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IODOCYCLIZATION REACTIONS OF α-ALLENIC ALCOHOL DERIVATIVES. STEREOSELECTIVE FORMATION OF Z-4-(1-IODO-2-ALKYL)ETHYLENE-2-TRICHLOROMETHYL-4,5-DIHYDRO-1,3-OXAZOLES

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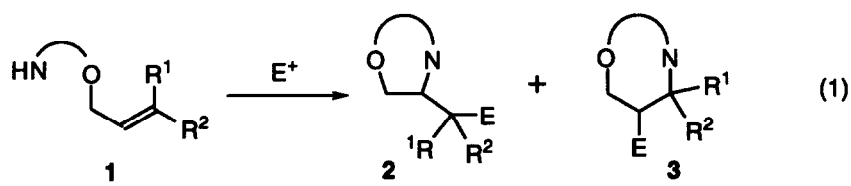
Abstract: The intramolecular iodoamination reactions of the trichloroacetimidates of primary α-allenic alcohols **4** provide the title compounds with a high degree of stereocontrol.

The electrophile initiated cyclization of allylic alcohol derivatives that contain a nucleophile tethered through the allylic oxygen has become a common method for the introduction of heteroatoms into cyclic and acyclic systems.[1] The preparation of amino alcohol derivatives via this type of cyclization stategy (eq 1) has been studied by a number of groups.[1,2] One of the general features of this reaction is that when acyclic, non-terminal trans olefinic alcohol derivatives (**1**; R^1 = H, R^2 = alkyl) are utilized, the formation of 1,3-amino alcohol derivatives (**3**) competes with the formation of the often desired 1,2-amino alcohols (**2**).[3] Thus, if one wishes to place these functional groups in a 1,2-relation, generally the cis olefins (**1**; R^1 = alkyl, R^2 = H) must be utilized as the acyclic precursor.[3]

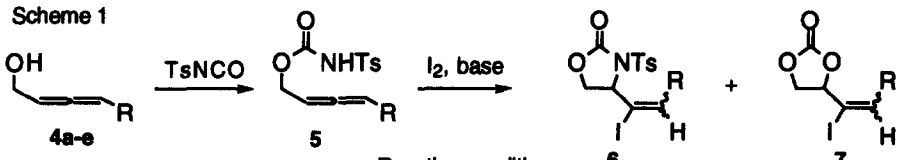


(1)

In connection with our interest in the halocyclization reactions of α-allenic alcohol derivatives,[4] we wished to study the reactions of the derivatives of primary α-allenic alcohols of 1,3-disubstituted allenes **4** for the preparation of vicinal amino alcohols (Scheme 1). These cyclization reactions were anticipated to form only those products of 1,2-functionalization and to proceed stereoselectively with respect to the emerging vinyl iodide.[5]

The requisite α-allenic alcohols **4** were prepared in excellent yield (approximately 90%) by a minor modification of the procedure described by Keck and Webb[6] wherein DMPU was substituted for HMPA.

Scheme 1



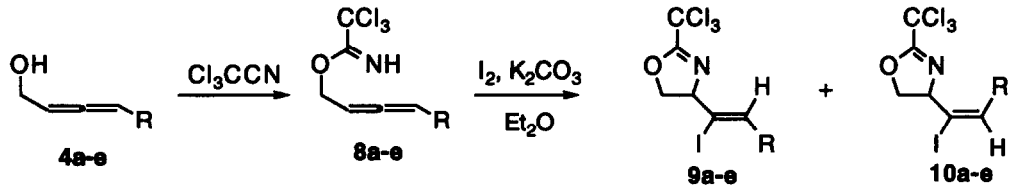
Reaction conditions	6	7
K_2CO_3, ether, rt	38%	16%
K_2CO_3, THF, reflux	44%	5%
$NaHCO_3$, aq CCl_4, rt	61%	16%
Ag_2CO_3, MeCN, rt	13%	60%

Treatment of **4a** (R = n-heptyl) with a small excess (1.1 eq) of TsNCO provided the carbamate **5** (Scheme 1). Iodocyclization[4] of **5** under a variety of reaction conditions, as described in Scheme 1, was quite disappointing since both **6** and **7** were isolated as E/Z mixtures in the yields indicated.[7] In light of these observations, we turned our attention to the trichloroacetimidate derivatives **8** since these compounds would not be plagued by problems of regioselectivity in the cyclization reaction.[8]

The trichloroacetimidates **8a-e** were prepared according to Urban and co-workers (Cl_3CCN, CH_2Cl_2, Cs_2CO_3)[9] in yields of 73-84% from the alcohols **4** (Table 1). Using the imidate **8a**, we surveyed a variety of reaction conditions in order to effect iodocyclization and provide the oxazolines **9a** and **10a**. The optimum conditions in terms of yield and stereoselectivity of cyclization were realized in ether (0.2M in allene) at room temperature in the presence of iodine (1.2 eq) and K_2CO_3 (2 eq). Iodocyclization of **8a-e** according to these standard conditions afforded the oxazolines very cleanly (Table 1). The ratios of the oxazoline stereoisomers **9:10** produced in the reactions were measured from well separated resonances in the integrated ^1H NMR spectra of the crude reaction mixtures. In each case, one major isomer was observed and subsequently identified (*vide infra*) as the Z-vinyl iodide **9**. Following standard aqueous workup, subjection of the crude reaction mixtures to column chromatography provided the major oxazolines **9** as pure compounds in yields of 58-80% (Table 1).

The major isomers were identified as the Z-olefins **9** by ^1H NMR spectroscopy. The vinyl proton resonances in the spectra of the major compounds **9** are observed upfield relative to the vinyl proton resonances of the corresponding minor isomers **10** (typically 0.3 to 0.5 ppm, Table 1). These observations are consistent with the trend observed for the vinyl proton resonances in the spectra of other Z- and E-trisubstituted iodo alkenes.[10] Furthermore, difference nOe experiments involving irradiation of the vinyl proton resonance in **9a** (δ 6.03) resulted in enhancement of the proton resonance attributed to C<u>H</u>N (δ 4.95), confirming the Z geometry in the major isomers. Similarly, irradiation of the allylic protons =C-C<u>H</u>$_2$-R' (δ 2.20) in **10a** resulted in enhancement of the resonance attributed to C<u>H</u>N (δ 5.07), confirming the E stereochemical assignment in the minor isomers.

Table 1: Iodocyclization of the Trichloroacetimidate Derivatives of Primary α-Allenic Alcohols

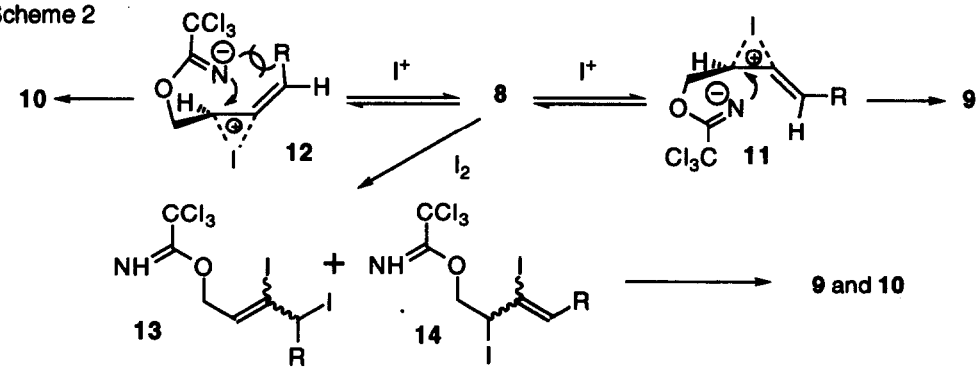


Entry	Substrate	Isolated Yield 8 (%)[a]	Ratio 9:10[b]	Vinyl Proton Chemical Shift (δ) 9; 10[c]	Isolated Yield 9 (%)[d]
1	**4a** R = $(CH_2)_6CH_3$	**8a** 76	33:1	6.03; 6.43	**9a** 80 (3)[e]
2	**4b** R = $CH_2CH(CH_3)_2$	**8b** 84	18:1	6.03; 6.45	**9b** 80
3	**4c** R = $(CH_2)_2C_6H_5$	**8c** 79	20:1	6.06; 6.44	**9c** 68
4	**4d** R = C_6H_{11}	**8d** 74	19:1	5.81; 6.30	**9d** 77
5	**4e** R = C_6H_5	**8e** 73	5:1	7.17; 7.56	**9e** 58

[a]Isolated yield from the alcohol **4**. These materials were characterized by ^1H NMR, ^{13}C NMR, IR and high resolution mass spectroscopy. [b]Measured from integrated ^1H NMR spectra of the crude reaction mixtures. [c]Chemical shift of the vinyl proton resonances ($CDCl_3$) observed in the crude reaction mixtures. [d]Isolated yield from the imidate **8**. These materials were characterized by ^1H NMR, ^{13}C NMR, IR and elemental analysis. [e]Yield in brackets refers to the isolated yield of the minor E-isomer **10a**.

The stereochemical outcome of the iodocyclization reaction is the result of a kinetically controlled process since treatment of pure **10a** under the conditions of the original reaction (I_2, K_2CO_3, ether) did not result in any of the Z-isomer **9a** being formed. Two pathways merit consideration when contemplating the mechanistic course of the cyclization reaction (Scheme 2).[11] The first pathway involves a rate limiting intramolecular attack of the imidate

Scheme 2



nitrogen on a rapidly equilibrating mixture of iodonium species such as **11** and **12**, wherein the steric interaction between the attacking nucleophile and the R group on the olefin, as in **12**, energetically disfavour transition states

that lead to the E-vinyl iodides **10**. We have carried out the cyclization reaction of **8a** using NIS as the iodonium source. Although the reaction mixture is not as clean as when using iodine, **9a** and **10a** are formed in a ratio similar to that observed in the Table, entry 1, lending support to the first mechanism. Alternatively, the formation of diiodide intermediates **13/14** followed by intramolecular S_N2/S_N2' displacement may provide **9** and **10**. When **8a** is treated with iodine, we observe the initial formation of four diiodide intermediates (by ^1H NMR) which are converted to the final products upon further reaction. In this case, iodine adds with low stereoselectively to both double bonds of the allene system.[10,11] Although this observation lends support to the second mechanistic proposal, the rationale for the cyclization stereoselectivity in this case is much less obvious. The reaction pathway is more complicated than anticipated initially and we are investigating in more detail the mechanistic course of this reaction.

Nevertheless, a stereoselective formation of the oxazoline derivatives of Z-2-amino-3-iodo-3-alken-1-ols has been developed via the iodocyclization of primary α-allenic alcohol trichloroacetimidates. The rich functionality present in these compounds enables one to consider a wide variety of subsequent synthetic operations in the context of the synthesis of polyfunctionalized acyclic materials.

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