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Carbohydrate Research 343 (2008) 1858–1862
Carbohydrate RESEARCH

Note

A stable, commercially available sulfenyl chloride for the activation of thioglycosides in conjunction with silver trifluoromethanesulfonate

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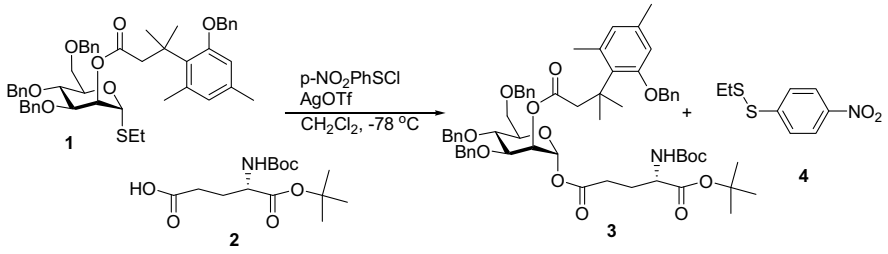
Received 8 February 2008; received in revised form 1 March 2008; accepted 4 March 2008
Available online 10 March 2008

Abstract—*p*-Nitrobenzenesulfenyl chloride is a stable commercially available sulfenyl chloride that, in conjunction with silver triflate, cleanly activates a wide range of thioglycosides for glycosylation at −78 °C in CH_2Cl_2.

Keywords: Glycosylation; Thioglycoside; Sulfenyl halide; Sulfenyl triflate

Thioglycosides[1] are some of the most popular glycosyl donors because they are easily prepared and are stable to most functional group modifications. Although many other thiophilic reagents, including NIS–TfOH,[2] iodonium dicollidine perchlorate (IDCP),[3] and methyl trifluoromethanesulfonate (MeOTf)[4] are known for the activation of thioglycosides, the sulfenyl/sulfonium class of thiophiles have gained considerable popularity since the discovery of dimethyl(methylthio)sulfonium triflate[5] (DMTST) as a promoter. Methanesulfenyl triflate (MeSOTf, MeSBr–AgOTf),[6] benzenesulfenyl triflate (PhSOTf, PhSCl–AgOTf),[7,8] and *p*-toluenesulfenyl triflate (*p*-TolSOTf, *p*-TolSCl–AgOTf)[9] have been investigated as powerful promoters capable of activating thioglycosides rapidly and cleanly at −78 °C with the formation of glycosyl triflates[8] as intermediates and stable disulfide byproducts. However, methanesulfenyl bromide (MeSBr), benzenesulfenyl chloride (PhSCl), and *p*-toluenesulfenyl chloride (*p*-TolSCl) are not commercially available owing to their limited shelf-life, and must be prepared and distilled prior to use. The 1-benzenesulfinyl piperidine (BSP)/trifluoromethanesulfonic anhydride (Tf_2O),[10] diphenyl sulfoxide (DPSO)–Tf_2O,[11,12] benzenesulfinyl morpholine–Tf_2O,[13] and dimethyl disulfide–Tf_2O[14] protocols have been developed as shelf-stable substitutes for this sulfenyl halide-based chemistry and have been employed widely in oligosaccharide synthesis. Herein, we report on the use of a stable, commercially available *p*-nitrobenzenesulfenyl chloride (*p*-NO_2PhSCl) as an activator for glycosylation



Scheme 1.

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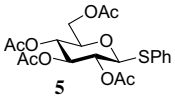
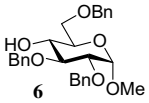
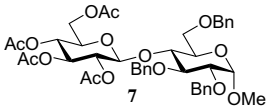
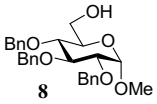
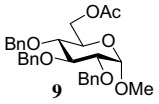
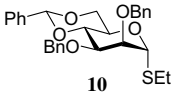
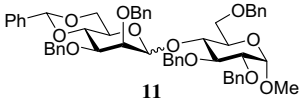
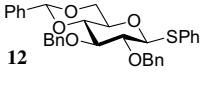
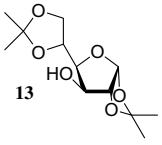
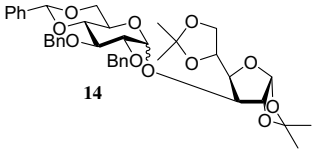
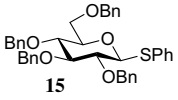
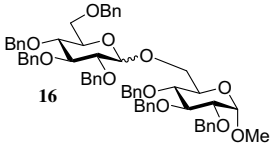
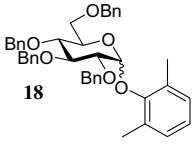
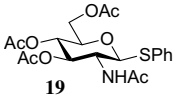
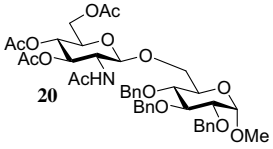
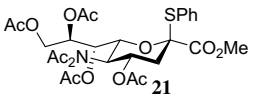
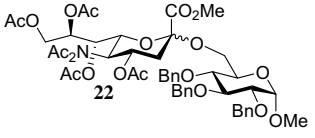
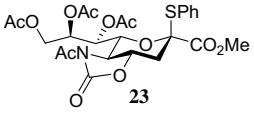
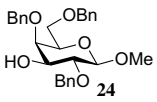
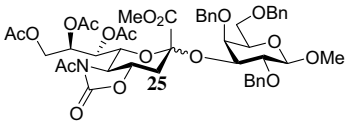
doi:10.1016/j.carres.2008.03.002

Table 1.

Entry	Donor	Acceptor	Coupling product	Yield[e] (%) (α:β)
1	 **5**	 **6**	 **7**	95[b,d] (β only)
2	**5**	 **8**	 **9**	75[b]
3 4	 **10**	**6**	 **11**	72[a,c] (1:13) 80[b,c,d] (1:5)
5	 **12**	 **13**	 **14**	88[a,c] (3:1)
6	 **15**	**8**	 **16**	85[a,c] (1:3)
7	**15**	 **17**	 **18**	82[a,c] (7:3)
8	 **19**	**8**	 **20**	20[b,d] (β only)
9	 **21**	**8**	 **22**	60[b,c,d] (1.5:1)
10	 **23**	 **24**	 **25**	77[a,d] (3:1)

[a] Preactivation.
[b] Pre-mixed.
[c] 1.2 equiv TTBP.
[d] 20% (v/v) acetonitrile.
[e] Determined by ^{1}H NMR analysis on the crude reaction mixture.

in conjunction with silver trifluoromethanesulfonate (AgOTf). *p*-Nitrobenzenesulfenyl chloride is an orange solid that has been previously employed as the precursor to photolabile sulfenate esters and, thus, as a source of alkoxy radicals.[15,16]

As a first demonstration of the method, the coupling of mannopyranoside donor **1** and an amino acid **2** was conducted using 1 equiv *p*-NO_2PhSCl–2.5 equiv AgOTf as a promoter in CH_2Cl_2. This reaction was complete in 30 min at −78 °C and gave the α-anomeric product in 80% yield. As expected, the disulfide **4** was also obtained in 83% yield (Scheme 1).

A number of other examples were then conducted employing 1.2 equiv *p*-NO_2PhSCl, 2.5 equiv AgOTf and 1.5 equiv acceptor in CH_2Cl_2, occasionally in admixture with acetonitrile[17,18] or 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[19] as additive. The acetate glucose donor **5** and acceptor **6** were pre-mixed and then activated to give disaccharide **7** in 95% yield (Table 1, entry 1). The formation of the β-isomer in this example relies on the neighboring group participation effect. The coupling of **5** with a primary alcohol **8**, the acetyl-transfer product **9** predominated (Table 1, entry 2). Preactivation of the 4,6-*O*-benzylidene mannopyranoside **10** followed by the addition of acceptor **6** gave a 13:1 (β:α) anomeric mixture of disaccharides in 72% yield; When **6** and **10** were pre-mixed before activation in the presence of 20% acetonitrile, only a 5:1 (β:α) selectivity was obtained (Table 1, entries 3 and 4). The preactivated 4,6-*O*-benzylidene glucopyranosyl donor **12** gave a 3:1 (α:β) anomeric mixture of disaccharides after preactivation and then the addition of acceptor **13** as expected on the basis of earlier work (Table 1, entry 5).[6,20] The tetra-*O*-benzyl glucosyl donor**15** exhibited a β-selective coupling with a primary alcohol (Table 1, entry 6) in keeping with the observation of Hashimoto[21] for a related coupling. However, with a less reactive partner **17** the more typical α-selectivity reasserted itself (Table 1, entry 7).

With the *N*-acetylglucosamine based thioglycoside **19** (Table 1, entry 8), oxazoline ring formation could not be suppressed; nevertheless, the glycosylation product **20** was formed in 20% yield. In the coupling of phenyl thiosialoside donor **21** and acceptor **8**, the anomeric ratio of the products was formed to be 1.5:1 (α:β) for a coupling conducted in the presence of acetonitrile, comparable to the result achieved with the DPSO/Tf_2O[22] promotion system. Encouragingly, the *p*-NO_2PhSOTf promoter could activate even the relatively inert phenyl thiosialoside donor **23** at −78 °C. Thus, premixing of donor **23** and acceptor **24** at −78 °C with acetonitrile as additive before activation afforded the α-sialoside (3:1) in good yield (Table 1, entry 10). This result is comparable to the NIS–TfOH[23] activated reaction using the more reactive 1-adamantanyl thiosialoside donor and the same acceptor.

In summary, the shelf-stable, commercially available *p*-NO_2PhSCl–AgOTf promoter works well with different kinds of donors. Both 1,2-*trans* and 1,2-*cis* products are formed as major products according to the choice of protecting group.

1. Experimental

1.1. General methods

Optical rotations were determined with an Autopol III polarimeter.^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, with chemical shifts reported downfield from tetramethylsilane. All solvents were dried by standard procedures. Commercial reagents were used without purification. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon or nitrogen using oven-dried glassware.

1.2. Typical procedure for coupling of pre-mixed donors and acceptors

1.2.1. α-*tert*-Butyl γ-{3,4,6-tri-*O*-benzyl-2-*O*-[3′-(2″-benzyloxy-4″,6″-dimethylphenyl)-3′,3′-dimethylpropanoyl]-α-D-mannopyranosyl}-*N*-*tert*-butyloxycarbonyl-L-glutamate (3) and 1-ethyl-2-(*p*-nitrophenyl)disulfane (4). A suspension of **1** (88 mg, 0.11 mmol), **2** (51 mg, 0.17 mmol), silver triflate (72 mg, 0.28 mmol) and 5 Å molecular sieves in anhydrous CH_2Cl_2 (1 mL) was stirred, with the exclusion of light, for 10 min at room temperature under N_2 before it was cooled to −78 °C. A solution of *p*-nitrobenzenesulfenyl chloride (22.3 mg, 0.11 mmol, 95% purity) in anhydrous CH_2Cl_2 (0.5 mL) was dropped into the above suspension at −78 °C. TLC analysis showed the reaction to be finished after stirring for 30 min at −78 °C after which a satd aq $NaHCO_3$ solution (0.2 mL) was added. The reaction mixture was diluted with CH_2Cl_2 (5 mL) to give a suspension, which was filtered through Celite and the Celite pad was washed with CH_2Cl_2 (10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (10:1→3:1, hexane–EtOAc) to first give **4** (20 mg, 0.09 mmol, 83%) as a light yellow color oil, and then **3** (92 mg, 0.09 mmol, 80%) in the form of a viscous oil. Compound **3**: $[\alpha]_D^{18}$ +22.5 (*c* 1.0, $CHCl_3$); lit.[24] $[\alpha]_D^{16}$ +22.2 (*c* 1.0, $CHCl_3$); ^{1}H and ^{13}C NMR spectral data matched that reported.[24] Compound **4**: ^{1}H NMR (500 MHz, $CDCl_3$): δ: 1.33 (t, $J = 7.5$ Hz, 3H), 2.80 (q, $J = 7.5$ Hz, 2H), 7.60 (m, 2H), 8.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 33.1, 124.2, 126.0, 146.4, 147.5; HRMS(EI): calcd for $C_8H_9NO_2S_2[M^+]$: 215.0075. Found: 215.0079.

1.3. Typical procedure for glycosylation with preactivation of the donor

1.3.1. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-α-D-glucopyranoside (11). A suspension of **10** (73 mg, 0.15 mmol), TTBP (44.0 mg, 0.18 mmol, 1.2 equiv), silver triflate (95 mg, 0.37 mmol, 2.5 equiv) and 5 Å molecular sieves in anhydrous CH_2Cl_2 (1 mL) was stirred, with the exclusion of light, for 10 min at room temperature under N_2 before it was cooled to −78 °C. A solution of *p*-nitrobenzenesulfenyl chloride (35.5 mg, 0.18 mmol, 1.2 equiv, 95% purity) in anhydrous CH_2Cl_2 (0.5 mL) was dropped into the above suspension at −78 °C. After 5 min, a solution of **6** (103 mg, 0.22 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (1 mL) was dropped into this suspension. TLC analysis showed the reaction to be finished after stirring for 1 h at −78 °C after which a satd aq $NaHCO_3$ solution (0.2 mL) was added. The reaction mixture was diluted with CH_2Cl_2 (5 mL) to give a suspension, which was filtered through Celite and the Celite pad was washed with CH_2Cl_2 (10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (9:1, toluene–EtOAc) to give **11** (95 mg, 0.11 mmol, 72%) in the form of a viscous oil. Compound **11**: $[\alpha]_D^{20}$ −26.3 (*c* 1.0, $CHCl_3$); lit.[25] $[\alpha]_D^{28}$ −26.4 (*c* 1.5, $CHCl_3$); ^1H and ^{13}C NMR spectral data matched that reported.[25]

1.4. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (7)

Colorless syrup; $[\alpha]_D^{20}$ −5.1 (*c* 1.1, $CHCl_3$); lit.[26] $[\alpha]_D^{20}$ −5.0 (*c* 1.0, $CHCl_3$); ^{13}C NMR spectral data matched that reported.[27]

1.5. 3-*O*-(2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (14α)

$[\alpha]_D^{18}$ +5.9 (*c* 1.0, $CHCl_3$); lit.[20] $[\alpha]_D$ +5.8 (*c* 0.8, $CHCl_3$); ^1H and ^{13}C NMR spectral data matched that reported.[20]

1.6. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (16β)

Colorless syrup; $[\alpha]_D^{20}$ +19.8 (*c* 1.0, $CHCl_3$); lit.[28] $[\alpha]_D^{24}$ +19.3 (*c* 0.2, $CHCl_3$); ^1H and ^{13}C NMR spectral data matched that reported.[28]

1.7. 2,6-Dimethylphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (18α)

Colorless syrup; $[\alpha]_D^{18}$ +36.5 (*c* 1.0, $CHCl_3$); lit.[8] $[\alpha]_D^{20}$ +36.7 (*c* 4.2, $CHCl_3$); ^1H and ^{13}C NMR spectral data matched that reported.[8] **18β** was isolated as a mixture together with **18α**, the ^1H and ^{13}C NMR spectral data matched that reported.[8]

1.8. Methyl 6-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (20)

Colorless syrup; $[\alpha]_D^{20}$ −19.9 (*c* 1.0, $CHCl_3$); lit.[29] $[\alpha]_D^{25}$ −20.1 (*c* 1.0, $CHCl_3$); ^1H and ^{13}C NMR spectral data matched that reported.[29]

1.9. Methyl [methyl 5-(*N*-acetylacetamido)-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (22α) and Methyl [methyl 5-(*N*-acetylacetamido)-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-non-2-ulopyranosylonate]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (22β)

22α and **22β** was isolated as an anomeric mixture, the ^1H and ^{13}C NMR spectral data matched that reported.[22]

1.10. Methyl [methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonate]-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (25α) and Methyl [methyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero-β-D-galacto-non-2-ulopyranosylonate]-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (25β)

25α and **25β** was isolated as an anomeric mixture, the ^1H and ^{13}C NMR spectral data matched that reported.[23]

Acknowledgment

We thank NIGMS (GM62160) for generous financial support.

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