An Anomalous Reaction of 2-Benzenesulfonyl-3-aryloxaziridines (Davis Reagents) with Indoles: Evidence for a Stepwise Reaction of the Davis Reagent with a π-Bond

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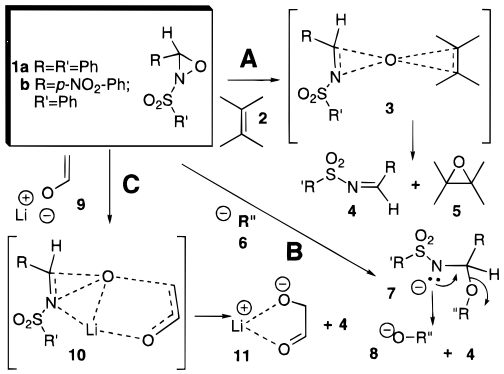
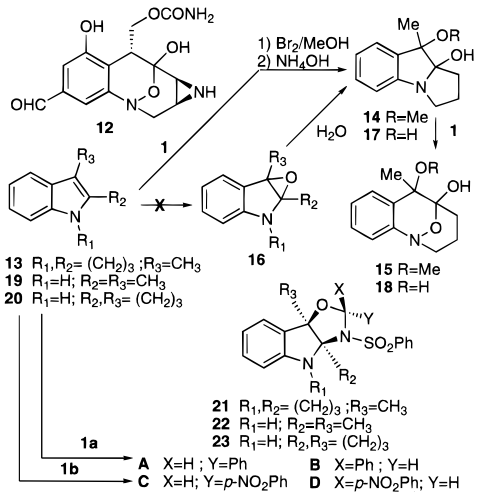
N-Sulfonyloxaziridines, **1**, have been shown to be versatile reagents for the oxygenation of a variety of organic functional groups.[1] The fact that such oxygenations can be performed with a high degree of asymmetric induction[2] has created considerable interest in the mechanism of the overall oxygen atom transfer process. Theoretical studies have led to the conclusion that, for neutral substrates such as sulfides[3a] and alkenes,[3b] the oxygenation process is a concerted S_N2-like reaction (mechanism A in Scheme 1) in which there is no intermediate and in which the substrate acts as a nucleophile and the *N*-sulfonylimine **4** acts as a leaving group. This direct oxygenation has been assumed to occur also in the reaction of *N*-sulfonyloxaziridines with tertiary amines to yield *N*-oxides,[4] with the π-bonds of TMS (trimethylsilyl) enol ethers to yield α-hydroxy ketones[5] and with the π-bonds of enamines to yield α-hydroxy and α-amino ketones.[6] For the hydroxylation of carbanions and enolates, a stepwise process involving a carbinolamine-like intermediate (**7**) which undergoes an elimination reaction to yield the oxygenated product **8** and the *N*-sulfonylimine **4** has been proposed (mechanism B).[7] More recently, however, Bach and co-workers[8] have proposed a concerted oxygen atom transfer mechanism for reactions with lithium enolates (mechanism C) based on *ab initio* calculations for the hypothetical reaction of the lithium enolate of acetaldehyde, **9**, with oxaziridine.

In connection with our interest in the total synthesis of antitumor antibiotic FR900482 (**12**),[9] we have reported an oxidative ring expansion of a model system (**14**) to yield **15** which incorporates the 1,5-epoxybenzazocine ring system present in **12**. The most efficient reagent for effecting this process was found to be *N*-(benzenesulfonyl)-3-phenyloxaziridine (**1a**). On the basis of the precedent outlined above, we expected that a pyrrolo[1,2-*a*]indole derivative such as **13** should react with the Davis reagent in the presence of water to yield the diol **17** via the epoxide **16**,[10,11] which should undergo oxidative ring expansion to **18** thus simplifying the transformation of pyrrolo[1,2-*a*]indoles into the FR900482 ring system.

Scheme 1



Scheme 2



We report herein, however, that the indole **13** reacts with **1a** to yield the unusual 1,3-oxazolidinoindole ring system **21** rather than the indole 2,3-epoxide **16** or derived products such as **17** or **18** and discuss the potential implications of these observations in the context of the oxidation of other electron rich systems by *N*-sulfonyloxaziridines (Scheme 2).

The diastereomeric adducts **21A** and **21B** were obtained in 71% isolated yield by reaction of **13** with **1a** in anhydrous or in 25% aqueous THF. The diastereomers were not readily separable chromatographically and were characterized by detailed spectroscopic analysis of the mixture.[12] That oxazolidine formation rather than monooxygenation was a general property of 2,3-dialkylindoles and was not exclusive to the pyrrolo[1,2-*a*]indole ring system was demonstrated by the observation that adducts similar to **21** were obtained upon reaction of **1a** with 2,3-dimethylindole (**19**) and 2,3-cyclopentanoindole (**20**). For the adducts **22A**/**22B**, it was possible to obtain a pure sample of one of the diastereomers by chromatography on silica gel. Single-crystal X-ray diffraction analysis established the structure of this diastereomer as **22A**.[13] Similarly, chromatography of the mixture of diastereomeric adducts **23A**/**23B** yielded a pure sample of one of the diastereomers shown to be **23B** by X-ray crystallography.[13]

(1) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
(2) (a) Davis, F. A.; Jenkins, R. H., Jr. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 4, pp 313−353. (b) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.
(3) (a) Bach, R. D.; Coddens, B. A.; McDouall, J. J. W.; Schlegel, H. B.; Davis, F. A. *J. Org. Chem.* **1990**, *55*, 3325. (b) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1410.
(4) Zajac, W. W., Jr.; Walters, T. R.; Darcey, M. G. *J. Org. Chem.* **1988**, *53*, 5856.
(5) Davis, F. A.; Sheppard, A. C. *J. Org. Chem.* **1987**, *52*, 954.
(6) Davis, F. A.; Sheppard, A. C. *Tetrahedron Lett.* **1988**, *29*, 4368.
(7) (a) Knipe, A. C.; McAuley, I. E.; Kansal, V. K. *Tetrahedron Lett.* **1984**, *25*, 1411. (b) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. (c) Davis, F. A.; Wei, J.; Sheppard, A. C.; Gubernick, S. *Tetrahedron Lett.* **1987**, *28*, 5115.
(8) Bach, R. D.; Anders, J. L.; Davis, F. A. *J. Org. Chem.* **1992**, *57*, 613.
(9) Dmitrienko G. I.; Denhart, D.; Mithani, S.; Prasad, G. K. B.; Taylor, N. J. *Tetrahedron Lett.* **1992**, *33*, 5705.
(10) For an example of an oxidation of a 1,2-dialkylindole with **1a** to yield a 2-hydroxyindol-3-one, see: Wang, Z.; Jimenez, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 4977.
(11) For studies of indole epoxides formed by reaction of indoles with dimethyldioxirane, see: (a) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867. (b) Adam, W.; Ahrweiler, M.; Peters, K.; Schiedeskamp, B. *J. Org. Chem.* **1994**, *59*, 2733 and references cited therein.
(12) HMQC, HMBC, selective TOCSY, and difference NOE NMR experiments allowed complete assignment of the ^{1}H and ^{13}C NMR signals of both diastereomers in this mixture.

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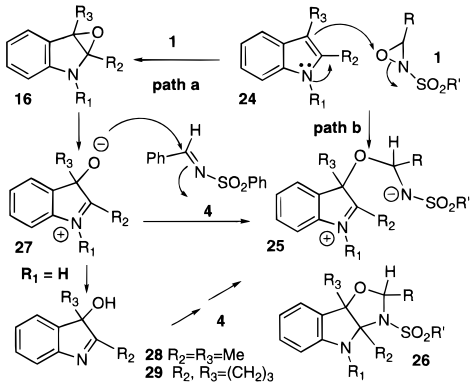
Scheme 3

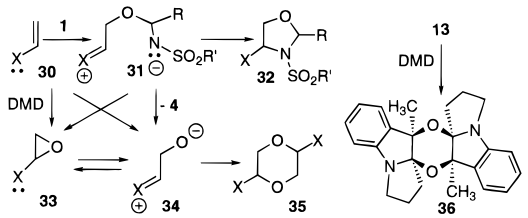


The simplest mechanistic interpretation of the formation of the indicated addition products was that shown in path b in Scheme 3 in which C-3 of the indole system **24** functions as a nucleophile to yield a zwitterionic intermediate (**25**) which cyclizes to give **26**. Knowledge of the extensive literature which suggested that the oxidative reactions of *N*-sulfonyloxaziridines involve direct oxygen atom transfer, however, caused us to consider alternative mechanisms for the formation of the observed adducts which did not involve an ionic intermediate such as **25** (path a). In particular, we considered the possibility that the reaction of **1a** with the indoles **13**, **20**, and **21** yielded the corresponding 2,3-epoxyindoles **16** which reacted subsequently with the imine **4** via the intermediates **27**, **28**, or **29** to produce the isolated 1,3-oxazolidines **26**.

In order to explore these mechanistic possibilities, we have reacted the indoles **13**, **20**, and **21** with 3-*p*-nitrophenyl-2-(benzenesulfonyl)oxaziridine (**1b**) to yield the corresponding diastereomeric mixtures of adducts **21C**/**21D**, **22C**/**22D**, and **23C**/**23D** and have carried out crossover experiments to test the possibility that these adducts are derived via the corresponding epoxyindoles. In particular, each of the indoles was reacted with the *N*-sulfonyloxaziridine **1a** in the presence of an equimolar amount of the *N*-sulfonylimine **4b** in THF solution at room temperature.[13] In each case, only the adduct obtained in the absence of the imine was observed and none of the nitro-substituted adducts was found. Essentially the same results were obtained when the imine **4b** was employed in a 10-fold molar excess. In parallel experiments in which each of the indoles was reacted with the nitro-substituted oxaziridine **1b** in the presence of the imine **4a**, only the adducts **21C**/**21D**, **22C**/**22D**, and **23C**/**23D** were observed. For 2,3-dimethylindole, it was also possible to demonstrate that the known 3-hydroxyindolenine (**28**, $R_2 = R_3 = CH_3$),[14] which could potentially be derived from the unstable epoxide **16** ($R_1 = H$; $R_2 = R_3 = CH_3$), was not an intermediate in the formation of the adducts **22A**/**22B** since no reaction was observed between equimolar amounts of the imine **1a** and **28**.

These observations represent the first convincing demonstration that *N*-sulfonyloxaziridines can react with nucleophilic π-bonds via a pathway other than direct oxygen atom transfer. Although our data do not demand a zwitterionic intermediate, the regioselectivity of these reactions is entirely consistent with a mechanism involving nucleophilic attack of the indole π-bond at the oxygen atom of the oxaziridine resulting in rupture of the O−N bond followed by intramolecular nucleophilic addition of the sulfonamido anion to the electron deficient carbon atom of the iminium bond of this intermediate.[15] It is reasonable to argue further that other electron rich olefins, especially enamines, which are more nucleophilic than indoles, may react in an analogous fashion. For enamines, the failure to detect either oxazolidines (**32**, X = NR_2) or oxiranes (**33**, X = NR_2) in the reaction with Davis reagents[6] may reflect the greater ability of the nitrogen lone pair electrons in enamines to stabilize a carbocation at the α-carbon, as in **31** and **34**, as compared with the ability of the lone pair electrons in indole systems to stabilize C-2 carbocations, as in **25**. The tendency of zwitterions such as **31** and **34** to collapse to the ring-closed forms **32** and **33**, respectively, may be relatively low (Scheme 4). Interestingly, in the reaction of *N*,*N*-dialkylenamines with dimethyldioxirane (DMD) under anhydrous conditions, oxiranes could not be detected spectroscopically even at low temperatures.[17] Instead, the stable dioxanes **35** (X = NR_2) were isolated. No such products have been reported in the oxidation of enamines with Davis reagents,[6] arguing against a common oxirane intermediate in the two oxidation processes. In parallel with these observations, we have found that the dioxane **36** analogous to **35** is formed in the reaction of **13** with DMD but is not observed in the reaction of **13** with Davis reagents.[21]

Scheme 4



In general, we feel that the reactions of oxaziridines with π-bonds may span a spectrum of mechanistic possibilities with the direct oxygen atom transfer and the zwitterionic pathways representing extremes. Experiments aimed at detecting the ionic intermediates in these reactions and theoretical studies including the essential electron-withdrawing *N*-sulfonyl substituent will be required to fully define these mechanistic possibilities.

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Supporting Information Available: Complete experimental details for all reactions and full X-ray data for compounds **22A**, **23B**, and **36** are provided (43 pages). See any current masthead page for ordering and Internet access instructions.

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(13) Full experimental details and X-ray data are provided in the Supporting Information.

(14) (a) Beer, S.; Donavanik, T.; Robertson, A. *J. Chem. Soc.* **1954**, 4139. (b) Berti, G.; Da Settimo, A.; Di Colo, G.; Nannipieri, E. *J. Chem. Soc. C* **1969**, 2703. (c) McLean, S.; Dmitrienko, G. I. *Can. J. Chem.* **1971**, *49*, 3642.

(15) Electron deficient, but not electron rich, olefins react with perfluoro-2-methyloxaziridine to yield oxazolidines in a process believed to involve diradical intermediates.[16] The fact that the oxazolidine formation observed in the present study involves the reaction of **1** with electron rich π-bonds argues in favor of a zwitterionic intermediate rather than a diradical one in these reactions. Our data do not, however, specifically exclude the possibility of involvement of diradicals.

(16) O'Brien, B. A.; Lam, W. Y.; DesMarteau, D. D. *J. Org. Chem.* **1986**, *51*, 4466.

(17) (a) Adam, W.; Peters, E.-M.; Peters, P.; von Schnering, H. G.; Voerckel, V. *Chem. Ber.* **1992**, *125*, 1263. (b) Isolated examples of enamine epoxides are known in which the nitrogen-assisted ring opening is sufficiently diminished by *N*,*N*-bis-silylation,[18] by incorporation of the nitrogen atom in an aziridine ring,[19] or by attachment of an electron-withdrawing group to the π-bond[20] to allow for spectroscopic detection at low temperature[18] or for isolation.[19,20]

(18) Adam, W.; Ahrweiler, M.; Paulini, K.; Reissig, H.-U.; Voerckel, V. *Chem. Ber.* **1992**, *125*, 2719.

(19) Stevens, C. L.; Pillai, P. M. *J. Am. Chem. Soc.* **1967**, *89*, 3084.

(20) Wasserman, H. H.; Frechette, R.; Rotello, V. M.; Schulte, G. *Tetrahedron Lett.* **1991**, *32*, 7571.

(21) This oxidation also produced a stereoisomer of **36** and two other dimers, analogous to the known dimeric autoxidation product of 2,3-dimethylindole,[14b,c] formed by condensation of **27** (R_1, $R_2 = (CH_2)_3$; $R_3 = CH_3$) with the enamine derived therefrom. For X-ray crystallographic data for **36** and a full experimental description, see the Supporting Information.