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Molecular Iodine-Catalyzed Facile Procedure for *N*-Boc Protection of Amines

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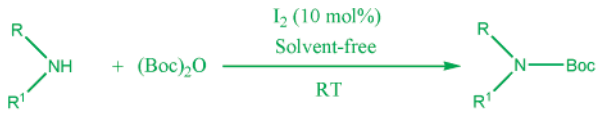

R, R^1= H, alkyl, aryl (57 examples)

An efficient and practical protocol for the protection of various structurally and electronically divergent aryl and aliphatic amines using $(Boc)_2O$ in the presence of a catalytic amount of molecular iodine (10 mol %) under solvent-free conditions at ambient temperature is presented.

The choice of the protection and deprotection strategy in a synthetic sequence is inevitable owing to chemoselective transformations in the presence of various functional groups.[1] Due to the desire to develop a mild, selective, and efficient protecting group, especially for amines, Boc protection has become one of the most useful steps due to its stability toward catalytic hydrogenation and extreme resistance toward basic and nucleophilic reactions.[2] Furthermore, removal of the Boc protecting group could be easily carried out with TFA within 5−10 min at room temperature on a bench scale and 3 M HCl in EtOAc or 10% H_2SO_4 in dioxane in large-scale operations. Although there are a variety of base-mediated reaction conditions available for Boc protection in the literature,[3] use of Lewis acid (LA)-catalyzed Boc protection of amines is limited because of the strong affinity of several LA's for amino groups which do not allow regeneration of the Lewis acids (LAs) in the reaction,[4] and moreover, they are decomposed or deactivated by the amines/their derivatives with the use of more than stoichiometric amounts.[5]

Due to the very attractive nature of the *N*-Boc group, apart from the classical base-induced procedures, only a few Lewis acids or reagents employing $Zn(ClO_4)_2 \cdot 6H_2O$, yttria−zirconia, $LiClO_4$, β-cyclodextrin, and $ZrCl_4$ have been implemented so far to effect the transformation.[6] However, some of these methods are associated with drawbacks such as use of costly reagents and limited substrate scope. To overcome the problems associated with protection of poorly reactive 1° or 2° arylamines and various side reactions such as biscarboamoylation/formation of isocyanates as well as urea,[7] there is further need for developing improved synthetic strategies for the synthesis of *N*-Boc amines which can be applied to a number of substrates in a catalytic process.

In this context, molecular iodine has drawn considerable attention lately as an inexpensive, nontoxic, nonmetallic, and readily available catalyst for effecting various organic transformations.[8] Another promising approach to environmentally friendly chemistry is to minimize or completely eliminate the use of harmful organic solvents in organic syntheses. This is because organic reactions run under solvent-free conditions are advantageous because of their enhanced selectivity, efficiency, ease of manipulation, and cleaner product formation as well as toxic or often volatile solvents are avoided.[9]

Thus, a paradigm shift from using solvents toward solvent-free reactions not only simplifies organic synthesis but also improves process conditions for large-scale synthesis. (**Note**: *Exothermicity of the reaction while carrying out the reaction on a large-scale operation should be controlled by maintaining the temperature and using the appropriate solvent depending on substrate reactivity and solubility, if necessary.*)

In a continuation of our efforts to develop new synthetic routes for carbon−carbon and carbon−heteroatom bond formation and heterocycles,[10]herein we disclose the first example of an efficient synthetic protocol for the selective *tert*-butoxycarbonylation of amines using iodine as LA under solvent-free conditions (Scheme 1).

Initially, we screened several mild Lewis acids such as silica gel, $InCl_3$, $FeCl_3$, CAN, $Yb(OTf)_3$, and molecular iodine (I_2)

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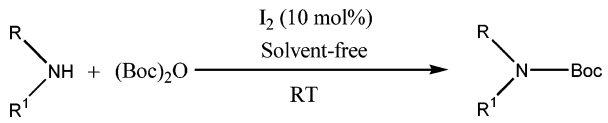
TABLE 1. Comparison of the Effect of Catalysts in *N*-Boc Protection of Aniline with $(Boc)_2O$ at Room Temperature (10 mol % as standard)

entry	catalyst	catalyst load (mol %)	time	solvent	isolated yield (%)
1	silica gel	50 mg/1 mmol	18 h	neat	69
2	$InCl_3$	10	30 min	neat	90
3	$FeCl_3$	10	1 h	neat	89
4	CAN	10	30 min	neat	74
5	$Yb(OTf)_3$	10	30 min	neat	89
6	I_2	10	30 min	neat	95[a]
7	yttria-zirconia[6b]	20	14 h	CH_3CN	90
8	$ZrCl_4$[6e]	10	3 min	CH_3CN	95
9	$Zn(ClO_4)_2 \cdot 6H_2O$[6a]	5	12 h	CH_2Cl_2	92
10	β-cyclodextrin[6d]	10	2.5 h	H_2O	75
11	uncatalyzed		48 h		60

[a] Conditions: Solvent-free (95%); MeOH (≅95%); acetone (85%); dichloromethane (55%); dichloroethane (60%); DMSO (≅78%); THF (90%); CH_3CN (≅90%).

SCHEME 1. Iodine-Catalyzed *N*-Boc Protection of Amines



R, R^1 = H, alkyl, aryl

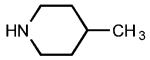
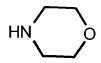
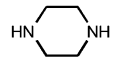
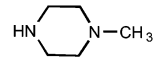
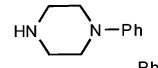
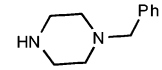
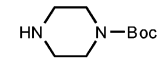
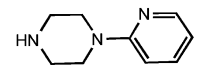
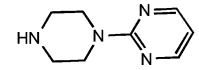
for this reaction. We deliberately chose these reagents because they are compatible with the capacity to retain their activity even in the presence of nitrogen-containing compounds. These catalysts are then screened for the model reaction between aniline (1 mmol) and $(Boc)_2O$ (1 mmol) at room temperature under solvent-free conditions,[7c] and the results are summarized in Table 1. The model reaction could also be carried out in different organic solvents such as MeOH (≅95%), acetone (85%), dichloromethane (55%), dichloroethane (60%), DMSO (≅78%), THF (90%), and CH_3CN (≅90%) for the specified time. It is clear from Table 1, most prominently, that I_2 was found to be the best catalyst in terms of reaction times and yields (95%, 30 min, entry 6, Table 1), although good results are obtained with other catalysts screened (entries 1−5, Table 1) and compared with the reported results using other LA's or additives (entries 7−10, Table 1), while conversion of aniline to the corresponding *N*-Boc derivative appears to be sluggish at room temperature without catalyst (entry 11, Table 1).

An optimum catalytic amount of 10 mol % of I_2 is sufficient to afford the desired product in excellent yield. To test the role of iodine for *N*-Boc protection, initially a mixture of Boc_2O and aniline were vigorously stirred under solvent-free conditions for 30 min without catalyst. There is no commencement of effervescence. Typically, shortly after introduction of a catalytic amount of I_2 into the reaction mixture there is evolution of heat and quick effervescence took place with concomitant formation of the corresponding *N*-Boc derivative (as confirmed by TLC).

With the optimized reaction conditions in hand, we then evaluated the scope of the reaction using a variety of structurally divergent *sec*-alicyclic amines and $(Boc)_2O$ (Table 2). All substrates smoothly reacted to give the corresponding *N*-Boc adducts in 30−140 min in excellent yields. All products were characterized by instrumental techniques such as IR, $^1H/^{13}C$ NMR, and mass spectrometry.

The reaction conditions employed also enable use of various aliphatic, aromatic, and heterocyclic amines as well, and the results are summarized in Table 3. The protection methodology was carried out under neat conditions for almost all substrates. In particular, for substrates (entries 24−26 and 29, Table 3) which solidify during the course of the reaction, the reaction mixture could be continuously stirred for the specified time by adding methanol (1 mL/1 mmol substrate).

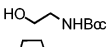
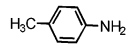
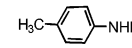
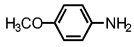
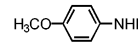
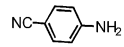
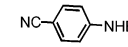
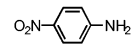
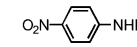
TABLE 2. Iodine-Catalyzed Boc Protection of Functionalized Amines

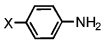
Entry	Amine	Time (min)	Yields (%)[a]
1		10	90[6e]
2		140	78
3		30	95[6c]
4		30	80[b]
5		20	96
6		45	95
7		30	96
8		60	82
9		60	94
10		45	98

[a] Yields refer to pure isolated products. [b] 2.2 equiv of Boc_2O is used.

Alkylamines (entries 1−9, Table 3) reacted faster and gave the monoprotected derivatives in good yields. In contrast, analogous reactions of primary and secondary arylamines (entries 10−15, Table 3) proceed in a sluggish manner. These results are not surprising because alkylamines are more nucleophilic than arylamines. It is important to note that in the case of primary amines any side reaction, such as formation of isocyanates or ureas, there were never any bis-Boc derivatives observed, as confirmed by ^1H NMR analysis of the crude products. In general, aromatic amines with electron-withdrawing substituents reacted slower than those with electron-donating substituents (see entries 11−14 and 21−23, Table 3). The present iodine-catalyzed *N*-Boc protection protocol is highly chemoselective: the amine group is exclusively protected in comparatively good yields even in the presence of alcohol (entry

TABLE 3. Iodine-Catalyzed Boc Protection of Amines

Entry	Amine	Product	Time (h)	Yield (%)[a]
1			1	82
2			3	70
3			0.5	97
4			0.5	95
5			0.75	90
6			1.5	85[7c]
7			1.5	88[6b]
8			0.5	94
9	$(PhCH_2)_2NH$	$(PhCH_2)_2NBoc$	2	78
10	Ph_2NH	Ph_2NBoc	5.0	82
11			2.5	90[6b]
12			1.5/12[b]	86/65[b]
13			4.5	77
14			4/24[b]	81/58[b]
15			6	57
16			4	85
17			1	88
18			6.5	68
19			*o*- 24 *m*- 12 *p*- 8	– 76 82

Entry	Amine	Product	Time (h)	Yield (%)[a]
20			0.2	95
21	 (X= Br)		Br- 1	94^{7a}
22	(X= Cl)		Cl- 2.5	90^{7a}
23			3	60^{7a}
24			2	78[c]
25			2.5	80[c]
26			12	45[c]
27			1.75	95
28			2	75^{6c}
29			6	88[c]
30			8.5	62
31			6.5	70
32			4.5	75
33	$CH_3SO_2NH_2$	CH_3SO_2NHBoc	3	82
34			1.5	76

[a] Yields refer to pure isolated products. [b] Reaction carried out without catalyst. [c] 1 mL/1 mmol MeOH was added.

5, Table 3) or phenolic −OH (entry 17, Table 3), thiophenol (entry 18, Table 3) groups. For entries 16−18, Table 3, the mono-*N*-Boc-protected products were obtained in good yields, and interestingly, the reaction times were also lower compared to those reported earlier using other catalysts.[6a,7a] However, 2-aminobenzoic acid did not furnish the corresponding product even after stirring for 24 h under the standardized conditions. On the other hand, 3- and 4-aminobenzoic acids gave the corresponding *N*-Boc-protected derivatives with acceptable results considering their low reactivities (entry 19, Table 3).[6a,7a] It is worth mentioning that heteroaromatic amines were also possible for the present reaction to give products in moderate to good yields (entries 20 and 24−27, Table 3).

On the basis of the reactivity differences of the amine group under various electronic and steric environments, few competitive experiments were conducted to study the efficacy of iodine-catalyzed selective *N*-Boc protection. Reaction of benzylamine (1 mmol) and *p*-methoxy aniline (1 mmol) with Boc_2O (1 mmol) afforded the corresponding *N*-Boc derivatives in 78% and 22% yields, respectively, after 30 min. Likewise, reaction of piperidine (1 mmol) and *p*-nitro aniline (1 mmol) with Boc_2O (1 mmol) afforded the corresponding piperidine *N*-Boc derivative exclusively in 90% yield after 10 min.

Moreover, chiral amine (entry 28, Table 3) gave optically pure *N*-Boc derivative.[11c] We then decided to test the utility of our protocol in reactions with hydrazines and sulfonamides (entries 29−33, Table 3). The corresponding mono-*N*-Boc products were obtained in reasonably good yields, although reaction times are slightly longer. Reaction of cyclic carbamate with Boc_2O afforded the corresponding *N*-Boc derivative in 76% yield after 1.5 h (entry 34, Table 3).

We further studied the iodine-catalyzed *N*-Boc protection protocol using a variety of amino acid esters and alcohols, and the results are summarized in Table 4. Free amino acids did not react under optimized conditions, maybe due to the presence of zwitterionic species, although trace amounts of products were observed after prolonged hours.

In the case of the corresponding amino acid alcohols (α-amino alcohols) esters (α-amino acid esters) were efficiently converted to their corresponding optically pure *N*-Boc products as determined by optical rotation and comparison with literature

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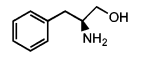
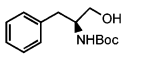
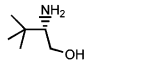
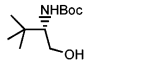
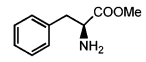
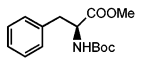
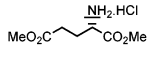
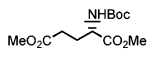
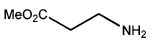
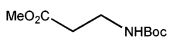
TABLE 4. Iodine-Catalyzed Boc Protection of Amino Acid Derivatives

Entry	Amine	Product	Time (h)	Yields (%)[a]	$[\alpha]^{25}_D$
1			2.5	78	-26.9 (c= 1, $CHCl_3$)
2			3	92	-7.0 (c= 1, $CHCl_3$)
3			3	85[6d]	-3.91 (c= 2, CH_3OH)
4			1	88	+ 12.5 (c= 2, $CHCl_3$)
5			1.5	90[6d]	–

[a] Yields refer to pure isolated products.

values under similar conditions (entries 1−4, Table 4).[6b,e,11] It is noteworthy that the reaction is chemoselective in the case with L-phenyl alaninol and L-*tert*-leucinol as the amines; *N*-Boc-protected products were solely obtained (not *O*-Boc derivatives) as, in general, alcohols are known to react with Boc_2O in the presence of DMAP to give *O*-Boc derivatives.[12]

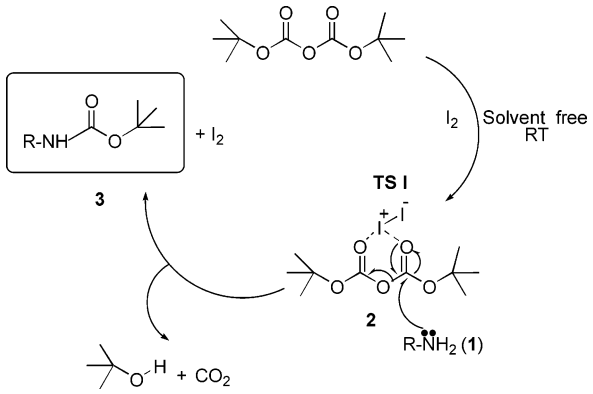
To explore the mechanism of the iodine-catalyzed *N*-Boc protection of amines (see Supporting Information), the IR spectrum of a mixture of 1 equiv of I_2 and 1 equiv of $(Boc)_2O$ was recorded. Two frequency bands of the C═O stretching vibration of carbonyl oxygen atoms were observed in the region of 1807.33 and 1761.20 cm^{-1}. Comparing the frequency of free carbonyl oxygen atoms of $(Boc)_2O$ at 1808.87 and 1761.91 cm^{-1} (a doublet due to Fermi resonance), the *shift of vibration frequency* implicated the possible coordination of I_2 with $(Boc)_2O$. The ^1H NMR spectrum of a mixture of 1 equiv of I_2 and 1 equiv of $(Boc)_2O$ in $CDCl_3$ showed that the chemical shift of the proton attached to the methyl protons of the *tert*-butyl group was 1.524. The chemical shift of the same proton in methyl protons of free $(Boc)_2O$ was 1.531.

The change of chemical shift also suggested possible coordination of I_2 with $(Boc)_2O$. As already mentioned, formation of *N*-Boc-protected amine **3** (IR frequency of C═O of **3** 1688.33 cm^{-1}a nd ^1H NMR value of **3** 1.514) occurs by addition of a catalytic amount of I_2 with exothermicity and commencement of effervescence (evolution of CO_2 is observed-Lime water test = +*ve*).

Thus, the following mechanism can be proposed for the reaction. Both carbonyl oxygen atoms of $(Boc)_2O$ are activated by iodine (TS I, **2**) initially, making the carbonyl group more susceptible to nucleophilic attack by amine **1** in one pot. This facilitates extrusion of *tert*-butanol and carbon dioxide as leaving entities, eventually leading to formation of *N*-Boc-protected amine **3** (Scheme 2).

In conclusion, molecular iodine shows promising results for the monoprotection of various electronically and structurally divergent open chain, cyclic aliphatic, aromatic amines, 1,2-diamines, heteroaromatic amines, hydrazides, sulfonamides, cyclic carbamates, amino alcohols, and amino acid esters as *N*-Boc derivatives in moderate to excellent isolated yields. In contrast to the existing methods using many Lewis acid catalysts/additives,[6,7] this new method offers the following competitive advantages: (i) it is mild and operationally simple; (ii) it is inexpensive, has lower catalyst loading, and is a readily available and environmentally benign catalyst under solvent-free conditions; (iii) it has high chemoselectivity; (iv) it has wide substrate scope and tolerability of labile functionalities; (v) it has no side reactions.

SCHEME 2. Proposed Mechanism for Iodine-Catalyzed *N*-Boc Protection of Amines



We believe that our protocol will be a valuable addition for the *N*-Boc protection of amines both in academia and industries.

Experimental Section

General Procedure. To a magnetically stirred mixture of amine (1 mmol) and $(Boc)_2O$ (1 mmol) a catalytic amount of iodine (10 mol %) was added under solvent-free conditions at room temperature. After stirring the reaction mixture for the specified time (Tables 2−4), diethyl ether (10 mL) was added. The reaction mixture was washed with $Na_2S_2O_3$ (5%, 5 mL) and saturated $NaHCO_3$ and dried over Na_2SO_4, the solvent was rotavaped under reduced pressure, and the residue was purified by silica gel column chromatography (60−120, 5−15% EtOAc in hexane) to afford the corresponding pure product.

Representative Examples. Entry 20, Table 3: IR (neat) δ 3364, 2975, 2930, 1725, 1699, 1502, 1308, 1165, 1070, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 9H), 7.02 (s, 1H), 7.33 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 85.6, 117.2, 130.3, 137.2, 147.4; EI-MS 168 (M^+); Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.11; H, 7.12; N, 16.69.

Entry 4, Table 4: IR (neat) ν 3436, 3025, 2965, 2981, 1732, 1714, 1682, 1657, 1503, 1369, 1168, 1068, 754, 629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.85−2.00 (m, 1H), 2.10−2.25 (m, 1H), 2.34−2.45 (t, 2H), 3.62−3.78 (s, 3H), 3.80−3.98 (s, 3H), 4.27 (dd, 1H, CH), 5.17 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7, 28.2, 30.0, 51.7, 52.3, 52.8, 79.9, 155.3, 172.6, 173.1; FAB-MS: 276 (M^+ + H). Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.26; H, 7.81; N, 5.05. $[\alpha]^{25}_D$: +12.5 (*c*= 2, $CHCl_3$). Optical purity: 96.89%. HPLC retention time (R_t) 4.683 min (purity (area %) 95.80 at 230 nm).[11a]

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Supporting Information Available: Experimental Section and IR, ^1H NMR, ^{13}C NMR, and mass spectral data for all compounds with representative copies of ^1H NMR spectra for selected compounds and proof of evidence for I_2-catalyzed *N*-Boc-protected amines. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0612473

(12) (a) Pozdnev, V. F. *Int. J. Pept. Protein Res.* **1992**, *40*, 407.