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Preparation and Reactions of Thiazole-fused 3-Sulfolenes. Useful Precursors to *o*-Dimethylene Thiazoles

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Abstracts: *Thiazole-fused 3-sulfolenes* ***8*** *and* ***9*** *have been efficiently prepared from 4-bromo-3-sulfolanone* ***7*** *in one step. These 3-sulfolenes react as synthetic equivalents to o-dimethylene thiazoles.*

o-Quinodimethane **1** and its derivatives have been widely used as reactive intermediates for the synthesis of complex molecules.[1] In contrast, much less studies have been reported about the preparation and properties of *o*-dimethylene heteroaromatics **2** (DMHA) which are the heterocyclic analogues of *o*-quinodimethane. Because most of the DMHA's have only been generated in situ by flash pyrolysis or by 1,4-elimination reaction from suitable precursors,[2] their synthetic applications have been so far limited , except for the case of *o*-dimethylene indole.[3] Since 3-sulfolenes are known to be excellent precursors to the corresponding dienes,[4] aromatic-fused 3-sulfolenes **3** should be ideal precursors to DMHA's as well. For this reason, there are a number of recent reports[5] dealing with the preparation of sulfolene-masked DMHA's by building a heteroaromatic ring on a five membered cyclic sulfone system.

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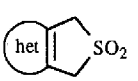

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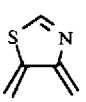

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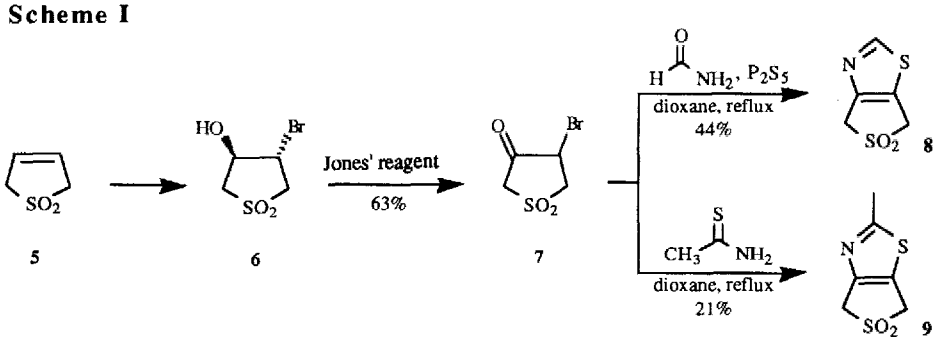
The thiazole DMHA **4** and its 2-phenyl derivative have been reported to be generated by flash pyrolysis (700 °C, 0.01 torr) of the *p*-chlorobenzoate esters of 4-methyl-5-(hydroxymethyl)thiazoles.[6] However, only insoluble polymers were obtained when attempts were made to collect the pyrolysates at low temperatures. The authors did not observe any dimerized products nor did they succeed in trapping these DMHA's with dienophilic olefins. The only evidence of the existence of these DMHA's was the adducts from the co-condensation of the

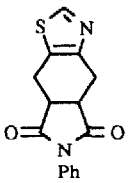
pyrolysates with thiophenol and sulfur dioxide. It was thought that one should be able to perform useful synthetic reactions of *o*-dimethylene thiazoles if thiazole-fused 3-sulfolenes could be prepared efficiently. And we report herein the success of this new strategy.

The synthesis of the thiazole-fused 3-sulfolenes is short and straight-forward (scheme I). The readily available 3-bromo-4-hydroxysulfolane **6**, easily prepared from 3-sulfolene **5**,[7] was oxidized with Jones' reagent to give the α-bromoketone **7** in 63% yield.[8] Treatment of **7** with formamide and P_2S_5 in refluxing dioxane yielded the desired product **8** in 44% yield as a white solid (mp 136-137 °C).[9] Synthesis of the 2-methyl analogue **9** under similar conditions was also easily achieved, albeit in lower yield (mp 131-132 °C). Both **8** and **9** are stable compounds which can be purified with column chromatography.

Scheme I



To test if compounds **8** and **9** are indeed precursors for the corresponding DMHA's, they were treated with typical dienophiles under thermal conditions. Reactions of **8** with N-phenylmaleimide or dimethyl fumarate in a sealed tube at 180-190 °C gave the desired Diels-Alder adducts **10** (74%) and **11** (73%), respectively. Similar treatment of **9** with dimethyl fumarate yielded the cycloadduct **14** (79%) as well. An attempted Diels-Alder reaction of **8** with a poor dienophile, cyclohexene, failed to give the desired cycloadduct but gave a mixture of two [4+2] dimerized products of **12**. In principle there are four possible [4+2] dimers of **4**, however, only two of them were obtained in this reaction in 47% and 4% yield.[10] It is interesting to compare the [4+2] dimerization reaction of *o*-dimethylene thiophene where only one of the four possible isomers was obtained.[2g-i] Whereas *o*-dimethylene furan,[2b,c] *o*-dimethylene pyrrole,[5b] and *o*-dimethylene oxazole[6] all dimerize in a symmetric [4+4] manner. The formation of the Diels-Alder cycloadducts **10**, **11**, and **14** and the dimers **12** clearly illustrates that the *o*-dimethylene thiazoles **4** and **13** were the reactive intermediates. And these cycloaddition reactions demonstrate the synthetic usefulness of **4** and **13** when they are generated thermally from the corresponding 3-sulfolenes.



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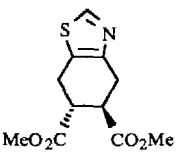

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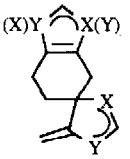
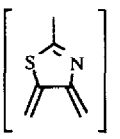


12, X=N or S



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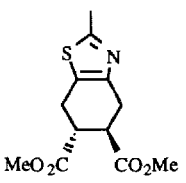

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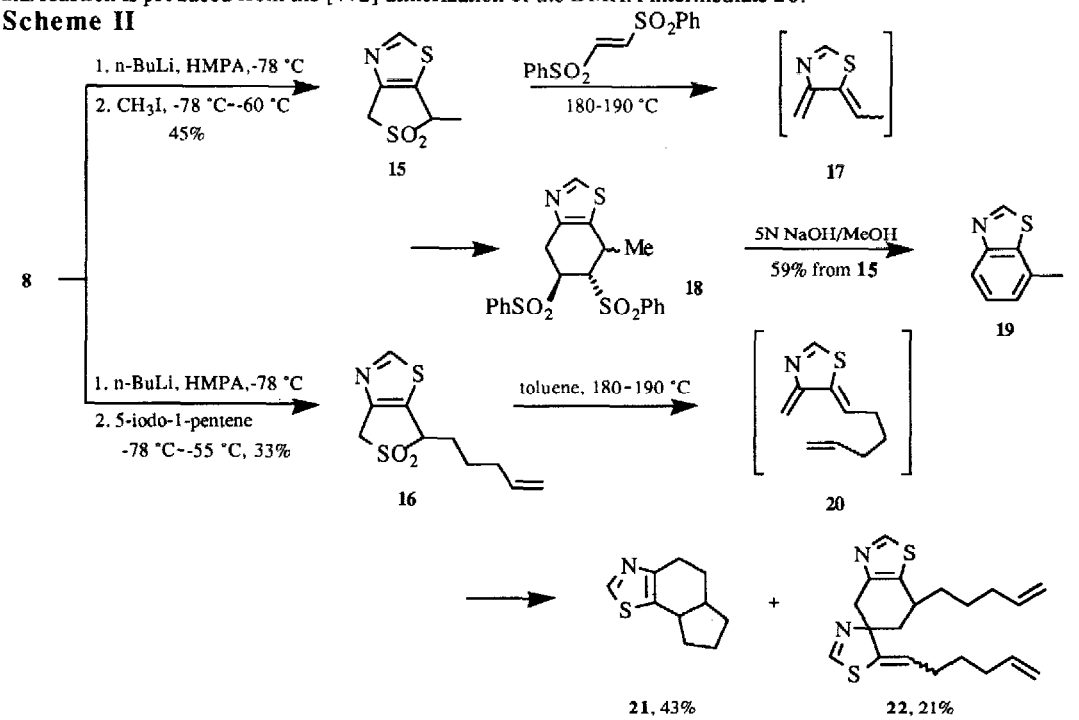
One very important advantage of using 3-sulfolenes as precursors for conjugated dienes is that substituents can be introduced directly by a deprotonation-alkylation process.[4] Thus, compound **8** was treated with n-BuLi at low temperature in the presence of HMPA as a co-solvent. The resulting carbanion could be alkylated regioselectively with an excess of MeI (2 equiv) to give **15** as the only product (Scheme II). 4-Pentenyl group could also be introduced regioselectively to yield **16**. The regioselective substitution reaction broadens the synthetic applications of *o*-dimethylene thiazoles. For examples, the reaction of **15** with 1,2-bis(phenylsulfonyl)ethylene followed by a base-induced elimination reaction produced the benzothiazole **19**. Whereas heating a solution of **16** in toluene at 180-190°C caused the extrusion of SO_2 followed by an intramolecular Diels-Alder reaction to give **21** (43%) as an 8 : 2 mixture of stereoisomers. The side product **22** in this reaction is produced from the [4+2] dimerization of the DMHA intermediate **20**.

Scheme II



Comparing the results described herein with those reported earlier, it can be concluded that the strategy of using thiazole-fused 3-sulfolene as the equivalent of *o*-dimethylene thiazole is more advantageous than the flash pyrolysis strategy for synthetic purpose. It should also be noted that the bromoketone **7** may be a very useful intermediate for the preparation of many more derivatives and analogues of **8**.

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8. All new compounds gave satisfactory spectral; analytical data.
9. ^{1}H NMR (200 MHz) δ 4.48 (s, 2H), 4.50 (s, 2H), 8.93 (s, 1H).
10. The two isomeric components (47%; 4%) could be isolated by HPLC (LiChrosorb column, EtOAc). The ^{1}H NMR (200 MHz) of the major product δ 1.65-2.16 (m, 2H), 3.02-3.14 (m, 4H), 5.22 (dd, 1H, J=1.8, 1.9 Hz), 5.38 (d, 1H, J=1.9 Hz), 8.05 (brs, 1H), 8.66 (s, 1H).

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