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A Traceless Linker Approach to the Solid Phase Synthesis of Substituted Guanidines Utilizing a Novel Acyl Isothiocyanate Resin

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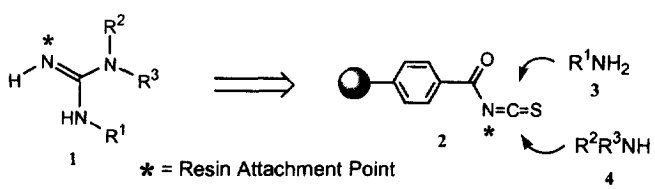
Abstract: *Solid phase synthesis of a series of substituted guanidines based on a novel acyl isothiocyanate resin is presented. This method provides both mono and disubstituted guanidines with a variety of sterically demanding and/or electron withdrawing substituents in good purities and yields.* © 1999 Elsevier Science Ltd. All rights reserved.

Key Words: solid phase synthesis, guanidines, EDC, combinatorial chemistry, isothiocyanate.

Solid supported combinatorial chemistry methods have proven to be useful for small molecule based library construction.[1] Substituted guanidine compounds (**1**) are well known to be responsible for the basis of a variety of pharmacological responses (*e.g.* anti-hypertensive, cardiotonic, H_2 antagonist/agonist, adrenoreceptor agonists, H+/K+ ATPase inhibition, NO synthase inhibition, anti-tumor activity) and there are several classical examples which have resulted in marketed drug substances.[2] For these reasons we became interested in devising a resin based route to this class of compounds that would be general enough to provide access to a variety of different types in this series via a traceless linker strategy.[3-5] Furthermore, we wanted an approach that would allow us to take advantage of the large number of commercially available and diverse amine-based building blocks (**3** and **4**) in both the aliphatic and aromatic categories (>2,000). We envisioned that an acyl isothiocyanate resin (**2**) would furnish the core guanidine attached directly to the resin thereby circumventing the need for a functional handle for resin attachment. This would be distinctly different than similar resin based guanidine synthetic methods since it would utilize a novel resin intermediate (*i.e.* **2**) in combination with an optimal choice of building block combinations (as both synthetic inputs) leading to a more diverse potential product portfolio.[6,7]



Resin bound isothiocyanates such as **2** should be highly reactive towards amines of all types, including those with very low nucleophilicity due to steric and electronic factors.[8] Amine addition to the acylated thiourea (**2** to **6**, Scheme 1) followed by subsequent amine condensation to an N-acyl guanidine (**6** to **7**) would furnish the guanidine compounds upon cleavage.[9] The benzoylated isothiocyanate (**2**), was chosen for the ability to act as an electron-withdrawing substituent, ease of formation, and stability of the acyl linkage and herein we report the first synthesis of this resin.[2a,3d,4d,10] Treatment of

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# Dedicated to the memory of our friend and colleague Hoang Do.

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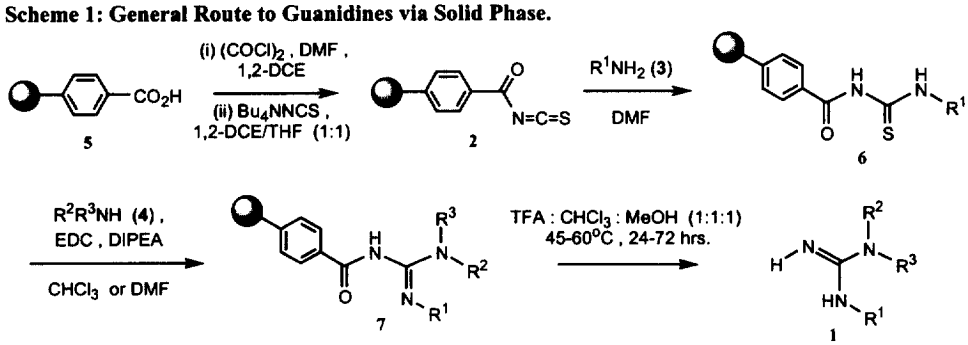
carboxypolystyrene (**5**) with oxalyl chloride (2.5 equiv.) and N,N-dimethylformamide (5% by volume) in 1,2-dichloroethane produces the acyl chloride, which is then followed by displacement with tetrabutylammonium thiocyanate in THF and 1,2-dichloroethane (1:1) to provide the target resin.[11] The appearance of strong and distinctive bands at 1970 cm^{-1} (N=C=S) and 1700 cm^{-1} (C=O) in the infrared spectrum confirms the assigned structure.

This precursor (**2**) is suitably activated to undergo addition reactions with a variety of amines (**3**) to form the corresponding acyl thioureas (**6**) under extremely mild conditions (monitored by the disappearance of the isothiocyanate band in the infrared spectrum). Even relatively hindered non-nucleophilic amines such as 2,6-dichloroaniline react suitably with this resin at ambient temperature. In the second step, resin bound guanidine formation is promoted through desulfurization with a suitable reagent in the presence of base.[3,7,9] Several reagents (diisopropyl carbodiimide (DIC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), Mukaiyama's reagent) were investigated, and all were found to facilitate the reaction. However, we found that EDC in either DMF or chloroform in the presence of Hunig's base (diisopropylethylamine, DIPEA) provided the best results. Reaction of the resin bound acyl thioureas with EDC and a second amine (**4** - can be either primary or secondary), resulted in the formation of the resin bound guanidine (**7**). At this stage we noticed the following exception: when either secondary amines or ammonia were utilized in the first step, although the formation of the thiourea (**2** to **6**) was successful, the subsequent reaction (**6** to **7**) failed to form the guanidine compounds upon reaction with EDC.[9d] This is consistent with the formation of an intermediary disubstituted acyl carbodiimide.[3b,9d] Cleavage of the acyl guanidine (**7**) was effected by treatment with trifluoroacetic acid (in $CHCl_3$ and MeOH (1:1:1)) at slightly elevated temperatures.[2a,3d]

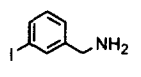
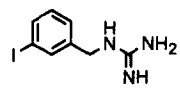
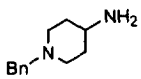
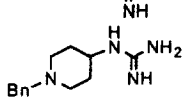
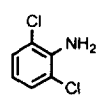
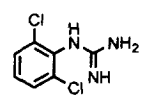
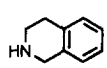
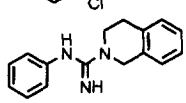
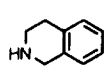
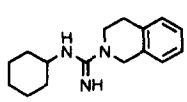
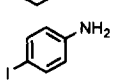
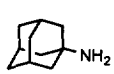
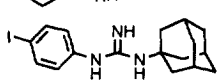
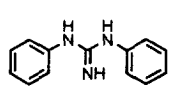
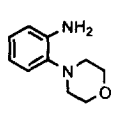
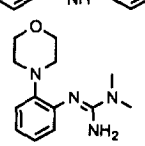
Scheme 1: General Route to Guanidines via Solid Phase.



Due to the general nature of the method, and to the large and diverse set of commercially available building blocks, we could easily benchmark the procedure with a resin based synthesis of several pharmacologically relevant and commercially available guanidines (Table 1). This allowed us to readily evaluate the potential of this procedure. The anti-tumor agent *m*-iodobenzyl guanidine (entry 1)[2d,12a], a potent sigma receptor antagonist (N-*p*-iodophenyl-N'-adamantyl guanidine, entry 6)[12b], and the insulin secretagogue N-(2-morpholino)phenyl-N',N'-dimethyl guanidine (**BTS 67,582**, entry 8)[2c] were all synthesized in good purities (>80%) and yields for the five step process (> 80% per step).

These examples, along with others illustrate the wide range of amine types we could utilize (Table 1).[13] For example, monosubstituted aryl and alkyl guanidines were synthesized (entries 1-3) by utilizing ammonia in the second step. In the case of disubstituted molecules, many examples of combinations of amine types were successful (entries 4-8), including aryl-alkyl (entries 4,6,8), aryl-aryl (entry 7), and alkyl-alkyl (entry 5). Most notable are the examples including electron withdrawing and sterically demanding substituents (entries 3 and 6).

Table 1: Guanidine Products and Yields from Scheme 1.[12,13]

Entry	R^1NH_2 (3)	R^2R^3NH (4)	Guanidine (1) [a]	Purity (%, ELS) [b]	Yield (%) from 5 [c,d]
1		NH_3		88	40 (83) [12a]
2		NH_3		85	42 (84)
3		NH_3		90	48 (86)
4				82	38 (83)
5				97	46 (85)
6				89	53 (88) [12b]
7				90	47 (86) [12c]
8		Me_2NH		84	74 (94)

[a] Isolated as the trifluoroacetic acid salts. [b] Refers to HPLC purity of crude reaction mixture after cleavage determined by evaporative light scattering (ELS) detection methods. Peak assignments based on isolated products and tandem HPLC-MS analysis. [c] Yield of purified compound from carboxypolystyrene (**5**) upon column chromatography for the five step process. All were >97% pure by HPLC after purification. Calculated as mono trifluoroacetic acid salts. [d] Yield per step in parenthesis.

In conclusion, we have provided general methodology to produce a number of diverse guanidine compounds utilizing a novel acyl isothiocyanate resin (**2**). We are currently utilizing this method for the production of libraries of these types. We are evaluating other acyl isocyanate linker types in this strategy, and looking at utilizing the acyl isothiocyanate resin for other scaffolds.

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11. Preparation of **2**: 850 mg of Carboxypolystryene (Advanced Chemtech, Louisville, Ky.; loading = 0.7 mmol/g) was swelled with anhydrous 1,2-dichloroethane (1,2-DCE; 2 X 10 mL), followed by the addition of 10 mL of 1,2-DCE, 0.5 mL of dimethylformamide, and 0.75 mL of oxalyl chloride/dichloromethane solution (added slowly over 5 minutes; 2M, Aldrich). After initial bubbling had subsided the vessel was agitated for 8 hours. After filtration, the process was repeated again overnight (14 hours). The resin was washed with 1,2-DCE (3 X 10 mL), and charged with Bu_4NNCS in 1,2-DCE/THF (1:1) solution (1.2 g in 10 mL), followed by shaking for 4 hours. This was repeated for another 5 hours, and the resin was washed (3 X 10 mL of THF; 3 X 10 mL of 1,2-DCE), followed by drying under nitrogen. Physical Data for **2**: IR (cm^{-1}): 3040, 2930, 1970 (N=C=S), 1700 (C=O), 1600, 1500, 1450, 1250, 1170, 1070, 1030, 910.
12. These compounds were identical by HPLC and TLC with authentic samples which were purchased from their corresponding vendors: (a) entry 1 - Sigma #I9890; (b) entry 6 - ICN #158938; (c) entry 7 - Aldrich #D20,775-6.
13. All guanidine products (**1**) in Table 1 were purified by flash column chromatography on silica gel and gave satisfactory ^1H NMR, ^{13}C NMR, ^{19}F NMR, MS, and HPLC spectra.