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LEWIS ACID AND HIGH PRESSURE PROMOTED DIELS-ALDER CYCLOADDITIONS OF N-ALKYL-N-SULFINYL DIENOPHILES

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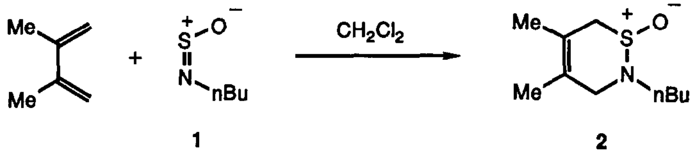
Summary: Normally unreactive N-alkyl-N-sulfinyl compounds act as dienophiles in both inter and intramolecular Diels-Alder processes in the presence of Lewis acids or optimally under high pressure.

Several reports from these laboratories have described new synthetic methodology[1] which utilizes Diels-Alder adducts of N-sulfinyl dienophiles and 1,3-dienes (eq 1).[2] These [4+2]-cycloadditions occur with great facility at room temperature or below provided the dienophile bears an electron withdrawing group (X) on nitrogen. N-Sulfinyl compounds containing electron donating substituents such as alkyl groups are normally unreactive as dienophiles. As part of our program of methodological studies, we became interested in effecting Diels-Alder reactions with simple N-alkyl-N-sulfinyl dienophiles.

$X = Ar, SO_2Ar, CO_2R, COR, CN, SO_2NR_2, \overset{+}{S}R_2$, etc

In some initial experiments N-sulfinylbutylamine (1)[3] and 2,3-dimethylbutadiene were treated with several Lewis acid catalysts at -78°C (Scheme 1) to afford dihydrothiazine oxide 2 in varying yields. The best catalyst proved to be boron trifluoride etherate, giving 2 in 68% yield. However, when the cycloaddition was effected under high pressure conditions[4,5] (12 kbar, 24h) in the absence of a catalyst a nearly quantitative yield of adduct 2 was produced.

Scheme 1



Conditions	Isolated Yield
TiCl$_4$/-78°C (1.0 equiv)	4%
SnCl$_4$/-78°C (0.5 equiv)	55%
BF$_3$-Et$_2$O/-78°C (1.0 equiv)	68%
12 kbar/room temp	96%

Cycloaddition of N-sulfinyl dienophile 1 and E,E-2,4-hexadiene was also investigated (**Scheme** 2). Once again, boron trifluoride gave the highest total yield of cycloadducts. Improved yields of products were obtained at 12 kbar. At 6 kbar a much reduced product yield was observed. Of the three solvents examined, methylene chloride gave the best results. It is possible that the lower yield of cycloadducts in ether and hexane is due to solidification of these solvents which occurs at room temperature at the pressure employed.[5]

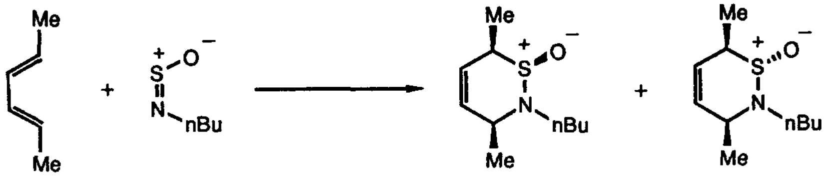
The stereochemistry of this cycloaddition was also studied. As anticipated, the reaction was <u>syn</u>-selective with respect to the diene, but provided varying mixtures of sulfur epimers 3 and 4 as shown in **Scheme** 2. The relative stereochemistry and conformations of adducts 3 and 4 were shown by ^{1}H NMR europium induced shift experiments to be as in **3A** and **4A**, respectively (relative induced shifts in parenthesis). We have previously shown that heterocycles of this type prefer conformations in which the S-O bond is quasi-axial, perhaps due to an anomeric effect.[6,7]

The high pressure reactions afforded isomer 4 as the major cycloadduct. Assuming that sulfinyl compound 1 reacts as the Z-isomer[2,8], adduct 4 is the result of exo approach, which probably occurs for steric reasons.

Interestingly, the cycloadditions catalyzed by boron trifluoride and titanium tetrachloride gave exclusively epimer 3. Stannic chloride yielded a mixture of 3 and 4. We believe these are kinetically controlled processes since exposure of cycloadduct 4 to the Lewis acids did not cause isomerization to 3.

We can only speculate as to why there is a reversal in stereochemistry going from the high pressure reactions to the two involving Lewis acids. One possibility is that some type of Lewis acid complexed N-sulfinyl dienophile reacts under steric control to give 3 predominantly. Another is that there is a difference in mechanism (i.e., concerted vs stepwise)[9] between the two sets of reaction conditions.

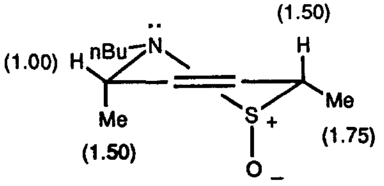
Scheme 2

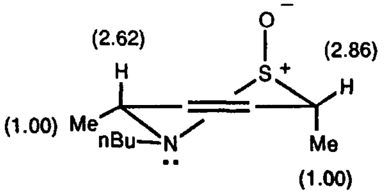


1 3 4

Conditions	Isomer Ratio	Isolated Yield
$TiCl_4/CH_2Cl_2$/-78°C (1.0 equiv)	100 : 0	27%
$SnCl_4/CH_2Cl_2$/-78°C (0.5 equiv)	40 : 60	47%
BF_3-Et_2O/CH_2Cl_2/-78°C (1.0 equiv)	100 : 0	54%
12 kbar/Et_2O/room temp	11 : 89	56%
12 kbar/hexane/room temp	12 : 88	66%
12 kbar/CH_2Cl_2/room temp	18 : 82	80%
6 kbar/CH_2Cl_2/room temp	15 : 85	22%

3A

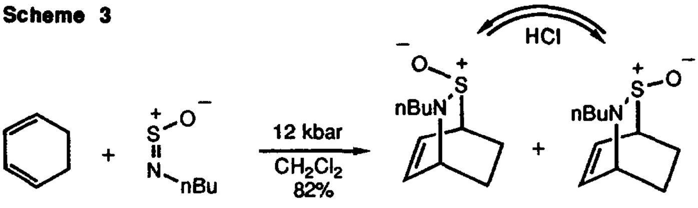




4A

1,3-Cyclohexadiene and dienophile **1** gave only a low yield (<10%) of cycloadducts in the presence of boron trifluoride etherate. However, at 12 kbar the reaction proceeded smoothly to afford a 95:5 mixture of endo and exo isomers **5** and **6**, respectively (**Scheme 3**) in good yield (82%). In this case the endo product would be anticipated to predominate if the reaction is sterically controlled. We also found that **5** and **6** could be equilibrated to a 1:1 mixture by treatment with a trace of HCl in chloroform. It is not clear at present how this isomerization occurs, although mechanisms involving a retro Diels-Alder reaction and/or dihydrothiazine oxide ring opening are feasible.

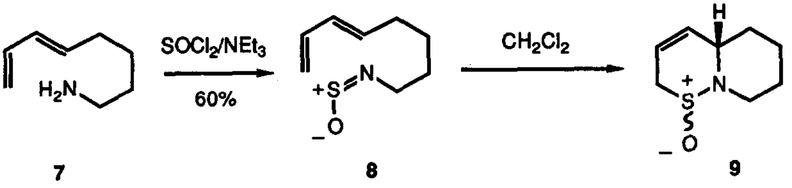
Scheme 3



1 5 (95 : 5) 6

It is also possible to effect these Diels Alder reactions intramolecularly (**Scheme 4**). Amino diene **7** was converted to N-sulfinyl compound **8** which showed no tendency to undergo thermal [4+2]-cycloaddition. When **8** was treated with BF_3 etherate, however, adduct **9** was formed as a 2:1 mixture of stereoisomers in 40% yield. At 12 kbar the same mixture of isomers of **9** was produced, but the yield improved to 82%.

Scheme 4



BF$_3$-Et$_2$O (1.0 equiv)/-78°C 40%
12 kbar/room temp/24 h 82%

We are currently investigating the scope of the chemistry described here, as well as its application to natural product synthesis.

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