Pergamon

Tetrahedron Letters, Vol. 35, No. 31, pp. 5709-5712, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01110-9

A One-pot Glycosylation of Tetrahydropyranyl (THP) Ether Intermediates

Stefano Manfredini*, Pier G. Baraldi, Rita Bazzanini, Mario Guarneri and Daniele Simoni

Dipartimento di Scienze Farmaceutiche, Università di Ferrara, Via Fossato di Mortara 17-19, I-44100 Ferrara, Italy

Abstract: tetrahydropyranyl (THP) derivatives of alcohols are converted in one-pot and in stereoselective manner into the corresponding 1-*O*-alkyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranosides on treatment with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and trimethylsilyl triflate (TMSOTf). The same protocol was also applyed on 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-glucopyranoside (α/β 9:1) to give, by reaction with 1-*O*-methyl-2,3,4-tri-*O*-benzyl-6-THP-α-D-glucopyranoside, the corresponding disaccaride (α/β 3:1). The reaction is high yielding and proceeds rapidly at very mild conditions (-30°C) on easily available starting materials.

The tetrahydropyranyl group (THP) is one of the most important protective group for the hydroxy function; it has been largely employing because of its low cost, the easy installation and the general stability under various non-acidic reaction conditions.[1]

The direct transformation of the THP moiety into other functionalities still remain undeveloped area, even if some stimulating studies are reported in literature: such as the THP-acetal linkage that decompones at room temperature with an excess of acetyl chloride in aprotic solvent, giving rise to the corresponding acetyl derivative[2] and tetrahydropyranyl ethers converted in one-pot reaction into benzyl and α-methoxyethoxymethyl ethers, benzoates, aldehydes and tosylates as well.[3]

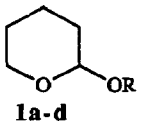
Recently, we found that N-THP-protected heterocycles (purines, pyrimidines and imidazoles) were directly glycosylated leading to nucleosides, by using 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in presence of hexamethyldisilazane (HMDS), trimethylsilyl chloride (TMSCl) and trimethylsilyl triflate (TMSOTf).[4] In view of these results we decided to deepen our knowledge about the synthetic utility of the THP-moiety transacetalization reaction and here we describe a new entry to glycosylation based on the one-pot transformation of THP-ethers into 1,2-trans alkyl glycosides.

Notwithstanding that a lot of work has been devoted to the study of the glycosylation reaction, and a number of glycosyl donors have been proposed,[5] the glycosyl acceptor has been scarcely considered being

usually represented by the alcohol. Hanessian and Banoub described in the past the use of N,N-dimethyl-formamide dialkyl acetals as sources of the aglycon portion,[6] and recently trimethylsilyl-protected alcohols has been used by Mukaiyama[7] and proposed as intermediates by Sinay[5] in the glycosylation step.

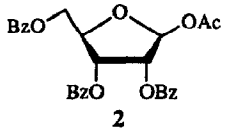
The method we have developed represents, to the best of our knowledge, the first direct glycosylation of THP-protected alcohols, amenable for the preparation of simple and complex glycosides. It possesses three suitable requisites: a) the reaction is effected on the protected alcohols (THP-derivatives) avoiding the unmasking step; b) glycosylation occurs at room temperature as well as at -30°C; c) the THP-derivatives and the starting glycosyl donor **3** are easily obtained by standard procedures, whereas **2** is commercially available.

The transformation was firstly studied on simple THP-derivatives (**1a-d**). Initial attempts involved the experimental protocol used for the glycosylation of N-THP-heterocycles,[4] but we found more suitable the use of the simple TMSOTf in dichloromethane or acetonitrile. On the contrary, these conditions were not successful in the case of the above reported nucleoside synthesis.



1a-d

a: R = Cyclohexyl, **b**: R = Benzyl,
c: R = Neopentyl, **d**: R = Isopropyl



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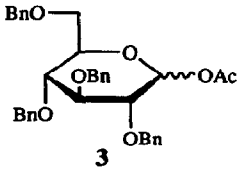

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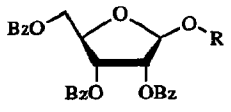
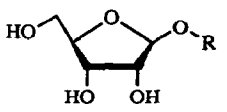
The procedure was simply performed as described: the appropriate THP-derivatives **1a-d** (1 equiv.) were dissolved in anhydrous dichloromethane and reacted at -30°C with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) (1 equiv.) in presence of TMSOTf (1.2 equiv.) under argon positive pressure. The reaction afforded, in stereoselective manner, the 1-β-D-alkyl-ribofuranoside tribenzoates **4a-d** in 60-85% yield. The structures of the prepared compounds were characterized by ^{1}H-NMR spectroscopy[8] and confirmed by comparison of the optical rotation with known compounds.[6,9-11] In order to further confirm the assigned structures, derivatives **4a,c** were deprotected with methanolic ammonia to give the corresponding ribofuranosides **5a,c**. The melting points and optical rotations of these debenzoylated derivatives were consistent with literature values.[6]



4a-d

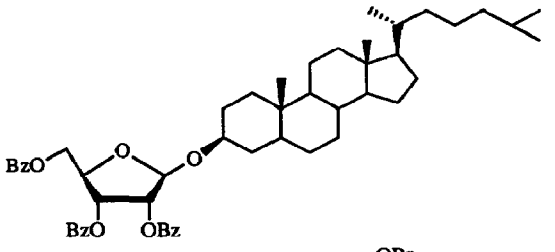


5a,c

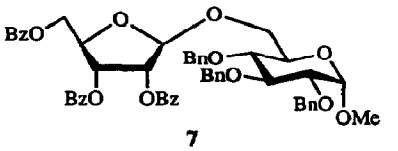
The mechanism of the reaction probably involves the activation of the sugar portion mediated by TMSOTf through the formation of an 1,2-acyloxonium intermediate, as described by Vorbrüggen et al. in the glycosylation of silylated heterocycles.[12] This intermediate can interact with the THP-derivative which is the source of the aglycone portion in the glycosides.

Having demonstrated the feasibility of this method on simple glycosides, we were interested to further investigate its behaviour toward more complex substrates and we focused our attention on compounds **6**,**7** and **8**. To this end the appropriate steroidal- and glucopyranosyl-THP derivatives were prepared and reacted to give the corresponding steroidal-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**6**) and disaccarides **7** and **8**.[10]

Compounds **6** and **7** were stereoselectively obtained as the solely β-anomers,[13] and compound **8** was prepared (α/β 3:1) by reaction of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-glucopyranoside (**3**) (α/β 9:1) with 1-*O*-methyl-2,3,4-tri-*O*-benzyl-6-*O*-THP-α-D-glucopyranoside.[10] The anomeric ratio of the mixture was determined by ^{1}H-NMR spectroscopy.



6



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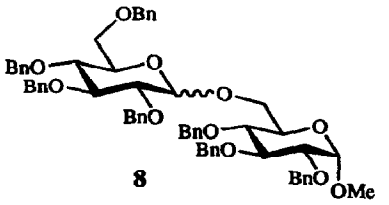

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In summary, the method here reported is a valuable one-pot procedure for glycosylation of protected alcohols which deserve a wide range of possible applications since it works with commercial or readily available reagents, under very mild conditions (-30°C) and is applicable for large scale preparation. In particular, the low temperatures the reaction can be conduced at in addition to the essentially neutral conditions, warrant the application of this procedure to complex and labile structures. Moreover, the possibility to convert a protected THP-alcohols directly into a glycosylic linkage, thus avoiding the acidic conditions characteristic of the unmasking step, confers to the methodology a particular synthetic value.

Acknowledgement: This work was supported by CNR (Piano Finalizzato Chimica Fine) and MURST (grant 40%) of Italy. We thank Dr. Cesare Iaccheri for his excellent assistance and Prof. Giorgio Catelani for helpfull discussions.

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* To whom correspondence should be addressed.

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7. Matsubara, K.; Sasaki, T.; Mukaiyama, T. *Chem. Lett.* **1993**, 1373-1376; Suda, S.; Mukaiyama, T. *Chem. Lett.* **1991**, 431-434.
8. As an example ^{1}H-NMR (δ, $CDCl_3$) of **4a** is reported: 7.30-8.07 (m, 15H), 5.88 (dd, J = 4.8 Hz, J = 6.5 Hz, 1H), 5.64 (d, J = 4.8 Hz, 1H), 5.42 (s, 1H), 4.60-4.71 (m, 3H), 3.58 (m, 1H), 1.21-1.95 (m, 10H).
9. Hanessian, S.; Banoub, J. *Methods Carbohydr. Chem.* **1980**, *8*, 243-245.
10. Data for compounds **4a-d**, **6**, **7** and **8**:

    4a: yield 80%; syrup; $[\alpha]_D$ = +26.1° chloroform, (lit.9 $[\alpha]_D$ = +26°, chloroform);

    4b: yield 85%; mp (EtOH) = 86°-87°C ; $[\alpha]_D$ = +18.1° chloroform [lit.11 mp (EtOH) = 87°-88°C; $[\alpha]_D$ = +14.9°, chloroform, (c 0.81) ; lit.5 mp = 65°C; $[\alpha]_D$ = +20°, chloroform];

    4c: yield 65%; syrup; $[\alpha]_D$ = +35° chloroform (lit.5 $[\alpha]_D$ = +35.5°, chloroform);

    4d: yield 77%; syrup; $[\alpha]_D$ = +45° chloroform (lit.5 $[\alpha]_D$ = +45° chloroform);

    6: yield 82%; syrup; $[\alpha]_D$ = +20.8° chloroform;

    7: yield 73%; syrup; $[\alpha]_D$ = +41.2° chloroform;

    8: yield 67%; syrup; (α/β 3:1). Similarly, reaction of compound **3** with **1a-d** gave the corresponding glycosides, as α/β mixture (3:1) as well, in 65-75% yields.
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12. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234-1255.
13. ^{1}H-NMR (δ, $CDCl_3$) Spectral data (H-1) for compounds **6**: 5.63 (d, J=4.8 Hz) and **7**: 5.62 (d, J=4.8 Hz)

(*Received in UK* 3 *December* 1993; *revised* 2 *June* 1994; *accepted* 10 *June* 1994)