SOLVENT FREE N-BOC PROTECTION OF AMINES USING AMBERLYST® A 21 SOLID BASE RESIN AS A REUSABLE HETEROGENEOUS CATALYST

SUNIL U. TEKALE, SUSHAMA S. KAUTHALE AND RAJENDRA P. PAWAR*

Department of Chemistry, Deogiri College, Aurangabad, 431005 (MS) India.

(Received: May 22, 2012 - Accepted: October 22, 2012)

ABSTRACT

An efficient, environmentally benign, highly facile and convenient synthetic protocol for the selective *t*-butyl carboxylation of aliphatic, aromatic and heterocyclic amines using Amberlyst® A 21 catalyst; a mild basic solid resin under solvent free conditions is reported. This method explores several advantages such as reusability of the heterogeneous catalyst, cleaner reaction profile, mild and solvent free system, short reaction time, operational simplicity, high conversions, excellent product yields and low cost of the catalyst. Furthermore since the catalyst is mild basic, decomposition of the carbamate formed is not observed if the reaction is continued for prolonged time as in the case of Lewis acid catalyzed N-Boc protection. This makes the present protocol a useful and attractive for N-Boc protection of amines.

Key words: Amberlyst® A 21, Amine, *t*-butyl dicarbonate, Carbamate, Heterogeneous catalyst.

INTRODUCTION

Technological progress with environmental safety is one of the key challenges of this millennium. The basic idea of clean production is to increase the production efficiency with minimization of wastes and emissions. Eco-efficiency and Green chemistry are the new principles guiding the development of next generation products and processes. Green chemistry is an essential and comprehensive programme to protect human health and environment. According to recent environmental considerations with safety concerns and economic views, the use of such reagents is undesirable. Hence there is still need for the generation of more efficient processes for the protection and deprotection strategies in chemo selective transformations.

Heterogeneous catalysis contributes more in synthetic organic chemistry as it provides not only an alternative to homogeneous catalysis but also an easy catalyst recovery, recycling ability, keeping the reaction conditions often mild, simple and easy product-catalyst separation. The development of efficient and versatile heterogeneous catalytic system has become an active ongoing research area recently due to the potential advantages of these materials over homogeneous systems.

Protection and deprotection strategy has emerged as a powerful tool in organic synthesis. Among the various protecting groups used for amines; di tertiary butyl dicarbonate i.e. (Boc)₂O¹⁻⁴ is the frequently employed protecting group mainly due to high stability of corresponding carbamates to different nucleophiles under alkaline conditions and their ease of labile nature under mild acidic conditions such as TFA/DCM, ethanolic HCl, 10% H₂SO₄ in 1,4-dioxane etc.

Protection of amines with (Boc)₂O has been carried out with or without solvent using various catalytic systems such as DMAP,⁵ NaOH,⁶ HClO₄-SiO₂,⁷ molecular iodine,⁸ sulfamic acid/ultrasound,⁹ yttria-zirconia,¹⁰ indion-190 resin,¹¹ saccharin sulfonic acid,¹² H₃PW₁₂O₄₀,¹³ LiClO₄,¹⁴ phosphomolybdic acid supported on silica gel,¹⁵ Bronsted acid ionic liquid methylimidazoliumtetrafluoroborate,¹⁶ ZrCl₄,¹⁷ organic solvents like 1,1,1,3,3,3-Hexafluoroisopropanol,¹⁸ Thiourea,¹⁹ 10% aq. AcOH,²⁰ iodine-CsF,²¹ indium(III) halides²² etc. The protection strategy in aqueous²³ medium has also been reported. Finally to avoid the use of hazardous organic solvents, attempts are being made to develop solvent free protocols.

The previous reported methods are associated with several limitations such as longer reaction time, use of costly reagents and limited scope. Further the Lewis acid catalyzed N-Boc protection of amines is of little significance due to strong affinity of the Lewis acid catalysts for amino groups which do not allow regeneration of the catalysts after completion of the reaction and more over they get decomposed or deactivated by the amines or their derivatives when used in more than stoichiometric amounts. In acid catalyzed reactions, the carbamate formed further decomposes if the reaction is continued for long duration of time. Therefore there is a scope for improvement towards facile and solvent free reaction conditions for N-Boc protection under mild and basic conditions.

Scheme 1

Recently the application of heterogeneous catalysts like ion-exchange resins, zeolites and clays have attracted much more attention in organic synthesis due to their operational simplicity, reusability, environmental compatibility, high selectivity, non-corrosiveness and easy availability of the reagents at low cost. Further the ion exchange resins facilitate the reaction profile quite simple, are environmentally friendly, economic and convenient. Hence they worked as the efficient catalysts for carrying out different organic transformations.

Amberlyst® A21 is particularly used for the removal of acidic impurities from non-aqueous solutions and mainly available in water-moist free solid basic bead form having surface area of about 25 m²g⁻¹, and ion exchange capacity of 1.3 meq ml⁻¹. It can sustain a maximum temperature of 383-393 K. Due to its inexpensive and commercially available solid form; it can be used for different organic transformations.

Herein we wish to disclose Amberlyst® A21 which is a bead form mild solid base resin as the non toxic environmentally friendly, cheap, reusable heterogeneous catalyst for N-Boc protection of amines under solvent free conditions and ambient temperature conditions.

EXPERIMENTAL

All the chemicals were purchased from commercial source (Aldrich) and used without further purification. Column chromatography was done using Merck silica gel (100-200 mesh). ¹H and ¹³C NMR spectra were recorded on Varian (400 MHz) spectrophotometer. IR spectra of the samples were recorded with Bruker Vector 22 FT-IR spectrophotometer and the samples were analyzed for ESMS on Shimadzu mass analyzer.

General experimental procedure for the N-Boc protection of amines using Amberlyst® A21 catalyst

Amberlyst® A21 (20 wt %) was added to a mixture of amine (1 mmole) and (Boc)₂O (1 mmole) and the mixture was stirred for the appropriate reaction time as specified in (Table 1). The progress of reaction was monitored by Thin layer chromatography (10-20% ethyl acetate: hexane) on TLC plates (Merck) precoated with silica. After completion of reaction, the reaction mass was diluted with methanol, filtered off the catalyst which was washed for several times and then dried at 80°C under reduced pressure for 1 hour and subjected to further recycle study (Table 4). It showed no much more decrease in the product yield indicating high activity of the catalyst. The filtrate was concentrated on rotavac and the product was purified by column chromatography to afford pure products.

The products were characterized by ^1H NMR, ^{13}C NMR, IR and ESMS. All the compounds gave satisfactory data.

Spectral Data of principal compounds *Tert-butyl 3, 4-difluorobenzylcarbamate (Entry 6, Table 1):*

White solid, M.P. 82-84 °C, ^1H (CDCl₃): δ 1.65 (s, 9 H), 4.25 (s, 2H), 4.93 (s, 1 H, broad), 6.97 (s, 1H), 7.3 (d, 2H, J = 7.2 Hz); ^{13}C (CDCl₃): 20.29, 43.59, 79.78, 116.25, 117.10, 123.10, 136.20, 148.99, 150.67, 155.83; IR (KBr): cm⁻¹ 645, 781, 821, 862, 1049, 1166, 1288, 1546, 1677, 2987, 3312, 3349, ESMS: 244 (M+1).

Tert-butyl-4-isopropylbenzylcarbamate (Entry 9, Table 1):

White solid, 93-95 °C, ^1H (CDCl₃): δ 1.26 (d, 6 H, J = 7.12), 1.5 (s, 9H), 2.9 (m, 1H), 4.28 (s, 2H), 4.78 (s, 1H, broad), 7.18 (d, 2H, J = 7.43), 7.20 (d, 2 H, 7.43); ^{13}C (CDCl₃): 23.92, 28.33, 33.71, 44.32, 79.20, 126.54, 127.47, 136.24, 147.89, 155.81; IR (KBr): cm⁻¹ 592, 841, 862, 927, 1055, 1165, 1267, 1440, 1522, 1687, 2925, 2964, 3013, 3389; ESMS: 250 (M+1).

Tert-butyl-4-bromo-2-methyl-1H-imidazolecarbamate (Entry 11, Table 1):

Colorless thick oil, ^1H (CDCl₃): δ 1.65 (s, 9H), 2.63 (s, 3H), 7.3 (s, 1H); ^{13}C (CDCl₃): 28.25, 80.92, 119.52, 121.77, 137.10, 144.43, 152.66; ESMS:

261 (M+1).

Tert-butyl-2-methyl-1H-imidazolecarbamate (Entry 12, Table 1):

Colorless thick oil, ^1H (CDCl₃): δ 1.65 (s, 9H), 2.64 (s, 3H), 6.85 (d, 1H), 7.3 (d, 1H); ^{13}C (CDCl₃): δ 16.71, 27.72, 84.84, 118.08, 127.09, 147.39, 147.86; IR (KBr) cm⁻¹ 669, 697, 744, 776, 848, 991, 1069-1302, 1140, 1353, 1480, 1552, 1756, 2984; ESMS: 183(M+1).

Tert-butyl-4-bromo-1H-imidazolecarbamate (Entry 13, Table 1):

White solid, M.P. 141-143 °C, ^1H (CDCl₃): δ 1.65 (s, 9H), 7.35 (s, 1H), 7.96 (s, 1H); ^{13}C (CDCl₃): 27.72, 86.45, 116.41, 117.38, 136.51, 145.80; IR (KBr) cm⁻¹ 604, 771, 840, 934, 1008, 1089, 1189, 1260, 1330, 1477, 1513, 1753, 2988, 3014, 3132; ESMS: 247(M+1).

Tert-butyl 2-chloro-4-(trifluoromethoxy) phenylcarbamate (Entry 15, Table 1):

White solid, M.P. 110-112 °C, ^1H (CDCl₃): δ 1.6 (s, 9H), 4.8 (s, 1H, br), 6.72 (d, 1H, J = 7.4), 6.8 (s, 1H), 7.83 (d, 1H, J = 7.4);

^{13}C (CDCl₃): 23.5, 77, 110, 113.2, 119.4, 121, 123, 128, 149, 153. ESMS: 312 (M+1).

The products were characterized by ^1H NMR, ^{13}C NMR, IR and ESMS. All the compounds gave satisfactory data.

Table 1. The yield of various N-Boc protected amines using Amberlyst[®] A21 as the catalyst.

Entry	Substrate	Product	Time (min)	Yield (%)	Reference
1			2	98	8
2			25	92	25
3			2	97	20
4			5	97	11
5			5	94	11
6			1	98	Present work
7			3	94	8
8			2	96	8

9			1	97	Present work
10			3	94	24
11			25	92	Present work
12			2	95	Present work
13			25	91	Present work
14			2	96	10
15			6 hr	<10	Present work
16			5	93	13
17			3	90	8

Table 2. The solvent screening for N- Boc protection.

Entry	Solvent	Catalyst (wt %)	Time (min)	Yield (%) [@]
1	CH ₃ OH	20	2	92
2	THF	20	3	87
3	DCM	20	4	82
4	DCE	20	3	88
5	CH ₃ CN	20	3	90
6	Dioxane	20	4	78
7	Neat	20	1	98

[@] Yields in case of entry 6 (Table 1).**Table 3.** The effect of catalyst concentration on the N-Boc protection of amines.

Entry	Catalyst (WT%)	Time (min)	Yield (%)
1	10	2	85
2	15	2	86
3	20	1	97
4	25	1	97
5	30	1	97

Table 4. Catalyst recycles study on some carbamates.

Entry	Carbamate	Recycle 1	Recycle 2	Recycle 3
1		95	94	93
2		96	94	94
3		97	96	96

Scheme 2

RESULTS AND DISCUSSION

The Amberlyst[®] A21 has some advantages over A-15 such as the basic reaction medium it offers and longer reaction times for decomposition of the carbamates formed. The present catalyst is basic in nature. In earlier reported methods almost all catalysts used were acidic in nature. A disadvantage of the acidic catalyst was; the traces of catalyst left with product after isolation further decomposes the carbamate product formed. Such decomposition of product is not observed in our process even after 18 hrs. Hence as per our knowledge, this process can be utilized as an industrial method.

To investigate the effect of solvent on the protection of amines (Table 2), several reactions were carried out on 3,4-difluorobenzyl amine as a model reaction using various solvents such as methanol, tetrahydrofuran, dioxane, dichloromethane, 1,2-dichloroethane etc which required longer reaction times

as compared to neat reaction. A catalytic amount (20 wt %) of the Amberlyst[®] A21 (Table 3) showed significant activity at ambient temperature and solvent free conditions to afford excellent results. Separation of the catalyst from reaction mass was performed by diluting the RM with methanol, filtering off the catalyst, washing it with methanol for several times followed by concentration of the filtrate to get crude product which was purified by column chromatography. Furthermore the N-Boc protection was found to be selective as observed in the case of amines (Entry 4, Table 1) possessing more than one NH₂ groups where only one rather than two is selectively protected.

The N- Boc protection of amines with Lewis acid catalysts is of little importance because; the carbamate obtained may be decomposed if the reaction is continued for prolonged time. Since Amberlyst[®] A21 is a mild basic resin; such kind of problem is not encountered in our present protocol (scheme 2) as on various carbamates formation (entries 5, 6, 11, 12, 13 etc in table 1). The N-Boc protection was observed to be sluggish in case of amines bearing electron withdrawing substituents, whereas amines bearing electron donating groups reacted smoothly to afford excellent results.

CONCLUSIONS

In summary we have developed an important protocol for the N-Boc protection using inexpensive and commercially available basic Amberlyst[®]

A21 resin as a green, efficient, reusable, versatile heterogeneous catalyst. This method offers several advantages such as short reaction time, simple work up procedure, easy product isolation, high yield and clean reaction profile. Solvent free strategy serves to be economical and environmentally beneficial.

ACKNOWLEDGMENTS

The authors are thankful to Principal; Deogiri College, Aurangabad (MS) India for providing the laboratory facilities during the process of our present work.

REFERENCES

- [1] C. Agami, F. Couty, *Tetrahedron* 58, 2701, (2002).
- [2] X. Y. Xiuo, K. Ngu, C. Choa, D. V. Patel, *J. Org. Chem.* 62, 6968, (1997).
- [3] T.W. Green, P.G. Wuts, *Protective groups in Organic synthesis*, 2nd Ed, Wiley: New York, USA, 503 and references therein (1999).
- [4] Theodoridis G., *Tetrahedron* 56, 2339, (2000).
- [5] B. J. Yochai, H. Alfred, *J. Org. Chem.* 65, 6368, (2000).
- [6] C. Lutz, V. Lutz, P. Knochel, *Tetrahedron* 54, 6385, (1998).
- [7] K. C. Asit, V.C. Sunay, *Org. Biomol. Chem.* 4, 2769, (2006).
- [8] R. Varala, S. Nuvula, S. R. Adapa, *J. Org. Chem.* 71, 8283, (2006).
- [9] D. J. Upadhyaya, B. Alessandro, S. Rachele, C. Giancarlo, *Tet. Lett.* 48, 8318, (2007).
- [10] R. K. Pandey, S. P. Dagade, R. K. Upadhyay, M. K. Dongare, K. A. Pradeep, *Arkivoc.* vii, 28, (2002).
- [11] A. Chaskar, S. Yewale, B. Langi, H. Deokar, *J. Korean Chem. Soc.* 53, 422, (2009).
- [12] F. Shirinia, M. A. Zolfigolb, M. Abedinia, *J. Iran. Chem. Soc.* 7, 603, (2010).
- [13] A. Heydari, R.K. Shiroodi, H. Hamadi, M. Esfandiyari, M. Pourayoubi, *Tet. Lett.* 48, 5865, (2007).
- [14] A. Heydari, S. E. Hosseini, *Advan. Synth. & Cat.* 347, 1929, (2005).
- [15] Y. Yadav, G. Rao, A.R. Reddy, A.V. Narsaiah, B.V.S. Reddy, *Lett. Org. Chem.* 5, 116, (2008).
- [16] S. Sadula, K. Sanjit, P. S. Reddy, B. N. P. Rachapudi, *Tet. Lett.* 49, 2527, (2008).
- [17] G. V. Sharma, J. J. Reddy, L. P. Sree, R. K. Palakodety, *Tet. Lett.* 45, 6963, (2004).
- [18] A. Heydari, S. Khaksar, M. Tajbakhsh, A. Heydari, S. Khaksar, M. Tajbakhsh, *Synthesis* 3126, (2008).
- [19] S. Khaksar, A. Heydari, M. Tajbakhsh, S. M. Vahdat, *Tet. Lett.* 49, 3527, (2008).
- [20] V. Perron, S. Abbott, N. Moreau, D. Lee, C. Penney, B. Zacharie, *Synthesis* 283, (2009).
- [21] N. Inahashi, A. Matsumiya, T. Sato, *Synlett* 294, (2008).
- [22] V. C. Sunay, A. K. Chakraborti, *Synthesis* 16, 2784, (2006).
- [23] V. C. Sunay, A. K. Chakraborti, *Org. Lett.* 8, 3259, (2006).
- [24] K.S. Kumar, J. Iqbal, M. Pal, *Tet. Lett.* 50, 6244, (2009).
- [25] L. Stephane, R. Renzo, *J. Fluor. Chem.* 117, 167, (2002).