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Note

Solvent and salt dependent 1,3-dipolar cycloaddition : Synthesis of isoxazolidino- and isoxazolino-carbocycles

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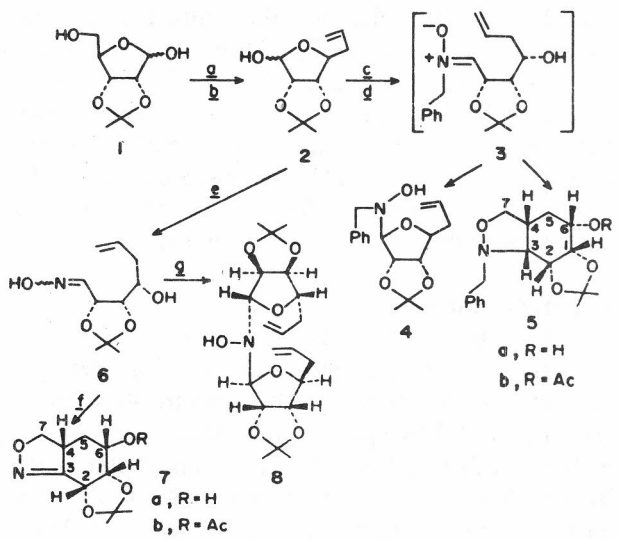
1,3-Dipolar nitrone/nitrile oxide cycloaddition of **2** in different solvents requires metal co-ordination to obtain high yields of desired products, isoxazolidino- and isoxazolino-carbocycles (**5** and **7**).

As a part of our programme on the synthesis of polyhydroxylated amino-carbocycles, intermediates for carbocyclic nucleosides[1] and a variety of glycosidase inhibitors[2], we have been using intramolecular nitrone[3] and nitrile oxide[4] cycloaddition reactions with sugar derivatives utilizing the carbon skeleton and the resident chirality of the starting sugars for the synthesis of enantiomerically pure non-carbohydrate compounds. Such 1,3-dipolar cycloaddition reactions have been shown, in simple intermolecular systems, to be solvent[5] and metal co-ordination[6] dependent and the use of non-co-ordinating solvents is essential for achieving excellent stereoselection. We have extended the results to polysubstituted, intramolecular systems and report herein the results of such reactions on compound **2** (Scheme I) in different solvents with or without added salts and a crown-ether.

The allylated sugar derivatives **2** were prepared from 2,3-*O*-isopropylidene-D-ribose **1**[7] in two steps following the procedure described for similar compounds[8]. Treatment of **2** with *N*-benzylhydroxylamine in benzene afforded only the undesired product **4** as an oil (92%), arising via *in situ* cyclization of the intermediate nitrone **3**. The same product was also formed when other solvents like acetonitrile, diglyme, THF, DMSO or DMF were used. On the other hand, no change in the starting material was noticed when polar protic solvents like EtOH and MeOH were employed. The desired 1,3-dipolar cycloaddition reaction could, however, be achieved by adding a small quantity of $NaHCO_3$ or $Mg(ClO_4)_2$ (a combination of $NaHCO_3$ and 18-crown-6 for benzene) to the reaction mixture yielding **5a** in a high yield.



Scheme I—(a) Allyl-MgBr, THF, 0°C, 2 hr; (b) $NaIO_4$, EtOH, 10°C, 45 min; (c) $PhCH_2NHOH$ (1.3 eq), C_6H_6, rt, 18 hr; (d) $NaHCO_3$, 18-crown-6; (e) $NH_2OH.HCl$, Py, rt, 6 hr; (f) chloramine-T (2 eq), EtOH, rt, 18 hr; (g) Δ, toluene, 6hr

Apparently, in solvents which cannot co-ordinate with the alcoholic group, the reaction results in cyclization involving the hydroxyl function; when metal salts were added to these solvents (using a crown-ether to solvate the salt with benzene/toluene), the hydroxyl group in **3** co-ordinates to the metal ion to prevent the formation of **4** and the desired 1,3-dipolar cycloaddition occurs. In co-ordinating solvents the nitrone intermediate **3** is not formed without the addition of salts which may co-ordinate with the alcoholic part of the allyl group to create a suitable condition for the reaction.

In the case of nitrile oxide cycloaddition, it was observed that attempted oxidation of oxime **6** using chloramine-T did not occur in apolar solvents like benzene or toluene. Under forcing condition (refluxing in toluene for 6 hr) also, only the dimer **8** could be obtained (10%; 22% by refluxing **6** or a mixture of **2** and **6** in toluene). However, when the reaction was carried out in dry EtOH, the expected isoxazoline derivative **7a** was formed (68%, identified as **7b**). Even in dry benzene, the desired transformation could be smoothly carried out with the incorporation of a small quantity of

18-crown-6, which perhaps acts by solvating the metal ion of the oxidant.

Regarding the structure and stereochemistry of **5b** and **7b**, the appearance of only one upfield triplet in the ^{13}C NMR spectra (at δ 24.9 in **5b** and 26.7 in **7b**) ruled out the bridged-ring structures. The absolute configuration at other centres being known, only those at C-3 and C-4 in **5b** and C-4 in **7b** remained to be determined. High-field NMR spectral analysis and molecular modelling studies using DTMM coupled with $3J_{HH}$ calculations showed preference for the indicated structures with boat-like conformation.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a JASCO-700 spectrophotometer. ^1H and ^{13}C NMR spectra were measured respectively on a JEOL FX-100 FT spectrometer and a Bruker AM 300L spectrometer using TMS as internal standard, and mass spectra on a JEOL AX-500 spectrometer at 70 eV.

5-Allyl-2-hydroxy-3, 4-*O*-isopropylidene-tetrahydrofuran 2. To a solution of allylmagnesium bromide [prepared from allyl bromide (3.70 g), Mg-turning (0.80 g) and a catalytic amount of iodine] in dry THF (30 mL) at 0°C was added dropwise a solution (20 mL) of **1** (1.90 g, 10 mmoles) in the same solvent. After stirring (2 hr at 0°C, then 1 hr at rt), the reaction mixture was decomposed (cold water) and filtered (Celite). The solvent was evaporated and the residue extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was dissolved in EtOH (40 mL), $NaIO_4$ (2.14 g, 10 mmoles) added to it portionwise and the mixture stirred for 45 min at 10°C, filtred, solvent evaporated and the product extracted with $CHCl_3$ (3 × 50 mL). Drying (Na_2SO_4) and solvent evaporation gave a gummy material which was purified by column chromatography using pet. ether-$CHCl_3$ (1:1) as eluent to afford **2** (1.56 g, 78%) as an oil: $[\alpha]_D^{24} - 3.9°$ (*c* 0.36, $CHCl_3$); IR (neat): 3400, 1641 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (s, 3H), 1.50 (s, 3H), 2.44 (m, 2H), 3.06 (brs, 1H), 4.28 (t, 1H, J = 8 Hz), 4.64 (brs, 2H), 5.14 (m, 2H), 5.46 (brs, 1H), 5.84 (m, 1H); EIMS : m/z 200 ($M^{+\cdot}$).

5-Allyl- 2 -(*N*-hydroxy-*N*-benzylamino)-3, 4-*O*-isopropylidene-tetrahydrofuran 4. *N*-Benzylhydroxylamine (800 mg, 6.3 mmoles) was added to a solution of **2** (1.00 g, 5 mmoles) in benzene (50 mL) and the mixture stirred at rt for 18 hr. After removal of solvent the residue dissolved in $CHCl_3$, and the solution washed (water), dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography over silica gel using pet. ether-$CHCl_3$ (1 : 4) to afford **4** (1.30 g, 92%) as a gum : $[\alpha]_D^{24} - 72.4°$ (*c* 0.30, $CHCl_3$); IR (neat): 3440, 1640, 732, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (s, 3H), 1.52 (s, 3H), 2.48 (m, 2H), 3.86 (d, 1H, J = 13.0 Hz), 4.10 (d, 1H, J = 13.0 Hz), 4.46 (dd, 1H, J = 4.0, 6.0 Hz), 4.80 (m, 3H), 5.18 (m, 2H), 5.88 (m, 1H), 7.34 (m, 5H); CIMS : m/z 306 ($M^+ + H$), 305 (M^+).

Isoxazolidinocarbocyclic derivatives 5a,b. To a solution of **2** (500 mg, 2.5 mmoles) in benzene (20 mL), $NaHCO_3$ (100 mg) and a catalytic amount of 18-crown-6 (5 mg) were added and the mixture was stirred for 30 min. *N*-Benzyl hydroxylamine (400 mg, 3.2 mmoles) was added and the mixture stirred for 16 hr at rt. Work-up in the usual way gave the crude product which on purification by column chromatography over silica gel using $CHCl_3$-MeOH (99 : 1) furnished **5a** as a gum (733 mg, 85%). Acetylation (Ac_2O-Py) of **5a** furnished the acetate **5b**: $[\alpha]_D^{24} + 54.6°$ (*c* 0.40, $CHCl_3$); IR (neat): 1731, 731, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.51 (s, 3H), 2.01 (m, 1H), 3.12 (dd, 1H, $J_{3,2}$ = 2.3 Hz, $J_{3,4}$ = 8.7 Hz), 3.70 (dd, 1H, $J_{7a,4}$ = 5.9 Hz, $J_{7a,7b}$ = 8.3 Hz), 3.68 (d, 1H, J = 3.9 hz), 4.06 (d,1H, J = 13.9 Hz), 4.17 (t, 1H, $J_{7b,4}$ = 8.1 Hz, $J_{7a,7b}$ = 8.3 Hz), 4.26 (dd, 1H, $J_{2,3}$ = 2.3 Hz, $J_{2,1}$ = 7.5 Hz), 4.44 (dd, 1H, $J_{1,6}$ = 3.2 Hz, $J_{1,2}$ = 7.5 Hz), 5.36 (dt, 1H, $J_{6,5b}$ = 3.1 Hz, $J_{6,1}$ = 3.2 Hz, $J_{6,5a}$ = 13.3 Hz), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.3, 23.9, 26.1 (3 × q), 24.9, 61.3, 72.0 (3 × t), 38.6, 65.4, 68.1, 72.7, 74.5, 127.4 (6xd), 128.3 (2xd), 128.8 (2 × d), 108.7, 137.1, 170.6 (3 × s); EIMS : m/z 347 (M^+), 332 ($M^+ - 15$), 253, 211, 163, 148, 121, 105, 91; Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found : C, 65.61; H, 7.29; N, 3.89%.

Oxime 6. To a solution of **2** (2.00 g, 10 mmoles) in pyridine (20 mL) was added $NH_2OH.HCl$ (742 mg, 0.7 mmoles) and the mixture stirred for 6 hr. The solvent was evaporated and the residue chromatographed over a silica gel column. Elution with $CHCl_3$-MeOH (19 : 1) afforded **6** (1.98 g, 92%); ^1H NMR ($CDCl_3$): δ 1.36 (s, 3H), 1.48 (s, 3H), 6.93 and 7.52 (2 × d, J = 6.0 Hz, *syn*- and *anti*-oxime).

Isoxazolinocarbocyclic derivatives 7a, b. Chloramine-T trihydrate (563 mg, 2 mmoles) was added to a solution of **6** (215 mg, 1 mmoles) in dry EtOH (10 mL) and the mixture stirred at rt for 18 hr, filtered, solvent evaporated and the residue purified by column chromatography using

$CHCl_3$-MeOH (49 : 1) as eluent to obtain **7a** (145 mg, 68%), characterized as acetate **7b**: m.p. 82-84°; $[\alpha]_D^{24}+62.9°$ (*c* 1.25, $CHCl_3$); IR (KBr): 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (s, 3H), 1.56 (s, 3H), 1.65 (m, 1H), 2.41 (m, 1H), 3.73 (m, 1H), 3.94 (dd, 1H, $J_{7a,7b}=8.3$ Hz, $J_{7a,4}=12.1$ Hz), 4.61 (dd, 1H, $J_{1,6}=2.5$ Hz, $J_{1,2}=7.3$ Hz), 4.70 (dd, 1H, $J_{7a,7b}=8.3$ Hz, $J_{7b,4}=11.0$ Hz), 4.89 (ddd, 1H, $J_{1,6}=2.8$ Hz, $J_{5a,6}=4.4$ Hz, $J_{5b,6}=11.1$ Hz), 5.07 (d, 1H, $J_{1,2}=7.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 20.9, 23.9, 25.8 (3×q), 26.7, 75.9 (2×t), 39.8, 67.9, 69.0, 75.5 (4×d), 111.2, 155.9, 169.8 (3×s); CIMS: m/z 256 ($M+H^+$), 240, 198, 180, 138; Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.39; H, 6.72; N, 5.41%.

***N*, *N*-Di-(5-allyl-3, 4-*O*-isopropylidene-tetrahydrofuran-2-yl)hydroxylamine 8.** A solution of **6** (1.10 g, 5 mmoles) in toluene (50 mL) was heated at reflux for 6 hr. The solvent was evaporated and the product purified by column chromatography using $CHCl_3$ as eluent to yield **8** (99 mg, 10%): m.p. 140-42°; $[\alpha]_D^{24}+30.0°$ (*c* 0.32, $CHCl_3$); IR (KBr): 3362, 1641 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.51 (s, 3H), 2.43 (m, 2H), 4.12 (dt, 1H, $J=3.6$, 7.1 Hz), 4.43 (dd, 1H, $J=3.6$, 5.9 Hz), 4.92 (m, 2H), 5.17 (m, 2H), 5.83 (m, 1H); CIMS: m/z 398 ($M^+ +H$), 382 ($M^+ -15$), 199, 183; Anal. Calcd for $C_{20}H_{31}NO_7$: C, 44.36; H, 5.77; N, 2.59. Found: C, 44.34; H, 5.78; N, 2.46%.

In a similar fashion, refluxing 1 mmole each of **2** and **6** in toluene (10 mL) for 6 hr and work-up as above gave **8** in 22% yield.

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