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A CONVENIENT IN SITU PROCEDURE FOR EFFECTING INTER- AND INTRAMOLECULAR DIELS-ALDER REACTIONS OF N-SULFONYL IMINES

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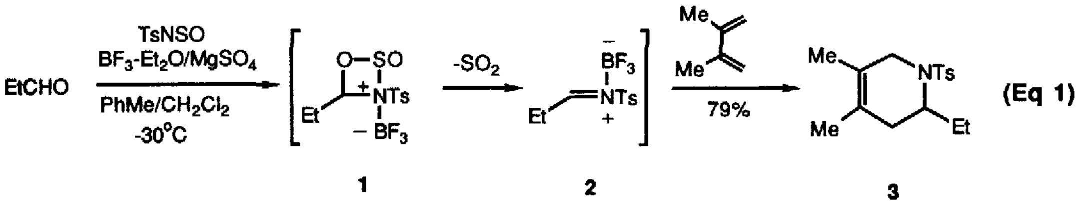
Summary: Treatment of an aldehyde and a 1,3-diene with N-sulfinyl-p-toluenesulfonamide/boron trifluoride etherate leads to products of an imino Diels-Alder reaction via an N-sulfonyl imine produced in situ.

Since its inception nearly five decades ago, the imino Diels-Alder reaction has become a powerful tool for construction of tetrahydropyridines.[1] Both inter- and intramolecular versions of the methodology have been widely utilized in alkaloid synthesis. A recent important advance in this area is the procedure of Grieco, et al., for in situ generation and Diels-Alder reaction of immonium salts under aqueous Mannich-like conditions.[2] We now describe a new one-pot method for effecting Diels-Alder cycloadditions of N-sulfonyl imines derived from a variety of aldehydes.

A number of years ago Kresze and co-workers reported that non-enolizable aldehydes could be converted to the corresponding N-tosyl imine using N-sulfinyl-p-toluenesulfonamide in the presence of a Lewis acid.[3] We recently used the Kresze reaction to generate N-tosyl imines from several enolizable aldehydes which underwent subsequent intramolecular electrophilic cyclizations with olefins.[4] We have now found that these in situ produced N-sulfonyl imines can be efficiently trapped by 1,3-dienes in a [4+2]-cycloaddition.

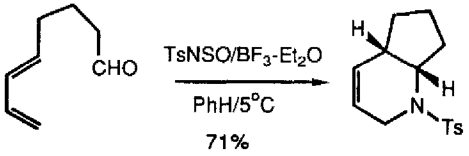
Thus, treatment of propionaldehyde with N-sulfinyl-p-toluenesulfonamide and BF_3 etherate followed by 2,3-dimethyl butadiene gives Diels-Alder adduct 3 in good yield (**Eq 1**). It was also



discovered that yields and reproducibility in the reaction are substantially improved if anhydrous magnesium sulfate is suspended in the reaction mixture. Molecular sieves (4 Å) also are effective but yields are slightly lower than with $MgSO_4$. Imine formation presumably involves an initial [2+2]-cycloaddition of the N-sulfinyl compound with the aldehyde affording an intermediate such as 1.[3] The reactive species in the cycloaddition may in fact be a Lewis acid complexed immonium salt 2.

The results of Diels-Alder cycloadditions using a number of different aldehydes and 1,3-dienes are shown in the **Table**. The reactions were conducted using the general procedure described below. Cycloadditions with unsymmetrical dienes were found to be fully regioselective. Only modest stereoselectivity was observed (cf entries 6-10). A useful feature of the methodology is that it is successful with a variety of relatively sensitive enolizable aldehydes. It should be noted that existing cases of [4+2]-cycloadditions of N-sulfonyl imines involve compounds derived from simple non-enolizable aldehydes such as chloral and glyoxylate.[3,5] Moreover, these reactions all utilize the neutral imines, which generally require higher temperatures than is necessary in our procedure.

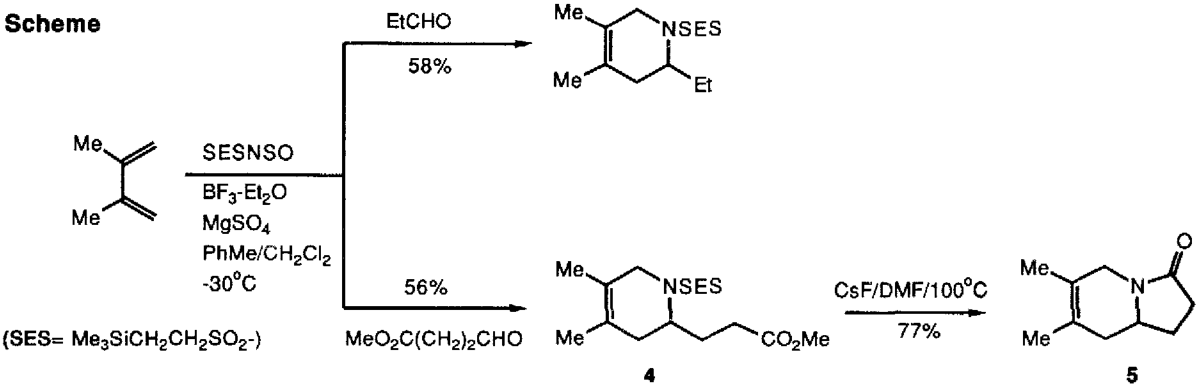
It is also possible to effect these cycloadditions intramolecularly as shown by the example in **Eq 2**. A single stereoisomeric product was obtained here which was tentatively assigned the cis-fused structure shown based upon NOESY experiments.



(Eq 2)

One can also perform these reactions with other N-sulfinyl sulfonamides such as the SES[6,7] series shown in the **Scheme**. In this case, sulfonamide cleavage can be effected under mild conditions. Thus, treatment of adduct **4** with fluoride[6] afforded the bicyclic lactam 5.[8] Compounds such as 5 are potentially useful in synthesis of indolizidine alkaloids.[9]

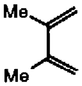
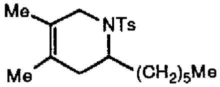
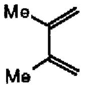
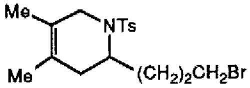
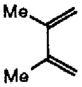
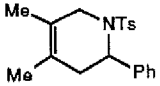
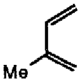
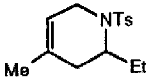
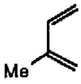
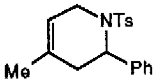
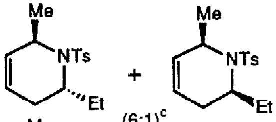
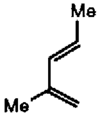
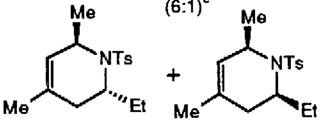
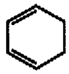
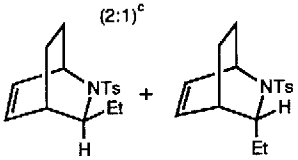
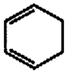
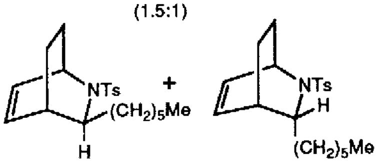
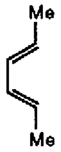
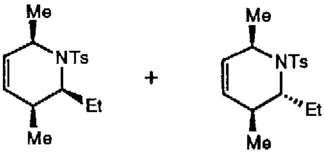
Scheme



(SES= $Me_3SiCH_2CH_2SO_2$-)

We are currently exploring extensions and applications of the methodology described here.

TABLE. Diels-Alder Cycloadditions of *in situ* Generated N-Tosyl Imines[a]

Entry	Aldehyde	Diene	Product(s)	Isolated Yield
1	$Me(CH_2)_5CHO$			63%
2	$BrCH_2(CH_2)_2CHO$			60%
3	$PhCHO$[b]			75%
4	EtCHO			63%
5	$PhCHO$[b]			60%
6	EtCHO		 (6:1)[c]	61%
7	EtCHO		 (2:1)[c]	68%
8	EtCHO		 (1.5:1)	73%
9	$Me(CH_2)_5CHO$		 (1.5:1)	74%
10	EtCHO		 (1:1)	44%

[a] see General Experimental Procedure

[b] reaction conducted at 0°C

[c] stereochemistry established by ^1H NMR NOEDS

General Experimental Procedure. To an oven-dried, 2-necked 25 mL flask fitted with a syringe cap was added 200 mg of $MgSO_4$ and 3 mL of dry toluene under an atmosphere of argon. N-Sulfinyl-p-toluenesulfonamide (0.3 mmol, 65 mg)[10] was dissolved in 2 mL of dry CH_2Cl_2 and this solution was added to the reaction flask. After cooling the mixture to -30°C, the aldehyde (0.5 mmol) and $BF_3 \cdot Et_2O$ (0.3 mmol, 0.037 mL) were added sequentially by syringe and the resulting solution was stirred for 5 min. The 1,3-diene (0.2 mmol) was added and the reaction mixture was stirred for 3 h at -30°C. The reaction mixture was diluted with 10 mL of saturated $NaHCO_3$ solution and extracted with 40 mL of ethyl acetate. The organic layer was washed with 20 mL of H_2O, dried over $MgSO_4$ and concentrated in vacuo. The product was purified by preparative TLC on silica gel. Isolated product yields are shown in the **Table**.

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