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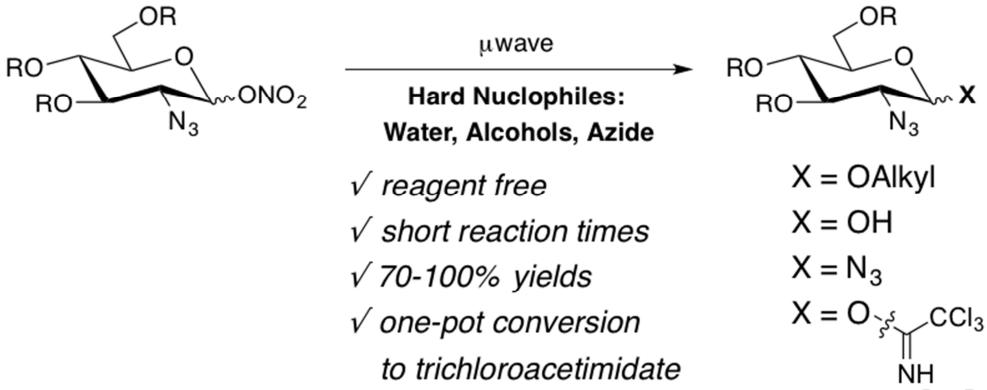

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Direct, Microwave-Assisted Substitution of Anomeric Nitrate-Esters

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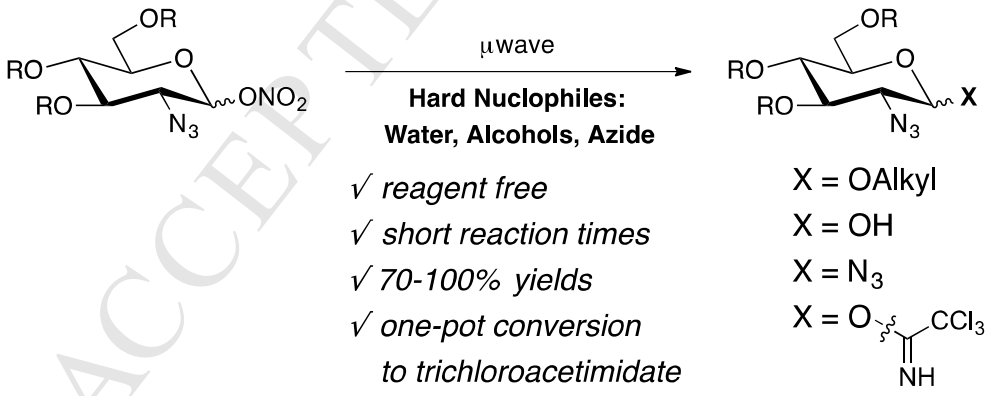
ABSTRACT

A series of carbohydrate 2-azido-1-nitrate-esters, protected at the C-3, C-4, and C-6 positions, were hydrolyzed thermally, under reagent free conditions. This preliminary result was extended to direct exchange of the 1-nitrate-ester modality for alcohol, alkoxy, and azide coupling partners with minimal purification. While direct glycosylation of nitrate esters ultimately proved unsuccessful, we have demonstrated that an anomeric nitrate-ester can be converted directly to a trichloroacetimidate in a short and simple one-pot procedure, bypassing lower-yielding two-step sequences.

GRAPHICAL ABSTRACT



KEY WORDS

Azido-Nitration
Nitrate-Ester
Hydrolysis
Glycosidation
Glycosylation
Trichloroacetimidate

Introduction

The Lemieux azidonitration of protected *O*-glycals is a valuable tool for synthesizing 2-amino-2-deoxy sugars; where the newly installed amino group is masked as an azide.[1-4] In the well-studied event (Figure 1A), a glycal (**1**) is reacted with sodium azide and ceric ammonium nitrate (CAN) in aqueous acetonitrile to produce a 2-azido-1-nitrate-ester (**2**). From this scaffold, a variety of synthetic maneuvers are available to exchange the nitrate-ester for a useful reactive handle (Figure 1B).[3-5] Traditionally, the nitrate-ester is converted to a latent leaving group directly or via the intermediacy of an anomeric alcohol, while the amine is revealed during the deprotection sequence and functionalized (i.e. to an acetamide), if desired.[1, 6-11]

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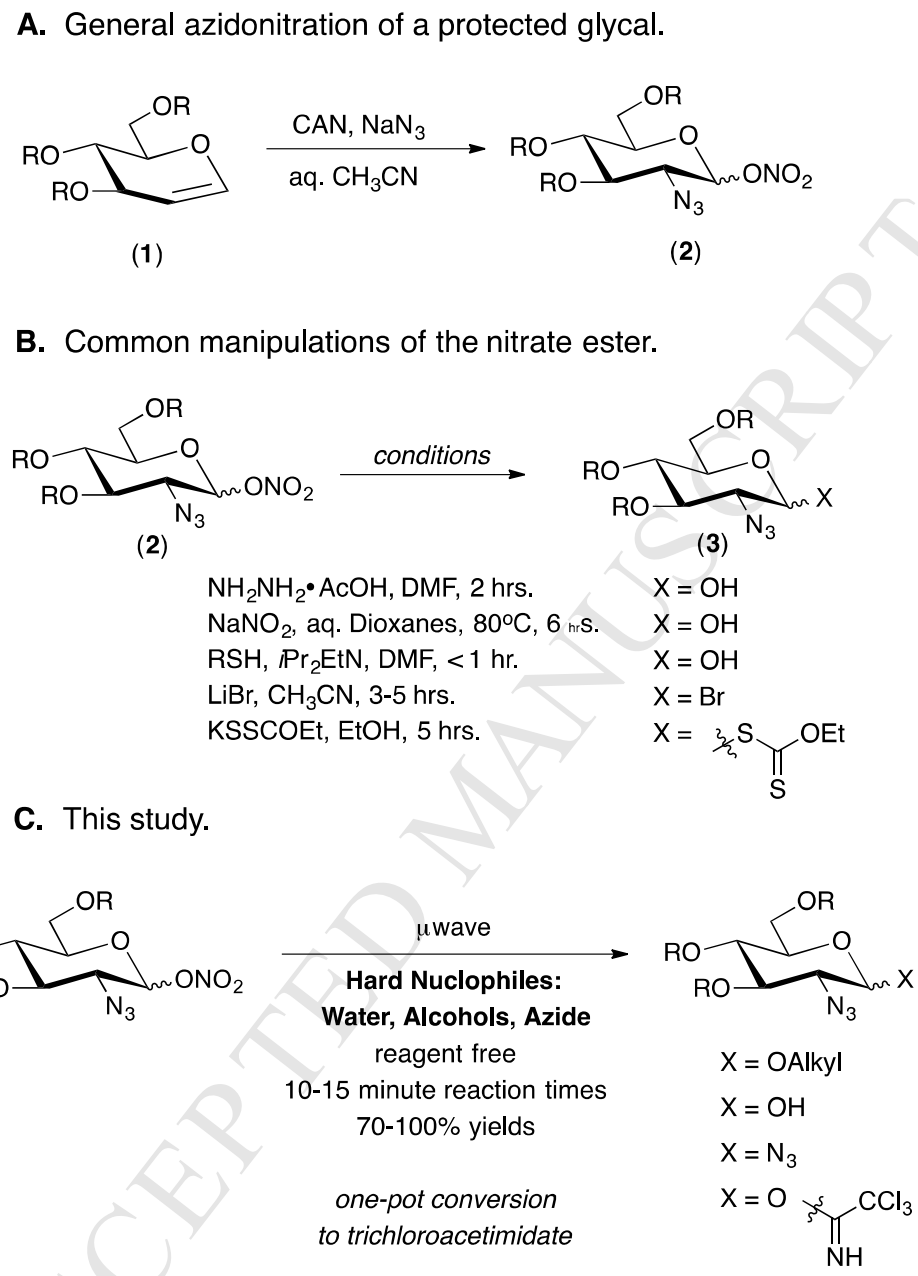

Figure 1. Lemieux's azido-nitration reaction and common manipulations of the nitrate-ester.

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The present study focuses on manipulation of the nitrate-ester and commenced with the observation that converting the group to useful functionality, in theory a trivial synthetic maneuver, is usually accomplished using strong nucleophiles under harsh reaction conditions. From a structural standpoint, we viewed the anomeric nitrate-ester as inherently unstable, a characteristic that should render the group susceptible to reaction under milder conditions. Thus, we hypothesized direct nucleophilic substitution should be feasible if nitrate-esters are treated with nucleophiles at elevated temperatures (Figure 1C).

Results and Discussion

The program commenced by examining the reagent free hydrolysis of a nitrate-ester. We believed successful completion of this reaction would provide an advance to the concept of amino-hydroxylation of glycals, as the reaction could be demonstrated, for the first time, without the use of strong nucleophiles. Moreover, as the reaction would produce nitric acid as a sole by-product, no column chromatography would be required, *vide infra*. The only additive to the reaction is pyridine, which acts as an acid scavenger. Importantly, acid stable substrates undergo reaction without addition of pyridine. In an orienting experiment (Table 1, entry 1) the per-benzylated azido nitrate-ester (**6**) was dissolved in aq. acetone and pyridine, and heated in a microwave reactor at 120 ^{o}C, for 10 minutes. In the event, we observed clean conversion of (**6**) to its corresponding alcohol (**7**) in quantitative yield. Conventional heating by oil bath, to the same temperature, required longer times and was low yielding (not shown). Similarly, the peracetylated azido nitrate-esters (**8**) and (**10**) (entries 2 and 3) were hydrolyzed in reactions that required 15 minutes of heating at 110 ^{o}C to give alcohols (**9**) and (**11**) in quantitative yield with no need for purification. In entry 5, a lactose derivative (**14**) was reacted in order to ensure glycosidic linkages would remain intact after microwave irradiation. Indeed, this substrate was stable to the

short reaction conditions as the alcohol (**15**) was obtained in 95% yield. The next phase of the study focused on exchanging the acetates for acid labile groups (entries 4 - 8) such as acetonides and silyl ethers. Each protective group pattern proved compatible with the reaction conditions, as we were able to observe yields ranging from 86% to greater than >95% yield.

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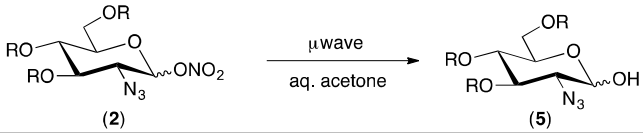
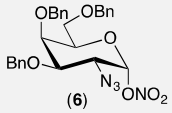
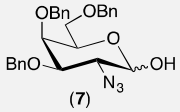
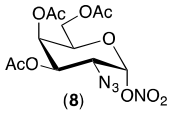
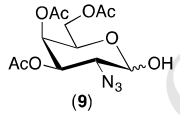
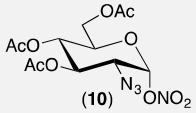
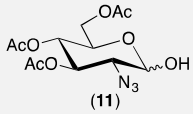
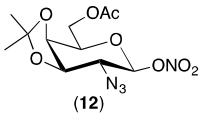
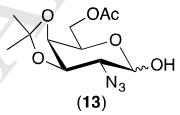
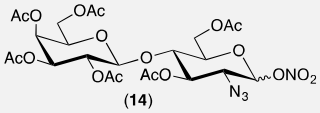
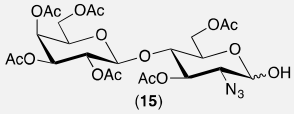
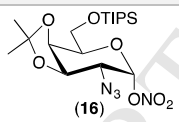
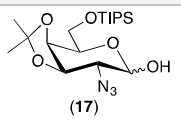
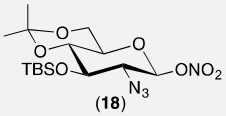
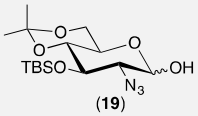
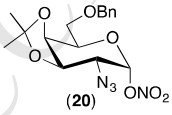
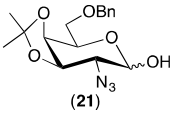
Table 1. Microwave-assisted removal of the nitrate-ester in aqueous solvent.



Entry	Nitrate-ester	Product	Conditions Yield
1	 (6)	 (7)	**120°C 10 min. >95%**
2	 (8)	 (9)	**110°C 15 min. >95%**
3	 (10)	 (11)	**110°C 15 min. >95%**
4	 (12)	 (13)	**100°C 10 min. 86%**
5	 (14)	 (15)	**120°C 10 min. >95%**
6[a]	 (16)	 (17)	**100°C 15 min. 93%**
7[a]	 (18)	 (19)	**120°C 20 min. >95%**
8	 (20)	 (21)	**100°C 15 min. 90%**

General Procedure: A 2-azido-1-nitrate ester (1.0 eq, 0.20 mmol) is dissolved in 20% aq. acetone (2.0 mL) and treated with pyridine (5.0 eq, 1.0 mmol). The reaction is heated by microwave irradiation to 120 °C until the starting material is consumed (usually 10 min.). The reaction mixture is transferred to a separatory funnel, diluted with EtOAc (20 mL) and washed with 1N HCl (1 x 5 mL), water (2 x 5 mL), and brine (1 x 5 mL). The organics are dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the anomeric alcohol as a yellow oil. Of note, other amine and inorganic bases such as triethylamine and sodium bicarbonate work equally well as an acid scavenger. [a]Acetonitrile or THF was used because the substrate was insoluble in acetone.

Mechanistically, nucleophilic attack at nitrogen or oxygen would trigger collapse of the nitrate-ester (Figure 2). Given that oxygen-based nucleophiles are hard bases, we speculated the nucleophile engages at carbon (Pathway B), as it is the harder electrophilic site.[12]

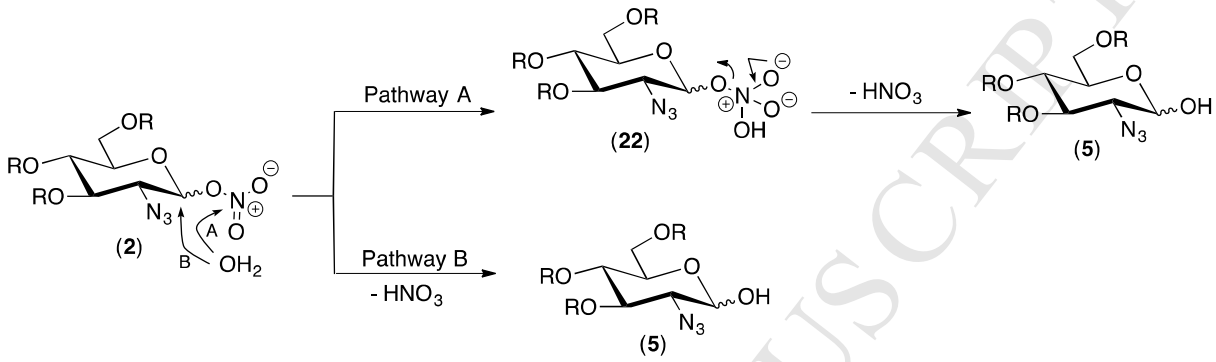


Figure 2. Mechanistic analysis of the azido-nitrate hydrolysis.

Based on this mechanistic analysis, we postulated that if the reaction proceeded through nucleophilic attack at carbon via an Sn1 or Sn2 pathway, the reaction could be extended to direct nucleophilic displacement, glycosidation, or glycosylation of nitrate-esters. Thus, the next step in our study involved evaluating direct reaction of the nitrate-ester with a pool of nucleophiles (Figure 3). In the first reaction, the peracetylated nitrate-ester (**8**) underwent effective methanolysis to provide methyl acetal (**26**) in quantitative yield. Similarly, reaction with isopropanol gave isopropyl acetal (**27**), similarly in quantitative yield. In an interesting reaction, a perbenzylated nitrate-ester successfully underwent substitution with NaN_3 to provide anomeric azide (**28**). This reaction in effect, produces the direct precursor to a 1,2-diamino sugar in a 2-step process from a glycal.[5, 13] Of note is that the reaction proceeds with complete anomeric stereo-control, providing only the β-isomer. As a final mechanistic control, a perbenzylated azido-nitrate ester (**6**) was reacted with NaCN, a soft nucleophile. Based on our analysis that hard nucleophiles attack directly at carbon, we anticipated this soft nucleophile would engage the mole-

cule at the nitrogen center to generate an anomeric alcohol. As expected, the reaction provided a quantitative yield of the previously synthesized hemiacetal (**7**) and no generation of cyanide (**29**).

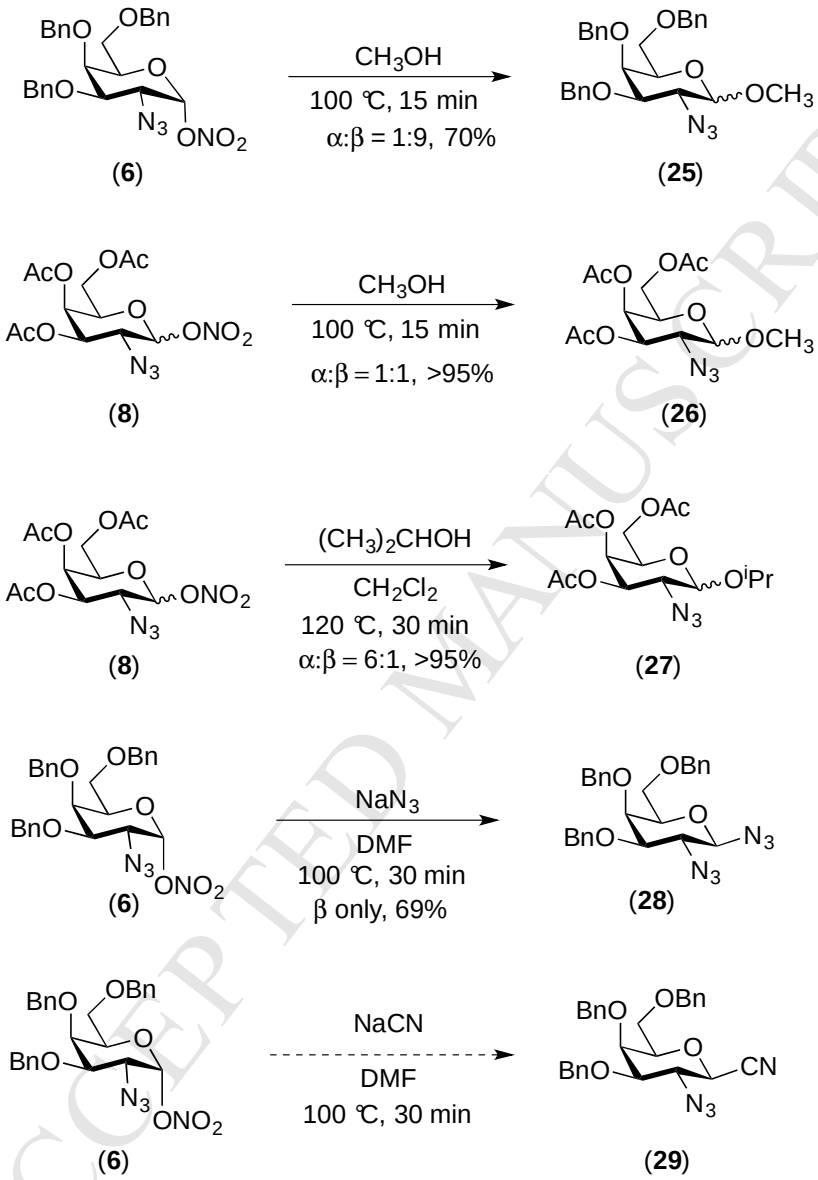


Figure 3. Direct substitution of the anomeric nitrate-ester.

The next segment of the program focused on using glycosyl acceptors as nucleophiles to study the direct glycosylation of a nitrate-ester. From the onset, it was our hope that a successful reaction between these substrates would produce a new glycosidic linkage, thereby enabling the

nitrate-ester to serve as a latent leaving group in glycosylation chemistry. Unfortunately, thorough screening of this reaction never provided the glycosidic linkage in a reasonable yield (Table 2).

A subset of the reaction conditions screened is listed below. The starting point was to use primary alcohol (**30**) as the acceptor in a reaction with nitrate-ester (**6**). As is shown in reaction 1, irradiation with equimolar donor and acceptor failed to generate the desired disaccharide. Extended irradiation for several hours led to polymerization of (**6**). In light of this observation, we moved forward and conducted additional reactions where we used excess amounts of both the donor and the acceptor. Still, only trace amounts of product formation, regardless of reaction conditions, was observed. Ultimately, the only productive system to give any isolable quantity of disaccharide (**31**) was one, which featured a 5:1 ratio of donor (**6**) to acceptor (**30**) in THF. This reaction mixture was heated in the presence of pyridine at 130 ^{o}C for 2 hours to yield 5% of (**31**) alongside unreacted acceptor (**30**) and uncharacterized polymerized byproducts.

In order to change the electronics of the system, a donor featuring electron-withdrawing acetate groups was examined (reaction 2). Additionally, a second donor compound (**33**), was examined (reaction 3). Both systems proved to be resistant to glycosylation.

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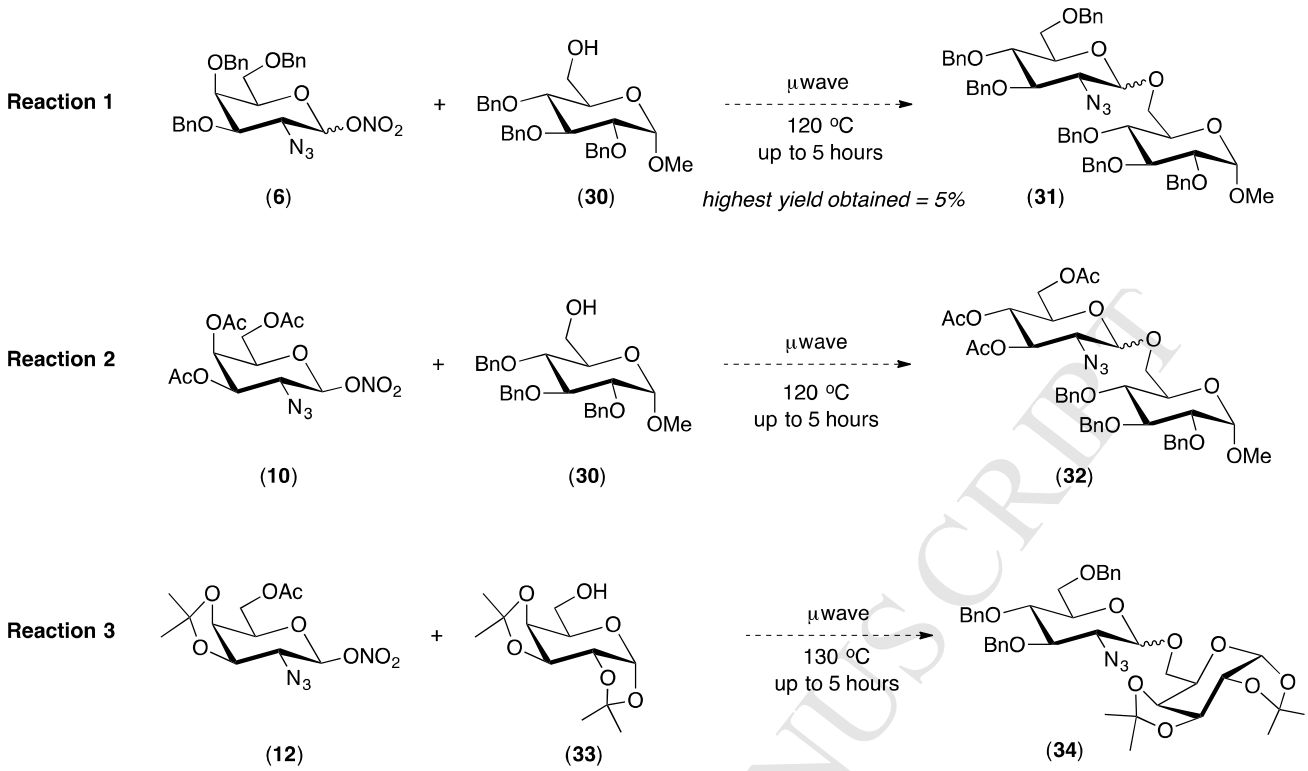

Figure 4. Attempted direct glycosylation of 1-nitrate esters.

Because the direct glycosylation of a nitrate-ester was unproductive, we felt it would be advantageous to use the chemistry described above, to improve on the conversion of a nitrate-ester to a trichloroacetimidate imidate. Typically, this sequence is carried out in a two-step process requiring two individual chromatographic purifications. Using microwave mediated reaction conditions; this transformation can be achieved in quantitative yield using a one-pot procedure shown in Figure 5.

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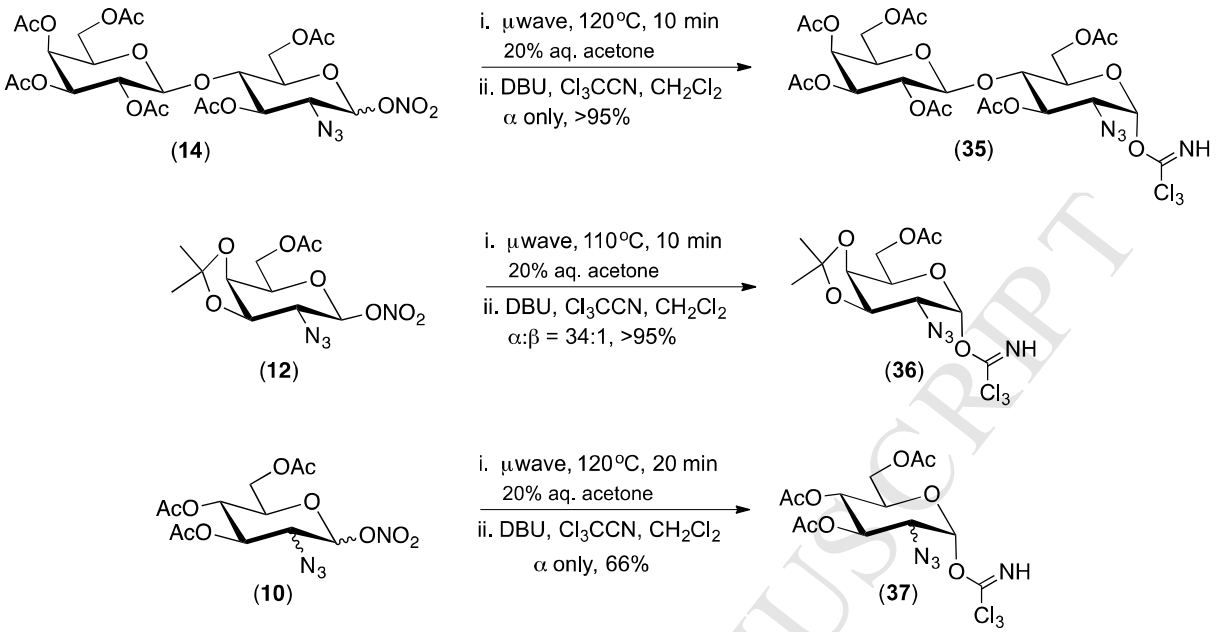

Figure 5. One-pot generation of a trichloroacetimidate glycosyl donor from an anomeric nitrate ester.

Conclusion

To close, we have demonstrated that anomeric nitrate-esters can be readily hydrolyzed or converted into useful building blocks under reagent free conditions. This methodology represents an advance from standard denitration reaction conditions that typically require the use of strongly basic or strongly nucleophilic reagents. These systems are often plagued by loss of product, due to unwanted side reactions. Here, thermal decomposition of the nitrate-ester, when occurring in the presence of water, hard nucleophiles, or alcoholic solvents produces, clean, high yields of the corresponding substituted saccharide with minor purification in short reaction times. While this reaction could not be extended to a useful glycosylation procedure, we were able to use the reaction conditions to quickly achieve a one-pot conversion of the anomeric-nitrate functionality to synthetically useful trichloroacetimidate donors in quantitative yields.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data (including spectra for new compounds). This material is available free of charge via the internet at http://pubs.acs.org

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- Short Reaction Times
- Minimal Reagents
- 70-100% yield
- One-Pot Conversion of a Nitrate-Ester to a Schmidt Imidate

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