Organic LETTERS

Letter

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# An Air- and Water-Stable Iodonium Salt Promoter for Facile Thioglycoside Activation

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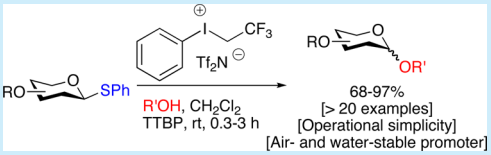
Supporting Information

**ABSTRACT:** The air- and water-stable iodonium salt phenyl(trifluoroethyl)-iodonium triflimide is shown to activate thioglycosides for glycosylation at room temperature. Both armed and disarmed thioglycosides rapidly undergo glycosylation in 68−97% yield. The reaction conditions are mild and do not require strict exclusion of air and moisture. The operational simplicity of the method should allow experimentalists with a limited synthetic background to construct glycosidic linkages.




The recognition of the critical roles that oligosaccharides and glycoconjugates play in an array of biological processes has led to significantly increased interest in glycobiology over the past two decades.[1,2] Despite this interest, the field is still in its infancy compared to genomics and proteomics. This is due in large part to the limited availability of oligosaccharides to serve as standards for biological analysis. A major reason for this is the difficulty associated with chemical glycosylation reactions.[3] In addition to the challenge of controlling stereochemistry in oligosaccharide synthesis,[4] many glycosylation reactions are extremely technically demanding and require the use of water/air sensitive reagents. As a consequence, extensive synthetic training is required to successfully execute oligosaccharide synthesis, limiting its use to highly specialized laboratories. We envisioned that if carbohydrate synthesis is to be adopted by the broader chemical biology community it will be necessary to develop protocols that utilize shelf stable donors and promoters under simple to use reaction conditions (room temperature, minimal effort to exclude moisture). After surveying various donors for oligosaccharide synthesis, we concluded that thioglycosides fit this profile well and decided to examine mild and shelf-stable thiophilic promoters for their activation. While many methods for thioglycoside activation have been reported, most require the use of toxic or unstable reagents, and/or extremely low reaction temperatures.[5] This has led to recent interest in developing milder approaches to glycosylation reactions using thioglycoside donors.[6,7] A major part of our research program is directed at developing facile yet highly efficient glycosylation procedures. Here we report the use of phenyl(trifluoroethyl)-iodonium triflimide (**1**) as a water- and air-stable thiophilic glycosylation promoter.

The iodonium salt **1** is a remarkably air- and water-stable crystalline solid that is readily synthesized in good yield in two steps starting from 1,1,1-trifluoro-2-iodoethane.[8] Not only does the preparation of **1** involve a final crystallization from ice water followed by drying under high vacuum, but it has also been shown to selectively alkylate amine nucleophiles in aqueous media.[9] In addition, longer chain analogues of **1** have been shown to rapidly alkylate the thioether of methionine, even during solid-phase peptide synthesis where nucleophiles display reduced activity.[9b] Furthermore, we anticipated that using **1** to activate thioglycosides would not result in the formation of electrophilic byproducts that can sometimes complicate glycosylations when using other thiophilic promoters (Scheme 1).[10] Based on these observations we anticipated that **1** would promote thioglycoside activation under particularly mild conditions.

Our preliminary study employed fully armed glucose thioglycoside donor **2**[11] and cholesterol (**3**) as coupling partners (Table 1). Pleasingly, dropwise addition of a solution

**Scheme 1. Phenyl(trifluoroethyl)iodonium Triflimide As a Glycosylation Promoter**

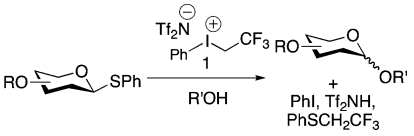
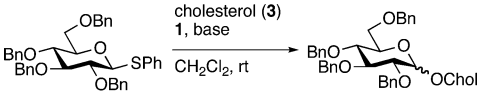



**Table 1. Reaction Optimization**




**2** **4**

| entry | time (h) | base | % yield | $\alpha$:$\beta$ |
|---|---|---|---|---|
| 1 | 0.2 | – | 63 | 1.9:1 |
| 2 | 24 | – | 0 | N/A |
| **3** | **1** | **TTBP** | **71** | **1:1** |
| 4[a] | 1 | TTBP | 55 | 1:1.2 |

[a]Reaction was run open to air. TTBP = 2,4,6-tri-*tert*-butylpyrimidine.

**Received:** February 7, 2014
**Published:** March 5, 2014

   dx.doi.org/10.1021/ol5004059 | *Org. Lett.* 2014, 16, 1780−1782

**Table 2. Reaction Scope with Fully Substituted Donors**

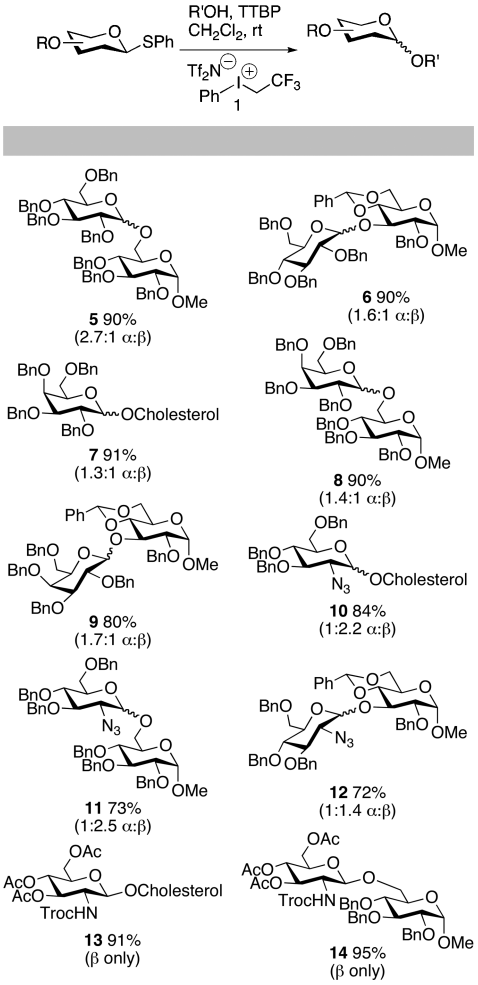
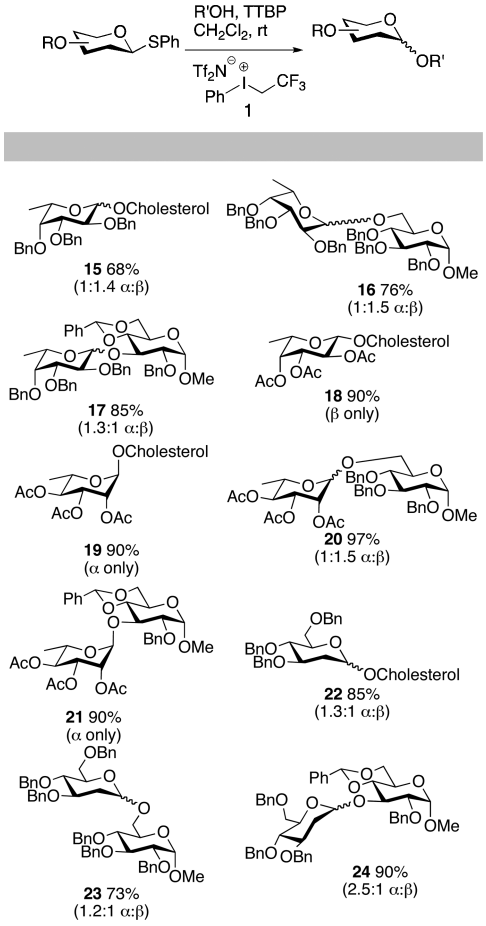



**Table 3. Reaction Scope with 2-Deoxy- and 6-Deoxy-sugar Donors**




of **1** (1.2 equiv) in dichloromethane to a premixed solution of the donor and acceptor at room temperature led to rapid formation (<20 min) of the desired glycosylation product in 63% yield (Table 1, entry 1). Importantly, additives normally used in glycosylation reactions to remove excess water, such as molecular sieves, were not necessary. Attempts to improve the yield through longer reaction times led to complete product decomposition (Table 1, entry 2). We reasoned that this was promoted by acidic trifluoromethanesulfonimide byproducts generated during the course of the reaction. Consistent with this rationale, adding the non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) to the reaction prevented any unwanted side reactions, thereby allowing for longer reaction times and an increase in yield (Table 1, entry 3). Finally, intrigued by the stability of the promoter and ease of setup we decided to assess the robustness of the reaction. To this end, we ran it exposed to open air (Table 1, entry 4). Under these conditions the product was obtained in slightly decreased yield (55%), indicating that strict exclusion of moisture is not entirely necessary to conduct this chemistry. This yield was less than optimal, however, due to competitive reaction of the activated thioglycoside with water to afford the corresponding hemiacetal. We therefore used an argon atmosphere for the rest of this study.

Having established optimal reaction conditions, we turned our attention to the scope of the reaction. As shown in Table 2, fully substituted thioglycoside donors all reacted smoothly with various acceptors in consistently good yields (72% to 95%). Importantly, both reactive and sterically hindered acceptors are competent coupling partners in the reaction. The promoter tolerates the presence of acetals, alkenes (e.g., cholesterol), ethers, esters, azides, and carbamates. In most cases a 1:2 donor-to-acceptor ratio was sufficient to promote complete glycosylation within 1 h.

When disarmed donors were used the reaction was slower, and both donor decomposition and byproduct formation again became a problem. In order to address this problem we decided to use the acceptor as the limiting reagent. Under these modified conditions, the reactions still took slightly longer to proceed (2 to 3 h). Despite this, the reaction now proceeded in synthetically useful yields (91−95%, products **13** and **14**).

Having established that the promoter could rapidly activate thioglycosides for glycosylation, we turned our attention to deoxy-sugar donors (Table 3). These sugars are an important component of many biological systems, including human glycoproteins,[12] bacterial polysaccharides,[13] and natural products.[14] The lack of oxygenation in these molecules, either at C2 or C6, destabilizes these glycosidic linkages relative to other sugars. As a result, product decomposition during the course of the reaction can be a problem if reaction conditions are too acidic.[15] Pleasingly, we found that **1** could promote glycosylations with both 2-deoxy- and 6-deoxy-sugar donors in good to excellent yield (68%−97%). As with the fully substituted sugars in Table 2, these studies used a 1:2 donor-to-acceptor ratio for thioglycosides possessing arming protecting


dx.doi.org/10.1021/ol5004059 | *Org. Lett.* 2014, 16, 1780−1782

groups. Once again, however, the presence of disarming protecting groups was problematic when the donor was used as the limiting reagent. As with our above study, this problem could be dealt with by modifying conditions so that the donor was used in excess. In all cases examined, under the optimal conditions product decomposition was not observed, even with highly reactive 2-deoxy-sugar donors.[16] The fact that we were able to use this promoter to make relatively unstable products such as **22** to **24** without incident or modification to the reaction conditions further demonstrates the effectiveness of this new promoter.

In conclusion, we have described the use of phenyl(trifluoroethyl)iodonium triflimide (**1**) as a representative of a new class of single-component thiophilic promoters. As a water- and air-stable white crystalline solid, the iodonium salt offers an advantage over other glycosylation promoters through its particular ease of handling. The salt is stable for 5 days at room temperature and will keep for more than 6 months if stored in the refrigerator in the dark. Furthermore, low temperatures or additives used to remove water from the reaction, such as molecular sieves, are not necessary to run this chemistry. The reaction is robust, and a wide array of thioglycoside donors were shown to cleanly and rapidly undergo glycosylations in high yields at room temperature. Due to the mildness of the reaction conditions, the procedure permits the construction of sensitive glycosides, such as 2-deoxy- and 6-deoxy-sugars. We envision that this approach will significantly facilitate oligosaccharide synthesis and ultimately lay the foundation for chemistries that will permit experimentalists with a limited synthetic background to construct their own oligosaccharide standards.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Tufts University and the National Institutes of Health (CA125033 to K.K.) for support of this work.

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