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Triflic acid-mediated synthesis of thioglycosides†

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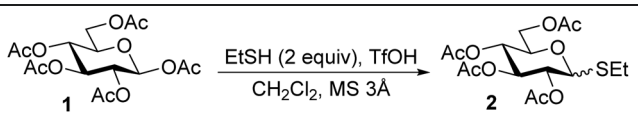
An efficient synthesis of thioglycosides from per-acetates in the presence of triflic acid is described. The developed protocol features high reaction rates and product yields. Some reactive sugar series give high efficiency in the presence of sub-stoichiometric trifluoromethanesulfonic acid (TfOH) in contrast to other known protocols that require multiple equivalents of Lewis acids to reach high conversion rates.

Carbohydrates are the most abundant biomolecules that play crucial roles in many biological processes and their involvement in all diseases has been proven.[1] However, the stereoselective synthesis of complex carbohydrates is still a challenge in glycosciences.[2,3] The key aspect of the oligosaccharide assembly is the attachment of various monosaccharide units *via* a glycosidic bond.[4–7] The linkage is constructed by a chemical glycosylation reaction that involves a nucleophilic displacement of a leaving group of the glycosyl donor with a hydroxyl moiety of the glycosyl acceptor in the presence of an activator.[8]

Since their invention in 1909 by Fischer,[9] thioglycosides have become key building blocks both for the modification of monosaccharides and for the construction of glycans.[10–15] Numerous methods for the preparation of thioglycosides have been established.[16–27] The most commonly employed pathway is Lewis acid-mediated thioglycosidation of per-acetylated sugars in the presence of stoichiometric amounts (2–5 equiv.) of TMSOTf, $BF_3{\cdot}Et_2O$, $ZrCl_4$, $SnCl_4$, *etc.*[28–30] A variety of other approaches such as one-pot acetylation-thioglycosidation of unprotected sugars,[17,26,27,31,32] including Brønsted-acid-mediated reactions are also known.[33] Although many of these conditions provide good stereoselectivity and yields, requirement of an excess of a promoter indicates the limitation of this methodology. Herein we report that even a sub-stoichiometric amount of triflic acid can promote thioglycosidation of per-acetates of different sugar series.

Our first attempt to standardize the reaction conditions involved common glucose pentaacetate **1** that was set to react with 2.0 equiv. of ethanethiol in dichloromethane at 0 °C. The key results of this study are surveyed in Table 1. Thus, when a catalytic amount of triflic acid (0.2 equiv.) was applied at 0 °C, thioglucoside **2**[34,35] was afforded in 26% yield in 4 h (entry 1). Prolonged experiments showed that the starting material was not consumed even after 24 h, and the product yield remained practically the same. Increasing the triflic acid to 50 mol% produced thioglycoside **2** in a respectable yield of 70% in 3 h (entry 2). These experiments were started at 0 °C, and the temperature was allowed to increase gradually after 1 h. Further increment in the amount of triflic acid to 80 mol% produced thioglucoside **2** in an excellent yield of 94% in 1 h (entry 3). Since many other thioglycosylations demand low temperature to maintain the stereoselectivity, we investigated the temperature effect on the outcome of the TfOH-promoted reaction. When essentially the same reaction in the presence of 0.8 equiv. of TfOH was set at rt, an excellent yield of 97% albeit compromised stereoselectivity (α/β = 1/5.0) were achieved (entry 4). These results confirm that low reaction temperature is

Table 1 Optimization of the reaction conditions for thioglycosidation of penta-acetate **1** with ethanethiol



Entry	*T* (°C)	Catalyst (equiv.)	Time	Yield of **2**, ratio α/β
1	0 → rt	TfOH (0.2)	4 h	26%, β only
2	0 → rt	TfOH (0.5)	3 h	70%, β only
3	0	TfOH (0.8)	1 h	94%, β only
4	rt	TfOH (0.8)	45 min	97%, 1/5.0
5	0	TfOH (1.0)	35 min	87%, β only
6	0	TfOH (1.2)	20 min	75%, β only
7	0 → rt	$BF_3{\cdot}OEt_2$ (0.8)	24 h	55%, β only

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required for maintaining the complete β-stereoselectivity of TfOH-catalyzed thioglycosidation of **1**.

A further increase in the amount of triflic acid to 1.0 and 1.2 equiv. reduced the reaction time to 35 and 20 min, but the yields declined to 87% and 75%, respectively (entries 5 and 6). Hence, we concluded that the reaction in the presence of 0.8 equiv. of TfOH (entry 3) offers the most advantageous combination of the reaction efficiency and rate. For comparison, when the same amount of boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) was used, thioglycoside **2** was obtained in a modest yield of 55% after 24 h (entry 7). This result is consistent with a common method of thioglycosylation that demands excess $BF_3{\cdot}Et_2O$ to drive this reaction to completion.[21,30]

Having standardized the reaction conditions for the synthesis of ethylthio glucoside **2**, we moved to expand the scope of this reaction to other sugar series and other aglycone types. The key results of this study are summarized in Table 2. Thus, the reaction of galactose pentaacetate **3** with ethanethiol in the presence of 0.8 equiv. of TfOH afforded thiogalactoside **4**[36,37] in 90% yield in 30 min (entry 1). Expectedly, the reaction with much less reactive mannose penta-acetate **5** was slow, and ethylthio mannoside **6**[26,37] was obtained in only 26% yield. To achieve the preparative outcome of this reaction, the amount of TfOH was increased to 2.0 equiv. In this case, thiomannoside **6** was isolated in a respectable yield of 85% (entry 2). Even under these fortified conditions, the reaction remained fairly sluggish and required 8 h to complete. Also 2-phthalimido glucose tetra-acetate **7**[38] required similar reaction conditions (2.0 equiv. of TfOH) to produce the corresponding ethylthio glycoside **8**[38,39] in 73% yield (β-only) in 4 h. When the amount of TfOH was increased to 2.5 equiv., this reaction produced thioglucoside **8** in 96% in 45 min (entry 3). Per-acetylated sialic acid **9**[40] produced the corresponding ethylthio sialoside **10**[41,42] in 70% yield (α/β = 1/1.0) in 45 min (entry 4). Our standard reaction conditions (0.8 equiv. of TfOH) were also employed for thioglycosidation of lactose octa-acetate **11**[43–45] to produce thiolactoside **12**[46] in 70% yield in 6 h (entry 5).

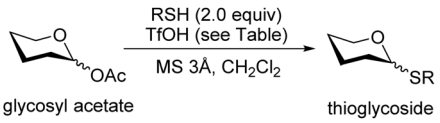
We then investigated glycosylation of other common thiols, thiophenol and *p*-thiocresol to generate SPh and STol glycosides, respectively. Glucose per-acetate **1** smoothly reacted with thiophenol (2.0 equiv.) under the standard conditions in the presence of 0.8 equiv. of TfOH at 0 °C. As a result, the desired phenylthio glucoside **13**[34] was obtained in 77% yield in 1.5 h (entry 6). Galactose per-acetate **3** very readily reacted with thiophenol under these conditions affording phenylthio galactoside **14**[18,37] in 88% yield in 30 min (entry 7). Thioglycosidation of mannose per-acetate **5** again required excess TfOH because the reaction under the standard conditions yielded only 31% of thiomannoside **15**.[18,47] In contrast, when this reaction was repeated in the presence of 2.0 equiv. of TfOH, phenylthio mannoside **15** was obtained in 75% yield (entry 8). As in the case of ethanethiol, the reaction was sluggish and required 9 h to complete. The introduction of the SPh anomeric group to sialic acid also required 2.0 equiv. of TfOH, but it was rather swift (45 min). As a result, phenylthio sialoside **16**[48,49] was obtained in 66% yield as an anomeric mixture (α/β = 1/2.0, entry 9).

First, thioglycosylations with *p*-thiocresol showed that the standard conditions provide somewhat lower efficiency than that seen for reaction with EtSH and PhSH. For instance, the reaction of glucose per-acetate **1** with *p*-thiocresol (2.0 equiv.) in the presence of 0.8 equiv. of TfOH at 0 °C provided STol glucoside **17**[26,34,50] in a modest yield of 70%. The utility of this reaction was enhanced by increasing the amount of TfOH to stoichiometric (1.0 equiv.). We have also observed that these reactions can be successfully performed at rt. When glucose penta-acetate **1** was reacted with *p*-thiocresol under these modified conditions, thioglycoside **17** was obtained in 88% yield in 30 min (entry 10). Galactose per-acetate **3** also reacted very readily with *p*-thiocresol affording tolylthio galactoside **18**[50,51] in 87% yield in 30 min (entry 11). Even thioglycosidation of mannose per-acetate **5** was very efficient under these conditions producing tolylthio mannoside **19**[27,33] in 88% yield in 2.5 h (entry 12). The introduction of the STol anomeric group to sialic acid **9** under these reaction conditions resulted in moderate efficiency for the synthesis of tolylthio sialoside **20**[33] (69%, α/β = 1/3.0), but it was rather swift (45 min). When this coupling was performed in the presence of excess TfOH (2.0 equiv.) at rt, tolylthio sialoside **20** was obtained both in a higher yield and higher stereoselectivity (85%, α/β = 1/4.0, entry 13). Also, lactose octa-acetate **11** reacted smoothly under similar conditions (1.0 equiv. of TfOH at rt) producing tolylthio lactoside **21**[33] in 4 h in a good yield of 80% (α/β = 1/10.0, entry 14).

We then briefly investigated the possibility of expanding this methodology to the synthesis of glycosyl thioimidates that found synthetic utility in recent years. The synthesis of *S*-thiazolinyl (STaz) imidate was also deemed possible, but required an excess of both HSTaz and TfOH, up to 3.5 equiv. each. The key results of this study are summarized in Table 3. Glucose per-acetate **1** produced the desired thioimidate **22**[34,52] in 76% yield in 6 h (entry 1). Galactose per-acetate **3** afforded STaz galactoside **23**[52] in 76% yield in 5 h (entry 2). The reaction of mannose per-acetate **5** again required a longer reaction time (16 h), but we managed to obtain STaz mannoside **24**[52] in 66% yield (entry 3). It should be noted that all of these reactions were completely stereoselective (Table 3), whereas previous syntheses of STaz imidates from per-acetates in the presence of excess $BF_3{\cdot}Et_2O$ at high temperature had often led to anomeric mixtures.[52]

In conclusion, we developed a simple methodology for the preparation of thioglycosides promoted by triflic acid. Many reactions still required stoichiometric TfOH, with a typical range from 0.8 equiv. for SEt introduction to 3.5 equiv. for STaz imidate synthesis. Our initial attempts to lower the amount of TfOH led to sluggish reactions (16–24 h or longer) and modest yields due to the inability to fully consume the starting material. The scope of this approach was investigated and found to be consistently effective for the synthesis of various thioglycosides in application to different sugar series. Complete stereoselectivity, high yields, and relatively fast reaction rates have been achieved. We have also demonstrated the compatibility of the developed protocol to multi-gram prepa-

Table 2 TfOH-promoted thioglycosidation of acetylated hexoses **1**, **3**, **5**, **7**, sialic acid **9**, and lactose **11**



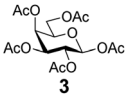
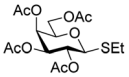
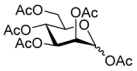
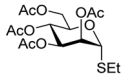
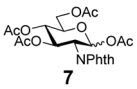
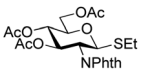
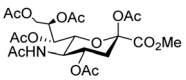
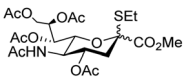
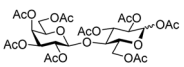
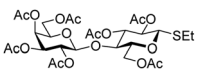
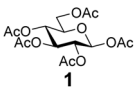
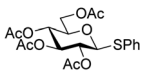
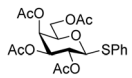
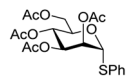
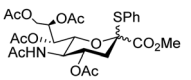
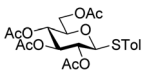
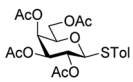
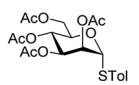
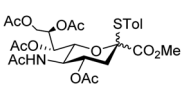
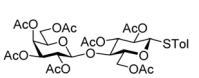
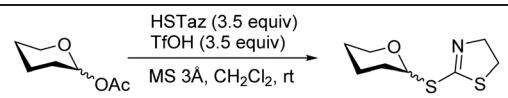
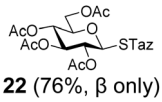
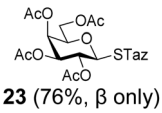
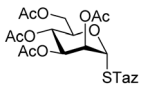
Entry	Substrate	Conditions, 0 °C → rt	Product (yield, α/β)
1	 **3**	EtSH, TfOH (0.8 equiv.), 30 min	 **4** (90%, β only)
2	 **5**	EtSH, TfOH (2.0 equiv.), 8 h	 **6** (85%, α only)
3	 **7**	EtSH, TfOH (2.5 equiv.), 45 min	 **8** (96%, β only)
4	 **9**	EtSH, TfOH (2.0 equiv.), 45 min	 **10** (70%, 1/1.0)
5	 **11**	EtSH, TfOH (0.8 equiv.), 6 h	 **12** (70%, β only)
6	 **1**	PhSH, TfOH (0.8 equiv.), 1.5 h	 **13** (77%, β only)
7	**3**	PhSH, TfOH (0.8 equiv.), 30 min	 **14** (88%, β only)
8	**5**	PhSH, TfOH (2.0 equiv.), 9 h	 **15** (75%, α only)
9	**9**	PhSH, TfOH (2.0 equiv.), 45 min	 **16** (66%, 1/2.0)
10	**1**	*p*-thiocresol, TfOH (1.0 equiv.), 30 min	 **17** (88%, β only)
11	**3**	*p*-thiocresol, TfOH (1.0 equiv.), 30 min	 **18** (87%, β only)
12	**5**	*p*-thiocresol, TfOH (1.0 equiv.), 2.5 h	 **19** (88%, α only)
13	**9**	*p*-thiocresol, TfOH (2.0 equiv.), 30 min	 **20** (85%, 1/4.0)
14	**11**	*p*-thiocresol, TfOH (1.0 equiv.), 4 h	 **21** (80%, 1/10.0)

Table 3 TfOH-promoted synthesis of STaz imidates **22–24** from per-acetates



Entry	Substrate	Time	Product (yield, α/β)
1	**1**	6 h	 **22** (76%, β only)
2	**3**	5 h	 **23** (76%, β only)
3	**5**	16 h	 **24** (66%, α only)

ration of thioglycosides (see the ESI† for details). We have also explored the possibility of conducting this reaction in the absence of molecular sieves. While most reactions were successful even without molecular sieves, the reaction yields were generally 10–20% lower due to competing hydrolysis leading to unreactive hemiacetal/hemiketal side products.

Experimental section

A general procedure for thioglycosidation of per-acetylated compounds 1, 3, 5, 7, 9 and 11 (see the ESI† for further details)

TfOH (0.8–3.5 equiv.) was added dropwise to a mixture containing a thiol (2.0 equiv. or 3.5 equiv. for HSTz), per-acetate (1.0 equiv.) in anhydrous CH_2Cl_2 (10 mL per gram of per-acetate) and freshly activated molecular sieves (3 Å) and the resulting mixture was stirred under argon for the time and at the temperature specified in tables. After that, the reaction mixture was diluted with CH_2Cl_2 and subjected to a conventional aqueous work-up. The organic layer was separated, dried, and concentrated under reduced pressure. The residue was purified either by crystallization (Et_2O–hexanes, mostly with Glc and Gal derivatives) or by column chromatography for most Man and aminosugar derivatives (gradient elution with EtOAc–hexanes) to give the target thioglycosides. The anomeric ratios (or anomeric purity) were determined by comparison of the integral intensities of relevant signals in the ^1H NMR spectra.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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