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Hydrogen bond catalyzed chemoselective *N*-*tert*-butoxycarbonylation of amines

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Abstract

A novel, chemoselective mono-*N*-Boc protection of various structurally diverse amines with di-*tert*-butoxypyrocarbonate $(Boc)_2O$ is described that relies on selective carbonyl activation by hydrogen bond formation. This mild, acid- and metal-free process requires only catalytic amounts of thiourea as hydrogen bond donor.

Keywords: Amines; $(Boc)_2O$; Chemoselective; Thiourea; Hydrogen bonding

In recent years, increasing attention has been paid to organocatalysts owing to their environmentally benign nature and other notable advantages (reactions catalyzed by organocatalysts often proceed under an aerobic atmosphere even in wet solvents; the organocatalysts are usually inexpensive and are commercially available).[1,2] In addition, and in contrast to metallic Lewis acids, these organocatalysts can be recovered and reused for a second reaction. Recently, Menche et al. demonstrated that thiourea efficiently activates imines.[3] Bearing in mind the usefulness and efficiency of organocatalysts, we decided to explore thiourea as a catalyst for the *N*-Boc-protection of amines. Among carbonic acid derivatives used as protecting groups, *tert*-butyl carbonates (*O*-Boc alcohols) and carbamates (*N*-Boc amines) are of great importance in organic chemistry. Boc-protected aryl amines are important intermediates in organic synthesis and have been used for the directed lithiation of aromatic rings and the preparation of unsymmetrical ureas amongst others.[4,5] However, various reagents and methodologies developed over the years to introduce this group using $(Boc)_2O$ have been carried out either in the presence of a base (DMAP,[6] aq NaOH,[7] NaHMDS[8]) or Lewis acid catalysts such as $Zr(ClO_4)_2 \cdot 6H_2O$,[9] $ZrCl_4$,[10] I_2,[11] $H_3PW_{12}O_{40}$,[12] sulfamic acid,[13] $LiClO_4$[14] and indium(III) halides.[15] These reports have demonstrated that the reaction of Boc_2O requires acidic or basic catalysts, extended reaction times,[16] elevated temperatures,[17] tedious work-up and anhydrous organic solvents. Despite improvements in performing *N*-*tert*-butoxycarbonylations, new and milder conditions are still required.

Herein, we report an efficient method for the chemoselective *N*-*tert*-butyloxycarbonylation of amines which relies exclusively on hydrogen bonding for carbonyl activation. This completely acid-free reaction is mediated by catalytic amounts of thiourea as a simple and readily modifiable organocatalyst and uses $(Boc)_2O$ as the reagent for the protection of amines. The general applicability of the method for the synthesis of a wide variety of diverse *N*-Boc-amines is demonstrated and the mechanistic background is studied.

In the presence of 10 mol % of thiourea, the reaction of aniline **1a** with $(Boc)_2O$ proceeded smoothly in toluene at 60 °C to afford the corresponding *N*-Boc aniline **3a** in an

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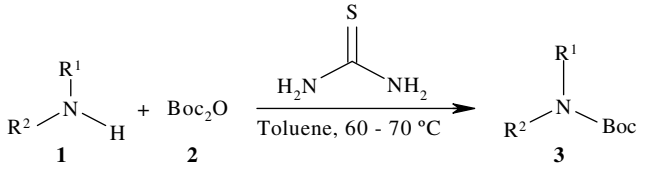
Table 1



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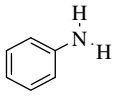
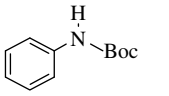
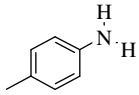
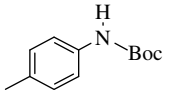
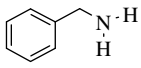
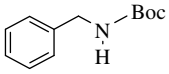
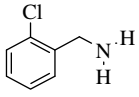
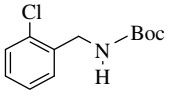
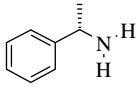
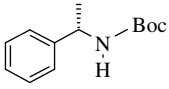
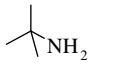
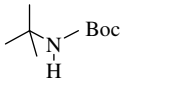
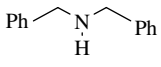
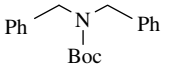
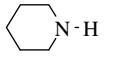
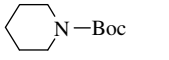
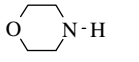
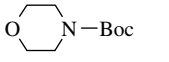
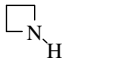
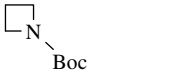
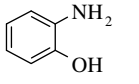
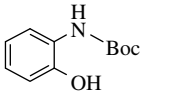
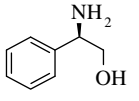
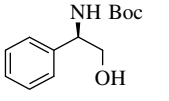
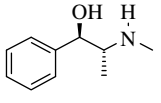
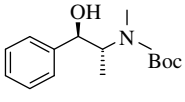
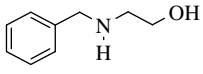
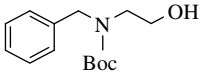
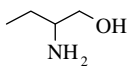
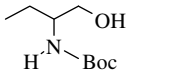
a		40		95
b		30		94
c		30		92
d		35		95
e		20		97
f		20		96
g		10		93
h		5		95
i		5		99
j		10		94
k		30		95
l		20		95
m		30		92
n		10		93
o		25		92

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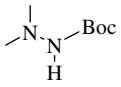
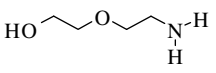
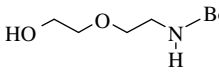
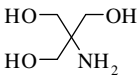
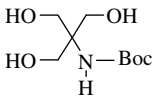
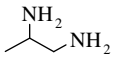
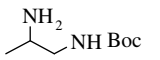
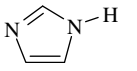
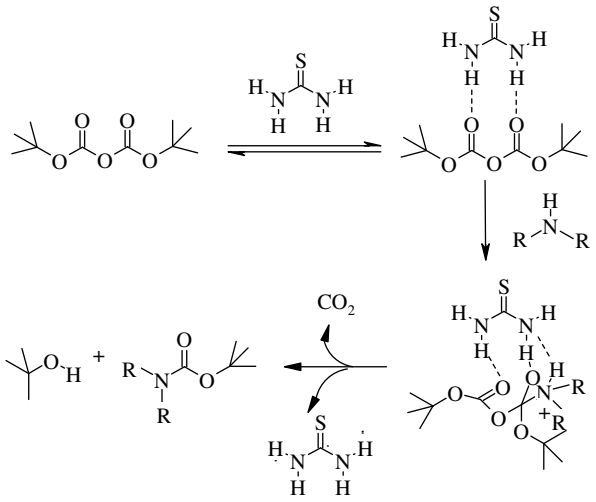
p		15		94
q		30		92
r		35		90
s		20		97
t		15		97
u		20		94

excellent isolated yield of 95% (Table 1). (**Note**: *The reaction of amines with (Boc)$_2$O cannot be performed in a closed glass or vial as CO_2 (g) is liberated during the reaction.*) Various amines and amine derivatives **1a**–**u** were treated with (Boc)$_2$O at 60 °C in toluene. No competitive formation of isocyanate, urea or *N*,*N*-di-Boc derivatives was observed (by NMR). Amines having an OH group afforded the corresponding *N*-Boc derivatives without *O*-Boc formation (by NMR). The chemoselectivity was further demonstrated in the cases of 2-aminoalcohols, which did not form oxazolidinones. The method can be applied for the conversion of sterically hindered *tert*-butylamine **1f**, to the corresponding *N*-Boc derivative. Similarly, 1,2-diamine **1s** was mono *N*-Boc-protected at the primary amine in excellent yield. In a further study, hydrazine **1p** and amino acid ester **1u** were converted to the corresponding *N*-Boc derivatives under similar reaction conditions in 20 min and in good yields. In all the cases, a remarkable rate acceleration effect was observed as demonstrated by the short reaction times and excellent yields of the corresponding *N*-Boc products. TLC was used to monitor the progress of reactions. The reactions could also be followed visually. In the case of secondary amines, an exothermic reaction took place immediately after the addition of (Boc)$_2$O to the amine with vigorous effervescence. For primary amines, commencement of slow effervescence took place with concomitant formation of the *N*-Boc derivatives.[18] However, aromatic amines with strong electron-withdrawing groups such as *p*-CN and *p*-NO$_2$ did not afford any significant amount of *N*-Boc derivatives as these groups decreased the nucleophilicity of the nitrogen atom of the amine group.



Scheme 1. Proposed mechanism of the hydrogen bond catalyzed chemoselective *N-tert*-butoxycarbonylation of amines.

The role of thiourea may be explained by Scheme 1.[3] Hydrogen bond formation between thiourea and the carbonyl oxygen atoms of $(Boc)_2O$ leads to 'electrophilic activation' (**TS1**) making the carbonyl group more susceptible to nucleophilic attack. The nitrogen atom of thiourea in turn forms a hydrogen bond with the hydrogen atom of the amine and increases the electron density at the nitrogen atom (nucleophilic activation). Electrostatic attraction between the carbonyl group and the nitrogen atom leads to **TS2**. Intramolecular nucleophilic attack by the nitrogen atom on the carbonyl carbon followed by the elimination of CO_2, *t*-BuOH and urea forms the carbamate.

In summary, we have developed the first hydrogen bond catalyzed chemoselective *N-tert*-butoxycarbonylation of amines, which allows the efficient synthesis of diverse *N*-Boc amines. The mild and nonacidic conditions together with the high chemoselectivity of this protocol should enable applications to complex or acid-sensitive substrates.

General procedure: N-tert-butoxycarbonylation of amines: A solution of the amine (1.00 mmol) and $(Boc)_2O$ (1 mmol) in toluene (5 mL) was treated with thiourea (0.100 mmol) and the mixture was stirred until complete conversion (5–40 min). After filtration, the solvent was evaporated and the residue purified by column chromatography (silica gel) eluting with hexane–EtOAc (1:1) followed by evaporation of the solvent. The physical data (mp, IR, NMR) of the known compounds were found to be identical with those reported in the literature.[16] Spectroscopic data for selected examples follows: Compound **3j**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.54$ (s, 9H), 2.18 (quin, $J = 6.5$ Hz, 2H), 3.94 (t, $J = 5.0$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 15.7$ (CH_2), 28.7 (CH_3), 44.1 (CH_2), 79.4 (C), 156.6 (C=O); compound: **3k** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.57$ (s, 9H), 6.69 (br s, 1H, OH), 6.89 (t, $J = 7.5$ Hz, 1H), 7.01 (d, $J = 9.5$ Hz, 1H), 7.06–7.11 (m, 2H), 8.17 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.69$ (CH_3), 82.43 (C), 119.06 (CH), 121.176 (CH), 121.71 (C), 125.87 (CH), 126.1 (CH), 147.75 (C), 155.4 (C=O); compound: **3n** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.51$ (s, 9H), 2.18 (br s, 1H, OH), 3.44 (m, 2H), 3.74 (m, 2H), 4.50 (s, 2H), 7.27–7.32 (m, 3H), 7.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.8$ (CH_3), 50.12 (CH_2), 52.40 (CH_2), 62.2 (CH_2), 80.94 (C), 128.0 (CH), 128.9 (CH), 138.68 (CH), 147.19 (C) 157.64 (C=O); compound: **3q** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.37$ (s, 9H), 3.24 (m, 2H), 3.47 (t, $J = 5.5$ Hz, 2H), 3.49 (t, $J = 4$ Hz, 2H), 3.65 (t, $J = 5$ Hz, 2H), 5.25 (br s, 1H, OH), 5.44 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 28.73$ (CH_3), 40.70 (CH_2), 61.71 (CH_2), 70.58 (CH_2), 72.67 (CH_2), 79.56 (C), 156.64 (C=O).

References and notes

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