The Nitro-Mannich Reaction and Its Application to the Stereoselective Synthesis of 1,2-Diamines†

Harry Adams,‡ James C. Anderson,*,‡ Simon Peace,‡ and Andrew M. K. Pennell§

Department of Chemistry, University of Sheffield, Sheffield S3 7HF, U.K., and GlaxoWellcome, Medecines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

Received August 20, 1998

The addition of alkyl nitronate anions to PMB imines, derived from benzaldehyde or straight-chain carbaldehydes, in the presence of a Bronsted acid, proceeds in greater than 90% yield with up to 10:1 diastereoselection favoring the anti isomer. The mechanism of this addition reaction is intriguing and is under investigation. The moderately unstable β-nitro amines can be reduced with samarium diiodide and the PMB group removed with CAN, in good overall yields, to give sensitive 1,2-diamines without erosion of diastereoselectivity. This protocol represents a new, stereoselective synthesis of certain 1,2-diamines.

The 1,2-diamine structural motif is important in biologically active natural products,[1] in medicinal chemistry,[2] and more recently in their use as chiral auxiliaries and chiral ligands in asymmetric catalysis.[3] While a number of intriguing reports have appeared detailing the stereoselective generation of 1,2-diamines, the diastereoselective synthesis of 1,2-disubstituted 1,2-diamines to date relies upon the conversion of alkenes via diols and diazides[4] or aziridines,[5] aza-pinacol-type coupling of two imines,[6] conversion of enantiomerically pure naturally occurring amino acids,[7] the addition of α-nitrogen carbanions to imines,[8] and the use of chiral auxiliaries.[9] The scope of these methods is limited due to the variability in diastereoselection and, where appropriate, the availability of enantiomerically pure starting materials, the nature of the chiral auxiliary, or in many cases the basicity of the reaction conditions.[23] Herein, we describe the nitro-Mannich reaction as part of a mild and general stereoselective method for the synthesis of 1,2-diamines that has the potential to produce enantiomerically pure products.

For our methodology to be as flexible as possible, we required a method of bringing two nitrogen-containing fragments together stereoselectively. To maximize the diastereoselectivity, we believed that we needed a reaction that proceeded through a six-membered, Zimmerman−Traxler-like transition state. We concentrated on transition states **1**, which involved the addition of an α-aza carbanion to an imine. Two possible scenarios required the addition of metalated hydrazones or nitronate anions to imines via transition states **2** and **3**, respectively.

1 **2** **3**

It is known that *tert*-butylhydrazones add to ketones to form α-hydroxy hydrazones.[10] Our attempts at the analogous addition reaction between *N*-benzylidene-*tert*-butyl- or -*tert*-butyldiphenylmethylhydrazone[11] and *N*-benzylidenebenzylamine were unsuccessful. However, deprotonation of nitropropane with *n*-BuLi followed by addition of *N*-benzylidenebenzylamine to the resultant nitronate ion (1.1 equiv with respect to imine) and quenching with acetic acid (AcOH) at −78 °C furnished the β-nitro amine **4**[12] in virtually quantitative yield with a diastereoselection of greater than 15:1 by ^{1}H NMR (Scheme 1). As the addition product **4** is analogous to those obtained from the diastereoselective nitroaldol studies of Seebach et al.[13] the major diastereoisomer was assigned on the basis of a similar ^{1}H NMR analysis. The

† This article is dedicated to my friend and colleague Professor Charles J. M. Stirling on the occasion of his retirement.

‡ University of Sheffield.

§ Glaxo Wellcome.

(1) (a) Pasini, A.; Zunino, F. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 615−24. (b) Otsuka, M.; Masuda, T.; Haupt, A.; Ohno, M.; Shiraki, T.; Sugiura, Y.; Maeda, K. *J. Am. Chem. Soc.* **1990**, *112*, 838−45.

(2) (a) Michalson, E. T.; Smuszkovicz, J. *Prog. Drug. Res.* **1989**, *33*, 135. (b) Reedijk, J. *J. Chem. Soc., Chem. Commun.* **1996**, 801−6.

(3) (a) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935−52. (b) Soai, K.; Niwa, S. *Ibid.* 833−56. (c) Jacobsen, E. N. in *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; p 159. (d) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−547.

(4) Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P. *Synthesis* **1990**, 1023−4.

(5) (a) Meguro, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.* **1994**, *35*, 7395−8. (b) Leung, W.-H.; Yu, M.-T.; Wu, M.-C.; Yeung, L.-L. *Ibid.* **1996**, *37*, 891−2.

(6) (a) Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609−10 and references therein. (b) Taniguchi, N.; Uemura, M. *Synlett* **1997**, 51−3.

(7) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103−6.

(8) (a) Kise, N.; Kashiwagi, K.; Watanabe, M.; Yoshida, J. *J. Org. Chem.* **1996**, *61*, 428−9. (b) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757−8.

(9) (a) Enders, D.; Wiedemann, J. *Synthesis* **1996**, 1443−50. (b) Alvaro, G.; Grepioni, F.; Savoia, D. *J. Org. Chem.* **1997**, *62*, 4180−2 and references therein.

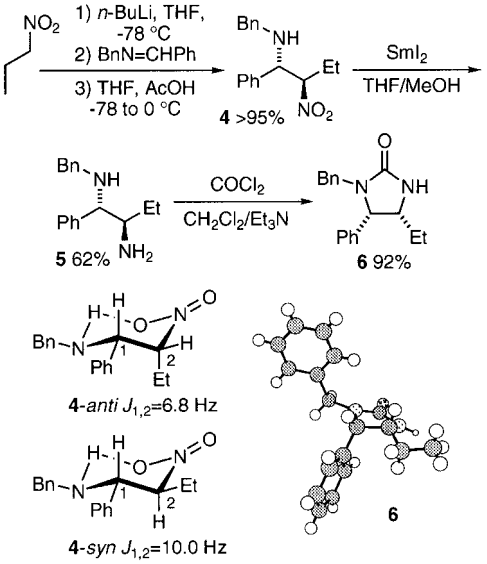
(10) Adlington, R. M.; Baldwin, J. E.; Bottaro, J. C.; Perry, M. W. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1040−1.

(11) Baldwin, J. E.; Adlington, R. M.; Newington, I. M. *J. Chem. Soc., Chem. Commun.* **1986**, 176−8.

(12) This class of product is similar to those that can be obtained by the classic nitro-Mannich reaction [see: Baer, H. H.; Urbas, L. In *The Chemistry of the Nitro and Nitroso Groups, Part 2*; Patai, S., Ed.; Interscience: New York, 1970; p 117]. However, there are few diastereoisomeric examples, and those that we could find combined *N*-phenylbenzylimine with either nitroethane (see: Hurd, C. D.; Strong, J. S. *J. Am. Chem. Soc.* **1950**, *72*, 4813−4) or nitropropopane (see: Kozlov, L. M.; Fink, E. F. *Trudy Kazan. Khim. Tekhnol. Inst. im. S. M. Kirova* **1956**, *21*, 163−6) to yield β-nitro amines both in 35% yield but gave no comment regarding diastereoselectivity.

10.1021/jo981700d CCC: $15.00
Published on Web 12/05/1998

Scheme 1



assumption was made that the more highly populated conformations are those in which there is a hydrogen bond between the vicinal NH and ON−O groups as in **4**-*anti* and **4**-*syn*. This same analysis was used in the assignment of future additions (vide infra) and was supported by a single-crystal X-ray analysis of the cyclic urea **6** derived from **5**.[14]

To produce the desired 1,2-diamine, we required the reduction of the alkyl nitro function to a primary alkylamine. Most common descriptions concerning the reduction of nitro compounds refer to aromatic systems. In addition, **4** is unstable to chromatography and prolonged periods in solution due to β-elimination.[15] Consequently, standard reducing systems invariably gave dibenzylamine as the chief reduction product. Fortunately, samarium diiodide gently reduces the nitro function to our desired primary amine **5**[16] in 62% yield.[15b,17] Hydrogenolysis of the *N*-benzyl group of **5**, to give the naked 1,2-diamine, caused many problems due to other sites being susceptible to cleavage. It was at this point that we optimized the reaction conditions using *N*-(4-methoxybenzyl)imines as the *N*-4-(methoxybenzyl) (PMB) group could be easily removed using ceric ammonium nitrate (CAN).[18] The general three-step sequence is outlined in Scheme 2 with a selection of representative examples in Table 1.

Scheme 2

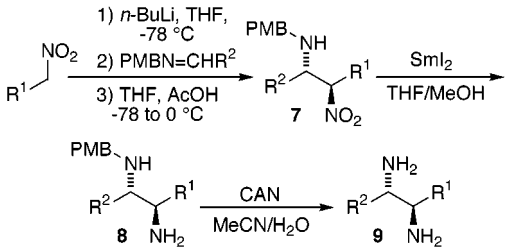


Table 1. Synthesis of Representative 1,2-Diamines

entry	R^1	R^2	yield[a] of **7** (%)	diastereoselectivity[b] anti/syn	yield[c] of **8** (%)	yield[d] of **9** (%)
1	Et	Ph	90	10:1	60	96
2	Et	*n*-Pn	95	9:1	66	100
3	Et	*c*-Hex	95	2:3	45	86
4	Me_2	Ph	60		48	86
5	Ph	Ph	74	1:15		
6	Et	CH_2OBn	95	3:2	77	100
7	Et	$(CH_2)_3Ph$	95	7:1	52	76

[a] Crude yield estimated from mass balance and NMR. [b] From 250 MHz ^1H NMR ($CDCl_3$). [c] Isolated yield over two steps with respect to imine. [d] Isolated yield.

Entries 1−3 examine which substituents are tolerated on the aldimine fragment. The success of the *n*-pentylimine in entry 2 is indicative of the mild reaction conditions of this method. Although steric hindrance in the imine partner does not appear to affect the yield of the coupling, the diastereoselection is drastically diminished (entry 3). Tertiary nitronate anions are tolerated (entry 4) and still accomplish a moderate yield for the three-step synthesis of this particular 1,2-diamine (**9**, $R^1 = Me_2$, R^2 = Ph). The reversal of stereoselectivity with phenyl nitromethane (entry 5) is curious, but we have verified this structural assignment by single-crystal X-ray analysis. An account of this anomaly awaits further mechanistic studies, which will elucidate a working transition-state model for these reactions. This addition product (**7**, R^1 = Ph, R^2 = Ph) was too unstable to survive even the mild reducing conditions employed in this sequence. An imine derived from 2-benzyloxyacetaldehyde gave poor diastereoselection (entry 6), but the corresponding carbon analogue gave the expected level of stereocontrol (entry 7). At present, the stereoselective nitro-Mannich reaction seems applicable to the synthesis of 1,2-diamines from the coupling of nitroalkyl compounds with PMB imines derived from benzaldehyde or straight-chain carbaldehydes.[19] Further studies concerning heteroatom substituents on the nitroalkyl fragment and imines derived from substituted benzaldehydes are underway to further define the limitations of this methodology.

The addition of a nitronate anion to an imine is thermodynamically impossible.[20] This reaction (Scheme 2) is only made possible by the presence of acetic acid.

(13) Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101−33.

(14) Crystallographic data (excluding structure factors) for structure **6** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101457. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: Int. code +(1223) 336−033; e-mail: deposit@chemcrys.cam.ac.uk).

(15) (a) Akhtar, M. S.; Sharma, V. L.; Seth, M.; Bhaduri, A. P. *Indian J. Chem.* **1988**, *27B*, 448−51. (b) Sturgess, M. A.; Yarberry, D. J. *Tetrahedron Lett.* **1993**, *34*, 4743−6.

(16) A forefather of this method for the synthesis of 1,2-diamines is the reduction, with Raney nickel and hydrogen (see Lambert, A.; Rose, J. D. *J. Chem. Soc.* **1947**, 1511−3), of products produced from the condensation between primary (see: Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10−12) or secondary amines (see: Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 12−14 and Johnson, H. G. *Ibid.* **1946**, *68*, 14−18), formaldehyde, and nitroalkanes. We have found no reports of this method with other aldehydes, which would produce diastereomeric products.

(17) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699−1702.

(18) Smith, A. B., III; Leahy, J. W.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Am. Chem. Soc.* **1992**, *114*, 2995−3007.

(19) Nitroamines **4** and **7**, protected diamines **5** and **8**, and diamines **9** have all been fully characterized except for satisfactory elemental analyses. We attribute this to the compounds' sensitivity, but satisfactory elemental analyses were obtained on the di-*N*-Boc derivatives (see the Supporting Information).

(20) As $\Delta G = -RT \ln K$ and if we approximate $K \approx \Delta K_a$ in this case, as the change in bond enthalpy is small, and we define pK_a's of 9 for nitropropane and 35 for the aza anion of **4** then at −78 °C we find $\Delta G \approx +97$ kjmol^{-1}!

Whether it is added to the nitronate anion or to the bulk reaction mixture, the outcome of the reaction is identical. Control experiments suggest that the diastereoselection is derived from the addition of the two reaction partners, not through equilibration to a tertiary nitronate anion and subsequent protonation.[21] Further studies are underway to determine whether a nitronic acid or a protonated imine is a key intermediate to elucidate the mechanism of this reaction.[22]

In summary, we have developed a three-step diastereoselective synthesis of 1,2-diamines that involves the coupling of alkyl nitro compounds and aldimines in good overall yields. Mechanistic studies, catalytic studies, and methods to control the absolute stereochemistry of the products, to further develop the stereoselective nitro-Mannich reaction, are underway and will be reported in due course.

(21) Treatment of **7** (R^1 = Et, R^2 = Ph, 10:1 anti/syn) with BuLi (*X* equiv) at −78 °C for 5 min and then addition of AcOH (2*X* equiv) followed by workup with saturated aqueous $NaHCO_3$ as before gave the following products by NMR: *X* = 1, 16% imine, 65% *anti*-**7**, 19% *syn*-**7**; X = 2, 40% imine, 45% *anti*-**7**, 14% *syn*-**7**. Control experiment with no BuLi, but 2 equiv of AcOH at −78 °C followed by workup with saturated aqueous $NaHCO_3$ as before gave a quantitative recovery of **7** with unaltered diastereomeric excess.

Acknowledgment. We thank GlaxoWellcome and the EPSRC for a CASE award (S.P.), Prof. C. J. M. Stirling and Dr. N. H. Williams of this department for helpful discussions, Mr. A. Jones and Ms. J. Stanbra for measuring microanalytical data, and Mr. S. Thorpe and Mr. N. Lewus for providing mass spectra.

Supporting Information Available: Experimental procedures, spectroscopic data, and proton NMR spectra for compounds **4**−**9** (32 pages). See any current masthead page for ordering information.

JO981700D

(22) Nitronic acids can be prepared by the treatment of alkali metal salts of nitroalkanes with strong mineral acid, although treatment with weaker acids such as AcOH is believed to give predominantly C-protonation [see: Nielsen A. T. In *The Chemistry of the Nitro and Nitroso Group, Part 1*; Patai, S., Ed.; Wiley Interscience: New York, 1969; pp 349], what may happen in THF at −78 °C is unpredictable. pK_a (propane−nitronic acid) = 4.6, pK_a (nitropropane) = 9.0 (in water, see: Nielsen, A. T. above and references therein). pK_a (acetic acid) = 4.7 and pK_a (*N*-benzylidenebenzylamine) ∼7 (see: Koehler, K.; Sandstrom, W.; Cordes, E. H. *J. Am. Chem. Soc.* **1964**, *86*, 2413−9. Cordes, E. H.; Jencks, W. P. *Ibid.* **1963**, *85*, 2843−8)

(23) For a recent review see: Lucet, D.; LeGall, T.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2580−2627.