Classical Synthesis of a New Class of Compounds *via* Coupling of Sugars and Amino Acids

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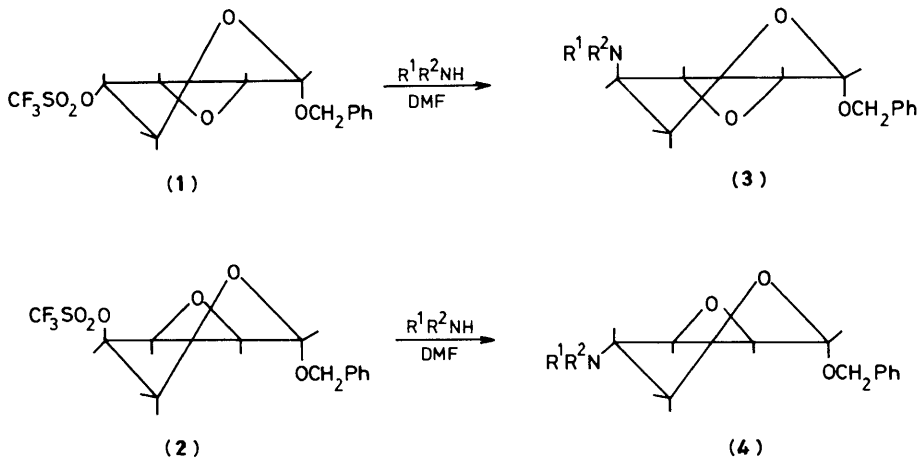
A new class of pharmacologically interesting compounds has been synthesized through a novel S_N2 displacement of the CF_3SO_2 group in benzyl 2,3-anhydro-4-trifluoromethylsulphonyl-α-D-ribopyranoside (**1**) and its β-L-isomer (**2**), by a variety of suitably protected naturally occuring amino acids: the reaction pathway also provides an efficient route to benzyl 2,3-anhydro-β-L- and -α-D-lyxopyranosides [(**3**) and (**4**) respectively].

Recently we have described a new approach for one pot syntheses of aminodeoxy sugars.[1] In the reaction sequence, direct displacement of the trifluoromethylsulphonyl group was affected by passing gaseous ammonia into acetone solutions of sugar trifluoromethanesulphonates. Further studies in this direction have now led to the synthesis of a new class of compounds by way of a novel C–N coupling reaction between partially blocked sugars and a variety of suitably protected amino acids. The free amino-functions of the latter were utilized as effective nucleophiles to cause smooth displacement of the CF_3SO_2 group in benzyl 2,3-anhydro-4-trifluoromethylsulphonyl-α-D-ribopyranoside[2] (**1**) and benzyl

2,3-anhydro-4-trifluoromethylsulphonyl-β-L-ribopyranoside[2] (**2**) respectively. The resulting 4-(protected amino acid)substituted products [benzyl 2,3-anhydro-4-deoxy-β-L-lyxopyranosides (**3**) and benzyl 2,3-anhydro-4-deoxy-α-D-lyxopyranosides (**4**)] gave expected molecular ion peaks in field desorption mass spectra and were shown by ^{1}H n.m.r. spectroscopy to exist almost entirely in the favoured half-chair conformation H_5^O. The same conformations are reported for the corresponding free anhydro sugars;[3] it may be deduced from this that the introduction of an amino acid moiety at position C-4 does not change the conformational stability.

The facile substitution at C-4 can be attributed to the excellent leaving properties of the CF_3SO_2 group,[4] the nucleophilicity of the protected amino acids, and the enhanced reactivity owing to the neighbouring oxirane ring.[5] Moreover, the approach of the attacking nucleophiles is favoured in the neighbourhood of the oxirane ring owing to the molecular geometry which shows a dipole moment in the



$-NR^1R^2$

a; -L-Leu-OMe
b; -L-Ala-OMe
c; -L-Phe-OMe
d; -L-Met-OMe
e; -L-Pro-OMe
OCH_2Ph
f; -L-Glu-OCH_2Ph
ε-CO_2CH_2Ph
g; -L-Lys-OCH_2Ph

Table 1. Physical constants of the reaction products of protected amino acids and sugar trifluoromethanesulphonates (**1**) and (**2**).

Amino acid ester	Substrate	Product[a]	Yield (%)[e]	M.p. (°C)	$[\alpha]_D^{25}$ (°)	R_f[i]
L-Leu-OMe	(**1**)	(**3a**)[b]	59	115—116	+44.3[f]	0.70
L-Leu-OMe	(**2**)	(**4a**)	78.4	32	+34.2[f]	0.69
L-Ala-OMe	(**1**)	[d]	26	180	+41.7[f]	0.39
L-Ala-OMe	(**2**)	(**4b**)[c]	58	142	+51.5[f]	0.53
L-Phe-OMe	(**1**)	(**3c**)[c]	46	163—164	+48.6[g]	0.54
L-Phe-OMe	(**2**)	(**4c**)[c]	54	134	+52.5[f]	0.53
L-Met-OMe	(**1**)	(**3d**)[c]	36	120	+22.5[f]	0.05
L-Met-OMe	(**2**)	(**4d**)	62.6	Oil	+35.6[h]	0.70
L-Pro-OMe	(**1**)	(**3e**)	68.2	Oil	+16.9[f]	0.56
L-Pro-OMe	(**2**)	(**4e**)[c]	70	140	+35.6[f]	0.62
L-Glu-OCH_2Ph OCH_2Ph	(**1**)	(**3f**)	22.5	Oil	+34.5[f]	0.58
L-Glu-OCH_2Ph ε-CO_2CH_2Ph	(**2**)	(**4f**)	55.6	Oil	+29.6[f]	0.61
L-Lys-OCH_2Ph ε-CO_2CH_2Ph	(**1**)	(**3g**)	23	Oil	+34.8[f]	0.58
L-Lys-OCH_2Ph	(**2**)	(**4g**)	45	75—76	+22.6[f]	0.71

[a] All the products gave correct elemental analyses. [b] Characterised as the hydrogen chloride. [c] Characterised as the hydrogen toluene-*p*-sulphonate. [d] Benzyl 2,4-dideoxy-2-bromo-4-(Ala-OMe)-β-L-xylopyranoside hydrogen bromide. [e] Yields are given for the isolated products after column chromatography. [f] $CHCl_3$. [g] Dimethyl sulphoxide. [h] C_6H_6. [i] Kieselgel 60 plates in solvent system acetone:CH_2Cl_2:toluene (1 : 1 : 1).

direction of the C–O bond and not parallel to the newly forming C–N bond.[6] The reactions described in the foregoing account invariably lead to lyxo-products owing to stereochemical inversion at C-4. The key evidence to this effect was provided by the coupling constants in the ^{1}H n.m.r. spectra, particularly $J_{3,4}$ and $J_{4,5}$. In the substrate sugars 3-H has a *cis* relationship with 4-H and a $J_{3,4}$ value of *ca.* 3.6 Hz is obtained[3] whereas in the products the two protons have a *trans* relationship and practically no coupling is observed. Moreover, for (**1**) the $J_{4,5}$ value of 8.1 Hz was obtained because of the quasi-axial,axial relationship between 4-H and 5-H while the $J_{4,5}$ values for the corresponding products (**3**) where 4-H and 5-H have a quasi-equatorial,axial relationship varied from 1—4 Hz.[3,7] The relationship between 4-H and 5-H is exactly reversed in the case of (**2**) and (**4**) and the observation of the $J_{4,5}$ value served again as a means of diagnosing the configurational inversion at C-4. The formation of these products can be rationalised by an S_N2 or ion pair mechanism. However, the observation that the reaction rates varied considerably with the nature and concentration of the nucleophiles, suggested strongly the operation of an S_N2 mechanism rather than a unimolecular process. Representatives of different classes of amino acids were used in the present work to demonstrate the scope of the reaction (Table 1). All of these were used to displace the CF_3SO_2 group in (**1**) and (**2**). The reactions were performed in dimethylformamide (DMF) with a 4-fold excess of amino esters by slowly warming the reaction mixtures from −20 °C to room temperature, followed by continuous stirring for a further 5 h. The substitution products were isolated by silica gel column chromatography and characterized as such or as their crystalline salts, except in one case where attempted salt formation with ethereal hydrogen bromide also resulted in epoxide cleavage to afford the corresponding 2-bromodeoxy derivative (Table 1).

In all the foregoing reactions, benzyl 2,3-anhydro-β-L-lyxopyranoside and benzyl 2,3-anhydro-α-D-lyxopyranoside were respectively obtained as side products from (**1**) and (**2**). The origin of these compounds could be rationalized through competing nucleophilic displacement of the CF_3SO_2 group by the moisture present in DMF. Deaminated (**3**) which was hitherto unreported, could also be obtained as a major product (60%) by stirring (**1**) in 98% DMF with a catalytic amount of pyridine or tetrabutylammonium nitrite, m.p. 83—85 °C, $[\alpha]_D^{25}$ +68.6° (*c* 0.13 in $CHCl_3$). The yield of deaminated (**4**) could likewise be improved to 70%, providing an alternative and efficient route to this epoxy sugar from L-arabinose, following the earlier synthesis reported by one of us, starting from D-xylose.[6]

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