Tetrahedron Letters 53 (2012) 5803–5806

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave assisted mild, rapid, solvent-less, and catalyst-free chemoselective *N-tert*-butyloxycarbonylation of amines

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ARTICLE INFO

Article history:
Received 22 June 2012
Revised 21 August 2012
Accepted 23 August 2012
Available online 31 August 2012

Keywords:
Amines
Boc anhydride
Boc protection
MWI
Solventless

ABSTRACT

Microwave assisted simple, rapid, solventless, and catalyst-free chemoselective method for the protection of amino group in aromatic, aliphatic, heterocyclic, aralkyl amines, phenyl hydrazine, and amino acid esters in good to excellent isolated yield (83–98%) in short reaction time (2–12 min) has been reported.

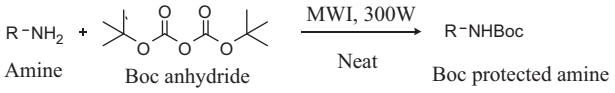
In organic synthesis, protection and deprotection of amino groups play an important role.[1] For choice of protecting group, simplicity, yield, ease of handling, and cost of the process are generally considered. Amine functionality is present in a wide range of biologically active compounds and hence the protection of amines is frequently needed in synthetic, organic, and medicinal chemistry.[2] The most easy method is acylation.[3] However, it requires harsh reaction conditions[4] to regenerate the amine from the acylated derivative and hence is not suitable for multifunctional substrates. Therefore, a protecting group that can be cleaved under mild reaction conditions is required. One of the most useful protecting groups is the *tert*-butoxycarbonyl (Boc) group[5] introduced using commercially available $(Boc)_2O$.[6]

N-tert-Butoxycarbonyl group is preferred due to its stability toward basic and nucleophilic attacks and the ease of removal by acid.[7] Conventionally, for Boc protection, amines are reacted with di-*tert*-butyl dicarbonate [$(Boc)_2O$] in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP)[8] or inorganic bases.[9] However, the reagents are toxic and the reaction takes a long time to complete. In base-catalyzed reactions, the formation of isocyanates,[10] ureas,[8] and *N,N*-di-Boc[11] derivatives is also reported. Methods using Lewis acids such as $ZrCl_4$,[12] $LiClO_4$,[13] $HClO_4$,[14] $Zn(ClO_4)_2 \cdot 6H_2O$,[15] and $La(NO_3)_3 \cdot 6H_2O$[16] are reported. However, these have limited applications and have drawbacks. $ZrCl_4$ is highly moisture sensitive and liberates hydrochloric acid fumes, perchlorate reagents are explosive and most Lewis acids are deactivated by amines, more than stoichiometric amounts are needed and hence not suitable.[17,18] Recently, $HClO_4/SiO_2$,[14] Montmorillonite K10 or KSF,[19] I2,[20] $H_3PW_{12}O_{40}$,[21] thiourea,[22a] HFIP,[23] sulfamic acid,[24] Amberlyst 15,[25] and H_2O[26] have been used. Most of these methods have limitations like high costs, toxicity, corrosiveness, limited applications, deprotection of other protecting groups,[27] difficulties in the isolation of products, lack of generality especially with deactivated (electron-deficient) amines, etc. Khaksar et al. have reported that thiourea, thioglycoluril, and guanidine hydrochloride can also catalyze *N*-Boc protection of various activated amines.[22b,c]

Microwave assisted organic synthesis has been widely used in organic synthesis.[28] Introduced in 1986 by Gedye[29] and Giguere,[30] it has advantages like reduction of reaction times,[31] enhancement of product yields, elimination of unwanted side products,[28] ability to precisely control the temperature, and pressure profiles of reactions, reproducibility,[32] etc.

In this Letter, we report the use of microwave for selective *tert*- butoxycarbonylation of various amines. It is a green chemistry approach for the synthesis of Boc-protected amines wherein the use of solvents and catalysts is avoided.

For model reaction, we reacted 1 mmol of aniline with 1.1 mmol di-*tert*-butyl dicarbonate [$(Boc)_2O$] in the absence of any catalyst



Scheme 1.

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0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.08.089

Table 1
N-tert-Butyloxycarbonylation of amines under microwave irradiation (MWI)

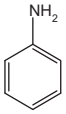
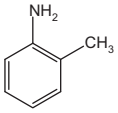
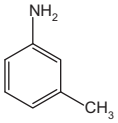
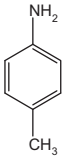
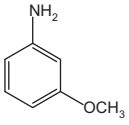
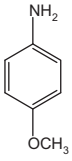
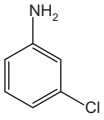
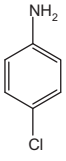
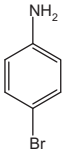
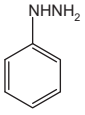
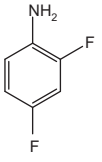
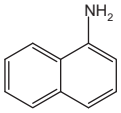
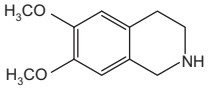
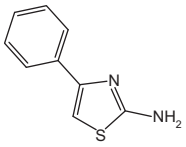
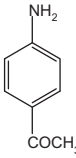
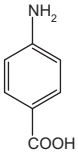
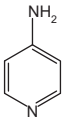
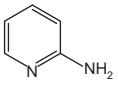
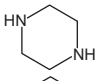
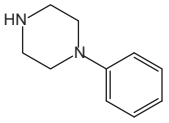
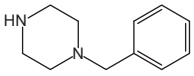
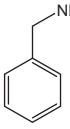
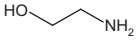
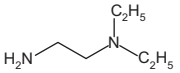
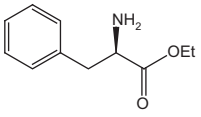
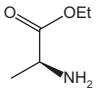
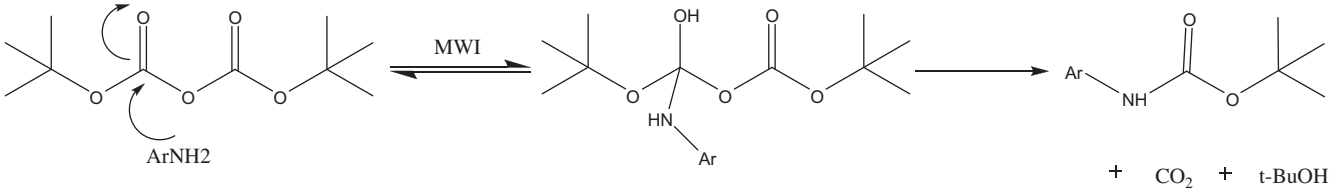
Entry	Amine	Time (min)	Yield[a] (%)
1		2	98
2		4	97
3		5	97
4		5	98
5		4	95
6		4	92
7		4	90
8		5	96
9		5	95
10		5	90
11		4	91
12		4	87
13		8	89

Table 1 (*continued*)

Entry	Amine	Time (min)	Yield[a] (%)
14		5	93
15		10	85
16		12	86
17		5	94
18		5	94
19		2	88
20		2	89
21		2	89
22		5	96
23		2	96
24		2	95
25		2	94
26		2	92
27		2	91
28		10	84
29		8	83

[a] Isolated yield.



Scheme 2.

with methanol as a solvent under microwave irradiation. The reaction was completed in just 2 min. We performed the reaction without methanol and got the same yield. Also, the time required for completion of the reaction was also the same (Scheme 1). Thus we concluded that the solvent does not have any role in this reaction and that microwave irradiation plays an important role.

To increase the scope of this reaction, we used substituted anilines, aliphatic amines, heterocyclic anilines, aralkyl amine, phenyl hydrazine, and also amino acid esters.[33] Results are shown in Table 1. In all cases, we obtained the product with excellent yield. We also used anilines having electron donating and electron withdrawing groups and all the products were isolated in good to excellent yield.

The following mechanism can be proposed for this reaction. Microwave irradiation not only quickly heats the system to very high temperature facilitating the reaction but also activates the carbonyl oxygen atom of $(Boc)_2O$ making the carbonyl group more susceptible to nucleophilic attack by the amine which forms the intermediate. This facilitates the removal of *tert*-butanol and carbon dioxide from the intermediate, eventually leading to the formation of *N*-Boc-protected amine (Scheme 2).

To summarize, we report the microwave assisted, efficient, and green method for *N*-*tert*-butoxycarbonylation of various structurally diverse amines in good-to-excellent isolated yields. In contrast to some existing methods using potentially hazardous catalysts/additives, this new method offers advantages like short reaction times, no use of catalyst, no use of solvent, ease of product isolation, no side reactions, and simple processing and handling.

Acknowledgment

This work has been carried out as a part of the Department of Science and Technology (DST) sponsored research project (SR/FT/CS-100/2009). We are thankful to DST, India for the financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.089.

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33. (General procedure for the *N*-*tert*-butoxycarbonylation of amines: Amine (1 mmol) and di-*tert*-butyl dicarbonate [$(Boc)_2O$] (1.1 mmol) were placed in a microwave reaction vial. The LG microwave oven MG 555f was programmed to 300 W at 100 °C. The reaction was monitored using TLC. After the reaction, ice water was added to the reaction mixture which resulted in the precipitation of the product. The solid product was merely filtered off and washed with excess cold water. The product was pure enough for all practical purposes. For characterization purpose, it was further purified by column chromatography (Neutral Alumina as adsorbent, solvent system: Hexane: Ethyl acetate (7.5:2.5)).
Spectroscopic data for few products are given below.
(1) Phenyl-carbamic acid *tert*-butyl ester (entry 1). IR (KBr) ν: 1685 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.54 (s, 9 H), 6.51 (bs, 1 H), 7.02–7.05 (m,1 H), 7.28–7.39 (m, 4 H). MS (EI): *m*/*z* 193 (M^+).
(2) o-Tolyl-carbamic acid *tert*-butyl ester (entry 2) IR (KBr) ν: 1693 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ : 1.54 (s,9H), 2.27 (s,3 H), 6.26 (bs, 1H), 7.01 (s, 1H), 7.15–7.28 (m, 2H), 7.78 (d, Hz,1H). MS (EI): *m*/*z* 207 (M^+).
(3) m-Tolyl-carbamic acid *tert*-butyl ester (entry 3) IR (KBr) ν: 1694 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ: 1.54 (s, 9H), 2.34 (s, 3H), 6.48 (bs, 1H), 7.09 (s, 1H), 7.16 (m, 3H); MS (EI): *m*/*z* 207 (M^+).
(4) p-Tolyl-carbamic acid *tert*-butyl ester (entry 4) IR (KBr) ν: 1690 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ: 1.53 (s, 9H), 2.31 (s, 3H), 6.44 (bs, 1H), 7.09 (d, 2H), 7.24 (d, 2H); MS (EI): *m*/*z* 207 (M^+).

(5) (4-Methoxy-phenyl)-carbamic acid *tert*-butyl ester (entry 6) IR (KBr) *v*: 1698 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ: 1.52 (s, 9H), 3.05 (s, 3H), 6.35 (bs, 1H), 6.84–6.87 (d, 2H), 7.26–7.28 (d, 2H); MS (EI): *m*/*z* 223 (M^+).

(6) (3-Chloro-phenyl)-carbamic acid *tert*-butyl ester (entry 7) IR (KBr) *v*: 1701 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ: 1.53 (s, 9H), 6.53 (bs, 1H), 7.00 (d, 1H), 7.15–7.28 (m, 2H), 7.53 (s, 1H); MS (EI): *m*/*z* 227 (M^+).

(7) Naphthalen-1-yl-carbamic acid *tert*-butyl ester (entry 12). IR (KBr) *v*: 1701 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.58 (s, 9 H), 6.89 (bs, 1 H), 7.45 (m, 3 H), 7.64 (d, 1 H), 7.86 (m, 3 H). MS (EI): *m*/*z* 243 (M^+).

(8) Pyridin-4-yl-carbamic acid *tert*-butyl ester (entry 17). IR (KBr) *v*: 1721 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.52 (s, 9 H), 7.32 (t, 2 H), 8.43 (t, 2 H). MS (EI): *m*/*z* 194 (M^+).

(9) 4-Phenyl-piperazine-1-carboxylic acid *tert*-butyl ester (entry 20) IR (KBr) *v*: 1685 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ: 1.54 (s, 9H), 3.13–3.16 (t, 4H), 3.58–3.61 (t, 4H), 3.51 (s, 2H), 6.88–6.93 (m, 3H), 7.27–7.32 (t, 2H); MS (EI): *m*/*z* 262 (M^+).

(10) 4-Benzyl-piperazine-1-carboxylic acid *tert*-butyl ester (entry 21) IR (KBr) *v*: 1698 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ: 1.45 (s, 9H), 2.37–2.40 (t, 4H), 3.38–3.42 (t, 4H), 7.24–7.32 (s, 5H); MS (EI): *m*/*z* 276 (M^+).

(11) Pyrrolidine-1-carboxylic acid *tert*-butyl ester (entry 23) IR (KBr) *v*: 1695 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ: 1.46 (s, 9H), 1.83–1.84 (s, 4H), 3.28–3.33 (s, 4H), MS (EI): *m*/*z* 171 (M^+).

(12) Morpholine-4-carboxylic acid *tert*-butyl ester (entry 24): Colorless oil, IR (Neat) *v*: 1695 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ : 1.46 (s, 9H), 3.39–3.42 (m, 4H), 3.62–3.65 (m, 4H). MS (EI): *m*/*z* 187 (M^+).

(13) 2-*tert*-Butoxycarbonylamino-3-phenyl-propionic acid ethyl ester (entry 28). IR (KBr) *v*: 1685 cmÀ1. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.24 (t, 3 H), 1.42 (bs, 9 H), 2.99 (t, 2 H), 4.16 (q, 2 H), 4.51 (d, 1 H), 5.00 (d, 1 H), 5.50 (bs, 1 H), 6.72 (d, 2 H), 6.97 (d, 2 H), MS (EI): 293 (M^+).