N-Benzyloxycarbonyl-2-methylaminothiazoline as a Selective Benzyloxycarbonylating Reagent of Amines

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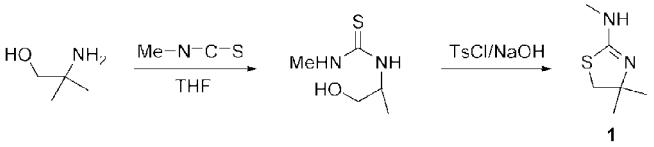
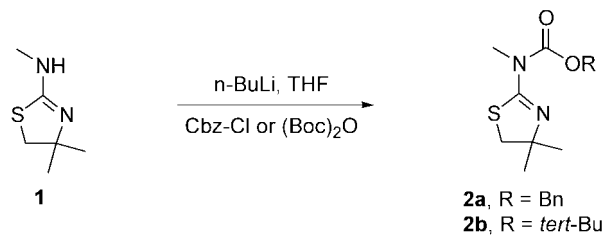
Chemoselective alkoxycarbonylation of amines is an important reaction for the protection in organic synthesis.[1] A variety of reagents have been developed by devising a leaving group such as chlorides,[2] imidazole,[3] imide,[4] oxime,[5] enolate,[6] and *N*-sulfonylanilide.[7] Each method has its advantages and disadvantages in any given situation. Thus the development of other reagents is necessary. Recently, we reported synthetic route to 2-methylaminothiazolines by the selective S-cyclization of *N*-(2-hydroxyethyl)-*N'*-methylthioureas.[8] Heterocyclic system of 2-methylaminothiazoline **1** is expected to be a good leaving group for alkoxycarbonylation reagent of amines. In this paper we report that *N*-benzyloxy and *N*-*tert*-butoxycarbonyl-2-methylaminothiazoline **2** serve as new reagents for the selective alkoxycarbonylation of a less hindered amines in the presence of a more hindered amines.

The synthesis of 4,4-dimethyl-2-methylaminothiazoline was readily performed by the reaction of 1,2-aminoalcohol with methyl isothiocyanate to give the corresponding *N*-(1,1-dimethylamino-2-hydroxy)ethyl-*N'*-methylthiourea, followed by the S-cyclization to the 2-methylaminothiazoline in 83% yield by a one pot reaction using *p*-toluenesulfonyl chloride and NaOH (Scheme 1).[9] Acylation of the 2-methylaminothiazolines can conceivably proceed through an attack upon acyl halide either by the *exo*-nitrgen to provide *N*-acylated-2-methylaminothiazolines or by the *endo*-nitrgon to give *N*-acylated 2-methyliminothiazolidine.[10] Alkoxycarbonylation of thiazolines **1** with benzyloxycarbony chloride (CbzCl) and *tert*-butoxycarbonyl chloride (BocCl) under *n*-BuLi gave only the *N*-benzyloxy and *N*-*tert*-butoxycarbonyl-2-methylaminothiazoline **2** (Scheme 2). After column chromatography, **2a** and **2b** were obtained as air storable oil in 96% and 93% yields, respectively.[11]



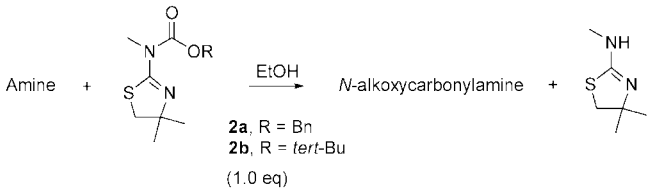
Scheme 1



Scheme 2

We next turned to our attention to the *N*-alkoxycarbonyl transfer potentiality of **2** to amine. Benzyloxycarbonylation of bezylamine with **2a** was examined first in a variety of solvents such as THF, CCl_4, and EtOH. No reaction occurred in refluxing THF and CCl_4 for 40 h. Even treatment of benzylamine with *n*-BuLi in THF to enhance the nucleophilicity of amine did not provide the desired carbamate. In refluxing ethanol, primary and secondary amines gave the corresponding carbamate in good yields (Table 1, entries 1-3). However, the reaction time required for the completion depended on

Table 1. Synthesis of Cbz- and Boc-amine with **2a** and **2b**



Entry	Reagent	R	Amine	Conditions	Yields (%)[a]
1	**2a**	Bn	Ph, NH_2	Reflux, 40 h	92
2	**2a**	Bn	Ph, NHMe	Reflux, 48 h	87
3	**2a**	Bn	Ph, NH_2	Reflux, 48 h	93
4	**2a**	Bn	Ph, NH_2	Reflux, 50 h	0
5	**2b**	*tert*-Bu	Ph, NH_2	Reflux, 60 h	62
6	**2b**	*tert*-Bu	Ph, NHMe	Reflux, 72 h	65
7	**2b**	*tert*-Bu	Ph, NH_2	Reflux, 72 h	0
8	**2b**	*tert*-Bu	Ph, NH_2	Reflux, 72 h	0

[a]Isolated yield by column chromatography

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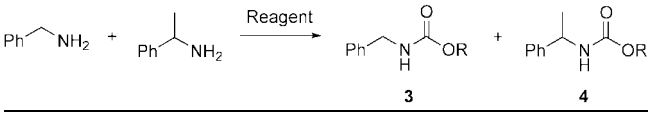
Table 2. Competitive alkoxycarbonylation



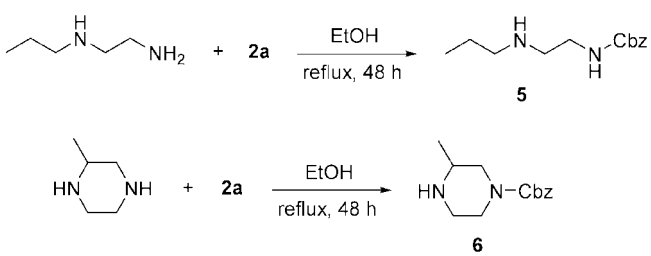
3 **4**

Entry	Reagent	R	Conditions	Yield (%)[a] Selectivity[b] **3** + **4**	**3** : **4**
1	**2a**	Bn	EtOH, reflux, 48 h	93	100:0
2	**2b**	*tert*-Bu	EtOH, reflux, 72 h	60	100:0
3	BnOCOCl	Bn	Et_3N, THF, 0 °C, 2 h	95	81:19

[a]Isolated yield by column chromatography. [b]Determined by ^{1}H NMR.

the bulkiness of amine. Very sterically hindered cumylamine did not yield Cbz-derivative in reflux for 50 h (Table 1, entry 4). Under the same conditions using **2b**, benzylamine and *N*-methylbenzylamine were converted to the Boc-derivatives in 86% and 85% yields, respectively. Hindered alkyl amines were not acylated even in refluxing EtOH for 72 h (Table 1, entries 7-8). These differences in reactivity between Cbz- and Boc-derivatives are due to the efficient bulkiness around the carbonyl group of **2b** by the *tert*-butoxy groups, indicating the reactivity of **2b** is more sensitive to the steric hinderence of the amines. The leaving group, 2-methylaminothiazoline **1** was almost quantitatively recovered for recycling simply by extracting with acidic aqueous solution. After washing, concentration of organic layer gave the crude alkoxycarbonylated product, which was purified by column chromatography or recrystallization. Comparison of the crude reaction product in each case was made with authentic samples of the possible carbamate product using NMR spectroscopy.[12] The substantial difference in reaction rate between hindered and less hindered amines prompted us to examine selective acylation of amines. We chose to investigate the selectivity in the acylation of a 1 : 1 mixture of a hindered primary amine and a less hindered primary amine with **2**. The results are summarized in Table 2. With both **2a** and **2b** high selectivity was observed. Benzyloxycarbonylation of the common reagent, BnOCOCl obviously gave a worse selectivity compared with the same reaction using **2a** (Table 2, entry 3). To test the above selective benzyloxycarbonylation in diamines by **2a**, benzyloxycarbonylation of *N*-propylethylene diamine and 2-methylpiperizine were performed to afford the mono-Cbz-derivatives (**5** and **6**) in 98% and 93% yields, respectively, which were only acylated product at the less hindered nitrogen (Scheme 3).

In conclusion *N*-benzyloxycarbonylated 2-methylaminothiazoline is very effective in selective *N*-benzyloxycarbonylation of amines. We believe that this novel benzyloxycarbonylating agent can be widely used for the selective protection of various polyamine compounds. The further development as a general acylating agent is in progress.



Scheme 3

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9. Synthesis of 4,5-Dihydro-4,4-dimethyl-*N*-methyl-2-thiazolamine **1**. To a stirred solution of *N*-[(1,1-dimethyl-2-hydroxy)ethyl]-*N*-methylthiourea (3.01 g, 19 mmol) in THF (20 mL) under nitrogen at room temperature was added a solution of NaOH (0.76 g, 2.2 mmol, 250 M%) in water (5 mL) and TsCl (3.89 g, mmol, 110 M%) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min at room temperature, quenched with water (30 mL), and extracted with ether (30 mL × 3). The organic layer was dried, filtered, and concentrated to give the crude product, which was purified by flash column chromatography to give the cyclized product **1** (2.3 g, 83% yield). White solid, mp 105-107 °C; R_f = 0.1 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 2H, SCH_2), 2.94 (s, 3H, NCH_3), 1.42 (s, 6H, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 73.1, 46.2, 31.4, 28.3. Anal Calcd for $C_6H_{12}N_2S$: C, 49.96; H, 8.39; N, 19.42; S, 22.23. Found: C, 51.22; H, 8.51; N, 18.93; S, 22.60. This method was more efficient in purification, compared to our previous work using Mitsunobu reaction (DEAD and triphenyl phosphine).[8]
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11. Synthesis of Benzyl *N*-(4,5-dihydro-4,4-dimethyl-2-thiazolyl)-*N*-methylcarbamate **2a**. To a stirred solution of **1** (0.51 g, 3.54 mmol) in dry THF (20 mL) under nitrogen at 0 °C was added a solution of n-BuLi (1.70 mL, 120 M%, 2.5 M solution in THF) dropwise with a syringe. After 30 min CbzCl (0.285 mL, 120 M%) was added and then the reaction mixture was stirred for 60 min at the same temperature, quenched with saturated NH_4Cl solution (20 mL), and extracted with ether (30 mL × 3). The organic layer was dried, filtered, and concentrated to give the crude product, which was purified by flash column chromatography to give the cyclized product **2a** (0.95 g, 96% yield). oil; R_f = 0.8 (ethyl acetate/hexane 3/7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.33 (m, 5H, Ar), 5.21 (s, 2H, OCH_2), 3.37 (s, 3H, NCH_3), 3.05 (s, 2H, SCH_2), 1.34 (s, 6H, $2CH_3$).
12. For benzyl *N*-(1-phenylethyl)carbamate, benzyl *N*-benzyl-*N'*-methylcarbamate, *N*-benzyloxycarbonyl-*N'*-propylethylenediamine **5**, and 1-benzyloxycarbonyl-3-methylpiperazine **6**, see: (a) Kondo, K.; Sekimoto, E.; Nakao, J.; Murakami, Y. *Tetrahedron* **2000**, *56*, 5843. For benzyl *N*-benzylcarbamate, see: (b) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755. For *tert*-butyl *N*-benzyl-*N'*-methylcarbamate and *tert*-butyl *N*-benzylcarbamate, see: (c) Alonso, E.; Ramon, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355.