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N-(Phenylthio)-ϵ-caprolactam: A New Promoter for the Activation of Thioglycosides

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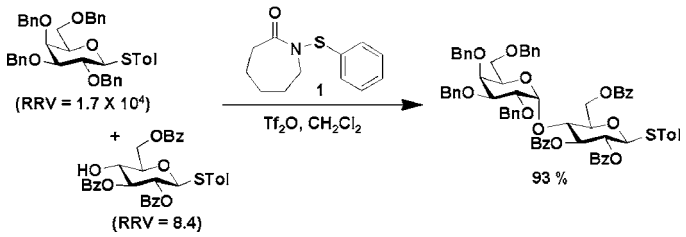
ABSTRACT



***N*-(Phenylthio)-ϵ-caprolactam (1) has been applied as a new promoter for the activation of thioglycosides. This proceeds by the reaction of 1 with trifluoromethansulfonic anhydride, which subsequently activates the thioglycoside for glycosidic bond formation. Notably, the reaction proceeds efficiently at room temperature and is adaptable to our reactivity-based one-pot oligosaccharide synthesis.**

Development of methods for glycosidic bond formation, arguably the most crucial step in oligosaccharide synthesis, has been the subject of investigation for many years. Though many methods are available to date, development of new reagents that promote glycosylations in a general and convenient manner is still very desirable. Recently, we reported a reactivity-based programmable one-pot method for complex oligosaccharide synthesis utilizing thioglycoside building blocks.[1] The generality of thioglycosides makes them convenient and attractive building blocks, due to their stability, accessibility, and compatibility.[2] Thioglycoside activators include *N*-iodosuccinamide/trifluoromethane-sulfonic (triflic) acid combination (NIS/TfOH),[3] dimethyl-(thiomethyl) sulfonium trifluoromethane sulfonate (DMTST),[4] methylsulfenyl triflate (MeSOTf),[5] benzeneselenyl triflate (PhSeOTf),[6] and iodonium dicollidine perchlorate (IDCP).[3] More recently, an excellent low-temperature reagent for thioglycoside activation was reported, which incorporates the reagent combination of benzenesulfinyl piperidine (BSP)/triflic anhydride.[7] This has been applied to our synthesis of oligosaccharides and has been shown to improve yields.[8] Although these promoters are convenient for the assembly of oligosaccharides, we have encountered several drawbacks and limitations mainly due to side reactions with byproducts resulting from the promoters. These issues, coupled with our interest in improving the one-pot oligosaccharide strategy, stimulated our search for a new promoter. Herein, we report the identification of a novel reagent, *N*-(phenylthio)caprolactam (**1**), for the activation of thioglyside donors and its application in our reactivity-based one-pot oligosaccharide method. In identifying a new promoter, several requirements

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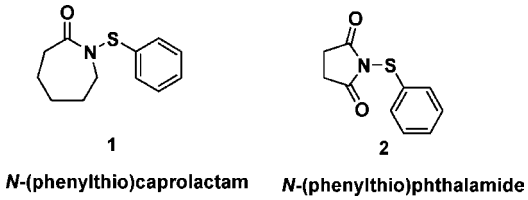
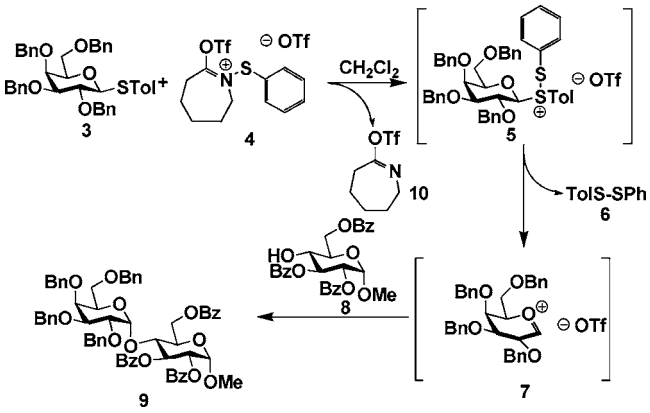


Figure 1. Reagents investigated as glycosylation promoters.

are critical. The new reagent must be thiophilic, amenable to our reactivity-based one-pot strategy, and most importantly, must not generate byproducts that will interfere with the course of the reaction. It is known that benzenesulfenyl triflate is an extremely powerful thiophilic reagent that can be used to couple thioglycosides with various acceptors.[9] Though it serves as a potent electrophile, it remains problematic due to its instability and its requirement for in situ preparation from benzenesulfinyl chloride and silver trifluoromethane sulfonate. A new reagent is needed to complement benzenesulfenyl triflate, with the added features of stability and convenient accessibility. To this end, we identified *N*-(phenylthio)caprolactam (**1**)[10] and *N*-(phenylthio)phthalamide (**2**).[11] Though *N*-(phenylthio)amides/phthalamides have not been used in glycosylations, they have been used as electrophiles in reactions with carbanions, enamines, silyl enol ethers and silyl ketene acetals to provide α-sulfenylated ketone and lactone products.[12] They have been demonstrated to be remarkably shelf stable and remain unreactive until exposure to reagents such as triflic anhydride or methyltrifluoromethane sulfonate. These properties prompted us to investigate their ability to activate thioglycoside donors for glycosylations and ultimately apply them in our reactivity-based one-pot strategy.

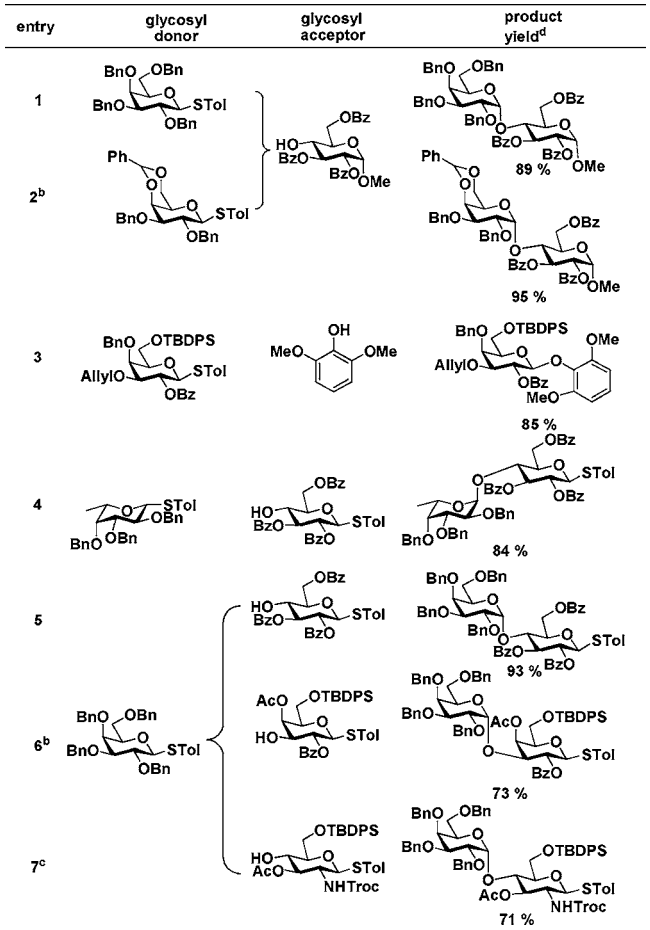
In competition experiments, it was determined that the caprolactam analogue **1** was more effective and significantly more reactive than its phthalamide counterpart **2**. A proposed reaction mechanism for this transformation involves initial O-triflation of the amide functionality within **1**, using triflic anhydride, to yield **4** (Scheme 1).[14] Activated promoter **4** is

Scheme 1. Proposed Mechanism for Thioglycoside Activation[13]



then susceptible to nucleophilic attack by the thioether functionality within thioglycoside **3**, yielding activated saccharide **5**. The activated species can then eliminate disulfide **6** to produce putative oxocarbenium species **7**,

Table 1. Glycosylations with *N*-(Phenylthio)Caprolactam (**1**) and Trifluoromethanesulfonic Anhydride[a]



[a] All reactions were carried out in dichloromethane. [b] TTBP was added to the reaction; yield was 71% without base. [c] β-Isomer (~5%) was also isolated. [d] Anomeric assignments determined by ^{1}H NMR analysis.

(9) (a) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702−1706. (b) Effenberger, F.; Russ, W. *Chem. Ber.* **1982**, *115*, 3719−3736.

(10) **1** is available from the Aldrich Chemical Co. (Rare Chemical Library); also, for the synthesis of **1**, see: Sosnovsky, G.; Krogh, J. A. *Synthesis* **1979**, *3*, 228−230.

(11) Behforouz, M.; Kerwood, J. E. *J. Org. Chem.* **1969**, *34*, 51−55.

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(13) We speculate that **1** reacts with electrophiles (i.e., Tf_2O, MeOTf) at the oxygen atom within amide bond-forming intermediate salts such as **4**. However, we cannot rule out other possible pathways for activation such as S-triflation. Mechanistic studies are currently underway to elucidate the pathway of this reaction.

(14) In a competition experiment at room temperature, the identical conditions were performed with the only difference being the presence of **1**. The reaction without **1** proceeded at a very slow rate to form **9** in addition to several byproducts, whereas **9** was formed cleanly (83%) within minutes with a mixture of **1**/Tf_2O.

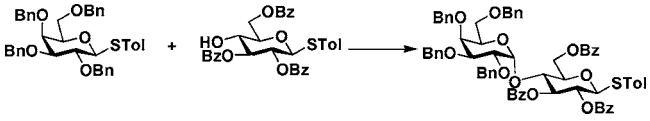
which then reacts with acceptor **8**, yielding the desired disaccharide **9**. Indeed, high yields can be obtained, while producing nonparticipating byproducts, triflyl imidate **10** and disulfide **6**.

Our initial investigations focused on determining whether activated phenylthioamides could serve as promoters for glycosylations using thioglycoside donors. Indeed, activated donors work exceptionally well, as several disaccharides were accessed using methyl glycoside acceptors, with yields up to 95% (entries 1−2). Another example is shown using 2,6-dimethoxyphenol as an acceptor (entry 3), a model for the vancomycin aglycon. This method suggests the potential for thioglycoside donors in the synthesis of vancomycin, which we have been investigating for some time, but we have been hindered by protecting group incompatibilities. This entry also demonstrates compatibility with several protecting groups, including TBDPS, benzyl, allyl, and benzoyl.

The next issue was to determine if we could apply **1** in a reactivity-based oligosaccharide synthesis. Indeed, this reagent works well, as we were able to synthesize various disaccharides using thioglycoside acceptors (Table 1, entries 4−7). In all the reactions, essentially equimolar concentrations of all the reagents were used to minimize the formation of side products, and exclusive activation of the donor was observed.

It is important to note that we also investigated the reaction at room temperature and were able to realize similar yields (Table 2, entry 1). In general, the reactions were extremely clean and complete within minutes at room temperature. This was an improvement over other methods (Table 2, entries 2−3).[15] If acid-sensitive functionalities are present, 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[16] can be used, which has not demonstrated a significant effect on the progress of the reaction. Finally, we were able to demonstrate a one-pot synthesis of trisaccharide **11** (Scheme 2), supporting that this novel promoter (**1**) can be used in our reactivity-based one-pot synthesis of oligosaccharides.[17]

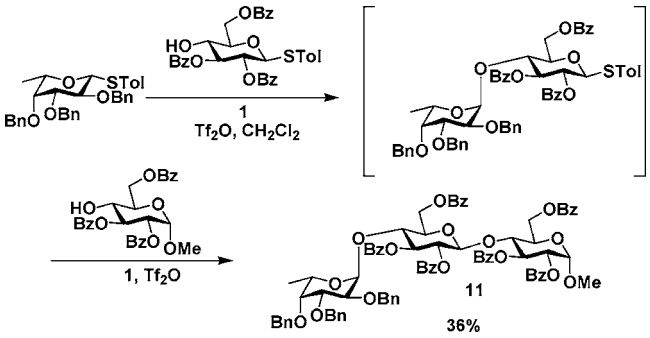
Table 2. Room-Temperature Glycosylations with **1**



entry	promoter system	yield[a]
1	*N*-(thiophenyl)caprolactam	83%[b]
2	benzenesulfinyl piperine/Tf_2O	<15%[c]
3	*N*-iodosuccinamide/TfOH	75%

[a] Conditions: 1:1:1 donor/acceptor/promoter, room temperature, 10 min. [b] Buffering reaction with TTBP gave comparable yields. [c] We rationalize that BSP yields electrophilic byproducts, which serve to further activate the products.[6] When using 0.5 equiv of BSP, the yield was 63%.

Scheme 2. Reactivity-Based One-Pot Glycosylation of **11**



In summary, we have identified *N*-(phenylthio)caprolactam (**1**) as a new reagent to selectively activate thioglycoside donors for glycosylation. This proceeds by the in situ activation of **1** with trifluoromethanesulfonic anhydride, which then serves to activate the thioglycoside for anomeric bond formation. This overcomes some limitations of the current methods and, most notably, proceeds efficiently at room temperature. We are currently attempting to define the scope of this new method and gain some mechanistic insight into this process.

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Supporting Information Available: Synthetic details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) BSP/Tf_2O is an excellent promoter for low-temperature anomeric bond formation and remains our reagent of choice when attempting low-temperature glycosylations. **1** requires higher temperatures: typically, the reaction is initiated at −45 °C and then allowed to warm to room temperature.

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(17) Same yield for **11** was obtained with BSP/Tf_2O.