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Thioglycoluril as a highly efficient, recyclable and novel organocatalyst for *N*-Boc protection of amines

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ABSTRACT

A simple and efficient protocol for the chemoselective mono-*N*-Boc protection of various structurally diverse amines with di-*tert*-butyl dicarbonate using thioglycoluril as the catalyst is described. The catalyst can be readily separated from the reaction products by simple filtration and recovered for reuse. No competitive side reactions, such as formation of isocyanate, urea, oxazolidinone, and *N*,*N*-di-Boc derivatives were observed.

1. Introduction

The term 'organocatalysis' describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound.[1] Interest in this field has increased as a result of both the novel approaches of the concept and, more importantly, by the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic reactions. Nowadays, ureas and thioureas are widely recognized as very useful templates on which powerful organocatalytic systems,[2] both mono- and bifunctional, can be constructed. However, the design and development of new, effective, and easily accessible bifunctional organic catalysts continue to be a major challenge. In 1989, Butler and co-workers reported that the condensation of thiourea and benzil in butanol yielded an insoluble white solid now known as thioglycoluril.[3] Recently, Wu and co-workers demonstrated that thioglycoluril, as a novel organocatalyst, efficiently promoted selective α-monobromination of 1,3-diketones and β-keto esters.[4] Bearing in mind the usefulness and efficiency of organocatalysts, we decided to explore thioglycoluril as a bifunctional organocatalyst for the *N*-Boc protection of amines.

N-*tert*-Butoxycarbonylation of amines has received considerable attention in synthesis due to the stability of the *N*-*tert*-butoxycarbonyl group toward basic and nucleophilic attack and its labile nature in the presence of acid.[5] 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)[6] or inorganic bases;[7] drawbacks include long reaction times and the toxicity of the reagents. Furthermore, the base-catalyzed reactions are often associated with the formation of isocyanates,[8] ureas,[6] and *N*,*N*-di-Boc derivatives.[9] Further, modified methods have been reported with amines and $(Boc)_2O$ in the presence of Lewis acids, such as $ZrCl_4$,[10] $LiClO_4$,[11] $HClO_4$,[12] $Cu(BF_4)_2 \cdot xH_2O$,[13] $Zn(ClO_4)_2 \cdot 6H_2O$,[14] and $La(NO_3)_3 \cdot 6H_2O$.[15] Although these methods circumvent the problems associated with the formation of side products, they are plagued by a number of other serious drawbacks and have limited applications in large scale preparation (e.g., $ZrCl_4$ is highly moisture-sensitive and liberates HCl fumes; perchlorate reagents are strong oxidants and explosive in nature). Moreover, it should be noted that most Lewis acids cannot be used in this reaction since they are consumed and deactivated by the amines.[16] Even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are needed, as the acids are trapped by the basic nitrogen.[17] In recent years, several new and efficient methods have been developed including the use of $HClO_4/SiO_2$,[12] Montmorillonite K10 or KSF,[18] I_2,[19] $H_3PW_{12}O_{40}$,[20] thiourea,[21] HFIP,[22] sulfamic acid,[23] Amberlyst 15,[24] and H_2O.[25] However, most of these methods still have limitations, such as high costs and the air-sensitive nature of the catalysts, toxicity and corrosiveness, restrictions for large-scale applications, deprotection of

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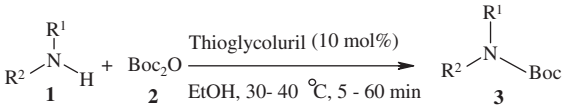
Table 1
Thioglycoluril-catalyzed *N*-Boc protection of amines



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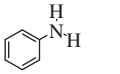
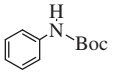
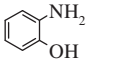
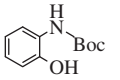
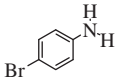
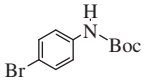
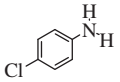
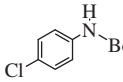
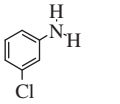
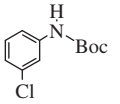
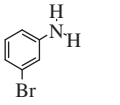
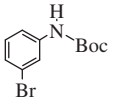
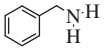
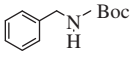
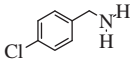
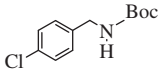
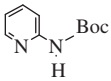
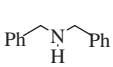
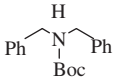
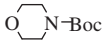
a		8		95
b		6		94
c		40		92
d		60		90
e		30		93
f		30		95
g		5		95
h		10		95
i		8		92
j		5		90
k		5		92
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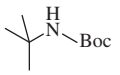
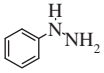
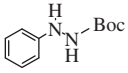
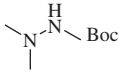
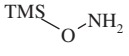
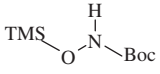
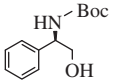
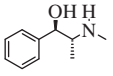
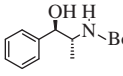
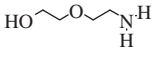
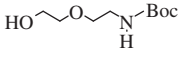
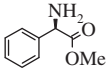
m		10		95
n		10		94
o		10		92
p		10		90
q		15		93
r		15		95
s		20		95
t		20		95

Table 1 (*continued*)

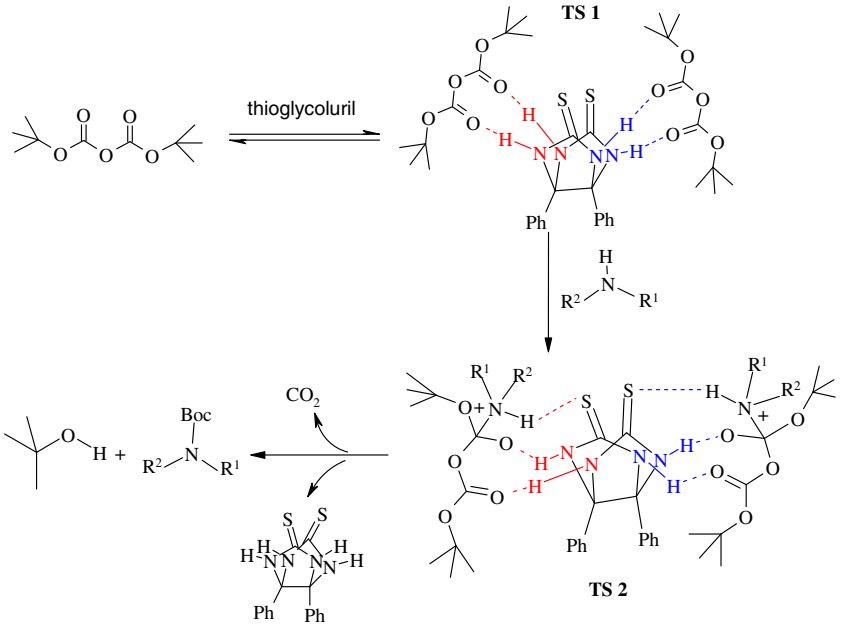
Entry	Substrate	Time (min)	Product	Yield (%) **3**[a]
u		10		80
v		10		80
w[b]		4 h		50
x[b]		6 h		40

[a] Isolated product.
[b] Without catalyst.

other protecting groups,[26] difficult product isolation procedures, lack of generality especially with deactivated (electron-deficient) amines, and difficulties in recovery of high-boiling solvents. We recently reported that thiourea can catalyze *N*-Boc protection of various activated amines in toluene at 60–70 °C.[21] Herein we report thioglycoluril as an excellent organocatalyst for the selective *tert*-butoxycarbonylation of various amines and amine derivatives. The general applicability of the method for the synthesis of a wide variety of diverse *N*-Boc-amines is demonstrated (Table 1).

In an initial endeavor, one equivalent each of $(Boc)_2O$ and aniline were stirred at ambient temperature in ethanol. After 4 h, only 50% of the expected product was obtained after work-up and recrystallization of the crude from ethanol. To improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of a catalytic amount of thioglycoluril (10 mol %) under similar conditions. Surprisingly, a significant improvement was observed and the yield of the expected product increased to 95% after stirring the mixture for only 8 min (Table 1, entry a). This study was extended to a wide range of structurally diverse amines including open-chain, cyclic, aromatic and heteroaromatic, as well as β-amino alcohols and α-amino acid esters all of which underwent reaction smoothly with $(Boc)_2O$. The method can be applied for the conversion of poorly reactive amines, such as 4-chloroaniline, as well as the sterically hindered *tert*-butylamine, into the corresponding *N*-Boc derivatives (entries d and m). Similarly, with 1,2-phenylenediamine the mono-*N*-Boc protected product was obtained in reasonably good yield (entry u). In addition, an amino acid ester was converted into the corresponding *N*-Boc ester under similar reaction conditions (entry t). It is noteworthy that this reaction is chemoselective in the cases of 2-phenylglycinol and ephedrine, where the *N*-Boc protected derivatives were obtained as the sole products (entries q and r) and neither *O*-Boc nor oxazolidinone derivatives were observed (by NMR). In all 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 the reactions which in some cases could also be followed visually, for example, with secondary amines, an exothermic reaction took place immediately after the addition of $(Boc)_2O$ to the amine with vigorous effervescence. For primary amines, commencement of slow effervescence took place with concomitant formation of the *N*-Boc derivatives.[27]

To extend the synthetic potential of this novel method for chemoselective protection of amines, we also examined its efficiency in reactions with hydroxylamines and hydrazines. As shown in Table 1, the corresponding mono-*N*-Boc products were obtained in good isolated yields (entries o and p).



Scheme 1. Proposed mechanism for the thioglycoluril-catalyzed chemoselective *N-tert*-butoxycarbonylation of amines.

The mechanistic role of thioglycoluril is illustrated in Scheme 1.[21,25] Hydrogen bond formation between thioglycoluril and the carbonyl oxygen atoms of $(Boc)_2O$ leads to 'electrophilic activation' (TS 1) making the carbonyl group more susceptible to nucleophilic attack. The sulfur atom of thioglycoluril 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 TS 2. Intramolecular nucleophilic attack by the nitrogen atom on the carbonyl carbon followed by elimination of CO_2, *t*-BuOH, and thioglycoluril yields the corresponding carbamate. A similar mechanism for the activation of carbonyl compounds by thioglycoluril has been reported.[4] Due to the poor solubility of thioglycoluril in ethanol and CH_2Cl_2 the catalyst can be separated easily after completion of the reaction and reused without any decrease in its activity. For example, the reaction of aniline (entry a) and $(Boc)_2O$ afforded the corresponding *N*-Boc product in 95%, 95%, and 94% isolated yields over three cycles. Although the amount of catalyst has been optimized to 10 mol %, lower amounts (5 mol %) also worked but with longer reaction times.

In summary, we have described an efficient method for *N-tert*-butoxycarbonylation of various electronically and structurally diverse amines in good-to-excellent isolated yields. In contrast to some existing methods using potentially hazardous catalysts/additives, this new method offers the following advantages: (i) avoids the use of any base, metal, or Lewis acid catalysts, (ii) short reaction times, (iii) ease of product isolation/non-aqueous work-up, (iv) high chemoselectivity, (v) no side reactions, and (vi) simple processing and handling. The recovered thioglycoluril can be recycled.

2. General procedure for the *N-tert*-butoxycarbonylation of amines

To $(Boc)_2O$ (1.0 mmol) and thioglycoluril (0.1 mmol) in ethanol (4 mL) was added an amine (1.0 mmol) and the mixture was stirred at room temperature for the time indicated in Table 1. After completion of the reaction (as indicated by TLC), CH_2Cl_2 (10 mL) was added and the catalyst was separated by filtration. The filtrate was collected and concentrated. The product was purified by flash chromatography (hexane–EtOAc). ^1H NMR, ^{13}C NMR, and IR spectra were consistent with the assigned structures.[11,24] Spectroscopic data for selected examples are given below. (**3a**)[19] White solid, mp: 130–132 °C; ^1H NMR (500.13 MHz, $CDCl_3$): δ 1.56 (s, 9H), 6.51 (br s, 1H), 7.06–7.09 (m, 1H), 7.30–7.41 (m, 4H); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 28.7, 85.5, 115.9, 123.4, 129.3, 138.7, 153.2. (**3b**) White solid, mp 142 °C, ^1H NMR (500.13 MHz, $CDCl_3$): δ 1.57 (s, 9H), 6.69 (br s, 1H, NH), 6.88–7.30 (m, 4H), 8.17 (br s, 1H, OH); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 28.6, 82.4, 119.0, 121.1, 121.7, 125.8, 126.0, 147.3, 155.3. (**3d**) White solid, mp: 102–104 °C; ^1H NMR (500.13 MHz, $CDCl_3$): δ 1.53 (s, 9H), 6.59 (br s, 1H, NH), 7.23–7.33 (m, 4H); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 28.3, 80.8, 119.7, 127.9, 128.9, 136.9, 152.6. (**3q**) Solid, mp 130–132 °C, ^1H NMR (500.13 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.69 (br s, 1H, NH), 3.85 (s, 2H), 4.51 (s, 1H), 5.30 (s, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 28.7, 52.2, 67.2, 80.4, 126.9, 128.1, 129.1, 140.1, 156.5.

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