Scandium Trifluoromethanesulfonate as an Extremely Active Acylation Catalyst

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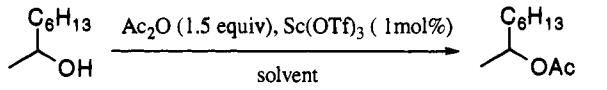
4-(Dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) are known to catalyze the acylation of alcohols with acid anhydrides and to increase the rate of acylation by a factor of 10^4.[1] Recently, Vedejs et al. reported tributylphosphine as a similar catalyst for the acylation of alcohols.[2] Although the mechanism of tributylphosphine catalysis is not yet clear,[2,3] the remarkable catalytic activity of these basic and nucleophilic catalysts can be interpreted by assuming the formation of ion pair intermediates such as *N*-acyl-4-(dimethylamino)pyridinium carboxylates. Besides the above catalysts, protic or Lewis acid is also known to catalyze the acylation of alcohols with acid anhydrides. Nevertheless, there is still great demand for acid catalysts to generate esters under mild conditions.[4-6] We anticipated that *acid* catalysts exist which have extremely strong catalytic potential similar to that of the basic catalysts (DMAP, Bu_3P), and we therefore investigated the possibility of developing new classes of stable acylation catalysts that are insensitive to protic substances like alcohols and carboxylic acids. This communication reports a new, practical, and very general approach to esters which is based on the use of a stable Lewis acid catalyst for acylation of alcohols with acid anhydrides or mixed anhydrides.

At first, we searched for various Lewis acids (1 mol %) which promote the model reaction of *sec*-phenethyl alcohol (1 equiv) with acetic anhydride (3 equiv) in dichloromethane. Among several stable metal triflates screened, we found scandium triflate to be quite effective:[7] the reaction proceeded even at 0 °C in the presence of scandium triflate, while the reaction almost did not proceed in the presence of lanthanide triflate at 0 °C. Although other Lewis acids such as $BF_3{\cdot}Et_2O$, $SnCl_4$, $TiCl_4$, etc. were also screened, scandium triflate proved the most effective catalyst for the present reaction.

The effect of solvents in the acetylation of 2-octanol (1 equiv) with acetic anhydride (1.5 equiv) under the influence of 1 mol % of scandium triflate is shown in Table 1. Under these conditions, the reaction proceeded faster in acetonitrile than in other organic solvents. Interestingly, the reaction was very slow in chloroform even at 23 °C.

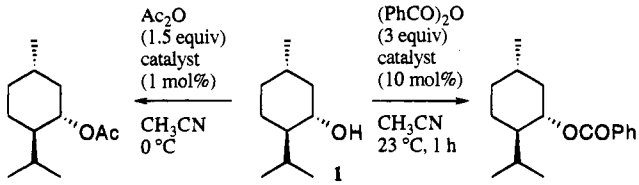
Table 1. Solvent Effect on Scandium Triflate Catalyzed Acetylation of 2-Octanol with Acetic Ahydride



solvent	conditns[a] and results: temp (°C), time (h), conversn (%)[b]
CH_3CN	−20, 2, >95
CH_3NO_2	0, 2, <5 → 23, 0.5, >95
toluene or CCl_4	0, 2, <5 → 23, 1, >95
CH_2Cl_2 or THF	0, 2, <5 → 23, 2, >95
$CHCl_3$	0, 2, 0, → 23, 23, 52

[a] A solution of 2-octanol (0.4 M) was used. [b] The conversion was determined by ^1H NMR analysis of the crude product.

Table 2. Comparison of Catalysts in the Acylation of Menthol with Acid Anhydrides



acetylation[a] conversn,[b] % (reacn time, min)	catalyst	benzoylation[a] conversn,[b] %
>95 (15 min)	$Sc(OTf)_3$	>95
75 (55 min)	DMAP/Et_3N (3 equiv)	ca. 75[c]
	DMAP	23[c]
	Bu_3P	88[c]

[a] A solution of **1** (0.25 M) was used. [b] The conversion was determined by ^1H NMR analysis of the crude product. [c] See ref 2a.

Following our demonstration of the remarkable catalytic activity of scandium triflate, three catalysts, DMAP, Bu_3P, and $Sc(OTf)_3$, were compared for the acetylation and benzoylation of menthol (**1**) under identical conditions. The results are summarized in Table 2. It was noted that $Sc(OTf)_3$ was not deactivated by the carboxylic acid byproduct of acylation. Vedejs and Diver have reported that the DMAP/Et_3N acetylation is ca. 10-fold faster than the Bu_3P/Et_3N reaction, and the acetylations by both catalysts under amine-free conditions are somewhat slower than with Et_3N present.[2a] Taking the experimental results independently reached by Vedejs' group and ours into consideration, we might conclude that $Sc(OTf)_3$ was the most effective acylation catalyst.

To explore the generality and scope of the above scandium triflate catalyzed acylation, the reaction was examined with various structurally diverse alcohols and acid anhydrides.[8] The results are summarized in Table 3. The high catalytic activity of scandium triflate was usable for acylating not only primary alcohols but also sterically-hindered secondary or tertiary alcohols with various acid anhydrides. Surprisingly, tertiary alcohols were easily acetylated under very mild conditions. In the acetylation of 2-methyl-2-dodecanol, elimination byproducts

(1) Reviews: (a) Höfle, G.; Steglich, V.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (c) Cherkasova, E. M.; Bogatkov, S. V.; Golovina, Z. P. *Russ. Chem. Rev.* **1977**, *46*, 246. Kinetics: (d) Connors, K. A.; Ebaka, C. J. *J. Pharm. Sci.* **1983**, *72*, 366. (e) Connors, K. A.; Lin, S.-F. *J. Pharm. Sci.* **1981**, *70*, 235.

(2) (a) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. (b) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286.

(3) Although several attempts were made to define the structure of the phosphine-activated acylating agent by Vedejs et al., the evidence did not prove that the phosphonium carboxylate was the key intermediate.

(4) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers, Inc.: New York, 1989; p 980.

(5) Recently, $CoCl_2$-catalyzed acetylation of alcohols with acetic anhydride was reported. Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, *57*, 2001.

(6) For references on the esterification reaction of trimethylsilyl ethers *via* acid anhydrides by the promotion of a catalytic amount of Lewis acid, see: (a) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728. (b) Miyashita, M.; Shina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516 and references cited therein.

(7) It was earlier reported that scandium triflate is a good Lewis acid catalyst for several reactions. Meerwein–Ponndorf–Verley type reductions: (a) Castellani, C. B.; Carugo, O.; Perotti, A.; Sacchi, D.; Invernizzi, A. G.; Vidari, G. *J. Mol. Catal.* **1993**, *85*, 65. Aldol and Michel reactions: (b) Kobayashi, S.; Hachiya, I.; Araki, M. *Synlett* **1993**, 472. Diels–Alder reaction: (c) Kobayashi, S.; Hachiya, I.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755. (d) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. Allylation: (e) Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958. Friedel-Crafts acylation: (f) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545.

(8) The following simple procedure illustrates the scandium triflate catalyzed acetylation of menthol. To a mixture of menthol (938 mg, 6 mmol) and acetic anhydride (849 μL, 9 mmol) in acetonitrile (24 mL) was added dropwise an acetonitrile solution (60 μL, 0.006 mmol, 0.1 M) of commercial scandium triflate, which was unpurified, at room temperature. After stirring at room temperature for 1 h, the solution was quenched with aqueous sodium hydrogen carbonate, and the product was extracted with ether. The organic layers were dried over magnesium sulfate, filtrated, and concentrated *in vacuo* to afford the crude product, which was sufficiently clean. Further purification was done by column chromatography on silica gel (1.17 g, 98% isolated yield).

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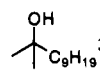
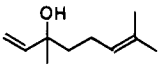
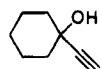
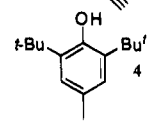
Table 3. $Sc(OTf)_3$-Catalyzed Acylation of Alcohols with Acid Anhydrides

entry	alcohol	$(RCO)_2O$ (equiv)	$Sc(OTf)_3$ (mol %)	condition [a] (°C, h)	yield [b] (%)
1	$PhCH_2CH_2CH_2OH$ 2	Ac_2O (1.5)	0.1	rt, 1	>95
2	PhMeCHOH	Ac_2O (1.5)	0.1	rt, 1	>95
3	1	Ac_2O (1.5)	0.1	rt, 1	>95
4		$(EtCO)_2O$ (1.5)	1.0	0, 1	>95
5		$(t\text{-}BuCO)_2O$ (1.5)	1.0	rt, 1	>95
6		$(PhCO)_2O$ (3.0)	1.0	rt, 20	>95
7	 3	Ac_2O (3.0)	1.0	rt, 1	56 (39)[c]
8		Ac_2O (5.0)	1.0	0, 0.8	85 (9)[c]
9		Ac_2O (5.0)	1.0	-20, 5.5	94 (1)[c]
10 [d]		Ac_2O (5.0)	[DMAP (1.0)]	rt, 5.5	< 1 (0)[c]
11		Ac_2O (5.0)	1.0	-20, 5	91 (9)[c]
12		Ac_2O [e]	0.5	-50--43, 1	66 (5)[f]
13		Ac_2O [e]	2.0	-45, 1	76 (14)[f]
14		Ac_2O [e]	2.0	-20, 2.5	68 (8)[f]
15		Ac_2O [e]	1.0	-40, 1.3	>95 (<1)[c]
16		Ac_2O (3.0)	1.0	-20, 0.5	>95
17	 4	Ac_2O (1.5)	1.0	rt, 1	>95

[a] Unless otherwise noted, an acetonitrile solution of substrate (0.25 M) was used. [b] Unless otherwise noted, the isolated yield by column chromatography on silica gel is indicated. [c] The isolated yield of olefins, which are produced by the elimination of the acetoxy group, is indicated in parentheses. [d] DMAP, 1.0 mol %, was used in place of $Sc(OTf)_3$. [e] Acetic anhydride as a solvent was used in place of acetonitrile. [f] The chemical yield of primary acetates, which are produced by the 1,3-migration of the acetoxy group, is indicated in parentheses. It was determined by ^1H NMR analysis of the crude product.

were produced together with the desired acetate (entry 7). When the reaction was carried out in the presence of excess acetic anhydride at as low a temperature as possible, the relative amount of acetylation only increased and the eliminations of hydroxy and acetyl groups were effectively prevented (entry 9).[9] For more acid-sensitive substrates such as allylic or benzylic tertiary alcohols, the reaction successfully proceeded using acetic anhydride as a solvent at as low a temperature as possible (entries 12−15). In most cases of DMAP-catalyzed acetylation of tertiary alcohols, it is necessary to use more than 10 mol % of DMAP and an excess of amine at conditions of high concentration (entry 9 vs entry 10).[1]

On the basis of the above results that the benzoylation (entry 6 in Table 3) of menthol with benzoic anhydride was relatively slow in comparison with the acylation using other aliphatic carboxylic acid anhydrides (entries 3−5 in Table 3), *we developed a convenient esterification between alcohols and carboxylic acids promoted by a catalytic amount of $Sc(OTf)_3$.*

The esterification between alcohols and aliphatic acids in the presence of an equimolar amount of benzoic anhydride would smoothly proceed if mixed anhydride were generated from aliphatic carboxylic acid and benzoic anhydride in the presence of a catalytic amount of $Sc(OTf)_3$.[6b,10] Actually, menthyl acetate was obtained in 85% yield with 99% chemoselectivity from menthol and acetic acid by the following experimental procedure: after a mixture of 2.0 equiv of acetic acid and 1.5 equiv of benzoic anhydride in acetonitrile was stirred in the presence of 5 mol % of $Sc(OTf)_3$ at room temperature for 12 h, menthol was added to the solution precooled to 0 °C and stirred at the same temperature for 10 h. In order to find the most suitable anhydride as additive, the phenyl ring substituent effect of benzoic anhydride was examined. The result was that a benzoic anhydride having an electron-withdrawing group such as a nitro group at the para position gave good reactivity and high chemoselectivity. In the reaction using *p*-nitrobenzoic anhydride, nitromethane was more effective than acetonitrile as a solvent with respect to its solubility. Several examples of the present esterification are demonstrated in Table 4. This method gave excellent results for the reaction between various alcohols except for tertiary alcohols and aliphatic carboxylic acids. It is noteworthy to point out that the experimental procedure is extremely simple and facile: only 1 mol % of $Sc(OTf)_3$ is employed at room temperature in a mixed solution of alcohols, carboxylic acids, and *p*-nitrobenzoic anhydride to afford the desired esters in high yield without preparing mixed anhydrides beforehand.

Table 4. Scandium Triflate Catalyzed Esterification of Alcohols with Carboxylic Acids

$$R^1OH\ (1\ \text{equiv}) + R^2CO_2H\ (1.1\ \text{equiv}) \xrightarrow[MeNO_2,\ rt^a]{Sc(OTf)_3\ (1\ \text{mol}\ \%)\ (p\text{-}NO_2C_6H_4CO)_2O\ (1.5\ \text{equiv})} R^2CO_2R^1\ (\mathbf{5}) + p\text{-}NO_2C_6H_4CO_2R^1\ (\mathbf{6})$$

entry	R^1OH	R^2CO_2H	time (h)	conversn (%)[b] 5	6
1	**2**	$EtCO_2H$	2	>95	0
2		*i*-$PrCO_2H$	3	>95	0
3	**1**	$EtCO_2H$	2	>95	0
4[c]		$EtCO_2H$	3	89	0
5		*i*-$PrCO_2H$	2	>95	<1
6		(*E*)-MeCH=CMeCO_2H	2	>95	0
7		*t*-$BuCO_2H$	3	>95	0
8	**3**	$EtCO_2H$	2	*d*	*d*
9	2,6-dimethyl-phenol	*i*-$PrCO_2H$	3.5	>95	0
10		*t*-$BuCO_2H$	4	90	0
11[e]	**4**	$EtCO_2H$	12.5	86	2

[a] Room temperature. [b] Isolated yield by column chromatography on silica gel. [c] 1 equiv of *p*-nitrobenzoic anhydride was used. [d] Although the esterification certainly proceeded, the acyloxy group of the ester produced was gradually eliminated under the same conditions. [e] 10 mol% of scandium triflate and 2.0 equiv of propanoic acid were used.

In summary, we have demonstrated that scandium triflate, which is commercially available, is a practical and useful Lewis acid catalyst for acylation of alcohols with acid anhydrides and esterification between alcohols and carboxylic acids in the presence of *p*-nitrobenzoic anhydride because of its remarkable catalytic potential (reaction conditions: 0.1−2 mol % of catalyst, below room temperature). The present method is especially attractive for large-scale synthesis (menthol (20 mmol), Ac_2O (30 mmol), CH_3CN (20 mL), $Sc(OTf)_3$ (0.002 mmol), room temperature, 1 h, 99% acetate after chromatography). Further studies on the application of the present reaction and its mechanism are in progress.[11]

Supplementary Material Available: Experimental procedures for acetylation of 3-methyl-1-dodecen-3-ol (entry 13 in Table 3) and for typical esterification between alcohols and carboxylic acids (Table 4) and compound characterization data (entries 13−17 in Table 3 and entries 4, 7, and 9−11 in Table 4) (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) It was ascertained by independent experiments that **3** and the corresponding acetate were gradually eliminated in the presence of $Sc(OTf)_3$.

(10) For a reference on esterification of alcohols with mixed anhydrides, see: Inanaga, J.; Hirata, K.; Saeki, T.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(11) Support of this research by the Ministry of Education, Science and Culture of the Japanese Government is greatly appreciated.