$HClO_4$–SiO_2 as a new, highly efficient, inexpensive and reusable catalyst for *N-tert*-butoxycarbonylation of amines

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Perchloric acid adsorbed on silica-gel ($HClO_4$–SiO_2) was found to be a new, highly efficient, inexpensive and reusable catalyst for chemoselective *N-tert*-butoxycarbonylation of amines at room temperature and under solvent-free conditions.

Introduction

Synthesis of *N-t*-butylcarbamates is an important and frequently needed exercise in synthetic organic/medicinal chemistry, as *N-tert*-butoxycarbonylation constitutes an efficient route for the protection of amines,[1] and *N-t*-butylcarbamates serve as key starting materials for various drugs and their intermediates. The common practice for *N-tert*-butoxycarbonylation is treatment of an amine with di-*tert*-butyl dicarbonate [$(Boc)_2O$] in the presence of DMAP,[2] organic/inorganic bases,[3] or Lewis acids.[4] Other procedures involve the reaction of an amine with 4-dimethylamino-1-*tert*-butoxycarbonylpyridinium chloride/tetrafluoroborate in aqueous NaOH,[5] 2-*tert*-butyloxycarbonyloxyimino-2-phenylacetonitrile in the presence of Et_3N in H_2O–dioxane,[6] *tert*-butyl-2-pyridyl carbonate in the presence of Et_3N in H_2O–DMF[7] or *tert*-butyl-1-chloroalkyl carbonates in the presence of K_2CO_3 in H_2O–THF.[8] However, these methodologies have various drawbacks such as long reaction times, special efforts required to prepare the *tert*-butoxycarbonylation reagents[5–8]/catalyst,[4] requirement of auxiliary substances (*e.g.* solvents and other reagents), potential hazards in handling the catalysts (*e.g.* the high toxicity of DMAP[9] does not qualify it, and the *tert*-butoxycarbonylation reagents derived from it, to be safe for use, the preparation of yttria–zirconia involves use of sulfuric acid at 500 °C,[4a] $ZrCl_4$ is highly moisture sensitive, decomposes on storing and liberates corrosive HCl fumes) *etc.* The base catalysed reactions often lead to the formation of side products such as isocyanate,[2d,10] urea,[2d] and *N*,*N*-di-Boc derivatives.[2d,11] These drawbacks necessitate the development of new synthetic methodology.

We felt that the formation of side products such as isocyanate, urea, and *N*,*N*-di-Boc derivatives would be avoided by the use of a Lewis acid catalyst, as the few reported Lewis acid-catalysed methods[4] of *N-tert*-butoxycarbonylation did not experience these side reactions. Recently, we have been engaged in the development of various catalysts for acylation[12] following the 'electrophilic activation' strategy. Subsequently, we observed that some of these catalysts were also found to be effective for thia-Michael addition,[13] 1,1-diacetate[14]/imine[15]/acetal[16]/dithiolane[17] formation and *N-tert*-butoxycarbonylation.[18] The tight legislation on the maintenance of greenness in synthetic pathways and processes demands the prevention of waste and avoidance of the use of auxiliary substances (*e.g.* solvents, additional reagents) and hazardous materials.[19] Thus, we kept this in mind while designing a new methodology. We planned to explore the efficiency of $HClO_4$–SiO_2 as a catalyst for *N-t*-Boc formation on the following grounds: (i) our experience revealed that it was the most effective catalyst for acylation, (ii) it is not associated with the problems encountered with some of the reported Lewis acid catalysts,[4] (iii) the increasing pressure from environmentalists has led to the development of sustainable chemistry and the leading contender for an environmentally acceptable alternative process is the use of supported reagents, (iv) the activity and selectivity of a reagent dispersed on a solid support is often improved, (v) supported reagents have good thermal and mechanical stabilities, can be easily handled, are easily separated from the reaction mixture through filtration and can be reused.

Results and discussion

Various aromatic, heteroaromatic, aliphatic and heterocyclic amines were treated with $(Boc)_2O$ (1 eq.) under solvent-free conditions at rt (~30–35 °C) in the presence of $HClO_4$–SiO_2 (1 mol%). The reactions were completed after 1 min–3 h affording excellent yields (Table 1). No competitive side reactions such as the formation of isocyanate,[2d,10] urea,[2d] or *N*,*N*-di-BOC derivative[2d,11] were observed. The catalyst was compatible with various functionalities such as F, Cl, Br, OH, SH, OMe, OBn, CO_2Me, and α,β-unsaturated carbonyl group. In most cases, the products obtained after the usual work-up were pure (spectral data).

Excellent chemoselectivity was observed for substrates with an OH/SH group (Table 1, entries 8 and 9) providing *N-t*-Boc derivatives as the sole product and no significant *O*/*S-tert*-butoxycarbonylation took place (IR).[2d,20] The chemoselectivity was further demonstrated by the reaction with amino acetaldehyde dimethyl acetal (Table 1, entry 20) that is sensitive to acids. The catalyst was recovered and reused after activation for *N-tert*-butoxycarbonylation of aniline (2.5 mmol) for four consecutive operations affording the product in 90, 90, 80 and 75% yields after 5, 5, 15 and 15 min.

We next planned to evaluate the effectiveness of this methodology for *N-t*-Boc formation of chiral amines, α-amino acid esters and a β-amino alcohol (Table 2). In each case, the corresponding optically pure (as determined by the optical rotation and comparison with literature values) *N-t*-Boc derivatives were formed

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Table 1 $HClO_4$–SiO_2-catalysed *N-tert*-butoxycarbonylation of amines[a]

Entry	Amine	Time/min	Yield (%)[b]
1	Aniline	5	100
2	4-Methylaniline	5	100
3	2,4-Dimethylaniline	30	95
4	2,4,6-Trimethylaniline	30	95
5	4-Methoxyaniline	5	98
6	4-Benzyloxyaniline	15	100
7	2,4-Dimethoxyaniline	30	90
8	4-Aminophenol	60	95
9	4-Aminothiophenol	30	92
10	4-Fluoroaniline	10	98
11	4-Bromoaniline	30	100
12	4-Bromo-2-methylaniline	30	100
13	3-Chloro-4-fluoroaniline	180	90
14	9-Ethyl-9*H*-carbazol-3-ylamine	15	90
15	4-Aminopyridine	15	100
16	2-Aminobenzimidazole	60	90
17	4-Aminoantipyrine	60	100
18	Benzylamine	1	100
19	Phenethylamine	2	100
20	2,2-Dimethoxyethylamine	1	100
21	Furfurylamine	5	100
22	2-Piperidin-1-yl-ethylamine	5	100
23	2-Morpholin-4-yl-ethylamine	5	100
24	Cyclohexylamine	15	100
25	*N*,*N*-Dicyclohexylamine	45	100
26	*N*,*N*-Dibenzylamine	10	100

[a] The amine (2.5 mmol) was treated with $(Boc)_2O$ (1 eq.) in the presence of the catalyst (1 mol%) under neat conditions at rt (~30–35 °C). [b] Isolated yield of the *N-t*-Boc derivative.

Table 2 $HClO_4$–SiO_2-catalysed *N-tert*-butoxycarbonylation of chiral amines, esters of α-amino acids and a β-amino alcohol[a]

Entry	Amine	Time/min	Yield (%)[b]
1	(*S*)-α-Methylbenzylamine	1	100
2	(*R*)-α-Methylbenzylamine	1	100
3	L–NH_2–Phg–OMe	10	95
4	L–NH_2–Phe–OMe	15	97
5	L–NH_2–Tyr–OMe	15	80
6	L–NH_2–Tyr–OEt	20	92
7	L–NH_2–Tyr–(OBn)OBn	15	95
8	L–NH–Pro–OMe	10	100
9	L–His–OMe	15	95
10	L–Phenylalaninol	15	90

[a] The amine (2.5 mmol) was treated with $(Boc)_2O$ (1 eq.) in the presence of the catalyst (1 mol%) under neat conditions at rt (~30–35 °C). [b] Isolated yield of the *N-t*-Boc derivative.

in excellent yields. Reaction with phenylalaninol (Table 2, entry 10) resulted in chemoselective formation of the *N-t*-Boc derivative without formation of oxazolidinone.[2d,21]

To compare the advantage of the use of $HClO_4$–SiO_2 over the reported Lewis acid catalysts, the reactions with aniline, dibenzylamine, aminoacetaldehyde dimethyl ether, (*R*)/(*S*)-α-methylbenzylamine and (*S*)-phenylglycine methyl ester were considered as a few representative examples. Treatment of aniline in the presence of yttria–zirconia (20% by weight) in MeCN afforded *tert*-butyl-*N*-phenylcarbamate in 90% yield after 14 h[4a] and 92% yield was obtained after 12 h in DCM in the presence of $Zn(ClO_4)_2$ (5 mol%).[4b] However, the use of $HClO_4$–SiO_2 (1 mol%) afforded a quantitative yield after 5 min under solvent-free conditions. The reaction of dibenzylamine afforded the product in 93% yield after 5.5 h in the presence of $Zn(ClO_4)_2$ (5 mol%) under solvent-free conditions[4b] and 90% yield after 5 h in DCM in the presence of $LiClO_4$ (20 mol%),[4d] whereas, a quantitative yield was obtained after 10 min under solvent-free conditions in the presence of $HClO_4$–SiO_2 (1 mol%). The *N-t*-Boc derivative of aminoacetaldehyde dimethyl ether was obtained in 90% yield after 16 h during the $Zn(ClO_4)_2$-catalysed (5 mol%) reaction[4b] compared to a quantitative yield obtained after 1 min in the presence of $HClO_4$–SiO_2 (1 mol%) under similar conditions. The $Zn(ClO_4)_2$-catalysed (5 mol%) *N-tert*-butoxycarbonylation of (*R*)-α-methylbenzylamine afforded the product in 97% yield after 2.5 h under solvent-free conditions.[4b] The *N-t*-Boc of (*S*)-α-methylbenzylamine was obtained in 85% yield after 5 h in the presence of $LiClO_4$ (20 mol%) in DCM.[4d] Compared to these results, quantitative yields were obtained with (*R*)- and (*S*)-α-methylbenzylamine under solvent-free conditions after 1 min in the presence of $HClO_4$–SiO_2 (1 mol%). Reaction of (*S*)-phenylglycine methyl ester provided an 88% yield of the product after 5 h in DCM in the presence of $LiClO_4$ (20 mol%)[4d] compared to 97% yield obtained after 15 min in the presence of $HClO_4$–SiO_2 (1 mol%) under solvent-free conditions. These results clearly demonstrate that $HClO_4$–SiO_2 is the best Lewis acid catalyst for *N-t*-Boc formation.

In conclusion, we have described herein $HClO_4$–SiO_2 as a new, highly efficient, inexpensive and reusable catalyst for chemoselective *N-tert*-butoxycarbonylation of amines. The advantages, such as: (i) the use of an inexpensive and easy to handle catalyst, (ii) solvent-free[22] and room temperature reaction conditions, (iii) short reaction times, (iv) high yields and (vi) ease of product isolation/purification fulfill the 'triple bottom line philosophy'[23] of green chemistry.

Experimental

Typical experimental procedure for *N-tert*-butoxycarbonylation of amines

To a magnetically stirred mixture of $(Boc)_2O$ (0.545 g, 2.5 mmol) and $HClO_4$–SiO_2[24] (50 mg, 0.025 mmol of $HClO_4$), aniline (0.235 g, 2.5 mmol, 1.0 eq.) was added and the mixture was stirred at room temperature (~30–35 °C) until completion of the reaction (5 min, TLC, IR, GCMS). The mixture was diluted with Et_2O (25 mL) and the catalyst allowed to settle down. The supernatant ethereal solution was decanted off, the catalyst washed with Et_2O (2 mL) and the combined ethereal solution concentrated under vacuum to afford *N-tert*-butylphenylcarbamate (white solid, 0.485 g, 100%, entry 1, Table 1), identical to an authentic sample.[2d] The catalyst was recovered, activated by heating at 80 °C under vacuum for 2 h and reused for four consecutive *N-tert*-butoxycarbonylations of aniline (2.5 mmol) affording 90, 90, 80, and 75% yields of the *N-t*-Boc derivative after 5, 5, 15 and 15 min, respectively. The remaining reactions were carried out following this procedure. In all cases, the crude products were found to be sufficiently pure (GCMS) and did not require any further efforts for purification. In a few cases wherein the solid crude product had a sticky appearance, the isolated product was triturated with 5% EtOAc in hexane to afford the product as a free flowing solid and on such occasions the isolated yields were less than 100%. The spectral data (IR,

NMR and MS) of all known products were identical with those of authentic compounds. The following compounds were unknown.

(9-Ethyl-9*H*-carbazol-3-yl)carbamic acid *tert*-butyl ester (Table 1, entry 14). Mp 161–162 °C; IR ν_{max} (KBr) = 3165, 2960, 1726, 1608, 1526, 1332, 1255, 1158, 1045, 999, 820 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.52 (9H, s, O-*t*-Bu), 1.55 (3H, s, Me), 4.33 (2H, d, *J* 7.10 Hz, CH_2), 6.55 (1H, s, NH_r), 7.19–7.45 (5H, m, Ph), 8.05–8.17 (2H, 2, Ph); δ_C (75 MHz, $CDCl_3$; Me_4Si) 13.80, 27.42, 37.58, 80.13, 108.41, 111.55, 118.56, 120.67, 122.76, 123.14, 125.72, 130.13, 136.13, 140.43, 153.129; MS (EI): *m*/*z* 310 (M^+); Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03; O, 10.31%. Anal. Found: C, 73.51; H, 7.15; N, 8.96; O, 10.24%.

Dicyclohexylcarbamic acid *tert*-butyl ester (Table 1, entry 25). Mp 58–59 °C; IR ν_{max} (KBr) = 2970, 2934, 2853, 1678, 1435, 1367, 1295, 1240, 1157 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.04–1.77 (m, 31H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 25.49, 26.22, 28.50, 31.21, 54.69, 78.84, 155.32; MS (APCI) *m*/*z*: 181 (M^+ − 100); Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 72.55; H, 11.10; N, 4.98%. Anal. Found: C, 72.48; H, 11.13; N, 5.08%.

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