# Preparation of Fused Aziridines by Intramolecular Cycloaddition

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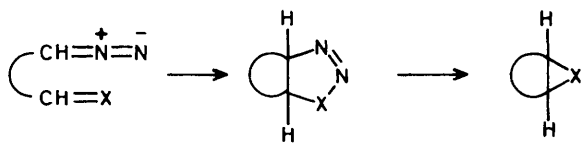
Heating the sodium salts of the tosylhydrazones (**3**) and (**7**) in boiling benzene gives fused aziridines (**4**) and (**8**) by a novel intramolecular cycloaddition to an oxime C=N bond.

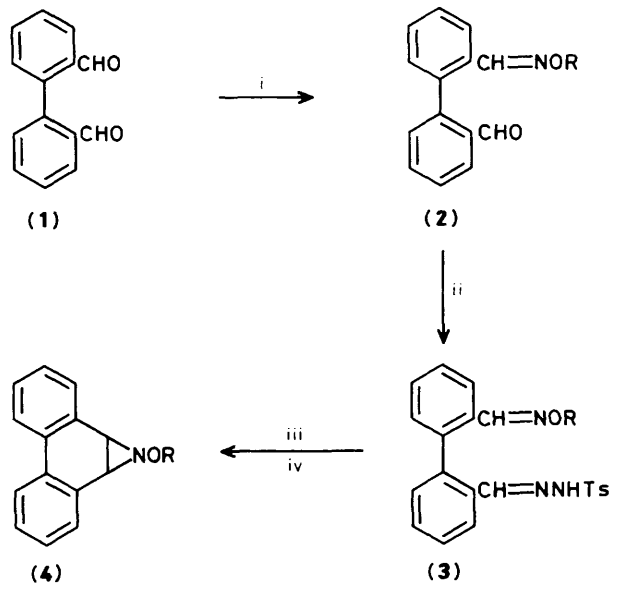
The chemistry of aziridines is dominated by their ring-opening reactions; this makes them versatile intermediates in the synthesis of various nitrogen-containing compounds,[1,2] and also accounts for the fact that many aziridines are biological alkylating agents.[1] If the aziridine ring is further strained by fusion to another ring, then the ring opening is often greatly facilitated; fused aziridines have been prepared by conventional routes from cyclic alkenes,[1,2] and, more recently, by intramolecular cycloaddition of nitrenes to C=C bonds.[3] We now report a new route to fused aziridines based on the previously unreported intramolecular cycloaddition of diazo compounds to oxime C=N bonds.

The use of intramolecular cycloaddition reactions to prepare polycyclic systems has become increasingly popular in recent years, and in this respect the intramolecular reaction of diazo compounds with alkenes (Scheme 1; X = $CR_2$) has been studied.[4] The reaction gives fused cyclopropanes,[5] either by way of an intermediate [3 + 2] cycloadduct pyrazoline, or, depending on the reaction conditions, by intramolecular addition of the derived carbene to the C=C bond. The corresponding route to fused aziridines (Scheme 1; X = NR) has not been firmly established;† indeed the formation of simple aziridines, either directly or indirectly *via* 1,2,3-triazolines, by *inter*molecular cycloaddition of neutral C=N bonds to carbenes or diazo compounds, is rare.[2,7,8] To investigate this new type of intramolecular cycloaddition reaction, we initially chose a relatively simple substrate (**3**), easily derived from biphenyl-2,2'-dicarbaldehyde (**1**). Reaction of the dialdehyde (**1**)[9] with *O*-methylhydroxylamine hydrochloride in pyridine in the presence of 4 Å molecular sieves gave the mono-*O*-

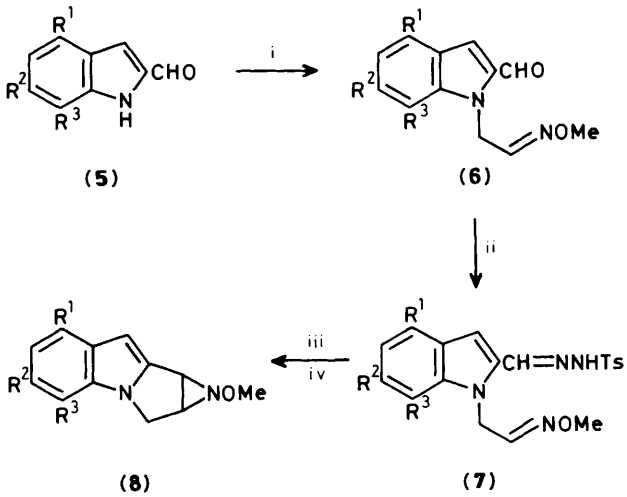



**Scheme 1**

† The intramolecular cycloaddition of a diazoalkane to an imine has been suggested as one of the possible mechanisms to explain the formation of a *minor* product in the thermolysis of 3-methoxycarbonyl-3,4,5-triazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene.[6]




**Scheme 2, a**, R = Me; **b**, R = $CH_2Ph$. *Reagents and conditions:* i, $RONH_3Cl$, pyridine, 4 Å molecular sieves; ii, $TsNHNH_2$, MeOH; iii, NaH, THF; iv, heat, benzene.




**Scheme 3, a**, $R^1 = R^2 = R^3 = H$; **b**, $R^1$ = Br, $R^2$ = OMe, $R^3 = OCH_2Ph$. *Reagents and conditions:* i, $MeON{=}CHCH_2Cl$, DMF, NaH; ii, $TsNHNH_2$, MeOH; iii, NaH, THF; iv, heat, benzene.

methyloxime (**2a**) (71%), condensation of which with toluene-4-sulphonohydrazide ($TsNHNH_2$) gave the required tosylhydrazone (**3a**)‡ (94%) (Scheme 2). The *O*-benzyl derivative (**3b**) was similarly prepared. Thermolysis of the sodium salts of the tosylhydrazones (**3**), formed by reaction with sodium hydride in tetrahydrofuran (THF), in boiling benzene gave the aziridinophenanthrenes (**4a**), m.p. 80—81 °C, and (**4b**), m.p. 65—66 °C, in 80 and 72% yield, respectively, with no evidence for any intermediate [3 + 2] cycloadduct. Although the aziridinophenanthrene ring system has been prepared previously from phenanthrene by conventional routes,[10] the present route demonstrates the viability of intramolecular cycloaddition of diazo compounds to C=N bonds.

This novel cycloaddition clearly has considerable potential as a route to the fused aziridine system of the mitomycin and mitosene antitumour antibiotics, and therefore we prepared the indole-based tosylhydrazones (**7**) (Scheme 3). Thus a mixture of indole-2-carbaldehyde (**5a**) and chloroacetaldehyde *O*-methyloxime[11] in dimethylformamide (DMF) was treated with sodium hydride to give the oxime (**6a**) (79%). Reaction of (**6a**) with $TsNHNH_2$ gave the tosylhydrazone (**7a**) (97%), decomposition of which under the usual conditions gave the desired aziridinopyrrolo[1,2-*a*]indole§ (**8a**) (61%), m.p. 97—97.5 °C. When the tosylhydrazone sodium salt was decomposed in boiling chlorobenzene, the yield of (**8a**) was increased to 73%. Similarly, the more highly substituted indole-2-carbaldehyde (**5b**)[12] was converted into the corresponding aziridinopyrrolo[1,2-*a*]indole (**8b**), m.p. 112 °C, the yield in the key intramolecular cycloaddition step being 64%.

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## References

1 O. C. Dermer and G. E. Ham, 'Ethyleneimine and Other Aziridines,' Academic Press, New York, 1969.
2 A. Padwa and A. D. Woolhouse, in 'Comprehensive Heterocyclic Chemistry,' eds. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 5, p. 47.
3 R. S. Atkinson and M. J. Grimshire, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1135.
4 A. Padwa in '1,3-Dipolar Cycloaddition Chemistry,' ed. A. Padwa, Wiley Interscience, New York, 1984, vol. 2, p. 277.
5 For a recent example, see: G. B. Jones and C. J. Moody. *J. Chem. Soc., Chem. Commun.*, 1988, 166.
6 A. C. Oehlschlager, R. S. McDaniel, A. Thakore, P. Tillman, and L. H. Zalkow, *Can. J. Chem.*, 1969, **47**, 4367.
7 M. Regitz and H. Heydt, in '1,3-Dipolar Cycloaddition Chemistry,' ed. A. Padwa, Wiley Interscience, New York, 1984, vol. 1, p. 393.
8 P. K. Kadaba, B. Stanovnik, and M. Tisler, *Adv. Heterocycl. Chem.*, 1984, **37**, 217.
9 P. S. Bailey and R. E. Erickson, *Org. Synth.*, 1961, **41**, 41.
10 For example, see: Y. Ittah, Y. Sasson, I. Shahak, S. Tsaroom, and J. Blum, *J. Org. Chem.*, 1978, **43**, 4271.
11 L. J. Stach, U.S. Pat. 3920772/1975.
12 R. E. Bolton, C. J. Moody, C. W. Rees, and G. Tojo, *J. Chem. Soc., Perkin Trans. 1*, 1987, 931.

‡ Satisfactory spectroscopic and analytical data were obtained for all new compounds.

§ $\delta_H$ (250 MHz; $CDCl_3$) 3.56 (2H, m), 3.64 (3H, s), 4.16 (1H, dd, *J* 12 and 4 Hz), 4.28 (1H, d, *J* 12 Hz), 6.46 (1H, s), 7.03—7.18 (3H, m), and 7.57 (1H, d, *J* 9 Hz); *m/z* (70 eV; 140 °C) 200 ($M^+$, 74%), 169 (100), and 155 (89). The structure was confirmed by *X*-ray crystallography, which showed that, in the crystalline state, the aziridine existed as a single invertomer with the methoxy group *cis* to the ring junction protons. Details will be published separately. We thank Dr. D. J. Williams for this result.