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The development of *N*-aryl trifluoroacetimidate-based benzyl and allyl protecting group reagents ☆

Sinele B. Tsabedze [a], Daniel E. K. Kabotso [b], Nicola L. B. Pohl [a,b,*]

[a] Department of Chemistry, Hach Hall, Iowa State University, Ames, IA 50011, USA
[b] Department of Chemistry, Simon Hall, Indiana University, Bloomington, IN 47405, USA

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ABSTRACT

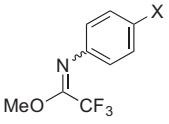
An exploration of the role of *para*-substituents on the balance between stability and reactivity of *N*-phenyl trifluoroacetimidates prompted the discovery of new reagents for the addition of allyl and benzyl protecting groups, namely *O*-allyl and *O*-benzyl *N*-(*p*-nitrophenyl)trifluoroimidates. These compounds are stable and crystalline at ambient temperature, making them ideal alternatives to existing benzylating and allylating reagents used under acidic conditions.

Introduction

The development of protecting group chemistries has allowed the synthesis of increasingly complex structures with dense functional group patterns, especially in the realm of carbohydrate synthesis.[1] Amongst the hydroxyl protecting groups, much effort has been focused on allyl and benzyl groups.[2] Unfortunately, the introduction of these protecting groups often involves employment of harsh acidic/basic conditions that can be problematic when other fragile groups are present in the compound being protected.[2h] Benzylation is one of the more common permanent protecting groups employed in oligosaccharide synthesis owing to its stability under both the acidic and basic conditions employed in typical glycosylation/deprotection reactions. A popular benzylating protocol uses benzyl bromide in the presence of sodium hydride and catalytic tetrabutylammonium iodide (TBAI).[2i] The utility of this reaction is limited when there are already base sensitive functional groups in the substrate such as the acetyl groups. For neutral conditions, benzylation in the presence of silver oxide[2h] can be successful, but the need for freshly prepared silver oxide to make this reaction reliable complicates the procedure. To employ acidic rather than basic conditions, benzyl trichloroacetimidate[2j] has been used, but this reagent usually requires in situ preparation due to its high reactivity. In the realm of glycosylation chemistry, several analogs of *N*-aryl trifluoroacetimidates have been used as glycosyl donors to circumvent the high reactivity of trichloroacetimidates.[3] The advantage of using these donors as opposed to the widely used trichloroacetimidate donors is that they are more stable and still very efficient and can thus be used in conditions where the less stable trichloroacetimidates fail.[3,4] Given these precedents, we decided to explore the possibility of modulating the reactivity of *N*-phenyl trifluoroacetimidates to find a balance between the stability and reactivity of this leaving group for use in reagents designed for benzylation and allylation reactions. Herein we report structure/function studies with these *N*-phenyl trifluoroacetimidates and the discovery of a leaving group that provides stable and crystalline reagents for the facile addition of benzyl and allyl groups under acidic conditions.

Methods

To find a more stable acetimidate, a systematic method to investigate the effect of changing a *para*-substituent on the



1 X = NO_2 (90%)
2 X = Cl (87%)
3 X = H (89%)
4 X = OMe (90%)

Figure 1. Synthesis yields of *para*-substituted *O*-methyl *N*-aryl triflouroacetimidates.

* Corresponding author. Tel.: +1 812 855 0298; fax: +1 812 855 8300.
E-mail address: npohl@indiana.edu (N.L.B. Pohl).

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N-phenyl group on the stability of the acetimidate under acidic conditions was sought. To start the study, a variety of *N*-phenyl trifluoracetimidates were made attached to methanol rather than benzyl for simplicity in the analysis by ^{1}H NMR (Fig. 1). Methyl 2,2,2-trifluoro-*N*-aryl acetimidates were synthesized by reacting methyl alcohol with *N*-aryl trifluoroacetimidoyl chlorides[5] under basic conditions. Several bases such as NaOMe, NaH, and K_2CO_3 were tested for their viability in this synthesis; K_2CO_3 was ultimately chosen for its ease of use while maintaining excellent (85–90%) yields.

After synthesis and subsequent purification of each compound **1**–**4**, a sample of 40 μmol of acetimidate was treated to 2% trifluoroacetic acid in DMSO-d_6 and allowed to react over the course of at least 120 min. Recordings of the reaction were taken by ^{1}H NMR every 5 min to determine which donor maintained the integrity of its structure the longest. The rate of transformation was quantified as the percent acetimidate peak divided by the total amount of aromatic peaks (starting material and product aromatic peaks). The difference between the aromatic peaks of the imidate and the degraded product is very distinct, making it very easy to quantify the rate of transformation (see Fig. 2).

Results and discussion

The percent imidate peak was plotted against time to get exponential graphs resembling Figure 3 below. From such graphs, the comparative rates of degradation were obtained. A comparison of nitro-substituted acetimidate **1** to the other analogs showed marked stability under acidic conditions. Compound **1** formed needle-like light yellow crystals at ambient temperature.

Given the superior stability of nitro-substituted *N*-phenyl trifluoroacetimidate, presumably because of the inductive effect of the electron-withdrawing group making nitrogen less basic, we next tested its reactivity as a leaving group in the context of a benzylation reaction. Obviously, to be a successful leaving group, the substituted *N*-phenyl trifluoracetimidate could not be too stable and thereby require harsh conditions for its transfer to a hydroxyl as a protecting group. A benzylating agent using the unsubstituted *N*-phenyl trifluoroacetimidoyl had already been reported,[2d] but this reagent, like its trichloroacetimidate counterpart,[2e,k] is also

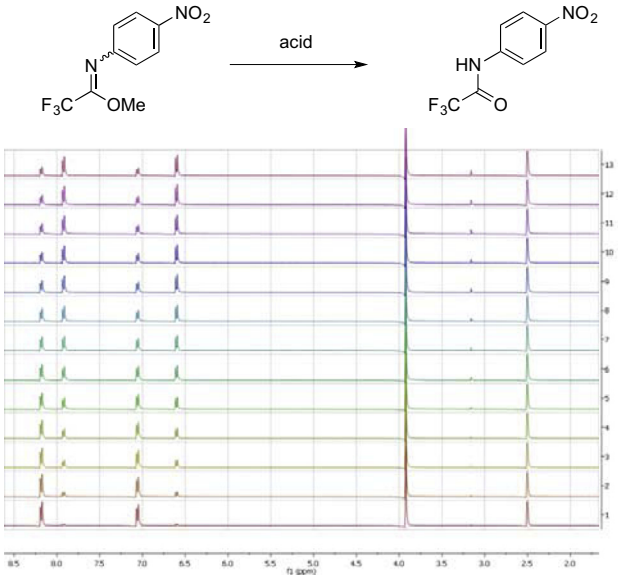


Figure 2. ^{1}H NMR depicting the change in structure of acetimidate **1** under acidic conditions.

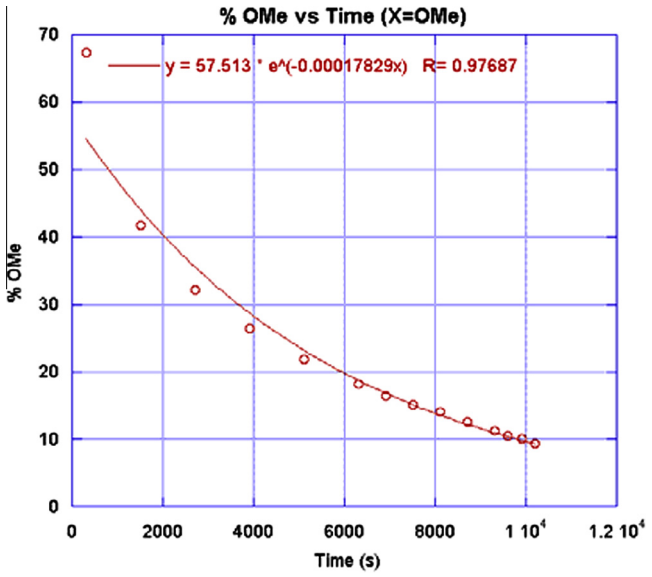


Figure 3. An example of a graph showing the % imidate aromatic peaks by ^{1}H NMR over time for compound **4**. Additional graphs are available in the Supplementary data.

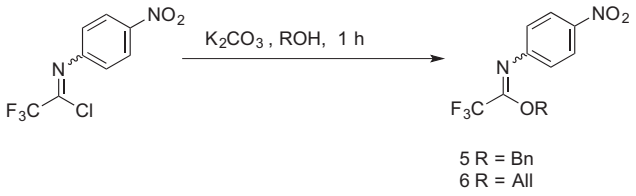


Figure 4. Synthesis of benzyl and allyl *N*-(nitrophenyl) trifluoroacetimidates.

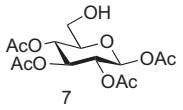
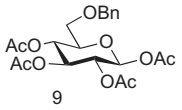
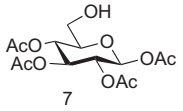
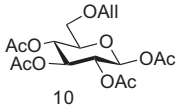
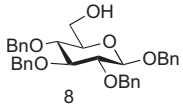
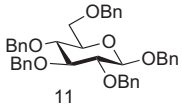
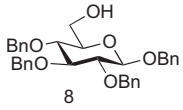
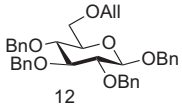
not particularly stable and therefore requires in situ preparation or stringent storage conditions. Prompted by the superior stability of nitro derivatives in the simple methanol study above, benzyl derivative **5** was synthesized in excellent (>90%) yield (Fig. 4). Interestingly, the reagent was crystalline and proved to be stable at ambient temperature for at least 10 days—properties that could make it more viable for commercial production than benzyl trichloroacetimidate.

An initial trial reaction showed that the new nitro-derivative **1** could indeed serve as a benzylation reagent. Given this promising initial data, allyl version **6** was also made. The reaction also proceeded in excellent yield to provide a crystalline product. These two new reagents were then used in reactions to protect alcohols **7** and **8**, representative of deactivated and activated carbohydrate hydroxyls, to form the known products **9**,[6a] **10**,[6b] and **11**,[6c] and the new product **12**. The benzylation and allylation reactions were first tried with $Zn(OTf)_2$ and $Yb(OTf)_2$. Though successful, the yields in these conditions were not satisfactory (~60%) compared to later reactions with TMSOTf (Table 1). All reactions were complete within 1 h compared to longer traditional methods and the yields were improved compared to using the less stable trichloroacetimidates.

Conclusion

After comparative monitoring of the rates of reaction associated with different *para*-substituents on *N*-aryl trifluoroacetimidates, the nitro-substitution was found to provide a perfect balance between stability and reactivity to aid in the development of a new reagent for the addition of benzyl and allyl protecting groups. These benzylating and allylating reagents are crystalline and stable

Table 1
Reactions of 1.2 equivalents *O*-allyl and *O*-benzyl *N*-(nitrophenyl)trifluoroimidates with different alcohols using catalytic amounts of TMSOTf as a promoter

Alcohol	Imidate	Product	Yield (%)
 7	**5**	 9	83
 7	**6**	 10	80
 8	**5**	 11	85
 8	**6**	 12	81

All reactions were complete within 1 h using CH_2Cl_2 as the solvent.

at ambient temperatures for days, thereby simplifying their use, and react with alcohols in high yields with catalytic amounts of TMSOTf comparable to the less stable allyl and benzyl trichloroacetimidate reagents. These new reagents should thereby provide attractive alternatives to the standard trichloroacetimidate reagents for acid-catalyzed additions of benzyl and allyl protecting groups.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.014.

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