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Synthesis of 3-(Arylsulfonyl)-3-pyrrolines from Allenyl Sulfonamides by Silver Ion Catalysis

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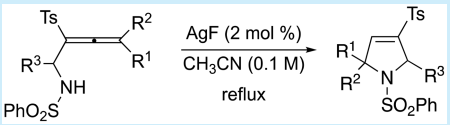
Supporting Information

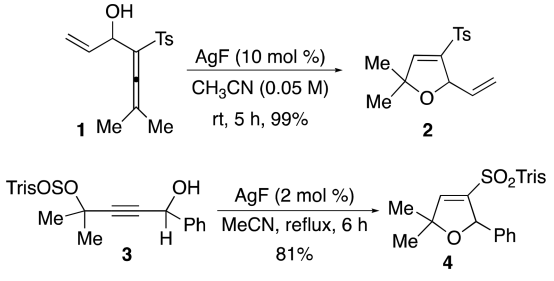
ABSTRACT: Treatment of allenyl sulfonamides with catalytic amounts of silver fluoride in acetonitrile at reflux afforded the corresponding 3-sulfonyl-3-pyrrolines in excellent yields by intramolecular hydroamination via a 5-*endo-trig* cyclization. The starting allenyl sulfonamides were prepared by lithiation of allenic sulfones and trapping with various *N*-sulfonylimines.



Five-membered ring heterocycles comprise a vast number of substructures that appear commonly in both natural products and man-made substances.[1] Those containing a single nitrogen atom include indoles and pyrroles, as well as reduced congeners of these compounds, and are significant enough to have attracted a great deal of attention from the synthetic community.[2] One class of compounds in which we have an interest are the 3-pyrrolines.[3] 3-Pyrroline-containing compounds possess many important biological activities including inhibitory activity against monoamine oxidase (MAO),[4] anticancer activity,[5] agonist activity at the NMDA receptor,[6] and K-agonist activity.[7] Owing to their pharmaceutical interest and synthetic utility, there have been many methods developed for the synthesis of 3-pyrrolines.[8] Among them, the metal-catalyzed cyclization of amino/amido allenes is of considerable interest.[9]

In the context of the exploration of metal-catalyzed cyclization of allenes, our group has recently reported the synthesis of 2,5-dihydrofurans from α-hydroxy allenes or hydroxy propargylic sulfinates by silver fluoride catalysis.[10] For example, treatment of **1** or **3** with silver fluoride under the conditions noted afforded the dihydrofurans **2** and **4** in 99% and 81% yields, respectively (Scheme 1). We envisaged that we could synthesize 3-pyrrolines from α-amino/amido allenes. Herein, we report the synthesis of 3-sulfonyl-2,5-disubstituted-3-pyrrolines from α-sulfonamido allenes via a 5-*endo-trig* cyclization.

Scheme 1. Dihydrofuran Formation



The cyclization of aminoallenes to pyrrolines catalyzed or mediated by various reagents has a long history, beginning with the first examples of aminoallene cyclizations catalyzed by silver cations.[11] This methodology continues to be investigated, with base-mediated processes,[12] phosphine-catalyzed processes,[13] metal catalysis combined with halogenation,[14] tandem metal-catalyzed cyclizations,[15] and micellar catalysis[16] being among the more recent developments in the area.[17] In spite of these important contributions, some gaps in the possible tactics one might use in this area still remain. For example, engaging substrates that might afford substituents on the product alkene that are novel or may be used as handles for further functionalization would be important. In undertaking our research, we decided to examine the reaction of lithiated allenic sulfones with sulfonyl imines and then assess the product of this addition reaction in cyclization chemistry to produce 3-pyrrolines.

The *N*-sulfonylimines needed for our studies were synthesized by the condensation of corresponding aldehyde and phenyl sulfonamide according to literature procedures.[18] We synthesized various allenylsulfonamides by the lithiation of allenyl sulfones and trapping with various *N*-sulfonylimines. We investigated the lithiation step by using both *n*-BuLi and LiHMDS as a base. Treatment of allenic sulfone **5a** in THF with *n*-BuLi followed by addition of *N*-sulfonylimine **6a** furnished the corresponding allenyl sulfonamide **7a** in only 54% yield. However, when LiHMDS was used as the base, **7a** was obtained in 86% yield (Scheme 2). We used either *n*-BuLi or LiHMDS for the preparation of all of our cyclization substrates. The results are shown in Table 1.

One result in this series was rather interesting and unexpected. When **5d** was treated with LiHMDS and then trapped with **6a**, a single stereoisomer of product was obtained in 82% yield (Table 1, entry 12). The process is depicted in Scheme 3. The organolithium obtained from deprotonation of **5d** is not configurationally stable. The sole product obtained resulted from inversion of configuration at the sulfone bearing

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Scheme 2. Effect of Base Change on Lithiation and Trapping of Allenic Sulfones

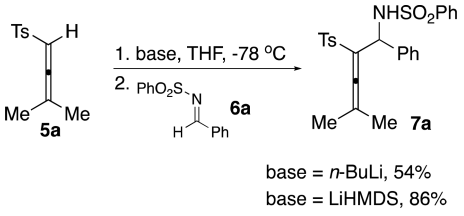
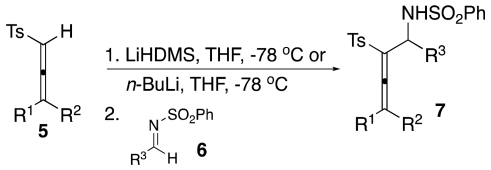


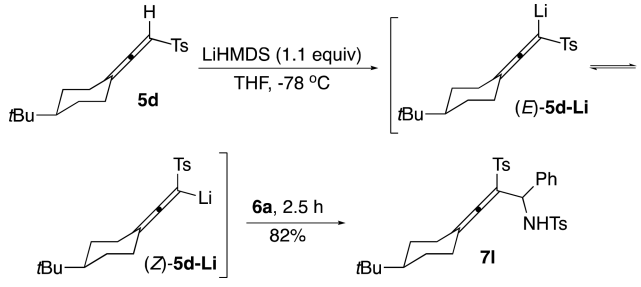
Table 1. Synthesis of Sulfamido Allenes



entry	R^1	R^2	R^3	product	yield (%)
1	Me	Me	Ph	**7a**	86
2	Me	Me	*c*-hexyl	**7b**	93
3	Me	Me	Me_2CHCH_2-	**7c**	92
4	Me	Me	*p*Tol	**7d**	97
5	Me	Me	*p*ClPh	**7e**	53[a]
6	Me	Me	*p*MeOPh	**7f**	97[a]
7	Me	Me	*p*NO_2Ph	**7g**	72[a]
8	Me	Me	2-furyl	**7h**	61[a]
9	Me	Me	PhCH=CH-	**7i**	64[a]
10	-$(CH_2)_4$-		Ph	**7j**	86
11	-$(CH_2)_5$-		Ph	**7k**	82
12			Ph	**7l**	82[b]
13	Ph	Me	Ph	**7m**	87[c]
14	Et	Me	Ph	**7n**	96[c]

[a]*n*-BuLi used as base. [b]Single stereoisomer. [c]dr = 1:1

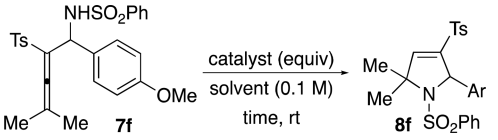
Scheme 3. Trapping an Allenic Organolithium with Inversion of Configuration



carbon. We conjecture that the organolithium derived from **5d** is rapidly equilibrating. A difference in the rates of the reaction of each diastereomer results in the formation of the product observed, an example of the Curtin–Hammett principle.[19] We have a small amount of evidence in support of this basic idea,[20] but we make no claim as to the veracity of our hypothesis.

To evaluate the cyclization reaction, we began by examining various catalysts using the substrate **7f**. The results are summarized in Table 2. We initially tested the cyclization

Table 2. Optimization of Cyclization Reaction Conditions



entry	catalyst (equiv)	solvent	time	yield (%)
1	$AuCl_3$ (0.1)	CH_2Cl_2	10 h	60
2	$HAuCl_4{\cdot}H_2O$ (0.1)	THF/H_2O[a]	4 d	88
3	$Ph_3PAuOTf$ (0.1)	CH_2Cl_2	9 h	20
4	$AgSbF_6$ (0.1)	CH_2Cl_2	3 h	32
5	$AgBF_4$ (0.1)	CH_2Cl_2	48 h	99
6	$AgNO_3$ (0.1)	THF/H_2O[a]	27 h	99
7	AgBr (0.1)	THF/H_2O[a]	4 d	nr
8	AgI (0.1)	THF/H_2O[a]	4 d	3
9	AgF (0.1)	CH_3CN	70 m	98
10	AgF(0.05)	CH_3CN	80 m	81
11	AgF (0.02)	CH_3CN	14 h	83
12	AgF[b] (0.02)	CH_3CN	10 m	99

[a]1:1 v/v. [b]At reflux.

with gold (I and III) catalysts. Treatment of **7f** with 10 mol % of $AuCl_3$ (Table 2, entry 1) produced the corresponding 3-pyrroline **8f** in 60% yield. The use of $HAuCl_4{\cdot}H_2O$ (Table 2, entry 2) gave **8f** in 88% yield. However, the use of gold(I) catalysts such as 10 mol % of $Ph_3PAuOTf$ (generated in situ from Ph_3PAuCl and AgOTf) (Table 2, entry 3) afforded **8f** in only 20% yield. We then examined various silver salts. Treatment of substrate **7f** with $AgSbF_6$ (Table 2, entry 4) produced **8f** in only 32% yield. However, when the substrate **7f** was treated with $AgBF_4$ and $AgNO_3$ (Table 2, entry 5 and 6), **8f** was produced in an excellent 99% yield in 48 and 27 h, respectively. The catalyst AgBr (Table 1, entry 7) showed no reaction even after 4 days, and the catalyst AgI (Table 1, entry 8) gave **8f** in only 3% yield. Silver fluoride (AgF) at levels of 10 and 5 mol % (Table 2, entries 9 and 10) afforded **8f** in 98% and 81% yields, respectively. The use of low catalyst loading (2 mol %, Table 2, entry 11) produced **8f** in 83% yield, but the reaction was slow compared to higher catalyst loading (Table 2, entries 9 and 10). Finally, we conducted the reaction using AgF at only 2 mol % loading (Table 2, entry 12) under reflux. This afforded the 3-pyrroline **8f** in 99% yield in only 10 min, and these conditions became what we used to produce additional examples of the reaction.

Using the aforementioned optimized conditions, we investigated the scope of 5-*endo*-*trig* cyclization of allenyl sulfonamide. The results are summarized in Table 3. Allenyl sulfonamides derived from the aliphatic substituted imines **7b** and **7c** (Table 3, entries 2 and 3) furnished the corresponding 3-sulfonyl-3-pyrrolines **8b** and **8c** in 97% and 95% yield, respectively, but relatively slowly, requiring 40 min for the completion of the reactions. The cyclization of phenyl-substituted allenyl sulfonamides **7d,e** (Table 3, entries 4–5) were completed within 5 min in excellent yields. To ascertain the electronic effects on this cyclization, various substitutions on the phenyl ring of the sulfonyl imine were examined. It appears that electron-donating groups on the phenyl group, such as a methyl or methoxy group (Table 3, entries 4 and 6),

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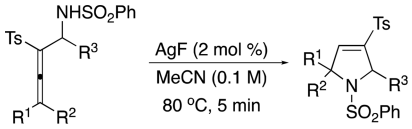
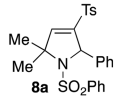
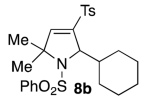
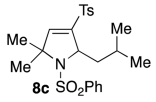
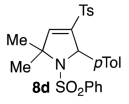
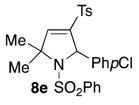
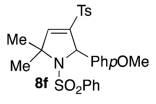
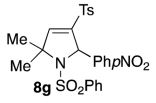
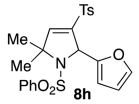
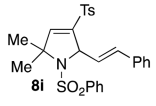
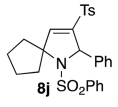
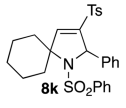
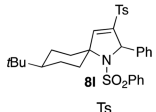
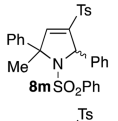
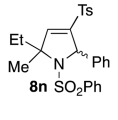
Table 3. Synthesis of Pyrrolines by Catalytic Ring Closure



entry	allene	time (min)	product	yield (%)
1	**7a**	5	 **8a**	97
2	**7b**	40	 **8b**	97
3	**7c**	40	 **8c**	95
4	**7d**	5	 **8d**	98
5	**7e**	5	 **8e**	78
6	**7f**	10	 **8f**	99
7	**7g**	15	 **8g**	99
8	**7h**	10	 **8h**	83
9	**7i**	5	 **8i**	78
10	**7j**	5	 **8j**	99
11	**7k**	5	 **8k**	98
12	**7l**	5	 **8l**	99
13	**7m**	5	 **8m**	98[a]
14	**7n**	5	 **8n**	99[a]

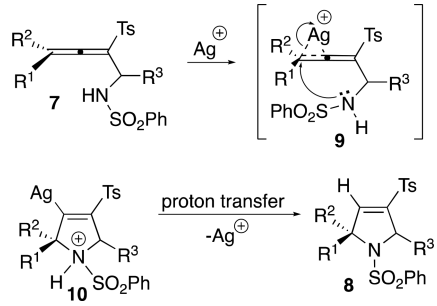
[a]dr = 1:1.

accelerated the reaction slightly, whereas an electron-withdrawing group such as the nitro group (Table 3, entry 7) slowed the reaction.

Heteroaromatic-substituted allenyl sulfonamide **7h** (Table 3, entry 8) gave **8h** in 83% yield. An allenyl sulfonamide possessing the cinnamyl group **7i** (Table 3, entry 9) produced **8i** in 78% yield. Cyclopentyl (**7j**) and cyclohexyl (**7k** and **7l**) systems afforded the desired cyclized products **8j–l** in excellent yields within 5 min (Table 3, entries 10–12). These results indicate that there are no substantial steric effects on this cyclization. Treatment of unsymmetrical allenyl sulfonamides **7m** and **7n** (dr 1:1) (Table 3, entries 13 and 14) with AgF furnished **8m** and **8n** (dr 1:1) in excellent yields (98% and 99%, respectively).

A plausible mechanism for the cyclization of an α-allenyl sulfonamide by silver(I) catalysis is shown in Scheme 4. First,

Scheme 4. Proposed Mechanism for Pyrroline Formation



silver ion coordinates to the distal, more electron-rich double bond of allene **7** and forms the intermediate **9**. The lone pair of electrons on the nitrogen then attacks the distal bond of the allene, undergoing a 5-*endo-trig* cyclization to give the 5-membered vinyl silver intermediate **10**. Finally, the loss of silver through a proton transfer affords the final product pyrroline **8**.

In conclusion, we have developed a new method for the synthesis of highly substituted, 3-(arylsulfonyl)-3-pyrrolines from α-allenyl sulfonamides by silver ion catalysis. While the vinyl sulfone group in the five-membered ring can be used to create various functional groups on the ring,[21] further development of the chemistry of the vinyl sulfone is warranted. Continuing studies of the scope of this process and the chemistry of the products will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02440.

Experimental procedures and ^{1}H and ^{13}C spectra (PDF)

Accession Codes

CCDC 1855814–1855815 and 1858620 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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