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Preliminary communication

N-Allyl and *N*-benzyl derivatives of 2-amino-2-deoxy-D-glucose*

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The isomerisation of the allyl group in dialkylallylamines with potassium *tert*-butoxide in dimethyl sulphoxide[2,3] and the isomerisation of allylamines and *N*-allyl-amides and -imides with various metal catalysts[4–6] have been investigated. *N*-Allyl groups have been used for protection in nucleoside chemistry[7] and the *N*,*N*-diallyl group has been used[8] for the protection of the amino function of *O*-methyl-L-tyrosine methyl ester. Allylation has also been used[9,10] for the protection of amides and imides, and the *N*-vinyl group has also been utilised[11] in this way.

We have investigated the allylation of *O*-protected 2-benzamido-2-deoxy-D-glucopyranose derivatives with allyl bromide and sodium hydride in *N*,*N*-dimethylformamide, which rapidly gave a mixture of the *N*-allylbenzamido derivatives and allyl imidates in which the former preponderated (~75%). Since allyl imidates rearrange[12] readily to the corresponding *N*-allylamides, conditions could probably be found to optimise the yields of the latter. The *N*-benzylbenzamido derivative **39** has been prepared[13] by slow benzylation of the benzamido derivative **38** with benzyl chloride and sodium hydride in tetrahydrofuran.

Allylation of benzyl 3-*O*-allyl-2-benzamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[14] (**1**) gave a mixture of the *N*-allylbenzamido derivative **2** {m.p. 124–126°, $[\alpha]_D^{26}$ −63° (*c* 1, chloroform)} and the imidate **3**, and allylation of allyl 2-benzamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[14] (**14**) gave a mixture of the *N*-allylbenzamido derivative **15** (syrup) and the imidate **16**. Similarly, benzyl 2-benzamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[15] (**26**) gave a mixture of **27** and **28**. The imidates were readily hydrolysed to the corresponding benzamido derivatives by the action of pyridinium *p*-toluenesulphonate in hot, aqueous pyridine, without loss of the benzylidene group. Since the benzamido derivatives **1**, **14**, and **26** are poorly soluble[14] in organic solvents, they were readily

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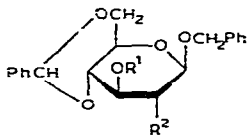
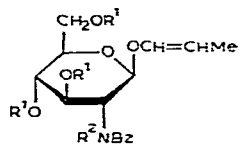
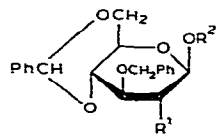


1 R^1 = $-CH_2CH{=}CH_2$, R^2 = NHBz
2 R^1 = $-CH_2CH{=}CH_2$, R^2 = N(Bz)$CH_2CH{=}CH_2$
3 R^1 = $-CH_2CH{=}CH_2$, R^2 = N=C(Ph)$OCH_2CH{=}CH_2$
4 R^1 = $-CH_2CH{=}CH_2$, R^2 = N(CH_2Ph)$CH_2CH{=}CH_2$
5 R^1 = $-CH{=}CHMe$, R^2 = N(CH_2Ph)$CH{=}CHMe$
6 R^1 = $-CH{=}CHMe$, R^2 = NHCH_2Ph
7 R^1 = $-CH_2CH{=}CH_2$, R^2 = N(CH_2Ph)$CH_2CH{=}CHMe$
8 R^1 = $-CH{=}CHMe$, R^2 = N(CH_2Ph)$CH_2CH{=}CHMe$
9 R^1 = $-CH{=}CHMe$, R^2 = N(CH_2Ph)$CH{=}CHEt$
10 R^1 = $-CH{=}CHMe$, R^2 = N(CH_2Ph)Ac
11 R^1 = H, R^2 = N(CH_2Ph)Ac
12 R^1 = H, R^2 = N(CH_2Ph)COR
13 R^1 = H, R^2 = NHCH_2Ph



38 R^1 = CH_2Ph, R^2 = H
39 R^1 = R^2 = CH_2Ph



14 R^1 = NHBz, R^2 = $-CH_2CH{=}CH_2$
15 R^1 = N(Bz)$CH_2CH{=}CH_2$, R^2 = $-CH_2CH{=}CH_2$
16 R^1 = N=C(Ph)$OCH_2CH{=}CH_2$, R^2 = $-CH_2CH{=}CH_2$
17 R^1 = N(CH_2Ph)$CH_2CH{=}CH_2$, R^2 = $-CH_2CH{=}CH_2$
18 R^1 = N(CH_2Ph)$CH{=}CHMe$, R^2 = $-CH{=}CHMe$
19 R^1 = NHCH_2Ph, R^2 = $-CH{=}CHMe$
20 R^1 = N(CH_2Ph)$CH_2CH{=}CHMe$, R^2 = $-CH_2CH{=}CH_2$
21 R^1 = N(CH_2Ph)$CH_2CH{=}CHMe$, R^2 = $-CH{=}CHMe$
22 R^1 = N(CH_2Ph)$CH{=}CHEt$, R^2 = $-CH{=}CHMe$
23 R^1 = N(CH_2Ph)Ac, R^2 = $-CH{=}CHMe$
24 R^1 = N(CH_2Ph)Ac, R^2 = H
25 R^1 = N(CH_2Ph)$CH_2CH{=}CHMe$, R^2 = H
26 R^1 = NHBz, R^2 = CH_2Ph
27 R^1 = N(Bz)$CH_2CH{=}CH_2$, R^2 = CH_2Ph
28 R^1 = N=C(Ph)$OCH_2CH{=}CH_2$, R^2 = CH_2Ph
29 R^1 = N(CH_2Ph)$CH_2CH{=}CH_2$, R^2 = CH_2Ph
30 R^1 = N(CH_2Ph)$CH{=}CHMe$, R^2 = CH_2Ph
31 R^1 = NHCH_2Ph, R^2 = CH_2Ph
32 R^1 = N(CH_2Ph)$CH_2CH{=}CHMe$, R^2 = CH_2Ph
33 R^1 = N(CH_2Ph)$CH{=}CHEt$, R^2 = CH_2Ph
34 R^1 = N(CH_2Ph)Ac, R^2 = $-CH_2CH{=}CH_2$
35 R^1 = NHAc, R^2 = $-CH{=}CHMe$
36 R^1 = N(CH_2Ph)Ac, R^2 = CH_2Ph
37 R^1 = NHAc, R^2 = CH_2Ph

separated from the ether-soluble *N*-allylbenzamido derivatives after the hydrolysis and could be recycled.

Reduction of the *N*-allylbenzamido derivatives **2**, **15**, and **27** with lithium aluminium hydride in ether at room temperature caused rapid and quantitative conversion[16] into the corresponding *N*-allylbenzylamino derivatives **4**, **17**, and **29**. Isomerisation of **4**, **17**, and **29** with potassium *tert*-butoxide in dimethyl sulphoxide at room temperature gave the corresponding *N*-(prop-1-enyl)benzylamino derivatives **5**, **18**, and **30**, the *N*-allyl groups rearranging at about the same rate as the *O*-allyl groups in **4** and **17**. T.l.c. of the reaction mixtures showed only the presence of the benzylamino derivatives **6**, **19**, and **31**, since the *N*-(prop-1-enyl) group was completely hydrolysed on the t.l.c. plate. However, addition of water to the isomerisation solution and then extraction with ether gave **5**, **18**, and **30**, which hydrolysed spontaneously in the air at room temperature. The N-(CH=CHMe) group in **18** absorbed at 1655 cm^{-1} and the O-(CH=CHMe) group absorbed at 1675 cm^{-1}. Earlier work indicated that enamines are highly acid-labile, but not that they hydrolysed spontaneously in the air. Carbon dioxide can effect *cis*→*trans* isomerisation[3] of the *N*-(prop-1-enyl) derivatives, which were also hydrolysed, on a preparative scale, with pyridinium *p*-toluenesulphonate in aqueous pyridine at room temperature.

Thus, **4** was converted into the prop-1-enyl ether **6** {m.p. 115–117°, $[\alpha]_D^{33}$ −73° (*c* 0.5, chloroform)}, **17** gave the prop-1-enyl glycoside **19** {m.p. 136–138°, $[\alpha]_D^{30}$ −20.5° (*c* 1, chloroform)}, and **29** gave the benzylamino derivative **31** {m.p. 128–129°, $[\alpha]_D^{36}$ −38° (*c* 1, chloroform)}. Compound **31** was also prepared in modest yield by direct reduction of the benzamido derivative **26** with lithium aluminium hydride in refluxing tetrahydrofuran during 12 h. Benzyl alcohol was also a product in this reduction, indicating some complete debenzoylation to give the free amine as observed[16] in the reduction of other benzamido derivatives.

The *N*-(but-2-enyl)benzylamino derivatives **7**, **20**, and **32** were prepared in a way similar to that for the *N*-allylbenzylamino derivatives. Treatment of **7**, **20**, and **32** with potassium *tert*-butoxide in dimethyl sulphoxide gave the corresponding *N*-(but-1-enyl)benzylamino derivatives **9**, **22**, and **33**. This behaviour is in contrast to that of *O*-(but-2-enyl) derivatives, which are cleaved[17] by this reagent, but similar to that of *S*-(but-2-enyl) derivatives[18]. The rate of isomerisation of the *N*-(but-2-enyl) derivatives is considerably less than that of the *O*-allyl and *N*-allyl derivatives, and hence it was possible to isomerise the *O*-allyl groups in **7** and **20** (reaction at room temperature for 30 min), without affecting the *N*-(but-2-enyl) groups, to give **8** and **21**. The *N*-(but-2-enyl) groups were isomerised to *N*-(but-1-enyl) groups at 50° during 4 h, in contrast to *O*-(but-2-enyl) groups which are cleaved[17] more rapidly than the *O*-allyl groups are isomerised. Previous work[19] suggested that potassium *tert*-butoxide does not affect *N*-(alk-2-enyl)dialkylamines, although stronger bases (BuLi, $NaNH_2$, and KH) cause[19] elimination of the alk-2-enyl groups to give dienes.

The *N*-(but-1-enyl) group in **9**, **22**, and **33** hydrolysed spontaneously in the air at room temperature to give the benzylamino derivatives **6**, **19**, and **31**. Acetylation of **6** and **19** with acetic anhydride–pyridine gave the *N*-benzylacetamino derivatives **10** and **23**, and hydrolysis[20] of the prop-1-enyl groups with mercuric chloride–mercuric oxide in aqueous acetone gave the alcohols **11** {m.p. 145–147°, $[\alpha]_D^{28}$ −69° (*c* 1, chloroform)} and **24** {m.p. 137–140°, $[\alpha]_D^{29}$ −3° (*c* 1, chloroform)}.

Hydrogenolysis of compound **11** in glacial acetic acid over 10% Pd/C removed the benzyl ether and benzylidene group during 3 h and then the *N*-benzyl group during 2 days. Acetylation of the product gave 2-acetamido-2-deoxy-D-glucose tetra-acetate. Previous work[9,21,22] has indicated the stability of *N*-benzylacylamino groups to hydrogenolysis, and sodium in liquid ammonia has been used[22] for the debenzylation of these groups. The rapid hydrogenolysis of a benzyl ether without affecting an *N*-benzylacetamido group may be of value in synthetic carbohydrate chemistry.

The foregoing reactions constitute a new method for the conversion of 2-benzamido-2-deoxy-D-glucose derivatives into 2-acetamido-2-deoxy-D-glucose derivatives. The use[15,23] of boiling acetic anhydride–acetic acid for this purpose has been adapted[24] (boiling trifluoroacetic anhydride–trifluoroacetic acid) for the deacylation of acetamido sugars and the cleavage of peptide bonds.

Acylation of **6** and subsequent depropenylation will give a variety of acyl derivatives **12**, which should be useful intermediates for the preparation of various *N*-acylmuramyl dipeptides for consideration as synthetic adjuvants[25,26]. The *N*-

benzylacylamino derivatives **12** should also be useful as intermediates for the preparation of the lipid A component of the bacterial lipopolysaccharides[26,27].

Benzylation of prop-1-enyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (prepared from the corresponding allyl glycoside[28]) with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide has also given **23**, which on mercuric chloride–mercuric oxide hydrolysis gave **24**. The corresponding 2-*N*-allylacetamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose has been prepared in a similar way. Both the *N*-allylacetamido and the *N*-benzylacetamido derivatives (and other *O*-protected derivatives) have potential in 1,2-*cis*-glycoside synthesis in the amino sugar series. Benzylation of benzyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(prop-1-enyl)-β-D-glucopyranoside has also been used to give **10**, which gave **11** on depropenylation. The allylation and benzylation of the acetamido sugars with alkyl bromides and sodium hydride in *N*,*N*-dimethylformamide yields only traces of the corresponding imidates, whereas ~25% of the imidate is formed with the benzamido derivatives.

Benzylation of allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[28] gave the *N*-benzylacetamido derivative **34**. Attempted isomerisation of **34**→**23**, using potassium *tert*-butoxide in dimethyl sulphoxide at room temperature, led to rapid elimination of the *N*-benzyl group and slower isomerisation of the allyl group to give the acetamido derivative **35**. This novel method of *N*-debenzylation was confirmed by the action of potassium *tert*-butoxide in dimethyl sulphoxide at room temperature on the *N*-benzylacetamido derivative **36** (prepared by acetylation of **31**), which was rapidly and quantitatively converted into known[15] benzyl 2-acetamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (**37**). This route represents an efficient method for the conversion of benzamido into acetamido derivatives and for cleavage of a protected acetamido group. The *N*-benzylacylamino derivatives **12** contain a protected nitrogen atom that allows vigorous *O*-alkylation conditions to be applied. Thus, with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide, **11** gave the ben zylether **36**, identical with the material obtained by acetylation of **31**.

Hydrolysis of the prop-1-enyl group from **6** with mercuric chloride–mercuric oxide gave **13** {m.p. 161–163°, $[\alpha]_D^{40}$ −68° (*c* 1, pyridine)}, and hydrolysis of the prop-1-enyl group from **21** gave the *N*-(but-2-enyl)benzylamino derivative **25** which may have potential in 1,2-*cis*-glycoside synthesis.

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