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Lewis Acid Catalyzed Cascade Reaction of 3-(2-Benzenesulfonamide)propargylic Alcohols to Spiro[indene-benzosultam]s

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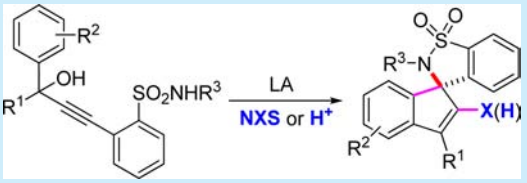
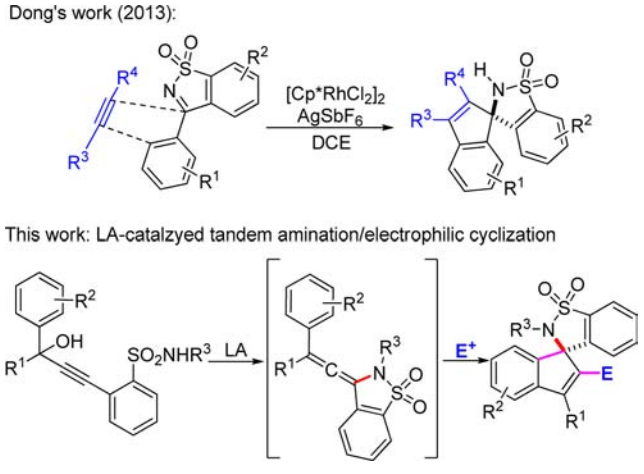
Supporting Information

ABSTRACT: A highly efficient and convenient construction of the spiro[indene-benzosultam] skeleton from propargylic alcohols has been developed. The reaction proceeded in a Lewis acid catalyzed cascade process, including the trapping of allene carbocation with sulfonamide, electrophilic cyclization, and intramolecular Friedel–Crafts alkylation. In the presence of NIS or NBS, iodo/bromo-substituted spiro[indene-benzosultam]s could be prepared in excellent yields.



Both indene[1] and benzosultam[2] are privileged motifs in pharmaceutically active compounds and also exist widely in nature. Although spiro indene and others, such as spiro[indene-indolin-3-one]s[3] or spiro benzosultam with spiro[benzo[*d*]-isothiazole-indane]s[4] are well documented in the literature, the connection of indene with benzosultam by sharing a spiro carbon has been seldom reported. As a successful example, Dong and co-workers reported a Rh-catalyzed [3 + 2] annulation of cyclic *N*-sulfonylketimines with internal alkynes to give synthetically challenging spiro[indene-benzosultam]s in the presence of $AgSbF_6$ in high yields (Scheme 1).[5]

Scheme 1. Approaches to Spiro[indene-benzosultam]s



Recent achievements on the cascade rearrangement of propargylic alcohols have attracted much attention to organic chemists because these reactions provide many efficient ways in making complicated organic compounds.[6] In comparison with the classical Meyer–Schuster rearrangement of propargylic alcohols to α,β-unsaturated ketones[7] via a 1,3-shift of the hydroxy group in the presence of Brønsted acid or Lewis acid, trapping of allenic carbocation by various nucleophiles presents more prosperous and diverse chemistry of propargylic alcohols and opens a new window to efficiently obtain various carbocycles and heterocycles in recent years.[8] Here, we report the synthesis of spiro[indene-benzosultam]s through an intramolecular trapping of allene carbocation and a sequential electrophilic cyclization (Scheme 1, this work). In this way, a spiro carbon was ideally constructed.

Based on this consideration, we designed the substrate **1a**, which integrated propargylic alcohol and sulfonamide in a single molecule. At room temperature, a Meyer–Schuster rearrangement of **1a** occurred in the presence of $BF_3{\cdot}Et_2O$ and afforded **2a** in 97% yield (Table 1, entry 1). When the reaction time was extended to 8 h, **2a** was still the predominant product (Table 1, entry 2). The situation changed when the reaction was conducted at 80 °C. Compound **2a** could be formed and isolated after the reaction was stirred for 5 min (Table 1, entry 3). Extension of the reaction time to 4 h, spiro[indene-benzosultam] (**3a**) was isolated in 95% yield (Table 1, entry 4). These time-controlled experiments also indicated that **2a** could be converted into **3a** at 80 °C under the reaction conditions. Without the addition of 4 Å molecular sieves, the yield of **3a** decreased to 78% (Table 1, entry 5). By altering the Lewis acid catalyst to $Yb(OTf)_3$ and AgOTf, a mixture of **2a** and **3a** was observed (Table 1, entries 6 and 7). Toluenesulfonic acid catalyzed the reaction but gave a relatively lower yield of **3a** (Table 1, entry 8). Finally, the optimal solvent was determined to be dichloroethane (DCE).

With the optimized reaction conditions in hand, we investigated the substrate scope (Table 2). Ten spiro[indene-benzosultam] compounds were prepared in yields varying from 57% to 95%. A variety of substituents, such as halogen, alkoxy, and alkyl, tolerated the reaction conditions. Chlorine-substituted

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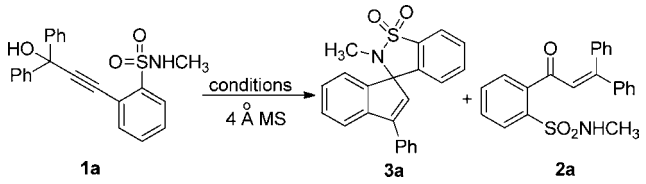
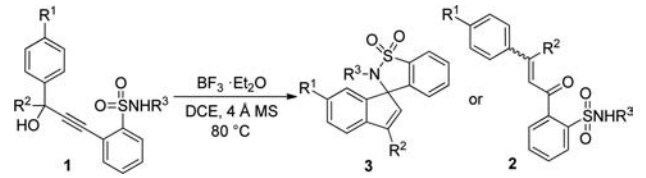
Table 1. Optimization of Reaction Conditions[a]

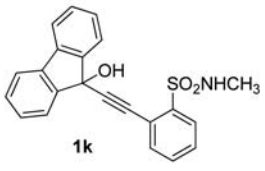


entry	catalyst	temp (°C)	time	solvent	3a/2a yield[b] (%)
1	$BF_3{\cdot}Et_2O$	25	5 min	DCE	0/97
2	$BF_3{\cdot}Et_2O$	25	8 h	DCE	0/96
3	$BF_3{\cdot}Et_2O$	80	5 min	DCE	0/97
4	$BF_3{\cdot}Et_2O$	80	4 h	DCE	95/0
5	$BF_3{\cdot}Et_2O$	80	4 h	DCE	78/0[d]
6	$Yb(OTf)_3$[c]	80	8 h	DCE	20/71
7	AgOTf[c]	80	8 h	DCE	35/47
8	TsOH[c]	80	6 h	DCE	76/0
9	$BF_3{\cdot}Et_2O$	80	3 h	MeCN	57/0
10	$BF_3{\cdot}Et_2O$	80	8 h	PhMe	83/0

[a]Reaction conditions: **1a** (0.1 mmol), catalyst (0.1 mmol), solvent (3 mL), 4 Å MS (100 mg). [b]Isolated yields refer to **1a**. [c]Catalyst (0.01 mmol) was used. [d]Without 4 Å MS.

Table 2. $BF_3{\cdot}Et_2O$-Mediated Electrophilic Spirocyclization of 1[a]



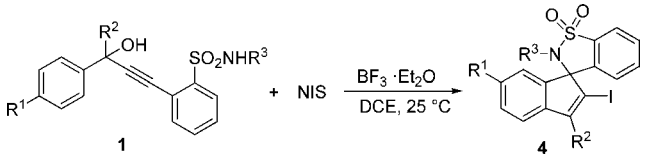
entry	1 ($R^1/R^2/R^3$)	product	yield (%)[b]
1	**1a** (H/C_6H_5/Me)	**3a**	95
2	**1b** (Cl/4-ClC_6H_4/Me)	**3b**	57[c]
3	**1c** (OMe/4-$MeOC_6H_4$/Me)	**3c**	66[d]
4	**1d** (Me/4-MeC_6H_4/Me)	**3d**	95
5	**1e** (H/Me/Me)	**3e**	85
6	**1f** (H/C_6H_5/H)	**3f**	87[e]
7	**1g** (Me/4-MeC_6H_4/H)	**3g**	88[f]
8	**1h** (H/C_6H_5/Et)	**3h**	93
9	**1i** (H/C_6H_5/$CH_2C_6H_5$)	**3i**	90
10	**1j** (H/C_6H_5/4-MeC_6H_4)	**2b**	95
11		**2c**	94
12	**1l** (H/4-$NO_2C_6H_4$/Me)	**3j**	85

[a]Reaction conditions: **1** (0.1 mmol), DCE (3 mL), 4 Å MS (100 mg), $BF_3{\cdot}Et_2O$ (0.1 mmol), 4 h. [b]Isolated yields refer to **1**. [c]8 h. [d]72 h. [e]56 h. [f]24 h.

substrate **1b** afforded the corresponding spiro compound **3b** in 57% yield. In this case, the reaction was conducted for 8 h (Table 2, entry 2). A longer reaction time (72 h) was required when the chloro was replaced by methoxy (Table 2, entry 3). When the substituent effect was moderate, such as methyl, **1d** was efficiently converted into **3d** in 95% yield (Table 2, entry 4). When the propargylic alcohol was derived from acetophenone, such as **1e**, spiro compound **3e** could also be prepared in 85% yield (Table 2, entry 5). Without the methyl on the nitrogen of sulfonamide, **3f** and **3g** were prepared in 87% and 88% yields, respectively (Table 2, entries 6 and 7). The substituent on the nitrogen of sulfonamide could be altered to other alkyl groups, such as ethyl or benzyl. Thus, **3h** and **3i** were produced in excellent yields (Table 2, entries 8 and 9). However, the substituent on nitrogen could not be changed into aryl group. For example, when 4-methylphenyl was substituted on the nitrogen (**1j**), instead of a spiro product we obtained α,β-unsaturated ketone **2b** in 95% yield (Table 2, entry 10). Similarly, the propargylic alcohol **1k** which was derived from fluorenone gave **2c** in 94% yield (Table 2, entry 11). The electronic effect on the nitrogen and the steric hindrance arising from the tertiary alcohol would largely influence the outcome of the product. Unsymmetrical acetylene **1l** was also examined, and the desired spiro product **3j** was isolated in 85% yield (Table 2, entry 12).

If we subjected additional electrophile, such as NIS, to the above reaction the electrophilic spirocyclization did occur and afforded the products with iodo substitution. For instance, when the reaction of **1a** in the presence of trifluoroboron etherate was conducted with an equivalent molar ratio of NIS at 25 °C for 30 min, **4a** was isolated in 99% yield (Table 3, entry 1). The

Table 3. $BF_3{\cdot}Et_2O$/NIS-Mediated Electrophilic Spirocyclization of 1[a]



entry	1 ($R^1/R^2/R^3$)	product	yield[b] (%)
1	**1a** (H/C_6H_5/Me)	**4a**	99
2	**1b** (Cl/4-ClC_6H_4/Me)	**4b**	62
3	**1c**(OMe/4-$MeOC_6H_4$/Me)	**4c**	90
4	**1d** (Me/4-MeC_6H_4/Me)	**4d**	78
5	**1e** (H/Me/Me)	**4e**	92
6	**1f** (H/C_6H_5/H)	**4f**	96[c]
7	**1g** (Me/4-MeC_6H_4/H)	**4g**	92[c]
8	**1h** (H/C_6H_5/Et)	**4h**	90
9	**1i** (H/C_6H_5/$CH_2C_6H_5$)	**4i**	84
10	**1j** (H/C_6H_5/4-MeC_6H_4)	**4j**	93
11	**1l** (H/4-$NO_2C_6H_4$/Me)	**4k**	57[d]

[a]Reaction conditions: **1** (0.1 mmol), NIS (0.1 mmol), DCE (3 mL), $BF_3{\cdot}Et_2O$ (0.1 mmol), 25 °C, 30 min. [b]Isolated yields refer to **1**. [c]Reflux. [d]48 h.

structure of **4a** was established by its single-crystal analysis.[9] Altering the acids or changing the reaction solvents would decrease the yield of **4a** (Table S1, Supporting Information). When other substrates (**1b**−**i**) were used, the corresponding spiro compounds **4b**−**i** were obtained in yields varying from 62% to 96% (Table 3, entries 2−9). In comparison with the yields observed for **3a**−**i** and the reaction time and temperature applied, a preliminary result could indicate that **4a**−**i** were easier to prepare with the aid of the additional electrophile (I^+). As evidence for this conclusion, **1j** provided the corresponding spiro compound **4j** with iodo substitution in 93% yield when the reaction mixture was reacted at 25 °C for 30 min (Table 3, entry

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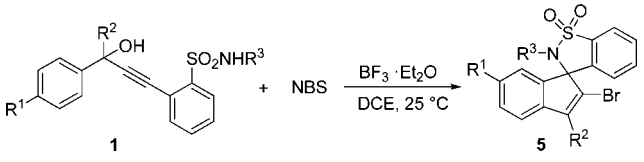
10). Without I^+, only the α,β-unsaturated ketone was obtained, although the reaction mixture was reacted at 80 °C for 4 h (Table 2, entry 10). Unsymmetrical acetylene **1l** gave the spiro product **4k** in 57% yield (Table 3, entry 11). By applying a similar strategy, we conducted this electrophilic spirocyclization in the presence of NBS. Accordingly, the corresponding bromo-substituted spiro compounds **5a–f** were obtained in yields varying from 63% to 98% (Table 4).

Table 4. BF_3·Et_2O/NBS-Mediated Electrophilic Spirocyclization of 1[a]

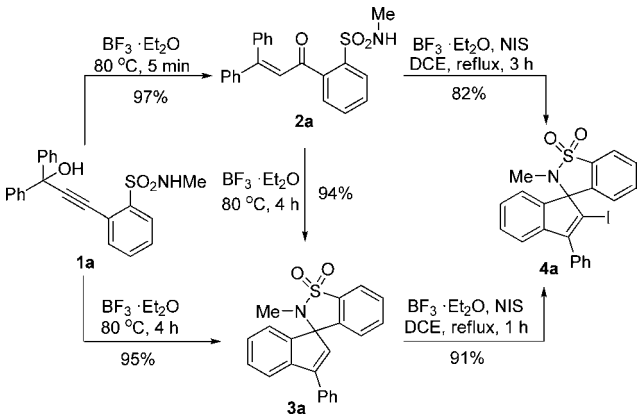


entry	**1** ($R^1/R^2/R^3$)	product	yield[b] (%)
1	**1a** (H/C_6H_5/Me)	**5a**	98
2	**1f** (H/C_6H_5/H)	**5b**	95[c]
3	**1j** (H/C_6H_5/4-MeC_6H_4)	**5c**	97
4	**1b** (Cl/4-ClC_6H_4/Me)	**5d**	63
5	**1c** (OMe/4-MeOC_6H_4/Me)	**5e**	89
6	**1l** (H/4-$NO_2C_6H_4$/Me)	**5f**	67[d]

[a]Reaction conditions: **1** (0.1 mmol), NBS (0.1 mmol), DCE (3 mL), BF_3·Et_2O (0.1 mmol), 25 °C, 30 min. [b]Isolated yields refer to **1**. [c]Reflux. [d]48 h.

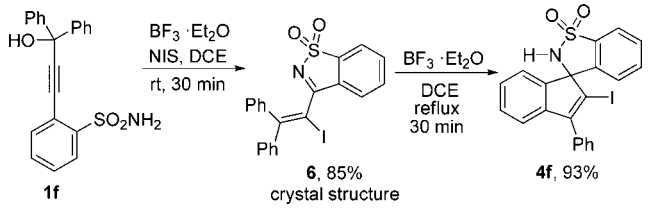
In order to understand the mechanism, we isolated the intermediates and did several condition-controlled experiments. As noted in the discussion of the screening of reaction conditions, **1a** could be converted into **2a** and **3a** by controlling the reaction time. Upon direct subjection of **2a** into the reaction, **3a** could also be prepared (Scheme 2). More significantly, **4a** could be prepared from either **2a** or **3a**.

Scheme 2. Transformations between 1a, 2a, 3a, and 4a



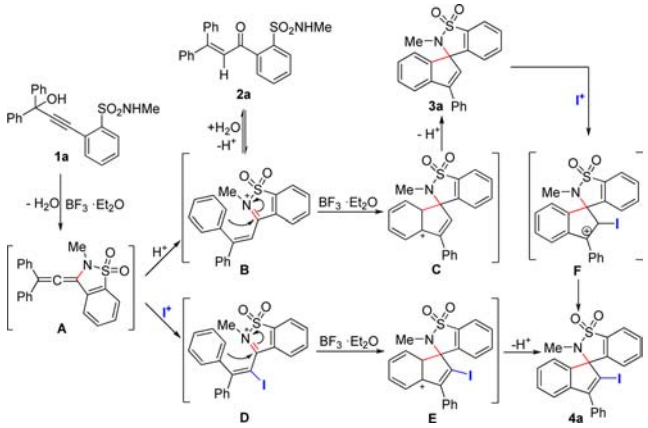
Without the substituent on nitrogen of sulfonamide, compound **1f** provided compound **6** in 85% yield when the reaction was carried out at room temperature for 30 min. The structure of **6** was established by its single-crystal analysis.[10] It is noteworthy that the isolated compound **6** could be further reacted and transferred into spirocyclized compound **4f** in 93% yield in the presence of trifluoroboron etherate at refluxing temperature for 30 min (Scheme 3).

Scheme 3. Formation of 4f via 6



Based on the above observations, we postulated a possible mechanism for this cascade process (Scheme 4). In the presence

Scheme 4. Proposed Mechanism for the Formation of 2a, 3a, and 4a



of trifluoroboron etherate, **1a** was converted into allenesulfonamide intermediate **A** by intramolecular trapping of allene carbocation formed from propargylic alcohol. Intermolecular trapping of allene carbocation with sulfonamide[11] or phosphoramide[12] had been realized in our previous studies. Without the additional electrophile, **B** was formed via an electrophilic cyclization. **B** equilibrated with **2a** by hydration and dehydration. Alternatively, **B** could be further spirocyclized via an intramolecular Friedel–Crafts alkylation, leading to the formation of **3a**. With the participation of additional electrophile, NIS or NBS, the allenesulfonamide **A** was converted into **D** via an electrophilic cyclization. Isolation of compound **6** was a good evidence for the existence of **D**. Through any intramolecular Friedel–Crafts alkylation, **4a** was formed via intermediate **E**. For the formation of **4a** from **3a**, electrophilic substitution on the electron-rich alkene was proposed.

Further studies indicated that halogen-substituted spiro[indene-benzosultam]s **4** and **5** could be transferred into aryl-substituted spiro[indene-benzosultam]s through transition-metal-catalyzed coupling reactions while maintaining the spiro structure. For instance, reaction between **4a** and arylboronic acid in the presence of $Pd(PPh_3)_4$ provided **7a–c** in high yields under the normal Suzuki coupling conditions (Scheme 5).

In conclusion, we have developed an efficient and convenient method for the construction of a spiro[indene-benzosultam] skeleton from propargylic alcohols using Lewis acid as a catalyst. The reaction proceeded in a cascade process, which included the trapping of allene carbocation with sulfonamide, electrophilic cyclization, and intramolecular Friedel–Crafts alkylation. In the presence of NXS, iodo/bromo-substituted spiro[indene-benzosultam]s were prepared in excellent yields. Moreover, these halogen-substituted products were converted into their

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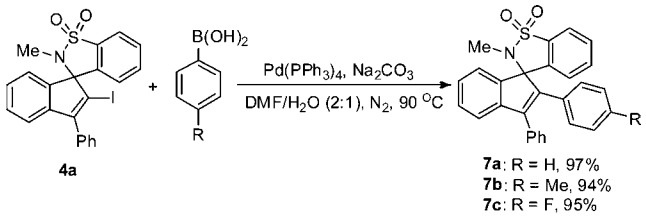
Scheme 5. Derivation of 4a



aryl-substituted derivatives without changing the spiro[indene-benzosultam] skeleton.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds and X-ray data (CIF) for compounds **4a** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) CCDC 1011642 contains the supplementary crystallographic data for **4a**.

(10) CCDC 1011643 contains the supplementary crystallographic data for **6**.

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