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A Mild and Efficient Method for the Preparation of Guanidines[1]

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Abstract: *A mild and efficient method for the preparation of guanidines by reaction of an acylated thiourea with an amine followed by removal of the acyl group(s) from the intermediate acylguanidine is reported.*

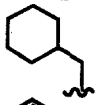
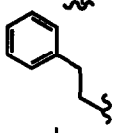
We recently required a mild and efficient method for the preparation of *N,N'*-disubstituted guanidines from amino acid residues. Classically, guanidines have been prepared by reaction of ammonia or an amine with S-alkylisothiouronium salts.[2] More recently, methods which employ reaction of ammonia or ammonia derivatives with cyanamides,[3] carbodiimides,[4] chloroformamidines,[5] dichloroisocyanides,[6] or aminoiminomethanesulfonic acids[7] have been described. Most of these methods, however, utilize starting materials which are corrosive, toxic, and/or highly moisture sensitive, or involve conditions, such as high temperature or strong base, which could compromise the stereochemical integrity of the amino acid residues needed in our substrates.

A report by Atwal[8] which described the synthesis of cyanoguanidines from cyanothioureas prompted us to explore the preparation of acylguanidines and guanidines from acylthioureas. It was reasoned that selection of a suitable acyl group, such as *tert*-butoxycarbonyl, which could be later removed, would allow for the direct preparation of guanidines.

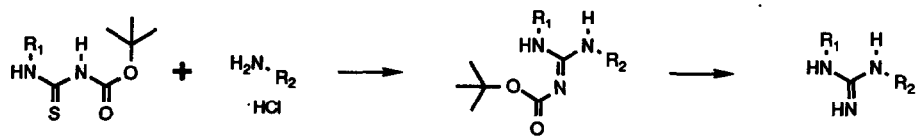
1 **2** **3** **4**

To this end, *N*-(*tert*-butoxycarbonyl)thioureas **4** were prepared by one of two methods. Compound **4a** (R_1 = benzyl) was synthesized from benzyl isothiocyanate and *tert*-butyl carbamate (NaH, THF, 43%). Yields by this method, however, were moderate and required the availability of the needed isothiocyanate. A more general and higher yielding procedure involved reaction of an amine **1b-d** with benzoyl isothiocyanate in chloroform to furnish benzoyl thiourea **2b-d**. Without purification, **2b-d** was deacylated (K_2CO_3, CH_3OH, H_2O) to provide thiourea **3b-d** (Table 1). Thiourea **3b-d** was then reacylated[9] (Boc_2O, NaH, THF) to give the desired *N*-(*tert*-butoxycarbonyl)thiourea **4b-d** (Table 1).

Table 1[10]

Entry	R_1	Yield of 3 (%) (from 1)	Yield of 4 (%)
b		86	82
c		75	88
d		82	95

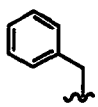
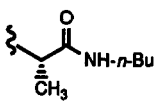
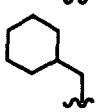
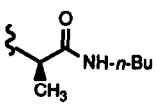
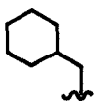
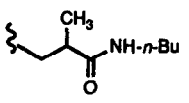
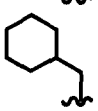
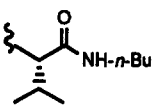
Combination of *N*-(*tert*-butoxycarbonyl)thiourea **4a-b** and amine hydrochloride **5a-d** in the presence of the water soluble carbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DMF, Et_3N)



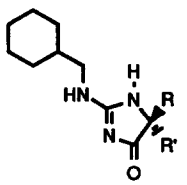
4 **5** **6** **7**

with stirring at room temperature cleanly provided *N*-(*tert*-butoxycarbonyl)guanidine **6a-d** in good yield[11] (Table 2). Removal of the *tert*-butoxycarbonyl group was then achieved by treatment of **6a-d** with acid to provide guanidine **7a-d**, which was typically isolated as a hydrochloride salt (Table 2).

Table 2[10]

Entry	R_1	R_2	Yield of 6 (%)	Yield of 7 (%) (Method)	Yield of 8 (%)
a			85	57 (HCl)[12]	40
b			94	42 (HCl)	56
c			90	90 (HCl)	0
d			88	94 (TMSOTf)	0

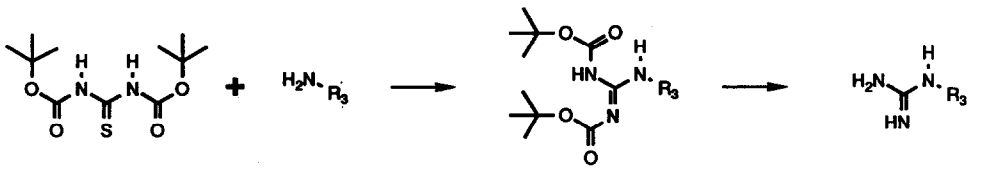
Due to the 1,5 relationship between the guanidine and the carbonyl moieties in **6a-b**, treatment with HCl in dioxane resulted in formation of a mixture of the desired guanidine **7a-b** and the cyclic acylguanidine **8a-b**.[12] If allowed to continue long enough, cyclic acylguanidine **8a-b** was the exclusive product from the reaction.



8a R = CH_3, R' = H
8b R = H, R' = CH_3

Formation of the cyclic product was not observed when TMSOTf in CH_2Cl_2 was used to remove the *tert*-butoxycarbonyl group as in **6d**. No cyclic acylguanidine product was observed when **6c**, which has a 1,6 relationship between the guanidine and the carbonyl moieties, was treated with HCl in dioxane.

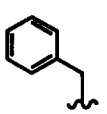
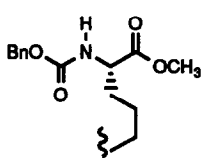
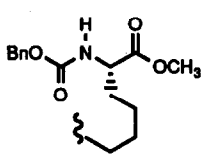
The current methodology has also been extended to prepare mono-substituted guanidines. Reaction of



9 **10** **11** **12**

thiourea with Boc_2O (NaH, THF, 95%) provided the di-*tert*-butoxycarbonyl derivative **9**.[9] Compound **9** readily combined with amine **10a-c** (DMF, Et_3N) to give the di-(*tert*-butoxycarbonyl)guanidine **11a-c** (Table 3). Treatment of acylguanidine **11a-c** with acid (CF_3CO_2H, CH_2Cl_2) furnished guanidine **12a-c** in good yield (Table 3).

Table 3[10]

Entry	R_3	Yield of 11 (%)	Yield of 12 (%)
a		80	91
b		73	84
c		71	87

The current methodology provides a mild and efficient means to prepare acylguanidines or guanidines from readily available amine starting materials. Application of this methodology to the preparation of acylamidines and amidines from acylthioamides is in progress.

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References and Notes:

1. Presented at the 203rd Meeting of the American Chemical Society, San Francisco, CA, April 1992, Abstract ORGN 424.

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8. Atwal, K. S.; Ahmed, S. Z.; O'Reilly, B. C. *Tetrahedron Lett.* **1989**, *30*, 7313.

9. Acylation with chloroformate derivatives, such as methyl chloroformate or benzyl chloroformate, gave a mixture of N and S acylated products. Attempted acylation with dibenzyl dicarbonate gave a complex mixture of products.

10. Yield refers to yield of pure isolated product.

11. The mechanism of this reaction is discussed in reference 8.

12. Before treatment with acid, the aryl ring in **6a** was reduced (H_2, Rh/Al_2O_3, EtOH, 98%) to the corresponding cyclohexyl ring.

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