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Preparation of *N,N'*-Bis-*tert*-Butoxycarbonylthiourea

Edwin J. Iwanowicz,* Michael A. Poss and James Lin

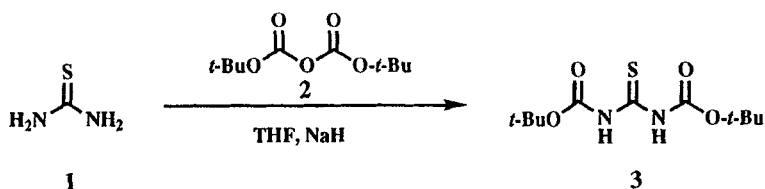
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ABSTRACT

The preparation of *N,N'*-bis-*tert*-butoxycarbonylthiourea from thiourea and di-*tert*-butyl dicarbonate in tetrahydrofuran is described.

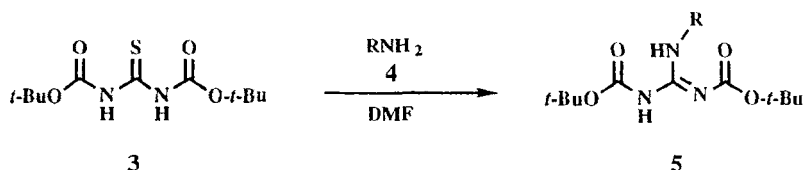
INTRODUCTION

Since our recent publication¹ on the preparation of guanidines, we have received several inquiries regarding the preparation of *N,N'*-bis-*tert*-butoxycarbonylthiourea **3**. Interest in this reagent has prompted us to describe its preparation. We have found that reacting the sodium salt of thiourea **1** with di-*tert*-butyl dicarbonate **2** in tetrahydrofuran at modest concentration gives **3** in high yield and free from *S* acylated products.^{2,3}



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N,N'-bis-*tert*-butoxycarbonylthiourea **3**, prepared by the procedure described below, was found to be satisfactory for the formation of di-(*tert*-butoxycarbonyl)-guanidines **5**.⁴



EXPERIMENTAL

The reagents were purchased from Aldrich Chemical Company, Fluka and Lancaster Synthesis. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl.

Preparation of **3**:

To a stirred colorless solution of thiourea **1** (0.571 g, 7.50 mmol) in THF (150 mL) under argon at 0 °C was added hexane washed NaH (1.35 g, 33.8 mmol, 60% in mineral oil). After five minutes, the 0 °C bath was removed and the reaction mixture was allowed to stir at room temperature for ten minutes. The reaction mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate **2** (3.60 g, 16.5 mmol) was added neat. After thirty minutes, the 0 °C bath was removed. A slurry formed within thirty minutes. The reaction mixture was stirred for another two hours at room temperature and was then quenched with an aqueous solution of saturated NaHCO₃ (10 mL). The reaction mixture was poured into water (250 mL) and extracted with ethyl acetate (3 X 70 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give **3**, 1.98 g (96%) as an off-white solid which was used without further purification.

mp 124-127 °C.

¹H NMR (CDCl₃) δ 1.61 (s).

¹³C NMR (CDCl₃) δ 177.73, 150.23, 84.06, 27.90.

MS *m/e* 277 (M+H)⁺, 221, 177.

IR (KBr) 3430, 3183, 2990, 1771, 1721, 1559, 1507, 1370, 1229, 1134 cm⁻¹.

REFERENCES

- 1) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933.
- 2) Reactions performed at higher concentrations were incomplete due to gel formation.
- 3) Reactions with other acylating agents gave mixed results. Acylation with chloroformate derivatives, such as methyl chloroformate or benzyl chloroformate, gave a mixture of N and S acylated products. In addition, attempted acylation with dibenzyl dicarbonate gave products in which alkylation (incorporation of a benzyl residue) was competitive with acylation.
- 4) *N,N'*-bis-*tert*-butoxycarbonylthiourea **3** was found to be >95 % pure by HPLC: YMC S-3 ODS (C-18) 6.0 x 150 mm, eluting with methanol, water and phosphoric acid, detected at 217 nm.