Monatsh Chem (2013) 144:969–973
DOI 10.1007/s00706-013-0964-0

ORIGINAL PAPER

Application of oxone immobilized on montmorillonite for an efficient oxidation of mannose thioglycoside

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Received: 13 December 2012 / Accepted: 10 March 2013 / Published online: 15 May 2013

Abstract A new solid system based on montmorillonite supported oxone has been developed and used for the oxidation of thiomannoside. The oxidation properties of oxone immobilized on montmorillonite were affected by polarity of the solvent, resulting in the different sulfoxide to sulfone ratios as the products. Toluene was the only solvent favouring sulfone formation over sulfoxide. X-ray crystal structures of the starting compound as well as the corresponding sulfoxide (major epimer *R*s) and sulfone are also reported.

Keywords Carbohydrates · Glycosides · Oxidation · Solid support · X-Ray structure determination

Introduction

Thioglycoside derived compounds, glycosyl sulfoxides and sulfones are valuable intermediates as well as target compounds in the field of carbohydrate chemistry. The sulfoxides have previously been widely used as glycosyl donors [1, 2]. Although they are able to react under mild conditions [3–5], their frequency of usage as glycosyl donors has been decreased due to a development of the thiol activation protocol that became a more convenient glycosylation alternative [6–9]. Nevertheless, carbohydrate sulfoxides still represent an interesting subject of choice in the synthesis of new derivatives with biological effects [10]. Sulfones have been synthesized for this purpose [10, 11], which moreover may function as the intermediates, for example in C–C bond formation and stereocontrolled group transformations [12, 13].

Due to the importance of sulfoxides as well as sulfones, various methods for their synthesis have been developed and reported. Both are prepared by an oxidation of the corresponding thioglycoside. For this purpose a number of oxidation agents have been employed. Among them the most common agent is *m*CPBA [10, 14–16]. Its use, however, is restricted by a limited solubility in dichloromethane and tedious removal of the reaction byproduct (*m*-chlorobenzoic acid). Moreover, a strict temperature control (below −30 °C) is required for sulfide oxidation to sulfoxide, i.e., to prevent overoxidation to sulfone. Various sulfides have been transformed to sulfoxides by means of other oxidation agents, e.g., magnesium monoperoxyphthalate (MMPP) [17], $NaIO_4$ [17], *tert*-butyl peroxide [18], oxone [18, 19], and hydrogen peroxide and AcOH or Ac_2O either in the presence or in the absence of urea [20]. Likewise, sulfones have been produced with the aid of numerous oxidants, such as $RuCl_3/NaIO_4$ [21], dimethyldioxirane [22], monoperoxyphthalic acid [23], oxone [15], OsO_4/tertiary amine *N*-oxide [24], $KMnO_4$/$CuSO_4{\cdot}5H_2O$ [25], and $HOF{\cdot}CH_3CN$ complex [26].

The use of many oxidation agents is restricted by their solubility in polar solvent(s) only and/or poor oxidation

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Electronic supplementary material The online version of this article (doi:10.1007/s00706-013-0964-0) contains supplementary material, which is available to authorized users.

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properties when used alone. These limitations can be sometimes overcome by combining the agent with a “wet” solid support, which mediates oxidant reactivity in a relatively non-polar solvent, such as dichloromethane [27]. Matrices having high specific surface area, in particular aluminum oxide and silica, are often chosen as the oxidant supports. Besides, bentonite [28], kaolin [29], and acidic montmorillonite K-10 [29] have also been shown to enhance the oxidant chemical reactivity.

There are several applications of the use of solid supports for the oxidation of carbohydrate based sulfides. The first one comprises an adsorption of MMPP, $NaIO_4$, or oxone on dry aluminum oxide or silica, followed by its moistening with an appropriate amount of water before the addition of sulfide solution [17]. Alternatively, the solid support is fully swallowed with water followed by an addition of the sulfide in an organic solvent and oxidant (oxone or 70 % aq. *tert*-butyl peroxide) thereto [18]. In addition, silica gel may be suspended in the organic solvent intended to be used for the reaction, that is started by the oxidant dissolved in water, e.g., 30 % hydrogen peroxide [20].

Smectites, i.e., clay nanoparticles with a layer structure, including montmorillonite, have specific surface areas similar to that of silica and aluminum oxide. The smectites are, thus, an interesting alternative to the more common reagent supports, although so far there is no information about their application as the support for oxidation agents in the field of carbohydrate chemistry. In this paper we report on a new solid phase system being prepared by oxone adsorption from aqueous solution to montmorillonite. For its evaluation, the mannoside having 2-phenylethyl function as aglycone has been selected as a substrate since the glycosides with phenylalkyl aglycone in its oxidized forms are valuable compounds in a design of potential glycosidase inhibitors [10, 30].

Results and discussion

The oxidation ability of montmorillonite supported oxone (supported reagent) was evaluated in four distinct solvents at rt for 24 h under an inert atmosphere, either without or in the presence of a small amount of water to reveal an influence of the solvent on the reaction course and the product distribution. For comparison, the same conditions were applied for the mixtures containing oxone alone as an oxidant. Two types of solvents, i.e., non-polar (toluene) and polar aprotic (THF, DCM, acetone) were chosen. The 2-phenylethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (**1**) was chosen as a model compound and its oxidized products, sulfoxide **2** and sulfone **3**, having previously been prepared by another procedure [10], were used as the standards.

There was no reaction observed in the solvents lacking either the substrate or the oxidation agent. Depending on the oxidation conditions used, sulfide **1** afforded the corresponding sulfoxide **2** (as an epimeric mixture) and sulfone **3** as products, accompanied with some amount of unreacted starting material (Scheme 1). The results of the conversion of sulfide **1** in the solvents used are summarized in Table 1.

As first, the reaction was screened in non-polar solvent toluene. The absence of solid support led to a low yield of the products (Table 1, entries 1, 2). Supported reagent without water facilitated the reaction slightly better, providing **2** and **3** in a ratio of 3.8:1 in overall 24 % yield (entry 3). Interestingly, addition of water (entry 4) significantly accelerated the oxidation, but also dramatically changed its selectivity favouring formation of sulfone **3** (59 %) over sulfoxide **2** (37 %) (ratio **2**:**3** = 1:1.6). Prolongation of the reaction time (48 h) led to a further increase in sulfone yield (entry 5) giving **2** and **3** in a ratio of 1:3.6. Another examined solvent was polar aprotic dichloromethane, which has only been employed in the previous studies [14, 15]. When oxone alone was used, sulfide **1** remained almost completely intact (entry 6). Neither the presence of water (entry 7) nor supported reagent alone (entry 8) promoted oxidation. The reaction was enhanced by simultaneous addition of the supported reagent and water when sulfoxide **2** along with sulfone **3** was yielded in a ratio of 5.1:1 and 3 % of unreacted **1** was left (entry 9). In summary, the use of water immiscible solvents resulted in an efficient oxidation only in the presence of both water and the support.

The course of oxidation reaction was also monitored in other polar solvents. Water fully miscible polar solvent, aprotic acetone, yielded an excellent conversion of starting sulfide **1** to sulfoxide **2** as a predominant oxidation product. In more detail, oxidation of **1** promoted by oxone alone afforded products **2** and **3** in the ratios 5.2:1 (entry 10) and 3:1 (entry 11) depending on the presence of water, which reduced the selectivity of the reaction and favoured the sulfone formation. The use of “dry” supported reagent (entry 12) led to a ratio of 17:1, i.e., the

Scheme 1

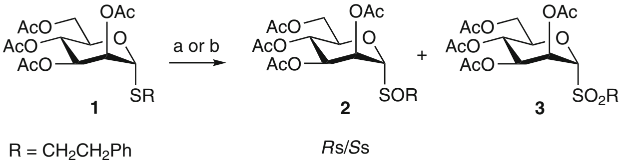

Table 1 Influence of reaction solvent, moisture, and the presence of montmorillonite as the oxone support on the reaction mixture composition

Entry	Solvent	Support	Water	Yield/%		
				Sulfoxide	Sulfone	Sulfide
1	Toluene	–	–	19		81
2		–	+	2		98
3		+	–	19	5	76
4		+	+	37	59	4
5	Toluene/48 h	+	+	21	76	3
6	Dichloromethane	–	–	3		97
7		–	+	3		97
8		+	–	4		96
9		+	+	81	16	3
10	Acetone	–	–	83	16	Trace
11		–	+	74	25	Trace
12		+	–	85	5	10
13		+	+	83	15	2
14	THF	–	–	15		85
15		–	+	74	7	19
16		+	–	13		87
17		+	+	56	5	39

The reactions were carried out in duplicate for 24 h at rt under an inert atmosphere. Values are the mean of two independent experiments

highest selectivity of sulfoxide **2** formation over sulfone **3** from all examined conditions where supported reagent was employed. In contrast, the oxidation promoted by "moist" supported reagent (entry 13) gave a comparable selectivity (ratio 5.5:1) as the reaction promoted by oxone alone. It was shown that the presence of the support helped prevent overoxidation to sulfone (10 % reduction). Besides, regarding the yield, the presence of water did not seem to be important in a water fully miscible solvent, aprotic acetone. On the other hand, another aprotic solvent, THF, which is moderately miscible with water, gave a distinct pattern. In this case, sulfoxide **2** was again a predominant oxidation product, but its formation was efficient only in the presence of added water (entries 15, 17) and not significantly affected by the support (entries 16, 17).

In summary, the use of supported reagent led in the most cases to the increased yield of the products. Although the oxidation was not selective, it might not be a limitation for the use of supported reagent, since the system is convenient to handle and the products are easily separable by column chromatography.

Under all conditions tested, sulfoxide was obtained as a mixture of *R*s and *S*s epimers, similarly as we observed previously in oxidation of the same substrate **1** with *m*CPBA [10]. The ratio of the epimers was distinguished based on integration of selected signals in ^{1}H NMR spectra [10]. In accordance with previous results [10, 31], the diasteromeric ratio *R*s/*S*s was found to be in an interval of 10:1–8.1 and not significantly affected either by solvent or by the support. Slight improvement in the selectivity was observed for supported reaction in DCM (entry 9) giving *R*s/*S*s ratio of 14:1. It was possible to obtain the major epimer by the crystallization from ethanol [10], therefore, its structure was also solved and confirmed by X-ray crystallographic analysis (Fig. 1). Besides, sulfide **1** and sulfone **3** were obtained as crystalline products [10] and their X-ray characterization was carried out as well (supplementary data, Figures S2 and S3).

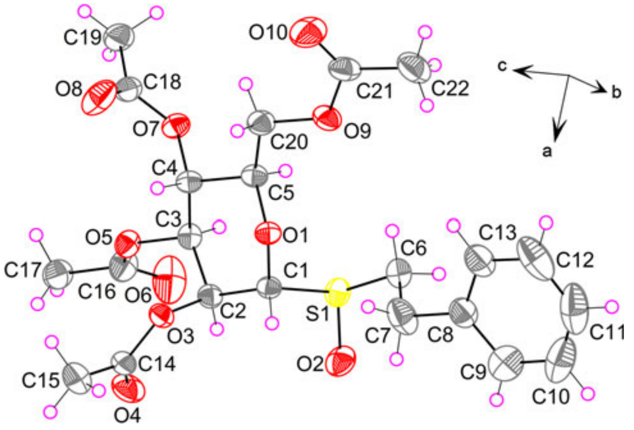

Fig. 1 X-ray of major epimer (*R*s) of **2** with crystallographic numbering. Displacement ellipsoids are shown at the 30 % probability level

Conclusion

In conclusion, this study was focused on the investigation of the capacity of montmorillonite clay as a support in oxidation of carbohydrate substrate. It was demonstrated that a new system, montmorillonite supported oxone, is compatible with the solvents of different polarity, which greatly affected substrate reactivity and oxidation reaction selectivity. Both supported reagent and moisture are required for an efficient oxidation in water-immiscible solvents, DCM and toluene. The non-polar solvent, toluene, is the only one favouring sulfone formation over sulfoxide, which was a predominant oxidation product under all other conditions used. Its most selective formation was observed in acetone in the presence of "dry" supported reagent. The choice of clays, such as montmorillonite, in combination with an oxone provides a new, cheap, and promising alternative for the combination of a solid support and the oxidation agent.

The study of montmorillonite to function as a support for other agents designed for an efficient oxidation of carbohydrate based substrates is in progress.

Experimental

^{1}H NMR spectra were recorded at 25 °C with a VNMRS 400 MHz Varian spectrometer. Chemical shifts are referenced to TMS ($\delta = 0.00$, $CDCl_3$ for ^{1}H). The TLC was performed on aluminium sheets precoated with silica gel 60 F_{254} (Merck). Anhydrous acetone, tetrahydrofuran, and toluene were purchased from Aldrich. Dichloromethane was dried (CaH_2) and distilled before use. All reactions were carried out under argon atmosphere. Powdered Kunipia clay was supplied by the Kunime, Japan. Peroxymonosulfate, which is available as a triple salt $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$ and commercially known as oxone, was obtained from Aldrich and used as an oxidant.

Fraction of the Na^+ saturated particles having diameter lower that 2 μm was separated from Kunipia bentonite (Japan). The obtained fraction identified by X-ray diffraction and FT-IR, corresponded only to a Na^+-montmorillonite. Its structural formula was $Na_{0.35}K_{0.01}Ca_{0.02}(Si_{3.89}Al_{0.11})(Al_{1.60}Mg_{0.32}Fe_{0.08})O_{10}(OH)_2{\cdot}nH_2O$.

Preparation of montmorilonite supported oxone

Montmorilonite supported oxone was prepared by a slow addition of cold (2–4 °C) 1 % oxone solution in distilled water (1 g/100 cm^3) to stirred cold (2–4 °C) 1 % dispersion of sodium exchanged Kunipia clay (1 g/100 cm^3) in distilled water (weight ratio oxone:clay = 1:1). After mixing, the viscous slurry was frozen to −20 °C and freeze-dried for 3 days. Dry powdered catalyst obtained from a single batch was used in all catalytic tests.

*Oxidation of 2-phenylethyl 2,3,4,6-tetra-O-acetyl-1-thio-α-D-mannopyranoside (**1**)*

To 5 cm^3 solvent (which in some cases contained 15 mm^3 H_2O corresponding to 20 % quantity (w/W) of montmorillonite supported oxone) 25 mg thioglycoside **1** (0.052 mmol, 1 eq) and 37.5 mg oxone (0.06 mmol, 1.15 eq) or 75 mg montmorillonite supported oxone were added. The reaction slurry was stirred at rt for 24 h under an inert atmosphere. The solid was then removed by filtration through a Celite pad and washed with 20 cm^3 EtOAc. The organic phases were pooled, washed with 10 cm^3 saturated aq. $FeSO_4$, dried (Na_2SO_4), filtered, and concentrated. The mixture was analyzed by ^{1}H NMR spectroscopy (supplementary data, Figure S1).

Acknowledgments This work was supported by the APVV-51-046505, APVV-0202/10, VEGA-2/0159/12, VEGA 1/0679/11 and VEGA-1/0962/12 grants and the Slovak State Program Project No. 2003SP200280203. Dr. Vladimír Puchart is appreciated for helpful discussion.

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