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N-tert-Butoxycarbonylation of amines using $H_3PW_{12}O_{40}$ as an efficient heterogeneous and recyclable catalyst

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This Letter is dedicated to Professor Mehdi Golshani on the occasion of his 70th birthday

Abstract—The commercially available heteropoly acid $H_3PW_{12}O_{40}$ (0.5 mol %) is a very efficient and environmentally benign catalyst for *N-tert*-butoxycarbonylation of amines (primary, secondary) with di-*tert*-butyl dicarbonate at room temperature in short reaction times (<10 min). No competitive side products such as isocyanates, ureas, *N*,*N-di-tert*-butoxycarbonyls, *O*-Boc and oxazolidinones were observed. Chiral α-amino alcohols and esters afforded the corresponding *N*-Boc derivatives chemoselectively in excellent yields.
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1. Introduction

As *N-tert*-butoxycarbonyl amino acids are resistant to racemization during peptide synthesis, the *N*-Boc moiety is one of the most important amine protecting groups.[1,2] The *tert*-butoxycarbonyl group is cleaved with CF_3CO_2H in 5–10 min at room temperature. Cheaper acids such as 3 M HCl in EtOAc or 10% H_2SO_4 in dioxane or hot formic acid can be considered for large scale deprotection. *N*-Boc-protected amino acids can easily be converted into the free amine and are useful in Merrifield's solid phase peptide synthesis. The stability of *N*-Boc to catalytic hydrogenation and its resistance towards basic and nucleophilic attack make carbamates and benzyl esters ideal orthogonal partners for protection of amines during the synthesis of multifunctional targets.[3] Various reagents and methods have been developed for *N-tert*-butoxycarbonylation of amines.[4] Most are carried out in the presence of a base, for example: 4-(dimethylamino)-1-*tert*-butoxycarbonylpyridinium chloride or tetrafluoroborate in aq NaOH,[5] *tert*-butyl-1-chloroalkyl carbonates/K_2CO_3,[1b] 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile/Et_3N,[1b] or di-*tert*-butyl pyrocarbonate in the presence of DMAP.[6] Commercially available di-*tert*-butyl dicarbonate is an efficient reagent for clean and rapid introduction of the *t*-Boc-protecting group. Although alkylamines are well known to give, without the assistance of any catalyst, the mono-protected derivatives on reaction with $(Boc)_2O$,[7a,b] the analogous reactions of poorly reactive primary and secondary arylamines, due to their reduced nucleophilicity, proceed sluggishly.[4,7c] Moreover, the base catalyzed reactions are often associated with the occurrence of various side reactions such as biscarbamoylation, or the formation of isocyanates and urea.[8] Further, the high toxicity of DMAP and reagents derived from it, limit their use.[9] Due to the very attractive nature of the *N*-Boc group, there have been many attempts to find alternative methodologies for this reaction, which do not suffer the drawbacks associated with the classical procedures.

There are limited number of reports on the use of Lewis acid catalysts to effect the above transformation. These include yttria-zirconia,[10] $Zn(ClO_4)_2{\cdot}6H_2O$,[11] $LiClO_4$,[12] $ZrCl_4$,[13] $Cu(BF_4)_2{\cdot}XH_2O$,[14] $HClO_4/SiO_2$[15] and Montmorillonite K10 or KSF.[16] Although these methods circumvent the problems associated with the formation of the above mentioned side products, they are plagued by a number of other serious drawbacks and have limited applications in large scale applications (e.g., the use of

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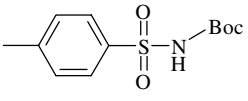
H_2SO_4 at 500 °C to prepare yttria-zirconia; $ZrCl_4$ is highly moisture sensitive and liberates HCl fumes; perchlorate reagents are strong oxidants and explosive in nature). Moreover, it should be noted that most Lewis acids cannot be used in this reaction since they are consumed and deactivated by the amines.[17] Even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are needed, as the acids are trapped by the basic nitrogen.[18]

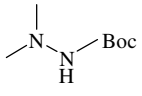
Over the past three decades, heteropoly compounds have been extensively studied as homogeneous and heterogeneous acid and oxidation catalysts for many reactions.[19] They also have found industrial applications in several processes as oxidants and acid catalysts both in solid and in solution reactions. Presently, four industrial processes utilize heteropoly compounds, propylene hydration, methacrolein and olefin oxidation and the polymerization of tetrahydrofuran.[20] Except for methacrolein oxidation, these industrial processes are based on polyoxometallate homogeneous catalysis with high conversion and selectivity at very low temperature. The use of heteropoly compounds in acid catalyzed reactions has opened new possibilities for processes requiring acidities greater than mineral acids, ion-exchange resins, zeolites, mixed oxides, H_3PO_4/SiO_2, CF_3SO_3H, PTS and CF_3COOH, in both heterogeneous and homogeneous systems. Furthermore, when using hetropoly acid (HPAs) fewer side reactions occur, which frequently take place with mineral acids. HPAs are non corrosive and environmentally benign. Dodecatungstophosphoric acid, $H_3PW_{12}O_{40}$ (PW), is an effective catalyst in the Keggin series. These HPAs can be reused or recycled, involve easy work up procedures, possess high structural and thermal stability and well defined acidic and redox properties, and have attracted much attention in synthetic chemistry.[21] Furthermore, $H_3PW_{12}O_{40}$ is found to retain its activity even in the presence of a number of organic substrates containing *N*, *S* or *O* atoms, that is, amino acids,[22] quinoline,[23] TTF[24] and crown ethers.[25] This prompted us to use this catalyst for the synthesis of *N*-Boc protected amines.

Herein we report that $H_3PW_{12}O_{40}$ is as an excellent catalyst for the selective *tert*-butoxycarbonylation of various amines and amine derivatives. The products obtained are summarized in Table 1. The method can be applied to the conversion of sterically hindered amines, such as *tert*-butylamine, as well as the poorly reactive 4-nitroaniline. With 1,2-phenylenediamine, only the mono *N*,*t*-Boc protected product was obtained in reasonably good yield (86%) under $H_3PW_{12}O_{40}$ catalyzed conditions. However, under conventional conditions the reaction of 1,2-phenylenediamine with Boc_2O in MeCN at rt afforded the *N*,*N*-di-Boc product in 95% yield after 24 h.[26] The use of Boc_2O in the presence of 0.5 equiv of 4-(dimethylamino)pyridine and 1,2-phenylendiamine afforded 1,3-di-*t*-Boc benzimidazolidinone in 50% yield and 50% of starting amine was recovered.[6b] In a further study, an α-amino acid ester was converted into the corresponding *N*-Boc ester under similar reaction conditions. It is noteworthy that the reaction is chemoselective in the case of 2-phenylglycinol, *N*-benzylethanolamine and ephedrine where the corresponding *N*-Boc protected products were obtained as the sole products, no *O*-Boc or oxazolidinone derivatives were observed, even though alcohols are known to react with Boc_2O in the presence of DMAP to give *O*-Boc-derivatives together with symmetrical carbonates.[27] Another notable feature of the reaction is that a secondary amine reacted smoothly to afford the desired product in high isolated yield. The insolubility of the catalyst (PW) in CH_2Cl_2 allows for easy separation of the product by simple filtration; PW was reused with only a gradual decrease in its activity observed. For example, the reaction of (*S*)-α-methylbenzylamine (**1c**) and $(Boc)_2O$ afforded the corresponding *N*-Boc derivative in 88%, 88% and 87% yields over three cycles (entry c).

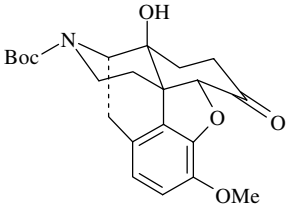
In continuation of this study, *p*-toluenesulfonamide and *N*,*N*-dimethylhydrazine underwent smooth *N*-Boc protection in the presence of PW (0.5 mol % in <10 min) to give **3r** and **3s**, respectively, in 90% and 89% yields. Furthermore, noroxycodone was converted into the corresponding *N*-Boc derivative **3t** under similar reaction conditions in 10 min in 90% isolated yield.



3r



3s



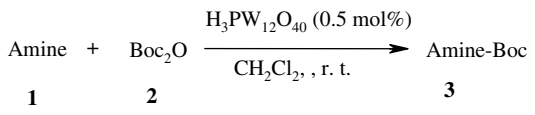
3t

In summary, this protocol represents a safer, and experimentally simple procedure for Boc-protection of amines.

2. General procedure: preparation of *N*-Boc amines

To a mixture of Boc_2O (218 mg, 1 mmol) and $H_3PW_{12}O_{40}$ (15 mg, 0.5 mol %) in 4 mL of CH_2Cl_2 was added 1.1 mmol of amine. After stirring for <10 min at room temperature, the resulting suspension was filtered and the solid residue washed with CH_2Cl_2 (10 mL). The filtrate was concentrated on a rotary evaporator to afford a crude product, which was purified by flash chromatography (hexane–ethyl acetate). ^1H NMR, ^{13}C NMR and IR spectra were consistent with the assigned structures and by comparison with those reported in the literature.[11] Compound **3d** is commercially available; **3t**[28] is a known compound. Spectral data for

Table 1. $H_3PW_{12}O_{40}$ catalyzed protection of amines



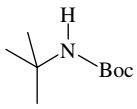
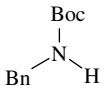
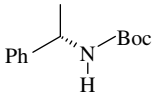
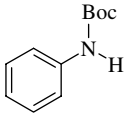
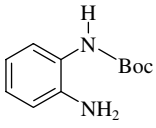
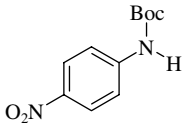
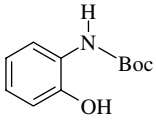
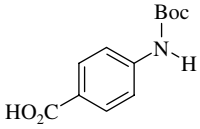
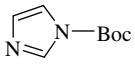
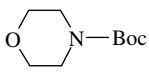
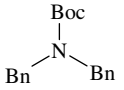
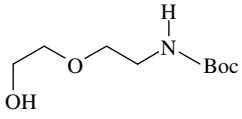
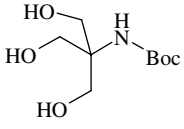
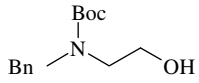
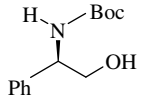
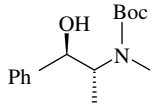
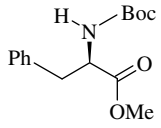
Entry	Product	Time (min)	Yield[a] (%)
a		8	84
b		3	92
c		4	88
d		8	85
e		6	86
f		12	80
g		3	88
h		10	84
i		10	85
j		7	83
k		6	91
l		5	90
m		4	94

Table 1 (*continued*)

Entry	Product	Time (min)	Yield[a] (%)
n		6	98
o		5	94
p		8	94
q		9	96

[a] Yields of pure products isolated by column chromatography.

selected products: **3l**: ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.5$ (s, 9H), 3.4 (m, 4H), 3.5–4.0 (m, 5H, NH and CH_2), 5.6 (br s, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$): 27.6 (CH_3), 39.7 (C), 60.6 (CH_2), 69.6 (CH_2), 71.8 (CH_2), 78.6 (CH_2), 156.2 (C=O); **3m**: ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.5$ (s, 9H), 2.4 (br s, 3H), 3.7 (s, 6H), 7.2 (br s, 1H); **3n**: ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.5$ (s, 9H), 2.9 (br s, 1H), 3.4 (d, $J = 9$ Hz, 2H), 3.7 (d, $J = 9$ Hz, 2H), 4.6 (s, 2H), 7.1–7.5 (br s, 5H); ^{13}C NMR (22.5, $CDCl_3$) 28.0 (CH_3), 49.3 (C), 52.2 (CH_2), 61.5 (CH_2), 80.4 (CH_2), 127.4 (CH), 127.8 (CH), 128.7 (CH), 138.4 (C), 156.7 (C=O).

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