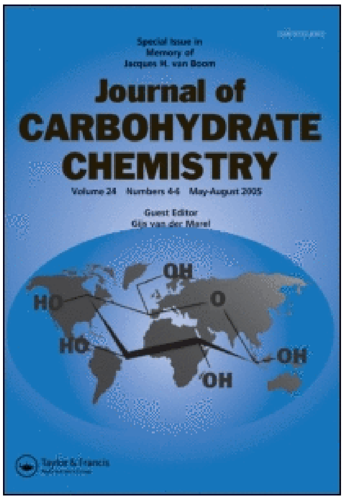

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A Simple Method for the Synthesis of Acylated Pyranoid Glycals Under Aprotic Conditions

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COMMUNICATION

A SIMPLE METHOD FOR THE SYNTHESIS OF ACYLATED PYRANOID GLYCALS UNDER APROTIC CONDITIONS[1]

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Per-*O*-acylated glycals[3] (1,4- or 1,5-anhydro-2-deoxyald-1-enitols, e. g., **9**) represent one of the most useful types of carbohydrate derivatives available for various syntheses. The classical method[4] for their preparation is the reaction of acetobromo sugars (e. g., **2**) with zinc dust in aqueous acetic acid, but the yields are variable and solvolysis products, among others, are formed in side reactions.[5]

Numerous attempts have been made to obtain glycals under aprotic conditions: introduction of good leaving groups at C-2 of glycosyl halides;[6] reactions of variously protected glycosyl halides with sodium,[7] potassium,[7] sodium naphthalenide,[7] zinc/silver-graphite,[8] potassium-graphite,[9] aluminum amalgam,[10] samarium(II) iodide[11] in tetrahydrofuran, with lithium in liquid ammonia,[12] with chromium(II) acetate in *N,N*-dimethylformamide;[13] reactions of 1-thioglycosides and glycosyl phenyl sulfones with lithium naphthalenide in tetrahydrofuran;[14,15] reactions of glycosyl phenyl sulfones with samarium(II) iodide in tetrahydrofuran/hexamethylphosphoric triamide;[11] radical induced eliminations from 1-thioglycoside-2-xanthates in toluene;[15] electrolysis of acetobromo sugars in *N,N*-dimethylformamide or acetonitrile.[16]

Since most of these methods suffer from one or more "inconveniences", e. g., problems with handling pyrophoric reagents,[8,9] requirement for special substrates[6,15] or inert atmospheres[7-9,11-15] or special techniques,[12,16] use of highly toxic reagents[10] or

Table 1. Reactions[19] of **2** with zinc dust and organic bases to give **9** of NMR purity

Solvent	N-base	Temperature	Reaction time
Benzene	4-Pic	reflux	1 hour
Ethyl-acetate	4-Pic	reflux	0.5 "
	MIM	reflux	0.2 "
Acetone	4-Pic	reflux	0.5 "
	MIM	reflux	0.5 "
Tetrahydro-furan	MIM	reflux	0.5 "
Dichloro-methane	4-Pic	reflux	4 "
	MIM	reflux	2 "
	MIM	r.t.	55 "
	MIM	r.t.	8 "*

4-Pic = 4-methylpyridine. MIM = 1-methylimidazole

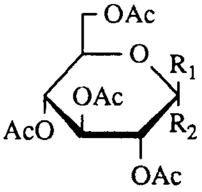
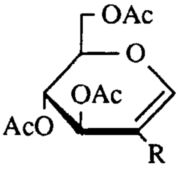
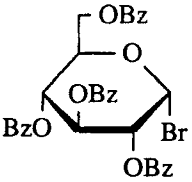
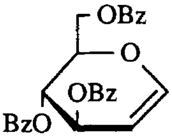
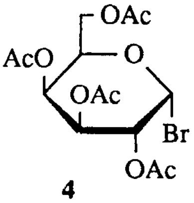
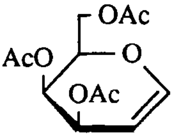
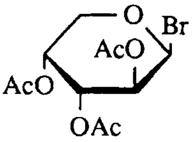
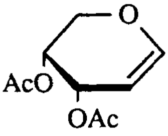
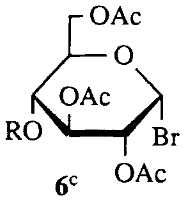
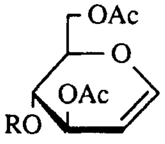
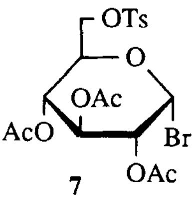
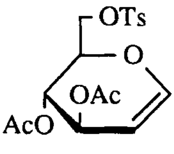
*By using a Zn/Cu-couple.[26]

solvents,[11] there is an obvious need for a simple aprotic procedure which is easy to perform on common substrates, and which is also suitable for scaling up.

We have found that the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**2**) with zinc dust in refluxing benzene in the presence of 1 equivalent of triethylamine[17] gives a mixture of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**9**) and penta-*O*-acetyl-β-D-glucopyranose (**1**) in 6:4 ratio (determined by ^{1}H NMR) which can be improved to 9:1 by the use of pyridine. Application of 4-methylpyridine (4-Pic) or 1-methylimidazole (MIM) gave **9** of NMR purity while use of 2,6-dimethylpyridine resulted in the formation of **1** and 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol (**8**), no **9** being detectable (TLC) in the reaction mixture. With 4-dimethylaminopyridine, 2,2'-bipyridyl, and *N,N,N',N'*-tetramethyl-ethylene-diamine **9**, **1**, and **8** could be detected (TLC) in the reaction mixtures.

4-Pic or MIM used in diverse solvents (Table 1) resulted in the formation of **9** of NMR purity as checked on the worked up reaction mixtures. MIM is superior to 4-Pic

Table 2. Preparation of acylated glycals

Substrate	Product	Yield (%) (mmol scale)
 **1** $R_1 = OAc$ $R_2 = H$ **2** $R_1 = H$ $R_2 = Br$	 **8** R = OAc **9** R = H	77[a] (2) 95[b] (100)[20]
 **3**	 **10**	89[b] (2)
 **4**	 **11**	82[a] (2) >95[b] (10)
 **5**	 **12**	65[a] (2)
 **6**[c]	 **13**[c]	75[a] (2)
 **7**	 **14**	81[b] (10)[27]

a. EtOac/4-Pic[19] b. EtOAc/MIM[19] c. 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl because it gives colourless solutions; a yellow colour develops during the reactions with 4-Pic necessitating chromatographic purification.

Any good quality zinc dust can be used. From among the several procedures[18] for activation of the zinc surface simple washing with hydrochloric acid[19] proved to be the best.

Applied to several acylated glycosyl bromides (**2-7**) the best reaction conditions[19] (Table 1) gave the corresponding glycals (**9-14**) in good to excellent yields (Table 2). A large-scale (100 mmol) reaction was also successful resulting in a quantitative yield of **9**.[20]

Glycosyl quaternary ammonium salts seem not to be intermediates in the reactions. This was checked by using 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) pyridinium bromide[21] which did not give any tri-*O*-acetyl-D-glucal under the applied conditions. Furthermore, zinc dust in the absence of N-base, and N-base in the absence of zinc did not give rise to glycal formation. Therefore, the role of the N-base is most probably to provide organozinc complexes[22] which may facilitate the formation of the glycosyl-zincbromides on one hand, and increase their reactivity by enhancing their carbanionic character on the other. This is supported by the finding that no glucal formation was observed when the hindered 2,6-dimethylpyridine was used as base.

In summary, a simple, large-scale, adaptable, aprotic procedure has been found for the preparation of acylated pyranoid glycals which constitutes an improvement on the classical Fischer method.[4]

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19. Glycosyl bromide (**2**-**7**, 2 mmol) was dissolved in a dry solvent (10 mL) and zinc dust (8-12 mmol, consecutively washed with 10% HCl, water, acetone, and ether, and then air-dried on a glass- filter just before use) was added. The mixture was stirred and heated under reflux and base (2 mmol) was added in one portion. After

TLC had indicated the disappearance of the glycosyl bromide the reaction mixture was cooled, filtered, the filtrate was washed with 10% HCl and then satd. aq. $NaHCO_3$, dried, and the solvent was evaporated. For chromatographic purification the reaction mixture was filtered, concentrated, and then applied to the silica gel column. Molecular sieves (4Å) can be added to the reaction mixture to remove traces of moisture which may be present in the zinc dust. This, however, was generally unnecessary.

20. For reactions on larger scales the following procedure proved to be most advantageous: Zinc dust (39.2 g, 0.6 mol, treated as indicated[19]) was suspended in EtOAc (400 mL) and 1-methylimidazole (7.95 mL, 0.1 mol) was added. The mixture was vigorously stirred and heated to reflux and, then a solution of **2** (41.1 g, 0.1 mol) in EtOAc (100 mL) was added dropwise over ~1 hour. Stirring and heating were then continued until TLC had indicated completion of the reaction (~30 min). The mixture was cooled, filtered through Celite, the filtrate was washed with 10% HCl, satd. aq. $NaHCO_3$, dried, and evaporated to a syrup (27.9 g) the ^1H NMR spectrum of which was essentially that of pure **9**. This syrup crystallized on standing, and recrystallization from MeOH-water gave **9** (25.8 g, 95%).

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22. It is known that Grignard compounds can be prepared in non-coordinating solvents in the presence of at least 1 equivalent of Et_3N, Et_2O, THF, etc.[23] Organozinc compounds also form rather stable complexes with (especially aromatic) nitrogen ligands,[24] and reactivity enhancement by complexation has been demonstrated.[25]

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26. Zinc dust was washed consecutively with 10% HCl, water, 10% $CuSO_4$, water, acetone, and ether, and then air-dried on a glass-filter just before use.

27. This experiment was performed by Andreas Tietze, Technical University of Darmstadt, Germany.