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Allenyl Sulfones and Allenyl Sulfides in the Synthesis of 3-Pyrrolines. A Novel Nucleophilic [3 + 2] Cycloaddition on Allenyl Sulfones Giving Rearranged Cycloadducts[||]

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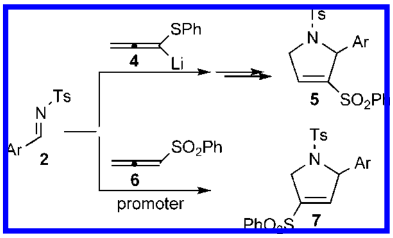
ABSTRACT



Efficient methodologies for the synthesis of regioisomeric 3-pyrrolines by reaction of electron-deficient imines and sulfur-containing allenyl derivatives are presented. Lithiated thioallenes give 2-aryl-3-phenylsulfonyl-3-pyrrolines, whereas allenyl sulfones furnish the isomeric 2-aryl-4-phenylsulfonyl-3-pyrrolines through migration of the sulfonyl group that catalyzes the nucleophilic [3 + 2] cycloaddition.

Nitrogen-containing heterocyclic systems have attracted widespread attention in organic and medicinal chemistry.[1] Many procedures for the construction of azacycles have been developed.[2] Allenes are useful building blocks in organic synthesis as a result of their unique reactivity that is governed by the type of substituents. Electron-donating groups activate C-3 for reactions with nucleophiles and C-2 for reactions with electrophiles. Allenes have also been involved in the synthesis of azacycles.[3] The smooth synthesis of 3-pyrroline derivatives by 1,2-addition of α-lithiated alkoxyallenes to imines and subsequent cyclization has been reported.[4] Thioallenes as another type of electron-rich allene have been less studied.[5] Electron-withdrawing substituted allenes, such as unsaturated systems, allow reaction at C-2 with nucleophiles by conjugate addition, and the resulting C-1 carbanion

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[||] Dedicated to Prof. P. Vogel on the occasion of his 65th birthday.

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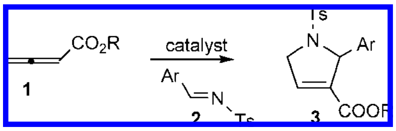
can interact with various electrophiles.[6] Allenyl esters **1** have been widely used as three-carbon zwitterions in nucleophile-catalyzed [3 + 2] cycloadditions with electron-deficient imines **2** as dipolarophiles, providing 3-alkoxycarbonyl 3-pyrrolines **3** (Scheme 1).[7] Phosphines have mainly been used as catalyst in these reactions, pioneered by Lu and co-workers[8] and also developed by many other groups.[9]

Scheme 1

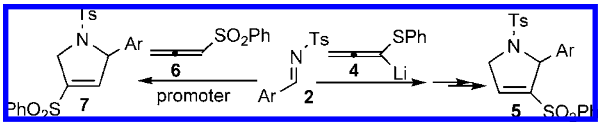


Unsaturated sulfones are versatile reagents. They easily give stabilized α-anions able to react with several electrophiles.[10] A sulfone substituent also activates an adjacent π-system toward several cycloaddition reactions, making unsaturated sulfones to act as excellent dienophiles in Diels−Alder[11] and [2 + 2][12] cycloadditions. Reactions of allenyl sulfones with diazomethane[13] and with *N*-phenylnitrones[14] and anionic [3 + 2] cycloaddition with electron-deficient alkenes[15] have also been described.

Despite the fact that the chemistry of allenyl sulfones has been widely studied[16] and that there is a similarity between conjugate additions and cycloadditions of allenyl sulfones and those of allenyl esters, as far as we are aware, anionic [3 + 2] cycloadditions of allenyl sulfones with electron-deficient imines have not been reported.

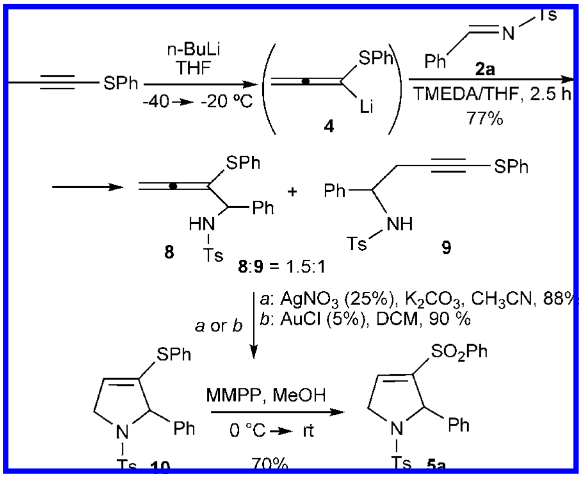
Here we report the synthesis of 3-pyrrolines of type **5** bearing a phenylsulfonyl moiety at C-3, which are analogues of alkoxycarbonyl pyrrolines **3**, by reaction of electron-deficient imines **2** with allenyl thioethers in a three-step procedure involving final oxidation. We also present for the first time the reaction of electron-deficient imines **2** and allenyl sulfones **6** that furnishes, in a promoted single step, regioisomeric 3-pyrrolines of type **7** (Scheme 2).

Scheme 2



Reaction of **4**[17] (generated in situ from 1-phenyl thioprop-1-yne)[18] with tosyl imine **2a** gave the desired α-adduct **8** together with γ-adduct **9** (77% combined yield) (Scheme 3). Subsequent 5-*endo* cyclization of **8** under $AgNO_3/K_2CO_3$ or AuCl catalysis afforded the corresponding 3-phenylthio-3-pyrroline **10**, which by oxidation with MMPP was converted into sulfone **5a**. When the transformation was carried out in a single step by reaction of **2a** with **6**[12,19] in the presence of a nucleophilic mediator, regioisomeric 2-aryl-4-(phenylsulfonyl)-1-tosyl-3-pyrroline **7a** was obtained.

Scheme 3



In our studies, we first screened conditions for the nucleophilic cycloaddition of **2a** and **6** in the presence of different nucleophilic mediators ($NaNO_2$, $NaSO_2Ph$, PR_3), solvents, temperatures, and order of addition of components. All of the reactions were carried out at room temperature with 25% promoter. Lower temperatures and a smaller amount of promoter slowed the reaction and gave inferior yields. In these cases, compounds of type **11** were detected by NMR (5% conversion). $NaNO_2$ or $NaSO_2Ph$ proved to be the best promoters giving similar yields, although reactions are slightly quicker with the latter. Because of the ambident character of this anion, we chose $NaNO_2$ for solvent screening conditions and mechanistic studies.[20] Anhydrous solvents gave poorer yields than those having traces of water (entries 4 and 5). Mixtures of THF and EtOH speeded reactions and increased the yields (entries 1 and 2 and 4 and 6). The order of addition of components is crucial for the

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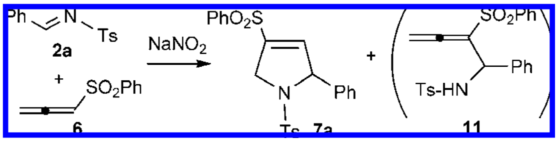
success of the reaction (best results obtained under conditions C) (Table 1).

Table 1. Screening of Reaction Conditions with $NaNO_2$



entry	solvent	reaction time (h)	yield (%) **7a**	addition order of reactants[a]
1	THF dry	20	25	**A**
2	THF/EtOH 2:1	3.5	43	**A**
3	THF/EtOH 2:1	10	38	**B**
4	THF dry	45	38	**C**
5	THF	40	50	**C**
6	THF/EtOH 2:1	8	60	**C**

[a] **A**: Solvent added to a mixture of promoter ($NaNO_2$) and reactants (molar ratio **2a**:**6** = 1.2:1). **B**: Solvent added to a mixture of promoter and reactants (molar ratio **2a**:**6** = 1:3). **C**: Excess of **6** (**2a**:**6** = 1:1.5−2.5) slowly added over a suspension of the promoter and imine in solvent.

Compounds **5a** and **7a** were fully characterized by their spectroscopic data. The major difference was found for the vinyl protons (6.9 ppm, m, for **5a** and 6.5 ppm, m, for **7a**) and for the corresponding carbons (136.9 ppm for **5a** and 139.3 ppm for **7a**) of the pyrroline framework. The structure of **7a** was unambiguosly confirmed by X-ray crystallography (Figure 1). Although under the reaction conditions **7a** was obtained as a racemate, each enantiomer separates into its own enantiomeric crystal by crystallization preferential, and one of them was selected from the crystals. The X-ray analysis indicated the 1,3-relationship between the phenyl and the phenylsulfonyl moieties.

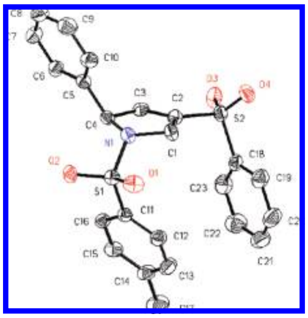
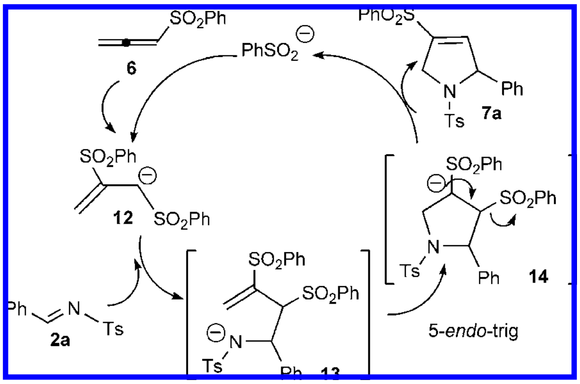


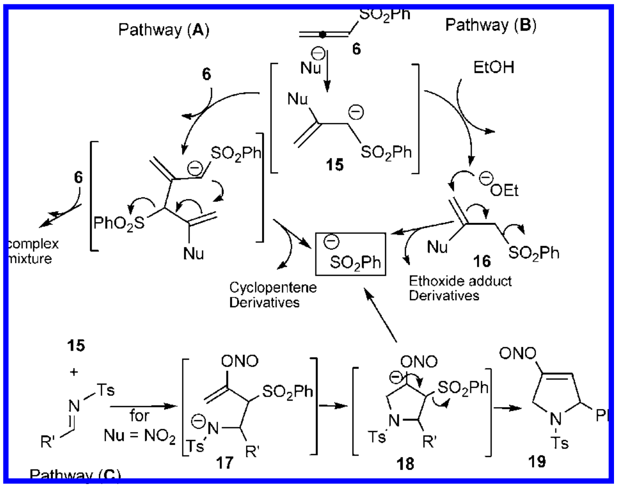
Figure 1. ORTEP drawing of compound **7a**.

A plausible mechanism for this nucleophile-catalyzed single-step preparation of **7a** is depicted in Scheme 4. To account for the high regioselectivity of the formation of **7a**, we required the participation of intermediate **12** in the process, which might be obtained by conjugate addition to **6** of the in situ generated benzenesulfinate anion. Nucleophilic addition of **12** to **2a** gave intermediate **13**, which after 5-*endo-trig* cyclization[21] followed by β-heteroatom elimination gave 3-pyrroline **7a**, since the sulfinate anion is both a good leaving group and a good nucleophile. As the reaction takes place with several promoters, we needed to invoke the formation of benzenesulfinate anion as initiator (see Scheme 5). The ORTEP drawing of compound **7a** is shown in Figure 1.

Scheme 4



Scheme 5



Plausible mechanisms for its generation in anhydrous solvent (pathway A) and in the presence of EtOH as cosolvent (pathway B) are indicated in Scheme 5. Thus, nucleophilic addition of the promoter to **6** gave intermediate **15**, which may subsequently react with **6**, resulting in a complex mixture, or cyclize to a five-membered ring, which after β-elimination released the benzenesulfinate anion (A). In the presence of EtOH, intermediate **15** may be protonated to give **16**, which upon addition of the ethoxide anion released benzenesulfinate anion (B). These pathways might

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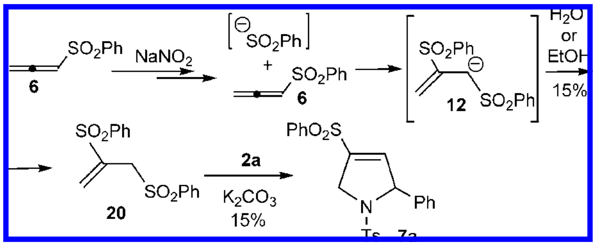
(20) See Supporting Information for more details.

(21) For other exceptions of the Baldwin rules, see: Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2006**, *47*, 2825.

explain the generation of the benzenesulfinate anion, the acceleration of the reaction when using EtOH as cosolvent, and the slower reactions and lower yields obtained in anhydrous solvents that may lead to allene polymerization. To verify the feasibility of these assumptions, an experiment with the allenyl sulfone **6** and $NaNO_2$ as promoter was performed (Scheme 6). The resulting benzenesulfinate anion generated through pathway A or B reacted with **6** to provide **12**, which generated known compound **20**.[22] Reaction of **20** with **2a** in the presence of K_2CO_3 afforded pyrroline **7a**. A similar behavior of allenyl sulfones triggered by Ph_3P generating benzenesulfinate anion was reported.[23] Another possibility that might be considered is the reaction of intermediate **15** with imine (pathway C) giving **17**, which may cycle to **18.** This specie could release the benzenesulfinate anion to furnish compound **19**, which could be detected in the ESI-MS spectra of the crude product but could not be isolated.

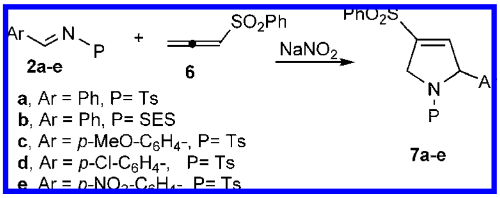
Scheme 6



The moderate yields obtained (best yield 60%) are not surprising considering the complexity of the overall pathways. The precursors can give undesired reactions, the imine being hydrolyzed to the corresponding aldehyde and the allenyl sulfone undergoing oligomerization. Additionally, part of the allenyl sulfone is consumed furnishing **20**. In fact this compound was detected in all of the reactions as side product.

To establish the scope of the reaction, a small library of aryl imines (see Supporting Information) were made to react with **6** under the optimized conditions. The reaction was found to occur with different substituted *N*-tosylimines and with *N*-(trimethylsilyl)ethanesulfonyl (SES) imine **2b** (Table 2). Reaction with the *p*-chlorophenyl imine **2d** delivered the best result. For the *p*-nitrophenyl derivative **7e** (entry 5) medium to poor yield was obtained. The higher reactivity of imine **2e** implies the formation of a byproduct coming from addition of EtOH (see Supporting Information). The use of THF alone does not increase the yield of the corresponding pyrroline **7e** (entry 6).

Table 2. Scope for Nucleophilic Cycloaddition of Imines **2** and **6** in THF/EtOH (2:1)



entry	Ar	P	reaction time (h)	**7a**−**e** yield(%)
1	Ph	Ts	8	60
2	Ph	SES	15	64
3	*p*-MeO-Ph	Ts	15	66
4	*p*-Cl-Ph	Ts	8	70
5	*p*-O_2N-Ph	Ts	7	39
6[a]	*p*-O_2N-Ph	Ts	15	38

[a] THF was used as solvent.

In summary, we have developed two procedures for the regiodivergent synthesis of isomeric 2-aryl-3-pyrrolines from allenes and electron-deficient imines. The three-step sequence employing a lithiated thioallene establishes a route to 2-aryl-3-phenylsulfonyl-3-pyrrolines. The one-pot procedure from allenyl sulfones implies migration of the sulfonyl group, which catalyzes an anionic [3 + 2] cyclization−elimination reaction. This represents a new, efficient, atom-economic, and mild route to synthesize 2-aryl-4-phenylsulfonyl-3-pyrrolines.

This behavior is different from that reported for alkoxycarbonyl-substituted allenes. Allenyl sulfones give sulfonyl rearranged 3-pyrrolines as a result of the ability of the benzenesulfinate anion to act as nucleophile as well as a leaving group. Efforts are underway to extend the scope of the reaction including chiral reactants.

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Supporting Information Available: Detailed experimental procedures, characterization data and spectra for all compounds. X-ray crystallographic data for **7a** and **7c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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