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Synthesis of 3-Sulfenyl- and 3-Selenylindoles by the Pd/Cu-Catalyzed Coupling of *N*,*N*-Dialkyl-2-iodoanilines and Terminal Alkynes, Followed by *n*-Bu_4NI-Induced Electrophilic Cyclization

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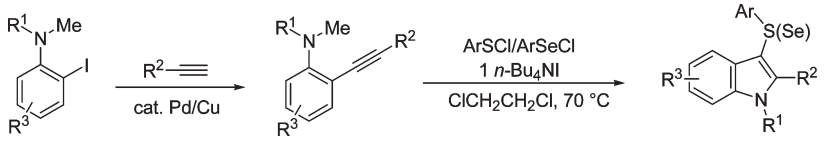

3-Sulfenyl- and 3-selenylindoles are readily synthesized by a two-step process involving the palladium/copper-catalyzed crossing coupling of *N*,*N*-dialkyl-*ortho*-iodoanilines and terminal alkynes and subsequent electrophilic cyclization of the resulting *N*,*N*-dialkyl-*ortho*-(1-alkynyl)anilines with arylsulfenyl chlorides or arylselenyl chlorides. The presence of a stoichiometric amount of *n*-Bu_4NI is crucial to the success of the electrophilic cyclization. A variety of 3-sulfenyl- and 3-selenylindole derivatives bearing alkyl, vinylic, aryl, and heteroaryl substituents have been prepared in good to excellent yields (up to 99%). By employing *N*,*N*-dibenzyl-*ortho*-iodoanilines, a 3-sulfenyl-*N*-*H*-indole has been successfully prepared. In addition, 3-sulfonyl- and 3-sulfinylindoles have also been successfully prepared by facile oxidation of the corresponding 3-sulfenylindoles.

Introduction

The indole ring is present in a wide variety of biologically active compounds and pharmaceutical agents.[1] Among the numerous indole derivatives known, 3-thioindoles have recently attracted considerable attention from both industry and academia due to their therapeutic value in a variety of diseases, such as HIV,[2] cancer,[3] obesity,[4] heart disease,[5] and allergies.[6] For instance, MK-886 is an inhibitor of 5-lipoxygenase and can augment the antitumor activity of celecoxib in human colorectal cancer.[7] L-737,126 is known to exhibit potent anti-HIV properties,[8] and the 3-(arylsulfenyl)indole **1** is not only an inhibitor of tubulin polymerization, but also capable of inhibiting human breast cancer cell growth.[9]

Because of their therapeutic potential, there has been growing interest in developing a general and versatile synthetic route to 3-thioindole derivatives. As a consequence, a number of synthetic approaches to 3-sulfenylindoles have been developed in the past few years, including the direct sulfenylation of indoles by disulfides[10] or quinone mono-*O*,*S*-acetals;[11] halide-catalyzed sulfenylation

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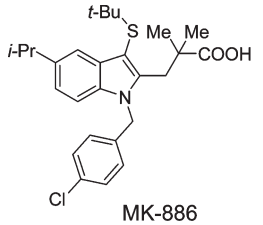
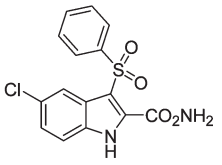
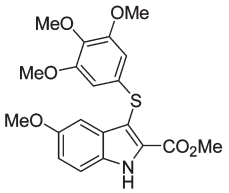
by *N*-thioalkyl(aryl)phthalimides;[12] sulfenylation using thiols activated in situ by *N*-chlorosuccinimide,[13] phenyliodine(III) bis(trifluoroacetate),[14] Selectfluor,[15] or transition-metal catalysts;[16] oxidant-promoted thiocyanation with ammonium thiocyanate;[17] and treatment of 3, 3′-dithiobisindoles with metalated aromatics or heterocycles.[18] In general, all these protocols have focused on direct sulfenylation at the 3-position of the indole nucleus by different sulfenylating agents.



MK-886



L-737,126



1

Recently, our group and others have reported the synthesis of a wide range of carbocyclic and heterocyclic compounds by electrophilic cyclization.[19] In the presence of halogen, sulfur, and selenium electrophiles, a wide variety of functionally substituted alkynes undergo electrophilic cyclization to form the corresponding heterocyclic and carbocyclic compounds, including indoles,[20] benzofurans,[21] benzothiophenes,[22] benzoselenophenes,[23] benzopyrans,[24] furans,[25] naphthols,[26] naphthalenes,[27] isoindolinones,[28] coumestans and coumestrols,[29] chromones,[30] isocoumarins and α-pyrones,[31] isochromenes,[32] isoquinolines,[33] quinolines,[34] isoxazoles,[35] polycyclic aromatics,[36] pyrroles,[37] furopyridines,[38] furanones,[39] and spiro[4,5]trienones.[40]

Although we had successfully prepared 3-sulfenyl-benzofurans[21a] and -benzothiophenes[22b,c] by electrophilic cyclization using arylsulfenyl chlorides as the electrophile, our early attempts to prepare 3-sulfenylindoles using similar methods were unsuccessful. The pharmaceutical interest in 3-sulfenylindoles, however, inspired us to explore this approach further. Our preliminary results have shown that in the presence of 1 equiv of *n*-Bu_4NI, 3-sulfenylindoles can be successfully prepared under standard electrophilic cyclization conditions.[41] Herein, we report our detailed results on the synthesis of 3-sulfenylindoles using this *n*-Bu_4NI-induced electrophilic sulfur cyclization chemistry.

Results and Discussion

The required starting material, *N*,*N*-dialkyl-2-(1-alkynyl)-anilines (**3**), is readily prepared by the Sonogashira coupling[42] of *N*,*N*-dialkyl-*ortho*-iodoanilines (**2**)[43] and terminal alkynes. The results of this palladium/copper-catalyzed

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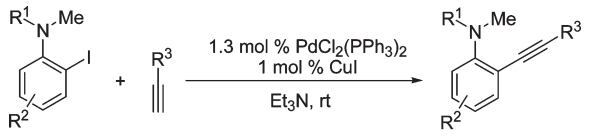
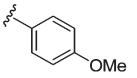
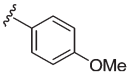
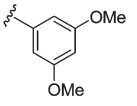
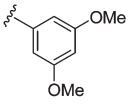
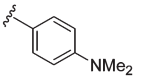
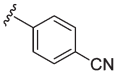
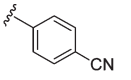
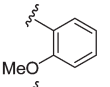
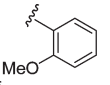
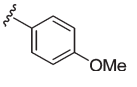
(43) The *N*,*N*-dialkyl-*ortho*-iodoanilines have been prepared by the dialkylation reaction. The detailed results are summarized in the Supporting Information.

TABLE 1. Preparation of *N*,*N*-Dialkyl-2-(1-alkynyl)anilines by Sonogashira Coupling[a]

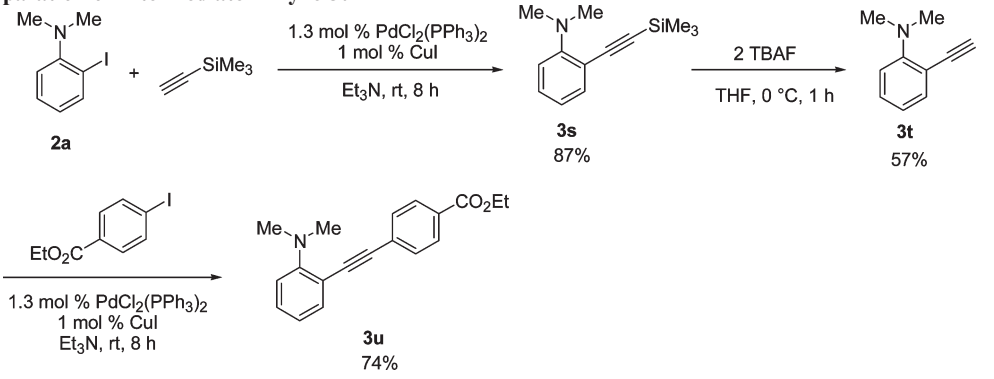


2 **3**

entry	**2**	R^1	R^2	R^3	time (h)	% yield[b] (**3**)
1	**2a**	Me	H	C_6H_5	8	89 (**3a**)
2	**2b**	Me	5-Me	C_6H_5	7	92 (**3b**)
3	**2c**	Me	4-Br	C_6H_5	5	76 (**3c**)
4	**2d**	Me	4-CO_2Me	C_6H_5	10	92 (**3d**)
5	**2e**	Me	5-CO_2Me	C_6H_5	10	93 (**3e**)
6	**2a**	Me	H		4	93 (**3f**)
7	**2c**	Me	4-Br		3	83 (**3g**)
8	**2a**	Me	H		5	85 (**3h**)
9	**2c**	Me	4-Br		6	84 (**3i**)
10	**2c**	Me	4-Br		4	86 (**3j**)
11	**2a**	Me	H		24	72 (**3k**)
12	**2c**	Me	4-Br		24	79 (**3l**)
13	**2a**	Me	H		6	98 (**3m**)
14	**2c**	Me	4-Br		5	81 (**3n**)
15	**2a**	Me	H		6	87 (**3o**)
16	**2a**	Me	H		4	82 (**3p**)
17	**2c**	Me	4-Br		5	86 (**3q**)
18	**2f**	C_6H_5	H		12	79 (**3r**)

[a] *N*,*N*-Dialkyl-2-iodoaniline (**2**, 2.0 mmol), terminal acetylene (2.2 mmol), $PdCl_2(PPh_3)_2$ (0.026 mmol), CuI (0.020 mmol), and 6 mL of Et_3N were mixed in a sealed 4-dram vial. The resulting mixture was flushed with Ar and stirred at room temperature for the indicated time. [b] Isolated yields after column chromatography.

SCHEME 1. Preparation of Intermediate Alkyne 3u



SCHEME 2. Reaction between 3a and 4-Nitrobenzenesulfenyl Chloride under Standard Electrophilic Cyclization Conditions

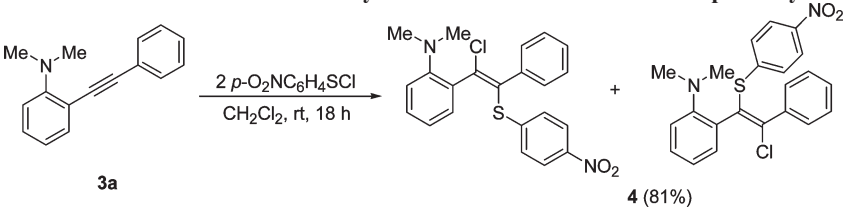
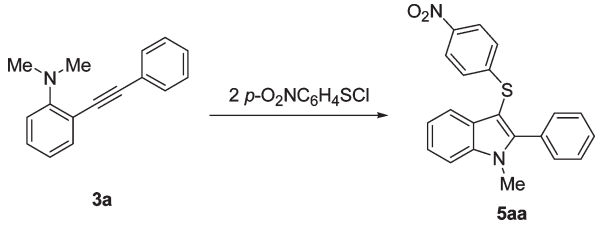


TABLE 2. *n*-Bu_4NI-Induced Electrophilic Cyclization of *N*,*N*-Dimethyl-(2-phenylethynyl)aniline with 4-Nitrobenzenesulfenyl Chloride[a]



entry	additive (equiv)	solvent	temp (°C)	time (h)	% yield[b]
1	*n*-Bu_4NI (1.0)	CH_2Cl_2	rt	60	86
2	*n*-Bu_4NI (1.0)	$(CH_2Cl)_2$	70	5	90
3	*n*-Bu_4NI (1.0)	CH_3CN	70	5	81
4	*n*-Bu_4NI (1.0)	toluene	70	5	13[c]
5	*n*-Bu_4NCl (1.0)	$(CH_2Cl)_2$	70	5	[d]
6	*n*-Bu_4NBr (1.0)	$(CH_2Cl)_2$	70	5	[d]
7	LiI (1.0)	$(CH_2Cl)_2$	70	5	trace[e]
8	*n*-Bu_4NI (0.5)	$(CH_2Cl)_2$	70	5	48[f]
9[g]	*n*-Bu_4NI (1.0)	$(CH_2Cl)_2$	70	5	72

[a] 4-Nitrobenzenesulfenyl chloride (2.0 equiv) was employed unless otherwise indicated. [b] Isolated yield of **5aa** after column chromatography unless otherwise indicated. [c] Yield determined by ^1H NMR spectroscopy. [d] No cyclized product was detected. [e] Only a trace amount (< 5%) of the desired cyclized product was detected by ^1H NMR spectroscopy. [f] Approximately a 40% yield of triple bond addition products **4** was obtained. [g] 4-Nitrobenzenesulfenyl chloride (1.5 equiv) was employed.

coupling process are summarized in Table 1. In general, this coupling reaction takes place smoothly between a variety of functionalized *N*,*N*-dialkyl-*ortho*-iodoanilines and terminal alkynes, affording high to excellent yields. A longer reaction time was required when electron-deficient 4-ethynylbenzonitrile was employed (Table 1, entries 11 and 12). Although it was found that the reaction rate in these cases could be significantly accelerated by means of either heating or adding a polar solvent, such as DMF, it is preferred that these reactions be carried out in Et_3N at room temperature to avoid the generation of cyclized indole byproduct.

Alkyne **3u** was prepared from *N*,*N*-dimethyl-2-iodoaniline (**2a**) by a three-step reaction sequence, namely, Sonogashira coupling, removal of the TMS group, and a second Sonogashira coupling (Scheme 1).

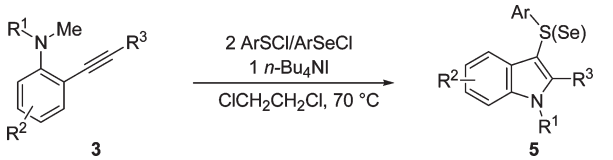
Our initial results indicated that under common electrophilic cyclization conditions, the reaction between *N*,*N*-dimethyl-(2-phenylethynyl)aniline (**3a**) and 4-nitrobenzenesulfenyl chloride leads exclusively to the simple triple bond addition products **4** (Scheme 2).[44] Our previous experience on the electrophilic cyclization chemistry of functionally substituted alkynes suggested that the successful cyclization reactions generally proceed by a stepwise mechanism involving electrophilic activation of the alkyne C−C triple bond, intramolecular nucleophilic attack on the cationic intermediate, and subsequent dealkylation by the in situ generated halide anion.[45] Based on this assumption and careful mechanism analysis, we envisioned that the failure in this electrophilic sulfur cyclization chemistry could be attributed to the relatively weak nucleophilicity of the in situ generated chloride anion, which should play a significant role in removal of the alkyl group after the intramolecular nucleophilic cyclization step had taken place. Thus, the nature of the halide might seriously impact indole ring construction. It is known that iodide anion is a better nucleophile than chloride anion due to its greater polarizability. For this reason, 1 equiv of *n*-Bu_4NI was added to the reaction of **3a** and *p*-$O_2NC_6H_4SCl$ as an external source of nucleophile. To our delight, in the presence of 1 equiv of *n*-Bu_4NI, the triple bond addition reaction was completely shut down and the reaction slowly produced solely the desired cyclization product **5aa** (Table 2, entry 1).

Our further study has revealed that this cyclization reaction can be substantially accelerated at an elevated temperature. Therefore, several higher boiling solvents were

(44) The ^1H NMR spectrum of the reaction mixture indicated that no cyclized indole product was formed.

(45) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141.

TABLE 3. Preparation of 3-Sulfenyl- and 3-Selenylindoles by *n*-Bu_4NI-Induced Electrophilic Cyclization[a]



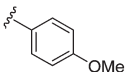
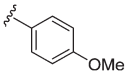
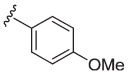
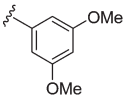
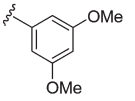
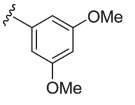
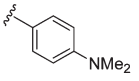
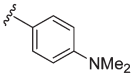
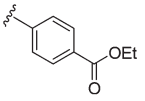
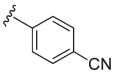
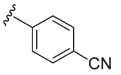
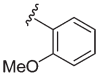
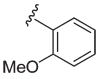
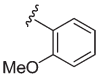
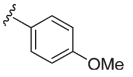
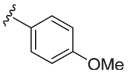
entry	3	R^1	R^2	R^3	ArSCl/ArSeCl	time (h)	5	% yield[b]
1	**3a**	Me	H	C_6H_5	*p*-$O_2NC_6H_4SCl$	5	**5aa**	90
2	**3a**	Me	H	C_6H_5	C_6F_5SCl	5	**5ab**	87
3	**3a**	Me	H	C_6H_5	C_6H_5SCl	6	**5ac**	87
4	**3a**	Me	H	C_6H_5	*p*-MeC_6H_4SCl	6	**5ad**	92
5	**3a**	Me	H	C_6H_5	*o*-$O_2NC_6H_4SCl$	5	**5ae**	52
6	**3a**	Me	H	C_6H_5	C_6H_5SeCl	5	**5af**	84
7	**3b**	Me	5-Me	C_6H_5	*p*-$O_2NC_6H_4SCl$	9	**5ag**	78
8	**3c**	Me	4-Br	C_6H_5	*p*-$O_2NC_6H_4SCl$	6	**5ah**	85
9	**3c**	Me	4-Br	C_6H_5	C_6H_5SCl	4	**5ai**	79
10	**3d**	Me	4-CO_2Me	C_6H_5	C_6H_5SCl	8	**5aj**	75
11	**3e**	Me	5-CO_2Me	C_6H_5	C_6H_5SCl	8	**5ak**	95
12	**3f**	Me	H		C_6H_5SCl	5	**5al**	71
13	**3f**	Me	H		*p*-MeC_6H_4SCl	6	**5am**	99
14	**3g**	Me	4-Br		C_6H_5SCl	5	**5an**	85
15	**3h**	Me	H		*p*-$O_2NC_6H_4SCl$	9	**5ao**	74
16	**3h**	Me	H		C_6H_5SCl	6	**5ap**	83
17	**3i**	Me	4-Br		C_6H_5SCl	5	**5aq**	83
18	**3j**	Me	4-Br		*p*-$O_2NC_6H_4SCl$	3	**5ar**	71
19	**3j**	Me	4-Br		C_6F_5SCl	2	**5as**	65

TABLE 3. Continued

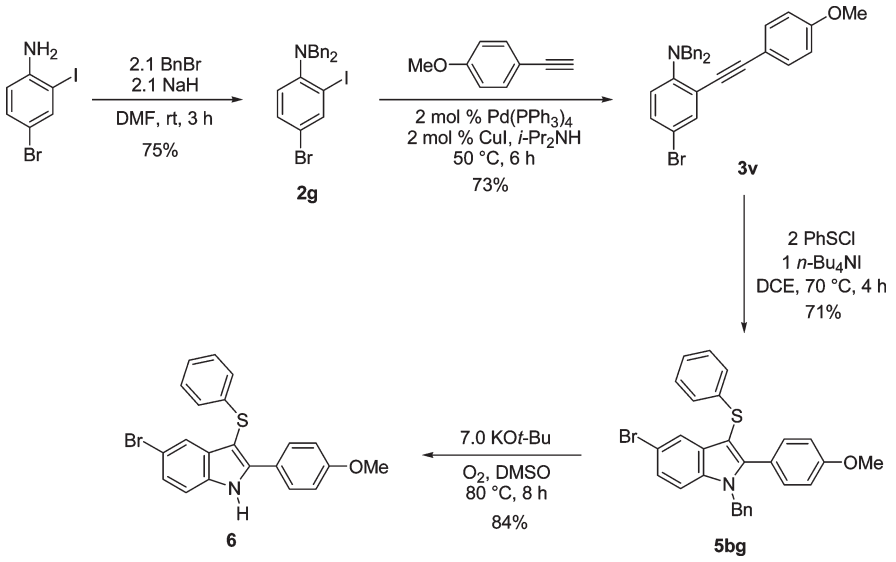
entry	3	R^1	R^2	R^3	ArSCl/ArSeCl	time (h)	5	% yield[b]
20	**3u**	Me	H		C_6H_5SCl	18	**5at**	66
21	**3k**	Me	H		C_6H_5SCl	50	**5au**	42
22	**3l**	Me	4-Br		C_6H_5SCl	55	**5av**	47
23	**3m**	Me	H		p-$O_2NC_6H_4SCl$	3	**5aw**	85
24	**3m**	Me	H		C_6H_5SCl	6	**5ax**	74
25	**3n**	Me	4-Br		C_6H_5SCl	4	**5ay**	91
26	**3o**	Me	H		p-$O_2NC_6H_4SCl$	3	**5az**	91
27	**3o**	Me	H		C_6H_5SeCl	5	**5ba**	76
28	**3p**	Me	H		C_6H_5SCl	4	**5bb**	79
29	**3q**	Me	4-Br		C_6H_5SCl	5	**5bc**	95
30	**3q**	Me	4-Br		p-$O_2NC_6H_4SCl$	7	**5bd**	81
31	**3r**	C_6H_5	H		p-MeC_6H_4SCl	3	**5be**	99
32	**3r**	C_6H_5	H		C_6H_5SCl	3	**5bf**	99

examined. When the reaction is run at 70 °C in dichloroethane (DCE), instead of room temperature in dichloromethane (DCM), a 90% yield of the desired 3-(arylsulfenyl)indole **5aa** was obtained in 5 h (Table 2, entry 2). An 81% yield was obtained when CH_3CN was employed (Table 2, entry 3). On the other hand, only a 13% yield of the desired indole product was obtained when the cyclization was carried out in toluene at 70 °C (Table 2, entry 4).

The role of the additive, n-Bu_4NI, was then investigated. None of the desired indole product was observed when either 1 equiv of n-Bu_4NCl or n-Bu_4NBr was employed (Table 2, entries 5 and 6). Indole **5aa** was generated only in trace amounts when n-Bu_4NI was replaced by LiI (Table 2, entry 7), possibly due to the extremely low solubility of the latter in DCE. An equimolar amount of n-Bu_4NI is found necessary for exclusive formation of the cyclization product. When 0.5 equiv of n-Bu_4NI is used, a mixture of both indole **5aa** and the triple bond addition products **4** is obtained in approximately a 1:1 ratio (Table 2, entry 8). An incomplete reaction was observed after 5 h when the electrophile 4-nitrobenzenesulfenyl chloride was reduced from 2.0 to 1.5 equiv (Table 2, entry 9).

The reaction scope was then explored under the optimal reaction conditions (Table 2, entry 2). This cyclization has proved to be a very general route to a variety of 3-sulfenylindoles (Table 3). Besides 4-nitrobenzenesulfenyl chloride, several other arylsulfenyl chlorides have also been successfully employed as electrophiles in this cyclization. When electron-deficient pentafluorobenzenesulfenyl chloride was employed, an 87% isolated yield of the corresponding indole was obtained (Table 3, entry 2). The more electron-rich arylsulfenyl chlorides phenylsulfenyl chloride and p-toluene-

SCHEME 3. Preparation of an *N*-*H*3-Sulfenylindole



sulfenyl chloride afforded similar high yields (Table 3, entries 3 and 4). When the more sterically demanding 2-nitrobenzenesulfenyl chloride was used, the yield of the cyclization product **5ae** decreased to 52% (Table 3, entry 5), although the starting material **3a** was completely consumed. Products of simple addition of the 2-nitrobenzenesulfenyl chloride to the triple bond of **3a** were also observed. Besides arylsulfenyl chlorides, an alkylsulfenyl chloride, trichloromethylsulfenyl chloride, has also been employed in this cyclization. However, this reagent only afforded a complex reaction mixture using our current optimized reaction conditions.

Despite our previous lack of success with the synthesis of 3-selenylindoles via analogous electrophilic cyclization chemistry,[20a] the cyclization of aniline **3a** by PhSeCl plus *n*-Bu_4NI was investigated. We were quite pleased to find that our current reaction conditions were equally suitable for the synthesis of 3-selenylindoles (Table 3, entry 6).

The electronic effect of the substituents on the aniline moiety in this electrophilic cyclization process has also been investigated. It turns out that this process is not particularly sensitive to the electronic effects of the aniline moiety, which is in good agreement with our previous experience with this type of electrophilic cyclization reaction, although the presence of a strong electron-withdrawing group on the aniline ring can significantly reduce the nucleophilicity of the dialkylamino group.[20a,b] Thus, this cyclization proceeds nicely in the presence of either electron-withdrawing or electron-releasing groups (Table 3, entries 7−11). In all cases examined, high yields have been obtained with reaction times similar to those of the parent system **3a**.

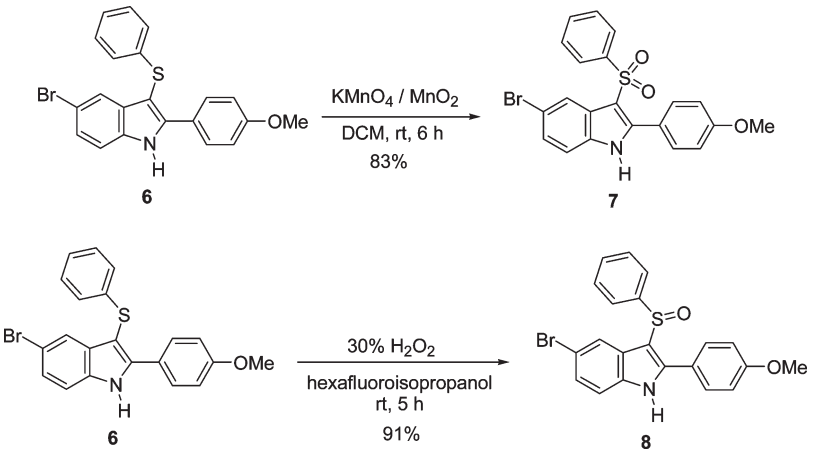
Besides 2-(phenylethynyl)anilines, other 2-(alkynyl)anilines have also been successfully employed in this process (Table 3, entries 12−32). In contrast to the effect of substituents on the aniline moiety, the substituents on the 2-alkynyl moiety display a significant electronic effect on this cyclization process. In general, the reaction is accelerated by the presence of electron-rich groups situated at the distal end of the 2-alkynyl triple bond, such as a 4-(*N*,*N*-dimethylamino)phenyl group (Table 3, entries 18 and 19), a thiophene ring (Table 3, entries 23−25), and a 4-methoxyphenyl group (Table 3, entries 31 and 32). The same high reaction rate was observed when a vinylic moiety, such as a 1-cyclohexenyl group, was present on the distal end of the triple bond (Table 3, entry 26). In this case, no product of addition of the 4-nitrobenzenesulfenyl chloride to the carbon−carbon double bond of the 1-cyclohexenyl moiety was observed, although such an addition reaction has previously been reported.[46] The same alkyne substrate **3o** also undergoes cyclization smoothly in the presence of a selenium electrophile leading to the corresponding 3-selenylindole in a 76% yield (Table 3, entry 27). The cyclization process was, however, significantly slowed by the presence of electron-withdrawing groups. When an ethoxycarbonyl group is situated at the *para*-position of the aryl group on the distal end of the alkyne triple bond, the cyclization takes as long as 18 h (Table 3, entry 20), affording product **5at** in a 66% yield. The effect is even more pronounced when the stronger electron-withdrawing cyano group is present (Table 3, entries 21 and 22). These cyclizations take more than 50 h and only afford modest yields ($< 50\%$) of the desired indole products. In both cases, a significant amount of the simple triple bond addition products are obtained.

We have previously shown that *ortho*-methoxyaryl alkynes undergo electrophilic cyclization in the presence of an arylsulfenyl chloride, without the addition of *n*-Bu_4NI, to form 3-sulfenylbenzofurans.[21a] We therefore investigated the reactivity of substrates **3p** and **3q** under our current cyclization conditions (Table 3, entries 28−30). Note that this alkyne contains an *ortho*-methoxyphenyl group at one end of the ethynyl functionality and an *ortho*-(*N*,*N*-dimethylamino)phenyl group at the other end. Thus, two cyclization paths are possible, leading to the formation of an indole, a benzofuran or possibly a mixture of both. In practice, the 3-sulfenylindoles **5bb**, **5bc**, and **5bd** were generated exclusively with no benzofuran products being observed.

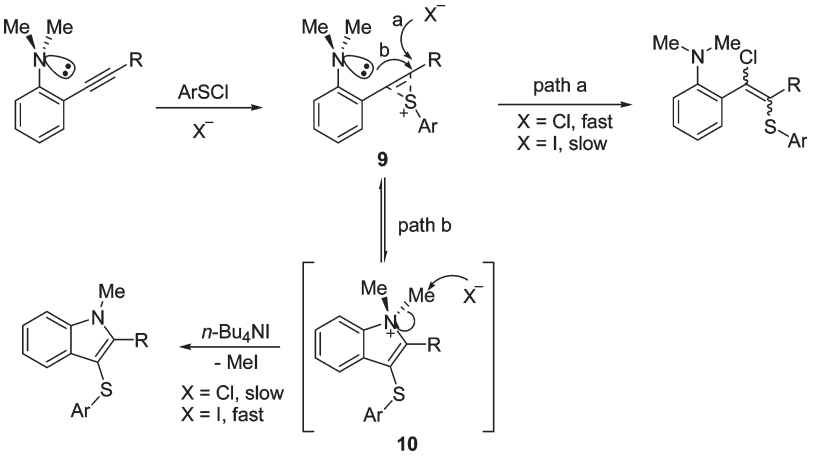
Substrate **3r** containing both a methyl and a phenyl group on the aniline nitrogen was also studied in this cyclization. As

(46) (a) Schmid, G. H.; Strukelj, M.; Dalipi, S.; Ryan, M. D. *J. Org. Chem.* **1987**, *52*, 2403. (b) Akguen, E.; Hartke, K.; Kaempchen, T. *Arch. Pharm.* (*Weinheim, Ger.*) **1981**, *314*, 72.

SCHEME 4. Oxidation of a 3-Sulfenylindole



SCHEME 5. Proposed Mechanism and Plausible Effect of *n*-Bu_4NI on the Electrophilic Cyclization



expected, the *N*-phenylindoles **5be** and **5bf** were produced exclusively in essentially quantitative yields (Table 3, entries 31 and 32).

The bromine atom present on the aniline ring of the starting internal alkynes **3c**, **3g**, **3i**, **3j**, **3 L**, **3n**, and **3q** (Table 3) has proved to be an ideal handle for further chemical elaborations by palladium-catalyzed coupling processes, after the cyclization, allowing the efficacious synthesis of a wide variety of substituted 3-thioindoles. Besides sulfenyl chlorides, sulfonyl chlorides and sulfinyl chlorides have also been examined in the current cyclization chemistry. However, none of the desired 3-substituted indole products were observed.

To prepare free *N*-H 3-thioindoles, we employed 4-bromo-2-iodoaniline bearing two benzyl groups on the aniline nitrogen in this cyclization (Scheme 3). The dibenzylated compound **2g** was converted to the internal alkyne **3v** by Sonogashira coupling in the presence of 2 mol % of Pd-$(PPh_3)_4$ and 2 mol % of CuI.[47] Subsequent electrophilic cyclization took place smoothly under our optimal reaction conditions, affording the *N*-benzylated indole **5bg** in a 71% yield. The latter product was readily converted to the corresponding *N*-*H*3-sulfenylindole **6** by employing Deaton−Rewolinski's debenzylation conditions.[48]

Although our attempts to prepare 3-sulfonyl- and 3-sulfinylindoles by direct sulfonyl chloride and sulfinyl chloride cyclization chemistry were not successful, these compounds were readily synthesized by simply oxidizing the corresponding 3-sulfenylindoles. Thus, 3-sulfonylindole **7** and 3-sulfinylindole **8** have been successfully prepared in 83 and 91% yields, respectively (Scheme 4).

Based on our previous experience with this type of electrophilic cyclization chemistry, we believe that the current process involves an *anti*-addition of the sulfur electrophile and the nitrogen moiety of the aniline to the alkyne triple bond to form a transient 3-sulfenylindolium salt **10** by a thiirenium intermediate **9** (Scheme 5, path b). In the presence of *n*-Bu_4NI, **10** undergoes methyl group removal via S_N2 displacement by the external iodide to complete indole ring construction after the loss of one molecule of MeI, which is possibly the driving force to shift the equilibrium from the thiirenium species **9** to the indolium intermediate **10**. In the absence of *n*-Bu_4NI, the harder counterion chloride is less nucleophilic and prefers *trans*-addition to the thiirenium intermediate to form the undesired olefin product

(47) About 15% of 1-benzyl-5-bromo-2-(4-methoxy-phenyl)indole was obtained alongside the desired cyclized product **5bg** when this Sonogashira coupling was carried out under the reaction conditions described in Table 1.

(48) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett.* **2002**, *43*, 399.

(Scheme 5, path a). However, our attempts to detect MeI and the indolium intermediate **10**[49] by ^{1}H NMR spectroscopy in a reaction between **3a** and 4-nitrobenzenesulfenyl chloride have been unsuccessful. These experiments have clearly shown the conversion of the starting materials to the desired 3-sulfenylindole product, but nothing else.[50] In addition, we have also prepared 1-[2-(phenylethynyl)-phenyl]pyrrolidine and examined its cyclization in the hope of obtaining the corresponding 3-sulfenylindole with a 4-iodobutyl chain attached to the nitrogen atom. Unfortunately, this reaction only afforded a complex reaction mixture with none of the desired indole product detected.

We cannot rule out activation of the arylsulfenyl chloride by *n*-Bu_4NI through halogen exchange to form the corresponding arylsulfenyl iodide (ArSI) as the real electrophile.[51] In the presence of the softer counterion iodide, the intramolecular cyclization (Scheme 5, path b) may take place much faster than addition to the triple bond (Scheme 5, path a), thus leading to the indole product.

The success of this cyclization reaction presumably relies on two factors, the presence of the two organic groups on the aniline nitrogen atom and the 1 equiv of *n*-Bu_4NI. In general, delocalization of the lone-pair of electrons on the aniline nitrogen into the aromatic ring π-electron system through orbital overlap dramatically decreases its basicity and nucleophilicity. However, the steric bulkiness of the two organic groups on the nitrogen and the *ortho*-substituted internal triple bond forces rotation of the aromatic C−N bond and reduces this orbital overlap, resulting in considerable enhancement of the nitrogen nucleophilicity. Inductive electron donation by the two organic groups on nitrogen also raises the nitrogen nucleophilicity. This hypothesis has been proved by our experimental data. No cyclization product was obtained when either the free *ortho*-amino (NH_2) containing alkyne or the *ortho*-*N*-monomethylamino (MeNH) containing alkyne analogue of **3a** was employed. In addition, the Boc-protected *ortho*-amino (NHBoc) containing alkyne analogue of **3a** has also been examined in this cyclization. However, no cyclized product was observed at all. With respect to *n*-Bu_4NI, it presumably provides the highly nucleophilic iodide ions needed to remove the methyl group from the indolium intermediate **10** and thus facilitates construction of the indole nucleus.

Conclusions

A synthetic approach to 3-sulfenylindoles and 3-selenylindoles by the *n*-Bu_4NI-induced electrophilic cyclization of *N*,*N*-dialkyl-2-(1-alkynyl)anilines by arylsulfenyl chlorides or arylselenyl chlorides has been described. A wide variety of *N*,*N*-dialkyl-2-(1-alkynyl)anilines undergo this cyclization process in good to excellent yields. Free *N*-*H*3-thioindoles have been successfully prepared using the present method and employing benzyl protecting groups. In addition, the 3-sulfenylindoles synthesized are readily converted to the corresponding 3-sulfonyl- and 3-sulfinylindoles by oxidation. A plausible mechanism for this cyclization has been proposed and the role of *n*-Bu_4NI has been discussed. This synthetic approach allows simultaneous construction of the indole ring system and the installation of a sulfenyl or selenyl functionality at the 3-position of the indole nucleus, and is a useful complement to the known literature protocols for preparing 3-sulfenyl- and 3-selenylindoles.

Experimental Section

General Procedure for Preparation of the *N*,*N*-Dimethyl-*o*-iodoanilines. These compounds were prepared according to a procedure reported by Cadogan.[52] To a solution of the corresponding *o*-iodoaniline (2.0 mmol) and iodomethane (0.85 g, 6.0 mmol) in DMF (10 mL) was added K_2CO_3 (0.55 g, 4.0 mmol). The resulting mixture was stirred at room temperature for 48 h. Water (10 mL) was added to the reaction mixture. The resulting solution was extracted with diethyl ether (3 × 10 mL). The organic layers were combined and washed with water to remove any remaining DMF and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

***N*,*N*-Dimethyl-4-bromo-2-iodoaniline (2c).** This compound was obtained as a light red oil in an 81% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 6H), 6.92 (d, J = 8.5 Hz, 1H), 7.40 (dd, J = 8.5, 2.4 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.0, 97.6, 116.4, 121.5, 132.0, 142.0, 154.3; HRMS (EI) calcd for C_8H_9BrIN, 324.8963; found, 324.8969.

General Procedure for Preparation of the *N*,*N*-Dialkyl-2-(1-alkynyl)anilines. To a 4-dram oven-dried vial was added $PdCl_2(PPh_3)_2$ (18.3 mg, 0.026 mmol), CuI (3.8 mg, 0.020 mmol), 2.0 mmol of the *N*,*N*-dialkyl-*o*-iodoaniline, 2.2 mmol of the terminal acetylene, and 6 mL of Et_3N. The resulting mixture was flushed with Ar and stirred at room temperature for the desired time. The reaction mixture was diluted with 15 mL of diethyl ether and washed with brine (15 mL). The aqueous phase was then extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product, which was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

***N*,*N*-Dimethyl-4-bromo-2-(phenylethynyl)aniline (3c).** This compound was obtained as a light yellow oil in a 76% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.98 (s, 6H), 6.78 (d, J = 8.8 Hz, 1H), 7.31−7.37 (m, 4H), 7.51−7.54 (m, 2H), 7.59 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.4, 87.7, 95.9, 112.1, 116.7, 118.5, 123.4, 128.4, 128.5, 131.4, 132.0, 136.4, 153.7; HRMS (EI) calcd for $C_{16}H_{14}BrN$, 299.0310; found, 299.0314.

General Procedure for Preparation of the 3-Sulfenyl- and 3-Selenylindoles. To a solution of 0.50 mmol of the *N*,*N*-dialkyl-2-(1-alkynyl)aniline, 0.50 mmol of *n*-Bu_4NI, and 3 mL of 1,2-dichloroethane (DCE) was gradually added a solution of 1.00 mmol of arylsulfenyl or arylselenyl chloride in 2 mL of DCE. The resulting mixture was stirred at room temperature for 5 min and then heated to 70 °C for the desired time. The reaction mixture was cooled to room temperature and diluted with 5 mL of dichloromethane (DCM). The mixture was then washed with 10 mL of satd aq NH_4Cl. The aqueous phase was extracted with diethyl ether (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash column chromatography on silica gel using either ethyl acetate/hexanes or chloroform/hexanes as the eluent.

1-Benzyl-5-bromo-2-(4-methoxyphenyl)-3-(phenylsulfenyl)indole (5bg). This product was obtained as a white solid in a 71% yield:

(49) For an example of the preparation and characterization of a 3-iodoindolium triiodide species, see ref 19d.

(50) We have been able to observe MeBr and the analogous selenium intermediate in our synthesis of benzoselenophenes. See ref 23a.

(51) For a selected example of the synthesis and reactivity of an arylsulfenyl iodide, see Goto, K.; Yamamoto, G.; Tan, B.; Okazaki, R. *Tetrahedron Lett*. **2001**, *42*, 4875.

(52) Cadogan, J. I. G.; Hickson, C. L.; Husband, J. B.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1891.

mp 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.34 (s, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 7.0 Hz, 2H), 7.04−7.12 (m, 4H), 7.19 (t, J = 7.4 Hz, 2H), 7.25−7.30 (m, 6H), 7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.7, 55.5, 99.9, 112.5, 114.1, 114.8, 122.1, 122.4, 124.8, 125.6, 125.96, 126.04, 127.7, 129.0, 129.1, 131.8, 132.1, 135.9, 137.3, 139.6, 147.5, 160.4; HRMS (EI) calcd for $C_{28}H_{22}BrNOS$, 499.0605; found, 499.0616.

5-Bromo-2-(4-methoxyphenyl)-3-(phenylsulfenyl)indole (6). This compound was prepared according to a procedure reported by Deaton-Rewolinski.[48] A solution of **5bg** (220 mg, 0.44 mmol) and KO-*t*-Bu (345 mg, 3.08 mmol) in DMSO (5 mL) was purged with O_2 at room temperature for 20 min. The reaction mixture was vigorous stirred at 80 °C for 8 h. The resulting mixture was diluted with EtOAc (10 mL) and washed with water (15 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product, which was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the corresponding product **6** in an 84% yield as a yellow oil, which solidified to a yellow solid upon standing: mp 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.94 (d, J = 8.8 Hz, 2H), 7.02−7.09 (m, 3H), 7.14−7.21 (m, 2H), 7.23−7.34 (m, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.74 (s, 1H), 8.50 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 98.3, 112.7, 114.5, 114.7, 122.4, 123.5, 125.0, 125.6, 126.2, 129.1, 129.6, 133.5, 134.5, 139.1, 143.6, 160.4; HRMS (EI) calcd for $C_{21}H_{16}BrNOS$, 409.0136; found, 409.0148.

5-Bromo-2-(4-methoxyphenyl)-3-(phenylsulfonyl)indole(7). This compound was prepared according to a procedure reported by Shaabani.[53] 5-Bromo-2-(4-methoxyphenyl)-3-(phenylsulfenyl)-indole (**6**; 0.195 mmol, 80 mg) were dissolved in CH_2Cl_2 (1.0 mL) and CH_3CN (1.0 mL). To the reaction mixture was added finely ground $KMnO_4/MnO_2$ (0.40 g) in portions over a period of 10 min. The mixture was stirred vigorously at room temperature, while the progress of the reaction was monitored by TLC. Upon completion of the reaction, the product was filtered through a sintered glass funnel to remove the solid precipitate. The product (in solution) was then filtered through a Celite pad and the solid residue was washed with CH_2Cl_2 (2 × 3 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the corresponding product **7** as a brown oil in an 83% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.48 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 8.8 Hz, 2H), 6.93 (t, J = 7.6 Hz, 2H), 7.02−7.14 (m, 4H), 7.79 (d, J = 8.8 Hz, 2H), 8.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 112.7, 118.6, 121.29, 121.31, 126.2, 128.2, 128.7, 129.8, 130.6, 131.0, 132.1, 136.1, 139.3, 152.4, 161.4, 175.1; HRMS (EI) calcd for $C_{21}H_{16}BrNO_3S$, 441.0034; found, 441.0044.

5-Bromo-2-(4-methoxyphenyl)-3-(phenylsulfinyl)indole(8). This compound was prepared according to a modification of a procedure reported by Xu.[54] To a solution of 5-bromo-2-(4-methoxyphenyl)-3-(phenylsulfenyl)indole (**6**; 80 mg, 0.195 mmol) and phenol (183.5 mg, 1.95 mmol) in HFIP (2.0 mL) was added 30% H_2O_2 (0.05 mL, 0.4 mmol). The reaction mixture was stirred at room temperature for 5 h. After complete disappearance of the reactant as monitored by TLC, the excess H_2O_2 was quenched with satd aq Na_2SO_3. Phenol was neutralized with 10% aq NaOH. The aqueous layer was extracted with EtOAc (2 × 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford the crude product, which was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the corresponding product **8** as a yellow oil in a 91% yield, which solidified to a yellow solid upon standing: mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 6.42 (d, J = 8.6 Hz, 2H), 6.92−7.05 (m, 2H), 7.03 (d, J = 8.6 Hz, 2H), 7.45−7.55 (m, 3H), 7.63−7.72 (m, 2H), 11.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 109.6, 114.0, 114.4, 114.5, 121.4, 122.2, 125.5, 126.1, 126.5, 129.4, 130.5, 130.6, 135.4, 142.9, 146.5, 160.9; HRMS (EI) calcd for $C_{21}H_{16}BrNO_2S$, 425.0085; found, 425.0089.

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Supporting Information Available: Experimental procedures, characterization data for the new compounds, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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