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Allyloxy and Propargyloxy Group Migration: Role of Remote Group Participation in the Synthesis of 5-C-Nucleosides and Other Sugar Derivatives

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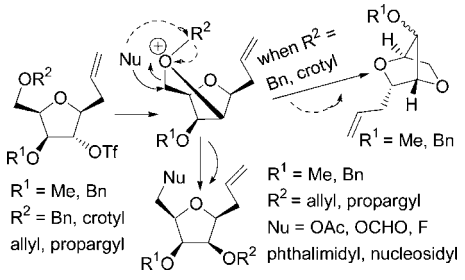
ABSTRACT



In 1-deoxy-xylofuranose derivatives possessing a good leaving group at 2-C, participation of allyloxy and propargyloxy substituents at 5-C results in loss of the 2-C substituent and attack of various nucleophiles at 5-C of the oxonium intermediate. Such participation of a benzyloxy or crotyloxy group leads to dioxabicyclo[2.2.1]heptane rings.

Protective groups play an important role in carbohydrate chemistry in controlling the regio- and stereoselectivities of target molecules. Various esters, commonly used as protecting groups in carbohydrate synthesis, sometimes undergo undesired migration and cleavage.[1−5] Several cases of 1,2-migration of, e.g., 2-oxoalkyl groups,[6] thio- or seleno-alkyl groups,[7−15] *N*-sulfonamides,[16−18] and triazoline-derived aziridines[19] in the stereoselective formation of glycosides have been reported. The participation of an (*S*)-(phenylthiomethyl)benzyl moiety at the 2-O or 6-O positions has proven useful in the stereochemical synthesis of α-glycosides.[20] Long-range participation of an acyloxy

(1) *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weiheim, Germany, 2000; Vol. 1.
(2) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1996.
(3) Oscarsson, S. *Topics in Current Chemistry: Glycoscience*; Driguuez, H., Thiem, J., Eds.; Springer: Berlin, Germany, 1997; Vol. 186.
(4) Lemieux, R. U. *Adv. Carbohydr. Chem.* **1954**, *9*, 1–57.
(5) Lemieux, R. U.; Brice, C.; Huber, G. *Can. J. Chem.* **1955**, *33*, 134–147.
(6) Shao, H.; Ekthawatchai, S.; Chen, C.-S.; Wu, S.-H.; Zou, W. *J. Org. Chem.* **2005**, *70*, 4726–4734.
(7) Auzanneau, F.-I.; Bundle, D. R. *Carbohydr. Res.* **1991**, *212*, 13–24.
(8) Pozsgay, V. *Carbohydr. Res.* **1992**, *235*, 295–302.
(9) Yu, B.; Yang, Z. *Tetrahedron Lett.* **2000**, *41*, 2961–2964.
(10) Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377–379.
(11) Jaurand, G.; Beau, J.-M.; Sina, P. *J. Chem. Soc., Chem. Commun.* **1981**, 572–573.
(12) Kaye, A.; Neidle, S.; Reese, C. B. *Tetrahedron Lett.* **1988**, *29*, 2711–2714.
(13) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75–78.
(14) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; Suzuki, H.; Fylaktakidou, K. C.; Baudin, O.; van Delft, F. L. *Chem.—Eur. J.* **2000**, *6*, 3095–3115.
(15) Lin, P.-C.; Adak, A. K.; Ueng, S.-H.; Huang, L.-D.; Huang, K.-T.; Ho, J. A.; Lin, C.-C. *J. Org. Chem.* **2009**, *74*, 4041–4048.
(16) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811–5819.
(17) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863–5864.
(18) Danishefsky, S. J.; Koseki, K.; Griffith, D. A.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Oriyama, T. *J. Am. Chem. Soc.* **1992**, *114*, 8331–8333.
(19) Dahl, R. S.; Finney, N. S. *J. Am. Chem. Soc.* **2004**, *126*, 8356–8357.
(20) (a) Boltje, T. J.; Kim, J.-H.; Park, J.; Boons, G.-J. *Org. Lett.* **2011**, *13*, 284–287. (b) Park, J.; Boltje, T. J.; Boons, G.-J. *Org. Lett.* **2008**, *10*, 4367–4370. (c) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090–12097. (d) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nat. Chem.* **2009**, *1*, 611–622.
(21) Abdel-Rahman, A. A. H.; Jonke, S.; El Ashry, E. S. H.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2972–2974.

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substituent followed by acyl group migration and epimerization is also common in sugar chemistry.[21,22]

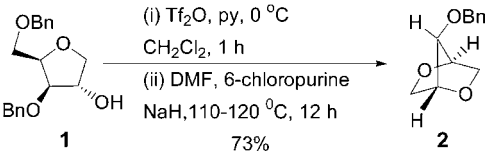
Participation of 3-*O*-axial esters at the anomeric carbon can lead to the stereoselective formation of β-glycosides through cyclic dioxanyl cation intermediates, which was convincingly proved by Crich et al.[23] The presence of 3-*O*-acetyl and 6-*O*-acetyl groups was found to direct the formation of α-mannosides through their remote participation at 1-C and subsequent nucleophilic attack by the hydroxyl group of sugar acceptors.[24] This participation was confirmed in one case by isolating a stable bicyclic trichlorooxazine ring through trapping the anomeric oxocarbenium ion with a 3-*O*-trichloroacetimidoyl group. Interaction between a 4-*O*-axial acetyl group and the C(2)-*O*Tf of a methyl β-D-galactoside derivative, followed by transfer of an Ac group to 2-C with inversion of configuration, has been evidenced in the synthesis of a methyl β-D-taloside derivative.[22] Displacement of a C(2)-OTf through the participation of a 3-*O*-Bn with formation of a benzyloxiranium intermediate and subsequent migration of the OBn group to C(2), followed by an attack of a nucleobase, to form the isonucleoside analogues, has recently been reported by our laboratory.[25] However, participation of 5-*O*-benzyl, -allyl, -crotyl and -propargyl groups in the displacement of leaving groups, as well as their migration to different sites, is not known in the literature. We now report such an unusual event in the displacement of a C(2)-*O*-triflate. The concomitant 1,4-migration of the allyloxy and propargyloxy groups allows generation of C(5)-nucleosides and other novel sugar derivatives using various nucleophiles.

As a part of a program on the synthesis of isonucleosides, we planned the S_N2 attack of a purine base nucleophile on the *O*-triflate ester of a 1-deoxy-2-hydroxyfuranoside derivative carrying a 4-CH_2OBn group. Surprisingly, we observed the formation of dioxabicyclo[2.2.1]heptane derivatives through participation of the C(5)−O−Bn group and loss of Bn. Thus the D-glucose-based tetrahydrofuran derivative **1**,[26] after triflate formation, reacted with 6-chloropurine in DMF to afford the bicyclic compound **2** (Scheme 1). Indeed, the reaction carried out in DMF alone at 110−120 °C, without the addition of 6-chloropurine, furnished the same product in very good yield. However, participation of the 3-*O*-Bn in the present case was not observed.

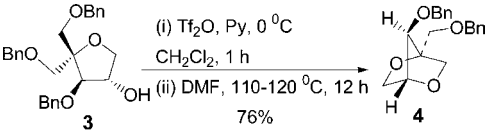
An analogous result was obtained when the triflate derivative of **3**[26] was heated in DMF. This afforded (Scheme 2) the dioxabicycloheptane derivative **4** through the participation of a β-benzyloxymethyl group at C(5) (*anti*-attack).

With a compound having a crotyloxy group at C(5) and C-allyl functionality at the C(1) position, a similar result

Scheme 1. Participation of Benzyloxy Group to Form **2**

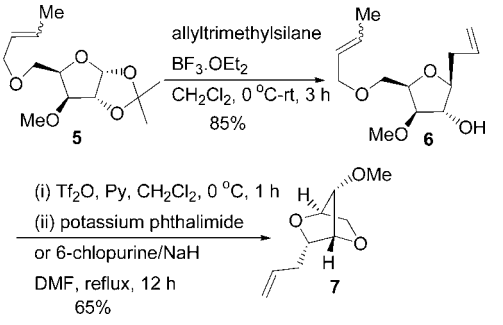


Scheme 2. Participation of β-C(5)-Benzyloxy Group



was obtained. Thus, treatment of **5** (derived via crotylation of 3-*O*-methyl-1,2-*O*-isopropylidene-α-D-xylofuranose[27] with crotyl bromide/NaH) with allyltrimethylsilane in the presence of a Lewis acid produced the allylated compound **6** (Scheme 3). Attempted nucleosidation and phthalimide insertion at C(2) of the triflate ester of **6** also failed to occur. In each of these cases, the dioxabicycle derivative **7** was obtained instead. The same product was also obtained from the ester by heating at reflux in DMF.

Scheme 3. Participation of Crotyloxy Group to Generate **7**



The results shown in Schemes 1−3 revealed that participation of the C(5)-benzyloxy and -crotyloxy moieties had occurred, leading to the formation of a dioxabicyclo-[2.2.1]heptane ring in the cyclized products **2**, **4**, and **7**. However, the presence of an allyloxy substituent in the same position of **9** produced a different outcome. Compound **8**, prepared via allylation of the corresponding hydroxyl derivative,[28] gave the C(1) allylated derivative **9** in excellent yield when treated with allyltrimethylsilane and $BF_3 \cdot OEt_2$ in CH_2Cl_2 for 3 h (Scheme 4). When the hydroxy group of **9** was activated as a triflate, and the

(22) Dong, H.; Pei, Z.; Angelin, M.; Byström, S.; Ramström, O. *J. Org. Chem.* **2007**, *72*, 3694–3701.
(23) Crich, D.; Hu, T.; Cai, F. *J. Org. Chem.* **2008**, *73*, 8942–8953.
(24) Baek, J. Y.; Lee, B.-Y.; Jo, M. G.; Kim, K. S. *J. Am. Chem. Soc.* **2009**, *131*, 17705–17713.
(25) Ghosh, R.; Maity, J. K.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **2010**, *75*, 2419–2422.
(26) Mukherjee, S.; Roy, B. G.; Das, S. N.; Mandal, S. B. *Tetrahedron Lett.* **2012**, *53*, DOI: 10.1016/j.tetlet.2012.06.121.
(27) Boto, A.; Hernández, D.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2006**, *71*, 1938–1948.
(28) Srihari, P.; Kumaraswamy, B.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 2903–2905.

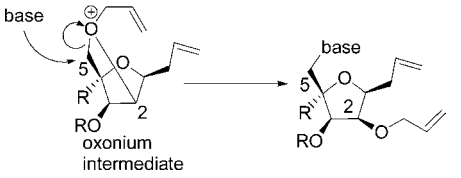
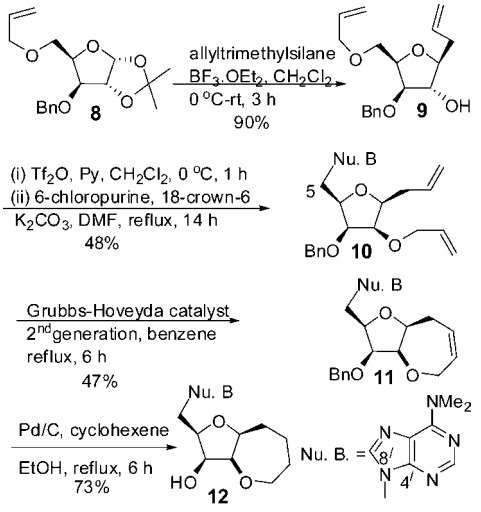


Figure 1. Mechanism for migration of allyloxy group.

Scheme 4. Synthesis of 5-C Nucleoside via Participation and Migration of Allyloxy Moiety

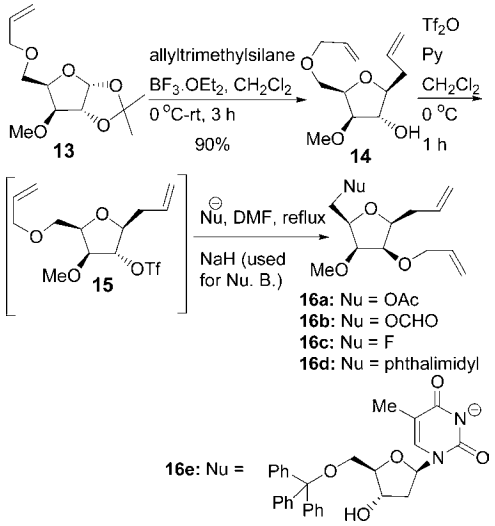


product was subjected to nucleosidation using 6-chloropurine and a crown-ether, in DMF at reflux, the C(5)-nucleoside **10** was obtained. It is interesting to note that the 6-chloro group was replaced by a dimethylamino functionality during this transformation. This can be attributed to the generation of dimethylamine from DMF under reflux conditions, as previously observed by us.[29] The formation of **10** is due to formation of an allyloxonium ion intermediate (Figure 1), generated through participation of the allyloxy group during the displacement of the substituent at C(2) of the sugar moiety; this then suffered subsequent attack by the purine base at C(5), leading to migration of the allyloxy group to the C(2) position. The structure of the product **10** was conclusively proved by 2D NMR and mass spectral analyses. The signals for the ipso protons for the carbon carrying the heterocyclic ring were easily identified through their characteristic HMBC correlations with 4-C and 8-C atoms of the purine ring.

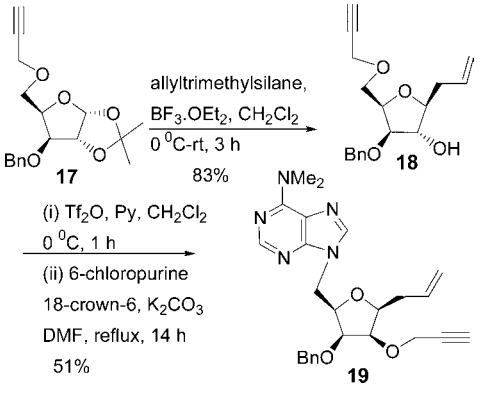
Ring-closing metathesis reaction of **10** using Grubbs catalyst (2nd generation) afforded the desired cyclized product **11**, proving the migration of the allyloxy group to C(2) of the furanoside. The olefin moiety could be reduced by hydrogenation to provide the bicyclic nucleoside analogue **12** (Scheme 4).

(29) Roy, A.; Chakrabarty, K.; Dutta, P. K.; Bar, N. C.; Basu, N.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **1999**, *64*, 2304–2309.

Scheme 5. Synthesis of 5-C-Substituted Nucleoside and Other Sugar Derivatives



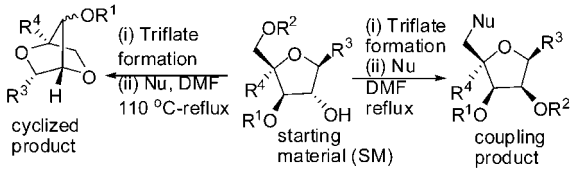
Scheme 6. Migration of Propargyloxy Group to 2-C



Similarly, use of various other nucleophiles such as acetyloxy, formyloxy, fluoride, phthalimidyl, and tritylated thymidinyl anions produced the corresponding C(5) substituted sugar derivatives. The 5-*O*-allyl sugar derivative **13**, derived from 3-*O*-methyl-1,2-*O*-isopropylidene-α-D-xylofuranose,[27] via allylation of the hydroxyl group, was C-allylated at C(1) using allyltrimethylsilane in the presence of boron trifluoride etherate to produce **14** (Scheme 5). When the intermediate triflate derivative **15** was treated with sodium acetate in DMF at reflux, it furnished **16a**. In like fashion, treatment of **15** with sodium formate, tetrabutylammonium fluoride, and potassiophthalimide gave the corresponding coupling products **16b**–**16d**. Most interestingly, the thymidine base was successfully introduced at C(5) of the sugar moiety using tritylated thymidine in DMF in the presence of sodium hydride, affording **16e**.

We next shifted our focus to the 5-*O*-propargyl sugar **18** to see whether this group could participate to produce the corresponding nucleoside with 6-chloropurine.

Table 1. Formation of Cyclized and Coupling Products



SM: **1** (R^1, R^2 = Bn, R^3, R^4 = H); **3** (R^1, R^2 = Bn, R^3 = H, R^4 = CH_2OBn)
6 (R^1 = Me, R^2 = crotyl, R^3 = allyl, R^4 = H)
9 (R^1 = Bn, R^2, R^3 = allyl, R^4 = H); **14** (R^1 = Me, R^2, R^3 = allyl, R^4 = H)
18 (R^1 = Bn, R^2 = propargyl, R^3 = allyl, R^4 = H)

entry	substrate	conditions	cyclized product (yield %)[a]	coupling product (yield %)[a,b]
1	**1**	6-chloropurine, NaH, DMF, 110−120 °C, 12 h	**2** (73)	–
2	**3**	DMF, 110−120 °C, 12 h	**4** (76)	–
3	**6**	potassium phthalimide, DMF, reflux, 12 h	**7** (65)	–
4	**9**	6-chloropurine, K_2CO_3, 18-crown-6, DMF, reflux, 14 h	–	**10** (48)
5	**14**	NaOAc, DMF, 15-crown-5, reflux, 12 h	–	**16a** (51)
6	**14**	NaOCHO, DMF, reflux, 10 h	–	**16b** (62)
7	**14**	TBAF, DMF, reflux, 16 h	–	**16c** (50)
8	**14**	potassium phthalimide, DMF, reflux, 12 h	–	**16d** (60)
9	**14**	tritylated thymidine, NaH, DMF, reflux, 11 h	–	**16e** (48)
10	**18**	6-chloropurine, K_2CO_3, 18-crown-6, DMF, reflux, 14 h	–	**19** (51)

[a] Product yields after purification. [b] Recovered starting material (8−10%) in each case.

To this end, the precursor **17**, obtained from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose[28] by treatment with propargyl bromide (Scheme 6), was converted to the C(1)-allyl sugar derivative **18**. Treatment of **18** with triflic anhydride/pyridine afforded the triflate intermediate, which subsequently furnished the nucleoside analogue **19** following participation of the propargyloxy moiety, and subsequent nucleophilic attack by the nucleobase. Replacement of the chloro group by dimethylamine was again observed in the product.

The yields of the cyclized and coupled products, under different reaction conditions, have been summarized in Table 1.

In conclusion, the work described herein documents an unusual remote participation of 5-*O*-allyl and -propargyl moieties during the displacement of a leaving group of 1-deoxy-xylofuranose sugar derivatives, followed by attack of nucleophiles at C(5), and migration of the participating groups to C(2), to afford 5-C-nucleoside analogues and other sugar derivatives. Similar participation and migration could provide a method for the synthesis of targeted sugar molecules. Use of 5-*O*-Bn or -*O*-crotyl derivatives, however, ended with loss of the *O*-alkyl groups from the oxonium ion intermediates, furnishing dioxabicycloheptane derivatives. The allyl/propargyl groups differ in their reactivity from benzyl/crotyl groups. We believe that the greater stability of the carbocations derived from the latter permits elimination of the corresponding alkyl groups before attack by the nucleophile at 5-C.

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Supporting Information Available. Experimental procedures for compounds **2**, **4**−**14**, **16**−**19**; their ^1H and ^{13}C NMR spectra including HSQC and HMBC spectra of **10** and **16d**. This material is available free of charges via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.