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SYNTHESIS OF 3-PYRROLINES VIA A [4+1]-ANNULATION STRATEGY

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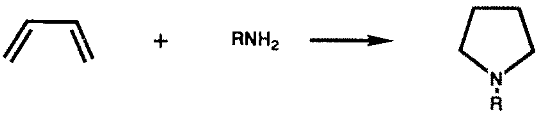
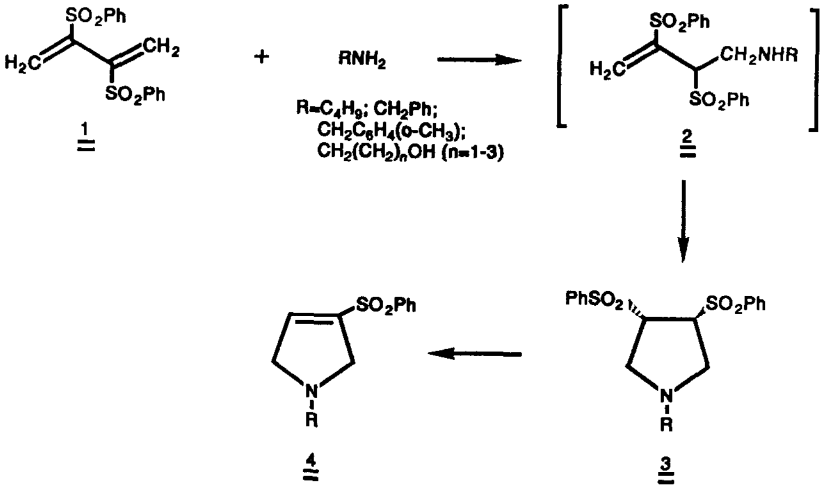
Abstract: The reaction of amines with 2,3-diphenylsulfonyl-1,3-butadiene produces 3-pyrrolines which are readily oxidized to 3-phenylsulfonyl pyrroles.

Five-membered nitrogen heterocycles constitute the central part of a large number of alkaloids.[1] Novel methodology for the general synthesis of pyrroles and pyrrolidines continues to receive significant attention. Particularly useful general approaches to these five-ring heterocycles are the intramolecular ene strategy developed by Oppolzer,[2] the electrophilic promoted cyclizations of unsaturated amine derivatives,[3] the 1,3-dipolar cycloaddition route,[4] the tandem cationic aza-Cope-Mannich cyclization synthesis of Overman[5] and the transition metal-catalyzed cyclization of unsaturated amines.[6] In connection with our ongoing synthetic program to develop new methods for alkaloid synthesis,[7] we thought it worthwhile to examine a route to 3-pyrrolines which involves a [4+1] annulation strategy.[8] The general synthetic approach is outlined in Scheme I. Successful application of this reaction to the synthesis of pyrrolidines where the product carries further functionality are rare. We report here on the reaction of 2,3-diphenylsulfonyl-1,3-butadiene[9] with various amines as a method for synthesizing these heterocycles in excellent yield.

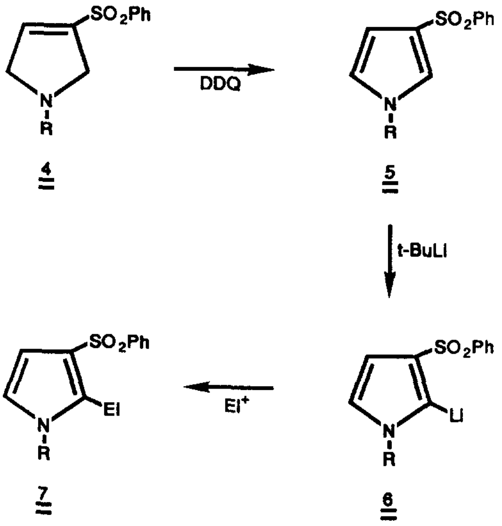
Scheme I



The importance of vinyl sulfones in organic synthesis is now well established.[10] Their diverse reactivity includes conjugate addition, cycloaddition and deprotonation reactions.[10] It seemed to us that 2,3-diphenylsulfonyl-1,3-butadiene (**1**) should be highly activated toward nucleophilic addition because of its markedly lowered LUMO energy level compared to butadiene. We have studied the reaction of **1** with various primary amines using a 1:1 methylene chloride-methanol mixture and found that pyrrolidine **3** was isolated as the exclusive product in 90% yield.[11] The formation of **3** proceeds through a two step sequence. The first step involves initial conjugate addition and this is followed by a 5-endo trig cyclization of the resulting amine onto the adjacent vinyl sulfone.[12] Pyrrolidine **3** undergoes ready elimination of phenyl sulfinic acid when treated with sodium methoxide to give the 3-pyrroline ring system in near quantitative yield.[13]

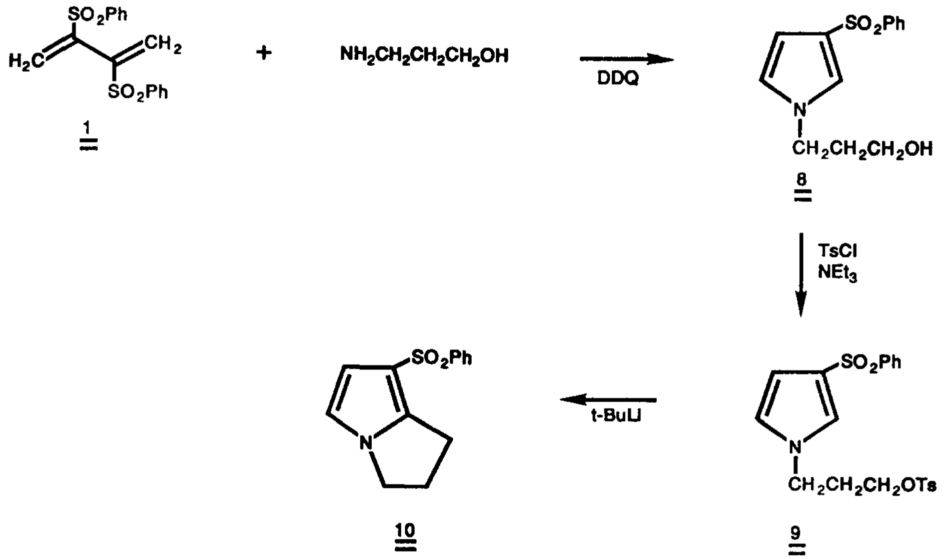


Heating a sample of pyrroline **4** in the presence of DDQ gave the expected pyrrole **5** in 80-95% yield. Heteroatom-facilitated ortho lithiation is a very popular and powerful technique which can lead to regiospecific attachment of an electrophile ortho to a heteroatom-containing substituent on an aromatic ring.[14] Recently some significant and creative applications of this methodology to the synthesis of several different classes of pyrroles have been reported.[15] We reasoned that under suitable conditions the sulfonyl group might stabilize an ortho lithium atom thus facilitating anion formation at the 2-position of the pyrrole ring.[16] Indeed, we found that adding 1.2 equiv of t-butyllithium in pentane to 1.0 equiv of pyrrole **5** in tetrahydrofuran readily generated the desired



carbanion. Quenching the lithiated pyrrole **6** with such electrophiles as methyl iodide, benzaldehyde, benzoyl chloride, dimethyl formamide and methyl acrylate led to 60-98% yields of isolated, purified 2,3-disubstituted pyrroles **7**. This sequence of reactions also allows for the synthesis of 2-substituted pyrroles since the phenylsulfonyl group can be readily removed by reductive methods.[10]

The ability of these 3-phenylsulfonyl pyrroles to undergo lithiation and subsequent alkylation in high yield suggested a facile synthesis of the pyrrolizidine pyrrole ring system. The process we envisioned and its successful implementation is outlined below. The sequence began by treating 3-aminopropanol with 2,3-diphenylsulfonyl-1,3-butadiene followed by a DDQ oxidation to give pyrrole **8**. This material was converted to the corresponding tosylate which was subjected to metallation using t-butyllithium to give **10** in 95% yield.[17]



In summary, 2,3-diphenylsulfonyl-1,3-butadiene is a useful synthetic reagent which undergoes a facile [4+1]-annulation reaction with primary amines to give 3-pyrrolines in excellent yield Other aspects of this reaction and its application to natural product synthesis will appear in forthcoming papers.

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References and Notes

1. A. R. Pinder in "The Alkaloids", M. F. Grundon, Ed.; Chemical Society: London, 1982, Vol. 12.
2. W. Oppolzer and V. Snieckus, **Angew. Chem. Int. Ed. Engl.** *17*, 376 (1978).

3. R. B. Webb and S. Danishefsky, **Tetrahedron Lett.** *1357* (1983); K. E. Harding and S. R. Burks, **J. Org. Chem.** *46*, 3920 (1981); D. L. Clive, V. Farina and A. Singh, **J. Org. Chem.** *45*, 2120 (1980).
4. P. N. Confalone and E. M. Huie, **J. Am. Chem. Soc.** *106*, 7175 (1984); T. Livinghouse and R. Smith, **J. Org. Chem.** *48*, 1554 (1983); E. Vedejs and F. G. West, **J. Org. Chem** *48*, 4773 (1983); R. Grigg, H. Q. Gunaratne and J. Kemp, **Tetrahedron Lett.** *99* (1984).
5. L. E. Overman, M. Kakimoto, M. E. Okazaki and G. P. Meier, **J. Am. Chem. Soc.** *105*, 6622 (1983).
6. B. M. Trost, **Pure Appl. Chem.** *53*, 2357 (1981); L. S. Hegedus, G. F. Allen, J. J. Bozell and E. L. Waterman, **J. Am. Chem. Soc.** *100*, 5800 (1978).
7. A. Padwa, M. Matzinger, Y. Tomioka and M. K. Venkatramanan, **J. Org. Chem.** *53*, 955 (1988); A. Padwa and W. Dent, **J. Org. Chem.** *52*, 235 (1987).
8. For an alternate [4+1]-annulation approach for pyrroline synthesis, see T. Hudlicky, J. O. Frazier and L. D. Kwart, **Tetrahedron Lett.** *3523* (1985); W. H. Pearson, J. E. Celebushi, Y. F. Poon, B. R. Dixon and J. H. Glans, **Tetrahedron Lett.** *6301* (1986).
9. W. H. Okamura and S. Jeganathan, **Tetrahedron Lett.** *4673* (1982).
10. P. D. Magnus, **Tetrahedron** *33*, 2019 (1977); T. Durstin, "Comprehensive Organic Chemistry", eds. D. R. R. Barton and W. D. Ollis, Pergmon, Oxford, Vol. 3, 1979, p. 197.
11. NMR **3** (R=n-C_4H_9) ($CDCl_3$, 300 MHz) δ 0.80 (t, 3H, J=7.0 Hz), 1.15 (m, 2H), 1.25 (m, 2H), 2.35 (m, 2H), 2.85 (dd, 2H, J=10.2 and 7.2 Hz), 3.03 (dd, 2H, J=10.2 and 4.2 Hz), 4.02 (m, 2H) and 7.50-7.95 (m, 10H); NMR **4** (R=n-C_4H_9) ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H, J=7.2 Hz), 1.15-1.33 (m, 4H), 2.46 (m, 2H), 3.51 (m, 2H), 3.55 (m, 2H), 6.65 (m, 1H) and 7.45-7.80 (m, 5H).
12. A very closely related reaction was recently reported to occur with α-(alkylaminoethyl)-acrylates, see B. Tarnchompoo, C. Thebtaranonth and Y. Thebtaranonth, **Tetrahedron Lett.** *6675* (1987).
13. The initially formed pyrrolidine **3** was also converted to 3-pyrroline **4** by further stirring with a slight excess of the primary amine.
14. H. W. Gschwend and H. R. Rodriguez, **Org. Reactions** *26*, 1 (1979).
15. R. J. Sundberg and H. F. Russell, **J. Org. Chem.** *38*, 3324 (1973); M. G. Saulnier and G. W. Gribble, **J. Org. Chem.** *47*, 757 (1982).
16. Recently, the 3-phenylsulfonyl group was found to direct metallation cleanly to the adjacent 2-position of furans, see G. D. Hartman and W. Halczenko, **Tetrahedron Lett.** *3241* (1987).
17. NMR **10** ($CDCl_3$, 300 MHz) δ 2.50 (m, 2H), 3.05 (t, 2H, J=7.4 Hz), 3.95 (t, 2H, J=7.2 Hz), 6.48 (d, 1H, J=2.9 Hz), 6.55 (d, 1H, J=2.9 Hz), 7.40-7.55 (m, 3H) and 7.90 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.7, 27.0, 47.1, 112.4, 112.4, 114.8, 115.6, 126.4, 128.8, 132.1, 141.6 and 144.2 ppm; mp 134-135°C.

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