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ArSCl Adducts of Glucal Derivatives in the Preparation of C-Glucosides

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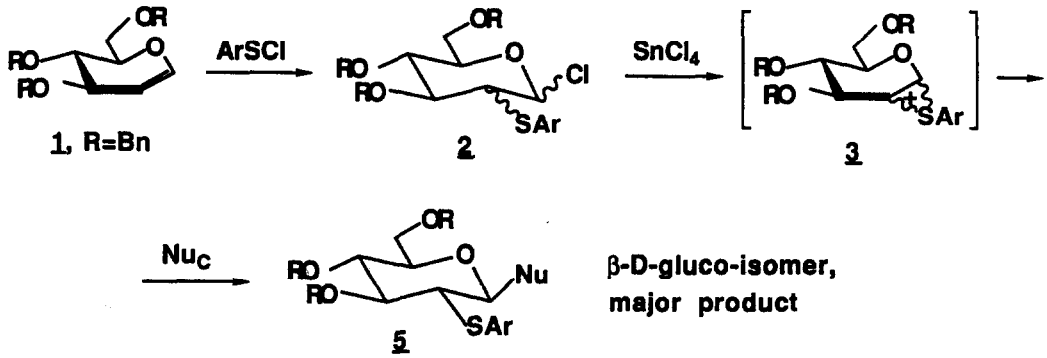
Abstract: Reaction of the ArSCl adducts formed *in situ* from the protected glucals with carbon nucleophiles in the presence of $SnCl_4$ is proposed as a novel route for a stereoselective synthesis of various C-β-D-glucosides.

Recently the interest in the synthesis of C-glycosides has risen dramatically owing both to the discovery of biologically active natural compounds of this type, e.g. C-aryl glycosides,[1] and also to the tremendous promise of carbohydrates bearing functionalized side chains as chiral precursors for the preparation of a plethora of biologically active compounds[2] including various non-hydrolyzable enzyme inhibitors.[3] The increased reactivity of anomeric acetal centers offers numerous opportunities for using carbohydrate derivatives as electrophiles in C-C bond forming reactions.[4] However, in many cases the scope of application of these reactions is rather limited due to the unsatisfactory stereoselectivity of C-glycosylation.[4] On the other hand, it is well known that a nearly complete stereospecificity of a closely related O-glycosylation process can be achieved with the intermediacy of bridged electrophiles generated from carbohydrate derivatives containing appropriate substituents at C-2.[5] These bridged intermediates are usually formed in the presence Lewis acids from the Ad_E adducts of protected glucals with various electrophiles.[6] To the best of our knowledge this sequence has never been employed for the preparation of C-glycosides, presumably because of the alleged low carbophilicity of the bridged electrophiles.

As was shown previously, episulfonium ions generated upon the action of Lewis acids at β-arylthioalkyl chlorides (Ad_E adducts of alkenes with ArSCl) are able to alkylate various carbon nucleophiles (Nu_C) with complete regio- and stereospecificity.[7] The tandem sequence of Ad_E reaction of 1-alkoxy alkenes with ArSCl and coupling of the formed *in situ* adducts with a set of π-donors has been elaborated as a novel procedure for the preparation of polyfunctional adducts from simple precursors.[8] It was anticipated that application of this reaction to unsaturated carbohydrate derivatives might offer novel opportunities for the preparation of chiral compounds, promising intermediates for the synthesis of C-glycosides. Here we report preliminary results attesting to the usefulness of this route.

The readily available tri-O-benzyl- (**1a**) and tri-O-acetyl- (**1b**) D-glucals were taken as model compounds. Reaction of **1a** with p-TolSCl proceeded readily upon mixing of the reagents in CH_2Cl_2 solution at ambient temperature and gave adduct **2a** which was used further without any purification.[9] We have found that in the presence of $SnCl_4$, **2a** is converted into an active electrophile, presumably **ESI 3**, which is capable of participating in C-C bond forming reactions with the set of standard π-donors **4a-g** used as Nuc (see general Scheme and Table). It was also noted that the presence of Lewis acid is unnecessary if more active nucleophiles like PhMgBr (**4h**) are utilized and in these cases the reaction can be carried out directly with **2a**. The respective 2-desoxy-2-arylthiosubstituted C-glycosides **5a-h** are formed in fair to good yields and with a high stereoselectivity (from 10:1 up to > 19:1 in favor of the β-isomer). The use of p-ClPhSCl gave essentially the same results as was shown for the preparation of the corresponding analog of **5c**. A similar sequence with **1b** required the use of a more polar solvent (CH_3CN) for the preparation of ArSCl adducts (**2b**, R=Ac). The interaction of the latter with **4c** gave **5i** as the nearly individual β-stereoisomer. However, the same reaction leading to **5k** proceeded in a non-stereoselective way and produced both β-D-gluco **5k** and α-D-manno **5l** isomers in comparable amounts.

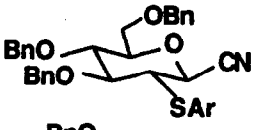
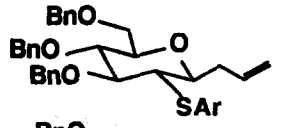
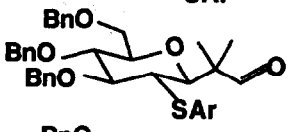
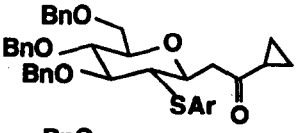
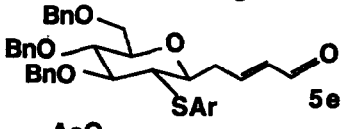
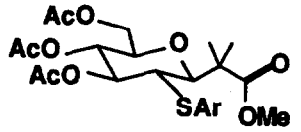
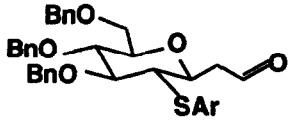
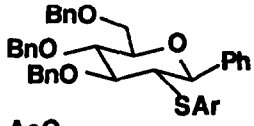
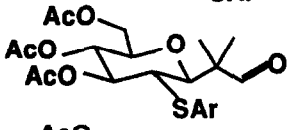
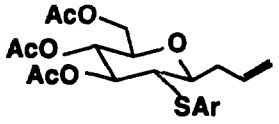
Scheme



The typical experimental procedure is as follows: To a solution of p-TolSCl (0.159 g, 1 mmol) in CH_2Cl_2 (1 ml) at room temperature was added a solution of **1a** (0.416 g, 1 mmol) in CH_2Cl_2 (10 ml). After 10 min the mixture was cooled down to -78° C and a solution of TMSCN (0.119 g, 1.2 mmol) in CH_2Cl_2 (2 ml) was added followed by a dropwise addition of $SnCl_4$ (0.14 ml, 1.2 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred for 30 min at -78°C, quenched with aq. $NaHCO_3$, and extracted with ether. Usual workup and preparative TLC on SiO_2 gave adduct 1-cyano-3,4,6-(tri-O-benzyl)-2-(p-tolylthio)-β-D-glucopyranoside **4a** (0.497 g, yield 88%), R_f 0.45 (ether-hexane, 1:1) as a colorless liquid (the presence of ca.3% of isomeric adduct, presumably with α-configuration was detected from PMR spectrum). ^1H NMR ($CDCl_3$, 200 MHz): 2.38 (s, 3H, CH_3), 3.21 (m, $J_{1,2}$=11.4, $J_{2,3}$=10.2, 1H, H^2), 3.40 (m, 1H, H^5), 3.53 (m, 1H, H^3), 3.73 (m, 3H, H^4, H^{6a}, H^{6b}), 4.08 (dd, $J_{1,2}$=11.4, J=1.1, 1H, H^1), 4.55, 4.62 (two d, J_{AB}=9.8, 2H, OCH_2Ph), 4.64, 4.67 (two d, J_{AB}=10.8, 2H, OCH_2Ph), 4.99, 5.20 (two d, J_{AB}=10.3, 2H, OCH_2Ph), 7.40 (m, 19H, H_{ar}). HRMS calcd for $C_{35}H_{35}SO_4N$ (M^+) m/e 565.2287, found m/e 565.2333.

Data given in Table demonstrate the broad scope of the suggested procedure for the synthesis of 2-arylthio-2-desoxy C-glycosides. In fact this method is applicable for the introduction of a set of substituents

Table. Synthesis of C-glucosides **5a-k** from glucals **1a,b**.

Entry	Glucal	Nu_C	Product[10]		Yield, %	Ratio of isomers, β:α
1	1a	TMSCN 4a		5a	88	>19:1
2	1a	TMS 4b		5b	79	>19:1
3	1a	OTMS 4c		5c	73	10:1
4	1a	OTMS 4d		5d	48	>19:1
5	1a	OTMS 4e		5e	31	10:1
6	1b	OTMS OMe 4f		5f	40	10:1
7	1a	OMe 4g		5g	63	10:1
8	1a	OMe 4h		5c	87	15:1
9	1a	PhMgBr 4i		5h	60	>19:1
10	1b	4c		5i	61	>19:1
11	1b	4b		5k	66	3:2

containing aliphatic, cycloaliphatic, or aromatic fragments bearing various functional groups into a molecule of a starting glucal derivative. One can easily envisage the obvious ramifications for the synthetic utilization of these products owing to the presence of the introduced functional substituents such as cyano or carbonyl groups, double bonds, aryl, or cyclopropylcarbonyl residue at C-1 as well as arylthio group at C-2.

A few additional comments are warranted for the adducts formed with the use of vinyl ethers **4g,h** as the nucleophiles. Here the nature of the final product depends on the manner of quenching of the reaction mixture. For example, aldehyde **5c** was obtained if water was used for the quenching. If the latter step was carried out under strictly anhydrous condition with abs. MeOH as the quencher, the respective dimethoxy acetal **5c'** was obtained in 76% yield. These data provide good reasons to suggest as a viable option for further studies the utilization of the next carbon nucleophile as a quencher at this step which would lead eventually to the creation of the second C-C bond in a way similar to that described earlier for the simpler models.[11]

The results described in this communication provide an entry for the elaboration of an efficient protocol for the general and stereocontrolled synthesis of various C-glycosides.

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References and Notes

1. For review on C-aryl glycosides, see: Postema, M.H.D. *Tetrahedron* **1992**, 48, 8545; Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1-65; Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201-206. For additional examples, see: Tius, M. A.; Gomez-Galeno, J.; Gu, X.; Zaidi, J. H. *J. Amer. Chem. Soc.* **1991**, *113*, 5775 and ref. cited therein.
2. Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach; Pergamon*, Oxford, 1983.
3. Shulman, M. L.; Shiyan, S. D.; Khorlin, A. Y. *Carbohydr. Res.* **1974**, *33*, 229. Cerretti, D. P. *ibid.* **1981**, *94*, C10. Chmielewski, M.; BeMiller, J.N.; Cerretti, D. P. *ibid.* **1981**, *97*, C1. See also: Somsak, L.; Mahmoud, S. H.; Kish, L. *XVI International Carbohydrate Symposium*, July 5-10, **1992**, Paris-France, Abstracts A014, p.49; Petrus, L.; BeMuller, J.; Koll, P.; Kopf, T.; Abeln, D. *ibid.* A123, p.158; Wittman, V.; Kessler, H. *ibid.* A233, p. 268.; Best, W.; Claeyssens, M.; Ferro, V.; Hoj, P. B.; Steck, R. V. *ibid.* A286, p. 321.
4. See, for example, Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Amer. Chem. Soc. 1982*, **104**, 4976 and ref. cited therein. Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydr. Res.* **1987**, *171*, 223. Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *ibid.* **1987**, *171*, 193.
5. For a review, see Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.
6. Ramesh, S.; Kaila, N.; Grewal, G.; Franck R. W. *J. Org. chem.* **1990**, *55*, 5 and nearly exhaustive list of references given therein.
7. Ibragimov, M. A.; Smit, W. A. *Tetrahedron Lett.* **1983**, *24*, 961. Patel, S. K.; Patterson, I. *ibid.* **1983**, *24*, 1315. Smit, W. A.; Smolyakova, I. P. *Izvestia Acad. Nauk SSSr, ser. khim.*, **1985**, 485. Ibragimov, M. A.; Smit, W. A.; Gybin, A. S.; Krimer, M. Z. *ibid.*, **1983**, 161. Ibragimov, M. A.; Lubinskaya, O. V.; Smit, W. A. *ibid.*, **1983**, 1204. Ibragimov, M. A.; Lazareva, M. I.; Smit, W. A. *Synthesis*, **1985**, 880.
8. Smolyakova, I. P.; Smit, W. A. *Izvestia Acad. Nauk SSSr, ser. khim.*, **1990**, 1680 and ref. cited therein.
9. Preuss, R., Schmidt, R.R. *Syhthesis* **1988**, 694.
10. Yields (not optimized) are given for the isolated products, their identity being ascertained by analytical and spectral data. The stereochemistry of the major β-D-gluco-isomers for **5a-5k** was deduced from the pattern of *vic* ^{1}H-^{1}H coupling constants between protons at C-1, C-2 and C-3 ($J_{1,2} \sim J_{3,2} \geq 10$ Hz). α-D-Manno-structure was tentatively ascribed for minor isomers. The latter structure was ascertained for the individual **5l** by ^{1}H NMR spectrum which revealed the following splitting pattern: $J_{1,2} = 5.75$, $J_{2,3} = 3.75$ Hz.
11. Smolyakova, I. P.; Smit, W. A.; Osinov, B. *Tetrahedron Lett.* **1991**, *32*, 2601.

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