

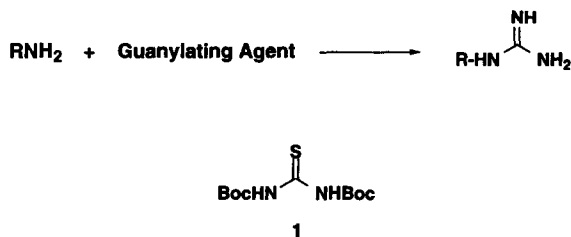
## Improved Method for the Preparation of Guanidines

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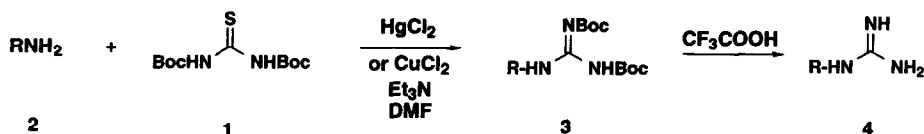
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**Abstract:** Use of N,N'-di-(*tert*-butoxycarbonyl)thiourea **1** in the presence of mercuric chloride provides a very efficient method for the bis-Boc protected guanidine formation of the amino compounds which are highly deactivated either sterically or electronically.

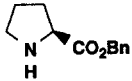
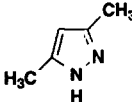
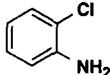
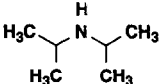
Classically, guanidines have been prepared by reaction of an amine with various guanylation agents.<sup>1</sup> We recently required an efficient method for the formation of guanidine analogs derived from very modestly reactive amines. Many known methods such as amidinesulfonic acid<sup>2</sup> were either ineffective or resulted in a poor yield. Recently new mild and efficient guanylation reaction using N,N'-di-(*tert*-butoxycarbonyl)thiourea **1** was reported.<sup>3</sup> However, this process was not effective for the substrates having a weak nucleophilic amino group. We felt that the reactivity of this reagent may be increased with the use of proper metal salts such as mercury or copper via a complex formation with the sulfur atom of **1**.



When amine **2** was reacted with bis-Boc-thiourea **1** in the presence of mercury (II) or copper chloride guanylation did proceed smoothly to afford the bis-Boc protected guanidine **3** in high yields as shown in the Table below. As reported by original authors<sup>3</sup> deprotection of two Boc-groups occurred uneventfully using trifluoroacetic acid to provide guanidine **4**.

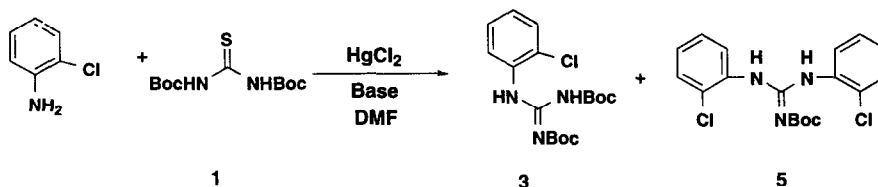


Table

<u>Amines</u>	<u>Metal Salt</u>	<u>Reaction Temp. and Time</u>	<u>mp (°C)</u>	<u>Isolated Yield of 3 (%)</u>
	HgCl <sub>2</sub>	0 °C, 20 min	112-113	90
	CuCl <sub>2</sub>	0 °C, 0.5 h; RT, 0.5 h		62
	HgCl <sub>2</sub>	60 °C, 2 h	90-91	87
CF <sub>3</sub> CH <sub>2</sub> NH <sub>2</sub>	HgCl <sub>2</sub>	RT, 1 h	136-137	89
	None	60 °C, 4 h		0
	HgCl <sub>2</sub>	RT, 2 h	135-136	78
		RT, 20 h*		92
	None	60 °C, 6 h		0
	HgCl <sub>2</sub>	0 °C, 0.5 h	104-105	90

\* Pyridine was used as a base in this case.

An interesting observation was made in the case of 2-chloroaniline. Under the same reaction condition as for other substrates at room temperature, the reaction produced a mixture of desired bis-Boc-guanidine **3** and di-2-chlorophenylguanidine **5** in an 82 : 18 ratio. The ratio was improved to 96 : 4 when the reaction was performed at 0 °C. However, when pyridine was used as a base instead of triethylamine the ratio improved to 99.6 : 0.4. This type of side product was not observed in the other substrates shown in the Table, and the cause for this discrepancy is not well understood.



Although we do not know the exact reactive intermediate of bis-Boc-thiourea in this reaction we suspect that *in-situ* generated bis-Boc-carbodiimide might be the reactive species which undergoes the guanylation for the very deactivated amines. When bis-Boc-thiourea is subjected to the similar reaction condition in the absence of amine it is rapidly transformed into a less polar compound within a few minutes and the spectroscopic data<sup>4</sup> are consistent with bis-Boc-carbodiimide or its complex with the metal. So far we were unable to obtain pure bis-Boc-carbodiimide which is free from mercury salts.

Typical experiment: To a mixture of L-proline benzyl ester hydrochloride salt (241.8 mg, 1 mmol), bis-Boc-thiourea (276.4 mg, 1 mmol) and Et<sub>3</sub>N (333.3 mg, 3.3 mmol) in dimethylformamide (2 mL) at 0 °C was added mercury chloride (298.6 mg, 1.1 mmol) with stirring.<sup>5</sup> The resulting mixture was stirred at 0 °C for 20 minutes, diluted with ethyl acetate (20 mL), and filtered through a pad of celite. The filtrate solution was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by flash chromatography column on SiO<sub>2</sub> eluting with hexane / ethyl acetate (3 / 1) to afford L-proline-bis-Boc guanidynyl benzyl ester<sup>6</sup> as a solid, 402 mg (90%), mp 112-113 °C.

#### Acknowledgment:

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#### References and Notes:

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4. A mixture of bis-Boc-thiourea (1.10g), mercuric chloride (1.09 g) and 2,6-lutidine (0.86 g) in tetrahydrofuran at 0 °C afforded a white solid **X** (1.40 g) after a normal procedure of work-up and triturating the crude product with hexane. The same product is also obtained in dimethylformamide solvent and it can even be purified by flash column chromatography on silica gel. When this compound was reacted with the amine by simply mixing the two components in a solvent it produced the same bis-Boc protected guanidine shown in the Table. A solution of this compound **X** in dichloromethane slowly deposits mercury metal in time which implies **X** might be a some kind of mercury complex of bis-Boc-carbodiimide. This compound has the following physical and spectroscopic data which matches the bis-Boc-carbodiimide or its metal complex.

**X:** mp 150 °C (dec.);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.49 (s, 18 H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  176.7, 82.6, 28.2 ppm (due to very slow relaxation one carbon peak was not observed); MS ( $\text{CI} / \text{NH}_3$ )  $m/e$  242 ( $\text{M}$  for bis-Boc-carbodiimide) $^-$ , 141 ( $\text{M-H-Boc}$ ) $^-$ .

5. In general, cupric chloride resulted in a lower yield than the mercuric chloride and mercuric oxide was much inferior for this reaction.
6.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  10.35 (s, 1 H), 7.34 (m, 5 H), 5.16 (s, 2 H), 4.71 (m, 1 H), 3.71 (m, 2 H), 2.26 (m, 1 H), 2.02 (m, 2 H), 1.90 (m, 1 H), 1.46 (s, 18 H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  171.5, 161.9, 153.8, 150.0, 135.4, 128.2, 127.9, 127.8, 81.6, 78.8, 66.6, 60.8, 49.1, 28.9, 27.8, 24.2 pp; MS ( $\text{CI} / \text{NH}_3$ )  $m/e$  448 ( $\text{M} + \text{H}$ ) $^+$ , 392, 348 ( $\text{MH} - \text{Boc}$ ) $^+$ ; 446 ( $\text{M} - \text{H}$ ) $^-$ , 356 ( $\text{M} - \text{H} - \text{Bn}$ ) $^-$ .

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