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THE UNCATALYZED DIELS-ALDER REACTION OF IMINES WITH BIS(PHENYLSULFONYL) SUBSTITUTED DIENES

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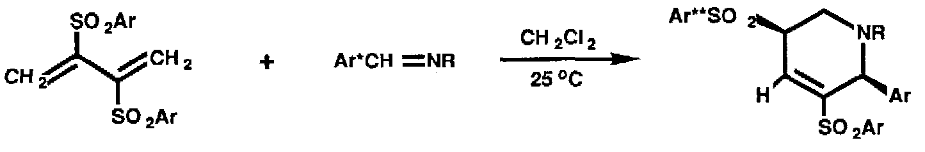
Abstract: *The reaction of 2,3-bis(phenysulfonyl)-1,3-butadiene with arylimines affords N-alkyl-3,5-bis(phenylsulfonyl)-1,2,5,6-tetrahydropyridines in high yield.*

Multifunctional 1,3-dienes often exhibit high regio and stereospecificity toward dienophiles and consequently these dienes are becoming well established as useful intermediates in organic synthesis.[1-5] Certain derivatives of imines have been employed in cycloaddition chemistry with several heterosubstituted dienes, opening new opportunities for the construction of aza heterocyclic compounds.[6] Typically, imino Diels-Alder additions are successful only if the imine is activated [7,8] in intramolecular additions[9] or involves the use of an iminium salt.[10] Our interest in this area is concerned with the uncatalyzed Diels-Alder cycloaddition of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**)[11] with various C-N pi-bonds. In an earlier report, we described our initial studies which focused on the reaction of **1** with oximes to give azaoxabicyclic adducts.[12] We have now studied the reaction of **1** with a variety of imines and find that a rather novel reaction occurs in excellent yield to give a rearranged Diels-Alder cycloadduct. This communication documents the results of these studies.

As our first model we investigated the Diels-Alder reaction of **1a** with N- benzylidenemethylamine. A typical reaction was carried out by simply stirring the two reagents in methylene chloride at 25°C for 24 h. The structure of the resulting cycloadduct **2a** (90%) was assigned on the basis of its characteristic spectral data and was further established by an X-ray single crystal structure analysis. This surprising result suggested a further study of **1a** with other imines so as to establish the generality of the process. Indeed compound **1a** participates as the diene component with several imines



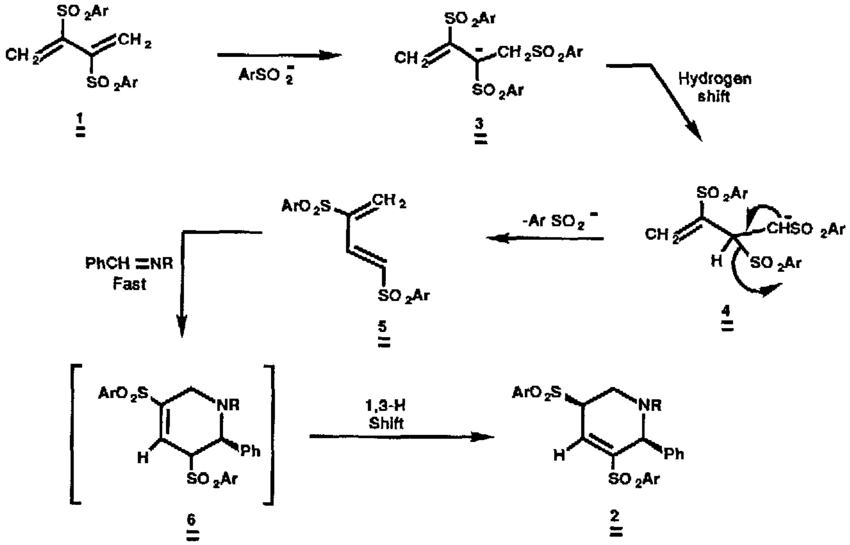
1a; Ar=Ph
1b; Ar=(o-NO_2)C_6H_4

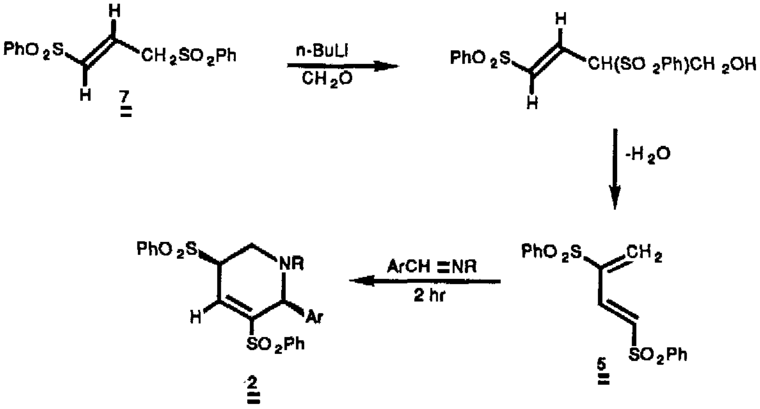
2a; Ar=Ar*=Ph; R=CH_3
b; Ar=(o-NO_2)C_6H_4; Ar*=Ph; R=CH_3
c; Ar=Ar*=Ph; R=CH_2Ph
d; Ar=(o-NO_2)C_6H_4; Ar*=Ph; R=CH_2Ph
e; Ar=Ph; Ar*=α-Naphth; R=CH_2Ph
f; Ar**=(o-NO_2)C_6H_4;Ar=Ar*=Ph;R=CH_3

under analogous reaction conditions. In all cases studied the cycloaddition afforded a single product (73-92%) corresponding to the rearranged cycloadduct.[13] Cycloaddition with formation of tetrahydropyridine **2** also occurred with the closely related 2,3-bis(*o*-nitrophenylsulfonyl) substituted diene (**1b**).

A mechanism which rationalizes the formation of **2** and which is consistent with all the data (vide infra) is outlined in Scheme I. Carbanion **3** is a probable key intermediate in this novel sequence of reactions. Proton transfer from **3** generates anion **4** which ejects the neighboring arylsulfinate group to produce a 1,3-bis(arylsulfonyl) substituted diene (i.e. **5**).[14] This material undergoes a facile 4+2-cycloaddition with the added imine and the initially formed Diels-Alder adduct **6** is transformed via a subsequent 1,3-hydrogen shift to the observed product.[15] Presumably a trace of aryl sulfinate anion was present in the reaction mixture and served as an initiator for the diene isomeriza-

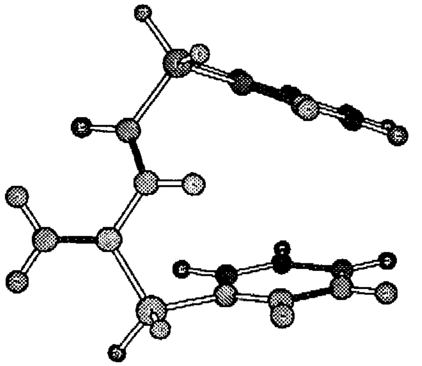
Scheme I





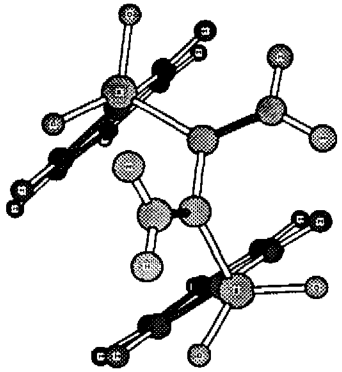
tion step. Supporting evidence for the proposed mechanism is provided by the observation that the reaction of a 1:1-mixture of dienes **1a** and **1b** afforded cycloadducts **2a** and **2b** as well as the mixed cycloadduct **2f** in 25% yield. This is perfectly compatible with the reaction sequence outlined in Scheme I. An additional piece of data which also supports the proposed mechanism is the observation that an independently synthesized sample of 1,3-bis(phenylsulfonyl)butadiene **5** readily undergoes cycloaddition with the same imines as was used with diene **1a** (25°C and 2h) and produced cycloadducts **2** in excellent yield.

All of our attempts to detect the rearranged 1,3-substituted diene (i.e **5**) starting from the 2,3-bis(phenylsulfonyl) substituted diene failed. This is undoubtedly related to the facility with which the 1,3-isomer reacts in the 4+2-cycloaddition process.[17] Molecular mechanics calculations using the Still-Steliou program[18] were carried out and the results indicate that the lowest energy conformer of the 1,3-isomer corresponds to the cisoid conformation necessary for the Diels-Alder reaction. The 2,3-substituted isomer, on the other hand, exists in the transoid form and possesses an enormous barrier (>50 kcal) for rotation about the 2,3-sigma bond. MNDO calculations also indicate that 1,3-diphenylsulfonyl-1,3-butadiene is more highly activated toward cycloaddition as a consequence of its markedly lowered LUMO energy level (-1.39 eV) compared with the 2,3-substituted isomer (-0.29 eV).



HOMO -11.21
LUMO -1.39

PhCH=NMe
HOMO -9.51
LUMO -0.19



HOMO -10.96
LUMO -0.29

The above results are suggestive of a broad potential of the imine-bis(phenylsulfonyl)-1,3-diene cycloaddition process. We are currently exploring the applicability of the reaction to more complex variations. Application of these activated dienes in the arena of alkaloid synthesis is also under investigation and will be reported on at a later date.

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13. The hydrogen at the 2-position of the ring (ca. δ 4.5 ppm) always appears as a singlet thereby establishing the 3,5-bis(phenylsulfonyl) substitution pattern in the resulting cycloadduct.
14. The addition-proton transfer-elimination process proposed for the conversion of **1** into **5** using benzenesulfinate anion has some literature precedence in the work of Taber; D.F.; Saleh, S.A. **J.Org. Chem.** *1981*, **46**, 4817
15. MM2 Calculations help rationalize the exclusive formation of *cis*-cycloadduct **2a** and also account for the 1,3-hydrogen shift from *cis*-**6a**. The calculations reveal a 3.2 kcal difference in steric energy between **2a** (27.81 kcal) and **6a** (31.01 kcal), which corresponds to the Diels-Alder cycloadduct derived from an *endo*-transition state.[16] The lower energy isomer corresponds to **2a** which presumably has fewer nonbonded interactions between the phenyl and phenylsulfonyl groups.
16. The steric energy difference between **2a** and the hypothetical *trans*-cycloadduct **6b** (*trans*-phenyl-phenylsulfonyl groups (*exo*-transition state) is also in favor of **2a** by 1.8 kcal.
17. Attempts to detect diene **5** in the absence of imine were also unsuccessful. Stirring for long periods of time led to uncharacterizable material.
18. MM2 Calculations were performed on a Vax 8550 using Model 2.94 with the "statistical-coordinate" option in TTY (i.e. Conf.) to write the appropriate batch files for minimization using BakModel to find the global minimum. We thank Professor Kosta Steliou for a prerelease version of this program.

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