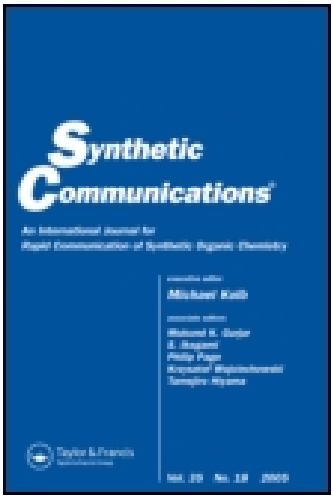

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One-Step Synthesis and Isolation of N-(tert-Butoxycarbonyl)-N′-methylthiourea on a Large Scale

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One-Step Synthesis and Isolation of N-(*tert*-Butoxycarbonyl)-N′-methylthiourea on a Large Scale

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Abstract: Simple preparation and isolation of N-(tert-butoxycarbonyl)-N′-methylthiourea on a large scale are described.

Keywords: 1,5-Dimethy-4,6-dithioxo-[1,3,5]-triazinan-2-one, guanidine, methyl isothiocyanate, N-methyl-thiourea, *tert*-butyl carbamate

INTRODUCTION

Recently a large quantity of N-(*tert*-butoxycarbonyl)-N′-methylthiourea (**2**) was required for preparation of a cyclic guanidine compound for our ongoing project. Guanidines can be prepared in many ways as described in a communication by Poss et al.[1] He also described how compound **2** could be prepared in two ways. However, the exact preparation and isolation of **2** was not detailed. In this article, we describe a one-step synthesis and isolation of a large quantity of this material. We also characterized the major unavoidable impurity, which was removed without chromatography separation.

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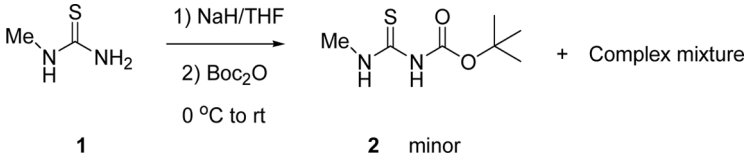
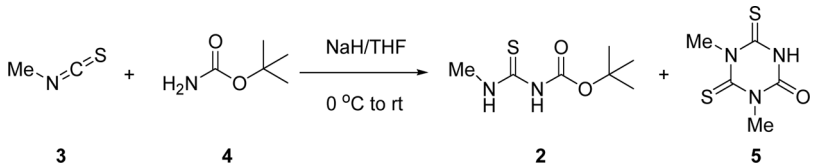


Scheme 1. NaH, THF, Boc_2O.

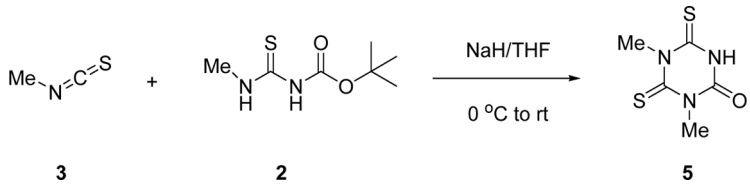
RESULTS AND DISCUSSION

According to Poss et al.,[1] N-propyl-thiourea can be acylated (Boc_2O, NaH, tetrahydrofuran [THF]) to give the desired N-(*tert*-butoxycarbonyl)-N′-propylthiourea in 95% yield. However, when we tried to acylate[2] N-methyl-thiourea **1** with Boc_2O in the presence of NaH in THF, an inseparable mixture containing minor amounts desired product **2** (Scheme 1) was obtained. This method was abandoned. [Note: We used 2 equivalents of NaH to acylate N-propyl-thiourea with Boc_2O in THF to obtain 93% of N-(*tert*-butoxycarbonyl)-N′-propylthiourea: The experiments were performed using 1 or 2 equivalents of NaH: To a slurry of NaH in THF at 0 °C was added 1 eq. of methyl-thiourea in THF. After stirring for 30 min at 0 °C, 1 eq. of Boc_2O in THF was added. The reaction was stirred at rt overnight. After usual workup, a complex mixture were found. Compound **1** was bought from Acros or can be prepared in two steps as described by Poss et al.[1] LC-MS and ^{1}H NMR analyses found the inseparable mixture to be a mixture of acylated thioureas, $NHBoc_2$, MeNHBoc, and desired product **2**].

The other method Poss described was a reaction of benzyl isothiocyanate and *tert*-butyl carbamate **4** in the presence of NaH in THF to give N-(*tert*-butoxycarbonyl)-N′-benzylthiourea in 43% yield. We used methyl isothiocyanate **3** to react with *tert*-butyl carbamate **4** in the presence of NaH (1.1 eq.) in THF. We found this method provided predominately a mixture of product **2** and by-product 1,5-dimethy-4,6-dithioxo-[1,3,5]triazinan-2-one **5** in a ratio of 3:1 (Scheme 2). (The reaction was acidified with saturated aqueous citric acid, and then extracted with



Scheme 2. NaH, THF, 0 deg. to rt.



3 2 5

Scheme 3. NaH, THF, 0 deg. to rt.

EtOAc. The ratio was measured by ^{1}H NMR of the corresponding methyl peaks).

The by-product **5** occurred during the reaction because product **2** competed with *tert*-butyl carbamate **4** for the electrophile **3** under the reaction conditions. This theory was validated by reacting **2** with methyl isothiocyanate **3** in the presence of NaH (1.1 eq.) in THF to give 73% isolated yield of **5** (Scheme 3). [Compound **5** (2.9 g) was also obtained by extraction with EtOAc (1×300 mL, 1×100 mL) from the acidified aqueous phase in a 10-g-scale reaction as described in method B].

The identification of triazine **5** as the major by-product explained the moderate yield of desired product **2**. Similar substituted triazine 2,4-dithiones can also be prepared according to the method of Joshua et al.[3]

Our first method (method A) in large synthesis of **2** was described previously. After an SiO_2 column separation, product **2** was isolated in 46% yield. This method requires a large amount of solvents and a large column separation. THF [(11 L) was used for 400 g of **4**, 250 g of **3**, and 210 g of NaH (60%)].

The second method (method B) is more efficient than the first one. We replaced THF with DMF and the amount of solvent was reduced by >65% (from 11 L to 3.5 L). DMF (3.5 L) was used for the same amount of chemicals. Column separation was eliminated after we found out that the triazine **5** was soluble in NaOH solution. Thus product **2** was directly extracted with diethylether in 51% yield from the reaction mixture after quenching with ice/water.

Our preferred method (method C) is to use 2 equivalents of NaH instead of 1, and compounds **3** and **4** have to be added together to a slurry of NaH in DMF at 0 °C. Either *tert*-butyl methyl ether or diethyl ether can be used for extraction. Using this variation, 58% of desired compound **2** was isolated. The extra equivalent of NaH increased the yield from 51 to 58%. A small-scale reaction (4 g of **4**) was run using method C and afforded 68% yield of **2**. It appears that the formation of di-anion **2** reacts with **3** slower than the mono-anion. Unfortunately, we were unable to increase the yield further regardless of changing temperature, inverse addition of NaH, using potassium *tert*-butoxide

instead of NaH, adding *tert*-butyl carbamate **4** first and then methyl isothiocyanate **3**, or adding both **3** and **4** together to a slurry of NaH in THF at 0 °C. An attempt to generate the anion of NH_2Boc with NaH in DMF at room temperature for an hour first, following addition of methyl isothiocyanate **3**, provided minor product **2**.

CONCLUSION

A simple preparation and isolation of N-(*tert*-butoxycarbonyl)-N′-methylthiourea **2** in a large quantity was developed for the first time in moderate yield. By using this method, a many similar substituted thioureas can be prepared easily. Further elaboration of substituted thioureas can lead to substituted guanidines.[1] The triazine impurity, like compound **5**, can be removed by basic aqueous washing.

EXPERIMENTAL

Starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. Melting points were determined with a MELT-TEMP instrument from Electrothermal. Column chromatography was performed on silica gel, 230–400 mesh. Chemical shifts (δ) are reported in parts per million. All ^{1}H NMRs were recorded with Varian 400-MHz spectrometer with solvents indicated. Mass spectra were obtained either from Waters-ZQ mass spectrometer or JUL Mstation magnetic factor mass spectrometer. Elemental analyses were performed by QTI Technologies Inc., Whitehouse, New Jersey.

Preparation of N-(*tert*-Butoxycarbonyl)-N′-methylthiourea 2

Method A

To a cold (2 °C) stirred suspension of 60% NaH (210 g, 5.3 mol, 1.55 eq.) in mineral oil in anhydrous THF (8 L) in a 22-L, three-neck, round-bottom flask under N_2 atmosphere, a solution of NH_2Boc **4** (400 g, 3.4 mol, 1.0 eq.) in THF (2 L) was added over 20 min. After stirring for 30 min, methyl isothiocyanate **3** (250 g, 3.4 mol, 1.0 eq.) in THF (1) was added over 20 min, keeping the temperature colder than 5 °C. The bath was removed, and the reaction was stirred overnight (~18 h) while warming up to room temperature. The reaction was chilled to 10 °C and acidified by pouring it in to a stirred solution of 10% citric acid (5 L). THF was

removed under reduced pressure, and the residue was extracted with EtOAc (2×6 L, 1×4 L). The combined organic phase was washed with brine (2×1 L), dried over $MgSO_4$, and then concentrated to give a crude product, which was chromatographed on an SiO_2 column, using 10 to 15% EtOAc in hexane to give compound **2** (296 g, 46%) as a white solid: mp 97–99 °C; ^{1}H NMR ($CDCl_3$) δ 9.7 (s, br. 1 H), 7.9 (s, br. 1 H), 3.1 (d, $J = 4.4$ Hz, 3 H), 1.4 (s, 9 H). Anal. calc. for $C_7H_{14}N_2O_2S$: C, 44.19; H, 7.42; N, 14.72; S, 16.85. Found: C, 44.32; H, 7.41; N, 14.52; S, 16.95.

Method B

To a cold (2 °C) stirred suspension of NaH (60% in mineral oil, 155 g, 3.8 mol, 1.1 eq.) in DMF (2.5 L) in a 12-L, three-neck, round-bottom flask under an N_2 atmosphere, a solution of NH_2Boc (400 g, 3.4 mol, 1.0 eq) and methyl isothiocyanate (246 g, 3.4 mol, 1.0 eq.) in DMF (1.0 L) was added in 2.05 h, keeping temperature colder than 5 °C. After complete addition, the bath was removed and, reaction was stirred overnight while warming it to room temperature. The reaction mixture was poured into a stirred mixture of ice (2 kg) and water (12 L) and extracted with Et_2O (2×10 L, 1×5 L, and 1×3 L). The combined Et_2O layers were dried over $MgSO_4$ and then filtered. Solvents were removed under reduced pressure until solids started to precipitate. Hexane (800 mL) was added, chilled in ice bath, and stirred vigorously. A white solid was collected by filtration to give **2** (332 g, 51%).

Method C

To a cold (0 °C) stirred suspension of NaH (60% in mineral oil), 315 g, 7.8 mol, 2.3 eq.) in DMF (2.4 L) in a 12-L, three-neck, round-bottom flask under N_2 atmosphere, a solution of NH_2Boc (400 g, 3.4 mol, 1.0 eq) and methyl isothiocyanate (246 g, 3.4 mol, 1.0 eq.) in DMF (1.1 L) was added in 1 h, keeping the temperature between −2 to 2 °C. After complete addition, the reaction was stirred overnight while warming it to room temperature. The reaction mixture was poured into a stirred mixture of ice (2 kg) and water (12 L) and extracted with TBME (5×6L). The combined *tert*-butyl methyl ether (TBME) extracts were washed with brine (1×10L, 1×5L), dried over $MgSO_4$, and then filtered. Solvents were removed under reduced pressure. The precipitate was triturated with pentane (500 mL), chilled in ice bath, and stirred vigorously. White solids were filtered to give **2** (379 g, 58 %).

Preparation of 1,5-Dimethy-4,6-dithioxo-[1,3,5]triazinan-2-one 5

To a cold (2 °C) stirred suspension of NaH (60% in mineral oil, 3.87 g, 97 mmol, 1.8 eq.) in anhydrous THF (200 mL), a solution of **2** (10.2 g, 54 mmol, 1.0 eq.) and **3** (8.4 g, 87 mmol, 1.6 eq.) in THF (80 mL) was added over 50 min. The temperature rose to 5.3 °C. The reaction was stirred at room temperature overnight. The reaction was chilled, and ice (100 g) was added. It was acidified to pH 3 with saturated citric acid. The precipitated solids were collected by filtration, washed with water, and dried over P_2O_5 in vaccum oven at rt to give **5** (7.4 g, 73%) as a light yellow solid: mp 179–181 °C; ^{1}H NMR ($CDCl_3$) δ 9.9 (s, br. 1 H), 4.1 (s, 3 H), 3.7 (s, 3 H); ^{13}C NMR ($CDCl_3$) 177, 174, 43, 36; MS: 190 (M + + H, 80%). Anal. calc. for $C_5H_7N_3S_2O$: C, 31.73; H, 3.73; N, 22.20; S, 33.88. Found: C, 31.90; H, 3.61; N, 21.80; S, 34.30.

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