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Fast and selective oxidation of thioglycosides to glycosyl sulfoxides using KF/*m*-CPBA☆

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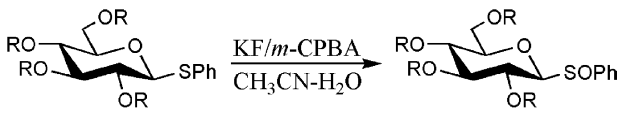
Abstract—A very fast and selective oxidation of thioglycosides to glycosyl sulfoxides has been achieved using KF/*m*-CPBA in CH_3CN–H_2O. This protocol has many advantages compared to the currently available methodologies for this transformation in terms of selectivity, yield, reaction time, control of temperature, etc. The yields obtained were excellent in all cases.

Selective and oxyfunctionalization of organic sulfides is a pivotal reaction in many organic syntheses of biologically active molecules.[1] Organic sulfoxides are an important class of synthetic intermediates used for C–C bond formation, and stereocontrolled functional group transformations.[2] In carbohydrate chemistry, the use of glycosyl sulfoxides as novel glycosyl donors in oligosaccharide syntheses was introduced by Kahne et al.[3] Currently, glycosyl sulfoxides hold a distinct position in synthetic carbohydrate chemistry in synthesizing oligosaccharides[4] and glycoconjugates[5] because of the mild reaction conditions under which they react,[6] their good to excellent anomeric stereo control[7] and their adaptabilities to both solution[8] and solid phase synthesis.[9] Moreover, the stereochemical outcome of glycosylation using glycosyl sulfoxides as glycosyl donors is independent of the configuration of sulfur atom, which eliminates the need to prepare diastereomerically pure glycosyl sulfoxide donors for their use in glycosylation reactions. Apart from being used as glycosyl donors, they have also been used to generate glycosyl carbanions for the synthesis of *C*-glycosides[10] and for the preparation of 2-hydroxy glycals.[11] In view of the importance of glycosyl sulfoxides, several oxidizing agents have been employed for the selective oxidation of thioglycosides to the corresponding glycosyl sulfoxides, which include, *m*-chloroperbenzoic acid (*m*-CPBA),[3] hydrogen peroxide–acetic anhydride–SiO_2,[12] oxone,[13] selectfluor,[14] magnesium monoperoxyphthalate (MMPP),[15] and *tert*-butyl hydroperoxide.[16] In general, the oxidation of thioglycosides to sulfoxides has been achieved most successfully using *m*-CPBA. However, this method suffers from a number of shortcomings including a requirement for strict control of temperature (below −38 °C), over-oxidation to sulfone, partial solubility of *m*-CPBA in dichloromethane and difficulty in removing the by-product (*m*-chlorobenzoic acid) from the sulfoxide. Other recently developed methods for the selective oxidation of thioglycosides to glycosyl sulfoxides also have notable drawbacks such as over-oxidation, requirement of a solid support,[12] controlling of temperature and oxidant and controlled microwave irradiation.[15] Therefore, there is still a need to develop a less stringent selective methodology for the transformation of thioglycosides to glycosyl sulfoxides. As a part of our ongoing program, we needed to prepare several glycosyl sulfoxides for their use in various glycosylation reactions towards the synthesis of oligosaccharides. In our hands, the use of *m*-CPBA and other oxidizing agents gave a mixture of glycosyl sulfoxide and sulfone in every case. We noted a few recent reports, which described an easy conversion of azides into nitro compounds using HOF·CH_3CN and the electrophilic oxygen atom of HOF·CH_3CN



Scheme 1.

Keywords: Glycosyl sulfoxide; Thioglycoside; KF; *m*-CPBA; Selective; Fast.

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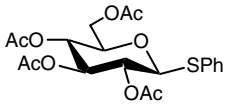
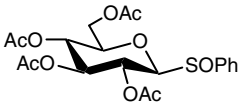
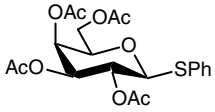
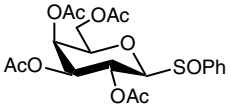
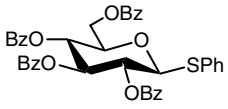
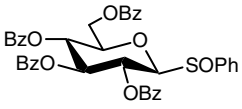
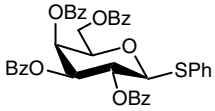
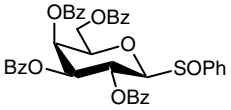
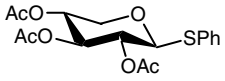
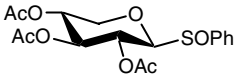
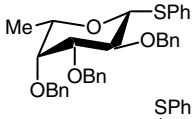
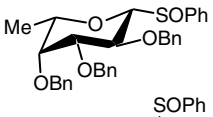
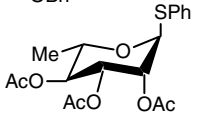
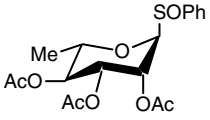
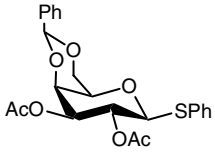
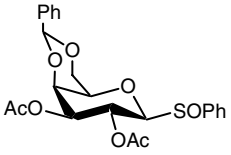
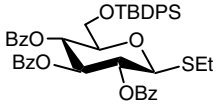
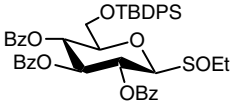
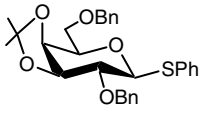
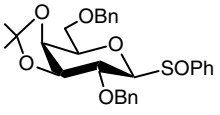
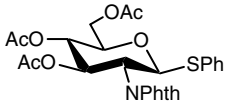
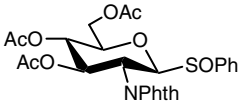
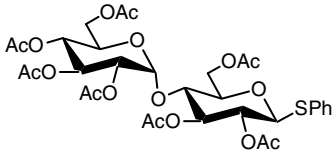
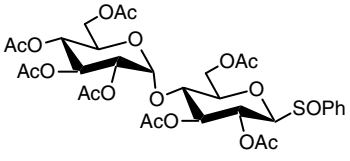
was also used for oxidation of sulfides.[17] In another report, a KF/*m*-CPBA complex was successfully employed for the selective oxidation of indolyl methyl sulfides to the corresponding sulfoxides, avoiding the formation of over-oxidized products.[18] Earlier, a KF/*m*-CPBA complex was successfully employed for the preparation of glycal epoxides.[19] We reasoned that KF/*m*-CPBA in CH_3CN–H_2O could produce KO-F·CH_3CN, which could selectively oxidize glycosyl sulfides to the corresponding sulfoxides utilizing the

Table 1. Oxidation of thioglycosides to glycosyl sulfoxides using KF/*m*-CPBA in CH_3CN–H_2O

Entry	Thioglycosides (1)	Glycosyl sulfoxides (2)	Time (min)	Yield (%)[a]	d/r[b]	Ref.
a			5	90	1:1	12
b			5	92	1:1	—
c			5	90	11:9	—
d			5	87	2.5:1	—
e			4	92	1:0	—
f			2	95	1:0	8b
g			5	85	1:0	—
h			5	88	1:1	—
i			5	85	2:1	—
j			3	95	2:1	—
k			5	90	2:1	12
l			5	88	2:1	—

[a] Isolated yield.

[b] Diastereomeric ratio based on the ration of integration values of anomeric protons in the ^1H NMR spectra.

electrophilic nature of oxygen atom of KOF·CH_3CN. In this letter, we disclose our findings on the treatment of the KF/*m*-CPBA combination with thioglycosides for a rapid generation of glycosyl sulfoxides with high selectivity and efficiency (Scheme 1).

The KF/*m*-CPBA combination has been employed to synthesize a series of glycosyl sulfoxides having a wide range of protecting groups, which are presented in Table 1. In every case, the reaction was exceptionally fast and exclusive formation of sulfoxide was observed in excellent yield without any trace of sulfone, in a few minutes. Acid-labile functional groups such as benzylidene acetal, isopropylidene, TBDPS groups remained intact under the reaction conditions. The rate of oxidation depends on the nature of the protecting group linked to C-2. 'Armed sugars' having an electron-donating group, such as a benzyl group at C-2 were oxidized at a faster rate than 'disarmed sugars' having an electron-withdrawing group, such as acetyl or benzoyl group at C-2. In most of the cases, a diastereomeric mixture of sulfoxides was formed. The diastereomeric ratio was determined from a comparison of integration value of H-1 in their ^1H NMR spectra. It is worth noting that among most frequently used solvents such as dichloromethane, dichloroethane, nitromethane, THF, CH_3CN used for this transformation, CH_3CN–H_2O was found to be the most effective in producing a high yield and a cleaner reaction. Since the reaction was carried out in CH_3CN–H_2O, there was no need to use anhydrous conditions and *m*-CPBA was completely soluble in the reaction mixture.

A typical experimental procedure is as follows: To a solution of KF (117 mg, 2.0 mmol) in CH_3CN–H_2O (4.0 ml; v/v 5:1), 70% *m*-CPBA (345 mg, 2.0 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. To the ice-cooled reaction mixture was added phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**1a**; 440 mg, 1.0 mmol) and the mixture was stirred at 0 °C for the appropriate time as specified in Table 1. After completion of the reaction, it was quenched with aq $FeSO_4$ solution and extracted with CH_2Cl_2. The organic layer was washed with aq $NaHCO_3$ and water successively, dried (Na_2SO_4) and concentrated under reduced pressure. The crude reaction mixture was purified over SiO_2 using hexane–EtOAc as eluant to furnish pure phenyl 2,3,4,6-tetra-*O*-acetyl-1-sulfinyl-β-D-glucopyranoside as a diastereomeric mixture. The ratio of isomers was determined from the integration values of anomeric protons in the ^1H NMR spectra.[20]

In conclusion, fast and exclusive generation of various glycosyl sulfoxides from the corresponding thioglycosides was achieved using KF/*m*-CPBA in CH_3CN–H_2O. The reaction is highly selective and efficient. Use of cheap, commonly available reagents, the exceptionally fast reaction rate, the absence of a need for strict control of temperature, high selectivity and no formation of over-oxidized product make this protocol an attractive alternative to the existing methodologies. The exploration of the synthetic utility of several glycosyl sulfoxides in oligosaccharide synthesis is currently in progress.

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20. Spectral data of phenyl 2,3,4,6-tetra-*O*-acetyl-1-sulfinyl-β-D-glucopyranoside **2a**: d/r 1:1; R_f 0.35 (hexane–EtOAc, 1:1); $[\alpha]_D^{25}$ −43.8 (*c* 1.6, $CHCl_3$); IR (KBr): 3021, 1754, 1371, 1218, 1044, 766, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66–7.54 (m, 5H, aromatic protons), 5.36–5.21 (m, 2H), 5.03–4.96 (m, 1H), 4.43 (d, $J = 9.1$ Hz, 0.5H), 4.29 (d, $J = 9.1$ Hz, 0.5H), 4.14–4.01 (m, 2H), 3.72–3.69 (m, 0.5H), 3.62–3.59 (m, 0.5H), 2.01, 2.00, 1.96, 1.91 (4s, 12H, $4COCH_3$); ESI-MS: 479 [M+Na]; Anal. Calcd for $C_{20}H_{24}O_{10}S$ (456): C, 52.62; 5.30. Found: C, 52.40; H, 5.50.