Pergamon

Tetrahedron Letters 39 (1998) 6561–6564

TETRAHEDRON LETTERS

Synthesis of Homochiral Propargyl Amines from Tetrahydro-1,3-Oxazines

Alastair Rae, James Ker, Alethea B. Tabor*

Department of Chemistry, University College London, 20 Gordon Street, London, WC1H OAJ

José L. Castro

Merck Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR

Simon Parsons#

Department of Chemistry, University of Edinburgh, Kings Buildings, West Mains Road, Edinburgh. EH9 3JJ

Received 27 May 1998; accepted 30 June 1998

Abstract: A direct method for the enantioselective synthesis of propargyl amines has been developed. 4-Substituted (*S*)-*N*-Boc-tetrahydro-1,3-oxazines were synthesised and the structure of one analogue determined by X-ray diffraction analysis. Ring-opening using alkynyl Grignard reagents in the presence of $BF_3.Et_2O$, followed by removal of the chiral directing group via oxidation and acid-catalysed retro-Michael reaction, gave the desired propargyl amines in good yield.

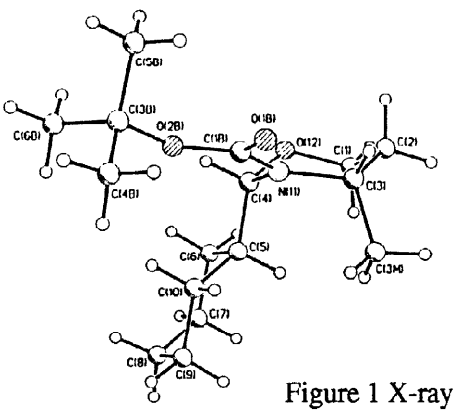
The ring-opening of chiral acetals with a variety of nucleophiles to give chiral alcohols has been extensively studied, and a range of procedures giving high yields and excellent stereoselectivities has been published.[1] In contrast, the analogous ring-opening of chiral aminals to give chiral amines has only recently received attention. Ring-opening reactions of 2-aliphatic[2] and 2-aryl[2,3] 1,3-oxazolidines with aliphatic Grignard and other organometallic reagents, followed by cleavage via hydrogenolysis or oxidative methods, have given chiral aliphatic and benzyl amines in moderate to good enantiomeric excess (ee). Addition of Grignard and organoaluminium reagents to bicyclic *N*-benzyl tetrahydro-1,3-oxazines derived from (+)-pulegone, followed by sequential treatment with P_2O_5 and hydrogenolysis, has also led to chiral aliphatic amines; the conformational rigidity of these tetrahydro-1,3-oxazines has resulted in high diastereomeric excess (de) on the ring-opening step.[4] However, little work has been reported on the functionalisation of oxazines or oxazolidines with unsaturated nucleophiles.[5] This may be attributed to the harsh conditions required in the deprotection and cleavage stages, which would not be compatible with sensitive unsaturated functionality.

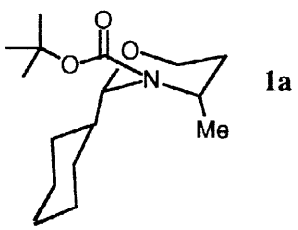
Chiral propargyl amines are of interest as enzyme inhibitors[6] and as precursors to chiral allylic amines;[7] direct and general methods for their synthesis are therefore important. In this paper, we report a method for the enantioselective synthesis of propargyl amines via the synthesis and ring-opening reactions of chiral 4-substituted *N*-Boc-tetrahydro-1,3-oxazines **1**.

It was envisaged that the tetrahydro-1,3-oxazines **1** would be synthesised from (*S*)-(*N*-Boc)-3-amino-butan-1-ol **2**, prepared from (*L*)-alanine via Arndt-Eistert homologation,[8] and an appropriate aldehyde. Surprisingly, all attempts to condense **2** directly with aldehydes, whether catalysed by mild acid,[9] or using $MgSO_4$[2,3] or Dean-Stark conditions[4] for removal of water, failed. Instead, acid-catalysed reaction of **2** with the corresponding diethyl acetals in refluxing benzene led to tetrahydro-1,3-oxazines **1a-1f** in good to excellent yields. In order to analyse the mechanism of ring-opening of these compounds, it was necessary to determine the

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01366-5

conformational preference of the substituents in the tetrahydro-1,3-oxazines **1**. We therefore determined the structure of **1a** by X-ray diffraction analysis (Figure 1).[10] The tetrahydrooxazine ring adopts a twist-chair conformation, with the cyclohexyl and methyl groups in pseudoaxial positions, and the Boc group in a pseudoequatorial position. This is in accord with previous structural work on *N*-tosyl tetrahydro-1,3-oxazines[11,12] in which substituents in the 2-, 4-, 5,- and 6-positions adopt axial positions in order to minimise steric interactions with the pseudoaxial tosyl group. However, it contrasts with the known structures of the *N*-methyl 2-aliphatic 1,3-oxazolidines,[13] in which the 2- and 4-substituents adopt pseudoequatorial positions, and with the bicyclic *N*-benzyl tetrahydro-1,3-oxazines, in which the 2-substituent also lies in the equatorial position.[4b,14] These structural differences presumably arise from the differing steric bulk of the nitrogen protecting group in each case.

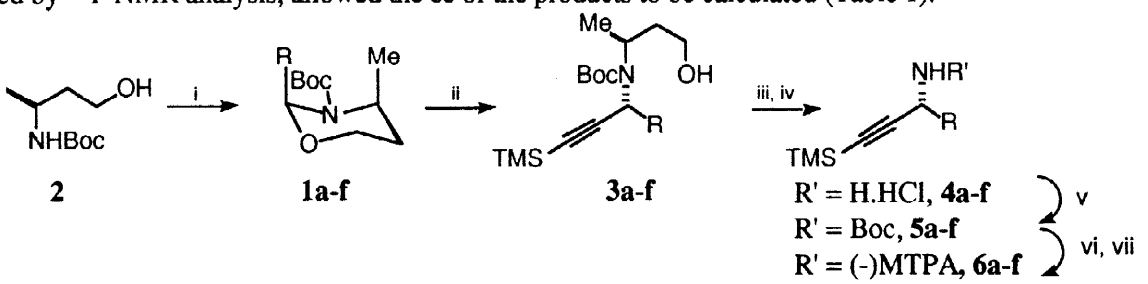




1a

Figure 1 X-ray crystal structure of aminal **1a**

Ring-opening of tetrahydro-1,3-oxazines **1a-1f** with alkynyl Grignard reagents, in the presence of $BF_3.Et_2O$, at elevated temperatures (Scheme 1) gave good yields of the required products (Table 1). This was shown to be the case for a range of substrates, including those with sensitive functionalities, such as the silyl ether **1d**. Removal of the chiral directing group, to reveal the propargyl amines, then proceeded as follows. Oxidation[15] of the ring opened alcohol to the corresponding aldehyde, followed by acid-catalysed retro-Michael reaction (Scheme 1) gave the required amines as the hydrochloride salts **4a-f**. As **4a-f** decomposed rapidly on isolation, the HCl salts were immediately reprotected with tert-butyl pyrocarbonate to give **5a-f** in good yields. Alternatively, conversion of these amines to their Mosher's amides **6a-f**[16] with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, followed by ^{19}F NMR analysis, allowed the ee of the products to be calculated (Table 1).



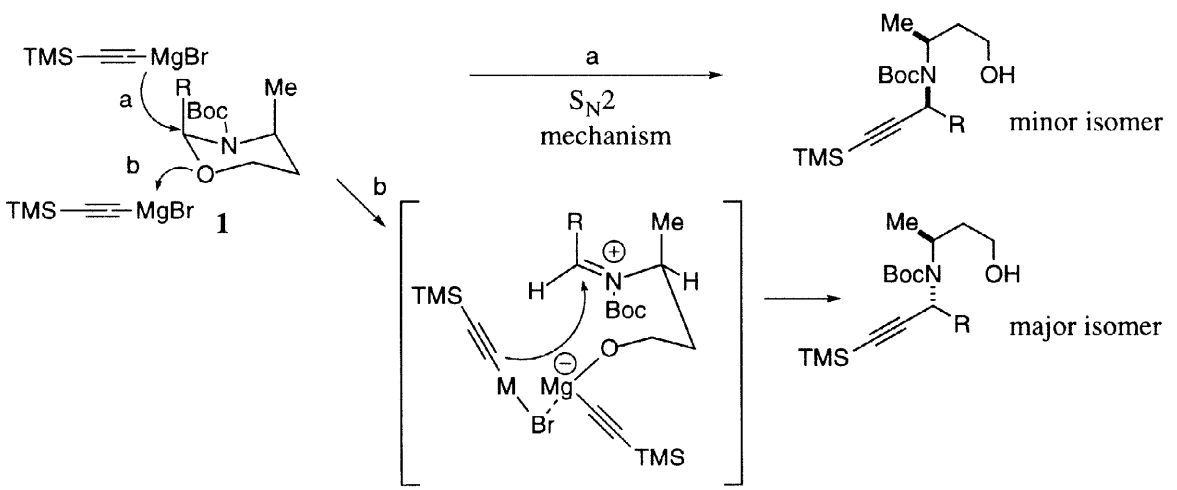
2 **1a-f** **3a-f**

Scheme 1 (i) $RCH(OEt)_2$ (1 equiv.), PPTS (cat.), C_6H_6, reflux, 2 hr; (ii) TMSCCMgBr (4 equiv.), $BF_3.OEt_2$ (1.1 equiv.), THF, 35°C, under N_2, 45 min; (iii) pyridine.SO_3 (3 equiv.), DMSO, THF, Et_3N, r.t, under Ar, 45 min; (iv) 2M HCl, THF, 100°C, 3 hr; (v) Boc_2O (2 equiv.), Na_2CO_3 (2 equiv.), dioxane/H_2O (1:1); (vi) CF_3COOH, MeOH, r.t.; (vii) pyridine, (*S*)-(+)-MPTA chloride.

Table 1

R	Yield (**3a-f**) / %	Yield (**5a-f**) / %	ee / %
cyclohexyl	73	70	40
hexyl	80	68	66
propyl	65	65	66
O-(TIPS)-pentyl	60	35	> 98
O-(TIPS)-propyl	45	38	62
isopropyl	48	64	90

The absolute configuration of the chiral centre formed in these reactions was then determined by correlation. Propargyl amine **5f** was converted to 1-(1'-methyl)-ethyl-*N*-(Boc)-2-propynamine, via acid-catalysed removal of the trimethylsilyl[16] and Boc groups followed by reprotection. Comparison of the optical rotation with the literature value[7] indicated that the major enantiomer had the (*R*)-configuration.[17] The ring-opening reactions of bicyclic *N*-benzyl tetrahydro-1,3-oxazines with Grignard reagents studied by Pedrosa[4b] have been shown to proceed via a S_N2-type mechanism; however, ring-opening of aminals **1** via such a mechanism would lead to the formation of the opposite stereoisomer (Scheme 2a). Instead, the stereochemical result of this ring-opening reaction is analogous to that reported by Pridgen[2a] for the ring-opening of 2-aryl 1,3-oxazolidines with an excess of Grignard reagent. We therefore postulate that a similar mechanism, involving initial aminal ring-opening to afford an iminium ion[2a] followed by intramolecular delivery of a second equivalent of anion[13] may account for the stereochemical outcome of the reaction (Scheme 2b). The role of the $BF_3.OEt_2$, which is essential for the reaction, is at present unclear.



Scheme 2

In summary, a novel, direct route to chiral propargyl amines has been reported, which extends the range of chiral amine functionalities available through ring-opening of chiral aminals. Further investigations of the mechanism of the ring-opening reaction, and the factors governing the stereoselectivity observed in this step, are in progress.

Acknowledgement. We thank the EPSRC and Merck Sharp and Dohme for a CASE Studentship (to A. R.), OSWEL DNA and Professor T. Brown (University of Southampton) for a studentship (to J. K.).

References

Author to whom enquiries concerning the X-ray structure should be directed.

(1) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry*, **1990**, *1*, 477.

(2) (a) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.*, **1991**, *56*, 1340. (b) Mokhallalati, M. K.; Muralidharan, K. R.; Pridgen, L. N., *Tetrahedron Lett.*, **1994**, *35*, 4267.

(3) (a) Higashiyama, K.; Inoue, H.; Yamauchi, T.; Takahashi, H. *J. Chem. Soc., Perkin Trans. I*, **1995**, 111. (b) Higashiyama, K.; Nakagawa, K.; Takahashi, H. *Heterocycles*, **1995**, *41*, 2007.

(4) (a) Alberola, A.; Andrés, C.; Pedrosa, R. *Synlett*, **1990**, 763. (b) Andrés, C.; Nieto, J.; Pedrosa, R.; Villamañán, N. *J. Org. Chem.*, **1996**, *61*, 4130.

(5) (a) Wu, M.-J.; Pridgen, L. N. *Synlett*, **1990**, 636. (b) Mokhallalati, M. K.; Wu, M.-J.; Pridgen, L. N. *Tetrahedron Lett.*, **1993**, *34*, 47.

(6) (a) Casara, P.; Danzin, C.; Metcalf, B. W.; Jung, M. J. *J. Chem. Soc. Chem. Commun.* **1982**, 1190. (b) Walsh, C. *Ann. Rev. Biochem.* **1984**, 53, 493.

(7) (a) Reginato, G.; Mordini, A.; Messina, F.; Degl'Innocenti, A.; Poli, G. *Tetrahedron*, **1996**, *52*, 10985. (b) Hauske, J. R.; Dorff, P.; Julin, S.; Martinellin, G.; Bussolari, J. *Tetrahedron Lett.*, **1992**, *33*, 3715.

(8) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta*, **1996**, *79*, 913.

(9) Meskins, F. A. J. *Synthesis*, **1981**, 501.

(10) The authors have deposited atomic coordinates for **1a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U. K.

(11) Burgess, K.; Ohlmeyer, M. J.; Whitmire, K. H. *J. Org. Chem.*, **1990**, *55*, 1359.

(12) Cherkauskas, J. P.; Klos, A. M.; Borzilleri, R. M.; Sisko, J.; Weinreb, S. M.; Parvez, M. *Tetrahedron*, **1996**, *52*, 3135.

(13) Takahashi, H.; Hsieh, B. C.; Higashiyama, K. *Chem. Pharm. Bull.*, **1990**, *38*, 2429.

(14) Eliel, E. L.; He, X.-C. *J. Org. Chem.*, **1990**, *55*, 2114.

(15) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. I*, **1990**, 47.

(16) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.*, **1973**, *95*, 512.

(17) Renaud, P.; Seebach, D. *Angew. Chem., Int. Edn. Engl.*, **1986**, *25*, 843.

(18) (*R*)-1-(1'-methyl)-ethyl-*N*-(Boc)-2-propynamine: $[\alpha]^{22}_{D}$ = +24.0° *c* = 0.25, $CHCl_3$. Literature value for (*S*)-1-(1'-methyl)-ethyl-*N*-(Boc)-2-propynamine: $[\alpha]^{22}_{D}$ = -45.3° *c* = 1.04, $CHCl_3$:[7a] $[\alpha]°$ = -59.9.[7b]