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SYNTHESIS OF OXAZOLIDIN-2-ONES USING CARBONATE ION ON A POLYMERIC SUPPORT

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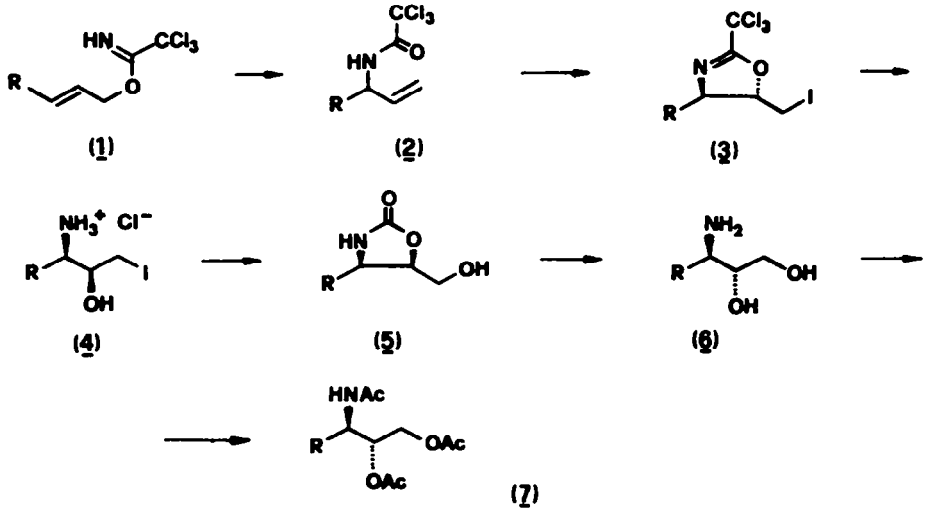
Abstract - Through the insertion of a carbon dioxide molecule, the oxazolidin-2-ones (5a) and (5b) were prepared by treatment of the salts (4a) and (4b) with carbonate anion on polymeric support. The hydrolysis under basic conditions of (5a) and (5b) afforded the erythro-3-amino-1,2-diols (6a) and (6b) which were fully acetylated: the 2-amino-2-deoxyerythritol derivative (7b) was obtained in 91% yield.

In a previous paper we reported the iodocyclization of allylic trichloroacetamides (2) that afford, under proper conditions, 4,5-dihydro-1,3-oxazoles (3). [1] The formation of the oxazole ring is a valuable reaction that results in a transfer of chirality from the secondary amide center to the carbon atom of the newly formed ring through the functionalization of the double bond. [2]

The major product (E)-(3), isolated from a diastereomeric mixture, was hydrolyzed under acidic conditions with 6N HCl in methanol, to give the corresponding salt (4) in a quantitative yield. We wish now to describe that on stirring the salts (4) with an excess of carbonate anion on a polymeric support (Amberlyst A 26) [3] in methanol at room temperature, the oxazolidin-2-one (5) were obtained in a very good yield, with the insertion of a carbon dioxide molecule.

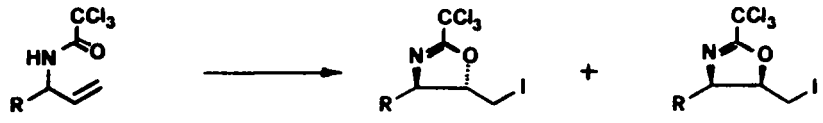
Scheme I



This result prompted us to study this new reaction which, through an intramolecular displacement of iodine allows to introduce the regio- and stereocontrolled moiety 3-amino-1,2--diol.

Thus, with the aim to synthesize aminosugars, a number of allylic trichloroacetamides (2) was prepared in good yield by thermal rearrangement of trichloroacetimidates (1).[4] According to the reported procedure [1], the iodocyclization of allylic trichloroacetamides was carried out with N-iodosuccinimide in $CHCl_3$ at room temperature and 4,5-dihydro-1,3-oxazoles (3) were obtained in a quantitative yield. The diastereomeric ratio reported in Table 1 was determined by g.l.c. analysis and ^{13}C NMR spectra of the reaction mixtures. The cyclization showed a good stereoselection for entries (2b), (2c) and (2d), while a lower stereoselection was observed in (2a) (R = n-C_3H_7). After silica gel chromatography of diastereomeric mixtures of 4,5-dihydro-1,3-oxazoles (3), the pure (E)-isomers were obtained.

Table 1



(2) E-(3) Z-(3)

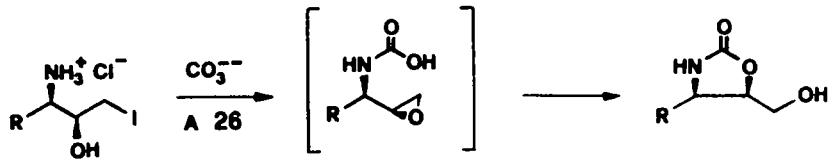
	Diastereomeric ratio E:Z*
a. R = n-C_3H_7	66 : 34
b. R = $PhCH_2OCH_2$	80 : 20
c. R = $HOCH_2$	95 : 5**
d. R = t-$BuPh_2SiOCH_2$	90 : 10

* Determined by g.l.c. and ^{13}C NMR ** The E configuration was assigned to the major isomer on the basis of its ^{13}C NMR spectrum[7]

Acidic cleavage with 6N HCl in methanol, removal of the solvent and washing of the residue with ethyl acetate afforded the salts (4) in very good yield. Under these conditions the labile protecting group t-butyldiphenylsilyl in (3d) [5] was removed to afford the salt (4c). The successive conversion to oxazolidin-2-ones (5) was carried out by treatment of (4a) or (4b) with an excess of Amberlyst A 26 in the CO_3^{--} form at room temperature in methanol. After stirring for 24 h, (5a) and (5b) were obtained in 84% and 87% yield, respectively, simply by filtering off the resin and evaporating the solvent. The presence of a five-membered cyclic urethane was evident from the i.r. spectra, that showed the carbonyl absorption at 1745 cm^{-1}. Moreover, starting from the threo-salts (4a) and (4b), only (Z)-oxazolidin-2-ones were obtained with invertion at C-5, as shown by ^1H NMR chemical shifts (Z-(5a): δ H-4, 4.0; H-5, 4.75; Z-(5b): δ H-4, 4.1; H-5, 4.7). [6] This assignment was further confirmed by ^{13}C NMR chemical shifts of (E,Z)-diastereomeric mixtures of (5a) and (5b) (E-(5a): δ_C 38.6 ($\underline{C}H_2CHN$), 63.3 ($\underline{C}H_2OH$); Z-(5a): δ_C 32.8 ($\underline{C}H_2CHN$), 60.8 ($\underline{C}H_2OH$). E-(5b): δ_C 63.5 ($\underline{C}H_2OH$), 72.4 ($\underline{C}H_2OCH_2Ph$); Z-(5b): δ_C 60.8 ($\underline{C}H_2OH$), 69.4 ($\underline{C}H_2OCH_2Ph$). [7]

To explain this result we suggest that, in the presence of CO_3^{--}, the iodide displacement occurred first to give an amino epoxide which was successively opened to afford exclusively

oxazolidin-2-ones with inversion of the original C-5 configuration through the insertion of a carbon dioxide molecule: [8]



(4) (5)

This hypothesis was supported by the isolation, in the early step of the reaction carried out with (4b), of a raw product which showed absorptions at 1745 cm^{-1} (-NH-COO-) in the i.r. spectrum and a characteristic oxirane pattern at δ 2.5 - 3.0 in the ^1H NMR spectrum.

Any attempt to obtain a oxazolidin-2-one from the salt (4c) failed, probably owing to the presence of a free hydroxyl group. The stereochemistry of (5a) and (5b) was successively exploited for the synthesis of a stereocontrolled 3-amino-1,2-diol moiety [9]. Thus the hydrolytic cleavage of (5a) under basic conditions (KOH/MeOH) [10] afforded quantitatively the aminodiol (6a) which was directly acetylated to the erythro-(7a) in 93% yield. Following the same reaction sequence, on (5b), the derivative of 2-amino-2-deoxy-erythritol (7b) was obtained in 91% yield.

EXPERIMENTAL

General Methods.

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ or sodium/benzophenone immediately prior to use. All reactions involving organometallic reagents were carried out under an argon atmosphere. Melting points (Pyrex capillary) were determined on a Buchi 510 hot stage apparatus and are uncorrected. I.r. spectra were obtained with a Perkin-Elmer Model 682 spectrophotometer either on film or, for solids, as Nujol mull. ^1H N.m.r. spectra were recorded on either a Perkin-Elmer R 12B (60 MHz) or a Varian XL-100 (100 MHz) or a Bruker WH 300 (300 MHz) for solutions in deuteriochloroform (tetramethylsilane as internal reference), unless otherwise reported. All chemical shifts were reported as p.p.m. downfield from the tetramethylsilane position on the δ scale. ^{13}C N.m.r. spectra (25 MHz) were recorded using a Varian FT 80-A spectrometer. All chemical shifts, δ (p.p.m.), were measured relative to tetramethylsilane assigned at zero. Mass spectra were obtained with a double focusing Varian MAT 112 at an ionizing voltage of 70 eV. Mass spectral data are tabulated as m/z values. Analytical g.l.c. was carried out on a Carlo Erba capillary gas chromatograph (Fractovap 4160) equipped with a SE-52 flexible glass capillary column (25 m x 0.3 mm i.d.; carrier gas He, p_{He} = 0.6 kg/cm^2). Chromatograms, peak areas and retention times were obtained by using a Perkin-Elmer Sigma 10 data processor. Thin-layer chromatography (t.l.c.) and column chromatography were carried out on Kieselgel GF_{254} (Merck). Solvent ratios are in volumes before mixing. Solutions were dried over anhydrous magnesium sulphate.

(E)-1-Trichloroacetimido-2-hexene (1a)

92% yield; colorless oil; i.r. (neat) 3340 and 1660 cm^{-1}; δ 0.95 (t, 3H, CH_3), 1.1 - 1.8 (m, 4H, CH_2), 4.8 (d, 2H, $CH_2OC(CCl_3)=NH$; J = 7 Hz), 5.6 - 6.1 (m, 2H, CH=CH), 8.3 (bs, 1H, C=NH).

(Z)-4-Benzyloxy-1-trichloroacetimidobut-2-ene (1b)

90% yield; colorless oil; i.r. (neat) 3300 and 1650 cm^{-1}; δ 4.15 (m, 2H, CH_2OCH_2Ph), 4.5 (s, 2H, $PhCH_2O$), 4.85 (m, 2H, $CH_2OC(CCl_3)=NH$), 5.85 (m, 2H, CH=CH), 7.3 (m, 5H, ArH), 8.3 (bs, 1H, C=NH).

(Z)-4-Trichloroacetimidobut-2-en-1-ol (1c)

60% yield; colorless oil; i.r. (neat) 3340 and 1660 cm^{-1}; δ 1.1 (s, 9H, $C(CH_3)_3$), 4.35 (d, 2H, CH_2OH; J = 7Hz), 4.7 (bs, 1H, OH), 5.0 (d, 2H, $CH_2OC(CCl_3)=NH$; J = 7Hz), 5.5 - 6.1 (m, 2H, CH=CH), 8.4 (bs, 1H, C=NH).

(Z)-4-t-Butyldiphenylsilyloxy-1-trichloroacetimidobut-2-ene (1d)

83% yield; colorless oil; i.r. (neat) 3340 and 1660 cm^{-1}; δ 4.35 (d, 2H, CH_2OSi; J = 6Hz),

4.7 (d, 2H, $CH_2OC(CCl_3)=NH$; J = 6Hz), 5.4 - 6.2 (m, 2H, CH=CH), 7.1 - 7.9 (m, 10H, ArH), 8.25 (bs, 1H, C=NH).

3-Trichloroacetamidohex-1-ene (2a)

83% yield; colorless oil; i.r. (neat) 3420, 3340, 1710, 1510 and 930 cm^{-1}; δ 0.95 (t, 3H, CH_3), 1.2 - 1.9 (m, 4H, CH_2), 4.25 - 4.80 (m, 1H, CHNH), 5.1 - 6.3 (m, 3H, $CH=CH_2$), 6.75 (m, 1H, NH).

4-Benzyloxy-3-trichloroacetamido-1-butene (2b)

88% yield; colorless oil; i.r. (neat) 3420, 3340, 1710, 1505 and 925 cm^{-1}; δ 3.6 (d, 2H, CH_2OCH_2Ph; J = 6 Hz), 4.2 - 4.7 (m, 1H, CHNH), 4.55 (s, 2H, $PhCH_2O$), 5.0 - 6.0 (m, 3H, $CH=CH_2$), 7.35 (m, 6H, ArH + NH).

2-Trichloroacetamido-3-buten-1-ol (2c)

75% yield; colorless oil; i.r. (neat) 3400, 3330, 1700, 1510 and 925 cm^{-1}; δ 2.8 (bs, 1H, OH), 3.8 (d, 2H, CH_2OH; J = 5 Hz), 4.35 - 4.75 (m, 1H, CHNH), 5.1 - 6.3 (m, 3H, $CH=CH_2$), 7.25 (d, 1H, NH).

4-t-Butyldiphenylsilyloxy-3-trichloroacetamido-1-butene (2d)

85% yield; colorless oil; i.r. (neat) 3410, 3335, 1705, 1505 and 930 cm^{-1}; δ 1.1 (s, 9H, $C(CH_3)_3$), 3.85 (d, 2H, CH_2OSi; J = 6 Hz), 3.75 - 4.4 (m, 1H, CHNH), 5.1 - 6.1 (m, 3H, $CH=CH_2$), 7.1 - 7.9 (m, 10H, ArH), 8.2 (m, 1H, NH).

General procedure for preparation of (3)

To a stirred solution of (2) (25 mmol) in $CHCl_3$ (100 ml), N-iodosuccinimide (27 mmol) was added at room temperature. After 8 h the reaction mixture was diluted with $CHCl_3$ (150 ml) and successively washed with 10% aqueous $Na_2S_2O_3$ and water, and then dried. The solvent was removed under reduced pressure to afford (3) in very good yield.

(E)- and (Z)-4-Propyl-5-iodomethyl-2-trichloromethyl-4,5-dihydro-1,3-oxazole (3a)

98% yield; colorless oil; (E):(Z) ratio 66:34; i.r. (neat): 1660 cm^{-1}; (Z)-isomer: δ 1.0 (t, 3H, CH_3), 1.4 - 1.9 (m, 4H, CH_2), 3.35 (d, 2H, CH_2I; J = 7 Hz), 3.8 - 4.3 (m, 1H, CHNH), 4.85 - 5.35 (dt, 1H, CHO; J = 7, J = 9 Hz); (E)-isomer: 1.0 (t, 3H, CH_3), 1.4 - 1.9 (m, 4H, CH_2), 3.35 (d, 2H, CH_2I; J = 7 Hz), 3.8 - 4.3 (m, 1H, CHN), 4.4 - 4.7 (dt, 1H, CHO; J = 7, J = 6 Hz).

(E)- and (Z)-4-Benzyloxymethyl-5-iodomethyl-2-trichloromethyl-4,5-dihydro-1,3-oxazole (3b)

96% yield; m.p. 81 - 83 °C; (E):(Z) ratio 80:20; (E)-isomer: i.r. (neat) 1660 cm^{-1}; δ 3.35 (d, 2H, CH_2I; J = 6 Hz), 3.6 (m, 2H, CH_2OCH_2Ph), 4.2 (m, 1H, CHN), 4.55 (s, 2H, $PhCH_2O$), 4.8 (q, 1 H, CHO; J = 6 Hz), 7.3 (m, 5H, ArH).(Z)-isomer: i.r. (neat) 1660 cm^{-1}; δ 3.3 - 4.0 (m, 4H, CH_2I, CH_2OCH_2Ph), 4.0 - 4.5 (m, 1H, CHN), 4.55 (s, 2H, $PhCH_2O$), 5.3 (dt, 1H, CHO; J = 4, J = 10 Hz), 7.35 (m, 5H, ArH).

(E)- and (Z)-4-Hydroxymethyl-5-iodomethyl-2-trichloromethyl-4,5-dihydro-1,3-oxazole (3c)

90% yield; colorless oil;(E):(Z) ratio 95:5; i.r. (neat): 3360 and 1655 cm^{-1}; (E)-isomer: δ 3.1 (bs, 1H, OH), 3.85 - 4.9 (m, 6H, CH_2I, CH_2OH, CHO, CHN); δ_C 6.0, 63.6, 74.1, 83.3.

(E)- and (Z)-4-t-Butyldiphenylsilyloxy-5-iodomethyl-2-trichloromethyl-4,5-dihydro-1,3-oxazole (3d)

93% yield; colorless oil; (E):(Z) ratio 90:10; i.r. (neat) 1660 cm^{-1}; (E)-isomer: δ 1.0 (s, 9H, $C(CH_3)_3$, 3.35 (d, 2H, CH_2I; J = 6 Hz), 3.5 - 4.4 (m, 3H, CH_2OSi, CHN), 5.0 (q, 1H, CHO; J = 6 Hz), 7.3 - 8.0 (m, 10H, ArH); δ_C 6.2, 26.8, 64.3, 74.0, 83.1, 127.8, 129.8, 135.5; (Z)-isomer: δ_C -1.8, 59.9, 69.0, 86.0, 127.8, 129.8, 135.5.

General procedure for preparation of (4)

A stirred solution of (3) (10 mmol) in methanol (5 ml) was treated with 6N HCl (3 ml) and stirred for 24 h at room temperature. After removal of the solvent under reduced pressure, the residue was washed with ether and (4) was obtained in a quantitative yield as a viscous oil.

(Threo)-3-amino-1-iodohexan-2-ol hydrochloride (4a)

i.r. 3330, 1610 and 1590 cm^{-1}; δ 1.0 (t, 3H, CH_3), 1.3 - 1.9 (m, 4H, CH_2), 3.1 - 3.8 (m, 4H, CH_2I, CHO, CHN), 4.85 (bs, 4H, OH, NH_3^+).

(Threo)-3-amino-4-benzyloxy-1-iodobutan-2-ol hydrochloride (4b)

i.r. (neat) 3350 and 1600 cm^{-1}; δ 2.8 (bs, 4H, OH, NH_3^+), 3.2 - 3.5 (m, 2H, CH_2I), 3.5 - 4.0 (m, 4H, CH_2OCH_2Ph, CHO, CHN), 4.6 (s, 2H, $PhCH_2O$), 7.4 (m, 5H, ArH).

(Threo)-3-amino-1-iodobutan-2,4-diol (4c)

i.r. (neat) 3250 and 1600 cm^{-1}; δ 3.2 - 3.5 (m, 2H, CH_2I), 3.5 - 4.1 (m, 4H, CH_2OH, CHOH, CHN), 4.8 (bs, 5H, OH, NH_3^+).

General procedure for preparation of (5)

To a stirred solution of (threo)-(4) (10 mmol) in methanol (40 ml), Amberlyst A 26 (CO_3^{--}) (11 g; 3.8 mequiv/g) was added and the suspension stirred for 48 h at room temperature. The resin was filtered off, the solvent removed under reduced pressure and (Z)-(5) was obtained in good yield after chromatography through silica gel (ethyl acetate as eluant).

(Z)-4-Propyl-5-hydroxymethyloxazolidin-2-one (5a)

84% yield; colorless oil; i.r. (neat) 3330 and 1745 cm^{-1}; δ 0.95 (t, 3H, CH_3), 1.2 - 1.7

(m, 4H, CH_2), 3.8 (d, 2H, CH_2OH; J = 7 Hz), 4.0 (dt, 1H, CHN; J = 5, J = 7 Hz), 4.75 (dt, 1H, CHO; J = 5, J = 7 Hz), 4.9 (bs, 2H, OH, NH); δ_C 14.2, 20.5, 32.8, 55.6, 60.8, 81.2, 161.9. Found: C, 52.79; H, 8.21%. $C_7H_{13}NO_3$ requires C, 52.81; H, 8.23%.

(Z)-4-Benzyloxy-5-hydroxymethyloxazolidin-2-one (5b)

87% yield; colorless oil; i.r. (neat) 3330 and 1740 cm^{-1}; δ 3.65 (m, 2H, CH_2OCH_2Ph), 3.85 (m, 2H, CH_2OH), 4.1 (dt, 1H, CHN; J = 5, J = 7Hz), 4.6 (s, 2H, OCH_2Ph), 4.7 (m, 1H, CHO; J = 5, J = 7 Hz), 4.9 (bs, 2H, OH, NH), 7.4 (m, 5H, ArH); δ_C 55.1, 60.8, 69.4, 74.2, 80.4, 128.6, 129.3, 139.0, 161.6. Found: C, 60.73, H, 6.35%. $C_{12}H_{15}NO_4$ requires C, 60.75, H, 6.37%.

General procedure for preparation of (7)

To a solution of (5) (5 mmol) in ethanol (20 ml), KOH (10 mmol) dissolved in ethanol (15 ml) was added and the mixture refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue (6) was treated with pyridine (2 ml) and Ac_2O (3 ml). After 12 h the excess pyridine and Ac_2O were removed under reduced pressure and the residue was chromatographed through silica gel (ethyl acetate as eluant) to afford the triacetate (7).

(Erythro)-3-acetamido-1,2-diacetoxyhexane (7a)

93% yield; colorless oil; i.r. (neat) 3270, 1745, 1655 and 1540 cm^{-1}; δ 0.95 (t, 3H, CH_3), 1.1 - 1.7 (m, 4H, CH_2), 2.0 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.1 (s, 3H, CH_3CO), 3.95 - 4.45 (m, 3H, CHN, CH_2O), 4.85 - 5.25 (m, 1H, CHO), 6.1 (d, 1H, NH, J = 8 Hz); δ_C 13.8, 19.0, 20.8, 21.0, 23.2, 32.7, 48.8, 63.2, 73.3, 170.2, 170.7, 170.8; MS(m/e) 259 (M^+), 214, 156, 139, 114, 72. Found: C, 55.55, H, 8.14%. $C_{12}H_{21}NO_5$ requires C, 55.58, H, 8.16%.

(Erythro)-3-acetamido-1,2-diacetoxy-4-benzyloxybutane (7b)

91% yield; colorless oil; i.r. (neat) 3280, 1745, 1650 and 1535 cm^{-1}; δ 2.0 (bs, 9H, CH_3CO), 3.5 (m, 2H, CH_2OCH_2Ph), 4.2 (m, 2H, CH_2OAc), 4.5 (s, 2H, $PhCH_2O$), 4.3 - 4.7 (m, 1H, CHN), 5.2 (m, 1H, CHOAc), 6.95 (d, 1H, NH; J = 10 Hz), 7.3 (m, 5H, ArH); δ_C 20.7, 20.8, 23.0, 48.2, 63.0, 68.2, 70.3, 73.2, 127.9, 128.4, 137.7, 170.1, 170.7; MS(m/e) 337 (M^+), 262, 250, 188, 170, 114, 91. Found: C, 60.49; H, 6.84%. $C_{17}H_{23}NO_6$ requires C, 60.52; H, 6.87%.

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