A HIGHLY STEREOSELECTIVE CONVERSION OF & ALLENIC ALCOHOLS TO SYN-1,2-DIOL DERIVATIVES

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Abstract: α -Allenic alcohols 4 are converted with high diastereoselectivity via an iodocyclization process into the syn-1,2-diol derivatives 10.

The stereocontrolled preparation of 1,2-diol moieties 1 in acyclic systems is a continuing challenge in organic synthesis.¹ One of the ways in which this issue has been addressed is by the electrophile (E) induced cyclization reactions of allylic alcohol derivatives 3 such as hemiacetals,² esters,^{2b} carbamates³ and carbonates⁴ (eq 1). In these reactions, the formation of the trans heterocycles 2 usually predominate although the diastereoselectivities associated with these processes in acyclic systems can vary greatly.



We have previously shown that the carbamates 5 derived from α -hydroxy allenes 4 can be utilized in a highly diastereoselective ($\geq 27:1$) synthesis of trans cyclic carbamates 9 (Scheme 1).⁵ This iodocyclization process involves the initial formation of a mixture of isomeric diiodides 6 and 7, resulting from the addition of iodine to the terminal double bond of the allene, followed by intramolecular S_N2' displacement of the allylic iodide. Under the basic reaction conditions (K₂CO₃), the carbamate nitrogen atom acts as the nucleophilic species. However, the ambident character of carbamate nucleophiles in intramolecular displacement reactions of epoxy carbamates, for example, is well documented⁶ and the regioselectivity that one observes is dependant on the nature of the reaction conditions.⁷ While basic reaction conditions favour nitrogen participation (S_N2 like), Lewis acidic reaction conditions favour participation of the carbonyl oxygen (S_N1 like).^{6,7} These observations suggested to us that reactions of 6/7 mediated by silver salts might provide cyclization products characteristic of the latter mode of reactivity via the generation of an allylic cation. If successful, the resulting vicinal diol vinyl iodides 10 would be potentially versatile synthetic intermediates. Herein, we describe the highly diastereoselective synthesis of *syn*-1,2-diols from α -allenic alcohols using this strategy.

Our initial investigations were concerned with the reaction conditions required to achieve regioselectivity in favour of participation of the carbonyl oxygen atom in this type of displacement reaction. Thus, the N-tosyl carbamate diiodide mixture **6a/7a** (E/Z 1:1) was prepared as described previously⁵ from the α -allenic alcohol **4a**⁸ (TsNCO, ether; I₂) and was subjected to a variety of reaction conditons, varying both solvent (ether, MeCN, CH₂Cl₂) and silver salt (AgBF₄, AgOTf, Ag₂CO₃). It quickly became apparent that Ag₂CO₃ was the salt of choice and the results obtained using this reagent are summarized in Table I, entries 1-5.⁹



Table I. Prena	ration of Ac	atviated syn-1.	2-Diols 10	from α -,	Allenic Alcohols	4
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Entry	Substrate 4 (R)	Cyclization Reaction Solvent ^a	Ratio 8:9 ^b	J _{a,b} (Hz) in 8	Overall Yield 10, % ^c
1	4a n-heptyl	ether	NR		10a 0
2		MeCN	1.7:1	6.8	10a 55 (34)
3		ether/MeCN (5:1)	10:1		10a 62 (5)
4		ether/MeCN (50:1)	28:1		10a 76 (3)
5		CH ₂ Cl ₂	>50:1		10a 82 (0)
6	4b TIPSOC ₄ H ₈	ether/MeCN (10:1)	>50:1	5.5	10b 78 (1)
7		CH ₂ Cl ₂	14:1		10b 80 (4)
8	4c BnOCH ₂ OC ₄ H ₈	ether/MeCN (10:1)	>50:1	6.1	10c 75 (2)
9	4d i-butyl	ether/MeCN (3:1)	13:1	6.8	10d 74 (4)
10		ether/MeCN (50:1)	20 :1		1 0d 60 (2)
11	4e c-hexyl	CH2Cl2	>50:1	5.3	10e 7 0 (0)
12	4f 3,4-(OCH2O)C6H3	ether/MeCN (10:1)	>50:1	6.1	10f 75 (1)
13	4g 4-MeOC ₆ H ₄	ether/MeCN (10:1)	đ	6.3	10g 29 (3)

^a Cyclization reactions carried out on approximately 0.2-0.3 M solutions of 4 using 1-1.5 eq Ag₂CO₃. ^b Measured from the integrated ¹H NMR spectra of the crude reaction mixtures. ^c Overall, isolated yields of analytically pure products 10 (characterized by IR, ¹H and ¹³C NMR, MS and elemental analysis) from allenic alcohols 4. Yields in brackets refer to the isolated yields of the corresponding amines 11. ^d Unable to determine.

While no reaction was observed in ether (Table I entry 1), presumably due to the insolubility of Ag₂CO₃ in ether, the reaction in MeCN did provide cyclized materials. However, the ratio of imino carbonate 8a to

carbamate 9a was low (Table I, entry 2). High degrees of regioselectivity favouring production of 8a over 9a were observed in ether/MeCN (Table I, entries 3 and 4) and CH₂Cl₂ (Table I, entry 5) solutions. Apparently, there is a subtle difference between the S_N2 pathway leading to 9a and the S_N1 like pathway leading to 8a that is highly solvent dependant.⁷ The ¹H NMR spectra of the crude reaction mixtures were extremely clean and free of byproducts. Furthermore, in each case only a <u>single</u> imino carbonate isomer 8a was observed in these spectra (diastereoselectivity >50:1). Difference nOe experiments¹⁰ performed on 8a clearly demonstrated that the substituents on the five membered ring are trans. For ease of isolation and purification, the crude cyclization products were hydrolyzed (K₂CO₃, MeOH) and acetylated (Ac₂O, pyridine, DMAP) to provide 10a and 11a. The integrated ratio of 8a:9a observed in the crude reaction mixtures was reflected in the isolated yield ratio of 10a:11a. Finally, it should be pointed out that the yields of diastereomerically pure acetylated syn-1,2-diol 10a reported in the Table are overall yields that are obtained starting from the α -allenic alcohol 4a.

This procedure (Scheme 1) was then applied to a variety of α -allenic alcohols **4b-g**⁷ and the overall yields from **4** to **10** are reported in Table I, entries 6-13.¹¹ The dependancy of the reaction regioselectivity on the nature of the reaction solvent was observed in all of the cases that we have studied. However, the results tend to vary with respect to the solvent composition that gives the optimum isolated yield of products derived from oxygen participation.

Several points regarding these entries deserve mention. The coupling constants $J_{a,b}$ in the imino carbonates 8 range from 5.3 Hz for 8e to 6.8 Hz for 8a. Again, difference nOe experiments clearly defined the trans configuration in 8e.¹⁰ By analogy, and since all of the $J_{a,b}$ values for the imino carbonates 8 fall in the range of 5.3 to 6.8 Hz, the cyclization reaction produces solely the trans diastereomers regardless of the steric size of the R group in the α -allenic alcohol 4. In addition, several alcohol protecting groups contained in the side chain R are compatible with the reaction sequence (entries 6-8 and 12).

Finally, the cyclization of 6/7 is expected to be a kinetically controlled reaction since iodide should be effectively removed from the reaction mixture by the precipitation of AgI, thus precluding iodide involvement in a reversible process. Cyclization of 6/7 via the developing allylic cationic intermediate A/B can then explain the observed stereoselectivity in the formation of 8. In this pathway, the rotomeric intermediates A and B can be generated from <u>either</u> of the E or Z diiodides 6 or 7. Due to the steric interactions between R and the vinyl iodide moiety in the cyclization transition state arising from conformer A, the alternative mode of cyclization out of conformer B would be the energetically more favourable pathway. This latter process results in the highly diastereoselective formation of the trans imino carbamate 8 regardless of the geometry of the starting diiodide 6 or 7.¹²



We have demonstrated that the α -allenic alcohols 4 can be easily converted, via a highly diastereoselective iodocyclization process, into syn-1,2-diol derivatives 10. Since one can also prepare syn-1,2-amino alcohol derivatives 11 in high diastereometric excess from the same carbamate substrate 5,⁵ it is becoming apparent that α -allenic alcohols are extremely useful substrates for carrying out internal asymmetric induction. We are continuing to explore the novel chemistry of allenic alcohols and pursuing the sythetic utility of compounds such as 10 and 11.

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- 9. A preliminary investigation into the effect of carbamate type indicated that the tosyl carbamate was the preferred species.
- 10. Irradiation of the signal assigned to the resonance of the methylene protons (RCH₂CH₈O, δ 1.80, CDCl₃) in 8a resulted in enhancement of the resonances of both protons Ha and Hb (δ 6.05 and 6.58). Such would be observed only in the case of a trans substituted imino carbonate 8a. Similarly, irradiation of Hb (δ 4.81, CDCl₃) in 8e resulted in enhancement of R₂CH₆CH₈O (δ 1.70), confirming the trans substitution.
- 11. The cyclization of each substrate was attempted in 2-3 solvent systems with the optimum results being listed. Typically, initial reactions were carried out in 10:1 ether/MeCN solutions.
- 12. A similar stereochemical outcome is predicted even if the reaction is not stepwise as shown (S_N1 like) but is a process in which iodide departure and oxygen attack are synchronous (more S_N2' like) (see ref. 5).