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FACILE CYCLOADDITION OF 2-PHENYLSULFONYL 1,3-DIENES TO INDOLES

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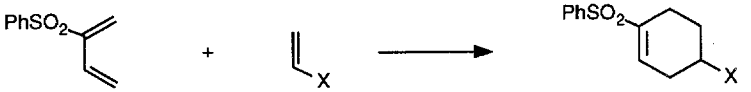
Summary: 2-Phenylsulfonyl 1,3-dienes react rapidly with the magnesium salt of indoles to give 3-(phenylsulfonyl)-1,4,4a,9a-tetrahydrocarbazoles via a formal [4+2] cycloaddition.

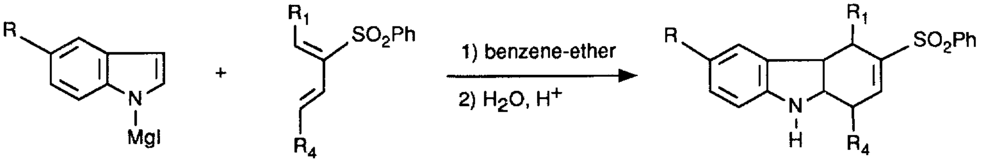
We have recently reported on the preparation and synthetic use of 2-phenylsulfonyl 1,3-dienes.[1-3] These dienes[4] have one electron deficient and one moderately electron rich double bond in conjugation, which leads to useful reactivity. For example they show a dual electron demand in their [4+2] cycloaddition (eq. 1) and hence react with both electron rich and electron deficient olefins. Enol ethers and enamines were used as dienophiles in the inverse electron demand Diels-Alder reaction.[1a,5]



(eq. 1)

X = OR, NR$_2$, or CO$_2$R

It is known that indole behaves as an enamine in its reactions with electrophiles.[6] The enamine-like reactivity is increased in the presence of weak bases[7] or on formation of the magnesium salt.[8] It therefore occurred to us that indole or its magnesium salt may serve as dienophile in the reaction with 2-phenylsulfonyl 1,3-dienes. Inverse electron demand Diels-Alder reactions between indoles and 3,6-dicarbomethoxy-1,2,4,5-tetrazenes have been reported.[9] We now report that 2-phenylsulfonyl 1,3-dienes react with the magnesium salt of indole in a [4+2] cycloaddition to give useful tetrahydrocarbazole systems (eq. 2)



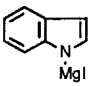
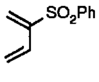
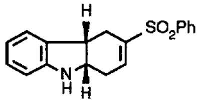
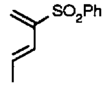
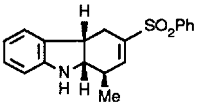
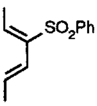
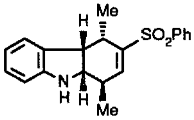
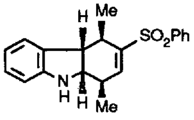
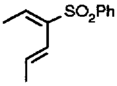
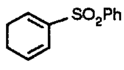
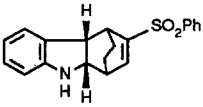
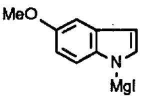
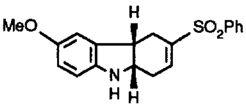
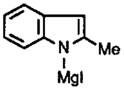
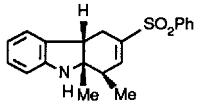
(eq. 2)

R = H, OMe

R$_1$ = H, Me
R$_4$ = H, Me

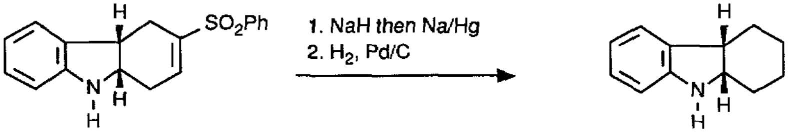
Reaction of 1-indolylmagnesium iodide[10] with the appropriate sulfonyldiene in benzene-ether (1:1) at 0 °C resulted in a cycloaddition and after workup the tetrahydrocarbazole product was isolated. Results from the reaction of a few 2-phenylsulfonyl 1,3-dienes are given in Table 1. In all cases only one regioisomer was formed and furthermore the stereochemistry at the bridge was *cis*. The regioselectivity conforms with that obtained from the reaction between phenylsulfonyl 1,3-dienes and enamines,[1a,11] *i.e.* the product formed is the one in which the nucleophilic carbon in the 3-position of indole has attacked the 1-position of the diene. The reaction of indolylmagnesium iodide with **1** and **2** afforded in each case only one stereoisomer, the ^{1}H NMR spectrum of

Table 1. Cycloaddition of 2-Phenylsulfonyl 1,3-Dienes to 1-Indolylmagnesium Iodide Derivatives[a]

IndolylMgI	diene	reaction time, temp.	product	% Yield[b,c]
	 **1**	5 min, 0 °C	 **6**	65
	 **2**	5 min, 0 °C	 **7**	62
	 **3**	3 h, 20 °C	 **8**  **9** 3 : 1	64
	 **4**	24 h, 20 °C	**8**[d] **9** 7 : 1	65
	 **5**	7 h, 20 °C	 **10**	42[e,f]
	**1**	10 min, 0 °C	 **11**	42
	**2**	1 h, 0 °C	 **12**	23

a. Unless otherwise stated the reaction was performed in benzene-ether (1:1); 1 equivalent of the sulfonyldiene was added to 1 - 2 equivalents of the indole magnesium salt during a few minutes. b. Isolated yield after flash chromatography. c. Yield based on the amount of sulfonyldiene used. d. In this case the fraction containing **8** was contaminated with small amounts of an isomer that was different from **9**. e. This product was a 3 : 1 mixture of the isomers where the ethylene bridge is cis and trans, respectively, to the indole bridge head protons (assignment by NOE). f. Benzene-ether (9 : 1) was used as solvent.

which is consistent with a *cis* configuration at the bridge.[12] The stereochemistry assigned was confirmed by transformation of **6** to hexahydrocarbazole **13** (eq. 3). The ^{1}H NMR spectrum of **13** was compared with the ^{1}H NMR spectra of *cis*- and *trans*-hexahydrocarbazole,[12a] and was found to be identical with that of the former.



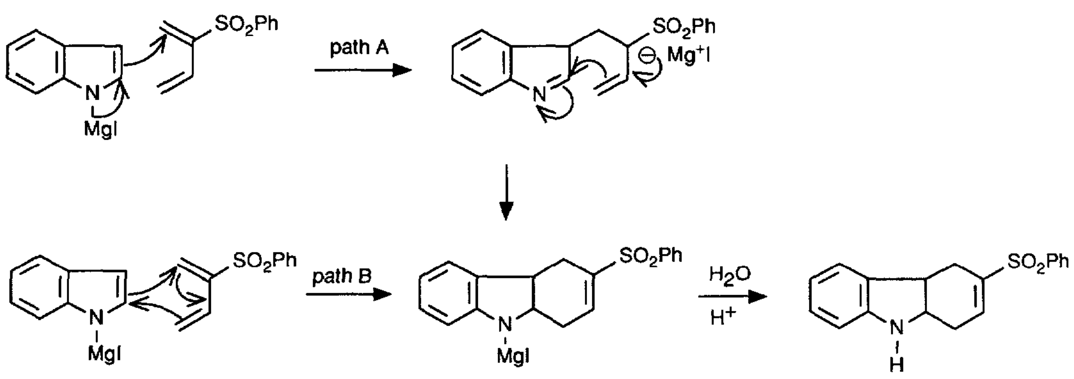
6 **13**

(eq. 3)

The reaction of the pure (2Z,4E) isomer **3** afforded a 3:1 mixture of isomers **8** and **9**. The (2E,4E) isomer **4** reacted much slower and afforded a 7:1 mixture of **8** and **9**. The expected products from a concerted reaction are **9** from **3** and **8** from **4**. Slow isomerization of **3** → **4** occurred during the reaction, but this isomerization is too slow to account for the product **8** in the reaction of **3**. Furthermore, the formation of **8** from the reaction of **3** was considerably faster than production of **8** from **4**, which excludes a major pathway **3** → **4** → **8**. We therefore conclude that the main part of **8** derives directly from **3**. The structural assignments for **8** and **9** are based on ^{1}H NMR spectroscopy.[13] A few other indole derivatives were also tested in the cycloaddition, the magnesium salt of 5-methoxy- and 2-methyl-indole affording adducts in moderate yield (Table 1). On the other hand, the magnesium salt of 5-nitroindole failed to give the desired cycloadduct with 2-phenylsulfonyl 1,3-dienes.

The mechanism of the cycloaddition described in this paper probably involves a two step reaction (path A, Scheme 1) although a concerted pathway cannot be completely excluded (path B, Scheme 1). The non-stereospecific formation of **8** and **9** is consistent with the major pathway being a two-step process.

Scheme 1



The results described in this paper extend the synthetic utility of 2-phenylsulfonyl 1,3-dienes, and the 3-(phenylsulfonyl)-1,4,4a,9a-tetrahydrocarbazoles, obtained in one step from indole, should be of interest for further synthetic transformations. Preliminary experiments show that it is possible to obtain selective carbon-carbon bond formation in the 1, 2, and 3-positions of these cycloadducts.

Acknowledgments. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged. We thank Dr. Adolf Gogoll for assistance and discussions concerning the NOE measurements.

References and Notes

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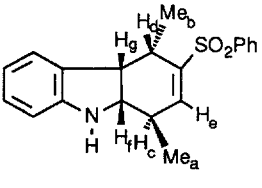
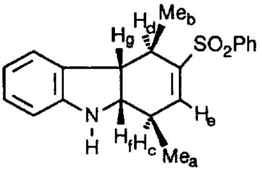
13. ^1H NMR, **8**: δ 7.96 - 7.46 (m, 5H, Ar-H), 7.02 (dt, 1H, indole-H), 6,96 (d, 1H, indole-H), 6.91 (d, J = 1.7 Hz, 1H, H-e), 6.69 (dt, 1H, indole-H), 6.56 (d, 1H, indole-H), 4.19 (br s, 1H, N-H), 3.79(dd, J = 10.5, 6.2 Hz, 1H, H-f), 3.38 (dd, J = 10.5, 5.9 Hz, 1H, H-g), 2.96 (m, J = 7 Hz, 1H, H-d), 2.67 (m, J = 7 Hz, 1H, H-c), 1.35 (d, J = 7.3 Hz, 3H, H-a), 0.58 (d, J = 7.2 Hz, 3H, H-b). **9**: δ 7.84 - 7.46 (m, 5H, Ar-H), 6.98 (d, J = 4.4 Hz, 1H, H-e), 6.92 (dt, 1H, indole-H), 6.57 (d, 1H, indole-H), 6.39 (dt, 1H, indole-H), 5.98 (d, 1H, indole-H), 3.88 (br s, 1H, N-H), 3.63 (dd, J = 7.3, 4.8 Hz, 1H, H-f), 3.27 (br d, J = 7Hz, 1H, H-g), 2.86 (br q, 1H, H-c), 2.29 (m, 1H, H-d), 1.42 (d, J = 7.0 Hz, 3H, H-b), 1.26 (d, J = 7.5 Hz, 3H, H-a). In both isomers there was a NOE on H_f when H_g was irradiated (5%, 7%), which is consistent with these protons being *cis* to each other. Furthermore, irradiation of Me_a gave a NOE on H_f in both isomers. Finally, the NOE on H_d in **8** (9%) but not in **9** on irradiation of H_g is consistent with the stereochemistry assigned for H_d and H_g in the two isomers. In agreement, irradiation of Me_b in **9** resulted in 6% NOE on H_g.



8 (J_{gf} = 10.5 Hz, J_{cf} = 6.2 Hz, J_{dg} = 5.9 Hz)
NOE(H_g^H_f) = 5%, NOE(H_a^H_f) = 3%
NOE(H_g^H_d) = 9%



9 (J_{gf} = 7.3 Hz, J_{cf} = 4.8 Hz, J_{dg} = 1 Hz)
NOE(H_g^H_f) = 7%, NOE(H_a^H_f) = 9%
NOE(H_g^H_d) ≤ 1%, NOE(H_b^H_g) = 6%

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