

# Silver Triflate Catalyzed Acetylation of Alcohols, Thiols, Phenols, and Amines

Rima Das, Debashis Chakraborty\*

Department of Chemistry, Indian Institute of Technology Madras, Chennai-600 036, Tamil Nadu, India  
Fax +91(44)22574202; E-mail: dchakraborty@iitm.ac.in

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**Abstract:** A variety of alcohols, thiols, phenols, and amines were subjected to acetylation reaction using acetic anhydride in the presence of catalytic quantity of silver triflate. The method described has a wide range of applications, proceeds under mild conditions, does not involve cumbersome workup, and the resulting products are obtained in high yields within a reasonable time.

**Key words:** acetylation, silver triflate, alcohol, phenol, thiol, amine

Functional group protection strategies are central to target molecule synthesis. The acetylation of hydroxy and amino groups is one of the most widely used transformations in organic synthesis, and a variety of acylating agents have been developed.<sup>1</sup> The protection of hydroxyl, mercapto, and amino groups by esterification constitutes the major backbone of many preparations of natural and synthetic products such as perfumes, flavors, food additives, cosmetics, pharmaceuticals, plasticizers, and polymers.<sup>2</sup> Generally, esterification is carried out by acylation of alcohols, thiols, phenols, and amines with carboxylic acids and more conveniently with anhydrides or acyl chlorides in the presence of basic catalysts.<sup>2c</sup> The use of acetic acid or a protic acid or acetic anhydride and pyridine is a common method for the synthesis of acetates.<sup>2b</sup> 4-(Dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) catalyze the acetylation of alcohols.<sup>3</sup> Further, other catalysts such as  $\text{CoCl}_2$ ,<sup>4</sup>  $\text{TaCl}_5/\text{SiO}_2$ ,<sup>5</sup>  $\text{ZnCl}_2$ ,<sup>6</sup>  $\text{ZnO}$ ,<sup>7</sup>  $\text{InCl}_3$ ,<sup>8</sup>  $\text{ZrCl}_4$ ,<sup>9</sup>  $\text{LiClO}_4$ ,<sup>10</sup> Ru-catalysts,<sup>11</sup>  $\text{Mg}(\text{ClO}_4)_2$ ,<sup>12</sup>  $\text{SmI}_2$ ,<sup>13</sup>  $\text{CeCl}_3$ ,<sup>14</sup>  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ ,<sup>15</sup> montmorillonite,<sup>16</sup>  $\text{TMSCl}$ ,<sup>17</sup>  $\text{PTSA}$ ,<sup>18</sup>  $\text{NH}_2\text{SO}_3\text{H}$ ,<sup>19</sup> distannoxane,<sup>20</sup> ionic liquids,<sup>21</sup> solid supported reagents and lipase enzymes,<sup>22</sup> and various triflates<sup>23</sup> have been used for acetylation. Recent reports include the use of molecular iodine,<sup>24</sup> 3-nitrobenzeneboronic acid,<sup>25</sup> and  $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ,<sup>26</sup> towards the acetylation; however, perchlorates, particularly of lithium, are known to be explosive and moisture sensitive. Although a large number of methods for acetylation are available, many suffer from limitations such as long reaction times, harsh reaction conditions, use of expensive, moisture sensitive and toxic catalysts, formation of side products, and poor yields of the desired products. In view of the demands of organic synthesis, there is still a need to develop mild and efficient protocols for acetylation. With increasing environmental concerns and the regulatory constraints faced in the chemical and pharmaceutical in-

dustries, the development of environmentally benign organic reactions has become a crucial and demanding area in modern organic chemical research. According to Wender, the 'ideal synthesis' is one in which the target components are readily obtained in one step and in quantitative yields from readily available starting materials in an environmentally acceptable process.<sup>27</sup> Our continued interest in environmentally benign process prompted us to explore the catalytic chemistry of Ag(I) salts.<sup>28</sup> Herein, we report that a number of alcohols, thiols, phenols, and amines can be acetylated with acetic anhydride, in excellent yields, in the presence of catalytic amounts of AgOTf under mild and solvent-free conditions.

Initial attempts to optimize the reaction conditions for acetylation reaction were performed with benzyl alcohol as a suitable substrate in the presence of acetic anhydride and different Ag(I) salts. The conversion of benzyl alcohol to benzyl acetate was found to be extremely facile in the presence of 1 mol% AgOTf at 60 °C. The reaction took longer time periods when performed under ambient conditions or in the presence of other Ag(I) salts (see Supporting Information).

Having optimized the reaction conditions, we continued our investigations with a variety of substrates namely alcohols, thiols (Table 1), phenols (Table 2), and amines (Table 3). A very large variety of alcohols, thiols, phenols and amines were subjected to acetylation reaction. The product from every reaction was isolated in very high yield after workup and column chromatography. The structural identity of all the products were ascertained on the basis of their spectral properties (<sup>1</sup>H, <sup>13</sup>C NMR, and mass spectra; see Supporting Information). In the absence of a catalyst, using the same reaction conditions, the corresponding products were obtained in low yields (25–30%) even after prolonged reaction time of 1.5 hours. The general applicability and efficiency of this reaction is evident from the wide range of compounds studied.

The kinetic studies of the acetylation reaction with catechol, cyclohexanol, 4-thiocresol, and 2,6-diisopropylamine was explored next. High-pressure liquid chromatography (HPLC) was used to determine the various starting materials and products present as a function of time. The concentrations of reactant and product for the acetylation of catechol are shown in Figure 1. The concentration of catechol decreases steadily while that of the product increases. The rates of such reactions were calculated. As an example, the acetylation of catechol can be considered. Van't Hoff differential method was used to determine the order (*n*) and rate constant (*k*) (Figure 2).

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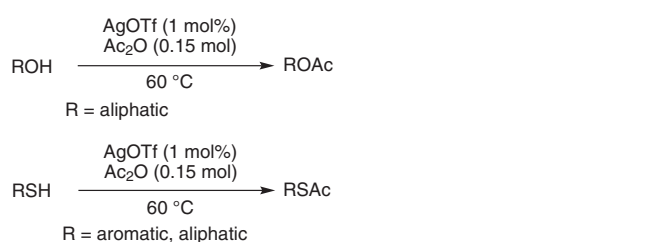
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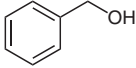
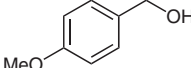
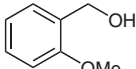
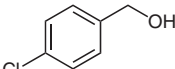
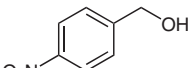
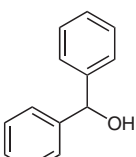
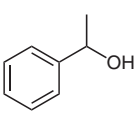
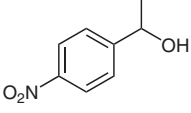
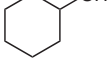
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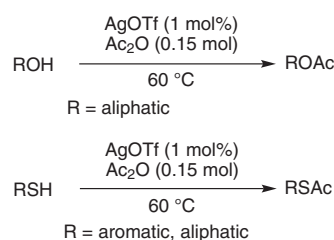
From Figure 1, the rate of the reaction at different concentrations can be estimated by evaluating the slope of the tangent at each point on the curve corresponding to that of catechol. With these data,  $\log_{10}(\text{rate})$  versus  $\log_{10}(\text{concentration})$  is plotted. The order ( $n$ ) and rate constant ( $k$ ) is given by the slope of the line and its intercept on the  $\log_{10}(\text{rate})$  axis. From Figure 2, it is clear that this reaction proceeds with second-order kinetics ( $n = 2.03$ ) and the rate constant  $k = 2.04 \times 10^{-2} \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ . For the other substrates, namely, cyclohexanol, 4-thiocresol, and 2,6-diisopropylamine, the order of the reaction  $n = \sim 2$  with rate constants ( $k$ )  $2.63 \times 10^{-2} \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ ,  $7.14 \times 10^{-2} \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$  and  $7.24 \times 10^{-3} \text{ L}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$ , respectively (see Supporting Information for details).



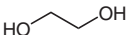

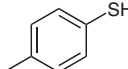
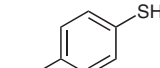
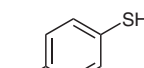

**Table 1** AgOTf-Catalyzed Acetylation of Alcohols and Thiols<sup>a</sup>



Entry	Substrate	Time (min) <sup>b</sup>	Yield (%) <sup>c</sup>
1		8	99
2		1	99
3		1	99
4		1.5	98
5		2	98
6		1.2	99
7		1	99
8		1.5	98
9		15	96

**Table 1** AgOTf-Catalyzed Acetylation of Alcohols and Thiols<sup>a</sup> (continued)



Entry	Substrate	Time (min) <sup>b</sup>	Yield (%) <sup>c</sup>
10		4	97
11		3	98
12		6	98
13		10	97
14		13	98
15		2	96
16		7	93
17		4 <sup>d</sup>	98

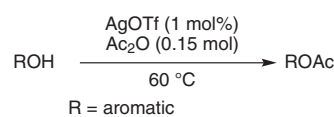
<sup>a</sup> Reactions performed in  $\text{Ac}_2\text{O}$  with 1 mol% AgOTf at 60 °C.


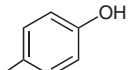
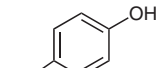

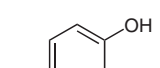
<sup>b</sup> Monitored using TLC until all the substrate was found consumed.

<sup>c</sup> Isolated yield after column chromatography of the crude product.

<sup>d</sup> Reaction performed at r.t.

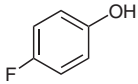
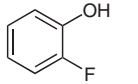
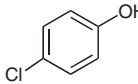
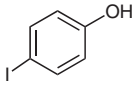
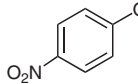
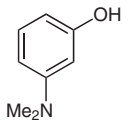
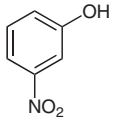
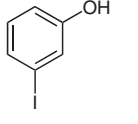
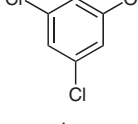
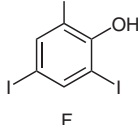
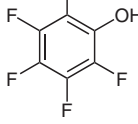
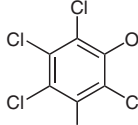
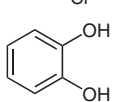
**Table 2** AgOTf-Catalyzed Acetylation of Phenols<sup>a</sup>



Entry	Substrate	Time (min) <sup>b</sup>	Yield (%) <sup>c</sup>
1		15	92
2		10	97
3		2	99
4		7	99
5		6	94

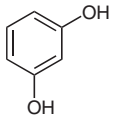
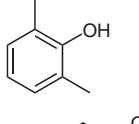
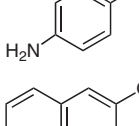
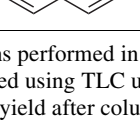
**Table 2** AgOTf-Catalyzed Acetylation of Phenols<sup>a</sup> (continued)

$$\text{ROH} \xrightarrow[60\text{ }^\circ\text{C}]{\text{AgOTf (1 mol\%)} \\ \text{Ac}_2\text{O (0.15 mol)}} \text{ROAc}$$
 R = aromatic

Entry	Substrate	Time (min) <sup>b</sup>	Yield (%) <sup>c</sup>
6		1	99
7		1	99
8		2	96
9		4	96
10		1	98
11		3	99
12		1	99
13		1.5	99
14		3	98
15		5	98
16		20	97
17		5	99
18		20	94

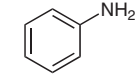
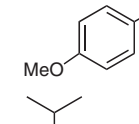
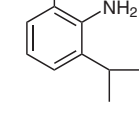
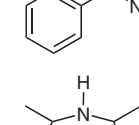
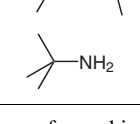
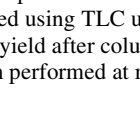
**Table 2** AgOTf-Catalyzed Acetylation of Phenols<sup>a</sup> (continued)

$$\text{ROH} \xrightarrow[60\text{ }^\circ\text{C}]{\text{AgOTf (1 mol\%)} \\ \text{Ac}_2\text{O (0.15 mol)}} \text{ROAc}$$
 R = aromatic

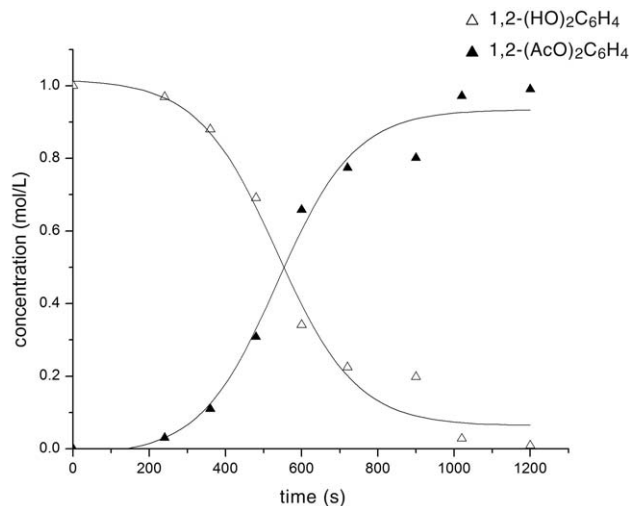
Entry	Substrate	Time (min) <sup>b</sup>	Yield (%) <sup>c</sup>
19		15	95
20		9	99
21		3	99
22		6	99

<sup>a</sup> Reactions performed in Ac<sub>2</sub>O with 1 mol% AgOTf at 60 °C.<sup>b</sup> Monitored using TLC until all the substrate was found consumed.<sup>c</sup> Isolated yield after column chromatography of the crude product.**Table 3** AgOTf-Catalyzed Acetylation of Amines<sup>a</sup>

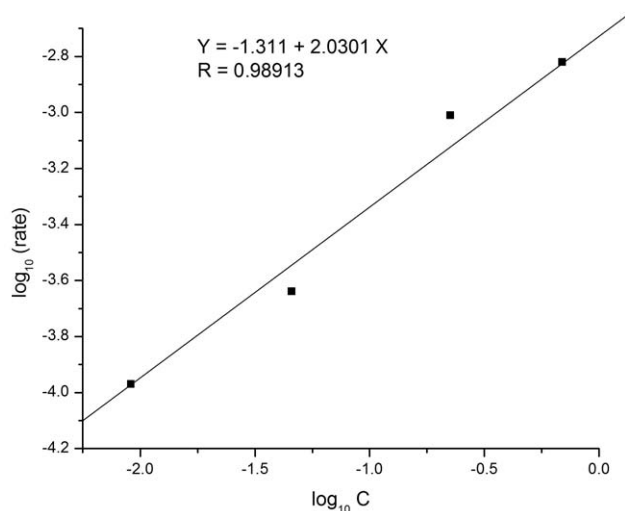
$$\text{RNH}_2 \xrightarrow[60\text{ }^\circ\text{C}]{\text{AgOTf (1 mol\%)} \\ \text{Ac}_2\text{O (0.15 mol)}} \text{RNHAc}$$
 R = aromatic, aliphatic

Entry	Substrate	Time (min) <sup>b</sup>	Yield (%) <sup>c</sup>
1		3	99
2		1	99
3		6	98
4		5	98
5		7	98
6		4	97 <sup>d</sup>

<sup>a</sup> Reactions performed in Ac<sub>2</sub>O with 1 mol% AgOTf at 60 °C.<sup>b</sup> Monitored using TLC until all the substrate was found consumed.<sup>c</sup> Isolated yield after column chromatography of the crude product.<sup>d</sup> Reaction performed at r.t.



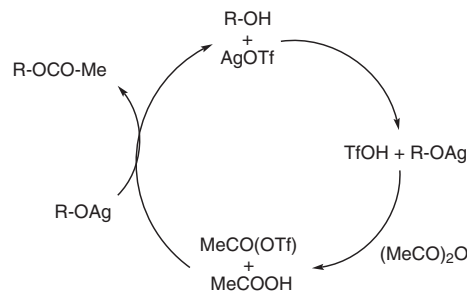
**Figure 1** Concentration versus time in the acetylation of catechol with acetic anhydride at 60 °C



**Figure 2** Van't Hoff differential plot for the acetylation of catechol with acetic anhydride at 60 °C

The proposed catalytic cycle for the acetylation of alcohols is shown in Scheme 1. According to this, TfOH is generated in situ from the reaction between AgOTf and the alcohol and is responsible for the further propagation of the reaction. To test this hypothesis, this reaction was performed in the presence of catalytic quantities of TfOH and it was found that the reaction takes much longer time period for completion. As an example in the case of benzyl alcohol, the reaction takes 20 minutes for completion, which is far higher than the time (8 min) required when AgOTf was used. This reveals once again that the Ag(I) plays a key role in substrate activation. A similar analogy may be thought for the acetylation reaction for thiols, phenols, and amines.

In summary, we have shown that AgOTf is an efficient and versatile catalyst for the acetylation of alcohols, thiols, phenols, and amines using acetic anhydride under sol-



**Scheme 1** Proposed catalytic cycle for acetylation of alcohols using AgOTf

vent-free conditions. The advantages of this method over earlier reported processes include its simplicity, clean and rapid reactions, high yields, and the absence of organic solvents.

All the substrates used in this study were purchased from Aldrich and used as received. The solvents used were purchased from Ranchem, India and purified using standard methods.  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded with a Bruker Avance 400 instrument. Chemical shifts were referenced to residual solvent resonances and are reported as parts per million relative to  $\text{SiMe}_4$ .  $\text{CDCl}_3$  was used for NMR spectral measurements. GC/MS analyses were recorded using Jeol JMS GC-Mate II instrument. HPLC analyses were done with Waters HPLC instrument fitted with Waters 515 pump and Waters 2487 dual  $\lambda$  absorbance detector.

#### Acetylation of Alcohols, Thiols, Phenols, and Amines; Typical Procedure

To a stirred mixture of alcohol/thiol/phenol/amine (0.10 mol) and  $\text{Ac}_2\text{O}$  (0.15 mol) was added AgOTf (1 mol%). The reaction mixture was heated to 60 °C and the progress was monitored by TLC (20% EtOAc in hexane) until all alcohol/thiol/phenol/amine was found to be consumed. After completion, the reaction mixture was washed with sat. aq  $\text{NaHCO}_3$  (15 mL) and extracted with EtOAc ( $3 \times 25$  mL). The EtOAc was evaporated, followed by flash column purification over silica gel (EtOAc–hexane) to obtain the pure product (Tables 1–3). The product was characterized using  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, and mass spectrometry. The data were found to be in accord with the literature (see Supporting Information).

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>.

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