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The preparation and cycloaddition reactions of new imidazoline nitrones are described. The imidazo[1,2-*b*]isoxazole alkene cycloadducts are formed *via* an *exo* approach. An example has been transformed into a pyrrolo[1,2-*a*]imidazole as a prelude to a new pyrrolidine synthesis.

J. Heterocyclic Chem., **37**, 481 (2000).

Introduction.

1,3-Dipolar cycloadditions offer routes to a wide range of heterocyclic targets with multiple stereogenic centres. Their utility depends largely on the potential for asymmetric induction *via* their highly ordered transition states. As part of an ongoing programme to develop chiral non-racemic heterocycloaddition reagents based on the imidazoline moiety [1-3], we have prepared the imidazoline nitrones **2** which are facially differentiated by virtue of the chiral templating nitron *N*-substituent being constrained within a heterocyclic ring.

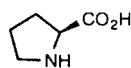
This lecture will present the context and background to our work, as an extension of our earlier synthesis of imidazolinium ylides **1** and their application to the assembly of homochiral pyrrolidines. We will describe an initial

unsuccessful approach to the key intermediate *N*-(2-aminoethyl)hydroxylamine **3**, based on 2-phenylglycine, that was thwarted by easy oxidation of the hydroxylamine, and then our successful synthesis from 2-chloroacetophenone.

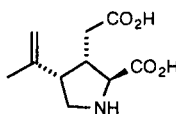
The results of cycloaddition studies will then be outlined. Alkyne dipolarophiles gave cycloadducts that underwent subsequent ring transformations. Electron-deficient alkene dipolarophiles did afford the expected (but rarely reported) imidazo[1,2-*b*]isoxazoles *via* an *exo* mode of approach to the dipole; the predominant regiochemistry favoured the dipolarophile activating group leading to 4-substitution in the isoxazolidine portion. The dimethyl 1,4-butyndioate cycloadduct has been transformed into a pyrrolo[1,2-*a*]imidazole by N-O cleavage and recyclisation, which opens a new and diastereoselective route to pyrrolidines.

1. Pyrrolidines and piperidines are important.

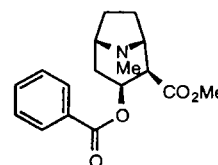
- For example, some biologically active natural products:



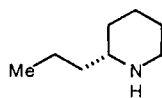
Proline



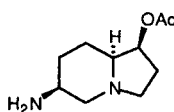
Kainic Acid



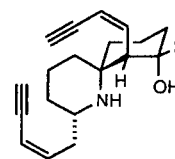
Cocaine



(-)-Coniine

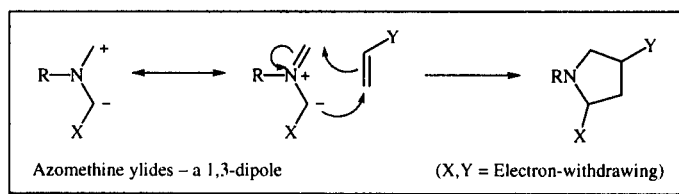


Slaframine

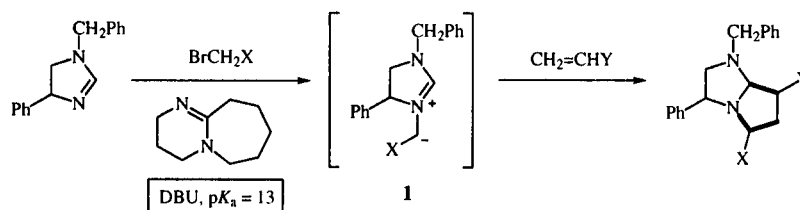


Histronicotxin

2. Five-membered rings by azomethine ylide cycloaddition.

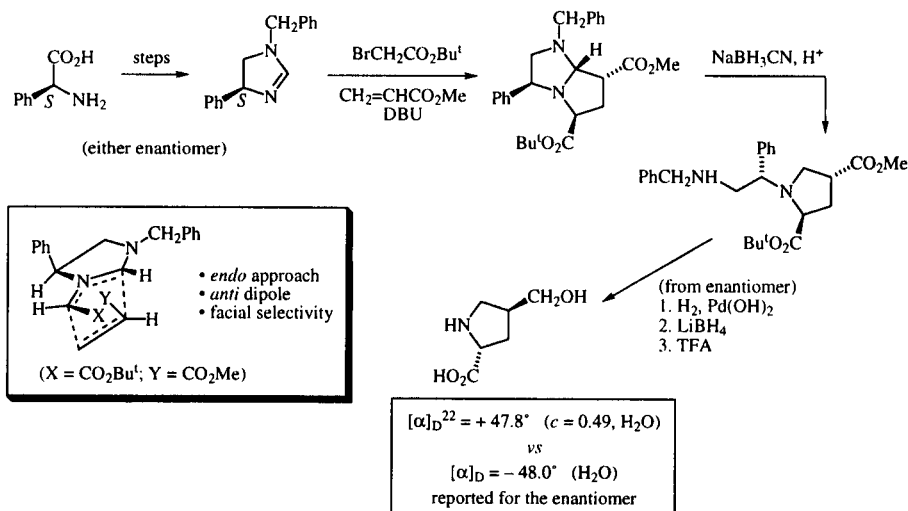


- Homochiral R substituent employed to induce asymmetry in the pyrrolidine.
- We use a 2-imidazoline as the template for the optically active dipole.

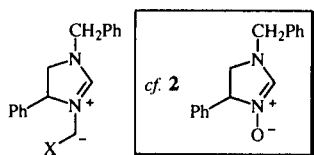


- Three (out of five) bonds of the new 5-membered ring (as indicated) are formed in one-pot.

3. Optically active pyrrolidines.



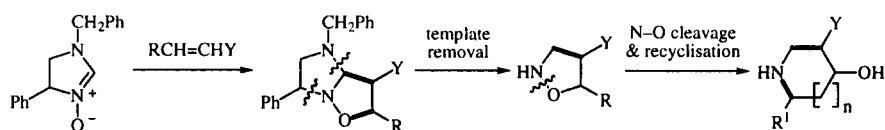
4. A chiral nitron 1,3-dipole?



Issues to consider

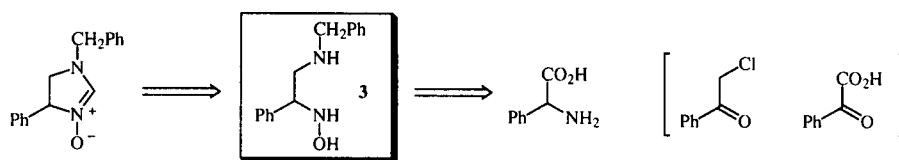
- Availability of the nitron?
- Reactivity of the imidazoline nitron?
- Regiochemistry of the cycloadditions?
- *endo* vs. *exo* Approach of dipole and dipolarophile?
- Facial selectivity of the dipole?
- Template removal from the cycloadducts?

- The proposed N–O cleavage/recyclisation strategy for use of the imidazole[1,2-*b*]isoxazole cycloadducts:

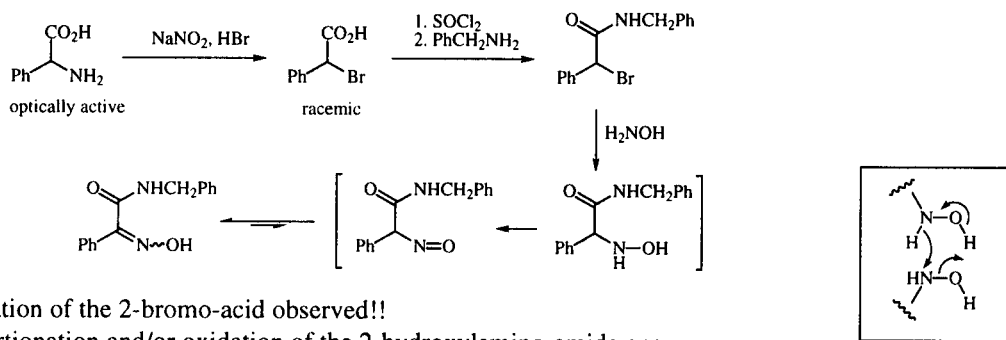


5. Retrosynthesis - precursors.

- Direct oxidation of 2-imidazoline unsuccessful.
- 2-Hydroxylamino-amine **3** as key precursor.
- Original plan: to use phenylglycine as precursor.
- Other possible "PhCC" precursors: 2-chloroacetophenone or benzoylformic acid.

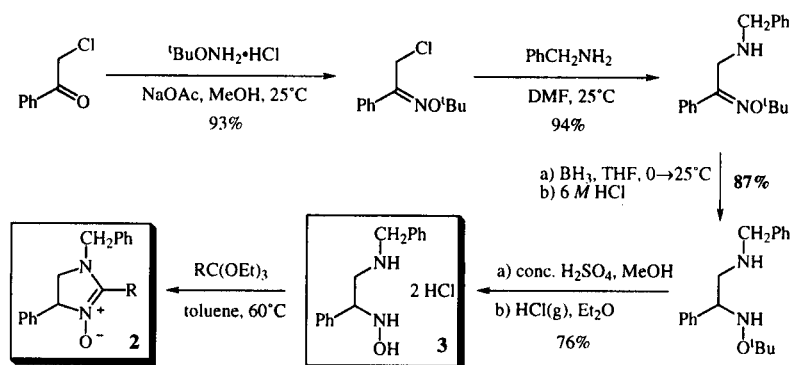


6. From phenylglycine?

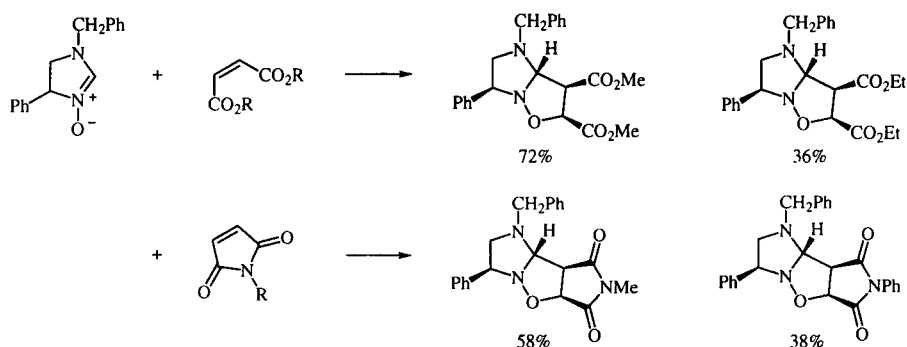


- Racemization of the 2-bromo-acid observed!!
- Disproportionation and/or oxidation of the 2-hydroxylamino-amide occurs.
- Alternative substitution by H₂NOCH₂Ph *very* slow.

7. Nitrones from 2-chloracetophenone.

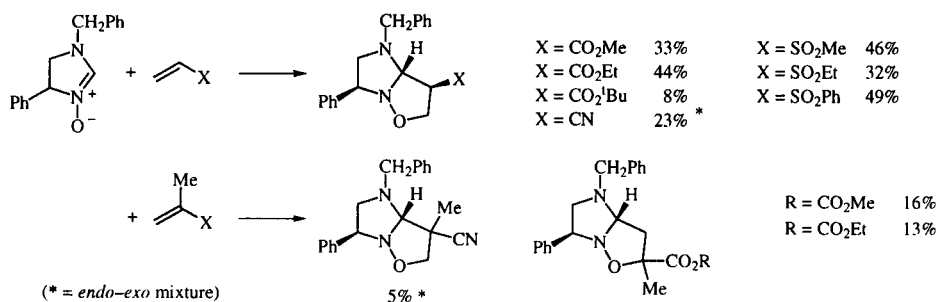


10. Reactions with alkene dipolarophiles (ii): Symmetrical alkenes.



11. Reactions with alkene dipolarophiles (iii): Unsymmetrical monosubstituted alkenes.

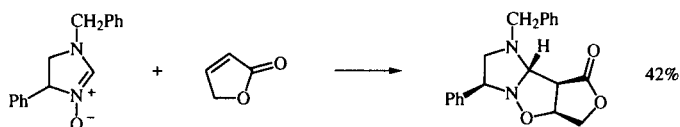
- Regiochemistry: Usually 4-substituted isoxazolidines;
Consistent with FMO control: HOMO(dipole)-LUMO(dipolarophile); Sustmann Type I,
Methacrylate esters give 5-substituted isoxazolidines; now steric control?



- Reactions are with electron-deficient alkenes; no cycloadditions seen with electron-rich alkenes.

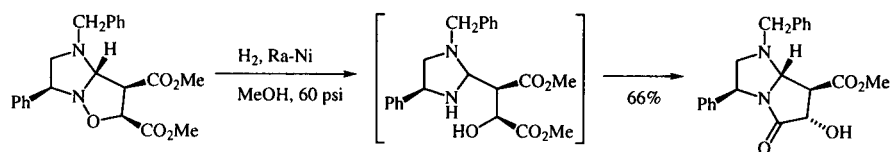
12. Reactions with alkene dipolarophiles (iv): An unsymmetrical 1,2-disubstituted alkene.

- 2(5*H*)-Furanone: An unsymmetrical 1,2-difunctional dipolarophile;
Potential for N—O cleavage and recyclisation?

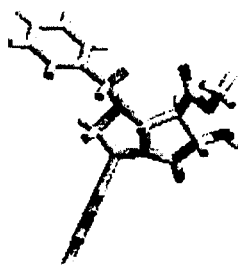


13. Template removal.

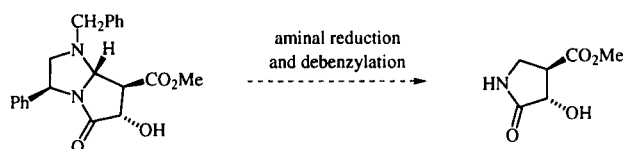
- Using 4,5-difunctional isoxazolidines, a pyrrolo[1,2-*a*]imidazole lactam has been prepared:



- X-Ray crystal structure of lactam confirms stereochemistry conserved.



- Template removal, as in the azomethine ylide work (see earlier, [1-3]), should lead to pyrrolidinones.



Conclusions.

We thus have developed a new chiral nitrene **2**, based on the imidazoline system, and explored its reactivity with a view to generating a new stereoselective route to pyrrolidines. The primary cycloadducts are imidazo[1,2-*a*]-isoxazoles, a largely unexplored ring system.

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- EPSRC National Mass Spectroscopy Service, Swansea

REFERENCES AND NOTES

- [1] R. C. F. Jones, K. J. Howard and J. S. Snaith, *Tetrahedron Letters*, **37**, 1707 (1996); R. C. F. Jones, K. J. Howard and J. S. Snaith, *Tetrahedron Letters*, **37**, 1711 (1996).
- [2] R. C. F. Jones, K. J. Howard and J. S. Snaith, *Tetrahedron Letters*, **38**, 1647 (1997).
- [3] R. C. F. Jones, K. J. Howard, J. R. Nichols and J. S. Snaith, *J. Chem. Soc., Perkin Trans. 1*, 2061 (1998).