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Tandem Reaction of Propargylic Alcohol, Sulfonamide, and *N*-Iodosuccinimide: Synthesis of *N*-(2-Iodoinden-1-yl)-arenesulfonamide

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ABSTRACT

An efficient and straightforward strategy for the synthesis of *N*-(2-haloinden-1-yl)arenesulfonamides from propargylic alcohols and sulfonamides is described. Allenesulfonamide is postulated to be the key intermediate for this tandem transformation.

Indenamine and indene moieties are key substructures in both targets and building blocks for various biologically active molecules[1] and functional materials.[2] Consequently, much attention has been paid to the synthesis of indene derivatives,[3] while synthesis of indenamines has been seldom reported. In a few examples in recent literature, indenamine derivatives could be synthesized by intramolecular Friedel−Crafts cyclization of β-aminoaldehyde,[4] by carbocyclization of *o*-indobenzaldimine and alkyne,[5] and by annulation of *N*-unsubstituted aromatic ketimine and internal alkyne.[6] Herein, we report a new convenient method for the synthesis of *N*-(2-haloinden-1-yl)arenesulfonamide from the corresponding propargylic alcohol, sulfonamide, and NXS (X = I or Br), which was catalyzed by $BF_3 \cdot Et_2O$.

In our ongoing efforts to construct the functionalized indenes, we tested the readily available 4-methylbenzenesulfonamide ($TsNH_2$) as the starting material instead of aziridine, which we previously used.[7] By screening various Lewis acids for the reaction between **1a** and **2a**, such as $Yb(OTf)_3$, AgOTf, $Sc(OTf)_3$, $BF_3 \cdot Et_2O$, and iodine chloride

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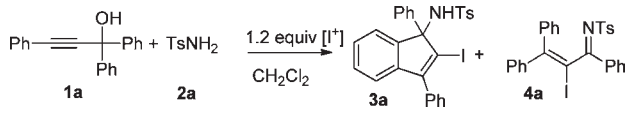
Table 1. Screening for the Reaction Conditions[a]



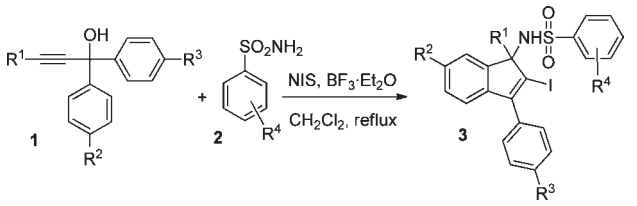
entry	[I$^+$] source	additive[b]	temp (°C)	time	**3a**/**4a** yield (%)[c]
1	ICl	none	reflux	24 h	32/11
2	I_2	none	reflux	24 h	n.d./n.d.
3	NIS	none	reflux	24 h	n.d./n.d.
4	I_2	H_2O[d]	reflux	72 h	46/15
5	ICl	$BF_3\cdot Et_2O$	reflux	1 h	61/0
6	I_2	$BF_3\cdot Et_2O$	reflux	1 h	11/0
7	NIS	$BF_3\cdot Et_2O$	reflux	1 h	72/0
8	NIS	$BF_3\cdot Et_2O$	reflux	2 h	71/0
9	NIS	$BF_3\cdot Et_2O$	reflux	40 min	62/12
10	NIS	$BF_3\cdot Et_2O$	rt	12 h	68/0
11	NIS	$BF_3\cdot Et_2O$	0	36 h	30/37
12	IPy_2BF_4	$BF_3\cdot Et_2O$	reflux	48 h	0/23
13	$I(coll)_2PF_6$	$BF_3\cdot Et_2O$	reflux	1 h	0/19

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), solvent (5 mL). [b] Equivalent molar to [I$^+$] source. [c] Isolated yields refer to **2**. [d] Water (2.5 μL) was added.

(ICl), we unexpectantly obtained a cyclized product (**3a**) in yield of 32% when the reaction was run with ICl and performed in the solvent of fresh CH_2Cl_2, redistilled from calcium hydride. The incomplete product **4a** was isolated in yield of 11%. Structures of **3a** and **4a** were established by X-ray analysis. To our delight, **3a** was indeed a *N*-(2-iodoinden-1-yl)arenesulfonamide derivative rather than a simple indene. To the best of our knowledge, this is the first example that produces 2-iodoindene by using the tandem strategy.

Exhaustive studies of the reaction conditions were first conducted (Table 1). Each reaction was performed with 1.2 equiv of the iodinating reagent to **2a** in fresh CH_2Cl_2 with a concentration of 0.1 M **2a**. Besides ICl, *N*-iodosuccinimide (NIS) and iodine were applied as iodinating reagents too. In fresh CH_2Cl_2, iodine was not effective even after 24 h based on the TLC tracking (Table 1, entry 2). The propargylic alcohol (**1a**) remained mostly, similar to the case of NIS (Table 1, entry 3). Liang et al. reported that a trace amount of water could react with I_2 to generate proton in situ, which eventually converted **1a** into an allenic carbocation.[8] On the basis of this consideration, we tested iodine with a trace amount of water. The reaction proceeded slowly and **3a** was isolated in yield of 46% after the reaction was conducted for 72 h (Table 1, entry 4). It is also noteworthy that various combinations of $BF_3\cdot OEt_2$ and iodinating reagent have recently been developed for efficient iodination (Wada's work[9]). Therefore, we tried to combine $BF_3\cdot OEt_2$ with iodine, NIS, and ICl, respectively (Table 1, entries 5−7). To our delight, the combination of $BF_3\cdot OEt_2$ and NIS gave **3a** in the highest yield. Moreover, incomplete product (**4a**) was not observed in all of these examples. Prolonging the reaction time to 2 h would barely influence the yield (Table 1, entry 8), while shortening the reaction time to 40 min would make the reaction incomplete (Table 1, entry 9). A similar situation was observed for the reaction temperature survey (Table 1, entries 10 and 11). Both combination of $BF_3\cdot OEt_2$ with bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) and combination of $BF_3\cdot OEt_2$ with bis(2,4,6-collidine)iodonium hexafluorophosphate ($I(coll)_2PF_6$) were not so effective for this transformation (Table 1, entries 12 and 13). Therefore, we selected the combination of $BF_3\cdot OEt_2$ and NIS as the iodinating reagent and refluxed the mixture in CH_2Cl_2 for 1 h.

Table 2. Tandem Synthesis of 2-Iodoindenamines[a]



entry	**1** ($R^1/R^2/R^3$)	**2** (R^4)	product	yield (%)[b]
1	**1a** (C_6H_5/H/H)	**2a** (4-CH_3)	**3a**	72
2	**1b** (4-*t*-BuC_6H_4/H/H)	**2a**	**3b**	76
3	**1c** (4-MeC_6H_4/H/H)	**2a**	**3c**	74
4	**1d** (3-MeC_6H_4/H/H)	**2a**	**3d**	73
5	**1e** (2-MeC_6H_4/H/H)	**2a**	**3e**	63
6	**1f** (4-BrC_6H_4/H/H)	**2a**	**3f**	58
7	**1g** (C_6H_5/Me/Me)	**2a**	**3g**	73
8	**1h** (C_6H_5/OMe/OMe)	**2a**	**3h**	53[c]
9	**1i** (C_6H_5/OMe/Cl)	**2a**	**3i**	45[c]
10	**1j** (C_6H_5/Cl/Cl)	**2a**	**3j**	41[d]
11	**1k** (*n*-Bu/H/H)	**2a**	**3k**	70
12	**1l** (H/H/H)	**2a**	**3l**	73
13	**1m** (H/Me/Me)	**2a**	**3m**	75
14	**1n** (H/OMe/OMe)	**2a**	**3n**	55[c]
15	**1o** (H/Cl/Cl)	**2a**	**3o**	40[d]
16	**1a**	**2b** (2-CH_3)	**3p**	70
17	**1a**	**2c** (4-H)	**3q**	63
18	**1a**	**2d** (4-OMe)	**3r**	77
19	**1a**	**2e** (4-*t*-Bu)	**3s**	75
20	**1a**	**2f** (4-Br)	**3t**	60
21	**1a**	**2g** (3-Br)	**3u**	61
22	**1a**	**2h** (4-Cl)	**3v**	57

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), NIS (0.6 mmol), $BF_3\cdot Et_2O$ (0.6 mmol). [b] Isolated yields refer to **2**. [c] 4 h. [d] DCE, 80 °C, 12 h.

With the optimized reaction conditions in hand, we subsequently tested the substrate diversity for this transformation. The results were presented in Table 2. With different aryl groups (R^1, **1a**−**f**) occupied on the propargylic alcohol, reactions proceeded smoothly (Table 2, entries 1−6). When the *para* position of the aryl was substituted by Br, **3f** was obtained in a decreased yield of 58% (Table 2, entry 6). In cases of entries 7−10,

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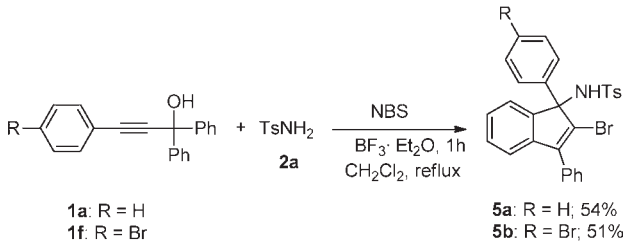
Scheme 1. Formation of 2-Bromoindenamines

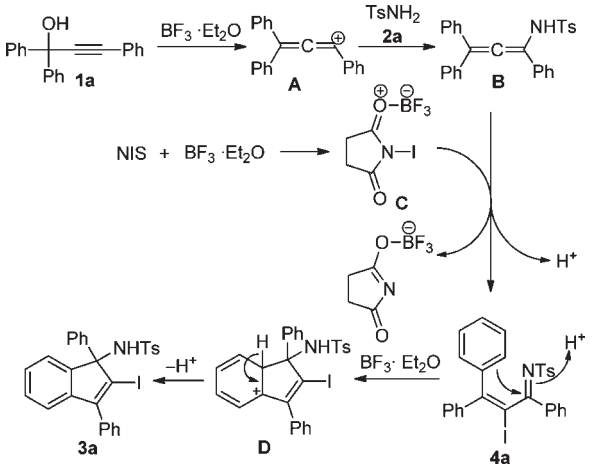


methoxy substitution (**1h**, **1i**) decreased the yields apparently in comparison with methyl substitution (**1g**), while chloro substitution (**1j**) only afforded α-iodo-α,*β*-unsaturated sulfonamide (**4b**) in refluxing CH_2Cl_2. By raising the reaction temperature to 80 °C by changing the solvent into dichloroethane (DCE), **3j** was expectantly obtained in a yield of 41%. Moreover, when the unsymmetrical ketone derived proparglic alcohol (**1i**) was used as the substrate, **3i** was regioselectively generated (Table 2, entry 9). The methoxy group would exclusively appear on the indene skeleton,[10] and the structure of **3i** was verified by crystal analysis. Aliphatic alkyne **1k** also afforded the corresponding product **3k** in a yield of 70%. Terminal alkynes **1*l*−o** gave the desired products **3*l*−o**, accordingly. A similar electronic effect was observed for cases of entries 12−15. By tuning the electron density of the arylsulfonamide part (**2b−h**), it was obvious that the electron donating (**2d**) on the arylsulfonamide would benefit the reaction (Table 2, entries 16−22).

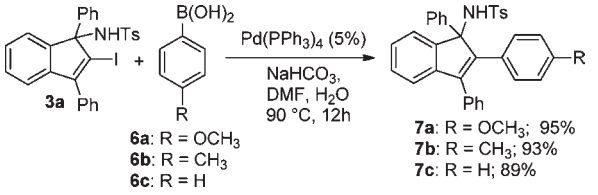
This reaction protocol could also be readily applied to the synthesis of *N*-(2-bromoinden-1-yl)arenesulfonamides by simply replacing NIS with *N*-bromosuccinimide (NBS) (Scheme 1). In this case, the yields were slightly lower.

On the basis of the aforementioned experiments, a plausible mechanism is outlined in Scheme 2. Propargyl alcohol (**1a**) was first converted to the allenic carbocation **A** via a Meyer−Schuster rearrangement.[11] Then, **A** was trapped by **2a** and the key intermediate allenesulfonamide **B** was afforded. Isolation of **B** was a futile effort because of its instability. Meanwhile, in the presence of $BF_3{\cdot}OEt_2$, NIS was activated to iodonium species **C**. The internal carbon of allenesulfonamide was electron rich because of the electron donating nature of the nitrogen (Hsung's review[12]). It reacted with active species **C** in situ to afford α-iodo-α,*β*-unsaturated sulfonimide **4a**.[13] **4a** was subsequently transferred into the final product **3a** via an intramolecular Friedel−Crafts

Scheme 2. Proposed Mechanism for the Tandem Transformation



Scheme 3. Further Elaboration of Compounds **3**



reaction promoted by $BF_3{\cdot}Et_2O$. As evidence for this proposed mechanism, **4a** could be isolated when the reaction was conducted at lower temperature (Table 1, entry 11) or in a shorter duration (Table 1, entry 9). More significantly, **4a** could also be quantitatively converted into **3a** in the presence of $BF_3{\cdot}Et_2O$. Consequently, three *σ*-bonds were efficiently constructed in this three-component reaction, including C−C, C−N, and C−I covalent bonds.

Having in mind that 2,3-diarylindenamines are known to exhibit high biological activities,[14] we decided to employ the synthesized *N*-(2-iodoinden-1-yl)arenesulfonamides as precursors for introduction of an aryl substituent at the 2 position of the indene moiety by a Suzuki cross-coupling reaction. In this way, 2,3-diarylindensulfonamides **7** were obtained in high yields (Scheme 3).

In summary, we have developed an efficient method to generate *N*-(2-iodo/bromoinden-1-yl)arenesulfonamides through a $BF_3{\cdot}Et_2O$ catalyzed tandem reaction of propargyl alcohol, sulfonamide, and NXS (X = I, Br). A

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possible mechanism for this reaction was proposed, which involves an active allenesulfonamide intermediate. Further research on the chemistry of allenesulfonamide is ongoing in our laboratory.

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Supporting Information Available. Detailed experimental procedures, characterizaton data, copies of ^{1}H, ^{13}C NMR spectra, and crystallographic information files (CIF) for compounds **3a**, **4a**, and **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.