Carbohydrate Research 402 (2015) 200–207

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Note

Synthesis of mixed glycosyl disulfides/selenenylsulfides using benzyltriethylammonium tetrathiomolybdate as a sulfur transfer reagent

Cheerladinne Venkateswarlu, Vibha Gautam, Srinivasan Chandrasekaran *

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

ARTICLE INFO

Article history:
Received 20 July 2014
Received in revised form 7 September 2014
Accepted 17 September 2014
Available online 28 September 2014

Keywords:
Tetrathiomolybdate
Sulfur transfer
Disulfide exchange
Glycosyl halide
Mixed glycosyl disulfide
Selenenylsulfide

ABSTRACT

An easy and mild method has been developed for the synthesis of mixed glycosyl disulfides/selenenylsulfides from glycosyl halides and diaryl/dialkyl dichalcogenides in the presence of benzyltriethylammonium tetrathiomolybdate [$(BnEt_3N)_2MoS_4$]. The salient feature of this method is the sulfur transfer from $[BnEt_3N]_2MoS_4$ to form glycosyl disulfides which with excess tetrathiomolybdate further undergo exchange reaction with other dichalcogenides in a one-pot operation.

The disulfide linkage plays an important role in carbohydrate chemistry for the study glycopeptides,[1] lectin binding,[2,3] and carbohydrate structure.[4,5] Moreover, in metabolic and other enzymatic studies, sugar disulfides are significantly important entities.[6,7] Many natural products and biologically active compounds have disulfide linkage as a vital functional motif.[8–10] Mixed glycosyl disulfides have received attention as a new class of glycosyl donors in solution and in solid phase synthesis.[11] Davis et al. reported the advantages of mixed disulfides over thioglycosides.[11] Due to the flexible nature of mixed disulfide linkage, the cleavage of disulfide bond could be adjusted according to the reacting partner.[12] When the mixed disulfide is used as a linker in solid-supported glycosylation, the anomeric mixed disulfide linkage would allow bidirectional (reductive or hydrolytic) cleavage, that would be of great advantage in both the analysis and use of solid supported glycosylation systems. Due to the presence of two sulfur atoms in mixed disulfides, the coordination potential of thiophile may offer enhanced reactivity over single sulfur thioglycoside systems. On the other hand, glycosyl selenenylsulfides have been used in protein glycoconjugation, which allows glycoconjugation with mono- and oligosaccharides of up to seven saccharide units in size at single and multiple sites in a variety of proteins.[13]

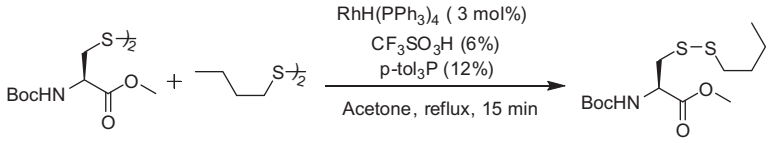
Usually, the synthesis of mixed disulfides involves the nucleophilic substitution of thiol onto sulfenyl derivatives. Sulfenyl derivatives such as sulfenyl halides,[14–18] sulfenic acids,[19] *S*-alkyl thiosulfates and *S*-aryl thiosulfates (Bunte salts),[20] *S*-(alkylsulfanyl)isothioureas,[21,22] benzothiazol-2-yl disulfides,[23] benzotriazolyl sulfides,[24] dithioperoxyesters,[25] (alkylsulfanyl)dialkylsulfonium salts,[26] alkyl aryldithiopyridine *N*-oxides,[27] *N*-alkyltetrazolyl disulfides, sulfenamides,[28] sulfenyl thiocyanates,[29] 4-nitroarenesulfenanilides,[30] thiolsulfinates and thiolsulfonates,[31,32] sulfanylsulfinamidines,[33] thionitrites,[34] sulfenyl thiocarbonates,[35] thioimides, thiophosphonium salts,[36,37] and thio-phthalimides[38] are used for this purpose.[39–45] Although sulfenyl derivatives are widely used, they have problems such as stability, multistep synthesis, and use of expensive reagents which limits the use of these reagents.

Disulfide exchange reaction is one of the useful methods for the synthesis of unsymmetrical disulfides which circumvents the use of malodorous thiols. Yamaguchi and Arisawa reported $RhH(PPh_3)_4$ catalyzed disulfide exchange reaction between two structurally different disulfides to give unsymmetrical disulfides (Scheme 1).[46] However, the limitation of this method is the use of expensive phosphine rhodium complex and it is applicability to only a few substrates. Hence, the search for alternative methods which are more convenient is clearly warranted.

Our continuing efforts to explore the utility of benzyltriethylammonium tetrathiomolybdate, $(BnNEt_3)_2MoS_4$ **1** as a reagent in

* Corresponding author. Tel.: +91 80 22932404; fax: +91 80 23600529.
E-mail address: scn@orgchem.iisc.ernet.in (S. Chandrasekaran).

http://dx.doi.org/10.1016/j.carres.2014.09.005
0008-6215/



Scheme 1. Functionalization of cysteine via unsymmetrical disulfide exchange reaction.

organic synthesis led to the discovery of a number of useful methodologies.[47–58] Earlier, we have demonstrated the synthesis of sugar disulfides using **1** as a sulfur transfer reagent.[48] Also, we have shown the application of **1** in tandem sulfur transfer reaction followed by Michael addition in a one-pot fashion.[49] Later the utility of **1** has been demonstrated in the synthesis of unsymmetrical β-sulfonamido disulfides from aziridines and disulfides.[47] To further explore the usefulness of the reagent **1**, we planned the synthesis of mixed glycosyl disulfides/selenenylsulfides via sulfur transfer-dichalcogenide exchange reaction in one-pot (Scheme 2).

Reaction of glucosyl bromide **2a** with disulfides **3** in the presence of **1**: We commenced our study by reacting glucose derived anomeric bromide **2a** (1 equiv) with tetrathiomolybdate **1** (2.2 equiv, CH_3CN, 25 °C, 2 h) followed by the addition of diphenyl disulfide **3a** (2 equiv),[59] and it gave the desired mixed disulfide **4aa** (3 h) in 70% yield (Scheme 3).

The mechanism of the reaction is similar to the one proposed in our earlier work on the synthesis of functionalized unsymmetrical β-sulfonamido disulfides from aziridines and disulfides in the presence of tetrathiomolybdate.[47] In light of this, it is visualized that the intermediate **A** formed during the reaction of **2a** with tetrathiomolybdate **1** undergoes an exchange reaction with disulfide **3a** (via intermediates **B** and **C**) to furnish the corresponding mixed disulfide **4aa** (Scheme 4).

Encouraged by this result, we further studied the scope of this reaction with other disulfides (**3b**–**3h**). The outcome of this detailed study is summarized in Table 1. It was observed that disulfides **3d**, **3e** bearing electron withdrawing groups (–Cl, $-NO_2$) gave the corresponding mixed disulfides **4ad** and **4ae** in lower yields (Table 1, entries 3 and 4)[60,61] compared to disulfides **3b**, **3c** containing electron donating groups (–Me, –OMe) (Table 1, entries 1 and 2). Heteroaromatic disulfide such as dipyridyl disulfide **3f** gave only 35% of the desired mixed disulfide **4af** (Table 1, entry 5). Aliphatic disulfides, dibenzyl disulfide **3g**, and dimethyl disulfide **3h** reacted smoothly with **2a** in the presence of **1** to give the corresponding mixed disulfides **4ag** and **4ah** respectively (Table 1, entries 6 and 7).

In general, most of the methods reported on the synthesis of mixed glycosyl dichalcogenides provide only moderate yields.[11,18,22,62] However, the methodologies that give very good yield of mixed dichalcogenides[19,24,38,63,64] use free chalcogenols as the reaction partner. Hence, the present protocol that avoids the use of free chalcogenols compares favorably with the existing methods.

Reaction of various glycosyl halides **2** and diphenyl dichalcogenides (**3a**, **3i**) in the presence of **1**: This methodology was further extended to various glycosyl halides (Scheme 5). The glycosyl halides **2b**–**2f** were studied for the disulfide exchange reaction with diphenyl disulfide **3a** in the presence of **1**.

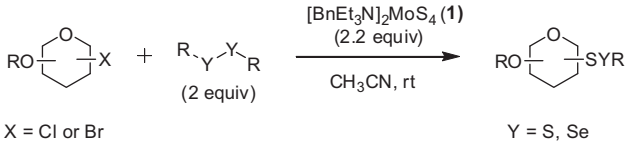
It was observed that the glycosyl halides **2b**, **2c**, **2e**, and **2f** in the presence of diphenyl disulfide **3a** and tetrathiomolybdate **1** underwent disulfide exchange reaction in 3 h to form the corresponding unsymmetrical mixed disulfides **4ba**, **4ca**, **4ea**, and **4fa**, respectively, in moderate to good yields (Table 2, entries 2, 3, 5, and 6) whereas glycosyl bromide **2d** having bromine atom at C-6 position took 8 h to furnish the mixed disulfide **4da** in 51% yield (Table 2, entry 4).

Further, we decided to extend this methodology to the synthesis of glycosyl (phenylselenenyl)sulfides. Accordingly, glycosyl halides **2a**–**2f** were treated with tetrathiomolybdate **1** (2.2 equiv) and diphenyl diselenide **3i** (2.0 equiv) in CH_3CN to give the corresponding selenenylsulfides **4ai**–**4fi** in moderate yields (Table 2). The mechanism of the reaction is similar to that of the disulfide exchange process. As in the synthesis of mixed disulfides, glycosyl bromide **2d** having bromine at C-6 position took a longer time (10 h) for sulfur-selenium exchange process and resulted in the corresponding selenenylsulfide **4di** in only 38% yield (Table 2, entry 4) compared to other glycosyl anomeric halides in which the reactions were completed in 4 h with moderate to good yields (Table 2, entries 1–3, 5, and 6).

The scope of the method was further extended to the synthesis of trisaccharide **4fj** and glycosyl amino acid **4ak** having mixed disulfide linkage. Initially lactose derived anomeric bromide **2f** was treated with **1** (2.2 equiv, CH_3CN, 25 °C, 2 h) followed by the addition of symmetrical glycosyl disulfide **3j** (2 equiv) to furnish the trisaccharide **4fj** in 51% yield (Scheme 6).

For the synthesis glycosyl amino acid mixed disulfide **4ak**, similar synthetic sequence was followed except that the starting materials were glucose derived anomeric bromide **2a** and cysteine derived Boc-Cys-OMe **3k** (Scheme 7).

In summary, we have presented a one-pot method for the synthesis of mixed glycosyl chalcogenides with sulfur transfer-dichalcogenide exchange reaction using tetrathiomolybdate **1**. The significance of this method is mild reaction conditions and avoiding the use of free chalcogenols. The application of the method has been demonstrated in the synthesis of a trisaccharide and glycosyl amino acid containing mixed disulfide linkage. Studies aimed at exploring the utility of these compounds are under progress in our laboratory.



Scheme 2. General scheme for the synthesis of mixed glycosyl disulfides and selenenylsulfides.

1. Experimental section

1.1. General methods

All the reactions were performed in oven dried apparatus and were stirred magnetically. Melting point values reported are uncorrected. Infrared spectra were recorded using an FTIR instrument and the frequencies are reported in wave number (cm^{-1}) and intensities of the peak are denoted as s (strong), m (medium), w (weak), and broad (br). ^1H and ^{13}C NMR spectra were recorded on a Jeol 400 MHz (100 MHz, ^{13}C) NMR spectrometer and calibrated using tetramethylsilane (TMS) for (^1H) or residual undeuterated solvent ($CDCl_3$) as an internal reference. Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet),