Heterocycles

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Facile Preparation of Indoles and 1,2-Benzothiazine 1,1-Dioxides: Nucleophilic Addition of Sulfonamides to Bromoacetylenes and Subsequent Palladium-Catalyzed Cyclization**

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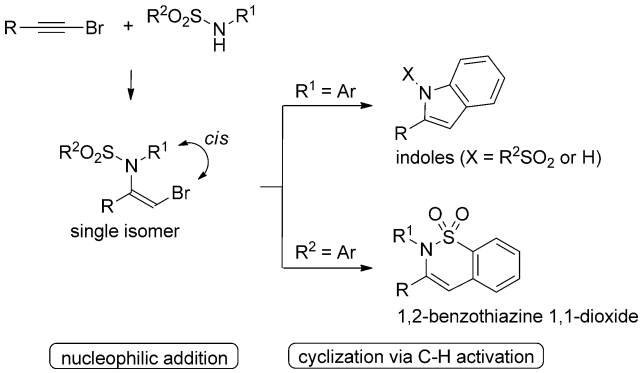
Nucleophilic addition to an electron-deficient carbon–carbon multiple bond is one of the most fundamental reactions in organic chemistry.[1] Among the various electron-withdrawing groups adjacent to an olefin or acetylene, thus making this process feasible, the weakest possible substituents, such as halogens, have recently attracted increasing attention.[2–7] We have already reported that certain nitrogen-containing compounds such as *N*-alkylsulfonamides,[8] imidazolines, or imidazoles undergo nucleophilic addition to 1-halo-1-alkynes.[5d,e] Furthermore, the synthetic utility of the adducts obtained by this reaction has been explored in a cyclization reaction affording nitrogen heterocycles.[5d] Our continuing efforts along these lines allow us to report herein, a novel entry to indole synthesis,[9] which consists of the nucleophilic addition of *N*-arylsulfonamides (i.e. *N*-sulfonylanilines) to bromoacetylenes with subsequent palladium-catalyzed cyclization of the resultant *cis*-2-(*N*-aryl-*N*-sulfonylamino)-1-bromoalkenes through aromatic C–H bond activation[10] (Scheme 1). A new synthesis of another interesting heterocycle, 1,2-benzothiazine 1,1-dioxide,[11] by a similar sequence is also described in this report.



Scheme 1. Facile preparation of two types of heterocycles by a novel synthetic strategy.

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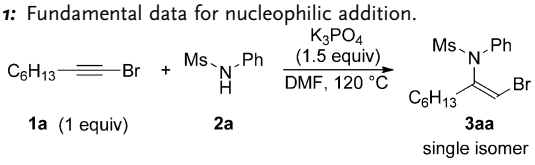
The nucleophilic addition of *N*-phenylmethanesulfonamide (**2a**) to 1-bromo-1-octyne (**1a**) proceeded under the same reaction conditions as reported previously for *N*-alkylsulfonamides,[5d] and gratifyingly the yield of the adduct **3aa** (85%, entry 1, Table 1) was higher than those in the previous cases (up to 78%). The reaction was highly regio- and stereoselective such that other isomers were not detected in the crude reaction mixture. Although an excess amount of the sulfonamide **2a** (3 equiv relative to **1a**) guarantees a good product yield, it could be reduced to 2 equivalents and still keep the yield within an acceptable range (entry 2). When 3 equivalents of **2a** was used, the unreacted **2a** was recovered in 97% yield and could be recycled; the yield of **3aa** based on the consumed sulfonamide **2a** was calculated to be 93% (entry 1).

Table 1: Fundamental data for nucleophilic addition.

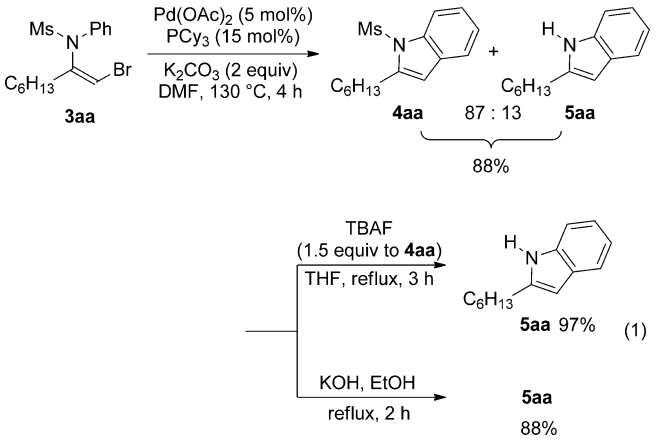


Entry	**2a** (equiv)	*t* [h]	Yield [%][a]	Recovery of **2a** [%][b]
1	3	6	85 (93)[c]	97
2	2	8	71	–

[a] Yield of isolated product is based on **1a**. [b] Yield of isolated product based on unreacted **2a**. [c] Yield based on consumed **2a**. DMF = *N*,*N*-dimethylformamide, Ms = methanesulfonyl.

The *cis* relationship between the bromide and sulfonylaniline moieties in the adduct **3aa** appears suitable for a variety of cyclizations,[12] one of which is the palladium-catalyzed ring closure through activation of the aromatic C–H bond as illustrated in Equation (1). In fact, treatment of **3aa** with $Pd(OAc)_2$[10i] effected the cyclization to give the *N*-sulfonylindole **4aa** contaminated with a small amount of desulfonylated **5aa** in 88% yield upon isolation. Despite considerable effort, the simultaneous production of **5aa** was hard to suppress and the ratio of **4aa** to **5aa** changed slightly from run to run. While **4aa** and **5aa** were separable by HPLC,[13] the mixture was subjected to either desulfonylation with TBAF (Bu_4NF)[14] or 10% ethanolic KOH,[15] thus leading to indole **5aa** in either 97 or 88% yield.[16]

Table 2 summarizes other results of the indole synthesis. In this sequence, the mixture of cyclization products **4** and **5** was directly submitted to the subsequent desulfonylation with TBAF. The yields of **4** and **5**, listed for reference, were estimated by ^{1}H NMR spectroscopy using an internal stan-



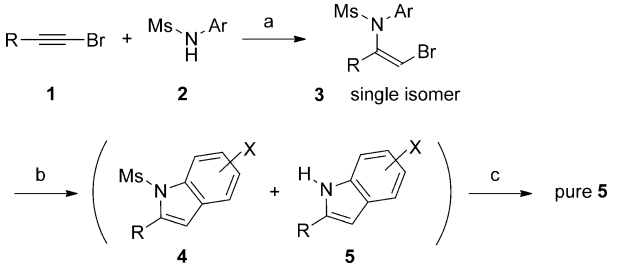
dard to determine the amount of TBAF needed to insure the desulfonylation step; typically 2 equivalents of TBAF were used relative to **4**. As far as the nucleophilic addition of *N*-phenylmethanesulfonamide (**2a**) to various bromoacetylenes (**1b–e**) is concerned, the corresponding adducts **3ba–ea** were obtained in good yields (entries 2–5). The mild reaction conditions allow the presence of representative functional groups, even an unprotected hydroxy group, on the side chain of bromoacetylenes. Likewise, 1-bromo-1-octyne (**1a**) and a variety of aniline derivatives, **2b–g**, afforded the desired products **3ab–ag** in good yields. The successful preparation of the adducts **3aa**, **3ba–ea**, and **3ab–ag** prompted us to investigate the generality of the subsequent cyclization through an intramolecular C–H activation (**3**→**4**+**5**). As previously described for the preparation of **5aa** from **3aa** [Eq. (1)], all reactions inevitably produced a mixture of sulfonylated indole **4** and a small amount of its parent indole **5**. The crude reaction mixtures were converted into indoles (**5aa**, **5ba–ea**, and **5ab–ag**) through desulfonylation with TBAF in good overall yields (entries 1–11). As a whole, these reaction conditions were compatible with various functional groups both on the acetylene side chain and aromatic ring, thus demonstrating broad applicability.[17]

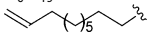
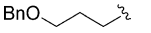
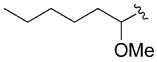
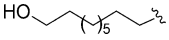
In Table 2, we separately listed each result for the nucleophilic addition and the subsequent cyclization/desulfonylation. However, more practically, these steps can be carried out in one pot without isolation of the intermediate products. Scheme 2 shows such an example in which indole **5aa** was obtained from the primary starting materials **1a** and **2a** in an excellent yield.

While the synthesis of unprotected indoles from *N*-arylmethanesulfonamides was established as above, sulfonyl-protected indoles could be cleanly produced from more robust *N*-aryl-*p*-toluenesulfonamides **6** as shown in Table 3. The nucleophilic addition of *N*-(*p*-toluenesulfonyl)aniline (**6a**) to bromoacetylenes **1a–e** (entries 1–5) required a longer reaction period (12 h) than that of the corresponding methanesulfonamides (6 h, see Table 2), but the product yields remained at a similar level. The longer reaction time might be due to the enhanced steric hindrance of **6.** The subsequent palladium-catalyzed cyclization of the adducts **7aa–ea** and **7ab** proceeded in the same way as that of methanesulfonamides to give sulfonylindoles **8aa–ea** and **8ab**, respectively, however the desulfonylated products were not detected in all cases (entries 1–6, Table 3). It should be emphasized that the palladium-catalyzed cyclization exclusively occurred on the *N*-aryl group in preference to the *N*-tosyl group, thus producing only *N*-sulfonylindoles **8**.

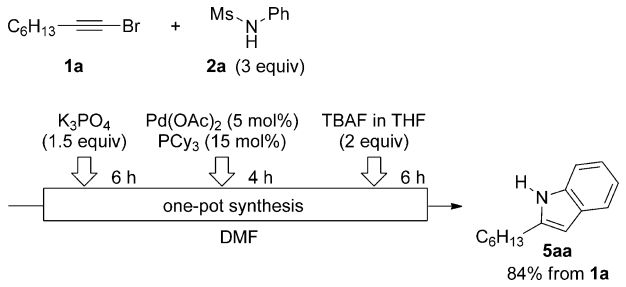
In conjunction with the indole synthesis discussed above, we noted in the preceding paragraph that the palladium-catalyzed cyclization of **7aa–ea** and **7ab** exclusively occurred at the aniline moiety to give **8aa–ea** and **8ab**, respectively, and the aromatic ring in the *p*-toluenesulfonyl group remained untouched. However, if the aniline moiety is not present in the molecule, then a similar cyclization did proceed toward the *p*-toluenesulfonyl group, thus leading to a new

Table 2: Preparation of indoles **5** from **1** and **2**.[a]



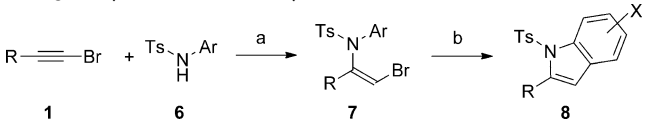
Entry	R		Ar	Yield [%][b]	Yield [%][c] **4/5**	Yield [%][d]
1	C_6H_{13}	(**1a**)	Ph (**2a**)	**3aa**: 85	94/6	**5aa**: 87
2		(**1b**)	Ph (**2a**)	**3ba**: 92	89/11	**5ba**: 84
3		(**1c**)	Ph (**2a**)	**3ca**: 87	83/17	**5ca**: 76
4		(**1d**)	Ph (**2a**)	**3da**: 64	53/47	**5da**: 79
5		(**1e**)	Ph (**2a**)	**3ea**: 82	44/23	**5ea**: 65
6	C_6H_{13}	(**1a**)	*p*-MeC_6H_4 (**2b**)	**3ab**: 79	90/10	**5ab**: 80
7	C_6H_{13}	(**1a**)	3,5-$Me_2C_6H_3$ (**2c**)	**3ac**: 85[e]	89/8	**5ac**: 78
8	C_6H_{13}	(**1a**)	*p*-$MeOC_6H_4$ (**2d**)	**3ad**: 92	89/11	**5ad**: 83
9	C_6H_{13}	(**1a**)	*p*-$(Me_2N)C_6H_4$ (**2e**)	**3ae**: 92[f]	95/5	**5ae**: 82
10	C_6H_{13}	(**1a**)	*p*-$(AcHN)C_6H_4$ (**2f**)	**3af**: 87	89/10	**5af**: 92
11	C_6H_{13}	(**1a**)	*p*-ClC_6H_4 (**2g**)	**3ag**: 78[g]	78/18	**5ag**: 85[h]

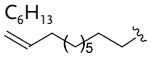
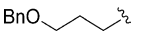
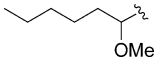
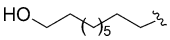
[a] Reaction conditioins: a) Bromoacetylene **1** (1 equiv), sulfonamide **2** (3 equiv), K_3PO_4 (1.5 equiv), DMF, 120°C, 6 h; b) $Pd(OAc)_2$ (5 mol%), PCy_3 (15 mol%), K_2CO_3 (2 equiv); DMF, 130°C, 4 h; crude reaction mixture was directly used in the next step; c) TBAF (2 equiv to **4**); THF, reflux, 4.5–5.5 h. [b] Yield of isolated product based on **1**. [c] Yield of crude product before desulfonylation and determined by ^{1}H NMR spectroscopy with an internal standard. These data are shown only for reference. [d] Overall yield of the isolated product from **3**. [e] The reaction period was extended to 8 h. [f] Unreacted **2e** was recovered in 97% yield upon isolation and may be recycled. Thus, the yield of **3ae** based on consumed **2e** was 94%. [g] The reaction period was extended to 12 h. [h] The cyclization was performed for 1 h. Bn = benzyl.



Scheme 2. One-pot synthesis of indole **5aa** from **1a** and **2a**. THF = tetrahydrofuran.

Table 3: Preparation of *N*-sulfonylindoles **8** from **1** and **6**.[a]



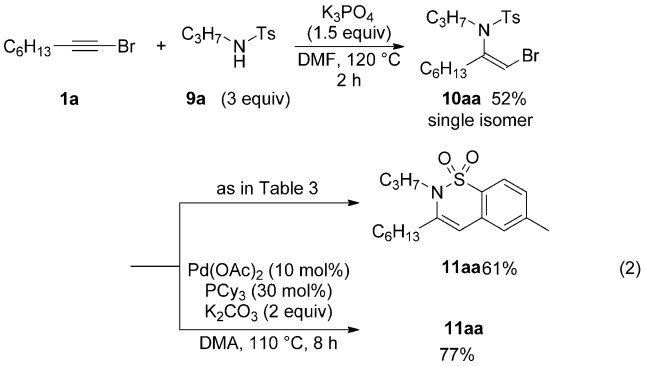
Entry	R		Ar	Yield [%][b]	Yield [%][c]
1	C_6H_{13}	(**1a**)	Ph (**6a**)	**7aa**: 80	**8aa**: 83
2		(**1b**)	Ph (**6a**)	**7ba**: 72	**8ba**: 77
3		(**1c**)	Ph (**6a**)	**7ca**: 70	**8ca**: 89
4		(**1d**)	Ph (**6a**)	**7da**: 69	**8da**: 88
5		(**1e**)	Ph (**6a**)	**7ea**: 81	**8ea**: 60
6	C_6H_{13}	(**1a**)	3,5-$Me_2C_6H_3$ (**6b**)	**7ab**: 72[d]	**8ab**: 70

[a] Reaction conditions: a) Bromoacetylene **1** (1 equiv), sulfonamide **6** (3 equiv), K_3PO_4 (1.5 equiv); DMF, 120 °C, 12 h; b) $Pd(OAc)_2$ (5 mol%), PCy_3 (15 mol%), K_2CO_3 (2 equiv); DMF, 130 °C, 4 h. [b] Yield of isolated product based on **1**. [c] Yield of isolated product from **7**. [d] The reaction period was extended to 14 h. Ts = 4-toluenesulfonyl.

preparation of 1,2-benzothiazine 1,1-dioxides as shown in Equation (2) (DMA = *N*,*N*-dimethylacetamide). For example, the *N*-alkyl-*p*-toluenesulfonamide **9a** underwent the nucleophilic addition to the bromoacetylene **1a** as described before[5d] to give exclusively the *Z*-bromoalkene **10aa**. Its cyclization under the same reaction conditions as those in Table 3 gave 1,2-benzothiazine 1,1-dioxide **11aa** in 61% yield, which was increased to 77% under a new set of optimized reaction conditions. As expected from the fact that the cyclization to the *p*-toluenesulfonyl group is a less favorable path, the optimized reaction conditions required a larger amount of the palladium catalyst (10 mol%) relative to the original indole synthesis (5 mol%) to attain comparable product yields.

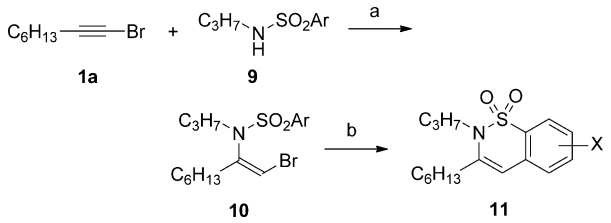
Results similar to those shown in Equation (2) are summarized in Table 4. 1-Bromo-1-octyne (**1a**) and *N*-alkylsulfonamides **9** derived from various arenesulfonyl groups afforded the corresponding *Z*-bromoalkenes **10aa–af** in good yields (entries 1–6). These products were successfully transformed into 1,2-benzothiazine 1,1-dioxides **11aa–af** (entries 1–6), wherein the cyclizations of **10ad** and **10ae**, having an electron-deficient aromatic ring (entries 4 and 5), were complete in shorter reaction periods than that of the others. Bromoalkene **10af**, having an unsymmetrical aromatic ring, cyclized to **11af** with a good regioselectivity (entry 6).

In conclusion, the nucleophilic addition of various sulfonamides to 1-bromo-1-alkynes took place in a highly regio- and



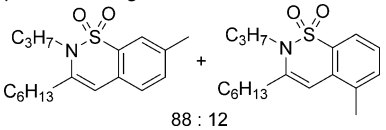
(2)

Table 4: Preparation of 1,2-benzothiazine 1,1-dioxides **11** from **1a** and **9**.[a]



Entry	Ar	Yield [%][b]	Yield [%][c]
1	*p*-MeC_6H_4 (**9a**)	**10aa**: 52	**11aa**: 77
2	Ph (**9b**)	**10ab**: 52	**11ab**: 71
3	*p*-$MeOC_6H_4$ (**9c**)	**10ac**: 48	**11ac**: 73
4	*p*-$NO_2C_6H_4$ (**9d**)	**10ad**: 53	**11ad**: 77[d]
5	*p*-ClC_6H_4 (**9e**)	**10ae**: 61	**11ae**: 58[e]
6	*m*-MeC_6H_4 (**9f**)	**10af**: 51	**11af**: 66[f]

[a] Reaction conditions: a) Bromoacetylene **1a** (1 equiv), sulfonamide **9** (3 equiv), K_3PO_4 (1.5 equiv); DMF, 120 °C, 2 h; b) $Pd(OAc)_2$ (10 mol%), PCy_3 (30 mol%), K_2CO_3 (2 equiv); DMA, 110 °C, 8 h. [b] Yield of isolated product based on **1a**. [c] Yield of isolated product from **10**. [d] The reaction period was 2 h. [e] The reaction period was 3.5 h. [f] Combined yield of the regioisomers as shown below.



stereoselective manner to give (*Z*)-2-(sulfonylamino)-1-bromoalkenes in good yields. The *cis* structure of sulfonylamino and bromo substituents in the products should be quite useful for a variety cyclizations, as demonstrated by the palladium-catalyzed cyclization involving aromatic C–H bond activation, thus providing a new and facile preparation of indoles, *N*-sulfonylindoles, and 1,2-benzothiazine 1,1-dioxides.

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