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Sonochemistry: A Powerful Way of Enhancing the Efficiency of Carbohydrate Synthesis

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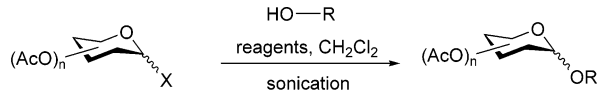

X = OAc, OC(NH)CCl$_3$, SPh, Br

Using sonication as a means of facilitating organic reactions in carbohydrate chemistry was explored under the conditions used for traditional organic synthesis. An array of representative reactions, including hydroxy group manipulation (acylation, protection/deprotection, acyl group migration), thioglycoside synthesis, azidoglycoside synthesis, 1,3-dipolar cycloaddition and reductive cleavage of benzylidene, commonly used in the synthesis of carbohydrate derivatives was examined. A series of glycosylation reactions that employ thioglycosides, glycosyl trichloroacetimidate, glycosyl bromide and glycosyl acetate as the glycosyl donors was also examined. Our results demonstrate that sonication can significantly shorten the reaction time, enhance the reactivity of reactant and lead to superior yield and excellent stereoselectivity. More importantly, a general protocol of glycosylation may finally be developed. Sonication is compatible to the conditions used for traditional organic synthesis. We believe that sonication can also be applied to other areas of synthetic processes.

Introduction

Owing to the remarkable biological relevance of carbohydrate,[1−3] the synthesis of oligosaccharides or carbohydrate derivatives has long been the goal pursued by researchers from various areas.[4,5] The complexity and diversity of carbohydrates found in nature, however, makes the synthesis of carbohydrates a challenging task despite numerous efforts documented in the literature. One of the reasons is that different carbohydrate scaffolds often manifest moderate to drastic different reactivity in various reactions thus resulting in the requirement of optimizing conditions for each individual carbohydrate scaffold. The vast number of developed and employed protecting groups further fuel the complexity in carrying out carbohydrate synthesis, one such example being glycosylation. Due to the difference in the reactivity of glycosyl donors as a result of the employed protecting groups and the intrinsic structure-associated reactivity, numerous methods designed for activating various glycosyl donors have been reported.[6−10] Sophisticated methods, like chemoenzymatic synthesis,[11] one-pot glycosylation,[12,13] solid-phase oligosaccharide synthesis,[14,15] and iterative glycosylation,[16] have been developed for the goal of alleviating the challenges in oligosaccharide synthesis.

On the other hand, the idea of promoting reactivity by using traditional synthetic methods, such as raising the reaction temperature, for less reactive or so-called "disarmed" glycosyl donors is considered to be less applicable, presumably because the reactive intermediates, such as oxycarbenium, are thought to be labile at higher temperature. To conveniently utilize the knowledge of carbohydrate chemistry in the literature, our group

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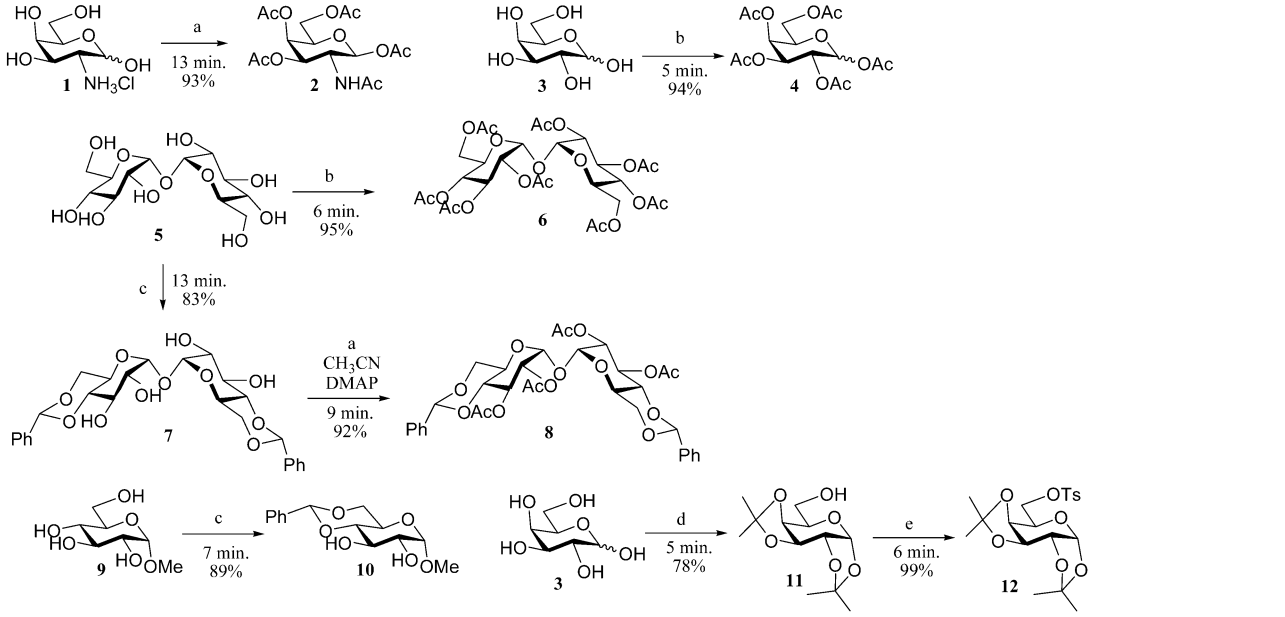
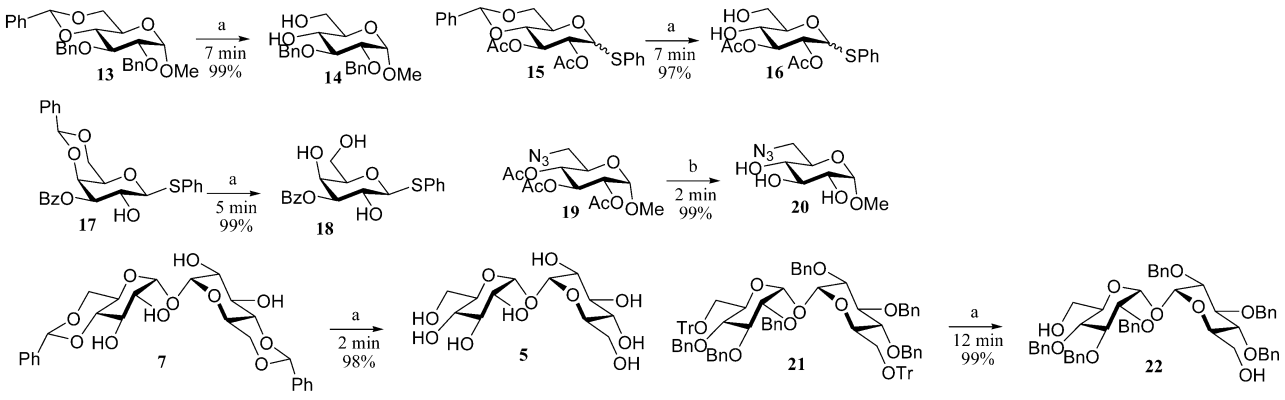
SCHEME 1. Hydroxy Group Manipulation

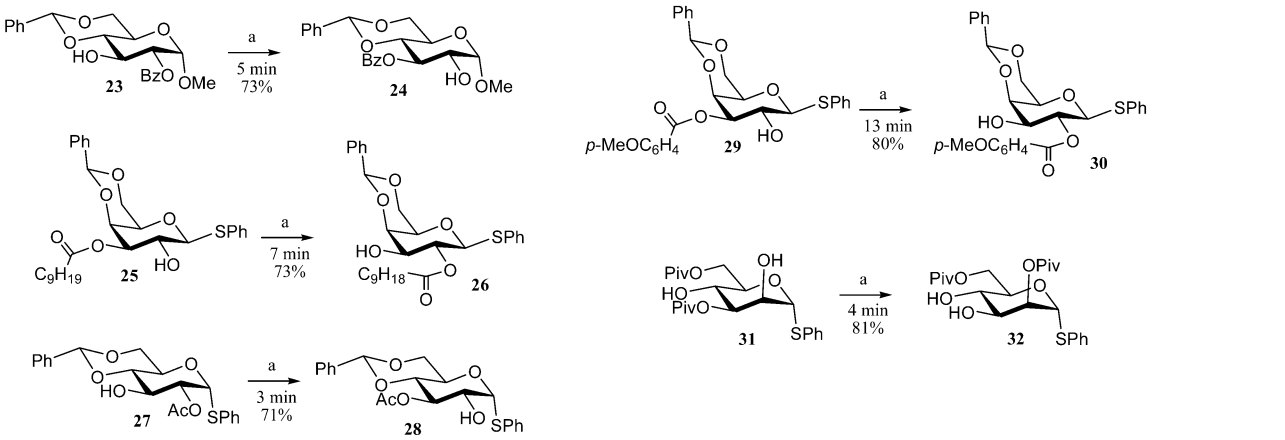
a. Protection reaction (acylation, diol protection and tosylation) and deprotection [a]



b. Deprotection reactions [b]



c. Acyl migration reaction [c]

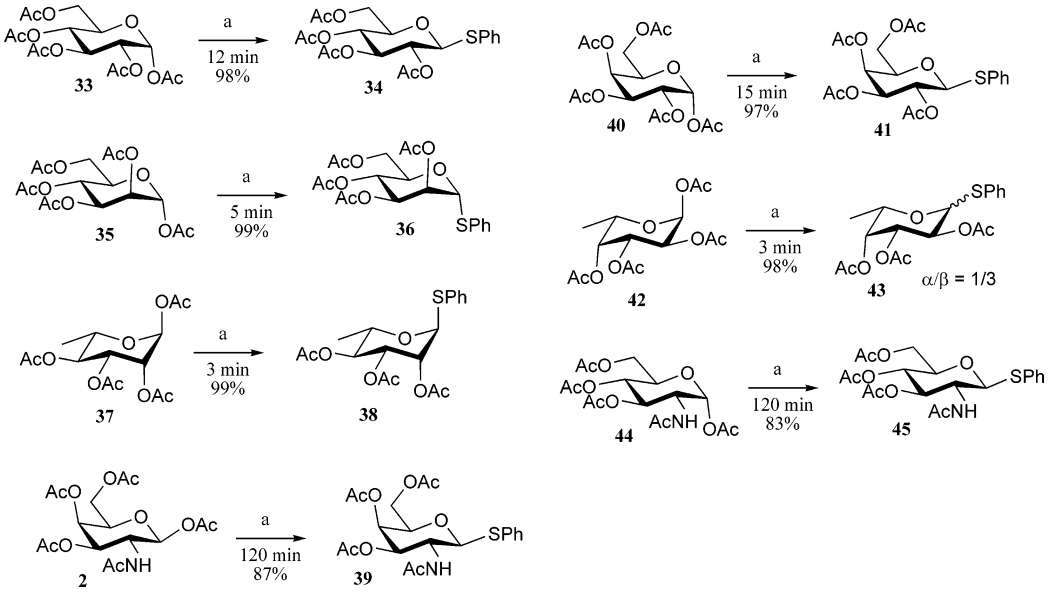


[a] Reagents and conditions: (a) Ac_2O, Et_3N; (b) Ac_2O, cat. H_2SO_4; (c) $PhCH(OMe)_2$, $TsOH-H_2O$, DMF; (d) $Me_2C(OMe)_2$, TsOH, DMF; (e) TsCl, py., DMAP. [b] Reagents and conditions: (a) $TsOH-H_2O$, MeOH; (b) NaOMe, MeOH. [c] Reagents and conditions: (a) Ag_2O, TBAI, DMF.

has devoted effort in developing general protocols for the systematic synthesis of unusual sugars.[17,18] Hence, the development of a general protocol for effective glycosylation is always a goal that we wish to pursue. With the development of such a general protocol, it is our hope that the complexity involved in carbohydrate synthesis can be minimized.

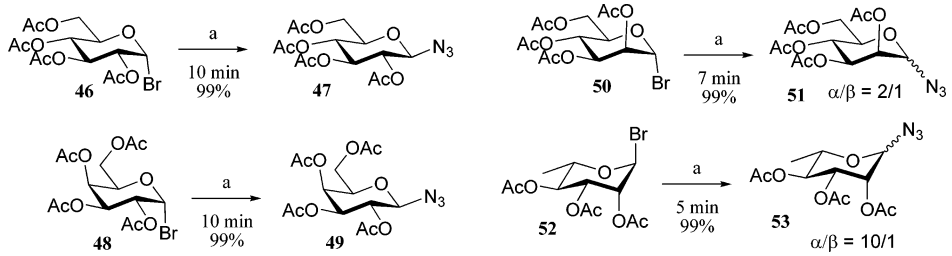
Sonication[19−23] and microwaves[24,25] have long been employed as the energy source for enhancing the rate of chemical reactions.

SCHEME 2. Synthesis of Thioglycosides[a]



[a] Reagents and conditions: (a) PhSH, BF_3-OEt_2, CH_2Cl_2.

SCHEME 3. Azidoglycoside Synthesis[a]



[a] Reagents and conditions: (a) NaN_3, DMF.

While the interest of using microwaves for assisting chemical reactions has reemerged recently, the use of sonication as the tool for organic synthesis is rather under-explored. For better efficiency, microwave-assisted synthesis is often performed without solvent, thus making this method not ideally compatible for syntheses involving molecules with high molecular weight or low solubility, such as in the case of carbohydrate synthesis. Sonication, on the other hand, may provide the needed energy to overcome the different reactivity among carbohydrates, and enable the development of general protocols for facilitating the synthesis of complex carbohydrates. Therefore, we have started to experiment with the use of sonication as an alternative energy source for carbohydrate synthesis.

Results and Discussion

We selected five types of commonly employed reactions in carbohydrate synthesis for our initial studies. These include hydroxy group manipulation (acylation, diol protection, tosylation, deprotection, acyl group migration) (Scheme 1),[26] thioglycoside synthesis (Scheme 2), azidoglycoside synthesis (Scheme 3),[27] 1,3-dipolar cycloaddition (Scheme 4),[28] and reductive cleavage of benzylidene (Scheme 5).[29] To our delight, all the sonication-mediated reactions are compatible with the traditionally employed conditions. Furthermore, the reaction time is dramatically shorter than previously required and with excellent yields in most of the cases. For example, acetylation of carbohydrate usually takes hours. For the trehalose derivatives, **7**, the reaction is hard to reach completion, probably due

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(27) Small molecular weight azido compounds are known to be explosive. Extreme safety measurements should be taken when carry out this reaction.

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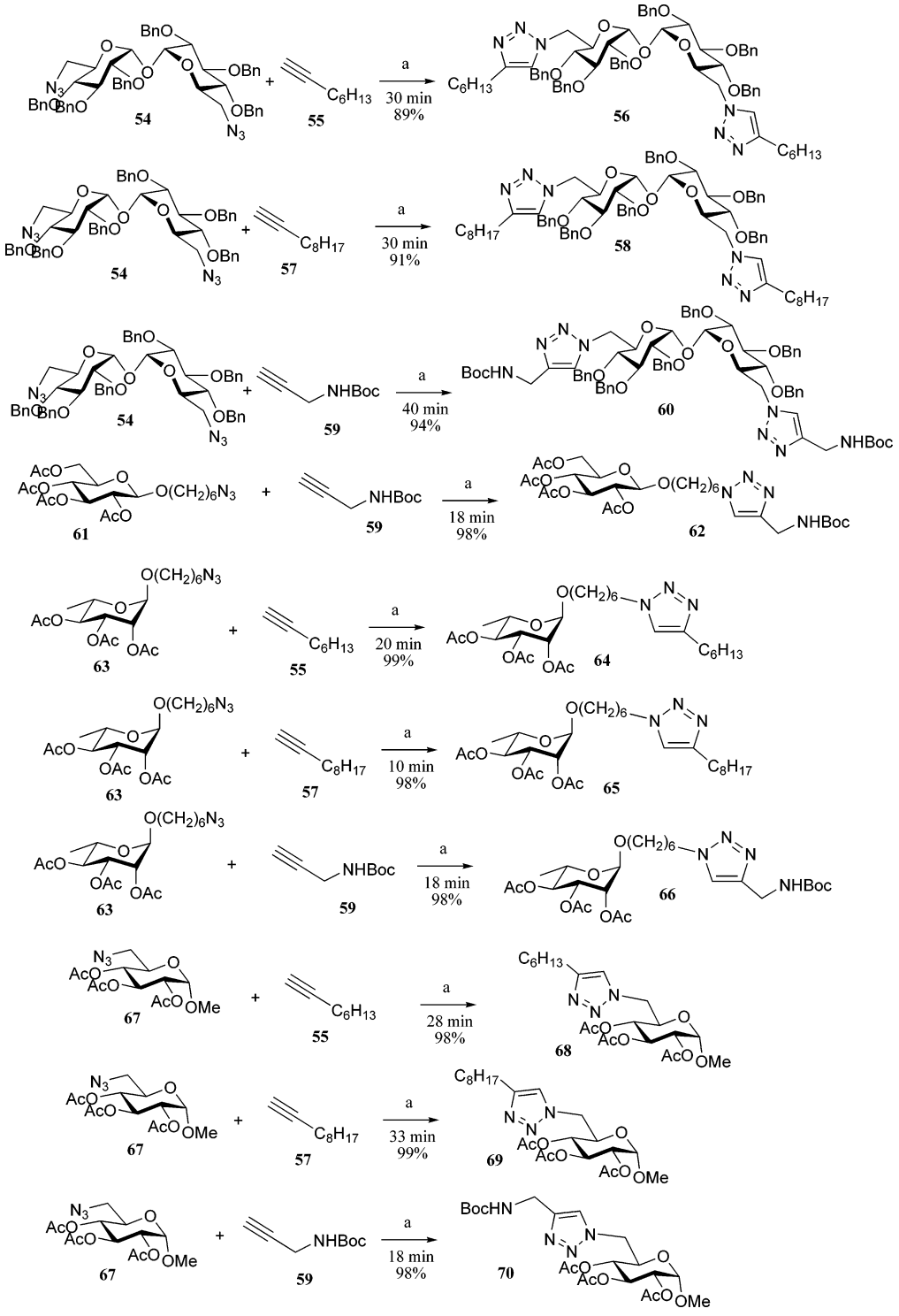
SCHEME 4. 1,3-Dipolar Cycloaddition[a]

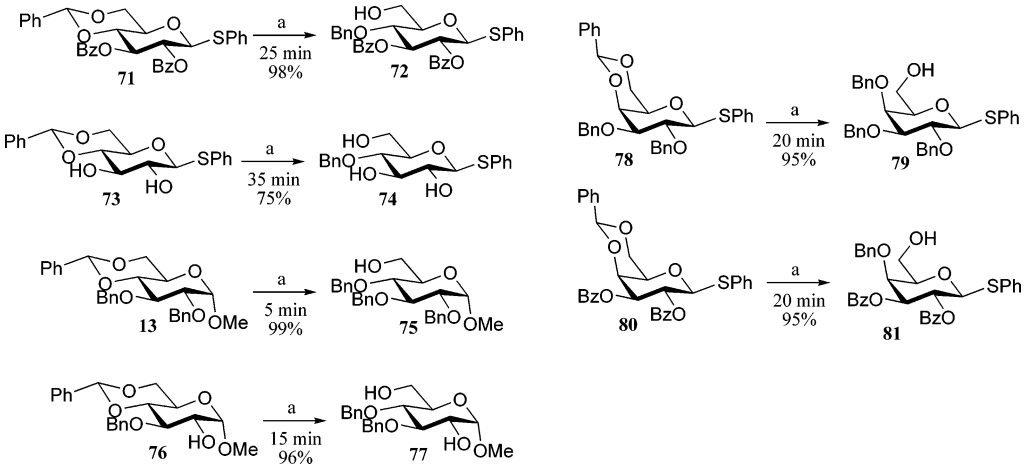


[a] Reagents and conditions: (a) $Cu(OAc)_2$, sodium ascorbate, MeOH, THF, H_2O.

to the steric hindrance. However, with the aid of sonication, the acetylation of all four hydroxyl groups of **7** can be accomplished in several minutes. Likewise, the deprotection of various protecting groups of the hydroxy group, such as acetyl, benzylidene, and trityl groups, can also be completed in a few minutes (Scheme 1b). We have recently developed a general protocol for regiospecific migration of acyl groups.[26] The reaction usually takes days to complete. Nevertheless, under the sonication condition, the reaction time can be shortened to only several minutes (Scheme 1c).

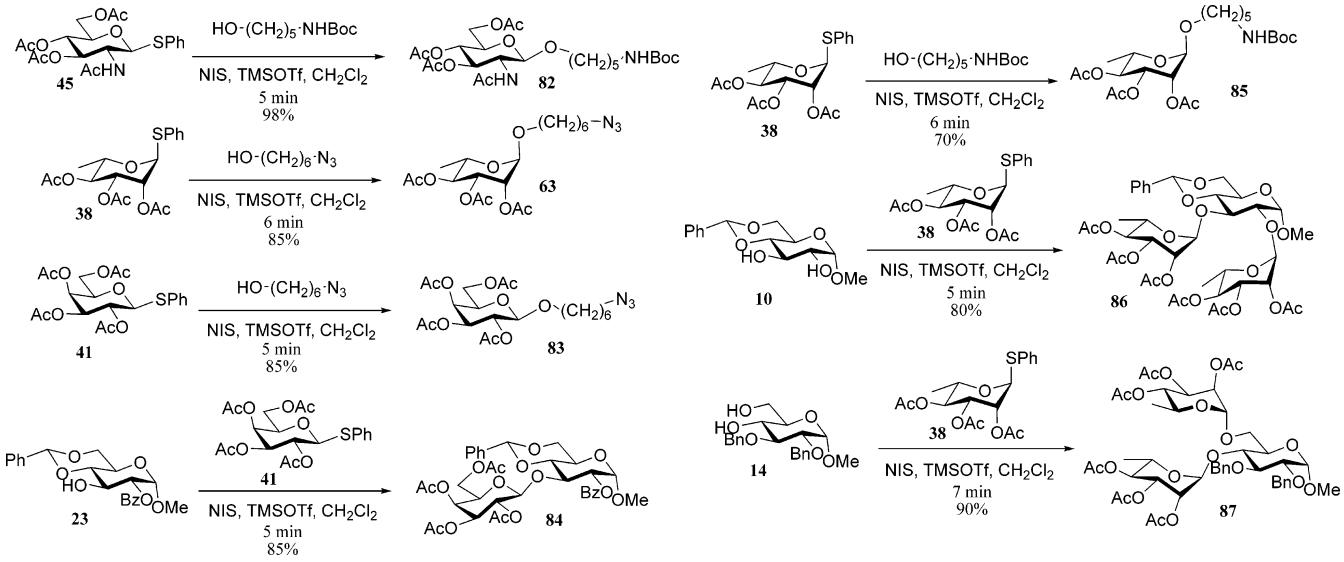
The synthesis of thioglycosides is another prominent example of utilizing sonication (Scheme 2). The synthesis of thioglycosides, the versatile glycosyl donor for glycosylation, is typically accomplished under Lewis acid-mediated condition for several hours or even days.[18] The reaction time for converting **44** to the corresponding thioglycoside, **45**, is even longer (as long as

SCHEME 5. Reductive Cleavage of Benzylidene[a]



[a] Reagents and conditions: (a) $Cu(OTf)_2$, BH_3−THF.

SCHEME 6. Glycosylation with Phenylthioglycosides



a week under traditional condition). However, under sonication, the reaction can be completed in several minutes up to 2 h. The rapidness in completing such a reaction may lead to the creation of environmentally friendly processes, emphasizing the role of employing ultrasound in Green chemistry.

Azidoglycosides have been commonly utilized for the synthesis of various *N*-glycosides. The synthesis of azidoglycosides often requires the use of $TMSN_3$ under the catalysis of Lewis acid for several hours.[30] By using sonication, azidoglycosides can be prepared from the corresponding glycosyl bromides in a few minutes via a substitution reaction even without the presence of Ag(I) (Scheme 3).[27]

The 1,3-dipolar cycloaddition (Scheme 4), the "click" reaction, has been the recent focus for incorporating carbohydrate components or for the preparation of glycomimetics. By using sonication, the reaction time can be shortened from days to less than an hour with excellent regioselectivity favoring the formation of 1,4-disubstituted 1,2,3-triazoles.

Regioselective reductive cleavage of the benzylidene protection group is commonly used for complex carbohydrate synthesis. Recently, Hung[31] reported that combination of $Cu(OTf)_2/BH_3$·THF can regioselectively reduce benzylidene in glucopyranoside. In our studies, all the tested reactions can be accomplished in minutes with high yields and excellent regioselectivity under similar conditions (Scheme 5). In particular, the so-called disarmed donor **80** still reacts smoothly in higher rate, yield and regioselectivity while the counterpart in the literature only gave moderate yield with longer reaction time (>20 h).

Encouraged by the success of these reactions, we began to examine the use of sonication for one of the most challenging reactions in oligosaccharide synthesis: glycosylation. Despite countless endeavors, the statement made by Paulsen in a review article[8] more than 20 years ago, "There are no universal reaction conditions for oligosaccharide syntheses", remains largely unchanged, particularly regarding the problem of glycosylation as we have pointed out previously. We selected "disarmed" phenylthioglycosides as the glycosyl donors for examining the effectiveness of using sonication based on the following reasons. First, phenylthioglycoside can be readily prepared in large

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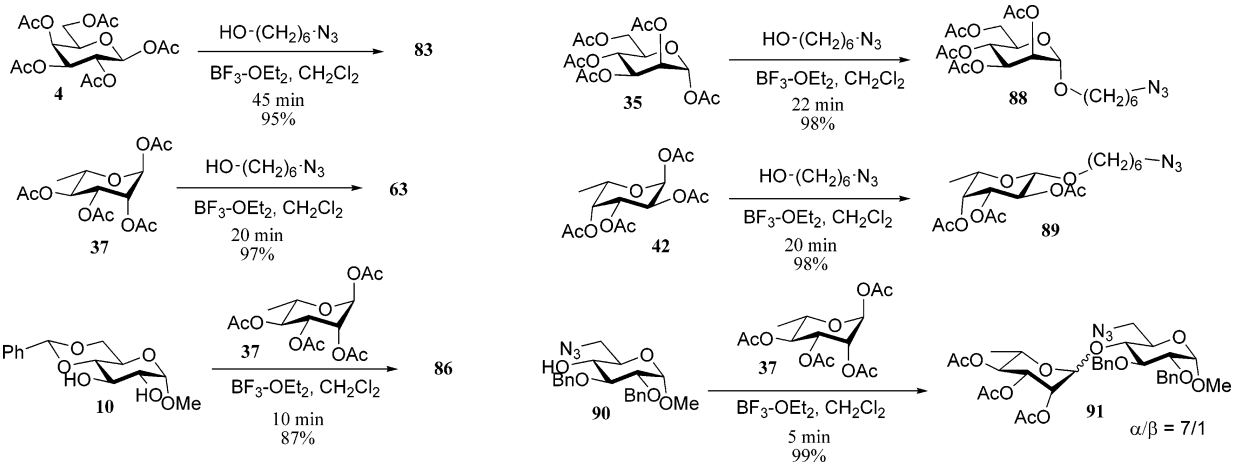
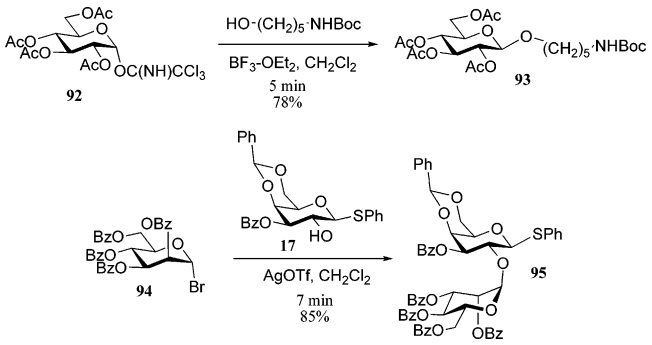
SCHEME 7. Glycosylation with Glycosyl Acetates



SCHEME 8. Glycosylation with Glycosyl Trichloroacetimidate and Glycosyl Halide



quantity, which is advantageous for complex carbohydrate synthesis. Second, phenylthioglycoside is stable in many chemical conditions needed for derivatization of the carbohydrate scaffold, which simplifies the synthesis of carbohydrate analogues, such as unusual sugars. Finally, phenylthioglycoside is known for its relatively lower reactivity as compared to the other glycosyl donors, such as glycosyl trichloroacetimidate and glycosyl halide, especially with the acyl protecting groups attached, which is termed "disarmed" donor. The lower reactivity of "disarmed" donor often results in the difficulty or unsatisfactory yields in glycosylation. Therefore, it will be a great improvement if we can use sonication to carry out glycosylation for such less reactive glycosyl donors, the "disarmed" donors.

The results from sonication-mediated glycosylation are very encouraging. All the examined reactions can be accomplished in minutes with high yield even for the donors of much lower reactivity (Schemes 6−8). Many sulfur-philic reagents have been developed for activating thioglycosides that have various degrees of relative reactivity.[10,18] Nevertheless, the reaction time typically ranges from hours to days, and the yield is often unsatisfactory, especially for "disarmed" donors such as **41** and **45**. In contrast, under standard NIS/TMSOTf condition for the activation of phenylthioglycosides, all the glycosylation can be accomplished in a short time with high yield. Steric hindrance often hampers the success of glycosylation. However, by using sonication, a diglycosylation at sterically hindered *trans*-1,2-diol was achieved in a short time and with excellent yield (Scheme 6, compound **86**). More significantly, the sonication protocol can even work on a much less reactive glycosyl donor, glycosyl acetate (Scheme 7). Most of the examined reactions can be completed in minutes although we do discover that longer reaction time is needed for a larger scale reaction. Finally, as expected, sonication is also applicable for a more reactive donor, glycosyl trichloroacetimidate, **92**, and glycosyl bromide, **94** (Scheme 8).

Conclusion

We have demonstrated that sonication can be an excellent energy source for accelerating a wide variety of organic reactions used for complex carbohydrate synthesis. Our results may lead to the revolutionized developments in this area. It is our belief that sonication can be applied to many other reactions in related areas. For example, sonication can be conveniently applied to the synthesis of complex glycoconjugates, which are decorated by specific terminal carbohydrates, such as mannose, fucose, or sialic acid. By using sonication, a general glycosylation protocol compatible with traditional solution organic synthesis is finally a goal within reach. We have begun to explore the application of using sonication in several advancing topics in organic chemistry. Large-scale applications are also being undertaken.

Experimental Section

General Procedure for Sonication. This general procedure was employed for hydroxy group manipulation (acylation, diol protection, tosylation, deprotection), thioglycoside synthesis, azidoglycoside synthesis, 1,3-dipolar cycloaddition, reductive cleavage of benzylidene, and glycosylation with phenylthioglycosides, glycosyl trichloroacetimidate, and glycosyl bromide. All the studied reactions were performed in the range of 0.1−0.2 g of starting material, according to the reported procedures and molar ratio of the materials in the cited references. The reactions were carried out in a 20 mL vial equipped with a sealed cap. The mixture was sonicated at ambient temperature until complete consumption of starting material (monitored by TLC). (**Caution:** Sonication of reaction for longer times (10 min or longer) may raise the temperature of the reaction vessel and thus increase the pressure inside. If longer reaction time is needed, it is recommended that the reaction vessel should be allowed to cool after sonication every 10 min before the next run.) After the reaction was quenched, the crude products were purified by gradient column chromatography.

General Procedure for Acyl Migration with Sonication. A solution of starting material (0.12 mmol), tetrabutylammonium iodide (TBAI) (4.2 mg, 0.012 mmol), and silver oxide (0.12 mmol) in anhydrous DMF (5 mL) was sonicated at ambient temperature. The reaction was monitored by TLC. When the appearance of byproduct was noted by TLC analysis, the reaction mixture was

subsequently filtered then concentrated. The filtrate was subject to flash column chromatography to yield the desired product.

General Procedure for BF_3-Mediated Glycosylation of Glycosyl Acetate with Sonication. A solution of glycosyl acetate (1 equiv), glycosyl acceptor (1 equiv), and $BF_3{-}OEt_2$ (1 equiv) in anhydrous CH_2Cl_2 (3 mL) was sonicated at ambient temperature until the complete consumption of the starting material (monitored by TLC). The reaction mixture was quenched by addition of $NaHCO_{3(s)}$ then filtered through Celite. The filtrate was subject to flash column chromatography to yield the desired product.

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Supporting Information Available: ^1H and ^{13}C spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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