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Magnetic Nanoparticles Catalyzed *N*-Tert-Butoxycarbonylation of Amines and Amine Derivatives

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Abstract: A simple and efficient protocol for the chemoselective mono-N-Boc protection of various structurally diverse amines with di-tert-butyl dicarbonate using magnetically recoverable γ-Fe_2O_3@SiO_2 nanoparticles is reported. The catalyst can be easily recovered and recycled without a significant loss in the catalytic activity. No competitive side reactions, such as formation of isocyanate, urea, oxazolidinone, and N,N-di-Boc derivatives were obsereved.

Keywords: $(Boc)_2O$, chemoselective, magnetic nanoparticles, protection, recycling.

INTRODUCTION

Because of increasing environmental concerns, the development of a clean synthetic procedure has become a crucial and demanding research. In this sense, heterogeneous organic reactions have many advantages, such as ease of handling, separation, recycling, and environmentally safe disposal [1]. Nanoparticles as heterogeneous catalysts have attracted a great deal of attention in recent years because of their interesting structure and high catalytic activities [2]. In this context, magnetic particles, in particular, have emerged as one of the most useful heterogeneous catalysts because of their numerous applications in nanocatalysis, biotechnology, and medicine [3]. Additionally, the magnetic properties make possible the complete recovery of the catalyst by means of an external magnetic field [4].

The choice of the protection strategy is of high importance in synthetic chemistry of multifunctional molecules including the total synthesis of natural products. Amines protection continues to attach a great deal of attention in a wide range of chemical fields, such as peptides, nucleoside, polymer and catalyst ligand synthesis [5]. A large variety of protective groups have been developed. Among them, the tert-butoxycarbonyl (t-Boc) group is frequently used as a protecting group for amine in synthetic organic/peptide chemistry due to its stability towards catalytic hydrogenolysis and extreme resistance to basic and nucleophilic conditions. Various reagents and methods have been reported for the N-tertbutoxycarbonylation of amines. N-tert-butyl carbamates using di-tert-butyl dicarbonate $(Boc)_2O$ have been carried out either in the presence of a base (DMAP [6] or inoeganic bases [7]) or more recently acid catalysts [8-17] and miscellaneous reagents. Some of the above procedures have certain drawbacks such as formation of side-products, the use of corrosive and moisture-sensitive reagents, limited applicabilities, and tedious work-up procedures. Moreover, many of these methods fail when amino acids or peptides are involved.

As a part of our ongoing research projects to develop new synthetic methodologies, particularly with a potential for using metal oxides [18], we have been interested in magnetic nanoparticles as an inexpensive, high corrosion resistive and as a potential reaction catalyst. γ-Fe_2O_3 Nanoparticles were synthesized by a chemical co-precipitation technique of ferric and ferrous ions in alkali solution [19]. SEM and TEM images of γ-Fe_2O_3 Nanoparticles are shown in Fig. (**1**). Herein, we roport γ-Fe_2O_3 as an efficient, heterogeneous and recyclable catalyst for the selective tertbutoxycarbonylation of various amines and amine derivatives. The general applicability of the method for the synthesis of a wide variety of diverse N-Boc-amines is demonstrated (Table **1**).

RESULTS AND DISCUSSION

Initially, Aniline reacted with $(Boc)_2O$ instantaneously at room temperature in the presence of 5 mol% γ- Fe_2O_3@SiO_2 under solvent free condition and a white precipitate of tert-butyl-N-phenyl carbamate is formed. No competitive side reactions leading to the formation of isocyanate, urea, or *N*,*N*-di-Boc derivatives were detected. The chosen amount of catalyst (5 mol %) was found to be sufficient for an optimal result, but increasing the quantity of catayst brought no substantial improvement. In the absence of catalyst, longer reaction time (90 min) was observed with lower isolated yield of tert-butyl-N-phenyl carbamate [20].

This study was extended to a wide range of structurally diverse amines including open-chain, cyclic, aromatic and heteroaromatic, as well as b-amino alcohols and a-amino acid esters which underwent the reaction smoothly with $(Boc)_2O$. The method can be applied for the conversion of poorly reactive amines, such as chloroaniline and

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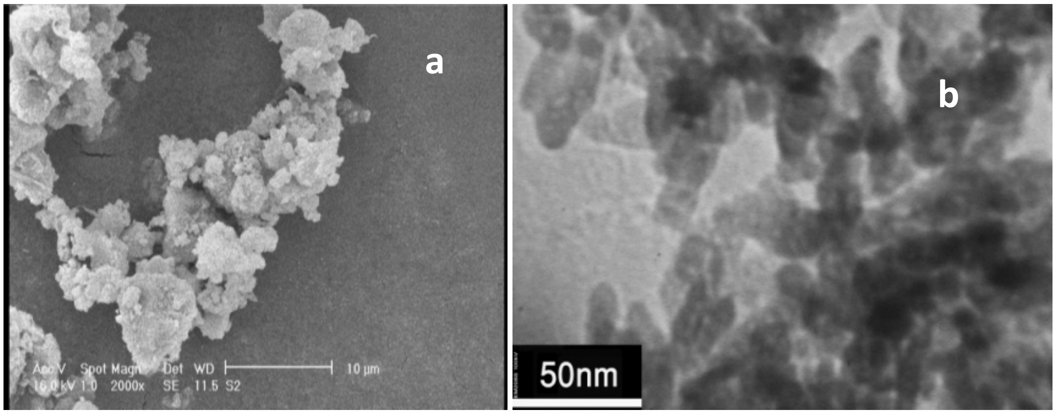
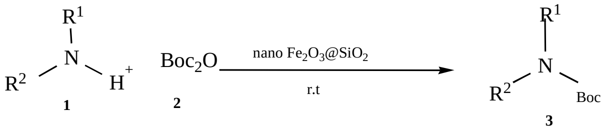


Fig. (1). The SEM (**a**), TEM (**b**) images of γ-Fe_2O_3.

Table 1. Magnetic Nanoparticles Catalyzed *N*-Boc Protection of Amines



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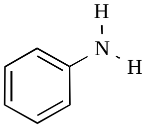
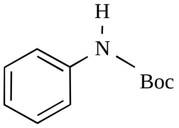
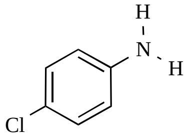
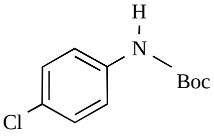
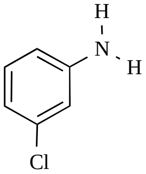
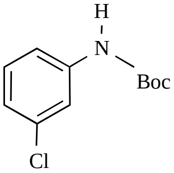
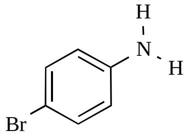
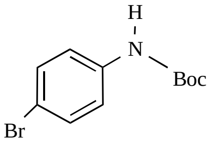
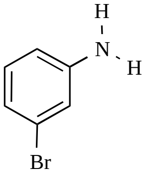
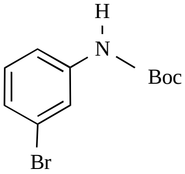
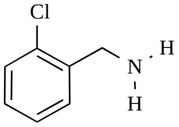
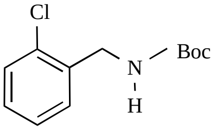
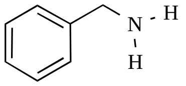
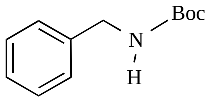
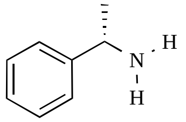
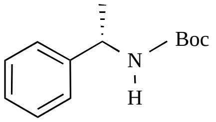
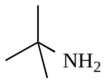
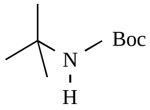
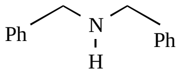
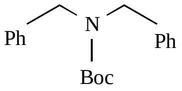
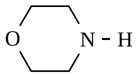
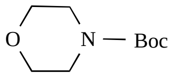
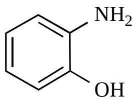
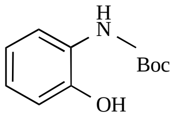
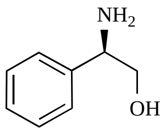
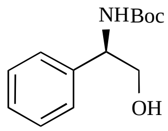
a		5		98
b		20		96
c		30		94
d		30		98
e		30		98
f		10		95

(Table 1). Contd…..

Entry	Amine	Time (min)	Product	Yield 3 %
		6		94
h		10		98
i		15		94
j		8		96
k		8		98
l		6		98
m		10		98

bromoaniline, as well as the sterically hindered tert-butylamine, into the corresponding *N*-Boc derivatives. The chemoselectivity of γ- Fe_2O_3 was assessed by performing NBoc protection of amines in bifunctional compounds. Excellent chemoselectivity was observed in the cases of aminoalcohols and aminophenols, where the corresponding *N*-Boc protected compounds were formed as sole products without competitive formation of O-Boc or oxazolidinone derivatives, even using an excess of $(Boc)_2O$ (Table **1**).

The mechanistic rule of magnetic nanoparticles catalyzed *N*-Boc protection of amines could be explained by the electrophilic activation of $(Boc)_2O$, making the carbonyl group susceptible to nucleophilic attack by the amine. Successive elimination of CO_2 and *tert*-BuOH results in the formation of *N*-Boc derivatives and regenerates γ-Fe_2O_3.

The ease of reusability is one of the important properties of this catalyst. The insolubility of catalyst in CH_2Cl_2 allows an easy separation of product by simple filtration. The catalyst was absorbed onto the external magnet. The catalyst was then washed with CH_2Cl_2, air-dried, and used directly with fresh substrates under identical conditions without further purification. It was shown that the catalyst could be used for five runs without noticeable drop in the product yield and its catalytic activity. A transmission electron microscopy (TEM) image of Fe_2O_3 showed that the average size and distribution of the Fe_2O_3 were not significantly altered, in good agreement with previously reported results that proved the unusual properties and potential applications of this magnetic material.

In conclusion, we have developed an efficient method for *N*-tertbutoxycarbonylation of various electronically and structurally diverse amines using γ-Fe_2O_3 in good-to-excellent isolated yields. The catalyst can be readily recovered by magnetic separation and reused. It is noteworthy that this reaction has some advantages in comparison with existing protocols. The rate of reaction for all substrates is faster than when there is no catalyst. Chemoselectivity of this reaction is the main advantage of this nano catalyst that could not happened without catalyst. In contrast to some existing methods using potentially hazardous catalysts/additives, this new method offers the following advantages: (i) short reaction times, (ii) ease of product isolation/non-aqueous work-up, (iii) high chemoselectivity, (iv) no side reactions, and (v) simple processing and handling. The recovered nano catalyst can be recycled.

EXPERIMENTAL SECTION

General Procedure for the N-Tert-Butoxycarbonylation of Amines

Amine (2 mmol) was added to a magnetically stirred mixture of $(Boc)_2O$ (2 mmol) and γ-Fe_2O_3@SiO_2 nano (5 mol%), and the mixture was stirred at room temperature. The reaction was monitored by TLC. After the completion of reaction, the *N*-Boc product was separated from the reaction mixture by extraction with CH_2Cl_2 and vacuum dried. Then the products were identified by using NMR in $CDCl_3$. The γ-Fe_2O_3 nanocatalyst was separated by external magnet and reused for further reactions. Afterward, the products were identified by NMR, and physical data (mp) by comparison with those reported in the literature [6]. Spectral data for the N-Boc products: (**3c**) White solid, mp: 102–104 ^oC; ^{1}HNMR (500 MHz, $CDCl_3$): d 1.53 (s, 9H), 6.59 (br s, 1H, NH), 7.23–7.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): d 28.3, 80.8, 119.7, 127.9, 128.9, 136.9, 152.6. (**3l**) White solid, mp 142 ^oC, ^{1}H NMR (500 MHz, $CDCl_3$): d 1.57 (s, 9H), 6.69 (br s, 1H, NH), 6.88–7.30 (m, 4H), 8.17 (br s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): d 28.6, 82.4, 119.0, 121.1, 121.7, 125.8, 126.0, 147.3, 155.3.

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