

Perchloric acid adsorbed on silica gel as a new, highly efficient, and versatile catalyst for acetylation of phenols, thiols, alcohols, and amines†

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Perchloric acid adsorbed on silica gel efficiently catalyses acetylation of structurally diverse phenols, alcohols, thiols, and amines under solvent free conditions.

The prevalence of phenol, thiol, alcohol, and amine functionalities in drugs and pharmaceuticals makes the protection of these functional groups a prime importance while carrying out reactions sensitive to such functionalities in a multifunctional substrate having one or more of these groups. Protection is usually achieved through acylation with anhydrides¹ due to the ease of deprotection.^{1,2} The poor nucleophilicity of hydroxylic compounds, particularly phenols, makes it essential to activate the anhydride. Recent procedures for acylation with anhydride include the use of Bu_3P ,³ metal triflates such as $\text{Sc}(\text{OTf})_3$,⁴ TMSOTf ,⁵ $\text{Sc}(\text{NTf}_2)_3$,⁶ $\text{Cu}(\text{OTf})_2$,⁷ $\text{In}(\text{OTf})_3$,⁸ $\text{Bi}(\text{OTf})_3$,^{9,10} clays,¹¹ zeolite,¹² Nafion-H,¹³ and yttria-zirconia.¹⁴ The limitations of the existing protocols realized in terms of longer reaction time, stringent conditions, use of halogenated solvents, use of hazardous materials (*e.g.* DMAP¹ is highly toxic, Bu_3P is flammable and air sensitive), use of costly and water sensitive catalysts (*e.g.* the triflates), special efforts required to prepare the catalyst (*e.g.* $\text{Bi}(\text{OTf})_3$, Nafion-H, yttria-zirconia), need to use excess acylating agent, potential side reactions with acid-sensitive substrates and in most of the cases being applicable to alcohols only make the necessity to develop a better acylation method in high demand.

Although recently the triflates have emerged as the most effective catalysts, the strong Lewis acid character of the triflates makes their use for acid-sensitive substrates difficult necessitating the use of a large excess of acylating agent and carrying out the reaction at low temperature to avoid potential side reactions. The high cost and susceptibility to aqueous medium of the metal triflates become a major concern for their industrial applications.

It has been proposed that during the triflate catalyzed acylation, the liberated TfOH acts as the actual catalytic agent.¹⁰ We reasoned that the large negative H_0 value of -14.1 of TfOH¹⁵ might be the reason for the potential competitive side reactions with acid-sensitive substrates during the use of metal triflates. Therefore, the use of a protic acid weaker than TfOH should permit acylation without any potential side reaction. Since HClO_4 is the next strongest protic acid known, we planned to evaluate its catalytic activity during the reaction of 2-naphthol with Ac_2O . Although the use of 0.1–1 mol% of aqueous HClO_4 resulted in almost quantitative formation of 2-naphthyl acetate in 15 min, acylation of acid-sensitive substrates such as geraniol and linalool catalyzed by aqueous HClO_4 led to the formation of rearranged products. Anticipating that the aqueous conditions might be the reason for the detrimental effect, we planned to use HClO_4 supported on silica gel ($\text{HClO}_4\text{-SiO}_2$).¹⁶ Moreover, the increasing pressure from environmentalists has led to a search for more friendly forms of catalysis. The leading contender for an environmentally acceptable alternative to the acylation processes is the use of supported

reagents. The activity and selectivity of a reagent dispersed on the surface of a support is improved as the effective surface area of the reagent can be increased up to one hundred times. The fact that supported reagents have good thermal and mechanical stabilities, can be easily handled as they are invariably low toxic, non-corrosive free flowing powders and are easily separated from the reaction mixture through filtration and reused make them suitable for industrial applications.

The results incorporated in Table 1 demonstrate the generality and scope of $\text{HClO}_4\text{-SiO}_2$ during the acetylation of structurally diverse phenols, thiols, amines and alcohols under solvent free conditions. The reaction could be carried out with one equiv. of Ac_2O at room temperature in 5–30 min. Sterically hindered and electron deficient phenols and amines (entries 3, 4, 8, 9, 18, and 19) are efficiently acetylated under solvent free conditions. Excellent chemoselectivity was observed in that secondary and tertiary alcohols do not experience any competitive dehydration (entries 22, 24–34) and no rearrangement took place for allylic and propargylic substrates (entries 30–34). Optically active substrates were efficiently acetylated without any detrimental effect on the optical purity (entries 25–27) demonstrating the mildness of the acetylation process. Sterically hindered alcohols could be effectively acetylated (entries 24, 28 and 34). The catalyst was recovered and reused five consecutive times giving excellent yields.¹⁷

The superiority of $\text{HClO}_4\text{-SiO}_2$ as acetylation catalyst over the metal triflates could be established while comparing the results obtained with a few representative acid-sensitive substrates. Thus, the $\text{Sc}(\text{OTf})_3$ ⁴ and TMSOTf ⁵ catalyzed acetylation of 1-methylcyclohexanol used 5 equiv. of Ac_2O at -20 and -10 °C respectively to afford comparable results obtained with 1 equiv. of Ac_2O at room temperature under the catalytic influence of $\text{HClO}_4\text{-SiO}_2$ (entry 24). The $\text{Bi}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$ and TMSOTf catalyzed acetylation of 1-ethynylcyclohexanol afforded 94, 88, and 62% yields in 4, 4, and 2 h, respectively, with 10 equiv. of Ac_2O ⁹ whereas the corresponding acetylated product could be obtained in 90% yields in 15 min with 1 equiv. of Ac_2O in the presence of $\text{HClO}_4\text{-SiO}_2$ (entry 34). The TMSOTf ⁵ catalyzed acetylation of linalool results in the formation of the rearranged product geranyl acetate and the $\text{Sc}(\text{OTf})_3$ ⁴ catalyzed reaction carried out at -20 °C affords a 68% yield of linalyl acetate and 8% geranyl acetate even with the use of Ac_2O as solvent. An 80% yield of linalyl acetate is obtained in the presence of $\text{Bi}(\text{OTf})_3$ with 10 equiv. of Ac_2O .⁹ Contrary to these findings, the $\text{HClO}_4\text{-SiO}_2$ catalyzed acetylation affords an 80% yield of linalyl acetate using 1 equiv. of Ac_2O . While the acetylation of 1-adamantanol with 10 equiv. of Ac_2O afforded 98, 99, and 94% yields in 6, 8.5, and 3.5 h, respectively, during the $\text{Bi}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$ and TMSOTf catalyzed acetylation,⁹ a 90% yield was obtained with 1 equiv. of Ac_2O in 15 min in the presence of $\text{HClO}_4\text{-SiO}_2$ (entry 28). To compare the catalytic activity of $\text{HClO}_4\text{-SiO}_2$ with the conceptually related $\text{H}_2\text{SO}_4\text{-SiO}_2$, linalool was treated with stoichiometric quantities of Ac_2O in MeCN for 1 h at room temperature. An 80% yield of the acetylated product was obtained under the catalytic influence of $\text{HClO}_4\text{-SiO}_2$ whereas no significant amount of acetylation took place in the presence of $\text{H}_2\text{SO}_4\text{-SiO}_2$.

† Electronic supplementary information (ESI) available: general experimental details, spectral data, comparison of $\text{HClO}_4\text{-SiO}_2$ with other reported catalysts. See <http://www.rsc.org/suppdata/cc/b3/b304178f/>

Table 1 HClO₄-SiO₂ catalyzed acetylation of phenols, thiols, amines and alcohols^{ab}

Entry	Substrate	Time/min	Yield (%)	Entry	Substrate	Time/min	Yield (%)
1	2-Naphthol	5	93	18	2-Nitroaniline	15	83
2	4-Methoxyphenol	15	94	19	2,4-Dinitroaniline	30	91
3	2,6-Di- <i>tert</i> -butyl-4-methylphenol	15	100 ^c	20	Benzyl alcohol	60	96
4	2,4,6-Trimethylphenol	15	94	21	2-Phenethyl alcohol	30	90
5	4-Bromophenol	30	92	22	1-Phenethyl alcohol	60	87 ^f
6	4-Hydroxyacetophenone	15	99	23	Benzoin	15	82
7	4-Hydroxymethylbenzoate	15	98	24	1-Methylcyclohexanol	30	92 ^f
8	4-Cyanophenol	15	92	25	α-D-Glucose	30	89 ^g
9	4-Nitrophenol	30	91	26	(-)-Menthol	5	90
10	Hydroquinone	5	83 ^d	27	(-)-Borneol	45	92
11	Catechol	15	97 ^d	28	1-Adamantanol	15	90
12	Resorcinol	10	91 ^d	29	Geraniol	60	90
13	Benzene 1,2,3-triol	10	89 ^e	30	Linalool	60	80 ^f
14	Benzenethiol	5	99	31	Propargyl alcohol	30	100
15	4-Methylbenzenethiol	15	92	32	2-Methyl-3-butyne-2-ol	30	100
16	4-Methoxybenzenethiol	15	95	33	3-Methylpent-1yne-3-ol	30	100
17	α-Toluenethiol	30	90	34	1-Ethynylcyclohexanol	15	90 ^f

^a The substrate was treated with Ac₂O (1 equiv. per OH/SH/NH₂ group except for entry 3) in the presence of HClO₄-SiO₂ (1 mol%) under neat conditions (except entries 22, 24, 30, 34) at room temperature. ^b Isolated yield of the corresponding acetylated product. ^c 1.5 equiv. of Ac₂O was used at room temperature. ^d Isolated yield of the di-acetate. ^e Isolated yield of the tri-acetate. ^f The reaction was carried out in MeCN at room temperature. ^g Isolated yield of the penta-acetate.

Table 2 HClO₄-SiO₂ catalyzed direct acetylation of alcohols with HOAc

Entry	Substrate	Method A ^a		Method B ^a	
		Time/h	Yield ^b (%)	Time/h	Yield ^b (%)
1	Benzyl alcohol	6	94	0.25	96
2	2-Phenethyl alcohol	2	90	0.5	93
3	1-Phenethyl alcohol	6	90	0.5	90
4	1-Phenyl-1-propanol	6	75 ^c	0.5	91
5	1-Ethynyl cyclohexanol	6	90	—	—
6	(-)-Menthol	6	97 ^d	0.5	95 ^d
7	(-)-Borneol	—	—	0.5	90 ^d
8	1-Adamantanol	—	—	0.5	80 ^e
9	Propargyl alcohol	6	85	—	—
10	2-Methyl-3-butyne-2-ol	6	87	—	—

^a The substrate was treated with HOAc (5 equiv.) in the presence of HClO₄-SiO₂ (1 mol%) at room temperature (Method A) or at 65 °C (Method B).

^b Isolated yield of the corresponding acetylated product. ^c A 2 mL of HOAc was used for 1 mmol of the substrate. ^d The reaction was carried out at 80 °C using 2 mL of HOAc per mmol of the substrate. ^e The reaction was carried out at 110 °C using 5 mL of HOAc per mmol of the substrate.

We next extended the use of HClO₄-SiO₂ for direct acetylation of alcohols with HOAc (Table 2). The superiority of HClO₄-SiO₂ is further established in the fact that direct acetylation of benzyl alcohol, 2-phenethyl alcohol, and 1-phenethyl alcohol with HOAc (5 equiv.) could be achieved in 6 h at room temperature (90–94% yields) or at 65 °C in 0.25–0.5 h (90–96% yields) under the catalytic influence of HClO₄-SiO₂ (1 mol%). The corresponding reactions catalyzed by Cu(OTf)₃⁷ or Sc(OTf)₃¹⁸ afforded comparable results under heating at 65 °C for 8–14 h using HOAc as solvent.

In conclusion, HClO₄-SiO₂ is a new and highly efficient catalyst for acetylation of phenols, thiols, alcohols and amines. The low cost, ease of handling and, with increasing environmental concern,¹⁹ the solvent free conditions employed in the present method, which make it “environmentally friendly”, fulfil the “triple bottom line philosophy”²⁰ and make it useful for industrial applications.

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- Preparation of HClO₄-SiO₂**: HClO₄ (1.25 g, 12.5 mmol, as a 70% aqueous solution) was added to the suspension of silica gel (23.75 g, 230–400 mesh) in Et₂O. The mixture was concentrated and the residue heated at 100 °C for 72 h under vacuum to afford HClO₄-SiO₂ (0.5 mmol g⁻¹) as a free flowing powder.
- Typical procedure of acetylation**: 2-naphthol (360 mg, 2.5 mmol) was treated with Ac₂O (0.24 ml, 2.5 mmol) in the presence of HClO₄-SiO₂ (50 mg, 0.025 mmol of HClO₄) for 5 min at room temperature under magnetic stirring. The mixture was diluted with Et₂O (25 ml) and the catalyst allowed to settle down. The supernatant ethereal solution was decanted off, the catalyst washed with Et₂O (2 ml) and the combined ethereal solution concentrated under vacuum to afford the product (432 mg, 93%), identical (mp, IR, ¹H and ¹³C NMR, and EIMS) to an authentic sample of 2-naphthyl acetate. The recovered catalyst was activated by heating at 80 °C under vacuum for 2 h and reused for acetylation of a fresh lot of 2-naphthol (2.5 mmol) affording 90% yield of 2-naphthyl acetate after 10 min. The recovered catalyst, after activation, was reused for four more consecutive acetylation reactions of 2-naphthol (2.5 mmol) affording 90, 85, 80, and 75% yields, respectively, in 15, 15, 15, and 30 min.
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