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Tetrahedron Letters 45 (2004) 4615–4618
Tetrahedron Letters

Fluorous thiols in oligosaccharide synthesis

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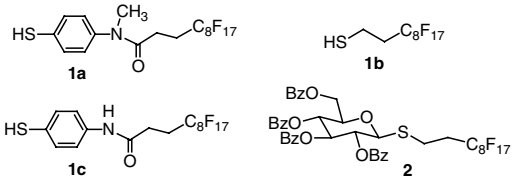
Received 30 March 2004; revised 21 April 2004; accepted 21 April 2004

Abstract—A new, almost odorless fluorous thiol is synthesized, which is utilized to prepare highly fluorinated thioglycosyl donors. These thioglycosides showed excellent reactivities in glycosylation reactions. The fluorous chain, stable under esterification, etherification, deacetylation, and glycosylation conditions, allowed facile purification of the thioglycosides by solid-phase extraction through fluorous silica gel. The fluorous thiol was readily recycled.

Traditional oligosaccharide synthesis is a time-consuming process mainly due to tedious chromatographic purification of multiple synthetic intermediates.[1] Resin based solid-phase carbohydrate syntheses[2] can help alleviate this problem but it suffers several disadvantages such as reduced reactivity, lack of a general method for real time monitoring of the reaction[3] and difficulty in purification of attached intermediates. Recently, fluorous chemistry has become an attractive alternative to solid-phase synthesis.[4] A highly fluorinated compound is readily separated from nonfluorinated substances by either binary fluorous/organic phase extraction or solid-phase extraction (SPE) through fluorous silica gel.[5] Fluorous technologies have been applied to carbohydrate synthesis,[6] primarily in development of highly fluorinated protective groups such as ester, acetal, silyl, and benzyl, where purification of desired products are greatly facilitated by fluorous moieties in the molecule.

Thioglycosides are one of the most popular glycosyl donors due to its high stability and high reactivities toward thiophilic promoters, which have been extensively utilized in stepwise and one-pot syntheses of complex oligosaccharides.[7] However, one drawback is the extremely unpleasant odor of thiols employed for thioglycoside formation, especially with the increasing environmental consciousness. We report here the development of a new fluorous thiol **1a**, which is almost odorless. Moreover, the fluorous moiety significantly aids the purification of corresponding thioglycosides and the fluorous thiol **1a** can be readily regenerated for further uses.



In designing the fluorous thiol, a suitable linker should be installed between the highly electron withdrawing fluorous chain and the nucleophilic sulfur atom. Crich and co-workers have demonstrated that a two methylene group spacer was enough to insulate the electron withdrawing power of the fluorous chain from the sulfoxide sulfur in the fluorous dimethylsulfide reagent for fluorous Swern oxidation reactions.[8] Our initial studies were carried out using the commercially available 1*H*,1*H*,2*H*,2*H*-perfluorodecane thiol **1b** with a two methylene linker.[8,9] The two methylene spacer in **1b** was found not sufficiently insulating as we failed to activate the disarmed thioglycoside **2** even with one of the most powerful promoters, *p*-toluenesulfenyl triflate (*p*-TolSOTf)[10] formed in situ by *p*-toluenesulfenyl chloride (*p*-TolSCl) and AgOTf. In order to increase the length of the linker, a fluorous *p*-amido thiophenol **1c** was prepared. However, the secondary amide moiety underwent undesirable benzoylation or benzylation under standard protective group manipulation conditions carried out on

Keywords: Fluorous thiol; Odorless; Glycosylation; Thioglycosides; Solid-phase extraction.
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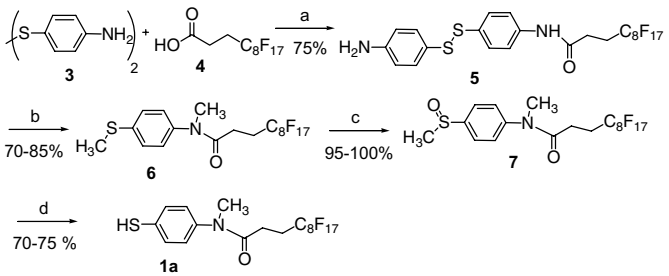
doi:10.1016/j.tetlet.2004.04.116

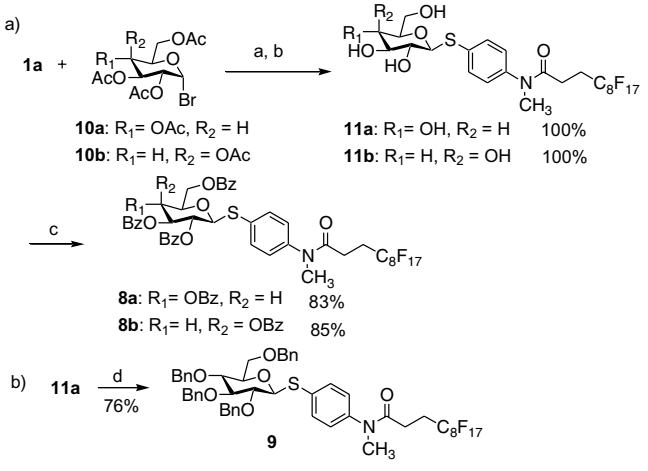


Scheme 1. Synthesis of fluorous thiol **1a**. Reagents and conditions: (a) BOP (1 equiv), TEA, DMF, 80 °C, 10 h; (b) CH_3I (20 equiv), KOH (20 equiv), tetrabutylammonium bromide (1 equiv), 1:1 THF–H_2O, rt, 15 h; (c) Selectfluor (1 equiv), 20:1 CH_3CN–H_2O, rt, 20 min; (d) TFAA, 40 °C, 50 min; 2 N NaOH, 0 °C, 2 h; 6 N HCl.

the corresponding thioglycosides. This led to the synthesis of the fluorous *p*-methylamido thiophenol **1a** (Scheme 1).

Mono-amidation of *p*-aminophenyl disulfide **3** with a fluorous carboxylic acid **4** in the presence of benzotriazol-1-yloxy tris(dimethylamino-phosphonium hexafluorophosphate) (BOP) and triethylamine (TEA) in *N*,*N*-dimethylformamide (DMF) gave disulfide **5** (75%), which was subsequently methylated with methyl iodide and potassium hydroxide under phase transfer conditions (PTC) to produce thioether **6** in 70–85% yield. In order to cleave the thiomethyl group, a two-step procedure was adopted. Oxidation by Selectfluor led to quantitative formation of sulfoxide **7**.[11] The usage of the popular oxidant *m*-chloroperoxybenzoic acid (*m*CPBA) formed substantial amount of undesired sulfone even with carefully controlled amount of oxidant at low temperature. Refluxing sulfoxide **7** in trifluoroacetic anhydride (TFAA),[12] followed by base and acid treatments yielded the desired fluorous thiol **1a** (70–75%),[13] which is almost odorless.

With the fluorous thiol **1a** in hand, disarmed (i.e., **8a**,**b**) and armed thioglycoside donors[14] (i.e., **9**) were prepared (Scheme 2). Displacement of bromide from



Scheme 2. Syntheses of fluorinated thioglycosyl donors. Reagents and conditions: (a) 1 M aq Na_2CO_3, EtOAc, rt, 2 h; (b) CH_3ONa, CH_3OH, rt, 5 h; (c) BzCl (20 equiv), DMAP (1 equiv), pyridine, rt, 15 h; (d) benzyl bromide, aq 50% NaOH, tetrabutylammonium bromide (1 equiv), CH_2Cl_2, rt, 20 h.

tetraacetyl-α-D-glucosyl bromide **10a** by thiol **1a** under PTC followed by removal of acetate produced the thioglucoside **11a** in quantitative yield (Scheme 2a). Benzoylation of **11a** with benzoyl chloride gave the disarmed thioglucoside **8a** (83%). Excess of benzoyl chloride (20 equiv) was necessary to drive the reaction to completion. Compound **11a** was successfully benzylated under PTC[15] to form armed donor **9** (76%) (Scheme 2b). Benzylation with sodium hydride and benzyl bromide in DMF gave low yield of the desired product presumably due to the amphiphilic nature of **11a**. Disarmed thiogalactoside **8b** was obtained in a similar fashion as the corresponding thioglucoside **8a** in 85% yield. All fluorinated compounds synthesized maintain normal chromatographic behavior on standard silica gel, allowing easy monitoring of the course of reactions by TLC. Purification of the desired glycosyl donor obtained from the multiple step syntheses was significantly aided by the fluorous moiety. The reaction mixture was subjected to solid-phase extraction (SPE) on fluorous silica gel. Excess reagents and side products were readily removed by washing with 80% methanol and water mixture, followed by elution of the fluorous compounds with pure acetone. The fluorous compounds can also be purified by normal silica gel chromatography if necessary, which is advantageous compared to solid-phase synthesis. The NMR signals originating from the fluorous chain do not interfere with the carbohydrate region, thus allowing facile characterization of the desired product.

The reactivities of these new highly fluorinated thioglycoside donors were examined next using acceptors **12** and **13** as examples of primary and secondary hydroxyl groups. Both disarmed donors **8a**,**b** and armed donor **9** underwent smooth glycosylation with **12** and **13** to form disaccharides **15** to **20** in excellent yields (Table 1). Promoter systems such as *N*-iodosuccinimide (NIS)/AgOTf, NIS/TfOH, and *p*-TolSCl/AgOTf[10] gave similar results indicating these highly fluorinated donors are compatible with multiple common glycosylation conditions.

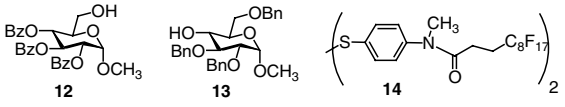
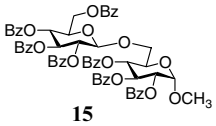
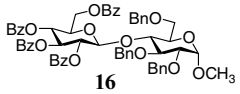
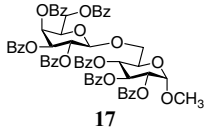
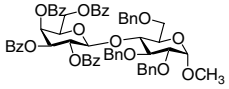
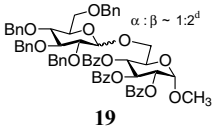
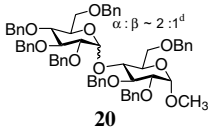


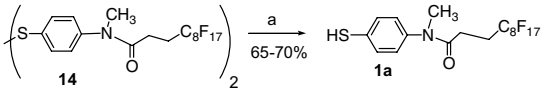
Table 1. Results of glycosylation using highly fluorinated donors

Entry	Donor+acceptor	Product	Yield (%)	Disulfide **14** recovered (%)
1	**8a+12**	 **15**	93[a]	75
2	**8a+13**	 **16**	87[b]	
3	**8b+12**	 **17**	91[a] 95[b]	86
4	**8b+13**	 **18**	88[a]	60
5	**9+12**	 **19**	92[c]	80
6	**9+13**	 **20**	85[a]	75

[a] Reagents and condition: NIS (2 equiv), AgOTf (0.2 equiv), CH_2Cl_2, MS-AW300, −78 °C.
[b] Reagents and condition: *p*-TolSCl (1 equiv), AgOTf (1 equiv), CH_2Cl_2, MS-AW300, −78 °C.
[c] Reagents and condition: NIS (2 equiv), TfOH (0.03 equiv), CH_2Cl_2, MS-AW300, −78 °C.
[d] Anomeric ratios were determined after comparison with literature data.[16]

The side product fluorous disulfide **14** from glycosylation reactions was facilely recovered by SPE with fluorous silica gel in 60–86% yields. Thiol **1a** can be regenerated (65–70%) through reduction of disulfide **14** with zinc dust (Scheme 3), which can be utilized further to form thioglycosyl donors.

In conclusion, we have prepared a new, almost odorless fluorous thiol **1a**, from which thioglycosyl donors were synthesized in good yields. Purification of glycosyl donors were greatly facilitated by fluorous moieties through SPE. Both armed and disarmed fluorinated thioglycoside donors showed excellent reactivities in glycosylation with primary and secondary acceptors. Fluorous group utilized was found compatible with etherification, esterification, deacetylation, and glycosylation conditions. The fluorous disulfide formed in glycosylation reactions was easily recycled to regenerate the fluorous thiol **1a**. Besides formation of thioglycosides, fluorous thiols can be potentially utilized in preparation of fluorinated glycosyl sulfoxide donors and as a ligand for metal catalysts. Further work is in progress to extend the application of fluorous thiols.



Scheme 3. Reagents and conditions: (a) Zn (10 equiv), AcOH, 60–70 °C, 15 h.

Acknowledgements

We thank The University of Toledo for supporting this research.

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13. Spectroscopic data for compound **1a**: ^{1}H NMR (399.95 MHz, $CDCl_3$) δ 2.30–2.47 (m, 4H, CH_2CH_2), 3.25 (s, 3H, NCH_3), 3.56 (s, 1H, SH), 7.04–7.34 (m, 4H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 25.49, 27.09 (t), 37.75 (NCH_3), 128.18, 130.97, 131.97, 141.21, 170.11. HRMS for $C_{18}H_{12}F_{17}NOS$ $[M+Na]^+$ calcd: 636.0266; found: 636.0262.
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