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Chromium(II)-complex mediated formation of *C*-glycosides from glycosyl halides under aqueous biphasic conditions

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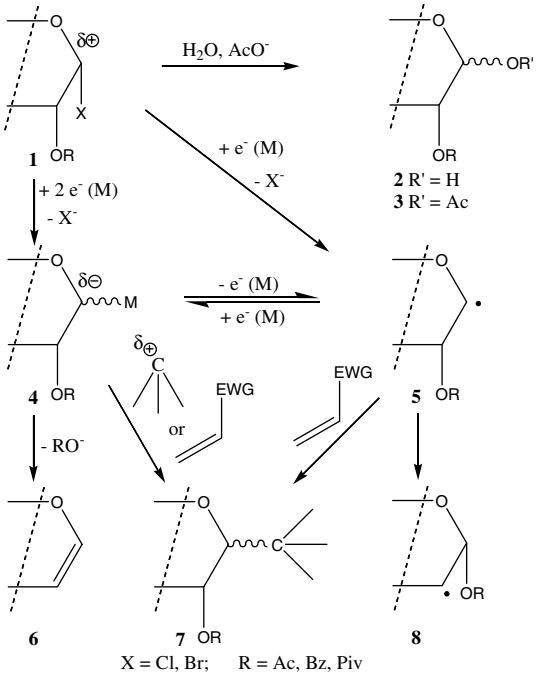
Abstract—*C*-Glycosyl compounds were formed in the reactions of hydrolytically sensitive glycosyl halides with electron deficient alkenes mediated by the complex $[Cr^{II}(EDTA)]^{2-}$ under aqueous conditions.

C-Glycosyl derivatives play an important role in carbohydrate and natural product chemistry, because: (i) there are numerous naturally occurring *C*-glycosides with important biological or pharmacological activities; (ii) these compounds can be considered as hydrolytically stable counterparts of *O*- and *N*-glycosides, and therefore suitable to mimic biologically important carbohydrate derivatives; (iii) the use of *C*-glycosides as intermediates is also of great importance in syntheses of complex structures of natural origin.[1] Therefore, formation of carbon–carbon bonds at the anomeric center of carbohydrate derivatives has received considerable attention.

Amongst numerous methods for the synthesis of *C*-glycosyl compounds[1] (Scheme 1, **7**) the generation of glycosyl anions[1i] **4** or radicals[1d,2] **5** offers possibilities for umpolung of the 'naturally' electrophilic reactivity of the anomeric center (cf. **1**).

Carrying out chemical transformations under aqueous conditions has attracted particular interest in the last decade because it offers several advantages: there is no need for anhydrous organic solvents; the burden of solvent disposal on the environment can be moderated; several protection-deprotection steps can be omitted from synthetic sequences; in metal ion assisted reactions separation of the organic product can be simplified; biochemical processes occur in the presence of water.[3]



Scheme 1.

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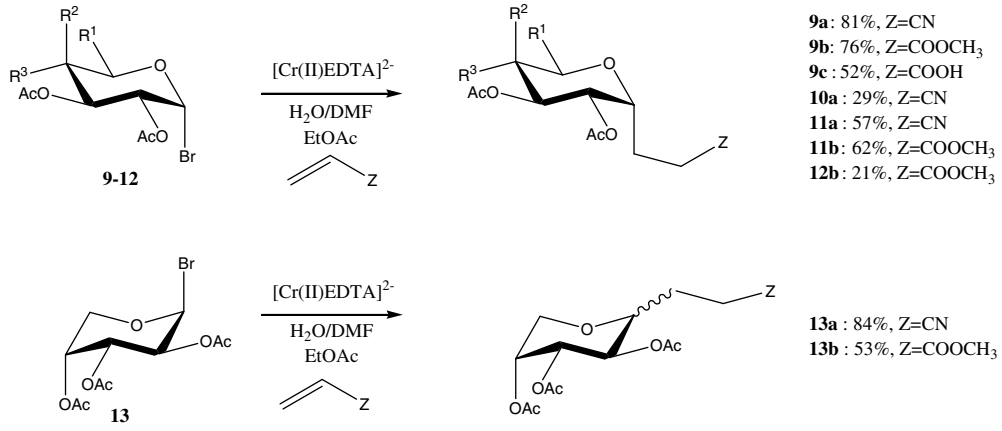
Although most 'classical' methods for the generation of (glycosyl) anions are incompatible with aqueous or even slightly protic circumstances,[1i] some years ago we demonstrated that glycosyl–chromium(III) species (**4**, M = Cr^{III}) were remarkably stable under aqueous conditions.[4a] Based on this finding a general method was elaborated for the preparation of pyranoid glycals **6** from per-O-acylated glycosyl chlorides or bromides **1** in water–DMF solvent mixture,[4b] and the transformation could also be performed in water.[4c] Under these conditions nucleophilic substitutions as side-reactions leading to **2** and **3** could be suppressed. Attempts to obtain *C*-glycosyl derivatives **7** from **4** with aldehydes were unsuccessful, the monomolecular $E1_{cb}$ type elimination being faster than the bimolecular reaction with the electrophile. Since glycosyl–chromium(III) (**4** M = Cr) must form via radical **5**[4b] we have investigated the possibility of tuning the above reaction conditions in order to trap nucleophile **5** with electron deficient alkenes to yield **7**. In doing this we were also encouraged by a report on the formation of *C*-(α-D-glucopyranosyl) derivatives (30% + ~60% glucal) in reactions of **9** with 20 equiv of methyl acrylate or methyl vinyl ketone mediated by $CrCl_3$/Mn/TMEDA under strictly anhydrous conditions.[5] Similarly, when the reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucoypranosyl 2-benzothiazolyl sulfone with $[Cr^{II}(EDTA)]^{2-}$ complex was performed in the presence of 60 equiv of acrylonitrile in H_2O/DMF = 1:1, formation of the corresponding *C*-(α-D-glucopyranosyl) derivative was observed (~40%).[6]

The reactions of various glycosyl halides (Scheme 2, **9**–**13**) were studied with the $[Cr^{II}(EDTA)]^{2-}$ complex in the presence of acrylic acid derivatives in neutral aqueous-DMF and under biphasic conditions. The complex was chosen on the basis of our earlier observations proving $[Cr^{II}(EDTA)]^{2-}$ to be the most efficient amongst Cr(II) amino-polycarboxylate complexes in glycal[4a–c] and carbon–carbon bond forming reactions.[4d] First, the reaction was studied under homogeneous conditions, in which both the complex and the solution of the glycosyl halide with acrylonitrile were prepared in H_2O/DMF = 1:1. In order to avoid the formation of glycals **6** due to high concentrations of Cr(II), the $[Cr^{II}(EDTA)]^{2-}$ complex[7] was prepared[8] in a separate reaction vessel and this solution was added dropwise to the solution of glycosyl halide **1** and acrylonitrile. During the first few minutes of addition of the complex, the colour of the reaction mixture turned brown indicating the rapid formation of glycosyl–Cr^{III} complex intermediate.[4a] Starting with **9**, under these conditions, the expected product **9a** was isolated in 44% yield, but by-products of type **2** and **3** were present in the worked up reaction mixture and a small amount of glycal **6** was also apparent (26%, 21% and 9%, respectively). With methylacrylate, a slightly better yield was achieved for **9b** (52%) together with the above by-products. The corresponding α-D-glucopyranosyl chloride, which is less susceptible towards nucleophilic attack, did not react completely and the products were the same as above.

To avoid these side-reactions the substrates and the reagent were placed into separate phases. When the complex was prepared in water and added dropwise to a solution of bromide **9** and acrylonitrile in ethyl acetate, starting material **9** (7%), **9a** (24%), hydrolyzed product **2** (60%) and glycal **6** (7%) were present in the mixture. However, no unreacted starting material remained when DMF was added to the solution of the Cr complex.[9] The role of DMF was most probably to help the reactants meet at the phase boundary.[4c] However, coupled product **9a** (39%) was still accompanied by side-products **2**, **3** and **6** (30%, 23% and 7%, respectively).



	Configuration	R^1	R^2	R^3
9	α-D-*gluco*	CH_2OAc	H	OAc
10	α-D-*cellobio*	CH_2OAc	H	$(AcO)_4$-β-D-Glc_p
11	α-D-*galacto*	CH_2OAc	OAc	H
12	α-D-*xylo*	H	H	OAc
13	β-D-*arabino*			

Scheme 2. The *C*-glycosyl derivatives were identified by comparing their ^1H NMR spectra with the literature data.[12] For optimized reaction conditions see Ref. 9.

Further optimization revealed that the organic solvent was also important with ethyl acetate being better than diethyl ether. More dilute reaction mixtures (lower concentration of $[Cr^{II}(EDTA)]^{2-}$) were also favourable (yield of **9a** 39% with a total volume of 40 ml of the solution of the Cr complex,[8] 44% with 60 ml). A faster dropping speed (20 drops/min instead of 7) resulted in an 81% yield of **9a** demonstrating that it was possible to suppress eliminative and nucleophilic side-reactions.

Under these optimized conditions several *C*-glycosyl derivatives **9**–**13** were obtained as shown in Scheme 2. The lower yields of **10a** and **12b** may be explained by the lower solubility of **10** and the higher sensitivity towards hydrolysis of **12**, respectively. Since arabinose derivatives show greater tendency towards conformational changes, **13a** and **13b** proved to be α/β anomeric mixtures in ~1:1 ratio.

The formation of *C*-glycosyl derivatives under the above conditions may occur either by radical (**5**→**7**) or ionic (**4**→**7**) pathways. The preponderance of the α-D-glycosyl derivatives infers a the radical pathway according to the known α-selectivity of glycosyl radicals.[2] Although the absence of 2-deoxyglycosyl products[10a,b] was considered to be an indication of non-radical reactions[5] one has to take into account that this rearrangement (**5**→**8**) is rather slow[11] and the end products (e.g. 2-deoxyglycosyl derivatives) can be obtained only if the trapping agents are present in very low concentration.[2] Therefore, we are in favour of the radical pathway but cannot exclude the ionic possibility on the basis of the present experimental data.

In summary, mild aqueous reaction conditions mediated by $[Cr^{II}(EDTA)]^{2-}$ have been developed and tuned to form *C*-glycosyl derivatives from hydrolytically sensitive acetylated glycosyl halides.

Acknowledgement

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8. *General procedure for the preparation of* $[Cr^{II}(EDTA)]^{2-}$ *complex*:[7,4b] $Na_2EDTA{\cdot}2H_2O$ (3.258 g, 8.75 mmol) was dissolved in a mixture of water and DMF (30 ml of each, total volume = 60 ml), and stirred under argon. A calculated amount of an aq KOH soln. (2.4446 M, 2.5 ml) was added to the solution to obtain pH ~6. After the solution had cleared (30 min), $[Cr(CH_3COO)_2{\cdot}H_2O]$ (1.372 g, 7.29 mmol) was added in one portion. Formation of the complex was indicated by a change of colour to blue. The pH of the solution was 6.5.
9. *Typical procedure*: $[Cr^{II}(EDTA)]^{2-}$ complex was generated in situ in H_2O/DMF = 1:1 as above[8] and added dropwise (20 drops/min) to a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide (**9**, 0.750 g, 1.82 mmol, 1 equiv) and acrylonitrile (2.16 ml, 32.83 mmol, 18 equiv) in EtOAc (15 ml). (In the first few minutes the colour of the reaction mixture was brown, and then it turned deep-violet.) The reaction vessel was then stoppered under a slight overpressure of argon, and stirred at room temperature for 18 h. The mixture was saturated with aqueous NH_4Cl solution and extracted with EtOAc (6 × 20 ml), the organic phase was washed with water (3 × 10 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting residue was examined by TLC (eluent: ether/hexane = 6:4) and ^1H NMR,[11] and separated by column chromatography (eluent ether/hexane = 1:1 to 3:1) to give **8a** in 81% yield as pale yellow crystals.
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