Monatsh Chem (2011) 142:1035–1043
DOI 10.1007/s00706-011-0534-2

ORIGINAL PAPER

An efficient and highly chemoselective *N*-Boc protection of amines, amino acids, and peptides under heterogeneous conditions

Fatemeh Jahani · Mahmood Tajbakhsh · Samad Khaksar · Mohamad Reza Azizi

Received: 2 October 2010 / Accepted: 30 May 2011 / Published online: 19 July 2011

Abstract A simple and efficient procedure for chemoselective mono-*N*-Boc protection of various structurally diverse amines, amino acids, and peptides with di-*tert*-butyl dicarbonate using Amberlyst-15 as catalyst in ethanol is described. The catalyst can be readily separated from the reaction products with simple filtration and recovered for direct reuse. No competitive side-reactions such as formation of isocyanate, urea, oxazolidinone, and *N*,*N*-di-Boc derivatives were observed.

Keywords Amberlyst-15 · Di-*tert*-butyl dicarbonate · Protection · Amine · Amino acid

Introduction

Chemical manipulation of complex polyfunctional molecules often requires sequential protection and deprotection of various functionalities. The presence of the amine moiety in a wide range of biomolecules makes protection of amines one of the most fundamental and useful transformations in organic synthesis, especially in peptide chemistry [1, 2].

Due to the stability of *tert*-butylcarbamates towards a wide range of nucleophilic reagents and alkaline reaction conditions, di-*tert*-butyl pyrocarbonate [$(Boc)_2O$] has become an important and popular protective group for amines [3]. *Tert*-butylcarbamates are easily introduced as well as readily removed under a variety of conditions [4, 5]. Besides, protection of amino groups in amino acids as *N*-Boc derivatives is an important strategy in peptide synthesis, as they can be easily converted into the free amines, and is also useful in Merrifield solid-phase peptide synthesis [6]. Furthermore, *N*-*tert*-butoxycarbonyl amino acids are resistant to racemization during peptide synthesis, making this protocol more applicable in multistep reactions [6–12]. A vast array of acidic, neutral, and basic reagents such as NaOH [13], K_2CO_3 [14], $Me_4NOH{\cdot}5H_2O$ [15], $NaHCO_3$ [16], hexamethyldizilazane sodium salt [17], dimethylaminopyridine [18–21], yttria-zirconia [22], $ZrCl_4$ [23], $Zn(ClO_4)_2{\cdot}6H_2O$ [24], $LiClO_4$ [25], $Cu(BF_4)_2$ [26], I_2 [27], $H_3PW_{12}O_{40}$ [28], montmorillonite K10 or KSF [29], sulfonic acid-functionalized silica [30], $La(NO_3)_3$ [31], thiourea [32], hexafluoroisopropanol [33], and guanidine hydrochloride [34] have been applied as catalysts for this transformation.

Some of these methodologies, although effective, have several drawbacks such as long reaction times, formation of side-products during the catalyzed reactions [19, 20], potential hazards (e.g., the high toxicity of DMAP and reagents derived from it), excess reagents in the case of Lewis acid-catalyzed reactions [36], and the problem of catalyst recovery and limited applicabilities (e.g., the use of 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, many of the *N*-Boc protection reactions do not show generality for amines; especially when amino acids are used as the amine moiety, the protection fails. Therefore, to overcome these problems, a new and more efficient protocol for synthesis of *N*-Boc amines, amino acids, and peptides, which can be applied to a number of substrates in a catalytic process, is still required.

F. Jahani · M. Tajbakhsh (✉) · M. R. Azizi
Department of Chemistry, University of Mazandaran, P.O. Box 453, Babolsar, Iran
e-mail: tajbaksh@umz.ac.ir

S. Khaksar
Chemistry Department, Islamic Azad University, Ayatollah Amoli Branch, PO Box 678, Amol, Iran

On the other hand, organic synthesis using heterogeneous acid catalysts has received much attention from the standpoint of green and sustainable chemistry because of the possibility of performing environmentally highly acceptable chemical processes [37–39].

In this context, Amberlyst-15, a sulfonic acid-based ion exchange resin, has been used as an acid catalyst in a wide variety of processes [40–43]. It has unique properties such as environmental compatibility, nontoxicity, reusability, noncorrosiveness, selectivity, and chemical and physical stability, and can be used over a prolonged period.

A very recent paper on the use of Amberlyst-15 as a catalyst for *N*-Boc protection [44] and its previous use as a catalyst for *N*-Boc deprotection [45] prompted us to report our own independent results.

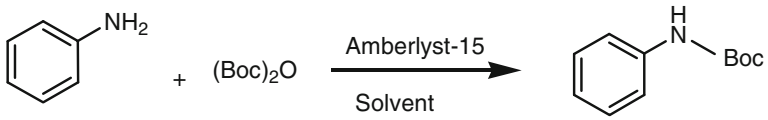
Results and discussion

Our initial experiments were carried out on aniline with 1.1 equiv $(Boc)_2O$ in the presence of Amberlyst-15 at room temperature, in order to find the best reaction conditions. The reaction was carried out in different organic solvents and monitored by thin-layer chromatography (TLC) (Table 1).

It is clear from Table 1 that protic solvents exert beneficial rate acceleration on the *tert*-butoxycarbonylation of amines as reported previously [46] (Table 1, entries 1–3). Reaction in other solvents needed longer time to give reasonable yield of the product (Table 1, entries 4–9). The lack of generality towards different substrates in water and the toxicity of methanol resulted in utilization of ethanol as a convenient solvent in this method. An optimum catalytic amount of 7–10% (w/w) of Amberlyst-15 was sufficient to afford the desired product in excellent yield. An increase in the amount of catalyst from 10% to 30% (w/w) did not improve the reaction time, and a smaller amount (2–5% w/w) led to a longer reaction time. In the absence of catalyst, longer time (38 min) was required for completion of the reaction (Table 1, entry 2).

Recently, Pal et al. [44] published a paper for *N*-Boc protection of amines in the presence of Amberlyst-15 under solvent-free conditions. They claimed that, in all cases, reactions were completed in 1–12 min. They have also reported *tert*-butoxycarbonylation of aniline in CH_2Cl_2, toluene, and CH_3CN in 1–3 min (Table 1, footnote c), but our effort to repeat the reaction under their reaction conditions led to formation of *tert*-butyl-*N*-phenyl carbamate in 72% yield after 6–7 min (Table 1, entry 10), and the reaction mixture became a mass which was very difficult to stir magnetically. Similarly, 4-chloro- and 4-bromoaniline with $(Boc)_2O$ under solvent-free conditions gave only 68% yield of the products after 30–35 min at 30–35 °C. Higher yield of the products would be obtained if the solid reaction masses were stirred manually or by mechanical stirrer for a long time. In general, the solvent-free condition was not effective. When other solid amines, especially amino acids and peptides, were employed, only low yield of the desired *N*-Boc products was obtained and excess amount of $(Boc)_2O$ was required to solve the stirring problem.

Table 1 Solvent screening



Entry	Solvent	Time/min	Yield/%[a]
1	H_2O	10	98
2	EtOH	12 (38)[b]	100
3	MeOH	12	100
4	CH_2Cl_2	50 (3)[c]	95 (95)[c]
5	$CHCl_3$	90	95
6	Dioxane	45	90
7	Toluene	60 (1)[c]	90 (80)[c]
8	CH_3CN	60 (1)[c]	90 (92)[c]
9	Tetrahydrofuran	60	95
10	–	6 (1 or 2)[c]	72 (99)[c]

[a] Yield refers to isolated products

[b] Without catalyst

[c] Values in parentheses are from [44]

However, with the optimized reaction conditions in ethanol, we evaluated the efficacy, applicability, and better potential of our protocol using a variety of structurally diverse amines. Various aliphatic, heterocyclic, and aromatic amines underwent smooth conversion into the corresponding mono-*N*-Boc products in excellent yields (Table 2).

No competitive side-reactions leading to formation of isocyanate, urea or *N*,*N*-di-Boc derivatives were detected by TLC or ^{1}H nuclear magnetic resonance (NMR) analyses of the crude products.

Reaction rates and yields are governed by the nucleophilicity of the amines. Primary and secondary aliphatic amines reacted instantaneously to give the *N*-Boc products in excellent yields (**1**–**6**). Sterically hindered *tert*-butylamine also underwent rapid and quantitative conversion (**6**). Similarly, aniline and electron-rich aromatic amines gave their *N*-Boc-derivatives under reaction conditions (**7**–**10**). In contrast, the presence of electron-withdrawing substituent groups, such as Cl, Br, CO_2H, COMe, and CN, decreased the nucleophilicity of the amines, and the corresponding conversion became quite slow (**11**–**15**), but in comparison with other catalysts reported in the literature, electron-deficient aromatic amines undergo *N*-Boc protection at much faster rates and in higher yields; for example, 4-chloroaniline using this method (**11**) required 80 min to form the corresponding *N*-Boc product (100%), which can be compared with 6 h required for the same conversion without catalyst in EtOH [46], 2.5 h (90%) in the presence of I_2 (10 mol%) under solvent-free conditions [27], and 6 h (96%) under solvent- and catalyst-free conditions [47]. A more interesting example is *N*-*tert*-butoxycarbonylation of 4-acetylaniline. $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%) catalyzed the reaction under neat conditions to generate *N*-Boc-4-acetylaniline in 60% yield after 24 h [26], whereas the desired product was obtained in 97% yield after 6 h when the reaction was carried out in the presence of Amberlyst-15 in ethanol (**15**). A notable feature of this method is the excellent chemoselectivity in the case of aminoalcohols, aminophenols, and aminothiophenol, where the *N*-Boc-protected compounds were formed as sole products without competitive formation of *O*-Boc or oxazolidinone derivatives, even using excess amount of $(Boc)_2O$ (**16**–**21**). Similarly, heteroaromatic amines underwent Boc protection in excellent yields (**21**–**26**). Moreover, the mildness of the protocol was exemplified by the conversion of a chiral amine (**29**) and α-amino acid esters (**27** and **28**) to their optically pure *N*-Boc derivatives as confirmed by measurement of their optical rotation values and comparison with those reported in the literature [22, 34, 48, 51, 52].

With these results, we decided to extend this method for protection of diamines. The results are tabulated in Table 3.

As indicated in this table, diamines were protected under reaction conditions in high yields. Clearly, when diamines were treated with 1 equiv $(Boc)_2O$, mono-*N*-Boc-protected diamines were formed, and with 2–2.5 equiv $(Boc)_2O$, rapid formation of di-Boc derivatives occurred (**30**–**35**). In the case of 3,4-diaminonitrobenzene, using 1 equiv $(Boc)_2O$ afforded only 65% of the mono-*N*-Boc product and introduction of 2.5 equiv $(Boc)_2O$ did not result in the di-Boc derivative as expected, but only the mono-*N*-Boc product in nearly quantitative yield (**36**). 4,4′-Diaminodiphenylether and 4,4′-diaminodiphenylmethane with 1 equiv $(Boc)_2O$ under the reaction condition afforded di-Boc derivatives as the sole products (5 min, 45%), but stepwise addition of $(Boc)_2O$ in 1.5 h selectively gave mono-*N*-Boc-protected products in moderate yields (**32**, **37**, and **39**). However, when 2 equiv $(Boc)_2O$ was employed, the corresponding di-Boc derivatives were formed in excellent yields (**33**, **38**, and **40**).

Since protection of the α-amino functionality of amino acids is one of the most important issues in peptide chemistry and is mandatory to prevent polymerization of the amino acid once it is activated, the utility of this protocol in reactions with amino acids and peptides was studied. In the initial experiments, we treated L-proline with 1.5–2.5 equiv $(Boc)_2O$ in the presence of Amberlyst-15 (7–10% w/w) in ethanol at 40–45 °C, and after only 5 min a quantitative yield of the *N*-Boc-L-proline was obtained. Measurement of the optical rotation value of the product and comparison with the literature [53, 54] showed that the configuration of the chiral center is not affected during the course of the reaction.

Encouraged by these results, *N*-Boc protections of amino acids and peptides were examined. Various amino acids and peptides were treated with $(Boc)_2O$ using the same approach, and the results are summarized in Table 4.

As seen in Table 4, amino acids, dipeptides (**41**–**50**), and glycylglycylglycine as a tripeptide (**51**) were efficiently protected with $(Boc)_2O$. Chemoselective protection of the α-amino group of DL-lysine was achieved in 85% under reaction conditions after 5.5 h (**47**). An interesting feature of this procedure was that the protection reactions of amino acids (but not L-proline) and peptides depicted in Table 4 could be followed visually. This is due to the poor solubility of the starting materials and solubility of the corresponding *N*-Boc derivatives in EtOH. Dissolution of the reaction mixture indicates completion of the reaction. This observation demonstrates the practical utility of this protocol, particularly in peptide synthesis.

After completion of the reaction, Amberlyst-15 can be easily separated from the product by filtration and reused without any decrease in its activity; for example, the reaction of 4-chloroaniline (**11**) and $(Boc)_2O$ afforded the

Table 2 Amberlyst-15-catalyzed protection of amines

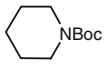
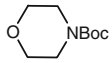
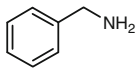
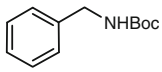
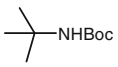
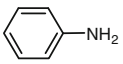
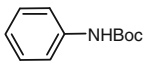
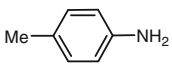
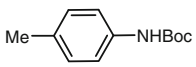
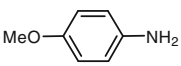
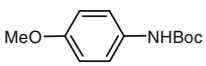
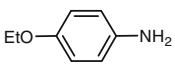
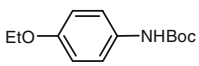
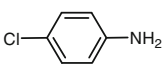
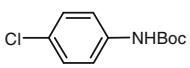
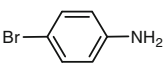
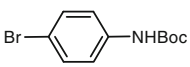
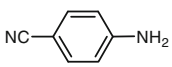
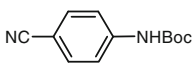
Comp.	Substrate	Product	Time/min	Yield/%[a]	M.p./°C found/reported
1			<1	100	Colorless oil [19, 48, 49]
2			<1	100	Colorless oil [48, 49]
3			<1	100	57–60/56–58 [19, 25, 48]
4			<1	100	52–54/55–57 [46, 48]
5	$(PhCH_2)_2NH$	$(PhCH_2)_2NBoc$	<1	100	Colorless oil [25, 27]
6			<1	100	42–45/– [25][b]
7			12	100	132/132 [29, 48]
8			15	100	84–85/86–87 [46, 48]
9			7	100	94–96/94–96 [27, 46]
10			6	100	110–112/110–112 [34]
11			80	100	102–104/102–103 [46]
12			45	100	100–103/102 [48]
13			6 h	65	112/113–114 [26]

Table 2 continued

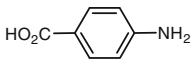
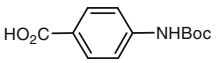
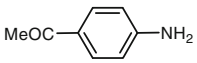
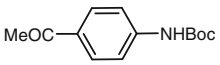
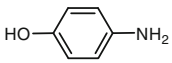
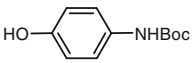
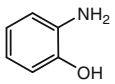
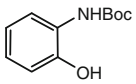
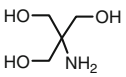
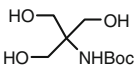
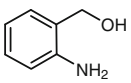
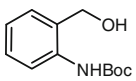
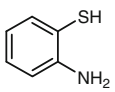
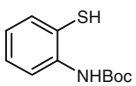
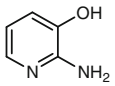
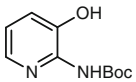
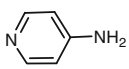
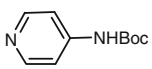
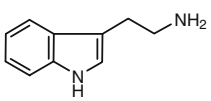
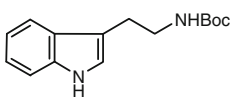
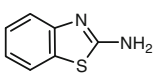
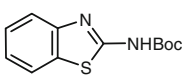
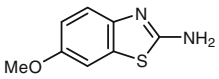
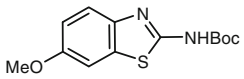
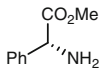
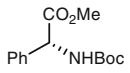
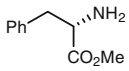
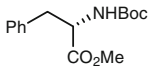
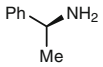
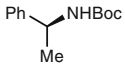
Comp.	Substrate	Product	Time/min	Yield/%[a]	M.p./°C found/reported
14			6 h	100	179–181/180–183 [50]
15			6 h	97	135–138/137 [26]
16			3	100	146/146 [48]
17			50	100	140–143/142 [33, 46, 48]
18			5	100	135–138/135–137 [28]
19			60	95	Oil [34]
20			60	83	83–84/– [27][b]
21			2.5 h	93	129–132/–
22			<1	100	46–48/42–45 [23, 24]
23			17	95	139–142/141–143 [34]
24			2	100	90–91/90–92 [34]
25			4 h	75	>240/–

Table 2 continued

Comp.	Substrate	Product	Time/min	Yield/%[a]	M.p./°C found/reported
26			5.5 h	100	>240/–
27			19	93[c]	107–109/110–111 [48]
28			16	95[d]	35–39/37–38 [48]
29			<1	100[e]	85–87/87–88 [25, 27, 46]

[a] Yield refers to isolated products

[b] Reference to NMR data

[c] $[\alpha]_D^{27} = +134.0°\ cm^2\ g^{-1}$ ($c = 0.8$, $CHCl_3$)

[d] $[\alpha]_D^{27} = -4.0°\ cm^2\ g^{-1}$ ($c = 2$, CH_3OH)

[e] $[\alpha]_D^{27} = -51.6°\ cm^2\ g^{-1}$ ($c = 1$, $CHCl_3$)

corresponding *N*-Boc product in nearly 100% isolated yield over three cycles.

In conclusion, we describe herein an efficient methodology for *N-tert*-butoxycarbonylation of various electronically and structurally divergent amines in good to excellent isolated yields. The method proceeds at ambient temperature in a convenient solvent, ethanol, with an easily recovered acid catalyst which can be used immediately without any activation.

Experimental

^1H and ^{13}C NMR spectra were recorded on 300 and 400 MHz Bruker spectrometers in $CDCl_3$ and dimethyl sulfoxide (DMSO)-d_6 using $SiMe_4$ as an internal standard. Chemical shifts are reported in ppm, and coupling constants (J values) are reported in Hz. Reactions were monitored by TLC (Merck) or gas chromatography (GC). Evaporation of solvents was performed at reduced pressure, using a rotary evaporator. Melting points were measured using the capillary tube method with a Bamstead Electrothermal 9200 apparatus. Infrared (IR) spectra were recorded from KBr disks on a Bruker Tensor 27 FT-IR spectrophotometer. All solvents and reagents were purchased from Aldrich or Merck with high-grade quality and used without any purification.

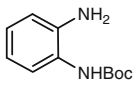
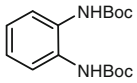
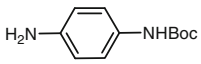
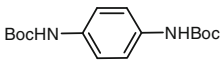
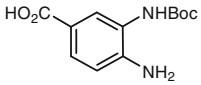
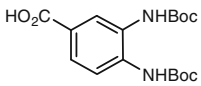
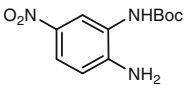
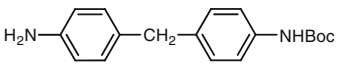
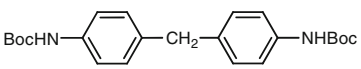
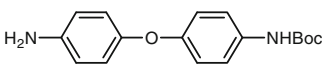
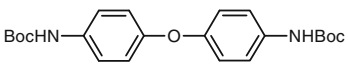
General procedure for preparation of N-Boc amines and amine derivatives

The amine or diamine (1 mmol) was added to a magnetically stirred mixture of Amberlyst-15 (7–10% w/w) and di-*tert*-butyl dicarbonate (1.1–2.5 mmol) in 1 cm^3 EtOH at room temperature. After completion of the reaction (followed by TLC), the catalyst was separated by filtration. The filtrate was concentrated on a rotary evaporator to afford the corresponding pure product. If necessary, the product was further purified either by recrystallization or silica gel column chromatography with EtOAc-hexane (1:6) as eluent. In the cases where excess $(Boc)_2O$ was used, the crude products were washed with *n*-hexane or petroleum ether before further purification.

General procedure for preparation of N-Boc amino acids and peptides

Amino acid or peptide (1 mmol) was added to a magnetically stirred mixture of Amberlyst-15 (7–10% w/w) and di-*tert*-butyl dicarbonate (2.5 mmol) in 1 cm^3 EtOH at 40–45 °C. The reaction mixture was stirred until a clear solution was obtained. After completion of the reaction (followed by TLC or visually), the catalyst was separated by filtration. The filtrate was evaporated under

Table 3 Amberlyst-15-catalyzed Boc protection of diamines

Comp.	$(Boc)_2O$ (equiv)	Product	Time/min	Yield/%[a]	M.p./ °C	Ref.[b]
30	1		20	90	110–113	[34]
31	2		60	100	104–106	[34]
32	1		30	80	112–114	[34]
33	2		12	100	189 (dec.)	[34]
34	1		2 h	70	190–192	–
35	2.5		4.5 h	95	195–197	–
36	1 2.5		6 h 8 h	65 97	190–192	[34]
37	1		90	60	126–129	–
38	2		70	100	191–194	–
39	1		90	60	188 (dec.)	–
40	2		60	100	208–210	–

[a] Yield refers to isolated products

[b] Reference to NMR data

vacuum, and the residue was washed with hexane (2×5 cm^3) to afford the pure product. If necessary, the crude product was further purified by recrystallization. The physical data (m.p.), ^1H, and ^{13}C NMR spectra of known compounds were found to be identical to those reported in the literature.

Table 4 Amberlyst-15-catalyzed Boc protection of amino acids and peptides

Comp.	Product	Time/h	Yield/%[a]	M.p./ °C found/reported
41	*N*-Boc-D-phenylalanine	20	93	Oil [55]
42	*N*-Boc-L-proline	5 min	100	132–134/135–137 [54, 56]
43	*N*-Boc-L-leucine	5	91	82–85/85–87 [34]
44	*N*-Boc-L-tryptophan	10	93	137–140/136–140 [54]
45	*N*-Boc-glycine	24	100	85–88/89 [54, 56]
46	*N*-Boc-L-arginine	35	87	121–124/–
47	N^{α}-Boc-DL-lysine	5.5	85	198–200/201–202 [35]
48	*N*-Boc-L-valine	40 min	97	72–75/76–78 [57]
49	*N*-Boc-glycylvaline	50 min	93	106–108/107–108 [34]
50	*N*-Boc-glycylglycine	19	95	126–130/128–131 [34]
51	*N*-Boc-glycylglycylglycine	10	91	125–127/125–127 [34]

[a] Yield refers to isolated products

2-(tert-Butoxycarbonylamino)-3-pyridinol
(**21**, $C_{10}H_{14}N_2O_3$)
Off-white solid, m.p.: 129–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.54$ (s, 9H), 7.00 (dd, $J = 8.0$, 4.7 Hz, 1H), 7.32 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.91 (dd, $J = 4.7$, 1.5 Hz, 1H), 9.31 (s, 1H, OH), 9.96 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.2$ (CH_3), 83.2 (C), 121.2 (CH), 127.8 (CH), 138.8 (CH), 140.3 (C), 143.8 (C), 156.1 (C=O) ppm.

2-(tert-Butoxycarbonylamino)benzothiazole
(**25**, $C_{12}H_{14}N_2O_2S$)
White solid, m.p.: >240 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.61$ (s, 9H), 7.03 (td, $J = 8.0$, 1.4 Hz, 1H), 7.42 (td, $J = 8.0$, 1.2 Hz, 1H), 7.81 (dd, $J = 8.0$, 0.8 Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.3$ (CH_3), 83.3 (C), 120.8 (CH), 121 (CH), 123.4 (CH), 125.7 (CH), 131.5 (C), 148.6 (C), 156.4 (C), 161.3 (C=O) ppm.

2-(tert-Butoxycarbonylamino)-6-methoxybenzothiazole
(**26**, $C_{13}H_{16}N_2O_3S$)
White solid, m.p.: >240 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.59$ (s, 9H), 3.87 (s, 3H), 6.98 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.27 (d, $J = 2.4$ Hz, 1H), 7.80 (d, $J = 8.8$ Hz, 1H), 11.4 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.3$ (CH_3), 55.8 (CH_3), 83.0 (C), 104.0 (CH), 114.5 (CH), 121.4 (CH), 132.7 (C), 142.9 (C), 152.8 (C), 156.4 (C), 159.4 (C=O) ppm.

4-Amino-3-(tert-Butoxycarbonylamino)benzoic acid
(**34**, $C_{12}H_{16}N_2O_4$)
Off-white solid, m.p.: 190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.46$ (s, 9H), 5.61 (s, 2H, NH_2), 6.67 (d, $J = 8.4$ Hz, 1H), 7.44 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.84 (s, 1H), 8.32 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 28.6$ (CH_3), 79.4 (C), 114.6 (CH), 118.0 (C), 122.8 (CH), 126.6 (C), 127.4 (CH), 146.2 (C), 154.1 (C=O), 167.8 (CO_2H) ppm.

3,4-Bis(tert-Butoxycarbonylamino)benzoic acid
(**35**, $C_{17}H_{24}N_2O_6$)
Off-white solid, m.p.: 195–197 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.47$ (s, 9H), 7.62 (dd, $J = 8.5$, 1.8 Hz, 1H), 7.70 (d, $J = 8.5$ Hz, 1H), 8.07 (br s, 1H), 8.70 (br s, 1H, NH), 8.75 (br s, 1H, NH), 12.8 (br s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 28.0$ (CH_3), 28.1 (CH_3), 79.6 (C), 80.0 (C), 122.0 (CH), 125.1 (CH), 125.3 (CH), 125.7 (C), 128.8 (C), 134.3 (C), 152.0 (C=O), 153.2 (C=O), 166.9 (CO_2H) ppm.

4′-(tert-Butoxycarbonylamino)diphenylmethan-4-amin
(**37**, $C_{18}H_{22}N_2O_2$)
White solid, m.p.: 126–129 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.52$ (s, 9H), 3.65 (s, 2H), 4.83 (s, 2H, NH_2), 6.47 (dd, $J = 6.4$, 2 Hz, 2H), 6.82 (d, $J = 8.4$ Hz, 2H), 7.03 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 9.19 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 28.6$ (CH_3), 40.6 (CH_2), 79.3 (C), 114.4 (CH), 118.7 (CH), 129 (C), 129.1 (CH), 129.4 (CH), 136.4 (C), 137.6 (C), 147.0 (C), 153.3 (C=O) ppm.

4,4′-Bis(tert-Butoxycarbonylamino)diphenylmethane
(**38**, $C_{23}H_{30}N_2O_4$)
White solid, m.p.: 191–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (s, 9H), 3.90 (s, 1H), 6.50 (br s, 1H, NH), 7.08 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.4$ (CH_3), 40.5 (CH_2), 80.5 (C), 118.7 (CH), 129.4 (CH), 136 (C), 136.4 (C), 152.9 (C=O) ppm.

4-Amino-4′-(tert-Butoxycarbonylamino)diphenylether
(**39**, $C_{17}H_{20}N_2O_3$)
White solid, m.p.: 192–194 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.45$ (s, 9H), 4.90 (s, 2H, NH), 6.56 (d, $J = 8.0$ Hz, 2H), 6.67 (d, $J = 9.2$ Hz, 2H), 6.78 (d, $J = 9.2$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 9.2 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 28.6$ (CH_3), 79.2 (C), 115.3 (CH), 117.7 (CH), 120.2 (C), 120.6

(CH), 134.4 (CH), 145.4 (C), 147.1 (C), 153.4 (C), 153.9 (C=O) ppm.

4,4′-Bis(tert-Butoxycarbonylamino)diphenylether (**40**, $C_{22}H_{28}N_2O_5$)
White solid, m.p.: 208–210 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (s, 9H), 6.46 (br s, 1H, NH), 6.91 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 8.8$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.3$ (CH_3), 80.5 (C), 119.1 (CH), 120.3 (CH), 133.6 (C), 153.0 (C), 153.03 (C=O) ppm.

N-Boc-L-arginine (**46**, $C_{11}H_{22}N_4O_4$)
White solid, m.p.: 121–124 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.35$ (s, 9H), 1.46–1.61 (m, 4H), 3.03 (m, 2H), 3.65 (m, 1H), 5.93 (d, $J = 6.8$ Hz, 1H, NH), 7.0–8.0 (br s, 4H, NH, NH_2), 9.20 (br s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 25.6$ (CH_2), 27.3 (CH_2), 28.6 (CH_3), 31.7 (CH_2), 55.0 (CH), 77.9 (C), 155.3 (C=NH), 157.7 (C=O), 176.1 (CO_2H) ppm.

Acknowledgments Financial support of this work by the Research Council of Mazandaran University is gratefully acknowledged.

References

1. Wuts PGM, Greene TW (2007) Greene's protective group in organic synthesis, 4th ed. Wiley, New York
2. Raghavendra NS, Kumar BP, Longquin H (2006) Tetrahedron Lett 47:389
3. Pope BM, Yamamoto X, Tarbell DS (1988) Org Synth Coll VI:418
4. Srinivasan N, Yurek-George AG (2005) Mol Diver 9:291
5. Longenecker K, Hamilton GL, Stewart K, Lai C, Kopecka H, von Geldern TW, Madar DJ, Pei Z, Lubben TH, Zinker BA, Tian Z, Ballaron SJ, Stashko MA, Mika AK, Beno DWA, Kempf-Grote AJ, Black-Schaefer C, Sham HL, Trevillyan JM (2007) Bioorg Med Chem Lett 17:2005
6. Merrifield RB (1964) J Am Chem Soc 86:304
7. Satori G, Ballini R, Bigi F, Bosica G, Maggi R, Righi P (2004) Chem Rev 104:199
8. Kocienski PJ (2000) Protecting groups. Georg Thieme Verlag, Stuttgart
9. Wuensch E (1974) Houben-Weyl, methods of organic chemistry, 4th edn. In: Mueller E, Bayer O, Meerwein H, Ziegler K (eds), Georg Thieme Verlag, Stuttgart, vol 15/1, p 46
10. McOmie JFW (1973) Protective groups in organic chemistry. Plenum Press, London
11. Gross E, Meienhofer J (1981) The peptides. Academic Press, New York
12. Merrifield RB (1963) J Am Chem Soc 85:2149
13. Lutz C, Lutz V, Knochel P (1998) Tetrahedron 54:6385
14. Handy ST, Sabatini JJ, Zhang Y, Vulfova I (2004) Tetrahedron Lett 45:5057
15. Khalil EM, Subasinghe NL, Johnson RL (1996) Tetrahedron Lett 37:3441
16. Eunhorn J, Einhorn C, Luche JL (1991) Synlett 1:37
17. Kelly TA, McNeil DW (1994) Tetrahedron Lett 35:9003
18. Darnbrough S, Mervic M, Condon SM, Burns CJ (2001) Synth Commun 31:3273
19. Basel Y, Hassner A (2000) J Org Chem 65:6368
20. Burk MJ, Allen JG (1997) J Org Chem 62:7054
21. Grehn L, Ragnarsson U (1985) Angew Chem Int Ed 24:510
22. Pandey RK, Dagade SP, Upadhyay RK, Dongare MK, Kumar P (2002) Arkivoc vii:28
23. Sharma GVM, Reddy JJ, Lakshmi PS, Krishna PR (2004) Tetrahedron Lett 45:6963
24. Bartoli G, Bosco M, Locatelli M, Marcantoni E, Massaccesi M, Melchiorr P, Sambri L (2004) Synlett 10:1794
25. Heydari A, Hosseini SE (2005) Adv Synth Catal 347:1929
26. Chankeshwara SV, Chakraborti AK (2006) Tetrahedron Lett 47:1087
27. Varala R, Nuvula S, Adapa SR (2006) J Org Chem 71:8283
28. Heydari A, Kazem Shiroodi R, Hamadi H, Esfandyari M, Pourayoubi M (2007) Tetrahedron Lett 48:5865
29. Chankeshwara SV, Chakraborti AK (2006) J Mol Catal A: Chem 253:198
30. Das B, Verkateswarlu K, Krishnaiah M, Holla H (2006) Tetrahedron Lett 47:7551
31. Suryakiran N, Prabhakar P, Srikanth Reddy T, Rajesh K, Venkateswarlu Y (2006) Tetrahedron Lett 47:8039
32. Khaksar S, Heydari A, Tajbakhsh M, Vahdat SM (2008) Tetrahedron Lett 49:3527
33. Heydari A, Khaksar S, Tajbakhsh M (2008) Synthesis 19:3126
34. Jahani F, Tajbakhsh M, Golchoubian H, Khaksar S (2011) Tetrahedron Lett 52:1260
35. Meienhofer J, Kuromizu K (1974) Tetrahedron Lett 15:3259
36. Ishihara K, Hasegama A, Yamamoto H (2001) Angew Chem Int Ed 40:4077
37. Trost BM (1991) Science 254:1471
38. Sheldon RA (1994) Chemtech 24:38
39. Anastas PT, Warner JC (1998) Green chemistry: theory and practice. Oxford University Press, UK
40. Tajbakhsh M, Heydari A, Alinezhad H, Ghanei M, Khaksar S (2008) Synthesis 3:352
41. Tajbakhsh M, Heydari A, Khalilzadeh MA, Lakouraj MM, Zamenian B, Khaksar S (2007) Synlett 15:2347
42. Lakouraj MM, Tajbakhsh M, Tashakkorian H (2007) Monatsh Chem 138:83
43. Tajbakhsh M, Hosseinzadeh R, Lasemi Z (2004) Synlett 4:635
44. Kumar KS, Iqbal J, Pal M (2009) Tetrahedron Lett 50:6244
45. Liu YS, Zhao C, Bergbreiter DE, Romo D (1998) J Org Chem 63:3471
46. Vilaivan T (2006) Tetrahedron Lett 47:6739
47. Jia X, Huang Q, Li J, Li S, Yang Q (2007) Synlett 5:806
48. Chankeshwara SV, Chakraborti AK (2006) Org Lett 8:3259
49. Dieter RK, Li S (1997) J Org Chem 62:7726
50. Norman MH, Rigdon GC, Hall WR, Navas F III (1996) J Med Chem 39:1172
51. Dondoni A, Perrone D, Semola T (1995) Synthesis 2:181
52. Green R, Taylor PJM, Bull SD, James TD, Mahon MF, Merritt AT (2003) Tetrahedron: Asymmetry 14:2619
53. Marcantoni E, Massaccesi M, Torregiani E (2001) J Org Chem 66:4430
54. Anderson GW, Mcgregor AC (1957) J Am Chem Soc 79:6180
55. Myers AG, Gleason JL, Yoon T, Kung DW (1997) J Am Chem Soc 119:656
56. Itoh M, Hagiwara D, Kamiya T (1975) Tetrahedron Lett 49:4393
57. Thaqi A, McCluskey A, Scott JL (2008) Tetrahedron Lett 49:6962