Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6739–6742

A rate enhancement of *tert*-butoxycarbonylation of aromatic amines with Boc_2O in alcoholic solvents

Tirayut Vilaivan*

Organic Synthesis Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Phayathai Road, Patumwan, Bangkok 10330, Thailand

Received 8 May 2006; revised 13 July 2006; accepted 20 July 2006
Available online 8 August 2006

Abstract—A rate enhancement of *tert*-butoxycarbonylation of aromatic amines by Boc_2O in alcohols compared to aprotic solvents was demonstrated. Kinetic analysis by NMR suggested that the reaction in CD_3OD was faster than in $CDCl_3$ by a factor of 70. Reactions between Boc_2O and various aliphatic and aromatic amines in ethanol provided the *N*-Boc derivatives in good to excellent yields in short reaction times.

Protection of amines is a frequently employed strategy for decreasing the nucleophilicity of the amino group in order to perform other transformations in molecules. Among various amine protecting groups, the *tert*-butoxycarbonyl (Boc) group is perhaps one of the most widely used due to its exceptional stability towards a variety of reagents and reaction conditions, yet it can be readily removed under moderately strong acidic conditions.[1] The Boc group has also been used as a directing group for *ortho*-metallation of aromatic amines.[2] Di-*tert*-butyl dicarbonate (Boc_2O, **1**)[3] is usually the reagent of choice for introduction of Boc groups due to its high reactivity and reasonable stability.[4] However, Boc-protection of poorly nucleophilic aromatic amines is generally not as efficient as that of aliphatic amines. N-Deprotonation of the aromatic amine using a strong base such as NaHMDS has been employed to increase the reactivity.[5] Other solutions to overcome the low reactivity of aromatic amines exist. These include the use of a high temperature, a nucleophilic catalyst such as DMAP[6] or NH_2OH,[7] and, more recently, Lewis acid catalysts such as Yttria-Zirconia,[8] $ZrCl_4$[9] and $Zn(ClO_4)_2$.[10] These procedures, although effective, have certain drawbacks including the formation of side-products such as isocyanates[11] and poly-acylated products,[6a] the requirement of unusual, highly reactive or environmentally harmful catalysts, and the necessity for chromatographic, or extractive work-up to isolate the product from the catalyst.

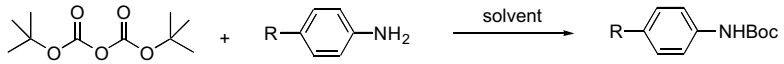
Although the unique role of water to mediate many organic reactions is currently attracting much interest,[12] the ability of alcohols to mediate or accelerate several reactions via general acid catalysis has not been widely appreciated. We have previously reported an interesting rate enhancement on the addition of organoindium reagents to imines in alcoholic solvents.[13] In this letter, a rate enhancement on the *tert*-butoxycarbonylation of aromatic amines in alcohols is reported. Boc protections of amines have been typically carried out in aprotic solvents such as dichloromethane or THF, often in the presence of a base such as triethylamine. Although the use of alcohols or aqueous alcohols as solvents for Boc protection of polar compounds such as amino acids is well known,[1,4] there has been no specific mention of rate enhancement. A model reaction between *p*-toluidine **2a** and Boc_2O (**1**, 1.5 equiv) was carried out in a variety of solvents (Table 1) without addition of base. TLC monitoring suggested that the reactions in methanol and ethanol were essentially complete within 0.5 h at 30 °C (entries 1 and 2). The same reactions in aprotic solvents were slower (4–6 h) (entries 3–5). Addition of triethylamine did not result in any rate improvement (entry 6). The same trend was observed with electron deficient *p*-chloroaniline **2b** as the substrate (entries 7–8). While the reaction in ethanol required 6 h to complete, the reaction in CH_2Cl_2 was only 50% complete after the same period of time.

From Table 1, it is clear that the alcoholic solvent exerts a beneficial rate acceleration on the *tert*-butoxycarbonylation of aromatic amines. In order to obtain a more

Keywords: Amine; Boc_2O; Protecting group.
* Fax: +66 2 2187598; e-mail: vtirayut@chula.ac.th

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.097

Table 1. Comparison of reaction time for *tert*-butoxycarbonylation of aromatic amines in various solvents[a]



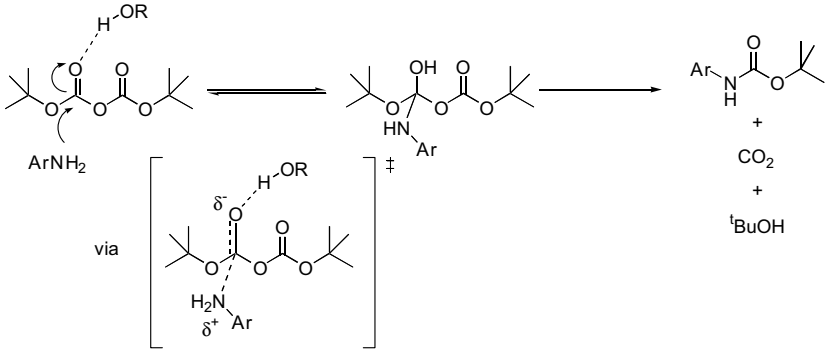
Boc_2O, **1** **2a** R = Me, **2b** R = Cl **3a** R = Me, **3b** R = Cl

Entry	Substrate	Solvent	Time (h)	Product (% yield)[b]
1	**2a**	MeOH	0.5	**3a** (93)
2	**2a**	EtOH	0.5	**3a** (96)
3	**2a**	MeCN	4	Not determined
4	**2a**	THF	6	Not determined
5	**2a**	CH_2Cl_2	6	Not determined
6	**2a**	$CH_2Cl_2 + Et_3N$	6	Not determined
7	**2b**	EtOH	6	**3b** (96)
8	**2b**	CH_2Cl_2	<50% at 6 h	Not determined

[a] Reaction conditions: 0.75 mmol of **1**, 0.5 mmol of **2a** or **2b**, 1 mL of solvent, 30 °C, progress monitored by TLC.
[b] Isolated yield.

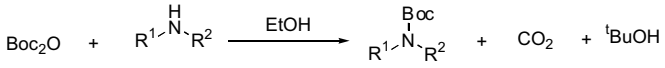
quantitative picture, reactions between *p*-toluidine **2a** and **1** were studied by ^1H NMR spectroscopy. While the reaction was essentially complete after 1 h in CD_3OD, the same reaction in $CDCl_3$ only proceeded to 50% extent after 12 h at 20 °C. Kinetic analysis suggested that in both cases the reactions follow a second-order rate law. From the calculated second-order rate constants of 1.3×10^{-2} and 1.8×10^{-4} l mol^{-1} s^{-1} in CD_3OD and $CDCl_3$, respectively, it was estimated that the rate in CD_3OD was enhanced relative to that in $CDCl_3$ by a factor of 70. This remarkable rate enhancement could be attributed to activation of the electrophilic C=O group in **1** by hydrogen-bonding with the hydroxyl group of the alcohol (Scheme 1). Furthermore, stabilization of the polar transition state of the initial tetrahedral intermediate resulting from attack of the nucleophile on the carbonyl group of **1** may also play a significant role. Interestingly, the rate in the more acidic alcohol, 2,2,2-trifluoroethanol, was comparable to that in acetonitrile. This is probably because of the diminished nucleophilicity of the amine as a result of acid–base interaction with the acidic solvent.

In order to study the generality and scope of the alcohol-assisted *tert*-butoxycarbonylation of amines, a number of aliphatic and aromatic amines (**2c**–**2u**) were employed as substrates (Table 2).[14] With few exceptions, the desired products were obtained in good to excellent yields and high purities after evaporation of the solvent without the requirement for chromatographic purification and/or acid–base extraction. Unhindered primary and secondary aliphatic amines usually reacted instantaneously to give the products in almost quantitative yields (Table 2, entries 1–5). The sterically hindered dicyclohexylamine gave a somewhat poorer yield (Table 2, entry 6). Electron-rich or moderately electron-deficient aromatic amines (Table 1, entries 1, 2, 7 and Table 2, entries 7–9) reacted within 6 h at room temperature. Sterically hindered and secondary aromatic amines (entries 10–14) reacted somewhat more slowly (up to 48 h). Electron deficient aromatic amines required stronger conditions (50 °C, 3–5 equiv of Boc_2O, a few days) and gave poorer yields (entries 16–18). The presence of phenolic and alcoholic hydroxyl groups was well tolerated. Both amino alcohols and amino phenols chemoselectively provided the *N*-Boc products even when **1** was added in excess (entries 3, 4, 8 and 11). Highly deactivated aromatic amines including diphenylamine and 4-chloro-2-aminobenzonitrile failed to react under these conditions. Interestingly, the reaction of 2-aminopyridine with Boc_2O in EtOH provided the ethyl carbamate instead of the expected Boc-derivative. This is most likely due to attack of the solvent on the isocyanate formed in situ.[11] Changing the solvent to *tert*-butanol gave Boc derivative **3u** in 72% yield (Table 2, entry 19). This behavior is unique to 2-aminopyridine since



Scheme 1.

Table 2. Yield of *N*-Boc products obtained from the *tert*-butoxycarbonylation of various aliphatic and aromatic amines in ethanol as solvent



1 **2** **3**

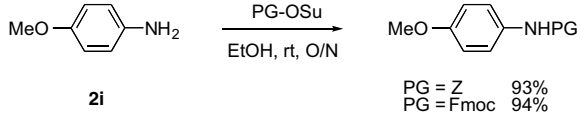
Entry	Amine	Product	R^1	R^2	Time	Yield[a] (%)
1	**2c**	**3c**	Bn	H	<1 min	92
2	**2d**	**3d**	(*S*)-PhCH(Me)	H	<1 min	98
3	**2e**	**3e**	$HOCH_2CH_2CH_2$	H	<1 min	98
4	**2f**	**3f**	D-Phenylalaninol		<1 min	>99
5	**2g**	**3g**	*N*-Phenylpiperazine		<1 min	95
6	**2h**	**3h**	[c]Hex	[c]Hex	2 h	76
7	**2i**	**3i**	4-$MeOC_6H_4$	H	0.5 h	94
8	**2j**	**3j**	2-HOC_6H_4	H	2 h	86
9	**2k**	**3k**	*o*-Phenylenediamine		2 h	>99[b]
10	**2l**	**3l**	C_6H_5	Me	12 h	86
11	**2m**	**3m**	C_6H_5	$HOCH_2CH_2$	24 h	>99
12	**2n**	**3n**	2,6-$Me_2C_6H_3$	H	48 h	>99
13	**2o**	**3o**	2,6-$^i Pr_2C_6H_3$	H	48 h	97
14	**2p**	**3p**	1-Naphthyl	H	24 h	99
15	**2q**	**3q**	3-$MeO_2CC_6H_4$	H	12 h	94
16	**2r**	**3r**	4-$O_2NC_6H_4$	H	72 h[c]	38
17	**2s**	**3s**	4-Cl-3-$O_2NC_6H_3$	H	72 h[c]	96
18	**2t**	**3t**	2-$HO_2CC_6H_4$	H	72 h[c]	88
19	**2u**	**3u**	2-Pyridyl	H	24 h[d]	72

[a] Isolated yield.
[b] Bis-Boc derivative.
[c] The reaction was carried out at 50 °C with excess of **1** (3.5 equiv) added.
[d] The reaction was performed in *tert*-butanol.

no ethyl carbamate formation was observed with other substrates. It should be noted that the alcoholic solution of **1** is fairly stable, no significant decomposition (<2%) of **1** was observed in CD_3OD by ^1H NMR after 8 h at 30 °C. However, significant decomposition was observed at higher temperature, therefore a large excess of **1** was required for the poorly reactive substrates which required heating. When **1** was used in excess, chromatographic purification or treatment of the reaction mixture with 3-morpholinopropylamine to form an acid-soluble by-product, which could be removed by simple extraction, was necessary.[15]

To explore further the scope of this reaction with other urethane-type amine protecting groups such as Z and Fmoc, it was observed that *p*-anisidine **2i** reacted smoothly with benzyl *N*-succinimidyl carbonate (ZOSu) and 9-fluorenylmethyl *N*-succinimidyl carbonate (Fmoc-OSu) in ethanol as a solvent to afford the Z- and Fmoc-protected *p*-anisidine derivatives (**3v** and **3w**) in 93% and 94% yields, respectively, after aqueous work-up (Scheme 2).

The present procedure for Boc as well as Z and Fmoc protection offers several practical advantages. The reaction provides improved or at least comparable results in terms of yield and reaction rate compared to Lewis acid mediated protocols.[16,17] The reaction conditions and isolation of the products are simple and involve a readily available and environmentally benign solvent. By-products from the reactions are volatile and relatively non-toxic. These features should make the reaction attractive for both laboratory and process chemists.



2i

Scheme 2.

Acknowledgements

Financial support from Rachadapisek Sompoj Endowment from Chulalongkorn University to Organic Synthesis Research Unit, and technical assistance by Miss Wanna Bannarukkul is acknowledged.

Supplementary data

Spectroscopic data of compounds **3a**–**3w** and details of the second-order rate constant calculations are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.097.

References and notes

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.
2. (a) Davies, A. J.; Brands, K. M. J.; Cowden, C. J.; Dolling, U.-H.; Lieberman, D. R. *Tetrahedron Lett.* **2004**,

45, 1721–1724; (b) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833–6837; (c) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798–4801.
3. Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. USA* **1972**, *69*, 730–732.
4. For a review see: Wakselman, M. In *Di-t-butyl Dicarbonate*; Paquette, L. A., Ed.; Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups; John Wiley and Sons: New York, 1999; pp 123–130.
5. Kelly, T. A.; McNeil, D. W. *Tetrahedron Lett.* **1994**, *35*, 9003–9006.
6. (a) Darnbrough, S.; Mervic, M.; Condon, S. M.; Burns, C. J. *Synth. Commun.* **2001**, *31*, 3723–3780; (b) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494–501; (c) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368–6380, and references cited therein.
7. Harris, R. B.; Wilson, I. B. *Tetrahedron Lett.* **1983**, *24*, 231–232.
8. Pandey, R. K.; Ragade, S. P.; Upadhyay, R. K.; Dongare, M. K.; Kumar, P. *Arkivoc* **2002**, *VII*, 28–33.
9. Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R. *Tetrahedron Lett.* **2004**, *45*, 6963–6965.
10. Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 1794–1798.
11. (a) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2497–2500; (b) Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett.* **1996**, *37*, 5861–5864.
12. (a) Grieco, P. A. In *Organic Synthesis in Water*; Thomson Science: London, 1988; (b) Li, C. J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68–82; (c) Lubineau, A.; Auge, J. *Tops. Curr. Chem.* **1999**, *206*, 1–39.
13. (a) Vilaivan, T.; Winotapan, C.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2001**, *42*, 9073–9076; (b) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464–3471.
14. Typical procedure for Boc-protection: To a solution of the amine (0.5 mmol) in EtOH (1 mL) was added Boc_2O (0.55 mmol). The reaction was stirred at 30 °C until the reaction was complete as indicated by TLC. The solvent was removed to provide practically pure product, which may be further purified by extraction or chromatography if desired.
15. For a related method to remove excess Boc_2O, see: Basel, Y.; Hassner, A. *Synthesis* **2001**, 550–552.
16. Boc protections of aniline and 2,4,6-trimethylaniline in MeCN at room temperature required 48 h and 168 h, respectively, to complete (Ref. 6c). In the presence of $Zn(ClO_4)_2$, the reaction time for 2,4,6-trimethylaniline decreased to 48 h (Ref. 10). In all cases, the products were isolated in >90% yields.
17. After submission of this manuscript, a related *tert*-butoxycarbonylation of amines in water is reported: Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259–3262.