A New Direct Glycosylation of Pyrimidine, Pyrazole, Imidazole and Purine Heterocycles *via* their *N*-tetrahydropyranyl (THP) Derivatives

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Pyrimidine, pyrazole, imidazole and purine *N*-tetrahydropyranyl (THP) derivatives have been converted in one-pot and in a regio- and stereo-selective manner into the corresponding β-D-2′,3′,5′-tri-*O*-benzoyl ribofuranosyl nucleoside derivatives on treatment with 1-β-acetyl-2′,3′,5′-tri-*O*-benzoyl-ribofuranose, hexamethyldisilazane (HMDS), trimethylsilyl chloride (TMSCl), and trimethylsilyl triflate (TMST).

The tetrahydropyranyl group (THP) is one of the most important protective groups employed in chemical synthesis, mainly because of its low cost, the easy of its installation, its general stability to most non-acidic reagents and the ease with which it can be removed.[1] Moreover, it has also been used in purine and nucleosides synthesis in view of its capability to increase the solubility of the heterocyclic derivatives in organic solvents and to provide a useful blocking group which prevents undesirable side reactions due the presence of the imidazole hydrogen.[2–6] The interesting antitumour activity of THP–pyrimidine and the use of purine derivatives as antitumour agents[7–9] are also well documented.

The THP–ether is one of the most extensively studied protecting forms of hydroxy groups, and although its acid-catalysed transacetalization with alcohols is well known, no references are reported in literature about the direct glycosylation of *N*-tetrahydropyranyl derivatives of heterocyclic ring for nucleosides synthesis.

As a part of an ongoing project aimed towards obtaining *N*-glycosylated derivatives of natural pyrazole nucleosides, we have previously reported the synthesis and antiviral activity of pyrazolo[4,3-d]pyrimidine nucleosides.[10] Recently we have described the preparation of the pyrazolo[4,3-d]triazinone isosters as well as simple pyrazole nucleoside analogues, which have interesting antiviral and antitumour properties.[11]

Here, we report a new glycosylation methodology which is amenable for scale preparation of a broad array of glycosylated heterocycles such as pyrimidine, pyrazole, imidazole and purine derivatives, starting from the THP–precursors **1a–i**.

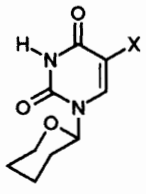
We were initially attracted by the possibility of studying a transglycosylation reaction in order to obtain nucleosides, starting from the corresponding THP-heterocycles, thus avoiding the required unmasking step of the THP–moiety. Initial attempts to perform this transformation by using trimethylsilyl trifluoromethanesulfonate (TMST) in acetonitrile, the known transglycosylation conditions first described by Miyaki and coworkers[12] and modified by Azuma and Isono,[13] gave rise, after work-up, to the deprotected heterocycle derivatives. Similar attempts to perform this reaction by the transglycosylation of the THP–intermediates, using 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-benzoyluracil, as a glycosyl donor,[14] failed.

Good results were achieved by simply refluxing the THP-derivatives **1a–i** with 1-β-acetyl-2′,3′,5′-tri-*O*-benzoyl-ribofuranose in anhydrous acetonitrile in the presence of hexamethyldisilazane (HMDS), trimethylsilyl chloride (TMSCl) and trimethylsilyl trifluoromethanesulfonate (TMST). These experimental conditions were similar to those employed by Vorbrüggen *et al.*[15] for the glycosylation of *N*-trimethylsilyl heterocycle derivatives.

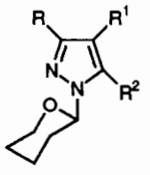
The THP derivatives **1a,b** and **1h,i** were obtained as described in the literature,[2,7] and compounds **1c–e** were readily prepared, in 60–85% yield, by treating the starting heterocycles with 2,3-dihydro-4*H*-pyran (DHP) in the presence of a catalytic amount of toluene-*p*-sulfonic acid (TsOH). Compounds **1f,g** were prepared in good yield by reaction of the imidazole derivatives with 2-chlorotetrahydropyran in the presence of sodium hydride.

The structures of the THP–pyrazole derivatives were assessed by ^{13}C NMR analyses on the basis of the different shift of C-3, C-4 and C-5 atoms, and were compared with the data reported for other THP–pyrazole derivatives.[4] In the case of **1g** the structure was attributed on the basis of ^{1}H and ^{13}C NMR data and confirmed by NOESY experiments.

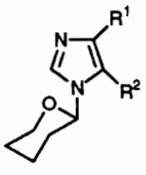
The glycosylation procedure was carried out as follows: the appropriate THP–derivatives **1a–i** (0.84 mmol) were treated at reflux conditions, (3–4 h, TLC), with 1-β-acetyl-2′,3′,5′-tri-*O*-benzoylribofuranose (0.50 g, 1 mmol) in anhydrous acetonitrile (10 ml) in the presence of HMDS (0.21 ml, 1 mmol), TMSCl (0.144 ml, 1.2 mmol) and TMST (0.17 ml, 1.2 mmol)



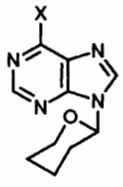
1a; X = H
1b; X = F



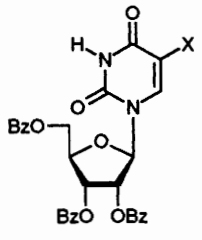
1c; R = CO_2Me, R^1 = I, R^2 = H
1d; R = CO_2Me, R^1 = CHO, R^2 = H
1e; R = Me, R^1 = NO_2 R^2 = H



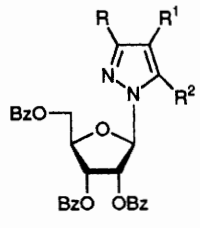
1f; R^1 = H, R^2 = H
1g; R^1 = NO_2, R^2 = Me



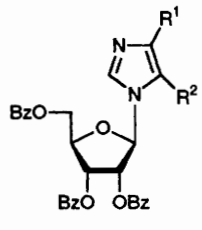
1h; X = Cl
1i; X = SMe



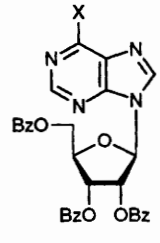
2a; X = H
2b; X = F



2c; R = CO_2Me, R^1 = I, R^2 = H
2d; R = CO_2Me, R^1 = CHO, R^2 = H
2e; R = Me, R^1 = NO_2, R^2 = H



2g; R^1 = NO_2, R^2 = Me



2h; X = Cl
2i; X = SMe

under argon atmosphere. After standard work-up all compounds were purified by silica gel column chromatography.

The reaction afforded, in regio- and stereo-selective manner, the N^1-β-D-ribofuranosylpyrazolo and imidazolo derivatives **2c–e,g** in 65–80% yield. The compounds were deprotected with methanolic ammonia to give the corresponding ribofuranosides.

In the case of compounds **1a,b**, the expected **2a,b** were obtained in 75 and 68% yield respectively together with the α-anomer (11 and 6%). Compounds **2h,i** were obtained in 77 and 64% yield respectively with traces of the N-7-isomers. The final compounds were confirmed, after deprotection, by comparison with an authentic sample of commercially available uridine, 5-fluorouridine, 6-chloro- and 6-methylthio-9-β-D-ribofuranosylpurine.

The regio- and stereo-chemistry of glycosylation reactions of pyrazole derivatives were determined by ^1H and ^{13}C NMR analyses on the deprotected compounds: it is well established that the C-5 of a N^1-glycosylated 5-carboxypyrazole nucleus are shifted to fields lower than the C-3 of the corresponding 3-carboxy isomer. Anomeric configurations were confirmed studying the H-1′ signal shift: α-anomers are observed at lower fields than that of β ones. These results were further confirmed by comparison with those obtained previously.[11]

In the case of the imidazole derivatives **1f** the reaction gave only complex mixtures. The regio- and stereo-chemistry of the glycosylation reaction on **1g**, to give **2g**, were established by NMR spectroscopy as reported above and on the basis of NOESY experiments as described for the THP–precursor **1g**.

The method reported here represents a new synthetic tool for the introduction of a glycosydic portion in a THP–heterocyclic intermediate showing that the protected functionality can be transformed without passing through an intermediary unmasked step,[5] thus avoiding harsh deblocking treatments.[4] The possibility of obtaining the pyrimidine derivative **2a** and the purines **2h** and **2i** starting from the corresponding THP–derivatives (**1a,h,i**) allows the preparation of more complex nucleoside derivatives of pharmacological interest by this method which is an alternative to other known synthetic procedures.

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