Asian Journal of Chemistry; Vol. 29, No. 6 (2017), 1313-1316

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20479

[TPA][Pro] Ionic Liquid as Efficient Reaction Medium for N-*tert*-Boc Protection of Amines

T. VIJAYA DURGA, A. RAMBABU, M. SRINIVASA REDDY and B. HARI BABU*

Department of Chemistry, Acharya Nagarjuna University, Nagarjunanagar-522 510, India

*Corresponding author: Tel: +91 863 2346575; E-mail: dr.b.haribabu@gmail.com

Received: 27 December 2016; *Accepted*: 17 February 2017; *Published online*: 10 April 2017; AJC-18345

A facile and efficient *N-tert*-Boc protection of amines is described by the reaction of various primary, secondary, benzylic and aryl amines with di-*tert*-butyl dicarbonate in the ionic liquid [TPA][Pro] at room temperature. All the *N-tert*-butylcarbamates are afforded in excellent yields. A catalyst-free method was developed and the ionic liquid [TPA][Pro] can be recovered and reused for several times without loss of its activity.

Keywords: Ionic liquid [TPA][Pro], Amines, *N-tert*-butylcarbamates, *N-tert*-butoxycarbonylation.

INTRODUCTION

Notwithstanding the unique advantages of ionic liquids (IL's) as reaction media and catalysts including biological systems, currently they have not been widely applied in industry. The reason for this is probably related to the high cost of ionic liquids, the difficulty in separation or recycling, the paucity of data with regard to their toxicity and biodegradability, *etc*. [1-5]. To overcome these disadvantages, recently some new ionic liquids have been prepared *via* simple and economic acid-base neutralizations. For example the preparation and application of the Brönsted acid-base ionic liquids from imidazole and *bis*(trifluoromethanesulfonyl)amide [6], a new class of ionic liquids by neutralization of 1,1,3,3-tetramethylguanidine with different acids have been reported [7]. Similarly, the synthesis of ionic liquids using quaternary ammonium hydroxide and chiral carboxylic acids have also been reported [8]. Although there are several reports on ionic liquids, the preparation of chiral ionic liquids using inexpensive starting materials is very limited.

Among carbonic acid derivatives used as protecting groups, *tert*-butylcarbonates and *tert*-butylcarbamates are of great importance in organic chemistry [9], because they are stable to wide range of nucleophiles in alkaline conditions and are very liable under moderately acidic conditions to give the parent alcohols and amines. Classically, introduction of *tert*-Boc group to an amine is generally achieved by reaction of amine with di-*tert*-butyl dicarbonate in the presence triethylamine in dry dichloromethane [10-14]. It has been reported that this can be promoted by di-*tert*-butyl dicarbonate in the presence of dimethylaminopyridine [15], *tert*-Boc transfer reactions using *tert*-Boc-imidazole [16] or *tert*-butoxycarbonyl-1,2-dihydroisoquinoline [17]. Although, various base mediated methods are available for the preparation of *N-tert*-butylcabamates using di-*tert*-butyl dicarbonate and also few reports on acid-mediated reaction Yttria-Zirconia [18], $Cu(BF_4)_2$ [19], $InBr_3$ [20], $HClO_4$-SiO_2 [21], $La(NO_3)_3{\cdot}6H_2O$ [22], $H_3PW_{12}O_{40}$ [23], $LiClO_4$ [24] and I_2 [25] as Lewis acids catalysts and also in water [26], sulfonic-acid-functionalized silica [27] as a catalyst for *N-tert*-butoxycarbonylation of amines. The catalyst free ionic liquid mediated *N-tert*-butoxycarbonylation of amines is not investigated so far. The selected ionic liquid, tetrapropylammonium L-prolinate [TPA][Pro] was reported as an efficient reaction medium for the synthesis of β-keto-sulfones, β-hydroxysulfones, *N*-benzyloxycarbonylation of amines [28,29]. We reported number of studies on molecular interactions between various ionic liquid's [30-33] and organic solvents, but in the present investigation an attempt was made to utilize ionic liquid [TPA][Pro] as an efficient reaction medium for *N-tert*-butoxycarbonylation of amines with di-*tert*-butyl dicarbonate.

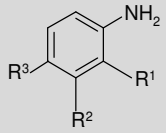
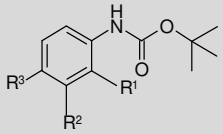
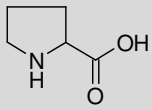
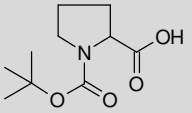
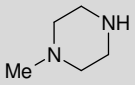
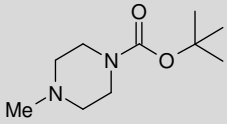
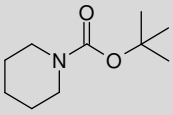
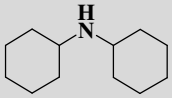
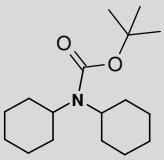
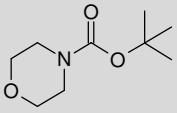
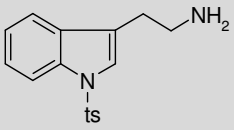
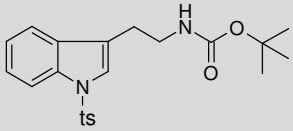
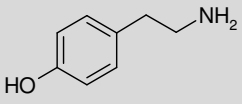
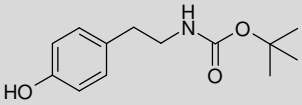
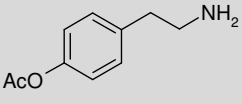
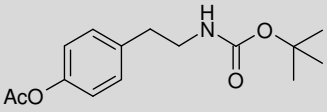
EXPERIMENTAL

All the chemicals used were of AR grade, purchased from Merck manufactures Pvt. Ltd. and were used as such. The melting points were calculated on Remi melting point apparatus. All the reactions were monitored by TLC and the yields refer to isolated products. The IR spectra were recorded on Shimadzu spectrophotometer using KBr pellet method, proton NMR spectra were recorded in $CDCl_3$ on Bruker instrument at 300 MHz and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker

spectrometer at 100 MHz. Mass spectra were recorded on Elegant LC-1100 series instrument.

General procedure for preparation of N-*tert*-butyl-carbamates: To the ionic liquid [TPA][Pro] (1 mL) was added amine (**1-14**; Table-1) (1 mmol) and di-*tert*-butyl dicarbonate (1.2 mmol). The reaction was stirred at room temperature for an appropriate time (Table-1). After completion of the reaction as monitored by TLC, water was added to the reaction mixture and the product was extracted into ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine solution and concentrated under reduced pressure to give crude product, which was purified over silica gel column to afford corresponding *N-tert*-butylcarbamate. The ionic liquid [TPA][Pro] in aqueous solution was recovered by removing water under reduced pressure and dried. The recovered ionic liquid was reused for five times without loss of its activity. Finally, all the compounds confirmed by their m.p.'s, IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis wherever needed.

TABLE-1
N-tert-BUTOXYCARBONYLATION OF AMINES USING IONIC LIQUID [TPA][Pro] CONDITIONS

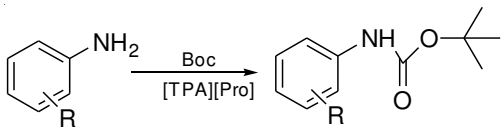
Entry	Substrate	Product	Time (min)	Yield (%)[a]
				
1	R^1 = H, R^2 = H, R^3 = H	R^1 = H, R^2 = H, R^3 = H	10	100
2	R^1 = CH_3, R^2 = H, R^3 = H	R^1 = CH_3, R^2 = H, R^3 = H	25	95
3	R^1 = OH, R^2 = H, R^3 = H	R^1 = OH, R^2 = H, R^3 = H	13	99
4	R^1 = H, R^2 = NO_2, R^3 = H	R^1 = H, R^2 = NO_2, R^3 = H	15	95
5	R^1 = H, R^2 = H, R^3 = NO_2	R^1 = H, R^2 = H, R^3 = NO_2	10	98
6	R^1 = H, R^2 = H, R^3 = F	R^1 = H, R^2 = H, R^3 = F	30	96
7			15	95
8			20	100
9			05	100
10			10	100
11			10	99
12			20	95
13			10	98
14			10	99

[a]Isolated yields after silica gel chromatography.

Spectral data of the compounds (Table-1) Entry 1: Solid, m.p.: 134 °C. FTIR (KBr, ν_{max}, cm^{-1}): 3314 NH, 1689 C=O. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.50 (s, 9H, Boc), 6.35 (bs, BocNH), 7.0 (t, *J* = 7.2 Hz, 1 Ar-H), 7.35 (m, 4 Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (CH_3), 80.3 (C), 118.5 (CH), 123 (CH), 128.9 (CH), 138.2 (C), 152.7 (C=O). EIMS: *m/z* 194 (M^+); **Entry 2:** Solid, m.p.: 82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.50 (s, 9H, Boc), 2.25 (s, 3H, CH_3), 6.20 (bs, 1 BocNH), 6.9 (m, 1 Ar-H), 7.0-7.24 (m, 2 Ar-H), 7.80 (d, 1 Ar-H); EIMS: *m/z* 207 (M^+); **Entry 3:** solid, m.p.: 142 °C. FTIR (KBr, ν_{max}, cm^{-1}): 3322 NH, 1691 C=O. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.56 (s, 9H, Boc), 6.63 (b s, 1H, OH), 6.81 (t, *J* = 7.5 Hz, 1 Ar-H), 7.0 (d, *J* = 9.5 Hz, 1 Ar-H), 7.03-7.09 (m, 2 Ar-H) 8.12 (bs, 1 BocNH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6 (CH_3), 82.4 (C), 121.17 (CH), 121.7 (CH), 125.85 (CH), 26.1 (CH), 147.78 (C), 155.38 (C=O). EIMS: *m/z* 209 (M^+); Anal. calcd. for $C_{11}H_{15}NO_3$; C, 63.13; H, 7.23; N, 6.70. Found: C, 63.21; H, 7.31; N, 6.73. **Entry 4:** Solid, m.p.: 95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ =1.50 (s, 9H, Boc), 7.5 (t, *J* = 7.2 Hz, 1 Ar-H,), 7.8-7.95 (m, 2 Ar-H), 8.66 (m, 1 Ar-H), EIMS: *m/z* 238 (M^+); **Entry 5:** Solid, m.p.: 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.50 (s, 9H, Boc), 7.5 (d, *J* = 6.5Hz, 2 Ar-H) 8.1 (d, *J* = 6.5 Hz, 2 Ar-H); EIMS: *m/z* 238 (M^+). **Entry 6:** Solid, m.p.: 125 °C. δ = 1.50 (s, 9H, Boc), 5.6 (brs 1 BocNH), 7.1 (m, 2 Ar-H), 7.4 (m, 2 Ar-H); **Entry 7:** Solid, m.p.: 123 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.40 (s, 9H, Boc), 2.1 (m, 4 Pyrldn-H), 3.4 (m, 2 Pyrldn-H), 4.4 (m, 1 Pyrldn-H), 9.0 (brs 1H BocNH); EIMS: *m/z* 215 (M^+); **Entry 8:** ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.45 (s, 9H, Boc), 2.2 (s, 3H, CH_3), 3.1 (m, 4H, Pip), 3.5 (m, 4H, Pip). EIMS: *m/z* 200 (M^+); **Entry 9:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (m, 2H, Pip), 1.45 (m, 4H, Pip), 1.45 (s, 9H, Boc) 2.8 (m, 4H, Pip); EIMS: *m/z* 185 (M^+); **Entry 10:** Solid, m.p.: 75 °C. FTIR (KBr, ν_{max}, cm^{-1}): 3090 NH, 1680 C=O. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04-1.79 (m, 29H). EIMS: *m/z* 171; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5 (CH_2), 26.2 (CH_2), 28.5 (CH_3), 31.1 (CH_2), 54.7 (CH), 78.9 (C), 155.4 (C=O) EIMS: *m/z* 299 (M^+); Anal. calcd. for $C_{18}H_{21}NO_3$; C, 72.552; H, 11.10; N, 4.98. Found: C, 73.15; H, 11.12, N, 4.88. **Entry 11:** Solid, m.p.: 58 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.49 (s, 9H, Boc), 3.4 (t, *J* = 7.5 Hz, 4H, Mor), 3.62 (t, *J* = 7.5 Hz, 4H, Mor). EIMS: *m/z* 187 (M^+); **Entry 12:** Solid, m.p.: 60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H, Boc), 2.2 (s, 3H, CH_3), 3.1 (m, 2H, CH_2), 3.3 (m, 2H, CH_2), 6.2 (brs, 1H, BocNH), 7.1 (m, 2H, Ind), 7.2 (m, 2H, Ind), 7.6 (m, 1H, Ind), 7.7 (d, *J* = 7.1Hz, 2H, Ar-H), 8.1 (m, 1H, Ind); EIMS: *m/z* 414 (M^+). **Entry 13:** solid, m.p.: 76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.49 (s, 9H, Boc), 2.70 (t, *J* = 6.1 Hz, 2H, CH_2), 3.30 (t, *J* = 6.1Hz, 2H, CH_2), 4.60 (bs, 1H, OH), 6.70 (d, *J* = 7.7Hz, 2H, Ar-H), 6.99 (d, *J* = 7.7 Hz, 2H, Ar-H). EIMS:*m/z* 237 (M^+). **Entry 14:** solid, m.p.: 65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.49 (s, 9H, Boc), 2.30 (s, 3H, CH_3), 2.80 (t, *J* = 7 Hz, 2H, CH_2), 3.40 (t, *J* = 7Hz, 2H, CH_2), 4.50 (b s, 1H, BocNH), 7.0 (d, *J* = 7.2, 2H, Ar-H), 7.20 (d, *J* = 7.2, 2H, Ar-H). EIMS: *m/z* 279 (M^+).

RESULTS AND DISCUSSION

In the present method (**Scheme-I**), we described a facile method for the protection of amines as *N*-Boc derivatives using the ionic liquid [TPA][Pro]. The present method is simple and no special care to exclude the moisture from the reaction medium and no by-products were observed. Further, the reaction medium *i.e.* the ionic liquid [TPA][Pro] was recovered and reused several times. We have prepared [28,29] the ionic liquid tetrapropylammonium prolinate [TPA][Pro] from readily available tetrapropyl ammonium hydroxide and proline in aqueous medium at 60 °C. Initially we have carried out the reaction of aniline (1 mmol) with di-*tert*-butyl dicarbonate (1.2 mmol) in the ionic liquid [TPA][Pro] at room temperature to give very rapidly the corresponding *N-tert*-butylcarbamate in good yield (Table-1, Entry 1). This achievement has encouraged us to extend the reaction on various primary, secondary and benzylic and aryl amines (Table-1) to yield the corresponding *N-tert*-butylcarbamates in a facile manner. From the foregoing results (Table-1) it is evident that ionic liquid [TPA][Pro] is an excellent reaction medium for *N-tert*-butoxycarbonylation of amines under very mild conditions.



Scheme-I

ACKNOWLEDGEMENTS

The authors are highly thankful to Acharya Nagarjuna University, Nagarjunanagar, India for constant encouragement and Laila Impex R&D Center, Vijayawada for their help in spectral data.

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