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Preliminary Communication/Communication

Protic ionic liquid [TMG][Ac] as an efficient, homogeneous and recyclable catalyst for Boc protection of amines

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Dedicated to Hossein Ali Motahari for his contribution in Iranian pharmaceutical industry.

ABSTRACT

An efficient and practical protocol for the chemoselective *N*-Boc protection of various structurally different aryl, aliphatic and heterocyclic amines was carried out with $(Boc)_2O$ using protic 1, 1, 3, 3-*tetra*-methylguanidinium acetate (10 mol%) as recyclable catalyst under solvent free condition at ambient temperature. No competitive side reactions (isocyanate, urea and *N, N*-di-Boc) were observed. α-Amino alcohols afforded the *N*-Boc-derivative without oxazolidinone formation.

1. Introduction

Nitrogen 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 [1]. Among the different means of the protection of amino group, N-tert-butoxycarbonylation has received the greatest attention due to extreme stability of the *N*-Boc group toward nucleophilic attack or alkali conditions and catalytic hydrogenation [2]. Various reagents and methodologies have been developed during the last years for the N-*tert*-butoxycarbonylation of amines. Most of them are carried out in the presence of an organic or inorganic base, for example: $(Boc)_2O$ in the presence of DMAP [3], 4-dimethylamino-1-*tert*-butoxycarbonyl pyridinium chloride/ tetrafluoroborate in aq. NaOH [4], 2-*tert*-butyloxy carbonyl oxyimine-2-phenylacetonitrile in the presence of Et_3N in H_2O-dioxane [5], *tert*-butyl-2-pyridyl carbonate in the presence of Et_3N in H_2O- DMF [6] or *tert*-butyl 1-chloroalkyl carbonates in the presence of K_2CO_3 in H_2O-THF [7]. However, these methodologies have various drawbacks such as long reaction times, preparation of the *tert*-butoxycarbonylation reagents, and requirement of auxiliary substances (e.g., solvents and other reagents). Furthermore, the base-catalyzed reactions are often associated with the formation of isocyanate [8], urea [3] and *N, N*-di-Boc derivatives [9]. Moreover, the high toxicity of DMAP and reagents derived from it, limits their use [10]. These disadvantages can be avoided by electrophilic activation of $(Boc)_2O$ in the presence of acids. There are examples of other modified methods for *N*-*tert*-butoxycarbonylation of amines with $H_3PW_{12}O_{40}$ [11], H_2NSO_3H [12], $Zn(ClO_4)_2.6H_2O$ [13], $ZrCl_4$ [14], $LiClO_4$ [15], $Cu(BF_4)_2$ [16], Montmorillonite K10 [17], sulfonic acid functionalized silica [18], I_2 [19], indium (III)halides [20], $HClO_4$-SiO_2 [21] and TFE [22]. These procedures, although circumventing the problem associated with the formation of the above-mentioned side products, have certain drawbacks: the reactions require highly reactive or environmentally harmful catalysts and anhydrous conditions (the use of H_2SO_4 at 500 °C to prepare Yttria-Zirconia, $ZrCl_4$ is highly moisture-sensitive and liberates HCl), use of solvents and

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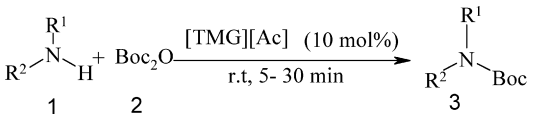
extractive work-up to isolate the product from the catalyst. Moreover, most Lewis acids are decomposed or deactivated by the amines and amine derivatives. Even when the desired reactions proceed, greater than stoichiometric amounts of Lewis acid are needed because the acids are trapped by nitrogen. Thus, the design of new, milder and effective methods for *N*-Boc protection still is an active topic in synthetic chemistry.

Currently, ionic liquids are extensively being used as green solvents for laboratory as well as industrial use due to their unique properties such as good solvating ability, variable polarity, negligible vapor pressure, and ease of recyclables [23]. In spite of advantages, there are few publications utilizing ionic liquids as green solvents for protection reactions. Moreover, the ionic liquids reported so far for protection reactions are mostly limited to salts of 1, 2-disubstituted imidazolium [24]. While considering ionic liquids as catalyst and their use in industrial processes, one major concern is cost. The cost of ionic liquid would be directly dependent on the price of the cations and anions that are used for their production [23]. Thus, the currently popular ionic liquids incorporating cations such as alkyl methyl imidazolium and dialkyl imidazolium as well as anions such as tetrafluoroborate and hexafluorophosphate are also expensive. Very recently, 1-methylimidazolium tertafluoroborate [$(HMIm)BF_4$], has been exploited as an efficient catalyst for chemoselective *N*-Boc protection of various amines using $(Boc)_2O$. However, ILs bearing perfluorinated anions have some disadvantages: (1) the presence of fluorine makes the disposal of spent ionic liquids (ILs) more complicated; (2) they may contain traces of halides arising from the preparation procedure. For these reasons, research on new ILs bearing inert low coordinating and non-fluorinated anions represents a field of intense investigation in the chemistry of ILs.

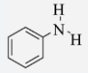
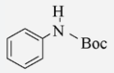
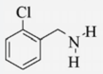
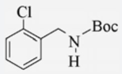
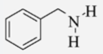
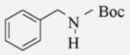
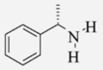
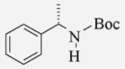
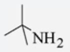
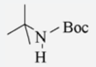
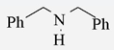
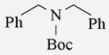
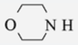
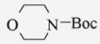
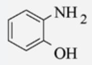
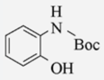
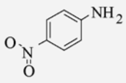
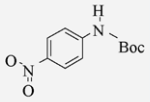
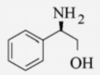
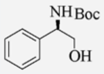
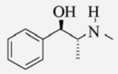
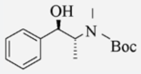
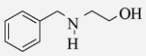
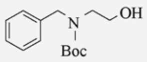
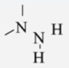
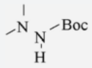
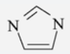
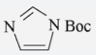
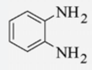
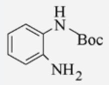
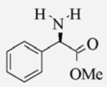
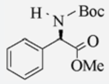
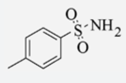
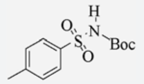
2. Results and discussion

Herein we report that (1, 1, 3, 3-*tetra*-methylguanidine [TMG])[Ac] [26] is an excellent catalyst for the *N*-*tert*-butoxycarbonylation of various structurally different amine derivatives (Scheme 1) and the results are summarized in Table 1 [27]. In an initial study, aniline (1 mmol) was treated with $(Boc)_2O$ (1 mmol) and [TMG][Ac] (0.018 g, 10 mol %) as a catalyst to isolate the corresponding mono *N*-Boc derivative within 5 min in 98% yield. The efficiency of our protocol was evaluated using a variety of structurally diverse amines (**1a–q**). The reactions were completed after 5–30 min, affording good to excellent yields (Table 1). Both primary and secondary amines worked well. In each case, only the mono *N*-Boc protected product was found. No isocyanide or urea formation was detected (by NMR of crude products). Aromatic amines



Scheme 1. *N*-Boc protection of amines catalyzed by [TMG][Ac].

Table 1
N-Boc protection of amines with [TMG][Ac].

Entry	Substrate	Time (min)	Product	Yield 3%
a		5		98
b		10		95
c		6		94
d		10		98
e		15		94
f		8		96
g		8		98
h		6		98
i		30		98
j		10		98
k		15		94
l		10		93
m		15		94
n		30		97
o		6		98
p		30		94
q		30		94

TMG: 1, 1, 3, 3-*tetra*-methylguanidine.