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Novel linker for the solid-phase synthesis of guanidines

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Abstract: A novel linker for the generation of alkyl-, acyl- and arylguanidines as an attachment point in solid phase synthesis has been developed. Introduction of a suitably functionalized thiourea to Wang resin via a carbamate linkage, followed by displacement of sulfur with a 1° or 2° amine affords resin bound guanidines suitably protected for further manipulation. Activation of the thiourea with Mukaiyama's reagent allows for the generation of arylguanidines. Mild acid treatment effects deprotection and liberation from the resin to afford guanidines in good yield and high purity.

Keywords: Thioureas; Guanidines; Solid-phase synthesis; Combinatorial chemistry.

Methods for immobilizing compounds to solid phase for combinatorial chemistry initially relied upon traditional solid-phase peptide linkers.[1] More recently there has been a surge in "traceless linkers"[1] and immobilization techniques which ultimately afford residual functional groups not previously accessible such as hydroxamic acids,[2] sulfonamides[3] and olefins.[4] Given our interest in tryptic serine proteinases, we embarked on a program to develop a general, high yielding and robust method for generating guanidinium bearing compounds by solid-phase synthesis.

Several methods for generating guanidines both in solution phase and on resin bound amines have been reported. Perhaps the most straightforward and effective method is the reaction of a bis-carbamate protected thiourea with a 1° or 2° amine.[5,6] In addition, the thiourea can be activated with silver or mercury salts,[7] or with Mukaiyama's reagent[6] for reactions with less nucleophilic amines. Herein we report a solid-phase linker which affords a residual guanidine moiety, derived from a 1°, 2° or aryl amine, suitably protected so as to be stable to a variety of synthetic transformations and yet liberated from the resin under mild conditions. The recent reports of a sulfonamide-based linker for the side chain immobilization of arginine,[8] the solid-phase synthesis of trisubstituted guanidines[9] and the functionalization of resin bound amines with *N,N'*-bis(*tert*-butoxycarbonyl)thiourea mediated by Mukaiyama's reagent[6] prompted us to report our findings.

The carbonylimidazole resin **1** was prepared from Wang resin (Colorado Biotechnology, 0.96 meq/g), as previously described.[10,11] In one pot, thiourea was deprotonated with two equivalents of sodium hydride, treated with the carbonylimidazole resin **1**, and then capped with *N,N''*-di-*tert*-butyldicarbonate to afford **2** (Scheme 1). Initially, the reactivity of **2** was checked with the set of amines shown in Scheme 1. The primary and secondary amines were found to react smoothly with the resin bound bis-urethane protected thiourea (**2**) and to afford, after

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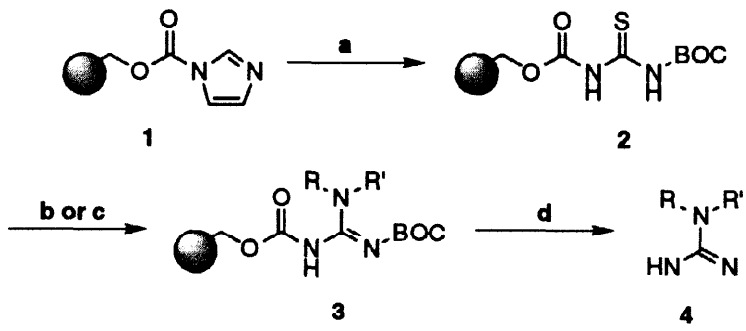
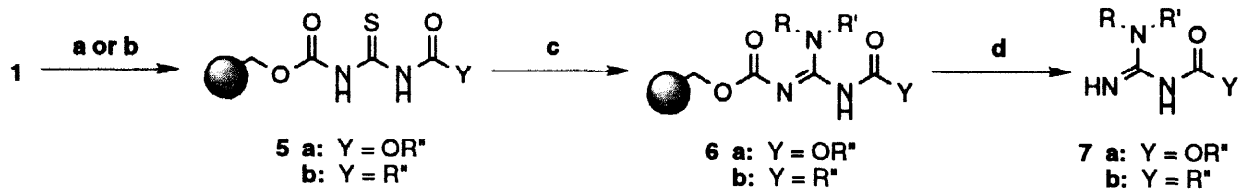
cleavage from the resin with CH_2Cl_2/TFA/$^iPr_3SiH$ (49:49:2), [12, 13] the desired guanidines **4** in greater than 85% yield and 90% purity.[14] We have examined the coupling of resin **2** with a more extensive set of forty primary and secondary amines (data not shown), and have found all to afford the desired product in good yield and purity. In the case of aryl amines, activation of the thiourea **2** with Mukaiyama's reagent[6] allowed for ready formation of aryl guanidines **4** (R = Ar) albeit in only fair yield (40-50%).[14]



RR'NH = benzylamine; *N*-benzylmethylamine; 4-benzylpiperidine; aniline; *N*-methylaniline.

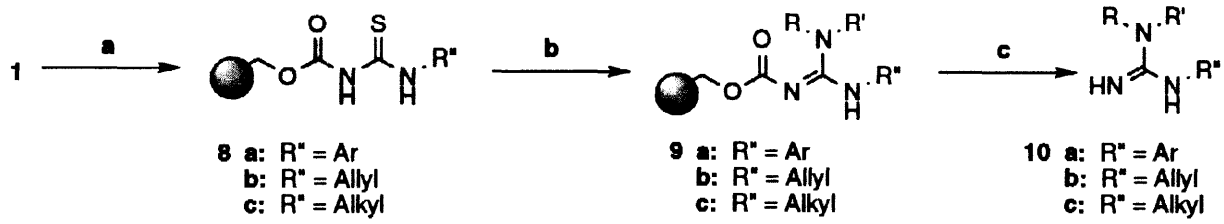
Scheme 1: a) (i) Thiourea, NaH, THF, (ii) **1**, THF, (iii) $(BOC)_2O$, THF; b) RR'NH (3 eq.), Et_3N, NMP or CH_2Cl_2; c) ArR'NH, 2-chloro-1-methylpyridinium iodide, Et_3N, NMP; d)TFA, $^iPr_3SiH$, CH_2Cl_2.

Mixed acyl/alkyl bis-substituted guanidines may also be accessed via this method (Scheme 2). By substituting a chloroformate (e.g. CbzCl) for $(BOC)_2O$, a mixed bis-urethane, resin bound thiourea **5a** (Y = OR") may be obtained (Scheme 2). Similarly, treatment of readily available acylthioureas (e.g. $AcNHC(S)NH_2$) with sodium hydride, followed by addition to the resin **1** affords the resin bound acylthiourea **5b** (Y = R"). For example, the resin **5b** (Y = Me) reacts efficiently with the set of forty primary and secondary amines to afford, after acid cleavage, the acyl/alkyl bis-substituted ureas **7b** (Y = Me) in >95% purity.[14]



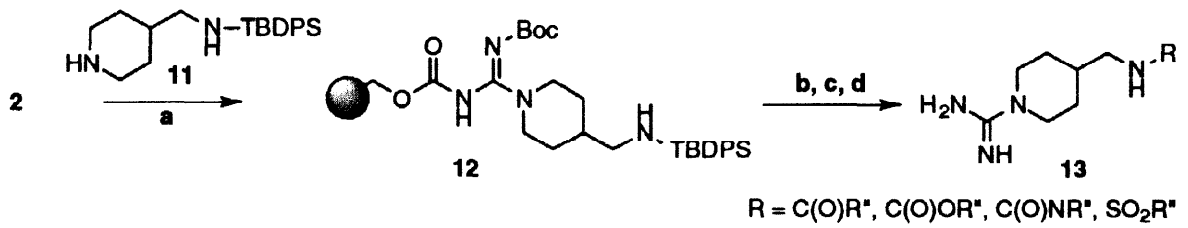
Scheme 2: a) (i) Thiourea, NaH, THF, (ii) **1**, THF, (iii) R"OC(O)Cl, THF; b) (i) $R"C(O)C(S)NH_2$, NaH, THF, (ii) **1**, THF; c) RR'NH (3 eq.), Et_3N, NMP; d) TFA, $^iPr_3SiH$, CH_2Cl_2.

Aryl-, allyl- or alkylthioureas can also be deprotonated and added to the resin **1** to afford the resin bound thioureas **8a**, **8b** and **8c** (R" = Ar, Allyl, Alkyl) (Scheme 3). Activation of the resulting mono-urethane thioureas **8** with EDC[15] and, reaction with primary and secondary amines affording the resin bound intermediates **9a**, **9b** and **9c**. Mild acid treatment cleanly delivers the bis-substituted guanidines **10a**, **10b** and **10c**. (R" = Ar, Allyl, Alkyl). Again, the forty amines were found to cleanly deliver (>95% purity) the desired product upon reaction with **8a** and **8b** (R" = Ph and allyl, respectively).[14]



Scheme 3: a) (i) $R"NC(S)NH_2$, NaH, THF, (ii) **1**, THF; b) RR'NH (3 eq.), Et_3N, EDC, NMP; c) TFA, $^iPr_3SiH$, CH_2Cl_2.

Having established a robust method for the generation of a variety of guanidines by solid-phase synthesis, we turned our attention to the compatibility of this linker strategy with other synthetic transformations. Reaction of the thiourea resin **2** with the *tert*-butyldiphenylsilyl protected[15] diamine **8** cleanly afforded **9** (Scheme 3). Cleavage of the silyl protecting group was readily accomplished with 3HF•Et_3N or HF•pyr in THF without noticeable diminution of resin loading, as judged by final yield of the cleaved products. The resulting primary amine may be readily functionalized with a variety of acylating and sulfonylating agents. Mild acid cleavage then afforded **10** in good yields and purity.[14]



Scheme 4: a) **11**, Et_3N, NMP; b) 3HF•Et_3N, THF; c) R"C(O)Cl, R"OC(O)Cl, R"NCO or $R"SO_2Cl$, NMM, CH_2Cl_2; d)TFA, $^iPr_3SiH$, CH_2Cl_2.

In conclusion, we have developed a robust and efficient method of generating a wide variety of guanidines by solid phase synthesis employing a novel guanidine generation/linker strategy.

References and Notes

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12. Higher percentage TFA resulted in decomposition of guanidines derived from secondary amines as evidenced by the presence of the secondary amine in HPLC, ES MS and NMR.
13. Deprotection of *N,N'*-bis(*tert*-butoxycarbonyl)guanidines with $SnCl_4$ has recently been reported. See: Miel, H.; Rault, S. *Tetrahedron Lett.* **1997**, *38*, 7865-7866.
14. Percent yields were determined by weight of the product relative to the loading of the original Wang resin. Purity was assessed by reverse phase HPLC, monitoring at 220 and 254 nm. All reaction products afforded ^{1}H and ^{13}C NMR, and positive ion ES MS consistent with the desired product.
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