Research Article

Iodine-Mediated Neutral and Selective *N*-Boc Deprotection

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A simple, efficient, and alternative method has been developed for the *N*-Boc deprotection of structurally diverse protected amines. Selective removal of *N*-Boc groups was achieved with excellent yields under a solvent-free condition or in a solvent using iodine as a catalyst. The methodology involving the first use of iodine for *N*-Boc deprotection of protected amines represents an effective and useful alternative to the previously reported methods.

1. Introduction

Amine is one of the commonly used functionalities in synthetic organic chemistry, and its protection in the form of an *N*-*tert*-butoxycarbonyl (*N*-Boc) derivative has become a regular strategy in the synthesis of complex natural products, peptides, or small organic molecules [1]. The key advantages of Boc group include its ease of installation and stability towards various nucleophiles including strong basic conditions in a number of chemical transformations [2–4]. Traditional methods for Boc-protection involve the reaction of amines with di-*tert*-butyl dicarbonate (Boc)₂O in the presence of 4-(*N,N*-dimethylamino) pyridine (DMAP) [5] or inorganic bases [6]. Several strategies have been developed for the *N*-Boc deprotection earlier. A variety of reagents have been employed to effect this transformation, including strong acids, Lewis acids, and neutral conditions assisted by microwave. Thus, *N*-Boc deprotection has been carried out successfully using mild acidic conditions [7] such as trifluoroacetic acid (TFA), HCl, H₂SO₄, aqueous phosphoric acid [8], or Lewis acids such as BF₃·OEt₂, TMSI, TMSOTf, TiCl₄, SnCl₄, AlCl₃, Sn(OTf)₂, and ZnBr₂ [9]. The use of montmorillonite K10 clay catalyst [10] and silica gel [11] or thermolytic conditions at high temperature [12, 13] have also shown to work. Cleavage of the Boc group can be achieved in some cases under basic conditions, where the amine is activated, such as pyrroles [14–16]. Microwave-assisted *N*-Boc deprotection under mild conditions using K₃PO₄·H₂O

in CH₃OH has been reported [17]. A catalyst-free *N*-Boc deprotection has been reported in subcritical water under pressure [18]. Recently, several *N*-Boc derivatives of aromatic amines and amino acids were deprotected in boiling water [19]. While many of these methods are quite elegant and effective, a few number of them however, suffer from drawbacks such as (i) longer reaction time, (ii) high temperature, (iii) low yield of products, and (iv) the use of expensive catalysts. Moreover, preparation of some of the catalysts requires cumbersome procedures. As an inexpensive and readily available reagent, iodine has attracted considerable interest due to its less hazardous nature and efficiency in various organic transformations [20]. Herein we report our preliminary results of newly found iodine-mediated *N*-Boc deprotection of various protected amines under a mild and solvent-free condition.

2. Experimental

2.1. General Method for *N*-Boc Deprotection of 1. A mixture of *N*-Boc protected amine **1** (1.0 mmol) and iodine (0.08 mmol) was grinded in a mortar for the time indicated in Table 2. After completion of the reaction (indicated by TLC), the mixture was diluted with CH₂Cl₂ (10 mL) and washed with saturated aqueous solution of sodium thiosulphate (2 × 5 mL) and then with saturated aqueous solution of NaCl (2 × 5 mL). The organic layer was collected, dried over anhydrous Na₂SO₄, and filtered and concentrated under low vacuum.

TABLE 1: Effect of solvents on iodine-mediated de-*N-tert*-butoxy-carbonylation of *N*-Boc-aniline (**1a**)^a.

Entry	Solvent	Time	Yield ^b (%)
1	DCM	5 h	94
2	CH ₃ CN	6 h	92
3	Benzene	9 h	88
4	Toluene	12 h	82
5	No solvent	30 min	98

^aAll the reactions were carried out using the *tert*-butyl phenylcarbamate (**1a**, 1.0 mmol) and iodine (0.08 mmol) at room temperature.

^bIsolated yield.

The residue was purified by column chromatography to afford the pure products **2a-o**.

3. Results and Discussion

In our initial study *tert*-butyl phenylcarbamate (**1a**) was reacted with 8 mol% of iodine at room temperature in a range of organic solvents separately. Results of this study are summarized in Table 1. A number of solvents such as DCM, CH₃CN, benzene, and toluene were examined (Table 1, entries 1–4) when the deprotected aniline (**2a**) was isolated in good yield.

While the duration of the reaction was 5–12 h in all these cases, in the absence of a solvent the reaction was completed within 30 min affording the desired product in 98% yield (Table 1, entry 5). These observations encouraged us to examine the generality and scope of this method. Accordingly, a variety of aliphatic and aromatic *N-tert* butylcarbamates (**2**) were treated with iodine under a solvent free condition when the corresponding amine (**1**) was isolated in good yield (Table 2). A variety of aryl (entries 1–9, Table 2), heteroaryl (entries 11–14, Table 2), and aliphatic amines (entries 10 and 15, Table 2) were deprotected following this methodology. We have also examined all these reactions in DCM, and the desired amines were isolated in good yields (Table 2). Notably, the present iodine-mediated *N*-Boc deprotection was found to be a slower process than the iodine-mediated *N*-Boc protection [21], perhaps due to the higher stability of the *N-tert* butylcarbamate moiety of **2** than the –OCO^tBu group of Boc₂O towards elemental iodine.

A plausible mechanism for iodine catalyzed *N*-deprotection of **1** is presented in Scheme 2. The reaction seemed to proceed via activation of the carbonyl oxygen of **1** by iodine leading to **E-1** which underwent the sequential cleavage of several bonds such as C–H, C–O and C–N bond. The interaction of molecular iodine with carbonyl oxygen has been described in the literature earlier [21, 22]. For example,

SCHEME 1: Iodine-mediated *N*-Boc deprotection of amines under solvent-free conditions.

SCHEME 2: Proposed mechanism for iodine catalyzed *N*-Boc deprotection of **1**.

nucleophilic addition of indole to a carbonyl compound was catalyzed efficiently by molecular iodine [23]. It was suggested that a halogen bond [defined as intermolecular non-covalent interaction between halogen atom and electron-donor atom such as O or N (similar to hydrogen bond)] [24] between the carbonyl oxygen and iodine molecule plays a key role in the catalytic effect of iodine observed in these reactions [25]. Nevertheless, the cleavage of C–H of the ^tBu group perhaps was facilitated by the iodine coordinated with the carbonyl oxygen. As a result the catalyst iodine was regenerated along with the extrusion of carbon dioxide and 2-methylpropene affording the desired amine **2**.

4. Conclusions

In conclusion, we have developed a simple, efficient, and alternative method for the *N*-Boc deprotection of structurally diverse protected amines. The selective removal of *N*-Boc groups was achieved with excellent yields under a solvent free condition using iodine as a catalyst. To the best of our knowledge, this is the first example of *N*-Boc deprotection of protected amines catalyzed by elemental iodine. The present deprotection methodology has potential to become an effective and useful alternative to the previously reported methods and may find applications in protecting group chemistry.

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TABLE 2: Iodine-mediated deprotection of *N*-*tert* butylcarbamates (**1**) (Scheme 1).

Entry	<i>N</i> - <i>tert</i> butylcarbamates (1)	Time (min)	Product ^a (2)	Yield ^b (%)	Yield ^c (%) DCM solvent
1	1a	30	2a	98	94
2	1b	50	2b	90	82
3	1c	90	2c	92	80
4	1d	120	2d	90	80
5	1e	90	2e	82	80
6	1f	120	2f	90	85
7	1g	150	2g	86	80

TABLE 2: Continued.

Entry	<i>N</i> -tert butylcarbamates (1)	Time (min)	Product ^a (2)	Yield ^b (%)	Yield ^c (%) DCM solvent
8	1h	60	2h	92	85
9	1i	120	2i	90	85
10	1j	90	2j	82	78
11	1k	100	2k	85	80
12	1l	150	2l	82	76
13	1m	180	2m	80	72
14	1n	240	2n	86	80
15	1o	120	2o	84	78

^a All the reactions were carried out using the *N*-tert butylcarbamate **1** (1.0 mmol) and iodine (0.08 mmol) at room temperature.

^b Isolated yield.

^c All the reactions were carried out using DCM (5 mL) at room temperature for 5-6 h.

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