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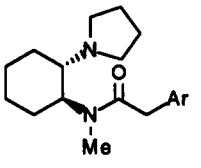
Unusual Chemo- and Stereoselectivity in the Addition of Chiral Aminoalcohols to Achiral Nitroalkenes

Michelle L. Morris, Michael A. Sturgess*
Dept. of Chemistry and Biochemistry, Univ. of Arkansas, Fayetteville AR 72701.

Abstract: Chiral aminoalcohols react with achiral nitroalkenes in a highly chemoselective manner depending on the aminoalcohol. Under optimum conditions, the addition reaction is almost stereospecific.

Keywords: Chiral amines, achiral nitroalkenes, facial selectivity, H-bonding.

Nitroalkenes have commonly been employed in the preparation of functionalized amines via the Michael addition of nucleophiles to the conjugated π-system, followed by reduction of the nitro unit to yield a functionalized primary amine. This approach has been applied to a wide range of species including aminosugars, aminoalcohols and diamines.[1] However, in such cases the facial selectivity of the initial conjugate addition was substrate controlled and was quite variable.[1c] In addition, the resulting nitronate anion was often quenched to give a mixture of products, which on standing or reduction readily interconverted leading to complex mixtures[2] of polar species which were difficult to separate. Although exceptions have been found wherein the thermodynamic product greatly predominated in the product mixture, or where the kinetic reduction product was the predominant species, in many cases such an addition/reduction process is not compatible with the stereochemical demands of modern synthetic chemistry.



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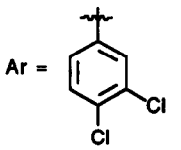
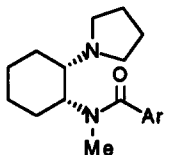




2

We have sought to understand the nature of intermolecular interactions involving nitroalkenes and nitroalkanes such that these factors may be utilized to control the relative stereochemistry of the reactions of such species, and also the absolute stereochemistry of the initial addition and the subsequent intermediates. Kinetic addition of amines to β-nitrostyrene results primarily in the *erythro* adduct, whilst the *threo* adduct is favored in the thermodynamic product mixture.[2] Corey has also noted the kinetic *cis* addition of ammonia to cyclic nitroalkenes, followed by slow equilibration to the thermodynamically preferred *trans* adducts.[3] We sought to investigate the influence of the structure of the amine(reagent) on the stereochemistry of addition to nitroalkanes with the goal of identifying those factors which may be employed to design an efficient asymmetric variant. Such a process would have tremendous potential in the preparation of analogs of the highly potent opioid κ and σ receptor antagonists **1**[4] and **2**.[5] Thus, while achiral nucleophiles had been partially explored, simple achiral amines had not been investigated.

Monofunctional amines 3-5 were expected to exhibit modest facial selectivity in the Michael addition to 1-nitrocyclohexene 6, based purely upon steric interactions (Table 1). Clearly minor steric interactions are insufficient at room temperature to efficiently direct the approaching nucleophile to one face of the π-system. Additionally once the attacking nucleophile is prevented from readily approaching the β-carbon, attack at the γ-protons becomes a relatively favorable pathway leading to competitive deprotonation. In all of these cases the nucleophilic addition was slow, and the observed selectivity was based upon slowing the rate of addition to the undesired face of the nitroalkene. Under such conditions the competing deprotonation will always be problematic. Accordingly we decided to investigate systems whereby approach to one face of the nitroalkene was highly favored by factors which ACCELERATED rather than RETARDED the reaction. We anticipated that H-bonding to the nitroalkene would reduce the electron density on the β-carbon leading to enhanced rates of addition, provided that the nucleophile was not similarly H-bonded. Such a scenario may be realized by the addition of 1,2-aminoalcohols since internal H-bonding within the nucleophile would be highly disfavored by geometric constraints. We chose as substrates the aminoalcohols 9-13 (Table 2). These amines may be divided into three categories; (1) those that do not react with 6 at room temperature, 9, (2) those that predominantly promote γ-deprotonation, 10 and 11, and, (3) those which cleanly add to the nitroalkene, 12 and 13.

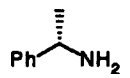
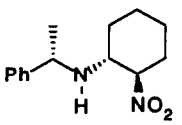
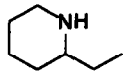
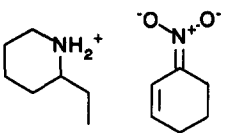
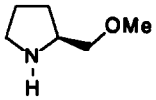
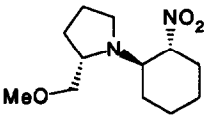
Entry	Amine	Result	Facial Selectivity	Rel. Time[6]	Product[7]	Yield(%)
1	 3	Add^{n}.	3 : 1 (trans : cis = 8 : 1)	40	 7	77
2	 4	Deprot^{n}.	-----	400		100
3	 5	Add^{n}.	2.5 : 1 (trans : cis = 7 : 1)	4	 8	76

Table 1

Reaction of aminoalcohols 10-13 with 6 was significantly faster than recorded for the simple amines 3-5, in this respect our concept may be regarded as successful. However, the chemoselectivity of these amines raises concerns as to the structural features necessary for clean asymmetric addition. We were particularly interested in the stereospecific addition of 13. The addition of 13 to 1-nitroalkenes 16 and 18[8] at room temperature yielded adducts 20(2:1) and 21(2:1) respectively as mixtures of diastereomers. Conversely addition of 13 to the 2-nitroalk-2-enes 17 and 19 appears to give predominantly one diastereomer(>10:1) as judged by 500MHz ^{1}H NMR. However, both adducts are unstable and have not yet been cleanly isolated. Reduction of 15 with samarium diiodide[9,10] gave diamine 22(95%). Recrystallization of the hydrogen iodide

salt of 22 allowed a crystallographic assignment of the stereochemistry of adduct 15. Both 15 and 22 exhibited ^{1}H NMR patterns for C_1 and C_2 of the cyclohexyl ring characteristic of a 1,2-*trans* diequatorial array of substituents. The crystal structure indicates that addition occurred to the *re*-face of the nitroalkene with concomitant cis proton transfer. By analogy the stereochemistry of the newly formed amine center of 14, 20 and 21 is R.

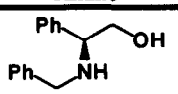
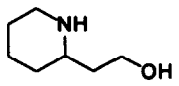
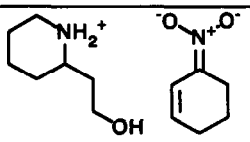
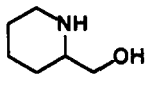
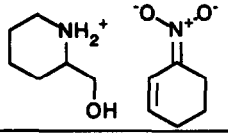
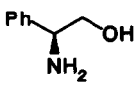
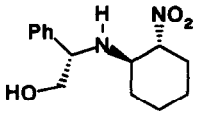
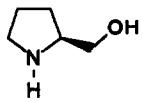
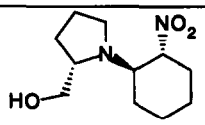
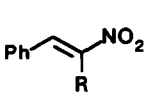
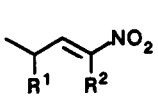
Entry	Amine	Result	Facial Selectivity	Rel. Time[7]	Product[8]	Yield(%)
1	 9	No Rxn	-----	-----	-----	-----
2	 10	Deprot^n.	-----	43		100
3	 11	Deprot^n.	-----	48		100
4	 12	Add^n.	2 : 1 (trans : cis 6 : 1)	10	 14	48
5	 13	Add^n.	>97 : 3 (trans :cis >99 : 1)	1.0	 15	95

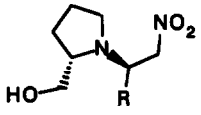
Table 2



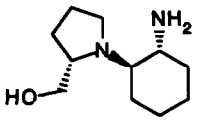
16 R = H
17 R = Me



18 R^1 = Me, R^2 = H
19 R^1 = H, R^2 = Me



20 R = Ph
21 R = i-Pr



22

Molecular modeling studies[11] suggest that if aminoalcohol 13 interacts with nitroalkene 6 by way of a H-bond to one of the oxygen lone pairs orthogonal to the π-system, addition should be favored on the *si*-face leading to the SSS diaminoalcohol. Alternatively H-bonding to the π-system of the nitro group leads preferentially to addition to the *re*-face and the RRS diaminoalcohol. Thus, it may be tentatively concluded that interaction of the alcohol and the nitro group occurs by way of H-bonding to the π-system, which is in good agreement with the acceleration of the rates of these reactions. We are currently pursuing this matter further by

way of locating the transition state, and thus evaluating the extent of H-bonding. Using this simple model as an approximation of the transition state (Figure 1) we can readily explain the propensity of **10** to promote γ-deprotonation. H-bonding of **10** to **6** as described above would result in a complex wherein the amine nitrogen is position precisely above the axial γ-proton. Thus, deprotonation should proceed rapidly (Table 2 Entry 2 vs Table 1 Entry 2) at the expense of addition. Similarly the amine nitrogen of aminoalcohol **9** is unable to approach either the β-carbon or the axial γ-proton due to severe steric interactions. Aminoalcohol **11** remains an enigma. Although structurally closer to **13** than **10**, it behaves analogously to **10**. We believe that this difference in behavior may be a result of the differing orientations of the nitrogen lone pair in the pyrrolidinyl and piperidinyl ring systems. Future work will focus upon investigating this point.

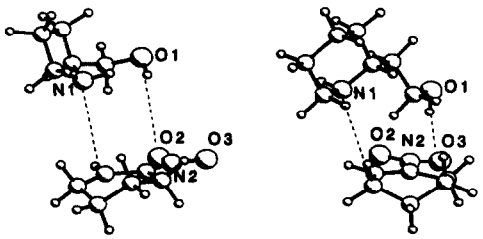


Figure 1 : Comparison of the approach of prolinol **13** (left) and piperidinylethanol **10** (right)

Although at present the extremely high facial selectivities are restricted to one type of nucleophile, this species hold great promise in the efficient asymmetric synthesis of novel analogs of the important opioid antagonists **1** and **2**, as well as the design and preparation of novel tridentate diamine ligands of interest in the area of *cis*-platin-like agents. Additionally, it is hoped that these principles may be employed in the design of future asymmetric additions to nitroalkenes. Furthermore, the concept of internal complexation, via either a hydrogen bond or a metal ion, to the π-system, rather than an orthogonal lone pair, raises interesting questions with respect to carbonyl based addition reactions.[12]

Acknowledgements: We thank the National Science Foundation for NSF #CHE 8900501 (MLM).

References:

1. For examples see, a) T. Sakakibara, T. Nakagawa, M. Funabashi Carbohydr. Res. 1987, **168**, 47; b) R.S. Varma, G.W. Kabalka Heterocycles 1986, **24**, 2645; c) H.H. Baer, T. Neilson J. Org. Chem. 1967, **32**, 1068.
2. P.L. Southwick, J.E. Anderson J.Am. Chem. Soc. 1957, **79**, 6222.
3. E.J. Corey, H. Estreicher J. Am. Chem. Soc. 1978, **100**, 6294.
4. J. Szmuszkovicz, P.F. VonVoigtlander J. Med. Chem. 1982, **25**, 1125.
5. J. Szmuszkovicz, P.F. VonVoigtlander U.S. Patent 4,801,604, issued Jan. 31 1989; M.A. Rogawski, R.J. Porter Pharm. Rev. 1990, **42**, 223.
6. All reactions were performed at r.t. and 0.44M concentrations where practical. Reaction times are given relative to the addition of prolinol **13** to **6** at r.t and 0.44M in CH_2Cl_2, which was complete within 30 mins, assuming second order kinetics for the addition.
7. All adducts were satisfactorally characterized by standard spectral methods, the salts were assessed by NMR.
8. R. Ballini, R. Castagnami, M. Petrini J. Org. Chem. 1992, **57**, 2160.
9. Adducts **14** and **15** were unstable at room temperature. All catalytic reduction protocols lead to a complex mixture of products, whilst $SnCl_2$/HCl reduction of **15** was not consistent. Modification of the recent SmI_2 process gave diamine **20** in good yield. This modified procedure will be reported independently.
10. A.S. Kende, J.S. Mendoza Tetrahedron Lett. 1991, **32**, 1699.
11. Molecular modeling was performed using PCMODEL 386 (V 4.0).
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