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Copper(II) chloride promoted transformation of amines into guanidines and asymmetrical *N,N′*-disubstituted guanidines

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ABSTRACT

We present a concise, less-toxic and broadly applicable method for coupling weakly nucleophilic amines with *N,N′*-di-(*tert*-butoxycarbonyl)thiourea, *N*-(*tert*-butxoycarbonyl), *N′*-alkyl/arylsubstituted-thioureas and *N,N′*-di-(*tert*-butoxycarbonyl)imidazolidine-2-thione in the presence of copper(II) chloride. Subsequent removal of Boc protecting groups affords guanidines, di-substituted guanidines and 2-aminoimidazolines in modest to excellent overall yields.

The guanidine functionality is present throughout nature, both in the amino acid arginine and many natural products. Its characteristic planar arrangement of a central carbon attached to three nitrogen atoms[1] attributes unique properties and chemistry. Guanidine is a superbase (pK_a 13.6),[2] can undergo π–cation interactions,[3] form salt bridges and donate hydrogen bonds. Its importance is illustrated by its presence in pharmacologically active molecules such as the natural product tetrodotoxin (sodium ion blocker)[4] and the commercially available therapeutics relenza (antiviral), famotidine (anti-ulcer) and clonidine (anaesthetic α2 adrenoceptor agonist) (Fig. 1).

We have been interested in the preparation of guanidine and 2-aminoimidazoline derivatives with varying pharmacological applications.[5,6] The synthetic approach involved the mercury(II) chloride promoted coupling of a primary aryl amine with either *N,N′*-di-(*tert*-butoxycarbonyl)thiourea to form guanidines, or *N,N′*-di-(*tert*-butoxycarbonyl)imidazolidine-2-thione to form 2-aminoimidazolines, as originally described by Kim and Qian[7] and by Dardonville and Rozas,[6] respectively. Generally, a thiourea bearing one or more electron-withdrawing groups is required for the reaction to proceed. Mercury(II) chloride is also necessary to promote the nucleophilic attack of the amine at the central carbon, by complexation to the thiourea sulfur atom.

The method works extremely well and despite the undesirable use of mercury salts, and the mercury-containing waste that ensues, it is the method of choice in late stage syntheses of guanidines, and is particularly useful when unreactive aryl amines need to be guanidylated. For example, in Du Bois' famous synthesis of (−)-tetrodotoxin, the guanidine is introduced in the penultimate step using $HgCl_2$ coupling of an amine and *N,N′*-di-(*tert*-butoxycarbonyl)thiourea, followed by Boc deprotection using trifluoroacetic acid.[8]

It is worth mentioning that none of the commercially available guanidine-containing drugs mentioned above (Fig. 1) use mercury(II) chloride in their synthesis, as it is not feasible for use on a large scale.

The synthesis of zanamivir (relenza, GSK) employs amidine sulfonic acid,[9] which is not successful with deactivated amines. The guanidine of famotidine is introduced using benzoyl isothiocyanate, which reacts with an aryl amine to give a benzoylthiourea,

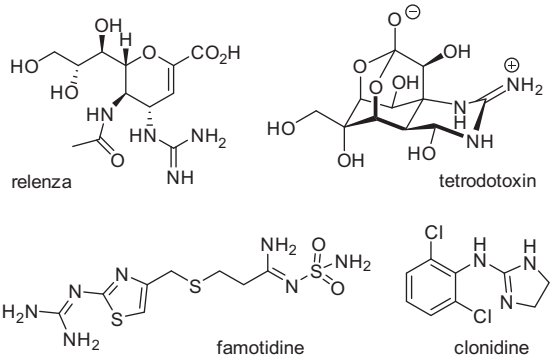

Figure 1. Structures of relenza, tetrodotoxin, famotidine and clonidine.

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which is subsequently *S*-methylated by methyl iodide and cleaved in two steps by ammonia to yield the guanidine.[10] The 2-aminoimidazoline moiety of clonidine is introduced from the corresponding aryl amine by first converting it into the thiourea using ammonium thiocyanate, then *S*-methylating with iodomethane and reacting with the powerfully nucleophilic ethylenediamine.[11] This is a clean synthesis but only works for the preparation of 2-aminoimidazolines and, like the synthesis of famotidine, still requires the use of light-sensitive and highly toxic iodomethane. Clearly, there is a need for safe and efficient syntheses of guanidines considering their potential as therapeutics and synthetically useful reagents.

While many methods exist for the introduction of the guanidine functionality, the prevailing problem is that they only work with aliphatic amines, and not with deactivated aryl amines. Mukaiyama's reagent[12] can also promote the coupling of amines with thiourea derivatives, while several reagents, such as protected pyrazole-1-carboximidamides, have a leaving group on a protected guanidine, which can react with amines yielding protected guanidines (Fig. 2).[9]

Thus, we sought to find a method which would allow the guanidylation of unreactive aryl amines without the need for mercury salts. The use of copper for guanidylation reactions has been explored by different authors. For example, Lai and co-workers used a CuI/*N*-methylglycine-catalysed reaction to couple guanidine nitrate with aryl iodides or bromides at 70–100 °C to afford symmetrical *N*,*N*′-diaryl guanidines with good to excellent yields.[13] Additionally, Terada and co-workers have reported, under mild conditions, the amination of *S*-methyl-*N*,*N*′-*bis*-Boc-isothiourea with either primary or sterically hindered secondary amines promoted by copper(I) chloride and K_2CO_3 resulting in *N*,*N*′-bis-Boc protected guanidines in good to excellent yields.[14]

During the synthesis of a related family of 1,4-dihydroquinazoline compounds,[15] copper(II) oxide was used in catalytic amounts as a desulfurizing agent to promote the intramolecular coupling of an aryl amine and *N*,*N*′-di-(*tert*-butoxycarbonyl)thiourea. With this in mind an investigation into the possibility of extending this methodology to intermolecular guanidine formation was undertaken. Under the same catalytic conditions, only trace amounts of product were isolated (<5%). Similarly, using a stoichiometric amount of copper(II) oxide gave very low yields (<5%). Use of a stoichiometric oxidant [*N*-methylmorpholine *N*-oxide (NMO)] was also attempted to examine if the catalytic species was being consumed in the reaction, but no yield improvements were observed. It seemed that a leaving group was required on the copper(II) species for the reaction to occur. Revisiting copper(II) chloride, which had been mentioned in Kim and Qian's original Letter,[7] but was thought to be less effective than mercury(II) chloride, the guanidylation of test compound aniline using stoichiometric copper(II) chloride and 2 equiv of Et_3N (Scheme 1) was effected in high yield (73%).

Notably, the yield matched exactly, published values for the same reaction promoted by $HgCl_2$ (73%).[5b] It should be noted that the commercially available *N*,*N*′-bis-(*tert*-butoxycarbonyl)-*S*-methyl isothiourea, which can often be used instead of *N*,*N*′-di-(*tert*-butoxycarbonyl)thiourea in $HgCl_2$ promoted guanidylations, was not successful when $CuCl_2$ was used. Besides, *N*,*N*′-di-(*tert*-butoxycarbonyl) thiourea (**1**) can be synthesised on large scale and in high yield (90%) from thiourea and di-*tert*-butyl dicarbonate.[16] To investigate the general applicability of this method (Scheme 1) different amines of varied reactivity were subjected to the conditions (Table 1).

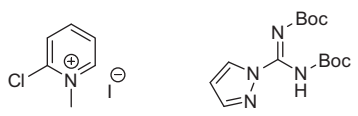
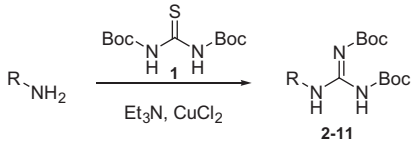


Figure 2. Reagents used in the synthesis of guanidines from aliphatic amines: Mukaiyama's reagent (left), and Boc-protected pyrazol-1-ylcarboximidamides (right).



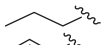
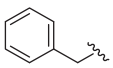
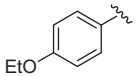
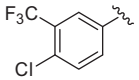
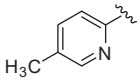
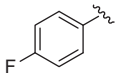
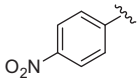
Scheme 1. General procedure for the guanidylation reaction of amines promoted by $CuCl_2$.

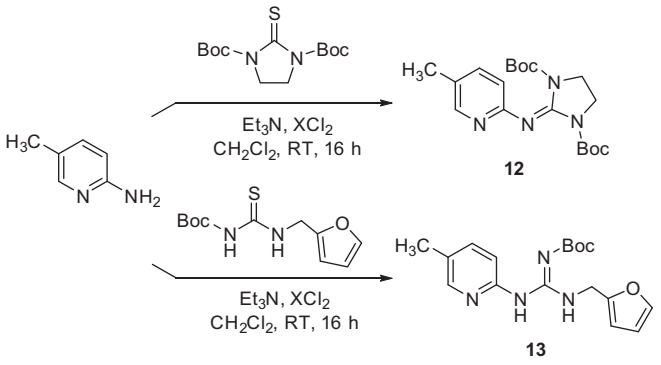
Where available, yields were compared to published values for the corresponding $HgCl_2$-promoted guanidylation. Reactions were carried out at room temperature in dichloromethane, but for more deactivated amines slightly more forceful conditions using dimethylformamide as the solvent and heating at 60 °C were employed, also yielding products in acceptable yields. It is worth noting that the guanidylation of *para*-nitroaniline to give **10**, which was not achieved in other studies, was accomplished using our method (41% yield). Furthermore, 4-aminopyridine was successfully guanidylated (26%) using $CuCl_2$ to give **11**, where this had not been possible in our hands with $HgCl_2$.

Based on these results we report that this method is at least as efficient and as high yielding as the $HgCl_2$-promoted guanidylation, and vastly more desirable as it obviates the need to use mercury salts. It is also applicable to both aliphatic and aryl amines, which are essential to its practicality.

Having shown that the method was successful in generating *N*,*N*′-di-Boc-protected guanidines we wanted to extend it to the synthesis of *N*,*N*′-di-Boc-protected 2-aminoimidazolines and

Table 1
$CuCl_2$ promoted coupling of amines with *N*,*N*′-di-(*tert*-butoxycarbonyl)thiourea (**1**). Published yields using $HgCl_2$ are given in parentheses

R	Conditions	Product	Yield (%)
	CH_2Cl_2, rt, 3 h	**2**	89
	CH_2Cl_2, rt, 3 h	**3**	89 (40)[17]
	CH_2Cl_2, rt, 3 h	**4**	83 (59)[18]
	CH_2Cl_2, rt, 5 h	**5**	76 (76)[19]
	CH_2Cl_2, rt, 16 h	**6**	73
	CH_2Cl_2, rt, 16 h	**7**	52
	CH_2Cl_2, rt, 16 h	**8**	67 (71)[19]
	CH_2Cl_2, rt, 16 h	**9**	62
	DMF, 60 °C, 16 h	**10**	41
	DMF, 60 °C, 16 h	**11**	26



Scheme 2. General 2-aminoimidazolidylation and *N*,*N*′-disubsituted guanidylation reactions of 2-aminopyridine (X = Hg or Cu).

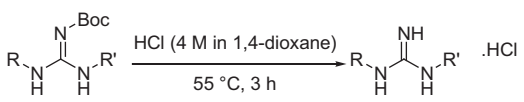
N-Boc-*N*′-substituted guanidines (as reported previously in our group).[20] The test amine was chosen as 2-amino-5-methylpyridine for both reactions as its use in the mercury-promoted guanidylation reaction gave moderate yields. Products **12** and **13** had previously been prepared in our group using $HgCl_2$ as the coupling agent (Scheme 2).

For both classes of reaction, favourable yields were obtained (Table 2). Using $CuCl_2$, **12** was obtained in almost exactly the same yield as the $HgCl_2$-promoted reaction, while for the formation of **13**, though the yield was low, it was slightly higher than for the analogous $HgCl_2$ reaction. This also proves that the method performs well for the coupling of troublesome amine and thiourea derivatives, allowing access to a wide range of guanidine-like compounds via this method.

The free guanidines, generally as their hydrochloride salt, are more useful pharmacologically, thus removal of the Boc groups was required. Previously, we carried out the deprotection of *N*,*N*′-di-Boc-protected guanidines and 2-aminoimidazolines by treatment with trifluoroacetic acid at room temperature overnight, followed by treatment with a basic anion exchange resin (Amberlite IRA-400) in its chloride activated form for 24 h.[5a] This lengthy procedure proved necessary as our experience of attempted deprotections in solutions of hydrochloric acid often led to hydrolysis of the guanidine moiety. For the compounds prepared in this work, deprotection was effected using HCl (4.0 M in dry 1,4-dioxane) (Scheme 3). The hydrochloride salts were obtained in good to excellent yields (80–100%) following reaction (6.0 equiv HCl per Boc group) for 3 h at 55 °C and removal of excess HCl and solvent under vacuum and purification of the salt using reversed phase silica chromatography with 100% H_2O as the mobile phase.

Table 2
Application of the $CuCl_2$-mediated coupling of 2-amino-5-methylpyridine with thiourea derivatives and comparison of the yields with $HgCl_2$ coupling

Coupling agent	Product	Yield (%)
$CuCl_2$	**12**	74
$HgCl_2$	**12**	75
$CuCl_2$	**13**	41
$HgCl_2$	**13**	32



Scheme 3. Deprotection of the Boc group to yield guanidine hydrochlorides.

Compared to the method developed by Lai and co-workers[13] the starting materials for our method, amino derivatives, are more readily available than the aryl halides used by them; their method did not give good results for heteroaromatic systems (they report only the reaction with 2-bromopyridine whereas, in this article, we report guanidylation of examples of 2-, 3- and 4-aminopyridines) and seems to work mostly for diarylation of guanidine. Compared to the guanidylation reported by Terada and co-workers[14] our method is more versatile since it requires the use of Boc-protected thioureas which can be aryl/alkyl substituted allowing the introduction of different substituents into the guanidinium system. As well, our conditions are milder (RT vs. 60 °C) and do not require an excess of the starting amines, base and copper reagent.

In conclusion, yields were on a par with the $HgCl_2$-promoted guanidylation to such a point that we now carry out these reactions with $CuCl_2$ instead of $HgCl_2$ in our laboratory, due to the cleanliness and reduced toxicity of the reagents involved. The relevant amines are readily available and the restrictions imposed by the necessary synthesis of the thiourea-containing reagent are minimal, being far outweighed by avoiding the use of mercury(II) salts.

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Supplementary data

Supplementary data associated with this article can be found, n the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.070.

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