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Diastereoselective Cycloadditions Involving Methyleneaziridines: Reactions with Tetracyanoethylene

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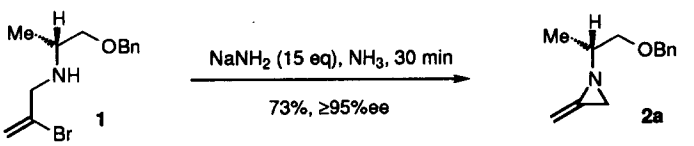
Abstract: 2-Methyleneaziridines **2a-e** containing a stereogenic centre on the *N*-substitutent undergo [2π+2π] cycloadditions with tetracyanoethylene to produce diastereomeric 5-azaspiro[3.2]hexanes **3a-e** and **4a-e** in moderate to good yields (32-82%). The diastereoselectivity of these cycloadditions (12-68% de) is shown to be dependent on the nature of the *N*-substitutent. The structure of 5-azaspiro[3.2]hexane **4a** has been unambiguously determined by X-ray crystallography.

Methyleneaziridines are small but densely functionalised heterocycles[2] which can be readily prepared by sodium amide induced cyclisation of the corresponding *N*-(2-bromoallyl)alkylamines.[3,4] We have recently used this chemistry to prepare a variety of chiral, nonracemic methyleneaziridines derived from chiral, nonracemic β-amino alcohols without racemisation at the adjacent stereogenic centre.[5] For example, vinyl bromide **1** can be transformed into homochiral methyleneaziridine **2a** in 73% yield (Scheme 1). As part of our ongoing studies to develop methyleneaziridines as useful intermediates for organic synthesis,[6] we wished to ascertain if the stereogenic centre in such systems could be used to exert any diastereocontrol on subsequent reactions of the methyleneaziridine ring system.



Scheme 1

Cookson *et al.* have shown that *N*-ethyl methyleneaziridine reacts with tetracyanoethylene (TCNE) to give 1,1,2,2-tetracyano-5-ethyl-5-azaspiro[3.2]hexane as a result of an intermolecular [2π+2π] cycloaddition across the double bond of the methyleneaziridine ring.[7] We have determined that thermolysis of methyleneaziridines **2a-2e**[8] with TCNE in refluxing acetone resulted in the formation of the corresponding 5-azaspiro[3.2]hexanes **3a-e** and **4a-e** (Scheme 2).[9] While the efficiency of all these cycloadditions is good as judged by ^{1}H NMR spectroscopy, modest isolated yields were obtained in some cases because of degradation of the highly strained 5-azaspiro[3.2]hexane products upon silica gel chromatography. In all cases, both possible diastereomeric cycloadducts were produced, the relative amounts of the two components was determined by analysis prior to purification (Table 1).

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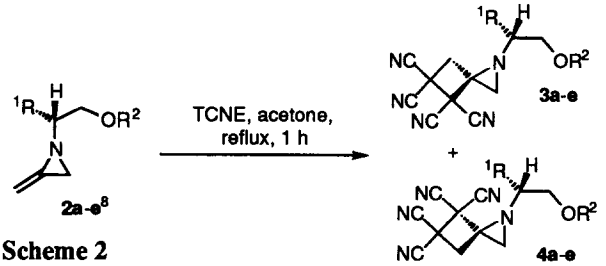
Our results suggest that stereochemical information contained within the *N*-substituent can be used to control the diastereoselectivity of these cycloaddition reactions and that the exact nature of the substituent impacts upon the level of diastereocontrol (12-68% de). Increasing the size of the R^1 substituent appears to improve the diastereoselectivity (Entries 1-3), although low selectivity was observed when R^1 = Ph (Entry 4). In the case of the TCNE cycloaddition of methyleneaziridine **2a**, we have unambiguously determined the relative stereochemistry of the minor cycloadduct **4a** by single crystal X-ray analysis (Figure 1).[10] Efforts to understand the stereochemical outcome of these reactions are complicated by the fact that **2a-e** exist as two diastereomeric nitrogen invertomers in solution. Low temperature ^{1}H NMR studies using **2a** indicate that these invertomers exist in near equal quantities (*ca* 54:46). The coalescence temperature has been determined to be approximately -50°C. Further work to explore the origins of the diastereoselectivity in these reactions, and to develop other cycloaddition chemistry of methyleneaziridines is ongoing and will be disclosed in due course.



Scheme 2

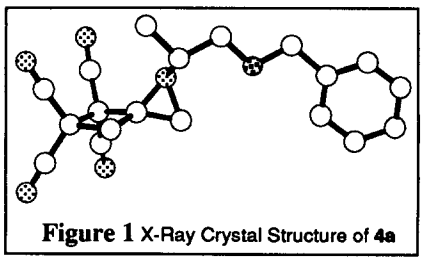


Figure 1 X-Ray Crystal Structure of **4a**

Entry	Methyleneaziridine	Isolated Yield[§]	Product Ratio[¶]
1	**2a** (R^1 = Me; R^2 = Bn)	82%	73 : 27 (**3a** : **4a**)
2	**2b** (R^1 = ^{i}Pr; R^2 = Bn)	48%	81 : 19 (**3b** : **4b**)[#]
3	**2c** (R^1 = ^{i}Bu; R^2 = Bn)	79%	84 : 16 (**3c** : **4c**)[#]
4	**2d** (R^1 = Ph; R^2 = Bn)	32%	63 : 37[†]
5	**2e** (R^1 = ^{i}Pr; R^2 = Si^{t}BuPh$_2$)	48%	56 : 44[†]

Table 1. [§] Isolated yields after column chromatography on silica gel. [¶] Determined by ^{1}H NMR analysis of the crude products. [#] Configuration of major diastereomer tentatively assigned by ^{1}H NMR shift comparisons with **3a** and **4a**. [†] Relative stereochemistry within the two cycloadducts could not be determined.

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REFERENCES & NOTES

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8. For clarity, all methyleneaziridines (and cycloadducts) are shown possessing the (*R*)-configuration of the *N*-substituent. In fact, these studies were performed using (*R*)-**2a**; (±)-**2b**; (*S*)-**2c**; (*R*)-**2d**; (±)-**2e**. All the cycloadducts are shown with correct relative configurations.
9. All new compounds gave satisfactory spectroscopic and high resolution mass spectral data.
10. The refined atomic coordinates for this structure have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.