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Note

Indium triflate catalyzed peracetylation of carbohydrates

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Abstract—Peracetylation is a very common protection strategy that is widely implemented in carbohydrate synthesis. Here, a method for the peracetylation of carbohydrates using catalytic $In(OTf)_3$ in neat acetic anhydride is reported. $In(OTf)_3$ has low toxicity and is mild and water tolerant, and the reactions are high yielding and efficient. Details regarding the scope and mechanism of the reaction are briefly discussed.

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Acetylation reactions are among the most common transformations in organic synthesis, and acetylation of monosaccharides is often the first step in the synthesis of complex carbohydrates. The peracetylation of sugars is most often performed using acetic anhydride and DMAP in pyridine.¹ Although this reaction works well, long reaction times (12 h) are required and pyridine is high boiling and noxious.

Numerous ways to avoid the use of pyridine in acetylation reactions have been devised. Some notable examples include the use of catalytic TMSOTf in $CH_2Cl_2^2$ and of catalytic Bu₃P in CH_2Cl_2 .³ Use of acetic anhydride as both the solvent and the acylating reagent has been demonstrated using a wide variety of catalysts including sodium acetate,⁴ montmorillonite K-10,⁵ molecular sieves,⁶ iodine,⁷ FeCl₃,⁸ 3-nitrobenzeneboronic acid,⁹ LiClO₄,¹⁰ HClO₄–SiO₂,¹¹ CuSO₄·5H₂O,¹² acetonyltriphenylphosphonium bromide,¹³ H₁₄[Na-P₅W₃₀O₁₁₀],¹⁴ La(NO₃)₃·6H₂O,¹⁵ and Mg(NTf₂)₂.¹⁶ Metal triflate catalysis of acetylation reactions has been reported using Cu(OTf)₂,¹⁷ Bi(OTf)₃,¹⁸ V(O)(OTf)₂,¹⁹ Sc(OTf)₃,²⁰ Ce(OTf)₃,²¹ and In(OTf)₃.²²

Most of the conventional metal salts that are used as Lewis acids are water sensitive and are often used in stoichiometric amounts. Metal triflates are an attractive alternative because of their low toxicity and non-corrosive nature.²³ Yamamoto's report of acetylation reactions using catalytic $Sc(OTf)_3$ in CH₃CN generated high interest in the area of metal triflate catalyzed acetylations.²⁴ In(OTf)₃ is a mild, water-tolerant Lewis acid that can be used in catalytic quantities for a variety of organic transformations.²⁵ Because In(OTf)₃ is considerably less expensive than Sc(OTf)₃, we are interested in its development as a catalyst for acetylation reactions. Frost reported the acetylation of alcohols and amines in acetonitrile using 0.1 mol % In(OTf)₃, but a chromatographic purification step was required and only one carbohydrate was evaluated.²² Here, we report the In(OTf)₃ catalyzed peracetylation of carbohydrates under solvent-free conditions.

We found that 0.05 equiv of $In(OTf)_3$ catalyzed the peracetylation of a number of sugars in acetic anhydride when the reactions were stirred for 1 h at 0 °C. The results are summarized in Scheme 1. For reaction workup, ethyl acetate was added to the flask and a 10% aqueous solution of Na₂CO₃ was added. After stirring for 20 min to 1 h to hydrolyze any unreacted acetic anhydride, the organic layer was collected and concentrated. The

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Scheme 1. $In(OTf)_3$ catalyzed peracetylation of carbohydrates. Conditions: $In(OTf)_3$ (0.05 equiv) in Ac₂O (30 equiv), 1 h, 0 °C (reactions 1–5) or 0 °C to rt (reactions 6 and 7).

crude products were normally of sufficient purity to be used without further purification. The reactions using lactose or *N*-acetyl glucosamine were warmed to room temperature because of the low solubility of the substrates in acetic anhydride at low temperature (reactions 6 and 7 in Scheme 1).

The compatibility of the $In(OTf)_3$ catalyzed peracetylation reactions with a number of commonly used protecting groups was explored. The benzylidene acetal and the TBDPS ether were stable to the reaction conditions (Scheme 2), but TMS and TBS groups were readily



Scheme 2. Protecting group compatibility studies.

hydrolyzed (and the corresponding acetylated sugars were obtained).

Investigation into the mechanism of the indium triflate catalyzed acetylation suggests that triflic acid is the active catalytic species. Acetylation of galactose occurred rapidly using 0.05 equiv of triflic acid (Table 1. entry 1). However, the reaction does not proceed when 2,6-di-tert-butylpyridine (DTBP) is added with In(OTf)₃, nor does acetylation occur when glucosamine is used as the substrate in a 1 h reaction (Table 1, entries 2-4). Thus, our results suggest that indium triflate can be used to provide low levels of triflic acid. Dumeunier and Markó observed a similar triflic acid mediated acylation using scandium triflate in a benzoylation procedure,²⁶ and free acid has also been proposed as the active catalyst in metal triflate mediated Friedel-Crafts reactions.²⁷ Loh and co-workers capitalized on the lability of the triflate on indium when forming chiral indium(III)-pybox complexes.²⁸ When we allowed our In(OTf)₃ catalyzed reaction with DTBP to stir at room temperature for one day, an 11% yield of peracetylated product was obtained (Table 1, entry 2). This result indicates that an indium triflate mediated reaction pathway may also be possible but is much slower than the triffic acid-catalyzed process. A similar dual pathway process has been proposed by Dumeunier and Markó for Sc(OTf)₃.²⁶

To further explore the role of the catalyst in the acetylation reactions, we investigated the effect of the choice of ligand on the behavior of the catalyst in the reaction. We compared In(OTf)₃ to InCl₃ and InBr₃. The acetylation of alcohols using indium chloride and ruthenium chloride catalysts has been reported previously.²⁹ RuCl₃ catalyzed reactions worked well without solvents for liquid substrates and were also successful for substrates compatible with acetonitrile (and slower in dichloromethane, chloroform, and tetrahydrofuran). Acetylations with carbohydrates were not explored.^{29a} InCl₃ catalyzed reactions were performed with only a small amount of catalyst and only one equivalent of Ac₂O at room temperature, and peracetylation of glucose was reported.^{29b} However, acetylation of glucose at 0 °C in our labs required 12 h using 0.05 equiv of InCl₃ (Table 1, entry 5). InCl₃ is a less reactive catalyst, and In(OTf)₃ may be better suited for acetylations performed below room temperature. InBr₃ catalyzed the acetylation of glucose at room temperature as shown in Scheme 1 (Table 1, entry 6). Thus, although InCl₃ and InBr₃ both effect the desired acetylation, the reactions are considerably slower with these catalysts than with In(OTf)₃. Our results indicate that the strength of the respective acids that are generated from the catalysts (TfOH, HBr, and HCl) correlates well with the reaction rate.

Overall, we found that carbohydrates that were soluble in acetic anhydride could be peracetylated very effec-

Table 1. Catalyst comparison^a

Entry	Substrate	Catalyst (equiv)	Time	Yield (%)
1	HO OH HO HOOH	TfOH (0.05 equiv)	10 min	84
2	HO HO HOOH	$In(OTf)_3$ (0.05 equiv) with DTBP ^b	24 h ^c	11
3	HO HO HOOH	$In(OTf)_3$ (0.05 equiv) without DTBP	1 h	99
4	HOO HOO HO	In(OTf) ₃ (0.05 equiv)	1 h	N.R. ^d
5	HO HO HOOH	InCl ₃ (0.05 equiv)	12 h	71
6	HO HO HO HO HO	InBr ₃ (0.05 equiv)	6 h ^c	86

^a Reactions were performed in 30 equiv Ac₂O.

^b DTBP = di-*tert* butylpyridine.

 $^{\circ}0 \,^{\circ}C$ to rt; all other reactions 0 $^{\circ}C$.

^d N.R. = no reaction.

tively using the $In(OTf)_3$ -mediated reaction conditions described in this report. Acetylation of sugars such as sorbose and fructose that were insoluble in acetic anhydride could not be performed using this methodology. Carbohydrates are also generally insoluble in solvents such as acetonitrile that are commonly reported for $In(OTf)_3$ -mediated acetylation of simple alcohols. Although smaller amounts of acetic anhydride could be used for the peracetylation of carbohydrates, we found reactions with 30 equiv of Ac_2O to be most convenient, and excess anhydride is easily removed using the described workup procedure.

In addition to the peracetylation reaction, the use of $In(OTf)_3$ to catalyze benzoylation reactions with carbohydrates was also briefly explored. Unfortunately, because benzoyl anhydride is a solid, solvent would be required for an analogous benzoylation reaction. Frost's work indicated that acetonitrile would be an appropriate solvent in which to invoke this transformation,²² but the low solubility of carbohydrate substrates in acetonitrile precluded product formation. In DMF, benzoyl protection of 1-methyl glucoside was performed using 0.05 equiv of In(OTf)₃ and 10 equiv of benzoyl anhydride at room temperature for 12 h, affording a 50% yield of fully benzoyl-functionalized 1-methyl glucoside.

Microwave irradiation to improve carbohydrate solubility in the perbenzoylation reactions was also evaluated. The use of microwave irradiation in glycosylations and in protecting group manipulations for carbohydrates has recently been reviewed.³⁰ We evaluated reactions using glucose and 10 equiv of benzoyl anhydride in acetonitrile with 0.05 equiv of $In(OTf)_3$. At temperatures ranging from 25 °C to 100 °C and with irradiations of 150 W to 300 W (all for 5 min), we were unable to achieve sufficient solubilization of substrates, and product formation was not observed.

We next tested microwave irradiation of the In(OTf)3catalyzed peracetylation reactions. Microwave conditions have been successfully applied by Limousin and co-workers to peracetylations using ZnCl₂, potassium acetate, or sodium acetate in acetic anhydride.³¹ An InCl₃-catalyzed peracetylation reaction using microwave irradiation in acetonitrile was reported by Das and coworkers.³² We found that the reactions that were performed according to our protocol described above (5 mol % In(OTf)₃, 1 h, 0 °C, neat acetic anhydride) could also be performed under microwave irradiation. We irradiated mannose and N-acetyl glucosamine for 5 min at room temperature in a sealed tube with 150 W to afford peracetylated products (Scheme 3). Although the yields we obtained were lower than those obtained without microwave irradiation, our results suggest that, with additional optimization, microwave irradiation could be used to successfully perform the transformations shown in Scheme 1. Reactions that were unsuccessful without microwave irradiation due to the insolubility of the sub-



Scheme 3. Peracetylation using microwave conditions.

strates in acetic anhydride were equally unsuccessful when irradiated.

In summary, the $In(OTf)_3$ -catalyzed peracetylation of carbohydrates in acetic anhydride works well for many carbohydrates. The new reaction conditions eliminate the need for unpleasant solvents such as pyridine, and $In(OTf)_3$ has the advantage of being affordable, nontoxic, and non-corrosive.

1. Experimental

1.1. General peracetylation procedure

Carbohydrate was added to Ac_2O (30 equiv), and the solution was cooled to 0 °C. $In(OTf)_3$ (0.05 equiv) was added, and the reaction was allowed to warm to room temperature while stirring for 1 h. EtOAc and 10% aqueous Na₂CO₃ solution were added, and the mixture was stirred for 1 h. Isolation of the organic layer, washing twice with satd aq NaHCO₃ solution, drying over MgSO₄, and removal of solvent in vacuo afforded the product.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres. 2008.04.009.

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