$La(OTf)_3$: An Efficient Promoter for Thioglycoside Activation in Conjunction with *N*-Iodosuccinimide

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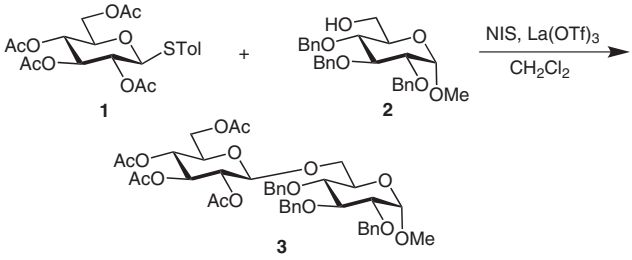
Dedicated to Professor Swapnadip Thakur, Department of Chemistry, University of Burdwan.

Abstract: Use of $La(OTf)_3$ as a Lewis acid promoter for *N*-iodosuccinimide-mediated activation of thioglycosides is reported. The glycosylation reactions proceeded smoothly with good to excellent yields and stereoselectivity.

Key words: thioglycoside, glycosylation, disarmed donor, Lewis acid, NIS

Glycosylation is the pivotal reaction for the construction of complex oligosaccharides. In recent years, significant developments have been made through reactivity tuning protocols based on the 'armed' and 'disarmed' concept,[1] orthogonal glycosylation strategies, and instrument-driven automated glycosylation techniques.[2] Among the various glycosyl donors, thioglycosides have proven to be the best so far due to their stability and compatibility with a wide range of protecting group manipulation strategies.[3,4] As a result, thioglycosides are currently the most commonly used glycosyl donors in oligosaccharide synthesis. Various promoter systems have been developed for efficient activation of thioglycosides to form glycosidic bonds with high stereoselectivity. Early methods of activation of thioglycosides with heavy metal salts in a Koenigs–Knorr type reaction[5] failed to achieve popularity because of the limitations associated with this protocol. Further developments saw the use of various organosulfur reagents, such as dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST),[6] methylsulfenyl triflate,[7] phenylsulfenyl triflate,[8] sulfenamides in conjunction with Lewis acids such as PhSNPhTh–TMSOTf,[9] MeSNPhTh–$TrB(C_6F_5)_4$,[10] *N*-(phenylthio)-ε-caprolactam–Tf_2O,[11] and sulfinates such as benzenesulfinyl piperidine (BSP),[12] benzenesulfinyl morpholine,[13] diphenyl sulfoxide.[14] Me_2S_2–Tf_2O is also been used as a promoter system.[15] However, the most common promoter system for the activation of thioglycosides is *N*-halosuccinimide in conjunction with a Lewis acid. The reagent system was first reported by van Boom et al. in 1990 whereby *N*-iodosuccinimide (NIS) and triflic acid (TfOH) were used for the activation of 'disarmed' thioglycosides.[16] In the same year, Fraser-Reid et al. used the same reagent system for the activation of *n*-pentenyl glycosides.[17] There are limitations to the TfOH-mediated reaction and thus TMSOTf has been used as an alternative Lewis acid. Further modifications of the system utilized silica-supported Brønsted acids, such as $HClO_4$ immobilized on silica[18] and H_2SO_4 immobilized on silica, which have been developed in our laboratory.[19] These systems work satisfactorily for various types of glycosylations. However, further improvements are still required to achieve ultimate efficiency. Recently we found $La(OTf)_3$ to be an efficient promoter for per-O-acetylation of sugars and further thioglycoside or *O*-glycoside formation.[20] Taking our cue from those experiments, we envisaged that $La(OTf)_3$ may serve as a better Lewis acid for the activation of thioglycosides in conjunction with NIS. Herein, we report the results of glycosylation reactions with 'disarmed' thioglycoside donors and various acceptors using NIS in the presence of $La(OTf)_3$.

Our initial studies started with *p*-tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**1**) as the thioglycoside donor. Compound **1** (1.2 mmol) was reacted with the primary alcohol of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**; 1 mmol) in the presence of NIS (1.1 mol equiv) and $La(OTf)_3$ (0.3 mol equiv). The reaction was complete in 90 min (TLC) at 0 °C and afforded the desired disaccharide **3** in 87% yield after isolation by flash chromatography (Scheme 1). Reducing the amount of $La(OTf)_3$ resulted in longer reaction time and lower yield.



Scheme 1 NIS–$La(OTf)_3$-mediated activation of thioglycosides

Once the reaction conditions were optimized, our next target was to establish the generality of the reagent system with various thioglycoside donors and acceptors. Therefore, a series of thioglycosides and acceptors was subjected to NIS–$La(OTf)_3$-mediated glycosylation in various combinations. Satisfactory results were obtained in all cases. The reaction was faster with 6-deoxy sugars due to

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their extra reactivity. Both thioethyl and thiophenyl glycosides proved to be equally good glycosyl donors as compared to *p*-tolyl thioglycosides. Acid-labile protecting groups, such as benzylidene, isopropylidene, and *p*-methoxybenzyl ethers, were stable during the glycosylation reaction. The yield was low in the case of the C-2 axial mannose donor due to hydrolysis of the orthoester formed during glycosylation. The results of these reactions are summarized in Table 1.

Table 1 Scope of the Reaction

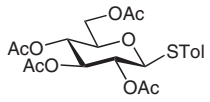
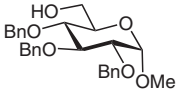
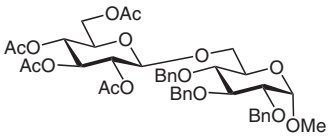
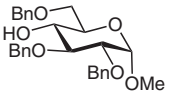
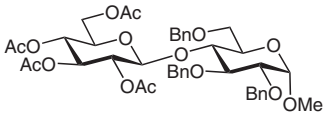
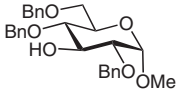
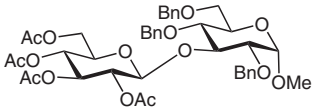
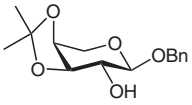
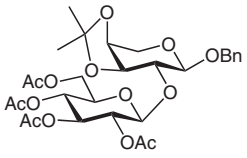
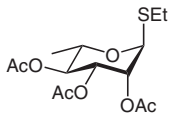
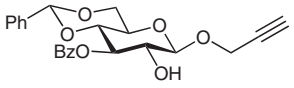
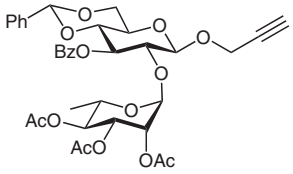
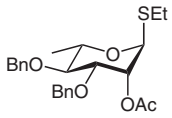
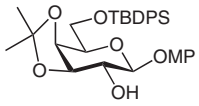
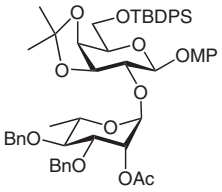
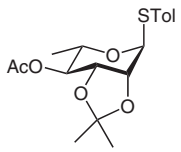
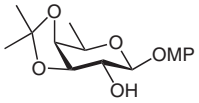
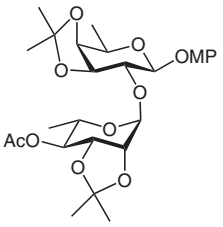
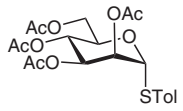
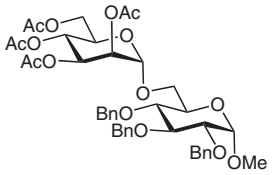
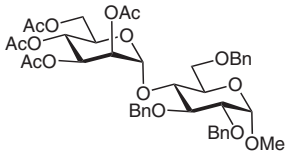
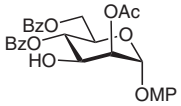
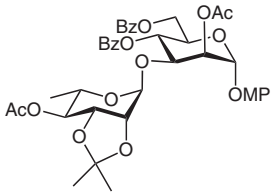
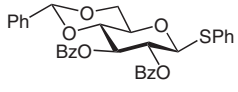
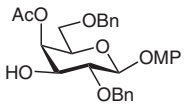
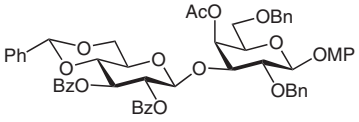
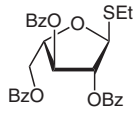
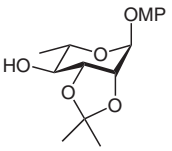
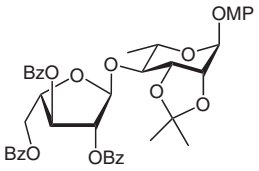
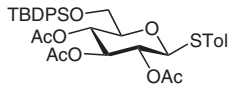
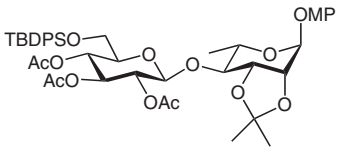
Entry	Donor	Acceptor	Product	Time (min)	Yield (%)	Ref.
1	 **1**	 **2**	 **3**	90	87	21
2	**1**	 **4**	 **5**	90	85	22
3	**1**	 **6**	 **7**	90	87	23
4	**1**	 **8**	 **9**	90	83	24
5	 **10**	 **11**	 **12**	45	89	19d
6	 **13**	 **14**	 **15**	45	82	25
7	 **16**	 **17**	 **18**	45	81	26

Table 1 Scope of the Reaction (continued)

Entry	Donor	Acceptor	Product	Time (min)	Yield (%)	Ref.
8	 **19**	**2**	 **20**	90	76	27
9	**19**	**4**	 **21**	90	71	27
10	**16**	 **22**	 **23**	45	83	28
11	 **24**	 **25**	 **26**	90	81	29
12	 **27**	 **28**	 **29**	60	83	19a
13	 **30**	**28**	 **31**	90	81	19c

In conclusion, La(OTf)$_3$, in combination with NIS, is an efficient catalytic system for activation of 'disarmed' thioglycosides.[30] The solid, moisture-tolerant catalyst is easy to handle in comparison with the traditional TfOH or TMSOTf. The yields are comparable or slightly better than those obtained by using $HClO_4$ immobilized on silica or H_2SO_4 immobilized on silica.

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(29) ***p*-Methoxyphenyl 2,3-Di-*O*-benzoyl-4,6-*O*-benzylidene-β-D-glucopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-glucopyranoside (26)**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.87, 7.83 (2 × d, 4 H, ArH), 7.38–7.13 (m, 21 H, ArH), 6.87, 6.68 (2 × d, 4 H, ArH), 5.67 (t, *J* = 9.5 Hz, 1 H, H-3′), 5.47 (s, 1 H, CHPh), 5.42 (d, *J* = 3.0 Hz, 1 H, H-4), 5.38 (dd, *J* = 8.0, 9.5 Hz, 1 H, H-2′), 5.17 (d, *J* = 8.0 Hz, 1 H, H-1′), 4.76 (d, *J* = 8.0 Hz, 1 H, H-1), 4.68 (d, *J* = 10.5 Hz, 1 H, CH_2Ph), 4.44, 4.40 (2 × d, *J* = 10.5 Hz, 2 H, CH_2Ph), 4.30 (d, *J* = 10.5 Hz, 1 H, CH_2Ph), 4.29 (m, 1 H, H-6a′), 3.92 (dd, *J* = 4.0, 9.5 Hz, 1 H, H-3), 3.89 (t, *J* = 9.5 Hz, 1 H, H-4′), 3.78 (m, 2 H, H-2, H-6b′), 3.68 (m, 2 H, H-4′, H-6a), 3.67 (s, 3 H, $ArCH_3$), 3.52 (m, 3 H, H-5, H-5′, H-6b), 2.11 (s, 3 H, $COCH_3$). ^{13}C NMR ($CDCl_3$, 500 MHz): δ = 170.4 (*C*OCH_3), 165.6, 165.1 (2 × *C*OPh), 155.4, 151.3, 137.8, 136.8, 133.3, 133.2, 129.8, 129.7, 129.4, 129.3 (2), 129.0, 128.5 (2), 128.4 (2), 128.3 (2), 128.2 (2), 128.0(2), 127.9 (2), 127.8 (2), 127.7 (2), 126.1 (2), 118.3 (2), 114.6 (2) (Ar*C*), 102.7 (*C*HPh), 101.4 (C-1′), 101.1 (C-1), 79.4, 78.6, 76.2, 75.1, 73.8, 73.0, 71.9, 69.7, 68.7, 68.6, 66.5, 55.6 (Ar*C*H_3), 20.8 (CO*C*H_3). HRMS: *m*/*z* calcd for $C_{56}H_{54}O_{15}Na$ $[M + Na]^+$: 989.3360; found: 989.3354.
(30) General procedure for glycosylation reactions: A mixture of acceptor (1.0 mmol), thioglycoside donor (1.2 mmol) and 4 Å MS in anhydrous CH_2Cl_2 (10 mL) was stirred under nitrogen for 30 min. $La(OTf)_3$ (0.3 mmol) was added and the mixture was stirred at 0 °C until TLC (*n*-hexane–EtOAc, 2:1) showed complete consumption of the starting material. The mixture was filtered through a pad of Celite and the filtrate was washed successively with aq $Na_2S_2O_7$ (2 × 20 mL), aq sat. $NaHCO_3$ (2 × 20 mL), and brine (20 mL). The organic layer was separated, dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was purified by flash chromatography using a suitable mixture of *n*-hexane–EtOAc as eluent to afford pure glycosylated products.