Cyclization

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Gold- and Indium-Catalyzed Synthesis of 3- and 6-Sulfonylindoles from *ortho*-Alkynyl-*N*-sulfonylanilines

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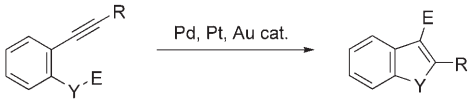
Sulfonylindoles are found in a wide variety of biologically active compounds, such as L-737126[1] and RO4368554.[2] However, it is difficult to synthesize sulfonylindoles directly from the corresponding unsubstituted indoles by electrophilic substitution because the electrophilicity of sulfonyl groups is much lower than that of acyl groups and halogens.[1] Although Yadav et al. recently reported that the indium-catalyzed reaction of indoles with sulfonyl chlorides leads to 3-sulfonylindoles,[3,4] the development of an efficient and robust method to synthesize sulfonylindoles, which could lead to the discovery of new bioactive compounds,[5] is still a challenge in organic synthesis.

Several groups, including ourselves, have recently reported that the reactions of *ortho*-alkynylanilines,[6] *ortho*-alkynylphenyl ethers,[6a,b,7] and *ortho*-alkynylphenyl sulfides[8] with a migrating group (E) on the heteroatom (Y) give the corresponding 2,3-disubstituted indoles, benzofurans, and benzothiophenes, respectively, in the presence of transition-metal catalysts [Eq. (1)].

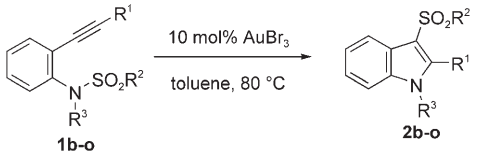


(1)

Y = NR', O, S
E = allyl, propargyl, acyl, α-alkoxyalkyl, MPM

Acyl, allyl, α-alkoxyalkyl, and methoxyphenylmethyl (MPM) groups can be employed as migrating groups. In this article, we report that the reactions of the *ortho*-alkynyl-*N*-sulfonylanilines **1b–o** give the corresponding 3-sulfonylindoles **2b–o** in good to excellent yields in the presence of a catalytic amount of $AuBr_3$ [Eq. (2)].

In addition, with $InBr_3$ as catalyst the cyclization of 2-alkynyl-6-methoxy-*N*-sulfonylanilines **1p–x** proceeds by an unprecedented 1,7-migration of the sulfonyl group to produce the 6-sulfonylindoles **3** as the major product in good to high yields [Eq. (3)].



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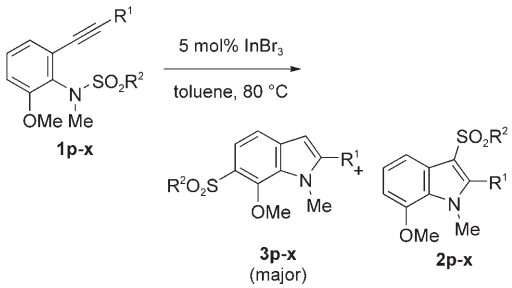
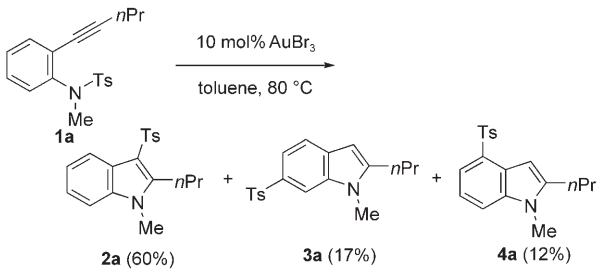


(3)

First, the catalytic activity of transition-metal compounds was tested with *N*-methyl-2-(1-pentynyl)-*N*-tosylaniline (**1a**) as substrate [Eq. (4)]. $AuBr_3$ showed the highest selectivity among the transition-metal complexes examined. Thus, the reaction of **1a** in the presence of 10 mol% $AuBr_3$ in toluene at 80 °C for one hour yielded *N*-methyl-2-propyl-3-tosylindole (**2a**) in 60% yield along with *N*-methyl-2-propyl-6-tosylindole (**3a**)[9] and *N*-methyl-2-propyl-4-tosylindole (**4a**), which are derived from an unprecedented sulfonyl migration to the benzene ring of the indole skeleton, in 17% and 12% yields, respectively. In our previous metal-catalyzed migration of *ortho*-alkynylacetanilides,[6d] *ortho*-alkynylphenyl acetals,[7f] and *ortho*-alkynylphenyl sulfides,[8] we did not observe substitution of the benzene ring by the migrating groups. The reaction of **1a** in the presence of $PtCl_2$ or $PdCl_2$ produced a 1:1 mixture of **2a** and **3a**, while the use of indium complexes led to a mixture of **2a**, **3a**, and **4a** (see the Supporting Information).

Next, we changed the tosyl group for a mesyl group. The results of the reaction of *ortho*-alkynyl-*N*-mesylanilines **1b–l**



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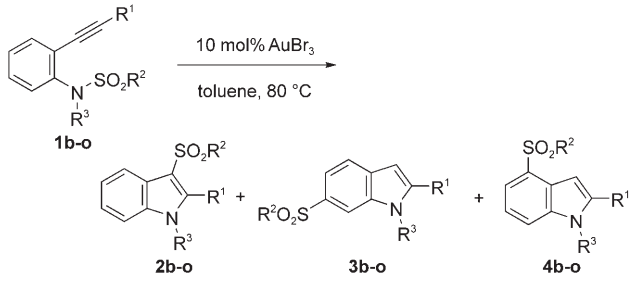
with $AuBr_3$ as catalyst are summarized in Table 1. The reaction of *N*-mesyl-*N*-methyl-2-(1-pentynyl)aniline (**1b**) in the presence of 10 mol% of $AuBr_3$ in toluene at 80°C for one hour gave 3-mesyl-1-methyl-2-propylindole (**2b**) in 95% yield (Table 1, entry 1). No other regioisomers derived from aromatic substitution were obtained. The reaction of **1b** in the presence of $AuCl_3$ or $PtCl_2$ gave **2b** in 85% and 93% yield, respectively. Substrates **1c** and **1d**, where R^1 is a cyclohexyl or *tert*-butyl group, were converted into **2c** and **2d** in 62% and 38% yields, respectively (Table 1, entries 2 and 3). The reaction of the 2-(arylethynyl)-*N*-tosylanilines **1f** and **1g**, where R^1 is an electron-rich aromatic ring, gave **2f** and **2g** in good yields, while the reaction with **1h**, which is substituted with an electron-deficient aromatic ring, produced **2h** in lower yield along with significant amounts of the other regioisomers (Table 1, entries 5–7). The terminal alkyne **1i** was converted into the 3-mesyl-substituted indole **2i** in 71% yield, while the reaction of the ynoate **1j** led to a mixture of unidentified products (Table 1, entries 8 and 9, respectively). The reaction of *N*-benzyl-*N*-sulfonylaniline (**1k**) and *N*-isopropyl-*N*-sulfonylaniline (**1l**) afforded the corresponding indoles **2k** and **2l** in moderate yields (Table 1, entries 10 and 11, respectively). The reaction of the arylsulfonanilides **1m–o** gave **2m–o** along with considerable amounts of the other regioisomers (Table 1, entries 12–14).

Table 1: $AuBr_3$-catalyzed cyclization of **1b–o**.[a]



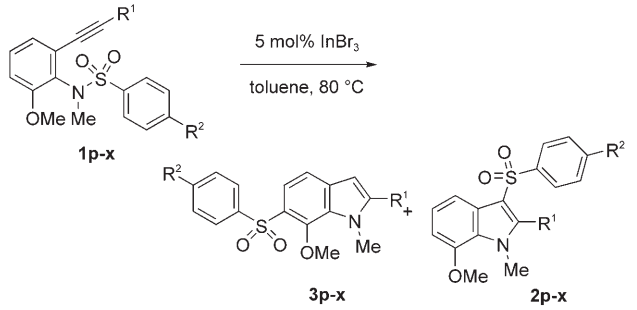
Entry	1	R^1	R^2	R^3	Yield [%] 2[b]	Yield [%] 3 and 4[c]
1	**1b**	*n*Pr	Me	Me	95	–
2	**1c**	cyclohexyl	Me	Me	62	25
3	**1d**	*t*Bu	Me	Me	38[d]	10
4	**1e**	Ph	Me	Me	92	2
5	**1f**	*p*-tolyl	Me	Me	87	–
6	**1g**	*p*-anisyl	Me	Me	81	5
7	**1h**	*p*-$F_3CC_6H_4$	Me	Me	51	20
8	**1i**	H	Me	Me	71	–
9	**1j**	CO_2Et	Me	Me	decomp[e]	
10	**1k**	*n*Pr	Me	Bn	44	–
11	**1l**	*n*Pr	Me	*i*Pr	60	–
12	**1m**	*n*Pr	Ph	Me	52	22
13	**1n**	*n*Pr	*p*-anisyl	Me	85	7
14	**1o**	*n*Pr	*p*-AcC_6H_4	Me	80	5

[a] The reaction of **1b–o** (0.25 mmol) was carried out in the presence of 10 mol% of $AuBr_3$ in toluene at 80°C for 1 h. [b] Yield of isolated product. [c] Yield of an inseparable mixture of **3** and **4** determined by GC. [d] Substrate **1d** was recovered in 29% yield. [e] A mixture of unidentified products was obtained.

Many attempts to synthesize 4- or 6-sulfonylindoles as the major products by varying the reactions conditions (solvent, ligands, additives, and temperature) only led to a mixture of **2**, **3**, and/or **4**. We then modified the substrate by adding functional groups. Among the substrates prepared, 2-alkynyl-6-methoxysulfonanilides **1p–x**, which have a methoxy group at the 6-position of the aniline moiety, were mainly converted into the corresponding 6-sulfonylindoles **3p–x** in the presence of catalytic amounts of $InBr_3$ [Eq. (3)]. The results are summarized in Table 2. The reaction of **1p** in the presence of 5 mol% of $InBr_3$ in toluene at 80°C for two hours gave an 87:13 mixture of **3p** and **2p** in 95% combined yield (Table 2, entry 1). The reaction of **1p** in the presence of $AuBr_3$ or $PdBr_2$ gave **3p** and **2p** with lower regioselectivities (Supporting Information). The reaction of **1q**, which has an electron-donating methoxy group on the arylsulfonyl moiety, produced the 6-sulfonylindole **3q** with higher regioselectivity than that of **1s**, which contains an electron-withdrawing nitro group (Table 2, entries 2 and 4, respectively). Substrate **1t**, which has a cyclohexyl group at R^1, was converted into **3t** with high regioselectivity (Table 2, entry 5). The ratio of **3** to **2** was not affected by the electronic properties of the R^1 substituent (Table 2, entries 6–8), although it was lower when terminal alkyne **1x** was employed as substrate (Table 2, entry 9). The reaction of the *N*-mesylaniline **1y** afforded a mixture of unidentified products, and **5a–c**, which have a methoxy group at the 3-, 4-, and 5-position, respectively, reacted sluggishly to give inseparable mixtures of unidentified products.

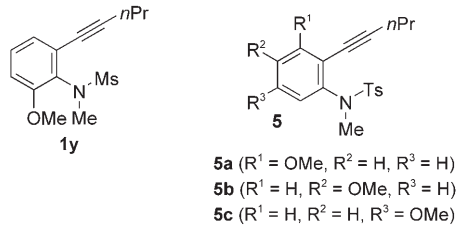
To find out if the migration of the sulfonyl group occurs in an intramolecular or intermolecular fashion, we performed crossover experiments [Eqs. (5) and (6)]. The reaction of a 1:1 mixture of **1e** and **1n** in the presence of a catalytic amount of

Table 2: $InBr_3$-catalyzed cyclization of **1p–x**.[a]

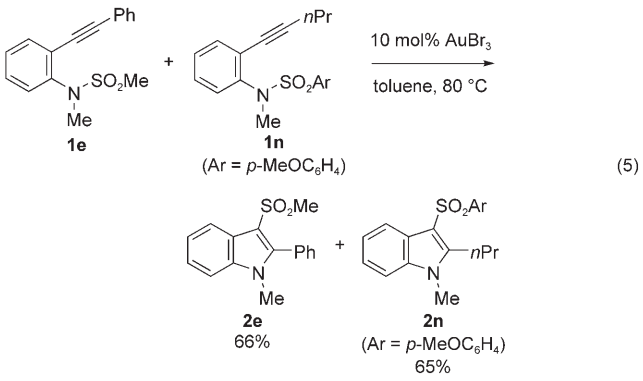


Entry	1	R^1	R^2	Yield [%][b]	3/2[c]
1	**1p**	*n*Pr	Me	95	87:13
2	**1q**	*n*Pr	MeO	99	84:16
3	**1r**	*n*Pr	H	98	78:22
4	**1s**	*n*Pr	NO_2	99	66:34
5	**1t**	cyclohexyl	Me	97	87:13
6	**1u**	Ph	Me	99	90:10
7	**1v**	*p*-$MeOC_6H_4$	Me	98	85:15
8	**1w**	*p*-$CF_3C_6H_4$	Me	88	83:17
9	**1x**	H	Me	73	54:46

[a] The reactions of **1p–x** were carried out in the presence of 5 mol% of $InBr_3$ in toluene at 80°C. [b] Yield of the isolated mixture of **2** and **3**. [c] The ratio was determined by ^1H NMR spectroscopy.

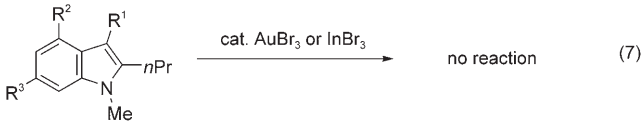


$AuBr_3$ gave the corresponding products **2e** and **2n** in 66% and 65% yields, respectively [Eq. (5)]; the crossover products were not detected by GC-MS or NMR spectroscopy.



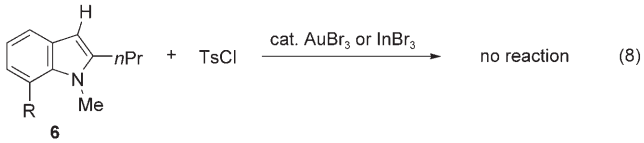
Furthermore, the $InBr_3$-catalyzed reaction of a 1:1 mixture of **1q** and **1w** afforded the products **3q** and **2q**, derived from **1q**, and **3w** and **2w**, derived from **1w** [Eq. (6)]; again, no crossover products were obtained. These results clearly indicate that the present reaction proceeds in an intramolecular manner.

The isolated products **2a**, **3a**, and **4a** remain unchanged in the presence of $InBr_3$ or $AuBr_3$ in toluene at 80 °C for two hours, thereby suggesting that interconversion between the products does not take place under the reaction conditions [Eq. (7)].

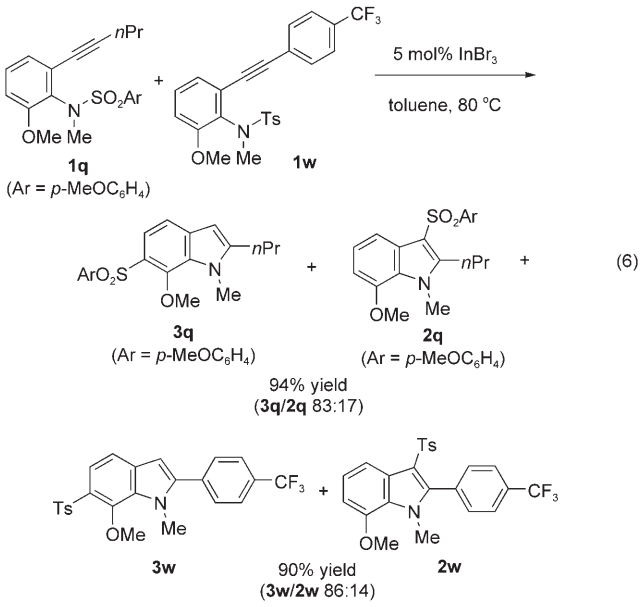


2a (R^1 = Ts, R^2 = R^3 = H)
3a (R^3 = Ts, R^1 = R^2 = H)
4a (R^2 = Ts, R^1 = R^3 = H)

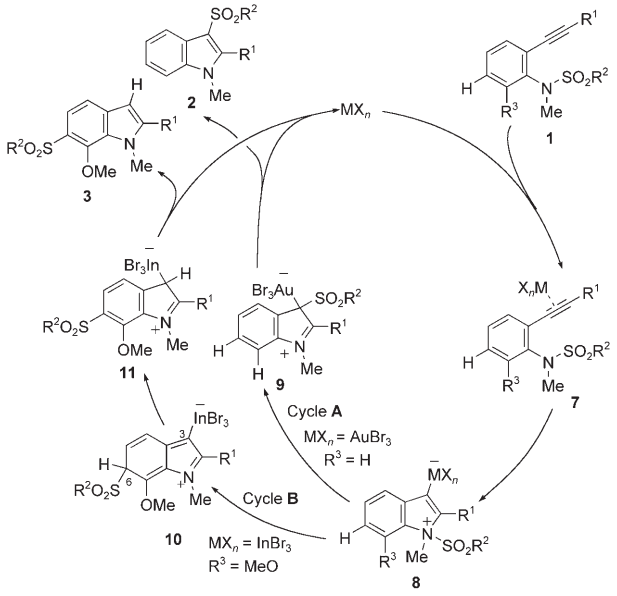
Mixing indoles **6a** and **6b** with tosyl chloride in the presence of $AuBr_3$ or $InBr_3$ did not give the corresponding sulfonylindoles **2**, **3**, and **4** [Eq. (8)].[3] Accordingly, it is unlikely that electrophilic substitution of the indole with tosyl halides occurs under these reaction conditions.



6a (R = H)
6b (R = OMe)



The above experimental results led us to propose the mechanism for the cyclization of **1** shown in Scheme 1. The Lewis-acidic transition metal coordinates to the triple bond of **1** to form the π-complex **7**. Nucleophilic attack of the nitrogen atom to the alkynyl moiety then leads to the cyclized intermediate **8**. For the gold-catalyzed reaction of **1a–o**, the sulfonyl group intramolecularly migrates to the 3-position of



Scheme 1. Proposed mechanism for the catalytic formation of **2** and **3** from **1**.

the indole skeleton (cycle **A**),[10] and elimination of $AuBr_3$ from **9** then gives the 3-sulfonylindole **2**. In the indium-catalyzed reaction of substrates **1p–x**, unprecedented consecutive 1,7-sulfonyl and 1,5-proton shifts take place instead (cycle **B**).[11] Elimination of $InBr_3$ from the resulting intermediate **11** then gives the 6-sulfonylindoles **3**. An interaction between the benzene ring on the sulfonyl group and the indium catalyst might play a crucial role in selectively producing 6-sulfonylindoles **3**, since the $InBr_3$-catalyzed reaction of *N*-mesylaniline **1y** gives a complex mixture of unidentified products.

The present reaction proceeds by formal addition of a nitrogen–sulfur bond to a triple bond, a so-called aminosulfonylation.[12] It is therefore likely that this method could be applicable in an efficient and environmentally benign synthesis of a wide variety of 3- and 6-sulfonylindoles.[13]

Experimental Section

$AuBr_3$-catalyzed cyclization of **1b**: Toluene (0.5 mL) was added to a mixture of $AuBr_3$ (0.025 mmol) and **1b** (0.25 mmol) in a pressure vial under argon. After stirring at 80 °C for 1 h, the reaction mixture was filtered through a short SiO_2 pad. The crude product was purified by silica gel column chromatography with hexane/ethyl acetate as eluent to afford **2b** (95 %).

$InBr_3$-catalyzed cyclization of **1p**: Toluene (1 mL) was added to a mixture of $InBr_3$ (0.0125 mmol) and **1p** (0.25 mmol). After stirring at 80 °C for 2 h, the reaction mixture was purified by Florisil column chromatography with hexane/ethyl acetate as eluent to afford **3p** (83 %) and **2p** (12 %). Further purification was performed by gel permeation chromatography.

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