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A HIGHLY STEREOSELECTIVE CONVERSION OF α-ALLENIC ALCOHOLS TO 1,2-SYN AMINO ALCOHOL DERIVATIVES VIA IODOCARBAMATION

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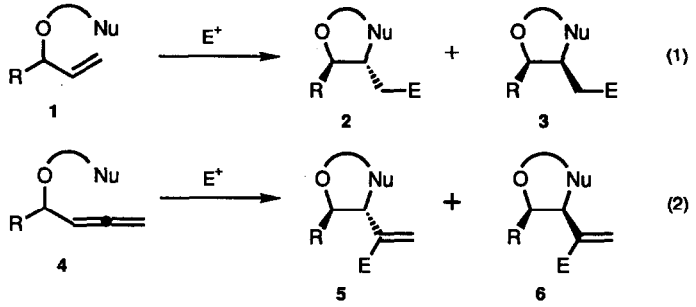
Abstract: The iodocarbamation of α-allenic alcohol O-carbamates is described. Reactions carried out in anhydrous Et_2O are highly diastereoselective, providing the cyclic carbamates trans-**8** and cis-**9** in ratios ranging from 21:1 to >99:<1. Hydrolysis and acetylation provide the corresponding amino alcohol derivatives syn-**10** and anti-**11**.

The electrophile mediated nucleophilic substitution of allylic alcohol derivatives has been the subject of much interest in recent years, both from the synthetic and mechanistic point of view.[1] In those cases in which the nucleophile is tethered through the oxygen atom, as in **1**, electrophilic cyclization provides the diastereomeric products **2** and **3** (eq 1).[2] The trans substituted heterocycle **2** usually predominates, with varying diastereoselectivities being observed. An interesting reversal of 1,2-asymmetry is observed for the N-tosyl O-carbamate derivatives (**1**, Nu = CONHTs). These materials provide preferentially, upon treatment with iodine, the cis cyclic carbamates **3** in ratios of about 3:1.[3]

Our interest in the preparation of polyfunctional, acyclic arrays led us to consider the corresponding reactions of α-allenic alcohol derivatives **4** (eq 2) for which there appears to be little literature precedent.[4] If successful, the resulting highly functionalized products **5** and/or **6** would be amenable to a variety of useful synthetic manipulations. In this report, we describe our results for the reactions of the N-tosyl O-carbamate derivatives of α-allenic alcohols (**4**, Nu = CONHTs) with iodine.

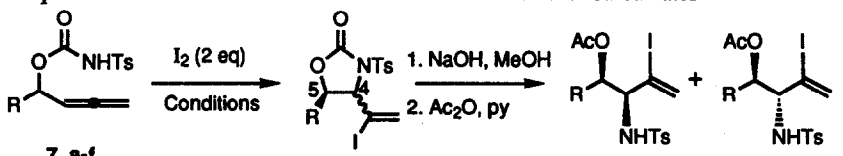


The requisite N-tosyl carbamates **7** were easily prepared in yields >85% by treatment of the α-allenic alcohols[5] with N-tosylisocyanate. Our initial investigations were concerned with the cyclohexyl derivative **7a** and the results are summarized in Table I, Entries 1-6. Thus, treatment of solutions of **7a** with base and molecular I_2 provided crude reaction mixtures that were analyzed by ^1H NMR. Examination of these spectra indicated, in all cases, the presence of two predominant products corresponding to the diastereomeric trans and cis cyclic carbamates **8a** and **9a**. Protons H4 and H5 are mutually coupled with coupling constants of 2.7 and 6.6 Hz for the major and minor diastereomers, respectively. On this basis,[6] the major isomer was assigned as the trans diastereomer **8a**. Unfortunately, **8a** and **9a** could not be efficiently

separated from other minor reaction products or from each other by column chromatography. However, hydrolysis (aqueous MeOH, NaOH) and acetylation (Ac_2O, py, DMAP) provided homogeneous mixtures of the acyclic N-tosyl amino alcohol derivatives syn-**10a** and anti-**11a** in combined, overall yields as indicated. Analysis of the integrated ^1H NMR spectra of these mixtures allowed us to accurately determine the diastereomer ratios. The ratios determined in this manner were consistent with the ratios that were measured in the spectra of the crude mixtures of the cyclic carbamates **8a/9a**.

Confirmation of the initial stereochemical assignment was made from an X-ray crystallographic study of the major acyclic N-tosyl amino alcohol derivative.[7] This analysis[8] demonstrated that the major product was indeed the syn isomer **10a**, having arisen from the trans cyclic carbamate **8a**.

Table I: Preparation of Amino Alcohol Derivatives from α-Allenic O-Carbamates



7 a-f **8 a-f trans** **9 a-f cis** **10 a-f** **11 a-f**

Entry	Substrate	Conditions (24h)	Overall Yield,% (**10**:**11**)
1	**7a** R = C_6H_{11}	aq $NaHCO_3$, Et_2O, rt (A)	33 (7.2:1)
2		aq $NaHCO_3$, THF, rt	35 (6.6:1)
3		aq $NaHCO_3$, CCl_4, rt	38 (15:1)
4		K_2CO_3, Et_2O, rt (B)	76 (40:1)
5		K_2CO_3, Et_2O, 0°C	68 (29:1)
6		K_2CO_3, CCl_4, rt	52 (12:1)
7	**7b** R = $CH_3(CH_2)_6$	A	62 (1.1:1)
8		B	78 (21:1)
9	**7c** R = $(CH_3)_2CHCH_2$	A	49 (1:1)
10		B	80 (27:1)
11	**7d** R = $(CH_3)_2CH$	A	47 (8.8:1)
12		B	79 (30:1)
13	**7e** R = $(CH_3)_3C$	A	18 (>99:<1)
14		B	60 (>99:<1)
15	**7f** R = C_6H_5	B	50 (10:1)

The three-step reaction sequence was then applied to a variety of α-allenic O-carbamates **7b-f**[9] and the results are summarized in Table I, Entries 7-15. Several points deserve mention. $J_{4,5}$ for the trans isomers **8** is in the range of 2.7 to 3.3 Hz while the cis isomers **9** exhibit $J_{4,5}$ of 6.6 to 7.4 Hz.[6] Reaction

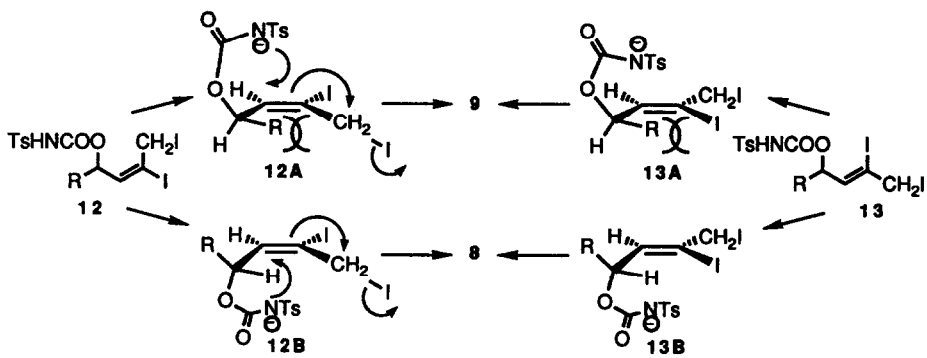
sequences in which the initial cyclizations were performed in anhydrous Et_2O were higher yielding and more diastereoselective than those carried out in aqueous solvents. In all cases, the major product was the syn isomer **10**. The ratio of syn:anti diastereomers for those reactions initially done in anhydrous Et_2O increases in the series from R = n-heptyl (1^o) to R = t-butyl (3^o) (compare Entries 4, 8, 10, 12 and 14). All the mixtures show similar chromatographic behaviour, with the syn products **10** being more polar than the anti materials **11**.

Of interest is the source of the high trans stereoselectivity (21-99:1) that is observed in the cyclization reactions that were carried out in anhydrous Et_2O. In these cases, the diastereoselectivity is greater and opposite to that observed in the analogous allylic O-carbamate series.[3]

In the event, **7b** was treated with K_2CO_3 and I_2 in dry Et_2O. Inspection of the reaction mixture after 30 min (tlc) revealed that **7b** was completely consumed but the new product did not correspond to the cyclic carbamates **8b** or **9b**. Isolation of this material indicated that I_2 had added non-stereoselectively to the terminal double bond of the allene system[10] to provide equimolar amounts of the E-and Z-diiodides **12b** and **13b**, respectively.[11] Resubjection of the diiodide mixture to the original reaction conditions, or simply stirring in dry Et_2O in the presence of K_2CO_3 for 24h, provided crude reaction mixtures of **8b/9b** whose ^1H NMR spectra were identical to those observed previously (ie. **8b**:**9b** 21:1, cf Entry 8). Evidence that this result was in fact a kinetic result, and not simply a thermodynamic preference of the trans isomer over the cis isomer, was obtained from the following reaction. Treatment of a 1:1 mixture of **8b** and **9b** (Entry 7) with I_2 and K_2CO_3 in dry Et_20 for 24h did not alter the trans:cis ratio.

Thus, the source of the high reaction diastereoselectivity is traced to a change in reaction mechanism. Instead of a concerted, intramolecular nucleophilic attack on an iodonium complex or intermediate,[2] a process that has been invoked to explain the asymmetric induction that is observed in cyclizations of allylic substrates, a S_N2' mechanism (illustrated for **12A** and **B**) appears to be operative (Scheme 1). S_N2' displacements that proceed out of conformers **12A** and **13A** are expected to have severe

Scheme 1



steric interactions between R and CH_2I or I in their respective transition states. These steric interactions are not present in transition states arising from cyclizations out of the conformers **12B** and **13B**. Therefore, these latter modes of S_N2' displacement would be energetically more favourable, providing the trans cyclic

carbamates **8** in preference to the cis isomers **9**. As expected, increasing the steric bulk of R results in a corresponding increase in the trans diastereoselectivity, reaching a maximum for R = t-butyl. Furthermore, irrespective of the E,Z-stereochemistry of the initially formed diiodides, the favoured mode of cyclization produces the trans cyclic carbamates **8**.

Thus, a highly diastereoselective process to produce syn amino alcohol derivatives **10** has been developed. The functionality inherent in **10** should prove to be useful in a variety of synthetic applications.

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4. The related cyclizations of γ-allenic alcohols and amines (to form 2-alkenyl tetrahydrofurans and pyrrolidines) has been studied. (a) J.-J. Chilot, A. Doutheau and J. Gore, *Bull. Soc. Chim. Fr.*, **1984**, 307. (b) R.D. Walkup and G. Park, *J. Am. Chem. Soc.*, **1990**, *112*, 1597. (c) S. Arseniyadis and J. Gore, *Tetrahedron Lett.*, **1983**, *24*, 3997. (d) R. Kinsman, D. Lathbury, P. Vernon and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, **1987**, 243.
5. The requisite α-allenic alcohols were prepared from the corresponding aldehydes and THP protected propargyl alcohol according to the two step procedure described by J.S. Cowie, P.D. Landor and S.R. Landor, *J. Chem. Soc., Perkin I*, **1973**, 720.
6. Similar $J_{4,5\ cis}$ and $J_{4,5\ trans}$ values (7.5 and 4.5 Hz, respectively) were observed in the ^1H NMR spectra of 4-alkyl-5-(iodomethyl)oxazolidin-2-ones (ref. 2c). See also, T.A. Foglia and D. Swern, *J. Org. Chem.*, **1969**, *34*, 1680.
7. Although the isomers **10** and **11** were isolated as homogeneous mixtures for determination of the diastereomeric ratios (column chromatography, elution with hexanes:ethyl acetate, 3:2 v/v), the major isomer (**10**) could be obtained as a pure compound by careful column chromatography (elution with hexanes:ethyl acetate, 4:1 v/v).
8. Full details of the X-ray crystal structure will be reported elsewhere. We would like to thank Dr. Alan Plough of this department for carrying out this structure determination.
9. All new materials (the carbamates **7a-f**, their precursor alcohols, and the major diastereomers **10a-f**) were characterized by ^1H and ^{13}C NMR, IR, high resolution mass spectra and/or elemental analysis.
10. The addition of iodine to the less substituted double bond of 1,1-disubstituted allenes occurs with excellent regioselectivity. C. Georgoulis, W. Smadja and J.M. Valery, *Synthesis*, **1981**, 572. The situation with monosubstituted allenes is much less clear. W. Smadja, *Chem. Rev.*, **1983**, *83*, 263.
11. **12b/13b**: FAB MS 642 $(M+Na)^+$: ^1H NMR (200 MHz, $CDCl_3$) δ **12b** 3.96 (d, 1H, J = 10.9 Hz), 4.72 (d, 1H, J = 10.9 Hz), 5.20 (dt, 1H, J = 9.5, 6.8 Hz), 5.92 (d, 1H, J = 9.5 Hz); **13b** 4.23 (dd, 1H, J = 0.8, 10.8 Hz), 4.37 (dd, 1H, J = 1.0, 10.8 Hz), 5.13 (dt, 1H, J = 7.8, 6.0 Hz), 5.86 (br d, 1H, J = 7.8 Hz).

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