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Graphical Abstract

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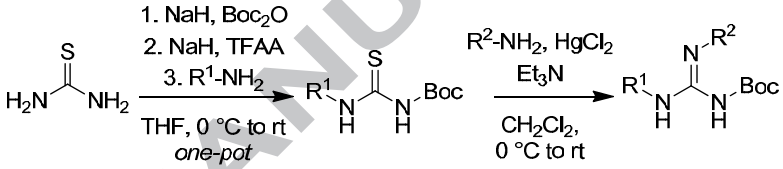

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A concise synthesis of asymmetrical *N,N′*-disubstituted guanidines

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Abstract—We present a new and concise method for the preparation of asymmetrical *N,N′*-disubstituted guanidines starting from thiourea *via* the reaction of *N*-Boc-protected *N′*-alkyl/aryl substituted thioureas with an amine in the presence of mercury(II) chloride and triethylamine.

Keywords*: Guanidine, thiourea, one-pot synthesis, N,N'-dialkyl/aryl guanidine*

Guanidine is a very relevant functional group present in Nature both in the common amino acid arginine and in a variety of natural products. This group possesses unique electronic and steric characteristics (superbasicity, ability to undergo π-cation interactions, etc.) due to the planar arrangement of the central C atom and the three N atoms attached to it. This important system is found in molecules of biochemical and pharmacological interest ranging from complex natural products such as saxitoxin (a potent neurotoxin acting as a sodium channel blocker[1]) to small molecule adrenoceptor ligands such as clonidine (an anesthetic α_2 adrenoceptor agonist). During the past 10 years, our group has been investigating the preparation of derivatives of guanidine and of 2-aminoimidazoline (a closely-related cyclic analogue) towards a variety of therapeutic applications.[2,3] Our standard synthetic approach is based on the nucleophilic attack of a primary aryl amine on either *N,N′-bis*-(*tert*-butoxycarbonyl)thiourea (for the preparation of guanidine derivatives), or *N,N′*-di(*tert*-butoxycarbonyl)imidazoline-2-thione (for the preparation of 2-aminoimidazoline derivatives) in the presence of mercury(II) chloride and excess triethylamine.[4]

Generally, the preparation of guanidine derivatives *via* primary amines is carried out using a thiourea bearing one or more electron-withdrawing groups in the presence of mercury(II) or copper(II) salts and a base.[5] Although more recent methods have included the catalytic preparation of symmetrically substituted *N,N′-bis*-arylguanidines[6] and the use of isothiocyanates for the preparation of sterically crowded and electron-deficient guanidines,[7] such methods are limited to the preparation of symmetrically substituted molecules or by the availability of the corresponding isothiocyanate. Other methods for the preparation of guanidines have also been developed,[8] but many of these procedures lack the generality of the original methodology utilizing a thiourea in the presence of a heavy metal. Recently, a solid support-linked guanidylating reagent was published by Goodman *et al.*[9] consisting of a urethane-protected trifyl guanidine attached to a solid support facilitating the synthesis of *N*-alkyl/aryl- or *N,N*-dialkylguanidines. This reagent allows guanidylation of secondary amines, but requires prior preparation and attachment to the resin and, after the guanidylation reaction, a cleavage process is necessary.

We sought to prepare a library of asymmetrical *N,N′*-disubstituted guanidines with different aliphatic and/or aromatic substituents. Therefore, in the present work, we report a new and robust procedure for their preparation *via* appropriately functionalised thiourea derivatives.

Yin *et al.* have described the preparation of *N*-Boc-*N′*-substituted thioureas by treatment of *N,N′*-di-Boc-substituted thiourea with sodium hydride and trifluoroacetic anhydride in the presence of an amine (R^1-NH_2).[10] Based in

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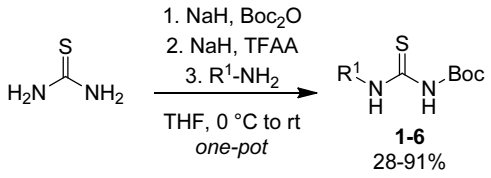
part on the mild conditions suggested by Yin, and considering the high cost of commercial *N,N′*-di-Boc-substituted thiourea, we have developed a simple one-pot procedure for the preparation of these *N*-Boc-*N′*-alkyl/aryl thioureas starting from inexpensive thiourea (Scheme 1).



R^1 = Pr (**1**), $(CH_2)_2OH$ (**2**), $(CH_2)_2OAc$ (**3**), Ph (**4**), 4-$Me_2NC_6H_4$ (**5**), 4-$EtOC_6H_4$ (**6**)

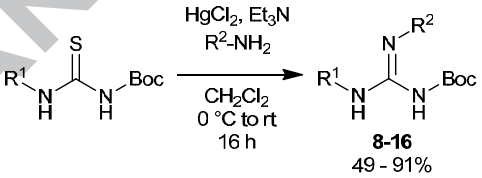
Scheme 1

First, 4.5 equivalents of sodium hydride (60% suspension in mineral oil) were added to a solution of thiourea in dry tetrahydrofuran under argon at 0 °C. This mixture was stirred at room temperature for 45 minutes to allow for complete formation of the thiourea anion, and then cooled again to 0 °C. At this point, 2.2 equivalents of di-*tert*-butyl dicarbonate were added and the mixture stirred at room temperature for 8 hours to form *N,N′*-di-Boc-protected thiourea, which was not isolated but used *in situ*. The reaction mixture was again cooled to 0 °C and a second portion of 60% sodium hydride (1.68 equivalents) added. One hour later, 1.54 equivalents of trifluoroacetic anhydride were added and the mixture stirred for one hour at 0 °C. Next, 1.54 equivalents of the appropriate amine (propylamine, hydroxyethylamine, acetoxyethylamine, aniline, *p*-ethoxyaniline or *p*-dimethylaminoaniline) were added, and the reaction stirred at room temperature for 18 hours. The mixture was again cooled to 0 °C and carefully quenched with H_2O followed by extraction with EtOAc. The organic phase was dried over $MgSO_4$, the solvents were removed under vacuum, and the residue purified by silica gel chromatography (hexane:EtOAc). Removal of solvents followed by recrystallisation from hexane afforded the product. The *N*-Boc-*N′*-substituted thioureas prepared in this work (see Table 1) were characterized by means of ^1H and ^{13}C NMR, IR and HRMS, and their purity assessed by HPLC (see Supporting Information).

Our one-pot procedure provided good results not only for aliphatic amines, but also for anilines which are less nucleophilic. Good yields were obtained (Table 1) and, in general, they were better for aliphatic than for aromatic amines. Moreover, the thioureas thus obtained provide an ideal substrate for guanidylation using our standard conditions in the presence of mercury(II) chloride and triethylamine and a second primary amine (R^2-NH_2), resulting in expedient access to asymmetrical *N,N′*-disubstituted guanidines (Scheme 2).

Notably, during the attempted guanidylation of *N*-Boc-*N′*-hydroxyethyl thiourea (**2**) with *p*-ethoxyaniline, we found that this reaction failed to produce the intended guanidine derivative. Instead, the hydroxyethyl moiety of thiourea **2** cyclised in the presence of mercury(II) chloride and Et_3N to produce *(E)*-oxazolidin-2-(*N-tert*-butoxycarbonyl)imine (**7**) (see Supporting Information). To avoid this unwanted reaction, two possible approaches were considered. In one approach, the corresponding *N*-Boc-*N′*-acetoxyethyl thiourea (**3**) was prepared instead of the hydroxyethyl derivative in order to avoid cyclization. In the second approach, we considered the preparation of the asymmetric *N,N′*-substituted guanidine derivatives **9**, **11**, **12** and **15** from the corresponding *N*-Boc-*N′*-arylthioureas **5** and **6** by reaction with propylamine, ethanolamine and aniline, respectively under the conditions shown in Scheme 2.

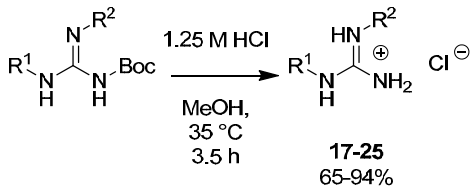
Introducing first an aliphatic or an aromatic amine in the thiourea system did not seem to affect the overall yield of the synthesis after treatment with the second primary amine. In all cases, the yields of this second nucleophilic attack ranged from good to excellent (49-91%), as can be seen in Table 1.



R^1, R^2 = Pr, $(CH_2)_2OH$, $(CH_2)_2OAc$, Ph, 4-$Me_2NC_6H_4$, 4-$EtOC_6H_4$, 6-(1,2,3,4-tetrahydronaphthalene).

Scheme 2

Previously, we have carried out the deprotection of *N*-Boc-protected guanidines and 2-aminoimidazolines by treatment with trifluoroacetic acid at room temperature overnight, later obtaining the hydrochloride salts by treatment with a basic anion-exchange resin (Amberlite) in its chloride form. This lengthy procedure proved necessary following our previous experience, in which deprotection of *N,N′-bis*-Boc-protected guanidines with a solution of hydrochloric acid often led to hydrolysis of the guanidine moiety. However, in the case of our present *N*-Boc-protected *N′*-substituted derivatives **8**-**16**, deprotection using a 1.25 M solution of HCl in methanol proceeded readily and without hydrolysis, affording the corresponding guanidine hydrochloride salts in good to excellent yields (see Table 1) in less than four hours at 35 °C (Scheme 3).



R^1, R^2 = Pr, $(CH_2)_2OH$, $(CH_2)_2OAc$, Ph, 4-$Me_2NC_6H_4$, 4-$EtOC_6H_4$, 6-(1,2,3,4-tetrahydronaphthalene)

Scheme 3

Our approach providing guanidines substituted with two different amino groups depends only on the availability of primary amines, whereas the Goodman approach yields guanidines doubly substituted at one of the amino groups depending on the availability of the corresponding secondary amines. Thus, our new and simple route to the *N,N′*-asymmetrical disubstituted guanidines is straightforward, affordable and shows the additional advantage of allowing the preparation of asymmetrical substituted *bis*-aryl guanidine derivatives, which have proven difficult to prepare in the past.[6,11]

Table 1. *N*-Boc-*N′*-alkyl/aryl substituted thioureas **1**-**6**, *N,N′*-disubstituted guanidines **8**-**16** and the corresponding hydrochloride salts **17**- **25** produced via Schemes 1, 2 and 3

Product	Thiourea/ guanidine	R^1	R^2	Yield (%)	NHBoc/NH.HCl	Yield (%)	Overall Yield (%)
1	-	$-(CH_2)_2CH_3$	-	-	NHBoc	-	71
2	-	$-(CH_2)_2OH$	-	-	NHBoc	-	43
3	-	$-(CH_2)_2OAc$[a]	-	-	NHBoc	-	91
4	-	$-C_6H_5$	-	-	NHBoc	-	46
5	-	$-C_6H_4$(*p*-NMe_2)	-	-	NHBoc	-	28
6	-	$-C_6H_4$(*p*-OEt)	-	-	NHBoc	-	49
8	**1**	$-(CH_2)_2CH_3$	$-C_6H_5$	91	NHBoc	-	65
9	**5**	$-C_6H_4$(*p*-NMe_2)	$-(CH_2)_2CH_3$	82	NHBoc	-	23
10	**1**	$-(CH_2)_2CH_3$	$-C_6H_3[-(CH_2)_4-]$	78	NHBoc	-	55
11	**6**	$-C_6H_4$(*p*-OEt)	$-(CH_2)_2OH$	49	NHBoc	-	24
12	**5**	$-C_6H_4$(*p*-NMe_2)	$-(CH_2)_2OH$	67	NHBoc	-	19
13	**3**	$-(CH_2)_2OAc$	$-C_6H_3[-(CH_2)_4-]$	75	NHBoc	-	68
14	**4**	$-C_6H_5$	$-C_6H_4$(*p*-OEt)	53	NHBoc	-	24
15	**5**	$-C_6H_4$(*p*-NMe_2)	$-C_6H_5$	88	NHBoc	-	25
16	**4**	$-C_6H_5$	$-C_6H_3[-(CH_2)_4-]$	84	NHBoc	-	37
17	**8**	$-(CH_2)_2CH_3$	$-C_6H_5$	-	NH. HCl	83	54
18	**9**	$-C_6H_4$(*p*-NMe_2)	$-(CH_2)_2CH_3$	-	NH. HCl	65	15
19	**10**	$-(CH_2)_2CH_3$	$-C_6H_3[-(CH_2)_4-]$	-	NH. HCl	73	40
20	**11**	$-C_6H_4$(*p*-OEt)	$-(CH_2)_2OH$	-	NH. HCl	94	23
21	**12**	$-C_6H_4$(*p*-NMe_2)	$-(CH_2)_2OH$	-	NH. HCl	80	15
22	**13**	$-(CH_2)_2OAc$	$-C_6H_3[-(CH_2)_4-]$	-	NH. HCl	87	59
23	**14**	$-C_6H_5$	$-C_6H_4$(*p*-OEt)	-	NH. HCl	87	21
24	**15**	$-C_6H_4$(*p*-NMe_2)	$-C_6H_5$	-	NH. HCl	70	18
25	**16**	$-C_6H_5$	$-C_6H_3[-(CH_2)_4-]$	-	NH. HCl	88	33

[a]Prepared from **2** using acetic anhydride (1.5 equiv), pyridine (3.0 equiv), DMAP (0.05 equiv) in CH_2Cl_2 over 2 h, 0 °C to rt.

Acknowledgements

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Supplementary Material

Supplementary material is available. Synthesis and spectroscopic data of all compounds prepared, and HPLC information of target compounds.