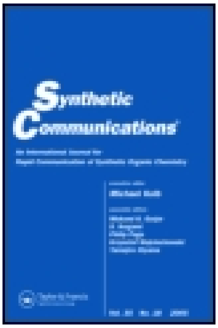

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Preparation of N,N'-bis-tert-Butoxycarbonylthiourea

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

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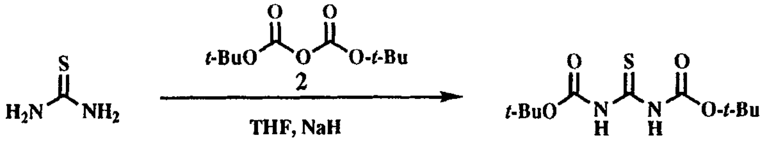
ABSTRACT

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

INTRODUCTION

Since our recent publication[1] 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]



1 **3**

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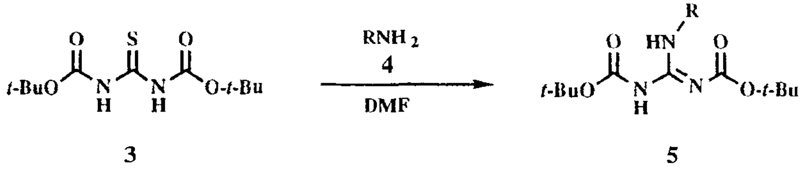
N,*N*'-bis-*tert*-butoxycarbonylthiourea 3, prepared by the procedure described below, was found to be satisfactory for the formation of di-(*tert*-butoxycarbonyl)-guanidines 5.[4]



3

5

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 $NaHCO_3$ (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 Na_2SO_4, 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.

^{1}H NMR ($CDCl_3$) δ 1.61 (s).

^{13}C NMR ($CDCl_3$) 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.