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THE SYNTHESIS OF OPTICALLY PURE β-LACTAMS DERIVED FROM SUGARS. HIGH-PRESSURE [2+2] CYCLOADDITION OF TOLUENE-4-SULPHONYL ISOCYANATE TO GLYCALS.

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Abstract: [2+2] Cycloaddition of toluene-4-sulphonyl isocyanate to glycals 1 - 4 at room temperature under 10 kbar pressure gave respective β-lactams 5 - 8 in good yields. The reaction proceeds regio- and stereospecifically to afford the four-membered ring in position trans to the acetoxy group at C-3 of the glycal moiety.

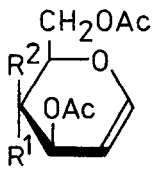
Addition of isocyanates to glycals is a potential way for the synthesis of enantiomerically pure β-lactams. Owing to the enol ether structure of glycals, [2 + 2] cycloaddition should lead to the formation of cyclic N-glycosylamido derivatives, which can be precursors of various β-lactams, particularly of oxapenams and oxacephams.

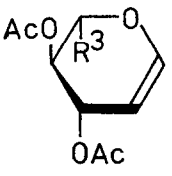
[2 + 2] Cycloaddition of isocyanates to 3,4-dihydro-2H-pyran derivatives has already been attempted several times,[1-3] but only in the case of unsubstituted[1] or 5-substituted[3] 3,4-dihydro-2H-pyran, the corresponding β-lactams were obtained. Glycals were found to be unreactive in cycloaddition of this type; isocyanate acts only as a Lewis acid, causing known dimerization of sugar substrate.[2]

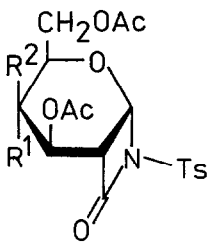
Despite these discouraging reports, we decided to return to the problem of [2 + 2] cycloaddition of isocyanates to glycals using the high-pressure technique. It is well known that high pressure accelerates the rate of reactions characterized by negative volumes of activation, and greatly enhances stereoselectivity, whereas it retards the retro-reaction. For [2 + 2] cycloadditions the volume of activation varies from -30 to -50 cm^3/mol, and this promises significant acceleration of the reaction by high-pressure.[4]

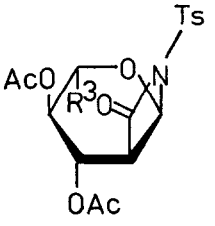
Toluene-4-sulphonyl isocyanate and glycals 1 - 4 were selected as model compounds. All high-pressure experiments were performed according to the technique described previously.[5] The isocyanate (1.5 equiv.) was condensed with glycals 1 - 4 (1 equiv.) in ether solution at room temperature under 10 kbar for 18 hrs. Except product 6 derived from galactal 2, products 5,7 and 8 crystallized from the reaction mixture in pure from in good yields (60-77%).[6] Compound 6 was obtained and characterized only as a crude syrup, spontaneously separated

from ether solution and evaporated to dryness. The β-lactam structure of compounds 5 - 8 was determined from their spectral and analytical data.[7] The cycloadditions proceeded regio- and stereospecifically, yielding a single isomer in each case; the isocyanate enters exclusively the trans position relative to the acetoxy group at C-3.









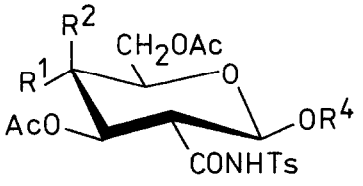
1:R^1=OAc, R^2=H
2:R^1=H, R^2=OAc

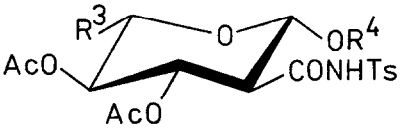
3:R^3=CH_3
4:R^3=H

5:R^1=OAc, R^2=H
6:R^1=H, R^2=OAc

7:R^3=CH_3
8: R^3=H

The configurations of 5 - 8 were assigned via opening of the β-lactam ring with alcohol or water. Upon heating in toluene solution, compounds 5 - 8 undergo retro-addition to afford the starting glycals. When treated with alcohols or water (tetrahydrofuran - water solution), 5 - 8 undergo at room temperature rapid opening of the β-lactam ring to give the respective glycosides 9 - 13[8] or free sugars 14 - 16[8]. The assignment of configuration to 9 - 16 is straightforward and hence it proves unequivocally also the configuration of β-lactams 5 - 8.





9:R^1=OAc, R^2=H, R^4=CH_3
10:R^1=OAc, R^2=H, R^4=C_2H_5
11:R^1=H, R_2=OAc, R^4=CH_3
14:R^1=OAc, R^2=R^4=H

12:R^3=R^4=CH_3
13:R^3=H, R^4=CH_3
15:R^3=CH_3, R^4=H
16:R^3=R^4=H

The high-pressure reaction between isocyanates and glycals is a new interesting contribution to the explanation of the nature of [2 + 2] cycloaddition; it permits the development of a simple, efficient and stereospecific method for β-lactam skeleton construction.

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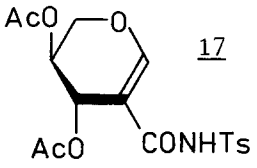
References and Notes

1. E.Effenberger and R.Gleiter, Chem.Ber., 97, 1576 (1964).
2. R.H.Hall, A.Jordaan, and G.J.Laurens, J.ChemSoc., Perkin I, 1973, 38; R.H.Hall, A.Jordaan, and O.G.de Villiers, ibid, 1975, 626.
3. A.G.M.Barrett, A.Fenwick, and M.J.Betts, J.Chem.Soc.,Chem.Commun., 1983, 299.
4. T.Asano and W.J.LeNoble, Chem.Rev., 78, 407 (1978).
5. All experiments were carried out in a piston-cylinder high-pressure apparatus described earlier: J.Jurczak, Bull.Chem.Soc.Jpn., 52, 2046 (1979). The reaction mixture (20-30% abs. ether solution) was placed in a Teflon ampoule which was inserted into a high-pressure vessel filled with ligroin as transmission medium.
6. The mother liquor contained (TLC) traces of substrate (1 - 4) and of a more polar compound which in case of cycloaddition to xylal (4) was isolated and characterized as 3-substituted xylal 17. Such rearranged products have been observed previously.[1,3] Elevation of the temperature of high-pressure cycloaddition to 60°C increases the content of amide 17 (TLC).



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7. All new compounds gave satisfactory spectroscopic and analytical data. Only selected data are given below. 5: m.p. 102-4°C; $[\alpha]_D$ + 80.3° (c 1, $CHCl_3$); IR (nujol): 1800 cm^{-1} (β-lactam); ^1H NMR ($CDCl_3$): 3.60 (dd, 1H, $J_{1,2}$ = 5.2, $J_{2,3}$ = 2.5 Hz, H - 2), 4,98 (t, 1H , $J_{3,4}$ = 4,8, $J_{4,5}$ = 5.9 Hz, H-4), 5.35 (m, 1H, H-3), 5.98 ppm (d, 1H, H-1).
6: syrup; IR ($CHCl_3$): 1810 cm^{-1}; ^1H NMR ($CDCl_3$): 3.40 (t, 1H, $J_{1,2} = J_{2,3}$ = 5.3Hz, H-2), 6.03 ppm (d, 1H, H-1).
7: m.p. 95-7°C; $[\alpha]_D$ -110.0° (c 1, $CHCl_3$); IR ($CHCl_3$): 1805 cm^{-1}; ^1H NMR ($CDCl_3$): 3.58 (bd, 1H, $J_{1,2}$ = 5.4 Hz, H-2), 4.77 (t, 1H, $J_{3,4}$ = 5.2, $J_{4,5}$ = 7.3 Hz, H-4), 5.30 (bd, 1H, H-3), 5.95 ppm (d, 1H, H-1).
8: m.p. 88-90°C; $[\alpha]_D$ -110.0° (c 1, $CHCl_3$); IR ($CHCl_3$): 1810 cm^{-1}; ^1H NMR ($CDCl_3$): 3.59 (bd, 1H, $J_{1,2}$ = 5.1 Hz, H-2), 4.98 (q, 1H, $J_{3,4}$ = 4.8, $J_{4,5}$ = 5.5, $J_{4,5'}$ = 5.7 Hz, H-4), 5.33 (m, 1H, w/2 = 10.0 Hz, H-3), 5.95 ppm (d, 1H, H-1).
17: m.p. 78-81°C; $[\alpha]_D$ + 56° (c 1, $CHCl_3$); IR ($CHCl_3$): 3200, 1750, 1725, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): 4.20 (bd, 1H, $J_{5,5'}$ = 12.7 Hz, H-5), 4.49 (bd, 1H, H-5'), 5.08 (bs, 1H, H-4), 5.51 (bs, 1H, H-3), 7.97 ppm (s, 1H, H-1).
8. 9: m.p. 92-3°C; $[\alpha]_D$ + 45° (c 1, $CHCl_3$); IR ($CHCl_3$): 3370, 1760 cm^{-1}; ^1H NMR ($CDCl_3$): 2.80 (dd, $J_{1,2}$ = 8.3, $J_{2,3}$ = 10.7 Hz, H-2), 4.51 (d, 1H, H-1), 4.99 (t, 1H, $J_{3,4}$ = 9.1, $J_{4,5}$ = 9.8 Hz, H-4), 5.47 ppm (t, 1H, H-3).
10: m.p. 63-5°C; $[\alpha]_D$ + 27.5° (c 1, $CHCl_3$); IR ($CHCl_3$): 3360, 1750 cm^{-1}; ^1H NMR ($CDCl_3$): 2.76 (dd, 1H, $J_{1,2}$ = 8.3, $J_{2,3}$ = 10.7 Hz, H-2), 4.60 (d, 1H, H-1), 5.00 (t, 1H, $J_{3,4}$ = 9.1, $J_{4,5}$ = 9.6 Hz, H-4), 5.51 ppm (t, 1H, H-3).

11: m.p. 61-5°C; $[\alpha]_D$ + 16.6° (c 1, $CHCl_3$); IR ($CHCl_3$): 3360, 1750 cm^{-1}; ^1H NMR ($CDCl_3$): 2.85 (dd, 1H, $J_{1,2}$ = 8.2, $J_{2,3}$ = 10.8 Hz, H-2), 4.44 ppm (d, 1H, H-1).
12: m.p. 58-60°C; $[\alpha]_D$ -60.6° (c 1, $CHCl_3$); IR ($CHCl_3$): 3380, 1755, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): 2.75 (dd, 1H, $J_{1,2}$ = 8.4, $J_{2,3}$ = 10.6 Hz, H-2), 4.46 (d, 1H H-1), 4.74 (t, 1H, $J_{3,4}$ = 9.0, $J_{4,5}$ = 9.1 Hz, H-4), 5.46 ppm (t, 1H, H-3).
13: m.p. 79-82°C; $[\alpha]_D$ - 29.2° (c 1, $CHCl_3$); IR ($CHCl_3$): 3370, 1755 cm^{-1}; ^1H NMR ($CDCl_3$): 2.70 (dd, 1H, $J_{1,2}$ = 7.6, $J_{2,3}$ = 10.0 Hz, H-2), 4.12 (d, 1H, H-1), 4.97 (m, 1H, $J_{3,4}$ = 9.5, $J_{4,5}$ = 5.3, $J_{4,5'}$ = 9.0 Hz, H-4), 5.43 ppm (t, 1H, H-3).
14: m.p. 121-2°C; $[\alpha]_D$ + 53.8° (c 1, $CHCl_3$); IR ($CHCl_3$): 3680, 3580, 3460, 3270, 1750 cm^{-1}; ^1H NMR (acetone-d_6): 2.81 (dd, 1H, $J_{1,2}$ = 8.1, $J_{2,3}$ = 10.6 Hz, H-2), 4.85 (t, 1H, $J_{3,4}$ = 8.7, $J_{4,5}$ = 9.9 Hz, H-4), 4.95 (d, 1H, H-1), 5.37 ppm (dd, 1H, H-3).
15: m.p. 134-5°C; $[\alpha]_D$ - 61.8° (c 1, $CHCl_3$); IR ($CHCl_3$): 3590, 3480, 3370, 1755, 1725 cm^{-1}; ^1H NMR ($CDCl_3$): 2.81 (dd, 1H, $J_{1,2}$ = 8.5, $J_{2,3}$ = 11.0 Hz, H-2), 4.79 (t, 1H, $J_{3,4} \approx J_{4,5} \approx$ 9.0 Hz, H-4), 5.01 (d, 1H, H-1), 5.45 ppm (t, 1H, H-3).
16: m.p. 96-7°C; $[\alpha]_D$ -8.6° (c o.57, acetone); IR ($CHCl_3$): 3640, 3580, 3480, 3260, 1740, 1715 cm^{-1}; ^1H NMR (acetone-d_6): 2.79 (dd, 1H, $J_{1,2}$ = 9.0, $J_{2,3}$ = 11.7 Hz, H-2), 4.82 (m, 1H, $J_{3,4}$ = 9.0, $J_{4,5}$ = 10.0, $J_{4,5'}$ = 5.7 Hz, H-4), 4.87 (d, 1H, H-1), 5.36 ppm (t, 1H, H-3).

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