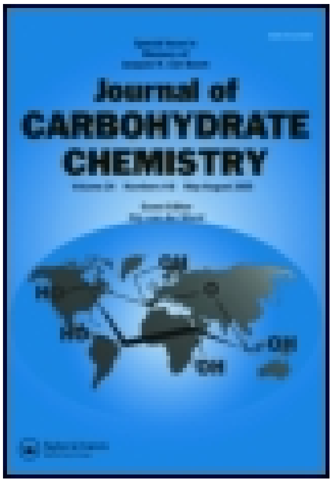

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Samarium Trifluoromethanesulfonate: An Efficient Moisture Tolerant Acylation Catalyst under Solvent-Free Condition

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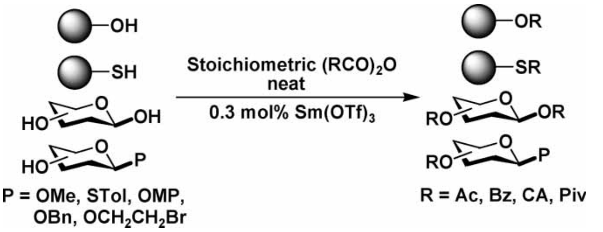
Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow, India

Samarium trifluoromethanesulfonate catalyzed the acylation of phenols, alcohols, thiols, free reducing sugars, and glycosides in excellent yields at ambient temperature under solvent-free condition using stoichiometric amounts of various anhydrides.



Keywords Acylation, Solvent free, Sugar acetates

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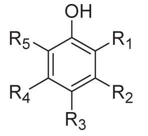
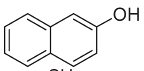
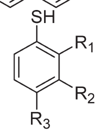
Address correspondence to Balaram Mukhopadhyay, Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, India. Present address: Indian Institute of Science Education and Research-Kolkata HC-7, Sector-III, Salt Lake City, Kolkata-700106, India. E-mail: sugarnet73@hotmail.com

Total synthesis of multifunctional targets often needs protection of a particular functionality in the presence of other functional groups; for example, phenols, alcohols, or thiols need protection since they are susceptible to other functional group transformations. Acetylation of such functional groups for temporary protection is very common in organic synthesis. Normally, acetylation is achieved by acylation with acetic anhydride in the presence of a suitable catalyst.[1] There is a plethora of catalysts reported in the literature that highlights the importance of this particular transformation.[2] However, many of these methods suffer from one or more of the following drawbacks: lack of atom economy (requirement of large excess of reagents), longer reactions and stringent conditions, difficulty of handling due to moisture sensitivity, use of highly toxic and/or expensive reagents, lack of compatibility with various protecting groups, etc. Therefore, the search for a suitable cost-effective catalyst that can be used under mild and stoichiometric conditions is far from over. In continuation of our effort toward simplifying organic reactions, here we report the successful use of samarium trifluoromethanesulfonate [$Sm(OTf)_3$] as a catalyst for acetylation of a range of phenols, alcohols, thiols, free reducing sugars, and glycosides using stoichiometric acetic anhydride.

Metal triflates have earned a great deal of attention as catalyst for acylation reactions.[3] Use of $In(OTf)_3$,[4] $Bi(OTf)_3$,[5] $Ce(OTf)_3$,[6] $Er(OTf)_3$,[7] LiOTf,[8] and $Cu(OTf)_2$[9] are already reported in the literature. However, all of them are either moisture sensitive or require excess reagents and other solvents for successful transformation. Although $Cu(OTf)_2$[10] has recently been used under stoichiometric conditions, moisture sensitivity of the catalyst is detrimental for large-scale preparations. On the other hand, $Sm(OTf)_3$ is known to be moisture tolerant[11] and thus attracts our attention to explore its catalytic activity for acylation reactions. We used 0.3 mol% of $Sm(OTf)_3$ in the reaction-unactivated phenol (e.g., 2-napthol) or electron-deficient phenol (e.g., *p*-nitrophenol) with stoichiometric Ac_2O under neat conditions at rt to afford the corresponding acetates in 95% and 97% yields, respectively. After complete conversion of the starting material, the reaction mixture was quenched with saturated aq. $NaHCO_3$ and the product was extracted with ether. General procedure for acetylation of phenols, alcohols, and thiols: To a slurry of the starting material (1 mmol) in Ac_2O (1 mmol for mono-ols and 2 mmol for di-ol), $Sm(OTf)_3$ (0.3 mmol) was added and the mixture was allowed to stir at rt until TLC (10:1 hexane-EtOAc) showed complete conversion of the starting material (Tables 1 and 2). Then saturated aq. $NaHCO_3$ was added to the reaction mixture until effervescence stopped. The whole mixture was transferred to separating funnel and the product was extracted with Et_2O (2×10 mL). Combined ethereal solution was dried (Na_2SO_4) and evaporated in vacuo to afford pure products (yields reported in Tables 1 and 2). Use of other solvents such as CH_3CN, CH_2Cl_2, CH_3NO_2, or

Table 1: $Sm(OTf)_3$-catalyzed solvent-free *O*-acetylation of phenols and thiols with stoichiometric acetic anhydride.[a]

Entry	Substrate	Time (min)	Yield
			
1	$R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OMe$	10	98%
2	$R_1 = R_2 = R_4 = R_5 = H$, $R_3 = COMe$	10	97%
3	$R_1 = R_3 = R_5 = H$, $R_2 = OH$, $R_4 = CO_2Me$	10	94%
4	$R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Cl$	15	99%
5	$R_2 = R_3 = R_4 = R_5 = H$, $R_1 = Cl$	15	98%
6	$R_1 = R_3 = R_4 = R_5 = H$, $R_2 = Cl$	15	96%
7	$R_2 = R_3 = R_4 = R_5 = H$, $R_1 = OH$	15	97%
8	$R_2 = R_3 = R_4 = R_5 = H$, $R_1 = Allyl$	10	99%
9	$R_2 = R_4 = R_5 = H$, $R_1 = Br$, $R_3 = Cl$	15	95%
10	$R_1 = R_4 = R_5 = H$, $R_2 = F$, $R_3 = NO_2$	10	98%
11	$R_2 = R_4 = H$, $R_1 = R_3 = R_5 = Me$	10	97%
12		15	96%
			
13	$R_1 = R_2 = R_3 = H$	15	97%
14	$R_1 = R_3 = H$, $R_2 = Me$	15	98%
15	$R_1 = R_2 = H$, $R_3 = Me$	15	96%

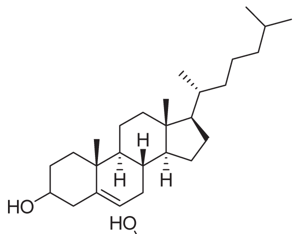
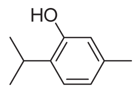
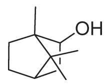
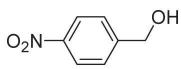
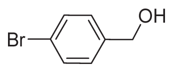
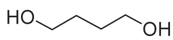
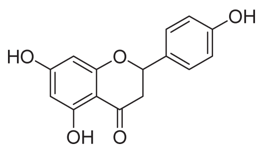
[a] With 1.0 molar equivalent of Ac_2O per hydroxyl group, 0.3 mol% of $Sm(OTf)_3$.

Et_2O was proved to be detrimental to the catalytic activity as the yields dropped to 20% to 30% after 1 h at rt with stoichiometric Ac_2O.

To explore the generality, structurally diverse phenols and thiols were subjected to acetylation under same reaction conditions (Table 1). The catalyst was proved to be compatible with variety of functional groups, such as OMe, NO_2, Cl, Br, F, COMe, and CO_2Et that are capable of complex formation and side reactions. Phenolic diols also transformed to the corresponding diacetate in excellent yield with 2 mol equivalent of Ac_2O.

Next, alcohols including benzylic also efficiently transformed to the corresponding acetates by $Sm(OTf)_3$-catalyzed acylation in neat Ac_2O. Target compounds were obtained in excellent yields without any side reactions such as dehydration or rearrangement (Table 2). It is worth noting that some of the solid substrate didn't dissolve in stoichiometric Ac_2O to start with, but after addition of the catalyst the reaction started immediately and the mixture turned liquid gradually.

Table 2: $Sm(OTf)_3$-catalyzed solvent free *O*-acetylation of phenols and thiols with stoichiometric acetic anhydride.[a]

Entry	Substrate	Time (min)	Yield
1		20	95%
2		15	97%
3		15	96%
4		25	94%
5		15	98%
6		15	96%
7		25	96%

[a]With 1.0 molar equivalent of Ac_2O per hydroxyl group, 0.3 mol% of $Sm(OTf)_3$.

Successful exploration of the catalytic activity of $Sm(OTf)_3$ for acylation of phenols, thiols, and alcohols prompted us to investigate its applicability for per-*O*-acetylation of free sugars. Thus, D-glucose was subjected to acylation with 5 mol equivalent of Ac_2O and 0.3 mol% $Sm(OTf)_3$ at rt. The exothermic reaction was started immediately leading to the per-*O*-acetylated compound in 98% yield as anomeric mixture within 30 min. Other monosaccharides also gave excellent yield of the corresponding per-*O*-acetates (Table 3). Deoxy sugars (rhamnose and fucose) and pentoses (arabinose and xylose) were reacted even faster than pyranoses. For disaccharides, initial heating at 80°C was necessary for rapid transformation presumably for the low reactivity of the sugars. After complete conversion of the starting material (TLC), saturated aq. $NaHCO_3$ was added to the reaction mixture and the product was extracted with CH_2Cl_2. General procedure for per-*O*-acetylation of free sugars and glycosides: In case of free sugars and glycosides, 1 mol equivalent

Table 3: $Sm(OTf)_3$-catalyzed solvent-free per-*O*-acetylation of sugar alcohols with stoichiometric acetic anhydride and catalytic $Sm(OTf)_3$.[a]

Entry	Sugar	Product	Time (min)	α/β	Yield
1	D-glucose	D-glucopyranose penta-acetate (**1**)	30	11:1	96%
2	D-galactose	D-galactopyranose penta-acetate (**2**)	30	11:1	97%
3	D-mannose	D-mannopyranose penta-acetate (**3**)	25	3:1	99%
4	L-rhamnose monohydrate	L-rhamnopyranose tetraacetate (**4**)	15	4:1	98%
5	L-fucose	L-fucopyranose tetraacetate (**5**)	15	10:1	97%
6	L-arabinose	L-arabinopyranose tetraacetate (**6**)	15	9:1	96%
7	D-xylose	D-xylopyranose tetra-acetate (**7**)	15	5:1	98%
8	D-maltose monohydrate[b]	D-maltose octa-acetate (**8**)	45	10:1	92%
9	D-lactose[b]	D-lactose octa-acetate (**9**)	45	10:1	93%
10	D-cellobiose[b]	D-cellobiose octa-acetate (**10**)	45	10:1	90%

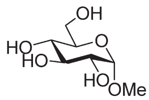
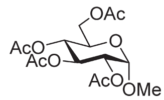
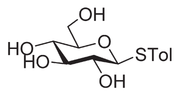
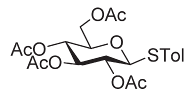
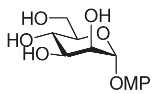
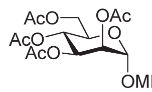
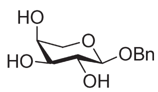
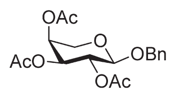
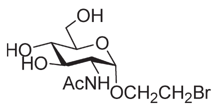
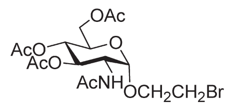
[a]With 1.0 molar equivalent of Ac_2O per hydroxyl group, 0.3 mol% of $Sm(OTf)_3$.
[b]In the cases of L-rhamnose and D-maltose, an additional 1 molar equivalent of Ac_2O was necessary since these sugars are commercially available only as monohydrates.

of Ac_2O per hydroxyl group has been used (for rhamnose and maltose, an extra 1 mol equivalent of Ac_2O was added since these are commercially available as monohydrates only). The remaining procedure is the same as above except CH_2Cl_2 was used as extracting solvent instead of Et_2O. Compounds obtained after evaporation of the solvent were sufficiently pure as determined by NMR and mass spectrometry.

To further per-*O*-acetylation of free sugars, various glycosides were also subjected to $Sm(OTf)_3$-catalyzed acylation in neat Ac_2O. Variety of glycosides such as methyl-, thio-, *p*-methoxyphenyl, benzyl, and 2-bromoethyl are proved to be compatible with this system (Table 4). All of them gave desired *O*-acetylated compounds in excellent yield. It is worth noting that protecting groups such as TBDMS, *p*-methoxybenzyl, benzylidene, or isopropylidene acetals did not stand in this condition. $Sm(OTf)_3$-catalyzed acetylation of substrates having these protecting groups resulted a complex mixture of degraded products.

Next, other acylating agents such as chloroacetic anhydride, benzoic anhydride, and pivalic anhydride were used for acylation of different alcohols, phenols, and sugars. Chloroacetylation of *p*-hydroxyacetophenone with a stoichiometric amount of chloroacetic anhydride proceeded smoothly to completion at rt in 30 min. For benzoylation with a stoichiometric amount of benzoic anhydride, heating at 80°C was necessary for complete conversion as the phenyl group reduced the electrophilic character of the carbonyl carbon of benzoic anhydride. Reactions with a stoichiometric amount of pivalic anhydride proceeded smoothly at rt, giving excellent yield. Results of these reactions are

Table 4: $Sm(OTf)_3$-catalyzed solvent-free per-*O*-acetylation of different glycosides with stoichiometric acetic anhydride.[a]

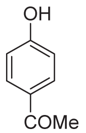
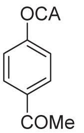
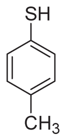
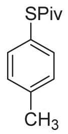
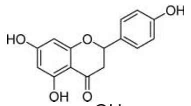
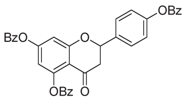
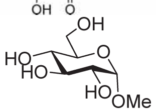
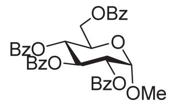
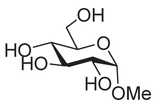
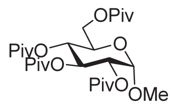
Entry	Sugar	Product	Time (min)	Yield[b]
1			30	95%
2			30	97%
3			30	96%
4			15	97%
5			15	95%

[a]With 1.0 molar equivalent of Ac_2O per hydroxyl group, 0.3 mol% of $Sm(OTf)_3$.
[b]Isolated yields after chromatographic purification.

summarized in Table 5. General procedure for acylation with anhydrides other than acetic anhydride: To a mixture of the starting material (1 mmol) in respective anhydride (1 mmol/OH or SH), $Sm(OTf)_3$ (0.3 mmol) was added and the mixture was stirred at rt or at 80°C (as mentioned in Table 5) until complete conversion of the starting material (TLC). The reaction mixture was cooled to rt, carefully neutralized with saturated aq. $NaHCO_3$, and extracted with CH_2Cl_2 (10 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by column chromatography (hexane-EtOAc).

In conclusion, we disclosed the applicability and scope of samarium trifluoromethanesulfonate as an efficient catalyst for the acetylation of phenols, alcohols, thiols, free sugars, and glycosides under solvent-free conditions using stoichiometric reagent giving the corresponding per-*O*. Furthermore, the catalyst showed to be equally effective for acylation with other anhydrides such as chloroacetic, benzoic, or pivalic anhydride. In our opinion, several unique properties of $Sm(OTf)_3$ such as high Lewis acidity, moisture tolerance, cost effectiveness, commercial availability, and simplicity of the reaction will definitely make $Sm(OTf)_3$ useful for catalytic application.

Table 5: $Sm(OTf)_3$-catalyzed solvent-free chloroacetylation, benzoylation, and pivaloylation.

Entry	Substrate	Product	Time (min)	Yield[a]
1		 CA = Chloroacetyl	30	94%
2			30	91%
3			20	93%
4			30	90%
5			45	86%

[a]Yield reported are those after chromatographic purification.

SUPPORTING INFORMATION AVAILABLE

Copies of ^1H and ^{13}C NMR spectra of compounds reported in Tables 1, 2, 4, and 5. Copies are available from the Corresponding author on request.

ACKNOWLEDGMENTS

BR, SD, and VKR are thankful to CSIR, New Delhi, for providing fellowship. Instrumentation facilities from SAIF, CDRI, are gratefully acknowledged. The work is supported by the Department of Science and Technology, New Delhi, India, through SERC Fast-Track Grant SR/FTP/CS-110/2005.

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