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Methyltrioxorhenium catalyzed domino epoxidation-nucleophilic ring opening of glycals

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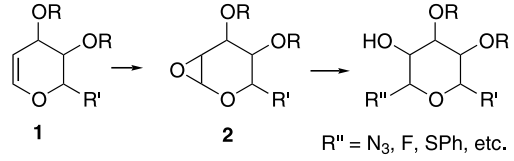
Abstract—The use of catalytic methylrhenium trioxide (MTO) and urea hydrogen peroxide in room temperature ionic liquid for the hydroxyglycosylation with glycals in a domino fashion is reported. Excellent conversions and good selectivities for the epoxidation reaction were observed. Application to the synthesis of glycosylphosphates, good glycosyl donors, has been studied.

Cell surface glycoconjugates are involved in many cell–cell recognition events connected to inflammation, immune response, cancer and viral infections.[1] In this respect, glycals **1** have recently found a wide application as synthetic building blocks in the construction of various glycoconjugates.[2] Direct epoxidation with glycals furnishes 1,2-anhydrosugars **2**, that behave as good glycosyl donors. In turn, 1,2-anhydrosugars **2** can be easily employed for the installation at C-1 of functional groups that impart glycosyl donor character to the anomeric carbon atom, such as azide, amine, fluoride, phenylthiol, etc.[3]



The epoxidation of glycals **1** to **2** is not a trivial task, due also to the sensitive nature of **2**, particularly in acidic media. This transformation is usually performed using dimethyldioxirane (DMDO);[4] other reagents have been proposed, namely methyl(trifluoromethyl)-dioxirane,[5] MCPBA/KF,[6] or perfluoro-*cis*-2,3-dialkyloxaziridines,[7] but always as stoichiometric oxidants. No general catalytic oxidation procedure has been reported so far for this type of transformation.[8] Recently, a C-2 hydroxyglycosylation with glycals that employs a reagent combination of Tf_2O and diphenylsulfoxide has been described.[9]

During the last years, we have been involved in the study of new convenient, practical, and environmentally friendly oxidation procedures, addressed in particular to the oxidation of nitrogen containing compounds.[10] During these studies, we have focused on the use of methylrhenium trioxide (CH_3ReO_3, MTO),[11] as the catalyst for the oxidation of secondary amines to nitrones by using as the stoichiometric oxidant the complex urea–H_2O_2 (UHP),[10c,12] which simplifies the work-up procedures and allows the use of non-aqueous solvents and safe reagents.

Methyltrioxorhenium has emerged in the last decade, in combination with hydrogen peroxide as the stoichiometric oxidant, as an important catalyst for the oxidation of many classes of substrates, among which the most important and studied reactions were epoxidation of olefins.[13] To our knowledge, however, no example of use of MTO as catalyst for the oxidation of enol ethers has been reported, apart from the oxidation of silyl enol ethers to α-hydroxy and α-silyloxy ketones.[14]

We decided to test methyltrioxorhenium (MTO), in combination with UHP as the stoichiometric oxidant, in the epoxidation of glycals, in view of the usefulness of 1,2-anhydrosugars and their uneasy preparation, requiring oxidants not immediately available. In this Communication we report the domino epoxidation-nucleophilic ring opening of glycals catalyzed by MTO.

Keywords: glycosyl phosphates; glycosyl donors; methyltrioxorhenium; ionic liquids; catalysis; oxidation.
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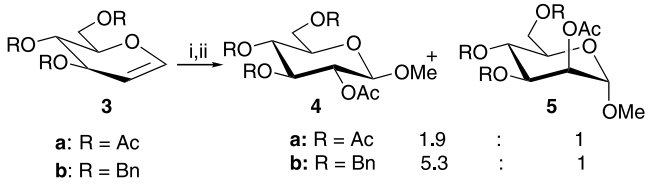


Scheme 1. *Reagents and conditions*: (i) MTO (2 mol%), UHP (3 equiv.), MeOH, rt, 20 h for **3**, 15 h for **4**; (ii) Ac_2O, py, rt, 15 h, **a**: 92%, **b**: 87%.

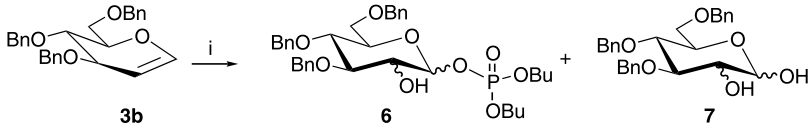
Reaction of tri-*O*-acetylglucal (**3a**) and tri-*O*-benzylglucal (**3b**) with MTO (2 mol%) and UHP (3 equiv.) in MeOH as solvent gave, with complete conversion of the starting glycals, a β/α mixture of methyl glycosides **4** and **5** (Scheme 1), deriving from methanolysis of the intermediate epoxides, not isolable under the reaction conditions. The diastereoselectivity of the epoxidation was determined by ^{1}H NMR analysis after acetylation of the crude product mixtures. As expected, with the bulkier benzyl groups a higher level of diastereoselectivity in favor of the α-epoxidation (anti to the OR group at C-3), with preferred formation of glucose derivative **4**, was observed.

All efforts to isolate the epoxides performing the oxidation reaction in non-nucleophilic solvents failed. Indeed, in CH_2Cl_2 or CH_3CN no appreciable conversion of the starting material occurred, while in acetone the 1,2-unprotected sugar **7** (as a mixture of 4 isomers) deriving from hydrolysis of the intermediate epoxides was formed in 72% yield (Table 1, entry 1). Use of 3 Å molecular sieves in the reaction mixture was not efficient in avoiding hydrolysis, ascribed to the formation of water in the reduction of UHP.

Glycosyl phosphates, recently prepared from 1,2-anhydrosugars and $HOP(O)(OR)_2$,[15] are powerful, albeit scarcely employed, glycosyl donors. They react with hindered glycosyl acceptors and furnish disaccharides in high yield, comparing favorably with other types of glycosylating agents.[16] Thus, the MTO-catalyzed epoxidation-nucleophilic ring opening was studied on tri-*O*-benzylglucal (**3b**) as model substrate by introduction of dibutylphosphate (DBP) in the reaction mixture (Table 1). With 3 equiv. of DBP, a 1:1 mixture of glycosyl phosphate **6** and 1,2-diol **7** was formed (entry 2); increase of the amount of DBP to 5 equiv., in order to suppress formation of **7**, however, resulted in lower conversions of glycal (entry 3), showing a detrimental effect of phosphate on the epoxidation rate. Switch to a room temperature ionic liquid[17] as solvent allowed to limit this effect, while increasing the selectivity towards formation of **6** (entry 4).[18] With $[BMIM]BF_4$ as solvent the glycosyl phosphate **6** was always the major product, and the reaction reached complete conversions by using 4 mol% of MTO and 5 equiv. of DBP at rt. The **6**:**7** ratio could be raised up to 4:1 drying the ionic liquid before use. These parameters were chosen as optimal reaction conditions (Table 1, entry 9). With 2 mol% of MTO, as well as at a temperature of 0°C, the reaction was slower, and use of minor (3 equiv.) or major (10 equiv.) amounts of DBP resulted in decreased **6**:**7** ratios (Table 1, entries 4, 12, 5 and 7). Apparently, the dibutyl glycosyl phosphate **6** undergoes slow hydrolysis under the reaction conditions, as showed by the lower ratio obtained when the reaction is stopped after 22 h (Table 1, entry 13 vs. 9).

The optimal reaction conditions (Table 1, entry 9), were then applied for the domino catalytic oxidation to

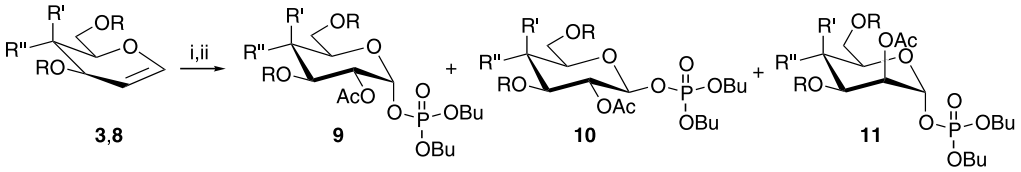
Table 1. Domino catalytic oxidation of tri-*O*-benzylglucal (**3b**) with MTO and UHP-nucleophilic ring opening with dibutylphosphate [a]



Entry	Solvent	MTO (mol%)	DBP (equiv.)	Time (h)	Temperature	**6**:**7** Ratio[b]	Conversion (%)[b]
1	acetone	2	–	1.5	rt	0:100	100
2	acetone	2	3	3	0°C	1:1	100
3	acetone	2	5	3	0°C	–	30
4	$[BMIM]BF_4$ [c]	2	5	3.5	rt	3:1	80
5	$[BMIM]BF_4$	4	3	5	rt	2:1	100
6	$[BMIM]BF_4$	4	5	3	rt	3:1	100
7	$[BMIM]BF_4$	4	10	5	rt	2:1	100
8	DBP	4	–	4.5	rt	1:1	100
9	$[BMIM]BF_4$ [c]	4	5	3.5	rt	4:1	100
10	$[BMIM]BF_4$ [c,d]	4	5	3.5	rt	4:1	100
11	$[BMIM]BF_4$ [c]	4	-	2.5	rt	0:100	100
12	$[BMIM]BF_4$ [c]	4	5	6	0°C	3:1	70
13	$[BMIM]BF_4$ [c]	4	5	22	rt	1.7:1	100

[a] *Reagents and conditions*: (i) MTO, UHP (3 equiv.), $HOP(O)(OBu)_2$(DBP), solvent, nitrogen atmosphere.
[b] Calculated by integration of the ^{1}H NMR spectra of the crude mixtures.
[c] Dried by heating at 80°C for 1 h under reduced pressure.
[d] In the presence of 3 Å molecular sieves.

Table 2. Catalytic oxidation of glycals to glycosyl phosphates in [BMIM]BF_4 with MTO and UHP [a]



Entry	Substrate	Reaction time (h)	Conversion (%) [b]	**9**:**10**:**11** ratio [b]	Yield (%) [c]	α/β Epoxidation selectivity [b]
1	**3a**: R = Ac, R′ = H, R″ = OAc	16	100	1.1:1:1.2	66	1.8:1
2	**3b**: R = Bn, R′ = H, R″ = OBn	3.5	100	8.3:1:1.7	58	5.5:1
3	**8a**: R = Ac, R′ = OAc, R″ = H	17.5	100	12.3:5.3:1	62	17.6:1
4	**8b**: R = Bn, R′ = OBn, R″ = H	4	100	10:1:0	41	>50:1

[a] *Reagents and conditions*: (i) MTO (4% mol), UHP (3 equiv.), DBP (5 equiv.), dry [BMIM]BF_4, nitrogen atmosphere, rt; (ii) py, Ac_2O, rt, 15 h.
[b] Calculated by integration of the ^1H NMR spectra of the crude mixtures.
[c] Isolated by flash column chromatography.

glycosyl phosphates of tri-*O*-acetylglucal (**3a**) and tri-*O*-acetyl and tri-*O*-benzylgalactals (**8a** and **8b**, respectively) (Table 2). Direct acetylation of the crude mixtures allowed determination of the diastereoselectivity of the epoxidation by ^1H NMR analysis. Satisfactory isolated yields (41–66%) were obtained in all cases.[19] Products **9** and **10**, that derive from the α epoxide, were always the major diastereomers, but the diastereoselectivity of the epoxidation is notably higher for galactals with respect to glucals (Table 2, entries 3,4 vs. 1,2) and with benzyl protecting groups with respect to acetyl protecting groups (Table 2, entries 2 vs. 1 and 4 vs. 3).

In conclusion, the first catalytic methodology to convert glycals into glycosyl phosphates employing safe, commercially available and inexpensive reagents and a 'green solvent' such as [BMIM]BF_4 is presented. Further work is in progress in our laboratories to widen the scope and application of this methodology.

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