl disulfide **2j**, reacted with 2-(2-phenylethynyl)benzenamine (**1a**), $PdCl_2$ and air smoothly in moderate to excellent yields (entries 1–9), but 1,2-dibenzyl disulfide (**2k**) was found to be an unsuitable substrate under the same conditions (entry 10). We were pleased to observe that several functional groups, such as methyl, methoxy, amino, cyano, trifluoromethyl, fluoro, chloro, and nitro groups, on the aromatic moiety of disulfides were perfectly tolerated, and disulfides having electron-deficient aryl groups gave the better results (entries 1–8). Substrate **2b** bearing a *para*-methyl group, for example, was treated with **1a**, $PdCl_2$ and air to afford the corresponding desired product **16** in 58% yield (entry 1). Gratifyingly, disulfide **2h** with an electron-withdrawing nitro group offered the product **22** in 96% yield (entry 7). Noteworthy is that a new fipronil analogue **19** is readily synthesized in high yield under the standard conditions (entry 4).[11] We were pleased to discover that the standard conditions were also compatible with 2-[2-(pyridin-2-yl)disulfanyl]pyridine (**2i**). In the presence of $PdCl_2$ and air, treatment of substrate **2i** with disulfide **1a** gave the desired product **23** in 74% yield (entry 8).

In summary, we have described the first example of synthesizing 3-sulfenylindoles by palladium-catalyzed annulation of 2-(1-alkynyl)benzenamines with disulfides under an air atmosphere. In the presence of $PdCl_2$ and air, a variety of 2-(1-alkynyl)benzenamines underwent the annulation reaction with disulfides smoothly to afford the corresponding 3-sulfenylindoles in moderate to good yields. It is worth noting that a new fipronil analogue is prepared in a good yield *via* the present protocol.[12] Efforts to explore the detailed mechanism and extend the applications of the transformation in organic synthesis are underway in our laboratory.

Experimental Section

Typical Experimental Procedure for Palladium-Catalyzed Annulation of 2-(1-Alkynyl)benzenamines (1) with Disulfides (2)

A mixture of 2-(1-alkynyl)benzenamine **1** (0.2 mmol), disulfide **2** (0. 1 mmol) and $PdCl_2$ (10 mol%) in DMSO (2 mL) was stirred at 80 °C under an air atmosphere for the indicated time until complete consumption of starting material as monitored by TLC and GC-MS analysis. After the reaction was finished, the mixture was poured into ethyl acetate, which was washed with saturated NaCl (5×3 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired product.

2-Phenyl-3-(phenylthio)-1*H*-indole (3): Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.57$ (brs, 1H), 7.78 (d, $J = 8.2$ Hz, 2H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.49–7.42 (m, 4H), 7.30–7.27 (m, 1H), 7.22–7.12 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.1, 139.3, 135.9, 131.4, 131.2, 128.9, 128.8, 128.7, 128.1, 125.6, 124.6, 123.4, 121.2, 120.0, 111.2, 99.4; LR-MS (EI, 70 eV): m/z (%) = 301 (M^+, 100), 268 (13), 223 (31); HR-MS (EI): m/z = 301.0925, calcd. for $C_{20}H_{15}NS$ (M^+): 301.0925.

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