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# Intramolecular Cycloaddition of Nitrones with Sulfur-Substituted Dienes and Its Synthetic Applications

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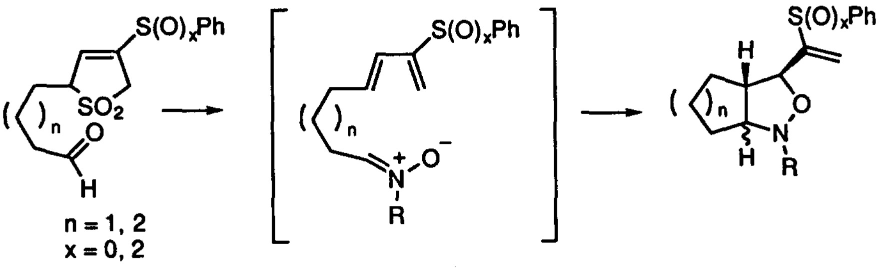
**ABSTRACT:** A series of sulfur-substituted dienyl nitrones were conviently prepared from the 3-sulfolene precursors. Intramolecular 1,3-dipolar cycloaddition reactions gave the fused bicyclic isoxazolidines. The regio- and stereochemical outcome of these reactions as well as the synthetic applications have been explored. © 1997 Elsevier Science Ltd.

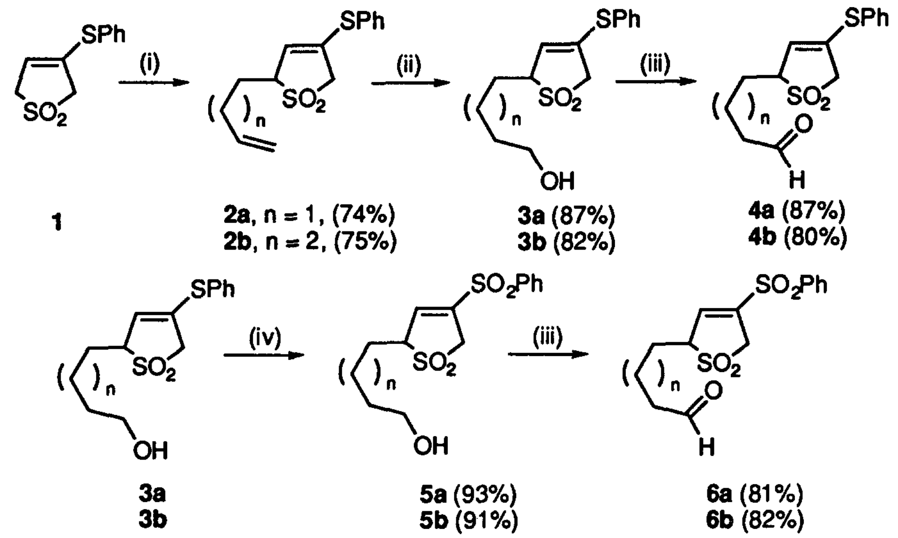
The 1,3-dipolar cycloaddition reaction of nitrones with alkenes is a powerful synthetic tool for the preparation of 1,3-amino alcohols,[1] and has attracted considerable attention as a convenient method for the rapid construction of widely varied classes of natural products.[2] In recent years, intramolecular nitrone-olefin cycloaddition has been of considerable synthetic interest because the resulting fused bicyclic isoxazolidine moiety can undergo many interesting transformations.[3] The regio- and stereochemistry of the intramolecular cycloaddition are influenced by many factors such as alkene polarity, ring strain, and nonbonded interactions.[4]

Although the intramolecular cycloaddition of nitrones with alkenes has been extensively studied, the corresponding reaction of nitrones with conjugated dienes has received little attention.[5] As an extension of our interest in the synthesis and reactions of sulfur-substituted dienes *via* 3-sulfolenes,[6] we herein report the first synthesis of sulfur-substituted dienes bearing the nitrone group from the corresponding 3-sulfolenes. The regio- and stereochemistry of the intramolecular 1,3-dipolar cycloaddition are studied, as well as some of the synthetic applications.



The sulfolene aldehydes required for this study were prepared by the reaction sequence as outlined in Scheme 1. Treatment of 3-(phenylthio)-3-sulfolene (**1**)[7] with BuLi (1 equiv) in THF at -105 °C in the presence of hexamethylphosphoric amide (HMPA, 4 equiv) followed by the addition of 4-iodo-1-butene or 5-iodo-1-pentene (2 equiv) gave the alkylated products **2** in good yield. Hydroboration of **2** with 9-BBN in THF followed by the oxidation with alkaline aqueous hydrogen peroxide produced the terminal alcohols **3** which were further oxidized to the corresponding aldehydes **4**. The sulfonyl aldehydes **6** could also be obtained in excellent yield by treatment of **3** with MCPBA (2.5 equiv) to give the sulfonyl alcohols **5** which were then oxidized with PCC.

**Scheme 1**



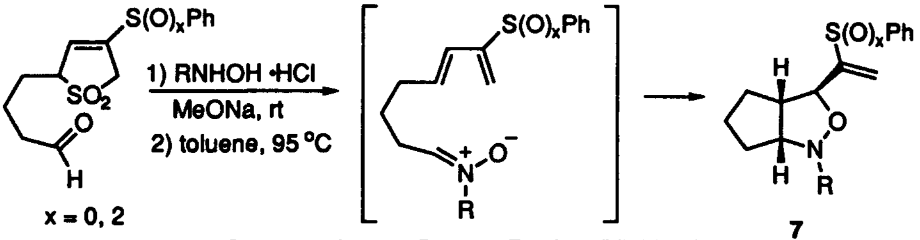
**Reagents :** (i) BuLi, HMPA, THF, -105 °C; $CH_2=CH(CH_2)_nCH_2I$, -90 °C to -50 °C;
(ii) 9-BBN, THF, 0 °C; NaOH, $H_2O_2$, 0 °C; (iii) PCC, $CH_2Cl_2$, rt;
(iv) MCPBA, $CH_2Cl_2$, 0 °C.

Once the sulfolene aldehydes were in hand, the targeted nitrones were readily prepared by condensation of the aldehyde group with an alkyl (methyl or benzyl) hydroxylamine hydrochloride salt (1.1 equiv) and NaOMe (1.1 equiv) in toluene. After the mixture was stirred at room temperature for 10 min, the nitrones formed were then heated at different temperatures, first to undergo the cheletropic removal of $SO_2$, and then the intramolecular 1,3-dipolar cycloaddition to give the isoxazolidine products (Scheme 2).

Whether it was the phenylthio or sulfonyl group on the diene, the 5-dienylnitrones **4a** and **6a** gave only the *cis*-fused [3.3.0] bicyclic isoxazolidines **7**. Apparently, the more strained *trans* isomer would proceed through a transition state of much higher activation energy.[4] However, in the case of 6-dienyl nitrones, the phenylthio-substituted **4b** gave a mixture of *cis*- and *trans*-fused products **8** and **9**, with the *cis* isomer slightly dominating. It is very interesting to note that the sulfone-substituted **6b** gave only the *cis*-fused product **8**. The transition state for the formation of the *trans* product **9** involves considerable steric repulsion between the phenylsulfonyl group and the substituent on the nitrogen (Scheme 2). The stereochemistry of the cycloadducts **7** - **9** was established by $^1H$ NMR decoupling experiment and NOE studies. It should also be mentioned that neither the adducts derived from the reaction of the nitrone group with the terminal olefin nor the bridged cyclization products were detected in any case.

We were also interested in the synthetic applications of these products. Reductive cleavage of the N-O bond in **7b** with Zn (10 equiv) in 50% aqueous HOAc[8] produced the amino alcohol **10**, not affecting the configuration of the stereocenters. After treatment with NaH (1.1 equiv) and MsCl (1.1 equiv) followed by the reaction with aqueous NaOH (3 equiv), the bicyclic azetidine product **11** was obtained in good yield.

**Scheme 2**



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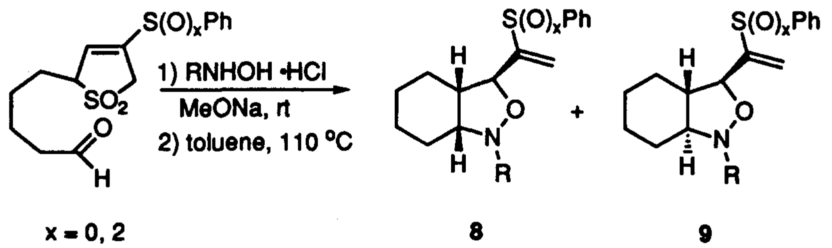
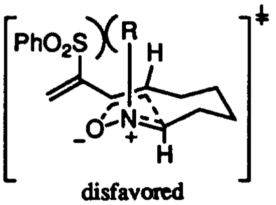
| Compound | R | Product (Yield, %) |
|---|---|---|
| 4a | $CH_3$ | 7a (73) |
| 4a | $CH_2Ph$ | 7b (61) |
| 6a | $CH_3$ | 7c (65) |
| 6a | $CH_2Ph$ | 7d (60) |



| Compound | R | Product (Yield, %) |
|---|---|---|
| 4b | $CH_3$ | 8a (38) + 9a (27) |
| 4b | $CH_2Ph$ | 8b (36) + 9b (18) |
| 6b | $CH_3$ | 8c (56) |
| 6b | $CH_2Ph$ | 8d (45) |



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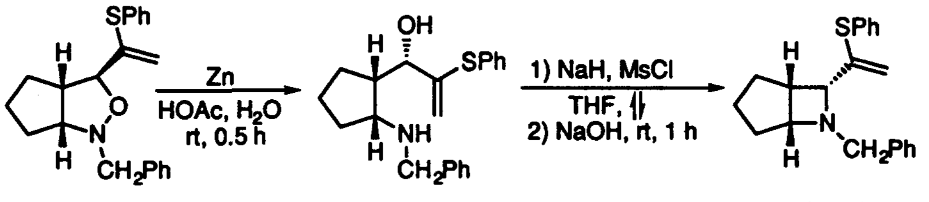
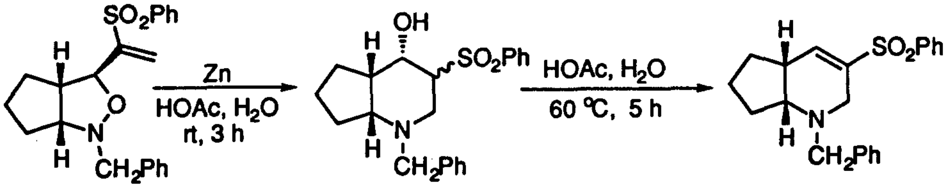


**7b** **10** (86%) **11** (75%)

On the other hand, the reaction of **7d** with Zn (3 equiv) in 50% aqueous HOAc produced directly the bicyclic piperidine product **12** as a diastereomeric mixture (1.3 : 1). After heating in 50% aqueous HOAc at 60 °C for 5 h, the dehydration product **13** was obtained in good yield.



**7d** **12** (75%) **13** (78%)

In summary, regiospecific intramolecular cycloadditions of nitrones with sulfur-substituted dienes have been conveniently carried out *via* the 3-sulfolene precursors. The stereochemical outcome of these reactions is influenced by the structure of the substituent (sulfide or sulfone) on the diene as well as the chain length connecting the diene and nitrone. The bicyclic products obtained from these reactions have been converted to some interesting heterocyclic compounds, and the functional group of vinyl sulfide or sulfone should be useful for further transformations.[9]

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