A Simple and Practical Method for Large-Scale Acetylation of Alcohols and Diols Using Bismuth Triflate

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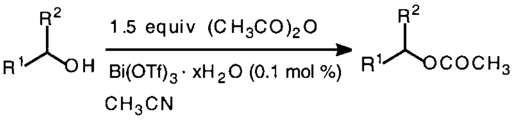
Received 7 June 2001; revised 21 August 2001

Abstract: A practical method for large-scale acetylation of 1° and 2° alcohols as well as diols has been developed. The acetylation proceeds smoothly in MeCN with as little as 0.1 mol% bismuth triflate in good yields.

Key words: bismuth and compounds, acylation, alcohols, diols

The conversion of alcohols to esters is an important synthetic transformation that has received considerable attention.[1] Conversion of an alcohol to the corresponding acetate is typically carried out using acetic anhydride or acetyl chloride in the presence of pyridine or triethylamine as a catalyst.[2] 4-(Dimethylamino)pyridine (DMAP) is known to cause a remarkable rate acceleration in this reaction.[3] In addition to catalysis by tertiary amines, Lewis acids have also been reported to catalyze the acetylation of alcohols. Examples include TMSCl,[4] $MgBr_2$,[5] $Sc(AcO)_3$–$(CF_3SO_2)_2NH$,[6] $TiCl_4$ + $AgClO_4$,[7] $CoCl_2$,[8] as well as $Sn(OTf)_2$, $Cu(OTf)_2$, and $In(OTf)_3$.[9] A highly efficient catalyst, $Sc(OTf)_3$, was introduced by Yamamoto.[10] However, many of these methods suffer from some drawbacks. Pyridine and DMAP are highly toxic while most metal triflates are very expensive. With increasing environmental concerns, it is imperative that new “environmentally friendly” reagents are developed.[11] Recently, bismuth compounds have become attractive candidates for use as reagents in organic synthesis for several reasons. Most bismuth compounds are relatively nontoxic, readily available at a low cost and are fairly insensitive to small amounts of water.[12] Bismuth has an electron configuration of $[Xe]4f^{14}5d^{10}6s^{2}6p^{3}$. Due to the weak shielding of the 4f electrons (Lanthanide contraction), bismuth(III) compounds exhibit Lewis acidity. The Lewis acidity of bismuth(III) salts, such as $BiCl_3$, has been recently exploited in organic synthesis. They have been used as catalysts for aldol and Michael reactions.[13] Bismuth triflate has been reported as a catalyst for Friedel–Crafts acylations,[14] sulfonylation of arenes,[15] Diels–Alder reaction[16] and the aza-Diels–Alder reaction.[17]

Recently, the use of bismuth triflate as a catalyst for the acylation of alcohols has been reported.[18] In this method, acetylation of alcohols is carried out on a small (1 mmol) scale using a large excess of acetic anhydride as the solvent (ten equivalents). In some cases, a small amount of a co-solvent is also used. However, this communication does not provide a detailed procedure for acetylation and only GC yields are reported for all but one example. In view of developing a practical method suitable for large scale acetylation of alcohols, we investigated the utility of bismuth triflate $[Bi(CF_3SO_3)_3{\cdot}xH_2O]$ for this purpose. We wish to report that the bismuth triflate catalyzed acetylation of 1° and 2° alcohols proceeds smoothly in acetonitrile in high yields using 1.5 equivalents of acetic anhydride (Scheme). We have also extended this method for acetylation of diols. In addition, some mechanistic findings are also presented.



Scheme

Bismuth triflate is not commercially available, but is easily synthesized from relatively inexpensive reagents following a literature method.[19] It is stable to air and has a good shelf life and thus requires no special handling. The results of this study are summarized in the Table.

The catalyst is highly efficient with both 1° and 2° alcohols as well as diols and the corresponding acetates are obtained in good yield with as little as 0.1 mol% catalyst. Acetylation was extremely slow in the absence of catalyst. In a few cases, the reaction mixture got slightly warm upon addition of the catalyst. Attempts to make the monoacetate from a symmetrical diol (entry 6) using one equivalent of acetic anhydride were not successful and instead, a statistical mixture of the monoacetate, diacetate and unreacted diol was obtained. However, formation of the diacetate proceeded smoothly in the presence of 3.0 equivalents of acetic anhydride. With diols containing a 1° and a 2° hydroxy group, a significant difference in the rate of acetylation of the 1° vs. 2° OH was not observed. Even with slow addition of 1 equivalent of acetic anhydride to a solution of the diol, a mixture of monoacetate, diacetate and the starting material was obtained. Again, the use of 3.0 equivalents of acetic anhydride afforded the diacetate in good yields (entries 7, 8, 10–12). The use of anhydrous acetonitrile did not increase the reaction rate or yield. The reaction was very slow in THF and diethyl ether. Under the reaction conditions employed, tertiary al-

Synthesis 2001, No. 14, 26 10 2001. Article Identifier:
1437-210X,E;2001,0,14,2091,2094,ftx,en;M03001SS.pdf.

ISSN 0039-7881

cohols did not undergo acetylation and the starting material was recovered unchanged (entry 13, 14). No dehydration product was observed with the tertiary alcohol linalool (entry 14).

In connection with a study of the mechanism of acetylation of alcohols catalyzed by TMSOTf, it has been reported that when a solution of menthol in CH_2Cl_2 was treated with acetic anhydride (1.5 equiv) and triflic acid (2 mol%), only a trace (<1%) of the acetate was formed.[20] In order to get some insight into the mechanism of acetylation catalyzed by bismuth triflate, we attempted the acetylation (using 1.5 equiv of Ac_2O) of phenethyl alcohol (entry 1), *sec*-phenethyl alcohol (entry 2) and menthol (entry 3) in MeCN, using triflic acid (2 mol%) instead of bismuth triflate. In contrast to the result in CH_2Cl_2, the corresponding acetate was obtained in good yield (90%) in all three cases. Based on our results, a possible mechanism is proposed. An exchange reaction between $Bi(OTf)_3$ and acetic anhydride can generate $MeCO_2Tf$ and triflic acid. Thus it is possible that triflic acid is the true catalyst for this reaction.[21]

Table Bismuth Triflate-Catalyzed acetylation of Alcohols in MeCN[a]

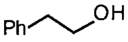
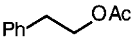
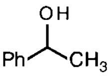
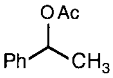
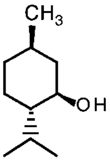
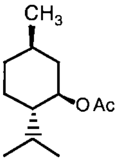
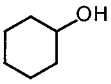
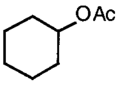
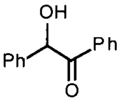
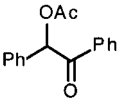
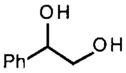
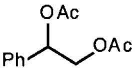
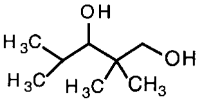
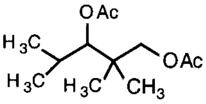
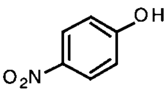
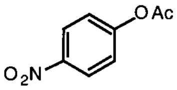
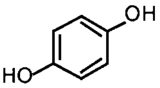
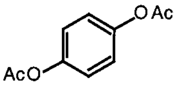
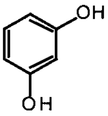
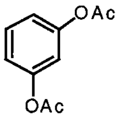
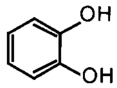
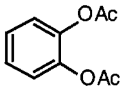
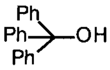
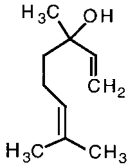
Entry	Alcohol	Time[b]	Product	Yield (%)[c,d]
1		25 min		88
2		45 min		86
3		45 min		87
4		30 min		86
5[e]		3 h		85
6[f]		45 min		80
7[f]		45 min		90
8[f]		1 h		87
9		30 min		90
10[f]		40 min		88
11[f]		15 min		92

Table Bismuth Triflate-Catalyzed acetylation of Alcohols in MeCN[a] (continued)

Entry	Alcohol	Time[b]	Product	Yield (%)[c,d]
12[f]		15 min		85
13[g]		12 h	NR	
14		12 h	NR	

[a] Reagent grade MeCN was used.

[b] All reactions were run at r.t. and reaction progress was monitored by TLC.

[c] Yields refer to that of isolated product.

[d] The crude product in each case was deemed to be of sufficient (> 98%) purity by ^{1}H and ^{13}C NMR spectroscopy and hence was not purified further.

[e] Reaction was carried out using 1 mol% catalyst.

[f] 3.0 Equivalents of Ac_2O were used for all diols.

[g] No reaction was observed even when the mixture was heated at reflux for 3 h.

In summary, this work demonstrates a practical preparative method for the acetylation of 1° and 2° alcohols and diols. The advantages of bismuth triflate include (1) ease of handling, (2) low cost, (3) fast reaction rates, (4) catalytic in nature and (5) insensitivity to air and small amounts of moisture, eliminating the need for anhydrous solvents.

sec-Phenethyl Acetate; Typical Procedure

To a stirred solution of *sec*-phenethyl alcohol (8.00 g, 0.0655 mol) in MeCN (80 mL) were added Ac_2O (10.0 g, 0.0982 mol) and bismuth triflate (42.9 mg, 6.55×10^{-5} mol, 0.1 mol%). After 1 h, MeCN was removed on a rotary evaporator and 10% aq Na_2CO_3 solution (40 mL) was added. The mixture was extracted with Et_2O (3×30 mL) and the combined organic extracts were washed with aq Na_2CO_3 solution until basic. The organic layer was washed further with brine (15 mL) and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to give 9.28 g (86 %) of a colorless liquid, which was identified to be *sec*-phenethyl acetate (>98% pure) by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

Acknowledgement

We wish to acknowledge funding by the National Science Foundation (NSF-RUI Grant 0078881).

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