Pergamon

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Tetrahedron Letters 44 (2003) 3521–3525

TETRAHEDRON
LETTERS

Fluoroboric acid adsorbed on silica gel as a new and efficient catalyst for acylation of phenols, thiols, alcohols, and amines

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Received 10 December 2002; revised 25 February 2003; accepted 7 March 2003

Abstract—Fluoroboric acid supported on silica gel efficiently catalyzes acylation of structurally diverse phenols, alcohols, thiols, and amines under solvent free conditions. Acid-sensitive alcohols are smoothly acylated without competitive side reactions.

Functional group manipulation through the protection–deprotection strategy is an unavoidable exercise in the synthesis of multifunctional target molecules. In this context protection of phenols, thiols, amines and alcohols becomes a frequently desired transformation due to the prevalence of these functionalities in drugs and pharmaceuticals. Protection of these functionalities is usually achieved through acylation with anhydrides[1] due to their ease of deprotection.[1,2] The poor nucleophilic properties of hydroxylic compounds, particularly phenols, necessitates activation of the anhydride. Various activators employed for the purpose include nucleophilic agents such as DMAP[3] and Bu_3P[4] and Lewis acids such as $CoCl_2$,[5] $Sc(OTf)_3$,[6] $Sc(NTf_2)_3$,[7] TMSOTf,[8] $Bi(OTf)_3$,[9] $Cu(OTf)_2$,[10] $In(OTf)_3$,[11] $TaCl_5$,[12] zeolites,[13] clays,[14] Nafion-H,[15] yttria-zirconia,[16] and $LiClO_4$.[17] However, these acylation methodologies suffer from one or more disadvantages such as long reaction times, stringent conditions, use of halogenated solvents, use of hazardous materials (e.g. DMAP is highly toxic, Bu_3P is flammable and air sensitive), use of costly catalysts (e.g. the triflates), the special efforts required to prepare the catalyst (e.g. $Bi(OTf)_3$, $Sc(NTf_2)_3$, Nafion-H, yttria-zirconia), the need to use an excess of acylating agent, side reactions with acid-sensitive substrates and in most of the cases being applicable to alcohols only. Thus, the development of a new acylation method is in high demand.

The ongrowing awareness on various issues related to environment pollution control has led to the search for more friendly forms of catalysts. The leading contender for an environmentally acceptable acylation process is the use of reagents adsorbed onto an insoluble inorganic or organic support (e.g. silica, alumina, clay or charcoal). As the effective surface area of the reagent dispersed on a support can be increased up to 100 times, the activity and selectivity of the reagent is improved. Additionally, supported reagents are easier to handle as they are invariably less toxic, non-corrosive free flowing powders. The ease of separation of the supported reagent from the reaction mixture by filtration, the feasibility of reuse, and good thermal and mechanical stabilities further add to the advantages. We reasoned that the use of fluoroboric acid, a weak protic acid, adsorbed on silica would circumvent the problem of side reactions for acid-sensitive substrates. The ready availability of HBF_4 and the ease of han-

Table 1. Acylation of **1** with Ac_2O under various conditions[a]

Entry	Activator	Solvent	Time (min)	Yield (%)[b,c]
1	HBF_4–SiO_2	Neat	5	90
2	HBF_4–SiO_2	$MeNO_2$	15	42
3	HBF_4–SiO_2	DCM	15	47
4	HBF_4–SiO_2	MeCN	15	5
5	HBF_4–SiO_2	THF	15	4
6	HBF_4–SiO_2	Toluene	15	42
7	HBF_4	Neat	5	90
8	SiO_2	Neat	30	30
9	$LiBF_4$	Neat	30	65

[a] The substrate was treated with Ac_2O (1 equiv.) in the presence of the activator (1 mol%) at room temperature.

[b] Isolated yield of 2-acetoxynaphthalene.

[c] Unreacted starting material was recovered.

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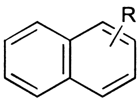
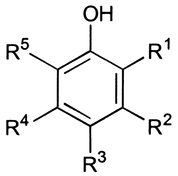
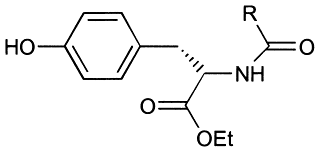
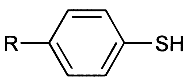
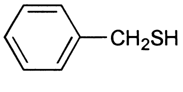
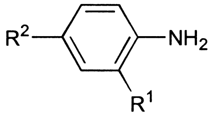
doi:10.1016/S0040-4039(03)00683-X

Table 2. HBF$_4$–SiO$_2$ catalyzed acylation of phenols, thiols, and amines[a]

Entry	Substrate	Time (h)	Yield (%)[b,c]
			
1	R = 2-OH	5 min	90(65)
2	R = 1-OH	0.25	91
			
3	$R^1 = R^2 = R^4 = R^5 = H; R^3 = OMe$	0.25	95(80)
4	$R^1 = R^3 = R^5 = Me; R^2 = R^4 = H$	1	90[d]
5	$R^1 = R^2 = R^4 = R^5 = H; R^3 = Br$	0.5	89
6	$R^1 = R^2 = R^4 = R^5 = H; R^3 = COMe$	0.25	82
7	$R^1 = R^2 = R^4 = R^5 = H; R^3 = CO_2Me$	0.25	95
8	$R^1 = R^2 = R^4 = R^5 = H; R^3 = CN$	0.5	89
9	$R^1 = NO_2; R^2 = R^3 = R^4 = R^5 = H$	1	92[e]
10	$R^1 = R^2 = R^4 = R^5 = H; R^3 = NO_2$	0.5	91(72)
11	$R^1 = R^2 = R^4 = R^5 = H; R^3 = OH$	5 min	85[f]
12	$R^1 = OH; R^2 = R^3 = R^4 = R^5 = H$	0.25	87[f]
13	$R^1 = R^3 = R^4 = R^5 = H; R^2 = OH$	0.5	94[f]
14	$R^1 = OH; R^2 = R^4 = R^5 = H; R^3 = {}^tBu$	6	98[f]
15	$R^1 = R^2 = OH; R^3 = R^4 = R^5 = H$	6	91[g]
			
16	R = Me	2	90
17	R = Ph	2	89
			
18	R = H	6	92
19	R = Me	1	82
20	R = OMe	3	95
21		3	85
			
22	$R^1 = NO_2; R^2 = H$	0.5	98
23	$R^1 = R^2 = NO_2$	0.5	80

[a] The substrate was treated with Ac$_2$O (1 equiv. per OH/SH/NH$_2$ group except for entry 4) in the presence of HBF$_4$ on SiO$_2$ (1 mol%) under neat conditions at room temperature.

[b] Isolated yield of the corresponding acylated product.

[c] The figure in parenthesis is the yield on carrying out the reaction in the presence of LiBF$_4$ (1 mol%) for 30 min.

[d] The substrate was treated with 1.5 equiv. of Ac$_2$O.

[e] The reaction was carried out at 80 °C.

[f] Isolated yield of the di-acetate.

[g] Isolated yield of the tri-acetate.

dling the adsorbed catalyst should make it cost effective. We disclose herein our findings on the catalytic effects of fluoroboric acid adsorbed on silica gel (230–400 mesh) (HBF$_4$–SiO$_2$) for acylation of phenols, thiols, alcohols and amines.

In a model study, 2-hydroxynaphthalene **1** was treated with Ac$_2$O (1 equiv.) in the presence of HBF$_4$–SiO$_2$ (1 mol%) under various conditions (Table 1). The reaction is best carried out at room temperature under neat conditions because the use of solvents such as MeNO$_2$, DCM, MeCN, THF, and toluene decreases the catalytic efficiency. The reaction works equally well using aq. HBF$_4$. However, inferior results are obtained with LiBF$_4$. The result incorporated in entry 8 shows that the catalytic activity of HBF$_4$–SiO$_2$ is not contributed to by SiO$_2$. In order to compare the effectiveness of aq. HBF$_4$ and HBF$_4$–SiO$_2$ we chose to carry out the acylation of an acid-sensitive substrate. Thus, while HBF$_4$–SiO$_2$ catalyzed the acylation of geraniol with 2 equiv. of Ac$_2$O to afford a 91% yield of acylated product in 6 h at room temperature in the absence of solvent, the corresponding reaction, carried out under similar conditions in the presence of aq. HBF$_4$ afforded an intractable product mixture. Thus HBF$_4$–SiO$_2$ is better suited for acylation of acid-sensitive substrates compared to aq. HBF$_4$.

To explore the generality and scope, structurally diverse phenols, thiols, and amines were subjected to acylation catalyzed by HBF$_4$–SiO$_2$ (Table 2). The reaction could be carried out with 1 equiv. of Ac$_2$O at room temperature. The catalyst could be recovered by diluting the reaction mixture with Et$_2$O and filtration and reused without any significant reduction of activity. Di- and tri-hydroxy aromatic compounds afforded the di- and tri-acetates, respectively, in excellent yields (entries 11–15). Electron deficient phenols were efficiently acylated (entries 5–10) but required longer reaction times due to their relatively poor nucleophilicity. The higher temperature required for acylation of 2-nitrophenol (entry 9) may be explained as the result of the steric effect of the *ortho*-nitro group in addition to the electron deficient nature of the substrate. A sterically hindered substrate (entry 4) required excess reagent and a longer reaction time. Substrates bearing ketone, ester, and cyanoamide functionalities[18] were smoothly acylated and no competitive Fries rearrangements[19] were observed. Acylation of optically active substrates were efficiently carried out without any detrimental effect on the optical purity (entries 16 and 17).

During the past eight years metal triflates have emerged as the most effective acylation catalysts. However, the high cost, susceptibility to moisture and commercial unavailability of some metal triflates do not make the metal triflates, in general, attractive for industrial use. Therefore, we planned to compare the advantages of HBF_4–SiO_2 over the metal triflates with a few representative examples. Thus, the $In(OTf)_3$ catalyzed reaction of 2-hydroxynaphthalene requires 1.5 equiv. of Ac_2O in MeCN whereas the use of HBF_4–SiO_2 affords a comparable result with stoichiometric amounts of Ac_2O in the absence of solvent. Acylation of electron-deficient phenols such as 4-bromophenol and 4-hydroxyacetophenone were carried out with 2 equiv. of Ac_2O in DCM for 2 h using $Cu(OTf)_2$ to afford comparable results to those obtained in 30 and 15 min, respectively, in the absence of solvent under the catalytic influence of HBF_4–SiO_2. The $Bi(OTf)_3$ catalyzed acylation of 2,4,6-trimethylphenol, a sterically hindered phenol, required 10 equiv. of Ac_2O in DCM for 2.5 h to afford a 95% yield. Contrary to this observation, the HBF_4–SiO_2 catalyzed reaction afforded comparable yields with stoichiometric amounts of Ac_2O in 1 h under neat conditions.

To generalize the catalytic efficiency of HBF_4–SiO_2 for other acylating agents, we employed 4-nitrophenol **2** as a representative example of an electron deficient phenol during the reaction with different acid anhydrides (Table 3). Acylation with propionic, *iso*-butyric, and pivalic anhydrides resulted in 81–91% yields in 0.5–3 h at room temperature under neat conditions. The reactions carried out at 80°C afforded 85–97% yields in 0.5 h (footnotes, Table 3). Acylation with benzoic anhydride could be carried out either in DCM at room temperature for 3 h (81% yield) or at 80°C under neat conditions for 0.5 h (85% yield).

As a logical extension of this methodology, we further investigated the potential of HBF_4–SiO_2 as a catalyst for the acylation of various alcohols (Table 4). Excellent chemoselectivity was observed in that secondary and tertiary alcohols did not experience any competitive dehydration (entries 3–7, and 13–15) and no rearrangement took place for allylic and propargylic substrates (entries 8, 9, and 11–15). Optically active substrates were efficiently acylated without any detrimental effect on the optical purity (entries 6 and 7) demonstrating the mildness of the acylation process.

Table 3. HBF_4–SiO_2 catalyzed acylation of **2** with various anhydrides[a]

Entry	Anhydride	Time (h)	Yield (%)[b,c]
1	Ac_2O	0.5	91
2	$(H_3CCH_2CO)_2O$	3	89 (95)
3	$[(H_3C)_2CHCO]_2O$	3	85 (97)
4	$[(H_3C)_3CO]_2O$	3	82 (90)
5	$(PhCO)_2O$	3	81[d] (85)[d]

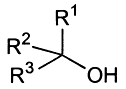
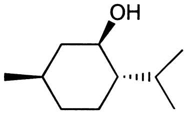
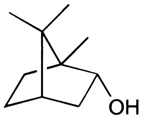
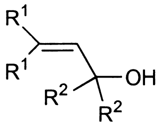
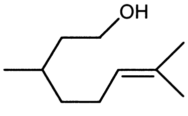
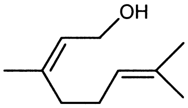
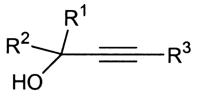
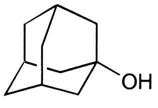
[a] The substrate was treated with the anhydride (1 equiv.) in the presence of HBF_4–SiO_2 (1 mol%) under neat conditions (except for $(PhCO)_2O$) at room temperature.

[b] Isolated yield of the corresponding acylated product.

[c] The figure in parenthesis is the yield obtained by carrying out the reaction at 80°C under neat conditions for 0.5 h.

[d] The reaction was carried out in DCM.

Table 4. HBF_4–SiO_2 catalyzed acylation of alcohols[a]

Entry	Substrate	Time (h)	Yield (%)[b]
			
1	$R^1 = R^2 = H; R^3 = Ph$	1	94
2	$R^1 = R^2 = H; R^3 = H_2CPh$	1	90
3	$R^1 = H; R^2 = Me; R^3 = Ph$	1	87[c]
4	$R^1 = Et; R^2 = H; R^3 = Ph$	6	95
5	$R^1 = Me; R^2,R^3 = (CH_2)_5$	2	77[c]
6		6	83
7		0.75	83
			
8	$R^1 = Me; R^2 = H$	2	90[d]
9	$R^1 = H; R^2 = Me$	2	90[d]
10		6	90
11		6	91
			
12	$R^1 = R^2 = R^3 = H$	2	100
13	$R^1 = R^2 = Me; R^3 = H$	2	100
14	$R^1 = Me; R^2 = Et; R^3 = H$	2	100
15	$R^1,R^2 = (CH_2)_5$	6	96
16		6	75[e]

[a]The substrate was treated with Ac_2O (1 equiv. per OH group) in the presence of HBF_4 -SiO_2 (1 mol %) under neat conditions (except for entries 3,5,8 and 9) at room temperature. [b]Isolated yield of the corresponding acylated product. [c]The reaction was carried out in MeCN at room temperature. [d]The reaction was carried out in DCM at room temperature. [e]The reaction was carried out with 1.5 equiv of Ac_2O at room temperature under neat conditions.

Although recently there has been an upsurge in the use of metal triflates for acylation reactions, the large H_0 value of −14.1 of triflic acid[20] makes the metal triflates very strong Lewis acids and hence unsuitable for their use in dealing with acid-sensitive substrates. This is exemplified by the necessity of a large excess of Ac_2O and/or low temperature (0 to −20°C) to suppress the competitive side reactions (e.g. dehydration and rearrangement) during the acylation of 1-methylcyclohexanol, 1-ethynylcyclohexanol and 3-methyl-1-pentyn-3-ol. The superiority of HBF_4–SiO_2 over the metal triflates during acylation of alcohols may be best demonstrated through comparison of the results of a few representative examples of acid-sensitive and sterically hindered substrates. Thus, acylation of 1-methylcyclohexanol carried out in the presence of $Sc(OTf)_3$ required 5 equiv. of Ac_2O at −20°C for 5 h to afford a 91% yield.[9a,b] The TMSOTf catalyzed acylation of the same substrate was carried out at −10°C in Ac_2O as solvent. The HBF_4–SiO_2 catalyzed reaction afforded a 77% yield with stoichiometric amounts of Ac_2O at room temperature for 2 h. The reaction of 1-ethynylcyclohexanol catalyzed by $Sc(OTf)_3$, $Bi(OTf)_3$ and TMSOTf required 10 equiv. of Ac_2O and MeCN/DCM as co-solvents to afford 94, 88, and 68% yields, respectively, in 2–4 h. Contrary to these, a 96% yield of the product could be obtained with 1 equiv. of Ac_2O for 6 h using HBF_4–SiO_2 in the absence of solvent. Quantitative acylation of 3-methyl-1-pentyn-3-ol takes place with a stoichiometric amount of Ac_2O in the absence of solvent at room temperature under the catalytic influence of HBF_4–SiO_2 but the corresponding TMSOTf catalyzed reaction required 2 equiv. of Ac_2O in DCM at 0°C to afford an 80% yield. Acylation of the sterically hindered *endo*-borneol required the use of 10 equiv. of Ac_2O in THF for 7 h in the presence of TMSOTf and the corresponding $Bi(OTf)_3$ catalyzed reaction required 10 equiv. of Ac_2O in THF to afford a 99% yield in 7 h. In contrast, the HBF_4–SiO_2 catalyzed reaction afforded comparable results in 45 min with 1 equiv. of Ac_2O in the absence of solvent.

While comparing the catalytic efficiencies of HBF_4–SiO_2 with other reported catalysts, we found that, HBF_4 on SiO_2 is superior as it is less costly[21] and the reactions are, in general, carried out with stoichiometric amounts of Ac_2O,[22] at room temperature,[23] and in the absence of solvent.[24]

In conclusion, HBF_4–SiO_2 is a new and efficient catalyst for the acylation of phenols, thiols, alcohols and amines. The low cost and with increasing environmental concerns;[25] the solvent free conditions employed in the present method will make it 'environmentally friendly' and potentially useful for industrial applications.

Preparation of HBF_4–SiO_2: A magnetically stirred suspension of silica gel (26.7 g, 230–400 mesh) in diethyl ether (75 ml) was treated with 40% aq. HBF_4 (3.3 g) for 3 h. The mixture was concentrated and the residue dried under vacuum at 100°C for 72 h to afford HBF_4–SiO_2 (0.5 mmol of HBF_4 g m^{-1}).

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18. Reaction with 4-hydroxybenzaldehyde resulted in a mixture of 4-acetoxybenzaldehyde, 4-hydroxybenzaldehyde-1,1-diacetate, and 4-acetoxybenzaldehyde-1,1-diacetate.
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21. Aldrich (India) 2000–2001 price (US $): $In(OTf)_3$ (50 g, 362.20); $Cu(OTf)_2$ (50 g, 384.80); $Sc(OTf)_3$ (50 g, 1590.00); estimated price (not available commercially) (US $): $Sc(NTf_2)_3$ (50 g, >4896.00); estimated price (not available commercially) (US $): $Bi(OTf)_3{\cdot}xH_2O$ (50 g, >315.95); HBF_4 (200 g, 3.6).

22. Ac_2O (equivalents) required for the reported catalysts: $Sc(OTf)_3$ (1.5—as solvent); $Sc(NTf_2)_3$ (1.5); clays (2.0); zeolite (2.0); TMSOTf (1.5—as solvent); $Cu(OTf)_2$ (2.0); $Bi(OTf)_3$ (1.5–10); $LiClO_4$ (2–10); HBF_4 (1).
23. High temperatures required for the reported catalysts: Yttria-zirconia 80°C; clays (40–80°C); zeolite (60°C); $LiClO_4$ (rt–40°C). Low temperatures required for acid-sensitive substrates: $Cu(OTf)_2$ (0°C); $Sc(OTf)_3$ (−20 to −50°C); TMSOTf (−10°C); HBF_4 (room temperature).
24. The reported catalysts require solvent: $Sc(OTf)_3$ (MeCN or Ac_2O); $Sc(NTf_2)_3$ (MeCN); clays (DCM or $CHCl_3$); Yttria-zirconia (MeCN); TMSOTf (DCM, MeCN/EtOAc, Ac_2O); $Cu(OTf)_2$ (MeCN), $Bi(OTf)_3$ (MeCN, THF, toluene, DCM); HBF_4 (no solvent is required).
25. Garrett, R. L. In *Designing Safer Chemicals*; Garrett, R. L.; De Vito, S. C., Eds.; American Chemical Society Symposium Series 640: Washington DC, 1996; Chapter 1.