A New Synthetic Approach to 3-Amino-1,2-diols from Allylic Alcohols *via* Trichloroacetimidates

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A new regioselective iodoamination reaction of allylic trichloroacetamides is described; the iodoaminoalcohols are obtained as the salts (**5**) *via* the corresponding 4,5-dihydro-1,3-oxazoles (**4**), and (**4a**) is converted by hydrolysis into the salt of the 3-amino-1,2-diol (**9a**).

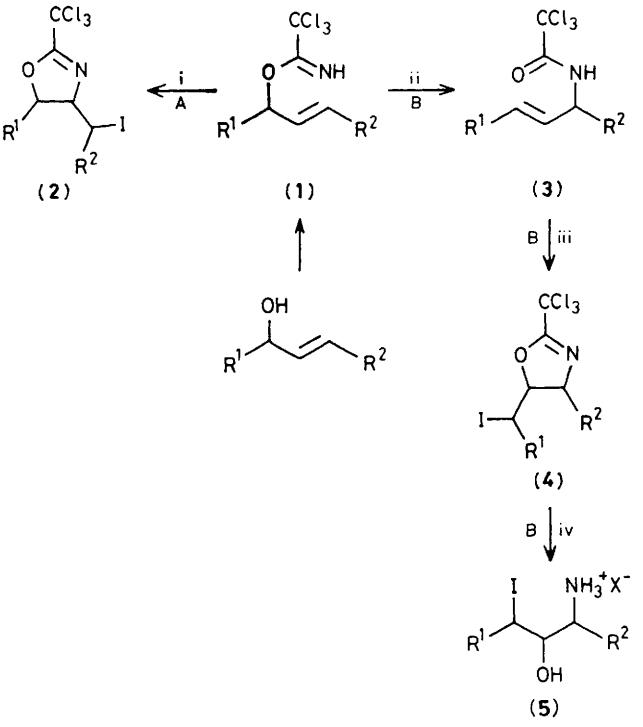
In recent papers we have described new methods for the introduction of functional groups to double bonds in the allylic or homoallylic position with respect to a hydroxy group, *via* an intramolecular ring closure allowed by the activation of the iodonium intermediate.[1] We realized that the polyfunctional sequences, 2-amino-1,3-diol and 3-amino-1,4-diol could be obtained by hydrolysis of iodo-4,5-dihydro-1,3-oxazoles (**2**) and iodo-1,3-oxazines, respectively[2] (Path A, Scheme 1).

We report here the synthesis of the iodo-4,5-dihydro-1,3-oxazoles (**4**), from allylic alcohols *via* allylic trichloroacetimidates (**1**) (Path B, Scheme 1). Thus treatment of (**3**), obtained from (**1**) by thermal rearrangement,[3] with *N*-iodosuccinimide in $CHCl_3$ afforded the iodo-4,5-dihydro-1,3-oxazoles (**4**) in good yield (Table 1).†

Only the 4,5-dihydro-1,3-oxazoles (**4**) were obtained in the cases shown in Table 1, although both five- and six-membered rings could be formed.‡ The diastereoisomeric ratios and stereochemical assignments were determined by v.p.c. and ^1H and ^{13}C n.m.r. spectroscopy.

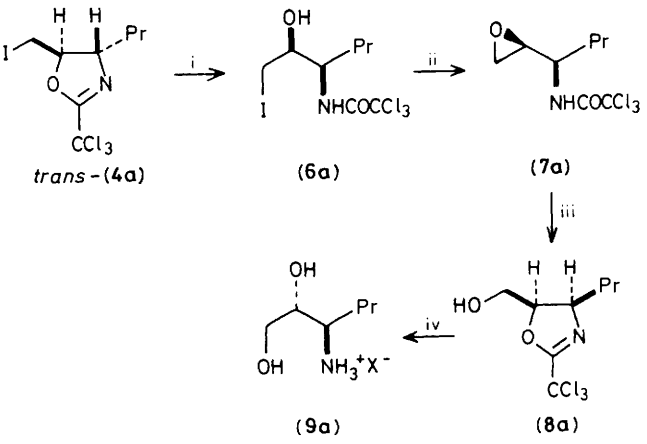
The subsequent hydrolysis of the 4,5-dihydro-1,3-oxazoles (**4**) was accomplished in methanol with an excess of 6 M HCl.[3] A mixture of trichloroacetates and hydrochlorides (**5**) of the corresponding iodoaminoalcohols was obtained in a quantitative yield (see Table 1).

The hydrolysis of pure isolated *trans*-(**4a**), performed under neutral conditions (H_2O–methanol 1 : 1; 8 h at reflux), gave the corresponding iodoamide (**6a**) in 87% yield. On stirring (**6a**) at room temperature for 5 min in methanol with an excess of carbonate anion on a polymeric support,[6] the epoxyamide (**7a**) was recovered in quantitative yield and identified by comparison with an authentic sample. However, on refluxing in



Scheme 1. i, I_2, pyridine, THF; ii, refluxing toluene; iii, *N*-iodosuccinimide, $CHCl_3$; iv, 6 M HCl.

R^1 = H, alkyl; R^2 = H, alkyl, phenyl
X^- = Cl^- : $CCl_3CO_2^-$ in a 1 : 1 mixture



X^- = Cl^- : $CCl_3CO_2^-$ in a 1 : 1 mixture

Scheme 2. i, H_2O–MeOH (1 : 1) at reflux; ii, Amberlyst A 26 in the CO_3^{2-} form, MeOH, room temp.; iii, Amberlyst A 26 in the CO_3^{2-} form, refluxing MeOH; iv, 6 M HCl.

† In a typical experiment, to a solution of the amide (**3a**) (2.4 g; 10 mmol) in $CHCl_3$ (70 ml) at room temp., *N*-iodosuccinimide (2.4 g; 10.5 mmol) was added and the mixture stirred for 4 h. The solvent was then removed *in vacuo*, the residue dissolved in $MeCO_2Et$ (100 ml), and the organic phase washed with water to remove the succinimide. The organic layer was then dried ($MgSO_4$) and the solvent removed *in vacuo*, to give the 4,5-dihydro-1,3-oxazole (**4a**) in 98% yield, *cis* : *trans* 34 : 66, determined by v.p.c.; i.r. (neat): 1660 (C=N) cm^{-1}; *cis*-isomer: ^1H n.m.r. ($CDCl_3$): δ 1 (t, 3 H), 1.4—1.9 (m, 4 H), 3.35 (d, 2 H, *J* 7 Hz), 3.8—4.3 (m, 1 H), 4.85—5.35 (dt, 1 H, *J* 7, 9 Hz); *trans*-isomer: ^1H n.m.r. ($CDCl_3$): δ 1 (t, 3 H), 1.4—1.9 (m, 4 H), 3.35 (d, 2 H, *J* 7 Hz), 3.8—4.3 (m, 1 H), 4.4—4.7 (dt, 1 H, *J* 7, 6 Hz). The 4,5-dihydro-1,3-oxazole (**4a**) (3.7 g; 10 mmol) was treated with 6 M HCl (10 ml) in refluxing methanol (30 ml) for 2 h. The solution was then evaporated and the salt (**5a**) (X^- = Cl^- : $CCl_3CO_2^-$ in a 1 : 1 mixture) was obtained after crystallization of the residue from acetone in 99% yield; ^1H n.m.r. (CD_3OD): δ 1 (t, 3 H), 1.3—1.9 (m, 4 H), 3.1—3.8 (m, 4 H), 4.85 (br.s, 4 H, OH, NH_3^+).

‡ The regioselection of carbamate cyclization, as reported in the literature,[4] depends on the electronic properties of the olefinic substituents. If an aryl substituent is present β to the methylcarbamoyl group, the intermediate cation is stabilized, affording the oxazolone, from a six-membered ring closure. The same results were observed by us for the cyclization of the trichloroacetimidates of cinnamyl and *p*-nitrocinnamyl alcohols.[5]

Table 1

Substrate (3)	Product yield, %[a]	Diastereoisomeric ratio *cis*:*trans*[b] (4)	Product yield, % (5)
a; R^1 = H, R^2 = Pr^n	98	34:66[c]	99
b; R^1 = H, R^2 = Ph	98	76:24[d]	99
c; R^1, R^2 = $-[CH_2]_3-$	97	91:9[e]	99

[a] Yields refer to pure isolated products. All new compounds gave satisfactory analytical and spectral data. [b] Determined by v.p.c. and ^1H and ^{13}C n.m.r spectroscopy. All ^1H n.m.r. data are in agreement with the assigned structures. [c] See text. [d] *cis*-Isomer: ^{13}C n.m.r.: 71.8 (C-4), 87.2 (C-5), 0.4 (CH_2I) p.p.m.; *trans*-isomer: ^{13}C n.m.r.: 88.5 (C-4), 75.5 (C-5), 5.8 (CH_2I) p.p.m. [e] *cis*-Isomer: ^1H n.m.r. ($CDCl_3$): δ C*H*O 5.15 (dd, *J* 6, 7 Hz) (ref. 5).

methanol for 1 h, (**7a**) underwent ring opening of the epoxide with participation by the neighbouring amide carbonyl group, to yield the *cis*-hydroxydihydro-oxazole (**8a**).[7,8] The expected *cis*-configuration of the oxazole ring was confirmed by ^1H n.m.r. spectroscopy ($CDCl_3$): δ 1 (t, 3 H), 1.2—1.8 (m, 4 H), 3.6 (br.s, 1 H, OH), 3.8 (d, 2 H, *J* 6 Hz), 4.0—4.7 (m, 1 H), 4.8—5.2 (dt, 1 H, *J* 6, 10 Hz). On hydrolysis with 6 M HCl, the salt (**9a**) was obtained in 99% yield (Scheme 2).

In conclusion, this method constitutes an effective route to compounds in which the neighbouring carbon atoms bear amino dihydroxy functionalities. Moreover this reaction is complementary to the previously reported iodoamination,[2] being a useful pathway to the 1-amino-2,3-diol moiety,[9] a sequence present in a number of biologically active compounds, such as β-adrenergic receptor blocking agents.[10]

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