Tetrahedron Letters 50 (2009) 6244–6246

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Amberlyst-15: a mild, efficient and reusable heterogeneous catalyst for *N-tert*-butoxycarbonylation of amines

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ARTICLE INFO

Article history:
Received 6 August 2009
Revised 31 August 2009
Accepted 3 September 2009
Available online 6 September 2009

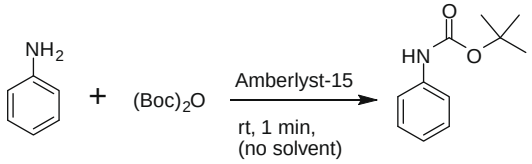
ABSTRACT

A mild and versatile method has been developed for the chemoselective *N-tert*-butoxycarbonylation of amines in the presence of Amberlyst-15 under solvent-free condition. The method is general for the preparation of *N*-Boc derivatives of aliphatic (acyclic and cyclic) and aromatic amines.

1. Introduction

The protection and deprotection of amines have become a very important and widely used strategy for many multi-step organic syntheses. Among the various groups reported for the protection of amines, the use of *N-tert*-butoxycarbonyl (*N*-Boc) group has become very popular.[1] Because of the stability of the corresponding *N-tert*-butylcarbamates to a wide range of nucleophiles under alkaline conditions this group can be exposed to a number of chemical transformations safely. Moreover due to its labile nature towards mild acidic conditions this group can be converted back to the parent amine easily.[2] Various reagents and methods have been reported for the *N-tert*-butoxycarbonylation of amines[3–11] in the absence or presence of Lewis acids.[12–26]Many of these methods suffer from several drawbacks, such as the requirement of longer reaction time and high temperature. Moreover, the preparation of catalysts is cumbersome in some cases. Therefore, the development of a new, facile and eco-friendly catalytic method was highly desirable. In recent years, heterogeneous catalysis has attracted much attention for various organic transformations.[27] As an inexpensive and commercially available heterogenous catalyst Amberlyst-15 attracted our attention due to its non-hazardous nature and easy removal from the reaction mixture, for example, via simple filtration. Herein we report an Amberlyst-15 mediated chemoselective *N-tert*-butoxycarbonylation of amines under a solvent-free condition (Scheme 1).

In our initial study, aniline was reacted with di-*tert*-butyl dicarbonate in the presence of Amberlyst-15 in DCM at room temperature for 3.0 min when the expected product was obtained in 95% yield (Table 1, entry 1). The use of other solvents such as toluene and CH_3CN did not improve the yield (Table 1, entries 2 and 3). However, better yield was achieved when the reaction was carried out in the absence of a solvent and the reaction was completed within 2.0 min affording the desired product in 99% yield (Table 1, entry 4). The catalyst recovered from the reaction mixture was also tested for its recyclability at least for three times and the desired product was isolated in good yield in each run (Table 1, entry 4).



Scheme 1.

This observation encouraged us to extend the scope and generality of this methodology. Thus a variety of primary, secondary and aryl amines were reacted with di-*tert*-butyl dicarbonate in the presence of Amberlyst-15 (Table 2). The reaction was completed within 2–12 min to give the corresponding *N-tert*-butylcarbamates in good to excellent yields. Aniline (Table 2; entry 1) and other aromatic amines containing electron-withdrawing groups underwent *N*-Boc protection at a faster rate (Table 2; entries 2–4 and 8–10) whereas aliphatic (cyclic and acyclic) primary and secondary

Table 1
N-tert-butoxycarbonylation of aniline in the presence of Amberlyst-15[a]

Entry	Solvent	Yield[a] (%)
1	DCM	95
2	CH_3CN	92
3	Toluene	80
4	Solvent free	99 (97, 96, 94)[b]

[a] Reaction conditions: aniline (1.0 mmol) and Boc_2O (1.0 mmol); Amberlyst-15 (15%, w/w); rt; 1.0 min.
[b] Catalyst was reused for additional three runs and figures within parentheses indicate the corresponding yield for each run.

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.09.018

Table 2
N-tert-butoxycarbonylation of aromatic and aliphatic amines in the presence of Amberlyst-15

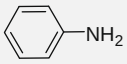
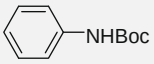
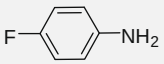
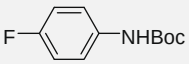
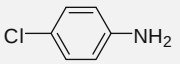
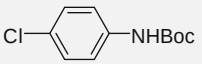
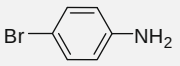
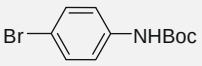
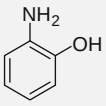
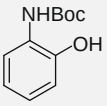
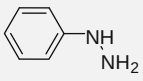
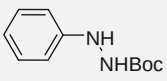
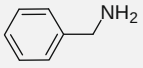
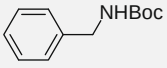
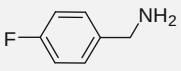
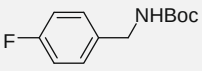
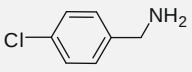
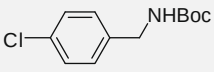
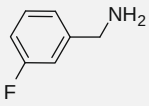
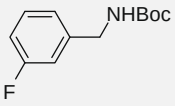
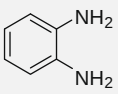
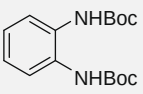
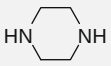
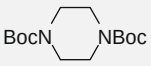
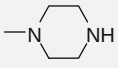
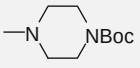
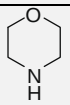
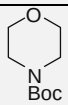
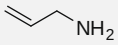
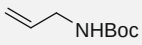
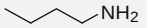
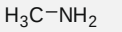
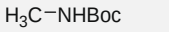
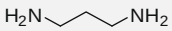
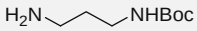
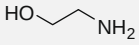
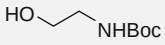
Entry	Amine	Product[a]	Time (min)	Yield[b] (%)
1			1	99
2			3	96
3			3	95
4			3	95
5			8	92
6			4	95
7			2	99
8			2	96
9			3	96
10			5	90
11			4	95
12			1	98
13			3	98
14			2	99

Table 2 (*continued*)

Entry	Amine	Product[a]	Time (min)	Yield[b] (%)
15			1.5	99
16			2	98
17			2	98
18			2	99
19			3	95
20			4	95
21			5	92
22			10	96

[a] All the products were characterized by IR, NMR and mass spectroscopy and compared with those reported in the literature.
[b] Isolated yields after column chromatography.

amines (Table 2; entries 12–22) provided the corresponding *N*-Boc products within 1–10 min. Notably, 2-aminophenol, and proline (Table 2; entries 5 and 22) reacted slowly with $(Boc)_2O$ in comparison with other amines. This method was found to be selective for the protection of amine as hydroxyl group was not affected during the reaction (Table 1, entries 5).

Since deprotection of Boc, protected primary and secondary aliphatic amines have been carried out using Amberlyst-15 earlier,[28] some of the protected amines prepared (e.g., Table 2, entries 8–10) were deprotected using similar reaction conditions as shown in Scheme 2.

In conclusion, we have developed a practical and general methodology for the preparation of *N*-Boc amines. The notable advantages of this protocol includes (i) regioselectivity, (ii) simple

Scheme 2.

operational procedure, (iii) the use of an inexpensive, heterogeneous and recyclable catalyst, (iv) solvent-free reaction conditions, (v) short reaction times and (vi) high yields of products. We strongly believe that this methodology would find wide usage in multistep organic synthesis.

2. Experimental procedure

To a mixture of $(Boc)_2O$ (1.0 mmol) and Amberlyst-15 (15%, w/w) was added an amine (1.0 mmol) and the mixture was stirred at room temperature for the time indicated in Table 2. After completion of the reaction (indicated by TLC), CH_2Cl_2 (10 mL) was added and the catalyst was separated by filtration. The filtrate was collected and concentrated. The residue was purified by column chromatography to obtain the pure product. The recovered catalyst was recycled for consecutive three times for the above reaction to furnish the product with a little variation in yields (Table 1, entry 4).

Acknowledgement

The authors sincerely thank the management of Institute of Life Sciences for continuous encouragement and support.

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