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Solid Phase Synthesis of Oligomeric Guanidiniums

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Abstract: Oligomers containing guanidinium linkages prepared via solid phase organic synthesis are of interest as possible therapeutic agents and in the assembly of supramolecular architectures. Efficient routes to these oligomers must be developed before their potential may be fully realized. Herein, four routes for their stepwise solid phase synthesis are described. In the first, a resin-bound thiourea was converted to a guanidinium using 2-chloro-1-methylpyridinium iodide. The second method utilized aza-Wittig couplings to prepare guanidiniums from resin-bound carbodiimides. Next, highly activated monomers prepared from bis-*tert*-butyloxycarbonythioureas and 2,4-dinitrofluorobenzene formed guanidiniums upon reaction with terminal amines. The optimum route, however, relied upon the 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride promoted coupling of a protected thiourea monomer with a resin-bound amine to produce the guanidinium linkage. The thiourea monomers for this method are easily prepared from mono-protected diamines and benzoyl- or Fmoc-isothiocyanate. The procedure is straightforward, proceeds cleanly in a relatively short period of time, and is compatible with several functional groups.

Keywords: Solid-phase synthesis; guanidines; thioureas; molecular recognition

INTRODUCTION

A growing number of synthetic oligomers have been prepared via solid phase synthesis in recent years.[1] The majority of these oligomers maintain the amide bond for which solid phase synthesis was originally developed.[2] These include polyamide nucleic acids (PNA),[3] peptoids,[4] β-peptides,[5] aedamers,[6] and pyrrole-imidazole polyamides.[7] More recently, oligomers containing unnatural linkages such as carbamates,[8] ureas,[9] thioureas,[10] isoxazolines,[11] azatides,[12] and sulfonopeptides[13] have been reported. These oligomers have been studied as antisense/antigene agents (PNA,[14] pyrrole-imidazole polyamides[15]), as synthetic ligands for biological receptors, antibodies, and peptides (peptoids,[16] carbamates,[8] ureas,[17] vinylogous sulfonyl peptides[18]) in the formation of novel secondary structures (β-peptides[19]), and as DNA intercalators (aedamers[20]).

The guanidinium group is of interest due to its biological activity, hydrogen bonding capabilities, stability, and positive charge integrity over a wide pH range.[21] The guanidinium functional group occurs naturally in guanine and arginine. Its molecular recognition features are used for DNA base pairing and in the active sites of many enzymes. Guanidiniums have recently been used to study the mechanism of phosphodiester hydrolysis, as anion receptors in synthetic sensors, and in the formation of novel secondary structure elements.[22] Guanidiniums are often synthesized from thioureas. Since we have prepared oligomeric thioureas via solid phase synthesis,[10] a natural extension of this work was the solid phase synthesis of

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oligomeric guanidiniums.

The growing interest in oligomeric guanidiniums may be gauged by the recent publication of a number of solid phase routes to terminal mono-, di-, and tri-substituted guanidiniums.[23] Novak has investigated the secondary structure of polymeric guanidines and Kagechika has studied the DNA binding of aromatic layered guanidines.[24] Bruice has prepared an oligonucleotide containing four guanidinium linkages in solution and studied its properties as an antisense/antigene agent.[25] He also published a method for the solid phase synthesis of guanidinium linked oligodeoxyribonucleotides (ODNs) based on a mercuric chloride desulfurization of protected thioureas.[26]

Due to the high nucleophilicity of a guanidine and the possibility of extensive hydrogen bonding networks in oligomers, we anticipated the solid phase synthesis of oligomeric guanidiniums would be challenging. In Figure 1, we present solutions to their preparation using Mukaiyama's reagent (Method A), aza-Wittig couplings (Method B), Sanger's reagent (Method C), and EDC couplings (Method D).

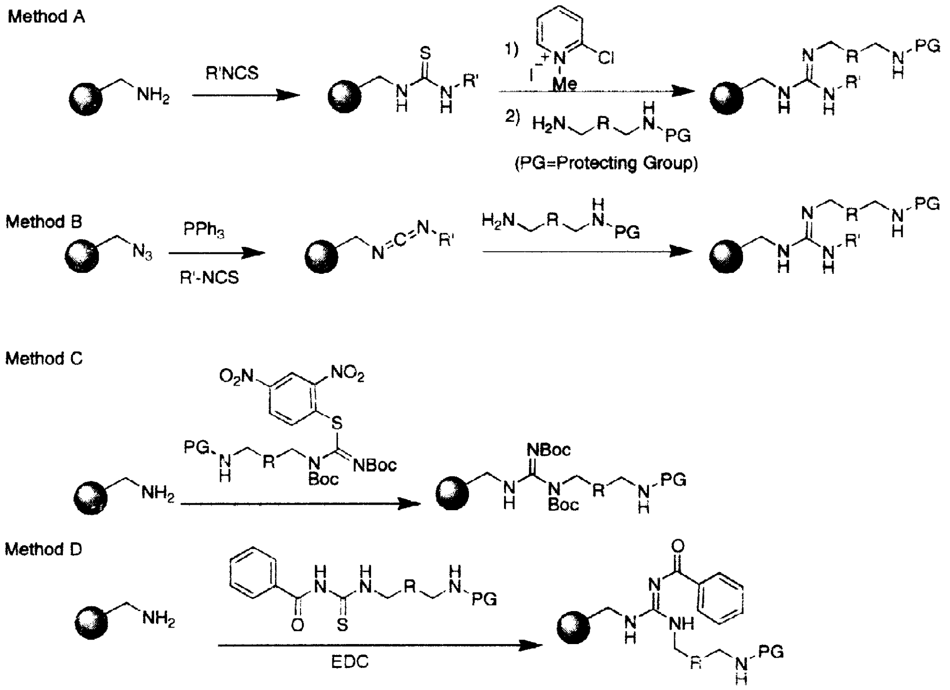


Figure 1. Four methods to form guanidinium linked oligomers on the solid phase: Method A: Mukaiyama's reagent; Method B: aza-Wittig coupling; Method C: Sanger's reagent; Method D: EDC coupling.

RESULTS AND DISCUSSION

A. Retrosynthetic Analysis

Numerous methods exist to prepare guanidiniums in solution. One of the most common is the reaction of *S*-alkylthiouronium salts with ammonia or an amine (Figure 2a).[27] Thioureas have also been activated by oxidation with hydrogen peroxide or peracetic acid (Figure 2b).[28] Inorganic thiophiles such as mercuric chloride, mercuric oxide, and lead oxide have been used to eliminate hydrogen sulfide from thioureas to form carbodiimides, which then react with amines (Figure 2c).[29] Ureas have been used to prepare guanidiniums using both phosgene and Burgess' reagent (Figure 2d).[30] Other non-thiourea methods for synthesizing guanidiniums include the use of cyanamides and reagents based on 1-*H*-pyrazole-1-carboxamidine hydrochloride (Figure 2e).[31]

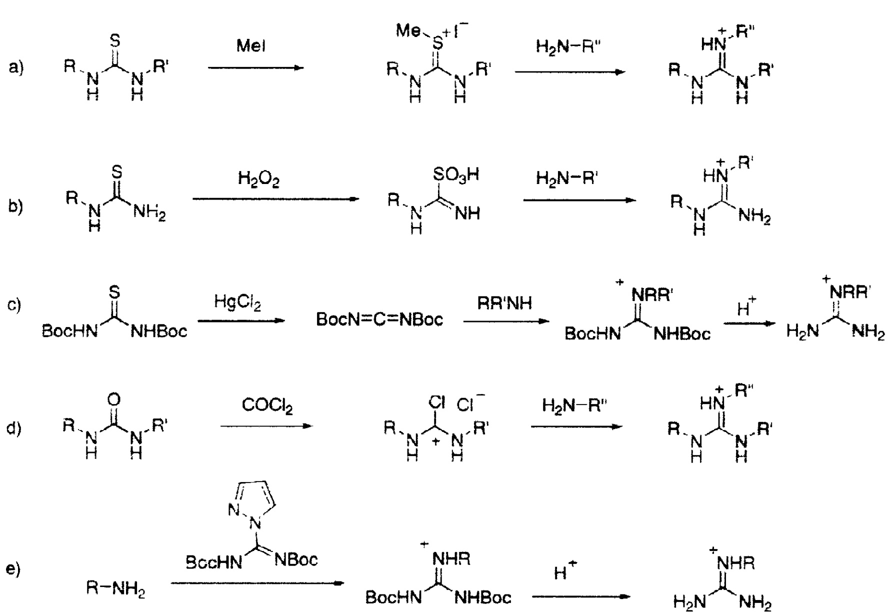


Figure 2. Standard methods to prepare guanidiniums in solution.

Two general approaches for the formation of guanidinium linked oligomers are shown in Figure 3. Terminal resin-bound moieties could be prepared on the solid phase that would then be converted into guanidiniums upon the addition of mono-protected diamine monomers. Alternatively, activated monomers could be synthesized that would form guanidiniums upon reaction with resin-bound amines. Both approaches were investigated. However, the latter method was most appealing because it allowed the reactions to be monitored by the Kaiser test.[32] There was also concern that the activation of resin-bound sites, such as the alkylation of resin-bound thioureas, might interfere with other functional groups present in the oligomer. Of the numerous methods in the literature for forming guanidiniums in solution, those that gave low to moderate yields, or required long reaction times or harsh conditions were eliminated from consideration. These were assumed to be unsuitable for solid phase synthesis. Lead and mercuric oxides and chlorides were not investigated in detail due to the limited solubility and toxicity of both the reagents and the byproducts. Phosgene and thiophosgene were also ruled out due to toxicity.

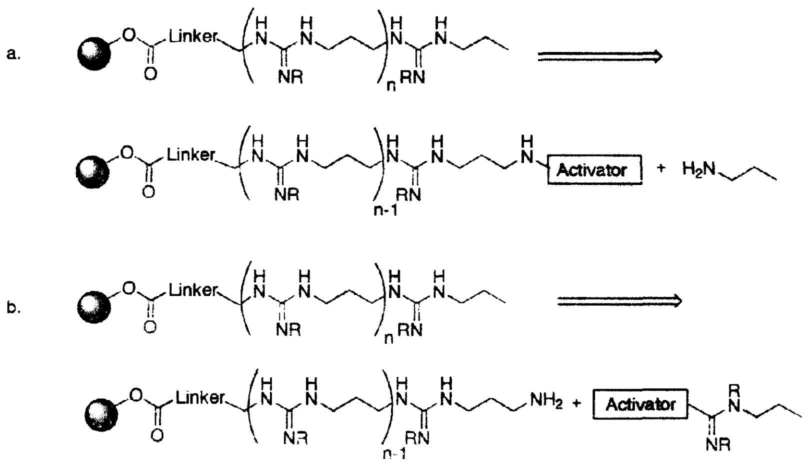


Figure 3. Retrosynthetic analysis for the formation of guanidiniums on the solid phase using a) an activated resin or b) an activated monomer.

B. Choice of Resin, Linker, and Protecting Groups

Several considerations were necessary in addition to the guanidinium formation. Resins, linkers, and protecting groups were needed that were compatible with each other and with the guanylation method. Though Merrifield resin was used initially, we soon switched to Wang resin due to the ease of cleavage from the resin with trifluoroacetic acid (TFA) and since Boc-protected guanidiniums could be deprotected at the same time. Wang resin was purchased preloaded with phenylalanine as a convenient handle.

The synthesis of guanidinium linked oligomers also required a rigid spacer between the resin-oligomer ester linkage and the first guanidinium. In acid, a guanidinium nitrogen δ to an ester or amide carbonyl can cyclize via an "Edman-like" degradation (Figure 4a).[33] Thus for Merrifield resin and acid labile Boc protecting groups to be used, a rigid spacer was needed to prevent cleavage from the resin during the deprotection; *p*-aminomethylbenzoate was chosen (Figure 4b). When acid sensitive Wang resins were used and TFA cleavage protocols were followed, the rigid spacer was only needed to prevent cyclization of the final product. Though this cyclization was generally not desired, due to the formation of two constitutional isomers, it may have applications in combinatorial libraries. We now use a commercially available 2-chlorotrityl resin that is preloaded with the desired rigid *p*-aminomethylbenzoate linker and is easily cleaved with 5% TFA in dichloromethane.

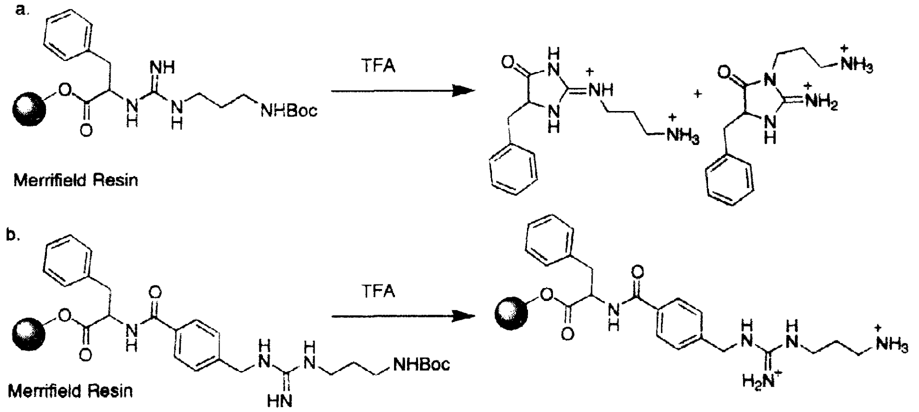


Figure 4. a) Guanidinium nitrogen's δ to an ester or amide carbonyl cyclize under acidic conditions. b) A rigid linker prevents this cyclization.

Two types of orthogonal protecting groups were needed for our synthesis. The solid phase synthesis of linear oligomers requires mono-protected bifunctional monomers. We intended to use Boc or Fmoc wherever possible to protect the *N*-terminus since we desired this method to be fully compatible with standard automated synthesis. While developing monomers for use with Sanger's reagent and EDC we also incorporated azido and phthalimido masked amines.

As with peptide and oligonucleotide solid phase synthesis, the guanidinium groups also required protection so they could not participate as nucleophiles during chain elongation. Boc, Fmoc, benzoyl, and veratryl protecting groups were considered for this purpose. Boc and benzoyl protecting groups are well precedented in this capacity.[34] These guanidinium protecting groups also serve a second purpose, that of facilitating guanidinium formation since their electron withdrawing character helped to further activate carbodiimide and alkylated thiourea intermediates toward nucleophilic attack. It was also anticipated that Fmoc and veratryl protecting groups could be introduced into thiourea precursors from the corresponding isothiocyanates. Fmoc would be removed via standard conditions of 20% piperidine in dimethylformamide (DMF). Based on previous experience with amidines, we anticipated that the veratryl group could be removed with TFA.[35]

C. Monomer Synthesis

Simple monomers that could rapidly be produced from commercially available diamines and their derivatives were used to develop this methodology. For methods A and B, which involved activation of the resin, the only monomer needed was a mono-protected diamine. To this end, sodium azide was used to convert 3-bromopropylamine hydrobromide to the mono azide derivative.[36] Several mono-protected diamines are now commercially available as well. Approaches that used activated thiourea monomers (Methods C and D), required initial protection of the *N*-terminus followed by formation of the activated thiourea. The syntheses of these monomers are discussed below.

D. Solid Phase Synthesis

Initial efforts involved the alkylation of thioureas with alkyl halides to activate the thiourea toward reaction with the resin. Benzyl thioureas were alkylated with methyl iodide, ethyl bromide, and benzyl bromide (Figure 5a). None reacted adequately with resin bound amines. The corresponding bis-Boc-protected thioureas were prepared but also failed to react (Figure 5b). Carbodiimide monomers were prepared and found to be ineffective as well (Figure 5c). Thus, the challenge was to find groups sufficiently activated for efficient couplings.

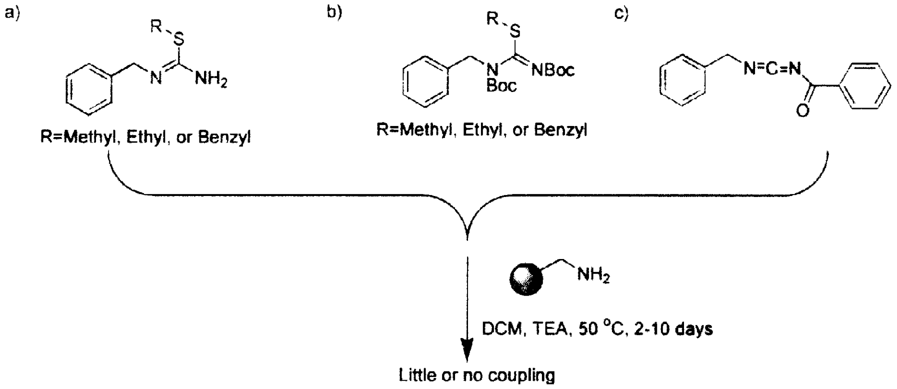


Figure 5. Monomers which failed to react with resin bound amines.

Four methods were chosen as candidates for the preparation of oligomeric guanidiniums due to their demonstrated use in solid phase synthesis or their rapid reaction in solution without insoluble by-products or harsh conditions. 2,4-Dinitrofluorobenzene (Sanger's reagent)[37] and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)[22d,33,38] were demonstrated to efficiently form disubstituted guanidiniums in solution and were compatible with solid phase synthesis. 2-Chloro-1-methyl-pyridinium iodide (Mukaiyama's reagent)[23g] and aza-Wittig couplings[23c-d] were shown to form terminal guanidiniums on the solid phase, and needed only to be adapted to the synthesis of oligomeric guanidiniums. Compounds prepared by these four solid phase methods are shown in Table 1.

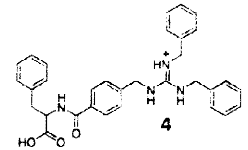
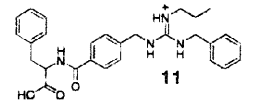
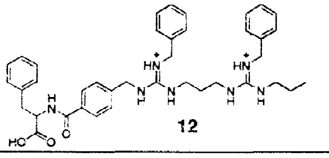
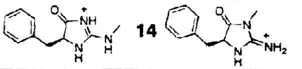
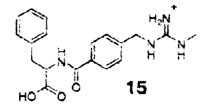
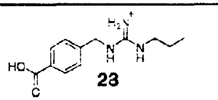
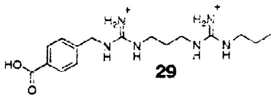
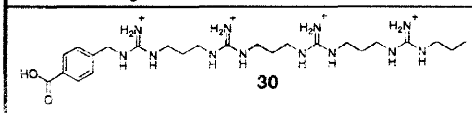
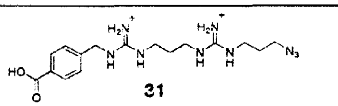
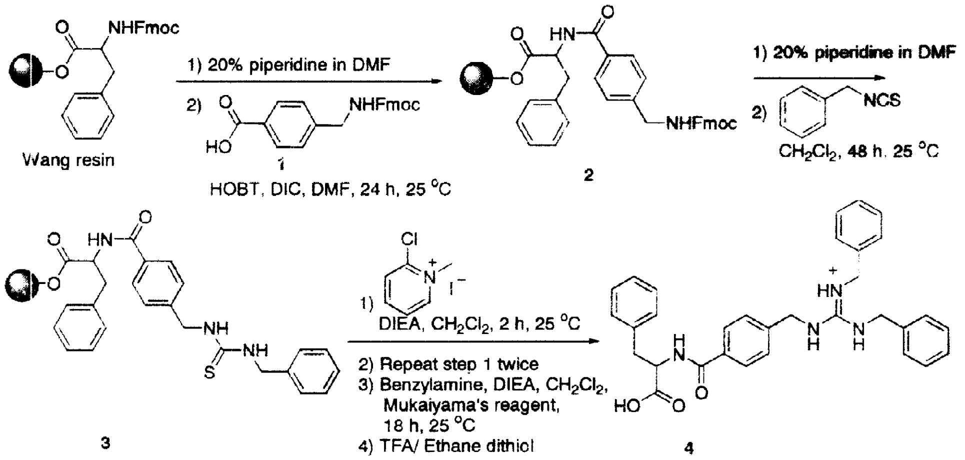
Oligomer	method	overall yield (%)
 **4**	A	59
 **11**	B	55
 **12**	B	<5
 **14**	C	28
 **15**	C	84
 **23**	D	84
 **29**	D	58
 **30**	D	26
 **31**	D′	13

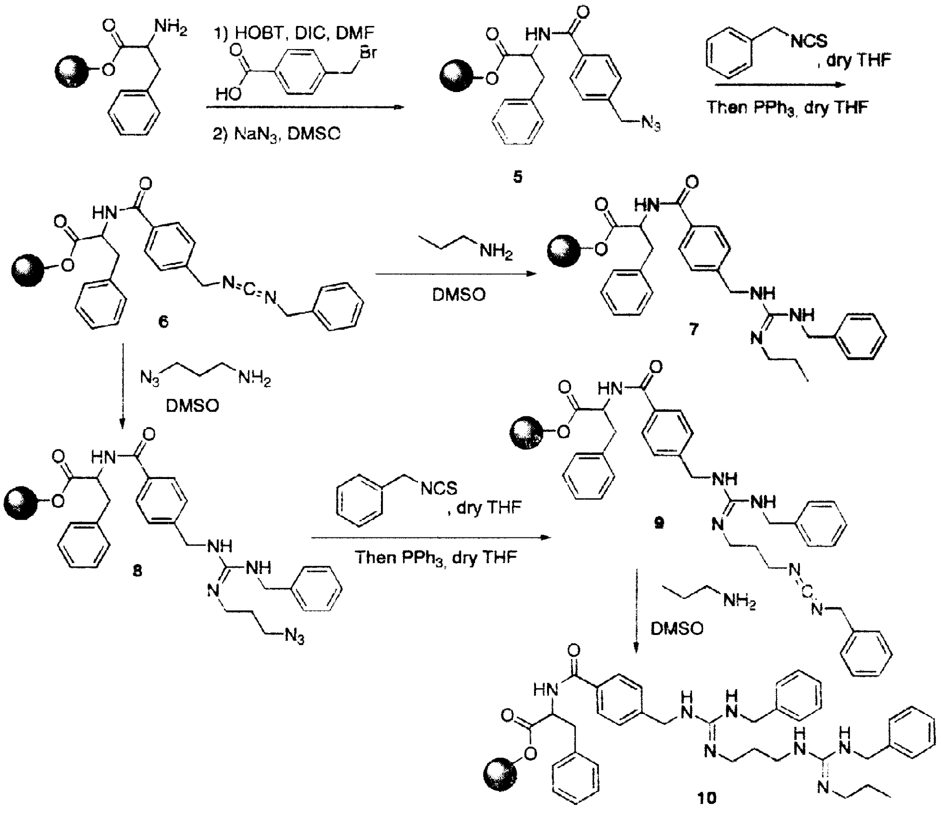
Table 1. Guanidinium linked oligomers prepared via four methods. Method A: Alkylation of resin bound thioureas with Mukaiyama's reagent; Method B: Aza-Wittig coupling; Method C: Thiourea monomers activated with Sanger's reagent; Method D: EDC coupling with benzoyl protected thioureas (or Fmoc protected thioureas for Method D′).

D.1. Method A. Lipton and coworkers reported the solid phase synthesis of protected monosubstituted guanidines using *N*,*N*′-bis-*tert*-butyloxycarbonylthiourea and Mukaiyama's reagent.[23g] Our attempts to use this method resulted in low yields and complications due to reaction of the reagent with resin-bound amines. Instead, we attached linker **1** to NH_2-Phe-Wang resin and then prepared resin-bound thiourea **3** in dichloromethane (DCM) using benzyl isothiocyanate as a model for protection with veratryl isothiocyanate (Scheme 1). Guanidiniums were to be generated by first alkylating **3** with Mukaiyama's reagent and subsequently adding an amine monomer. However, when **3** was only treated once with Mukaiyama's reagent, the major product after cleavage and isolation, was the corresponding unreacted thiourea. To alleviate this problem, **3** was alkylated three times with Mukaiyama's reagent prior to the addition of benzylamine. Subsequent cleavage with TFA produced monoguanidinium **4** in 59% yield. Attempts to form a bis-guanidinium oligomer were inconsistent. The reactions appeared successful by the Kaiser test but the desired products could not be isolated; possibly due to reaction of the first guanidine with Mukaiyama's reagent. Further studies with veratryl isothiocyanate were not performed.



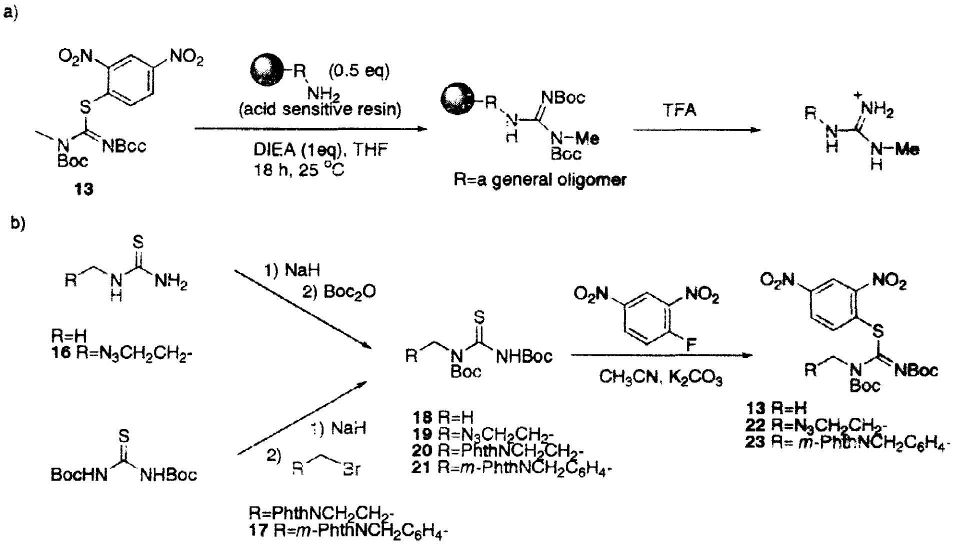
Scheme I. SPOS of guanidiniums using Mukaiyama's reagent.

D.2. Method B. Two groups have reported the use of aza-Wittig couplings between resin-bound iminophosphoranes and aryl isocyanates or aryl isothiocyanates to form resin-bound carbodiimides.[23c-d] These carbodiimides formed tri-substituted monoguanidiniums when allowed to react with secondary amines. Attempts to modify these methods to form oligomeric disubstituted guanidiniums were made. To switch from tri-substituted to di-substituted guanidiniums an isothiocyanate containing a removable guanidinium protecting group was desired. Chain elongation was accomplished using bifunctional, protected monomers. Drewry *et. al.* noted that the reaction was dependent on the electronic and steric nature of the isothiocyanate and halocarboxylic acid used, but tolerant of the amine.[23c] They found that aryl isothiocyanate gave higher yields and cleaner products than alkyl isothiocyanates. However, since we desired a removable protecting group, we again chose benzylisothiocyanate as a model for veratryl isothiocyanate. Carbodiimide **6** was prepared from azide **5**, benzylisothiocyanate, and triphenylphosphine, and was treated with amine monomers as shown in Scheme II. Propylamine was used to prepare guanidine **7** which, following cleavage, produced mono-guanidinium **11** with a yield of 55% (Table 1). Dimer **10** was prepared from **6** using 1-azido-3-aminopropane for the first coupling and propyl amine for the second coupling. However, due to the low yield (<5%) and poor purity of the cleaved dimer **12** (Table 1), further studies with veratryl isothiocyanate were not performed.



Scheme II. SPOS of guanidiniums using aza-Wittig couplings.

D.3. Method C. Ratcliffe and coworkers described the alkylation of bis-*tert*-butyloxycarbonyl protected methylthiourea by 2,4-dinitrofluorobenzene (Sanger's reagent) to prepare the strongly activated thiourea **13** that reacted rapidly with aryl amines in solution to form di-substituted guanidiniums.[37] It was expected that **13** would also react readily with resin bound amines and that the protecting groups could be easily removed during TFA cleavage of the oligomers from Wang resin. In fact, two equivalents of **13** in the presence of an external base quantitatively reacted with resin-bound alkyl and benzyl amines in under 18 h at room temperature (Scheme IIIa). To test the methodology and confirm that an "Edman-like" degradation (see figure 4) occurs in the absence of a rigid linker, cyclized guanidinium **14** was synthesized in 28% yield (mixture of isomers, Table 1). Using linker **1**, guanidinium **15** was prepared in 84% yield (Table 1). These reactions were accompanied by a rapid color change from yellow to red as the dinitrophenyl sulfide group was released.

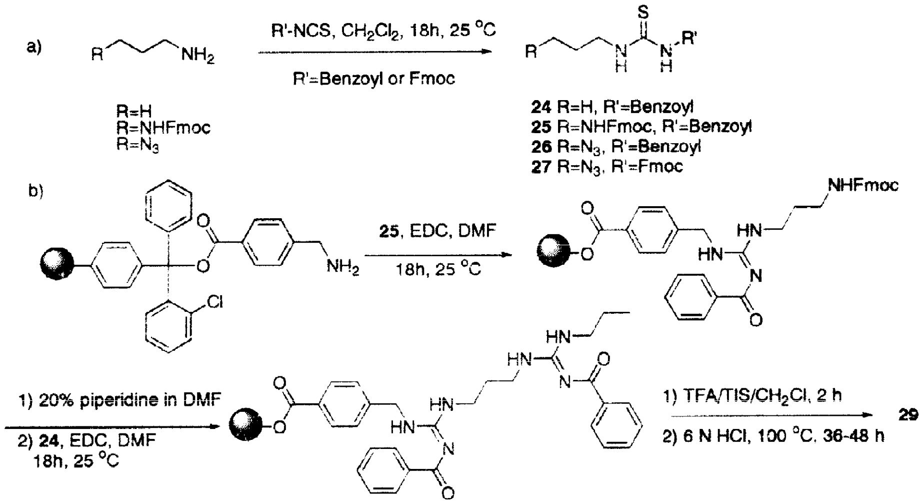


Scheme III. a) SPOS of guanidiniums via thioureas activated with Sanger's reagent. b) Synthesis of monomers.

Having demonstrated that guanidiniums were efficiently formed on the solid phase by this strategy, we next attempted to prepare bifunctional monomers. Unfortunately standard Fmoc and *tert*-butyloxycarbonyl protection were not appropriate for this method. Fmoc was not stable to the preparation of the bis-*tert*-butyloxycarbonyl protected thiourea and subsequent activation with Sanger's reagent. To prevent side reactions with the guanidiniums during chain elongation, it was desirable to leave the guanidiniums protected until just prior to cleaving the oligomer from the resin. Thus, *tert*-butyloxycarbonyl protection was not used for the terminal amine since the protecting group could not be selectively removed from the terminal amine without deprotecting the guanidiniums as well. Phthalimido and azido masked amines were chosen because it was anticipated that they would be compatible with the synthesis of the bis-*tert*-butyloxycarbonyl activated thiourea moiety and their conversion to amines on the solid phase was known.[39] Alkyl-bis-*tert*-butyloxycarbonylthioureas **19-21** were prepared via the Boc protection of an alkylthiourea or via the alkylation of *N,N'*-bis-*tert*-butyloxycarbonylthiourea[40] with alkyl or benzyl bromides (Scheme IIIb). The protected thioureas were then treated with 2,4-dinitrofluorobenzene to form activated thioureas. Thiourea **19** was activated to form the azido protected monomer **22**. However thiourea **20** could not be alkylated successfully due to competing side reactions on the phthalimido group. Separating the phthalimido group from the thiourea, as in **21**, with an aromatic group enabled isolation of the activated thiourea **23**. Unfortunately these monomers could not be prepared in high yield and were difficult to isolate. When added to resin-bound amines, they appeared to react, as indicated by the Kaiser test, but unmasking the azide and phthalimide groups was unsuccessful. Undesirable side reactions appear responsible for the negative Kaiser tests. Thus this method is useful for the solid phase preparation of di-substituted terminal guanidiniums but not for longer oligomers.

D.4. Method D. The similarity between the elimination of H_2S from thioureas to form guanidinium linkages and the elimination of H_2O from amino acids to form amide linkages led us to investigate peptide coupling reagents for the formation of guanidiniums. Several coupling reagents including DCC, DPPA, BOP and PyBOP were studied with various thioureas and amines. Guanidinium formation was observed in solution couplings with DCC and BOP, but did not proceed to completion on the solid phase even after several days at 50 °C.

Reports that EDC efficiently coupled amines and acylated thioureas to form guanidiniums[22d,33,38] led us to reinvestigate this strategy. Monomers **24-26** were readily prepared by the reaction of the appropriate amine with benzoyl isothiocyanate in dichloromethane (Scheme IVa). Addition of three equivalents of protected thiourea and three equivalents of EDC in dry DMF to resin-bound amines cleanly formed guanidines at room temperature in 18 to 24 h (Scheme IVb). The reaction was also successful with DCC as the coupling reagent but extended reaction times and elevated temperatures were required. Using EDC as the coupling reagent, oligomers containing one, two, and four guanidinium linkages were prepared. Fmoc, Boc (unpublished results), and azide protecting strategies were all successful and many other protecting groups should be compatible with these mild conditions as well. Following cleavage from the resin, the benzoyl groups were removed via acid hydrolysis with 6 N HCl at 100 °C for 18-36 h[34b] to give the deprotected oligomers in 26-84% overall yield (**28-30**, Table 1).



Scheme IV. a) Synthesis of protected thiourea monomers. b) Synthesis of a bis-guanidinium using EDC as the coupling reagent. TIS= triisopropylsilane.

Since many functional groups are not stable to these deprotection conditions, an alternate protection strategy was employed using protected thioureas prepared from Fmoc-NCS.[41] It was anticipated that mono-azido-mono-amine monomer **27** would allow the guanidiniums to remain protected until just prior to cleavage. Monomer **27** did indeed form guanidiniums with resin bound amines in the presence of EDC. Though **27** required 48 h to react completely, the resulting oligomer did not require deprotection after cleavage. Dimer **31** was prepared in this manner in 13% overall yield. We are currently using this method to prepare PNAs in which the amide linkages have been replaced by guanidiniums.

SUMMARY

Several approaches were investigated for the preparation of guanidinium linked oligomers, the results of which are summarized in Table 1. A mono-guanidinium was synthesized via activation of a resin-bound thiourea via Mukaiyama's reagent (Method A) but longer oligomers could not be made in this manner. Similar results were achieved using an aza-Wittig coupling (Method B). Protected dimers were successfully prepared but in very low yield. Only strongly activated thioureas reacted with resin bound amines in a synthetically useful manner. Sanger's reagent (Method C) was such an activating group, but the difficulty in incorporating it into bifunctional monomers made it unsuitable for preparing oligomers. The highest yields and purities were achieved using EDC to couple benzoyl or Fmoc-protected thioureas with resin-bound amines (Method D). These thioureas were readily prepared from easily synthesized or commercially available mono-protected diamines. Mono through tetra-guanidinium oligomers were prepared in 13 to 84% yield. This mild method is compatible with several standard protecting group strategies and should find numerous applications.

EXPERIMENTAL SECTION

General Information.

All ^1H and ^{13}C NMR spectra and low-resolution and high-resolution mass spectra were measured at the spectral facilities on the campus of the University of Texas. Melting points were measured on a Thomas Hoover capillary melting-point apparatus and are uncorrected. Preparative flash chromatography was performed on Whatman 60 Å 230-400 mesh silica gel. Analytical high performance liquid chromatography was performed on a Waters 990 system using a RP C_{18} 90Å Vydac column. Preparative reversed-phase liquid chromatography (LC) was performed on RP C_{18}-modified silica gel[42] 55-105 µm using a Pharmacia LKB-FRAC-100 LC system.

Supplies.

All resins were purchased from NovaBiochem as was mono-Fmoc-1,3-diaminopropane hydrochloride. All reagents were purchased from Aldrich except diisopropylcarbodiimide (Fluka). All solvents were purchased from EM except DMF (Aldrich), DMSO-d_6 (CIL), CD_3OD (Isotech), and $CDCl_3$ (Isotec), and were used as purchased, except as noted below. All solid phase reactions were carried out in dry solvents, except where noted below. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl radical. Dichloromethane was distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. Anhydrous DMF was used as supplied in a Sure/Seal™ bottle from Aldrich and used without further drying. *N,N′*-Bis-*tert*-butyloxycarbonylthiourea,[40] 1-azido-3-aminopropane,[36] and Fmoc isothiocyanate[41] were synthesized by literature procedures.

Spacer Synthesis. Benzoic acid, 4-[*N*-(9-fluorenylmethyloxycarbonyl)aminomethyl] (1). 4-Aminomethylbenzoic acid (2.89 g, 19.1 mmol) was dissolved in a mixture of dioxane (50 mL) and 10% sodium bicarbonate (200 mL) and cooled to 0 °C with vigorous stirring. A solution of 9-fluorenylmethyl chloroformate (5.44 g, 21.0 mmol) in dioxane (50 mL) was added dropwise over 15 min. The ice bath was removed and the suspension was allowed to stir for 3 h. Water (500 mL) was added and the mixture was extracted with ether (3 x 150 mL). The aqueous layer was cooled to 0 °C and carefully acidified with concentrated hydrochloric acid to pH 3. The resulting white precipitate was extracted into ethyl acetate (3 x 150 mL). The combined organic layers were washed with water (3 x 200 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield a white solid (4.86 g, 68.1%). mp 209-211 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 7.90 (m, 6 H), 7.69 (d, J=7.2 Hz, 2 H), 7.41 (t, J=7.4 Hz, 2 H), 7.32 (t, J=7.2 Hz, 2 H), 4.37 (d, J=6.6 Hz, 2 H), 4.24 (d, J=6.3 Hz, 2 H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 167.1, 156.4, 144.9, 143.8, 140.8, 129.3, 129.3, 127.6, 127.0, 126.9, 125.1, 120.1, 65.3, 46.8, 43.5; HRMS-CI$^+$ m/z calcd. for $C_{23}H_{20}NO_4$ (M+H$^+$) 374.1392, obsd. 374.1391.

Monomer Syntheses. [*N*-3-(azido)propyl-*N′*-benzoyl] thiourea (26). Benzoyl isothiocyanate (1.48 mL, 11.0 mmol) was added dropwise to 1-azido-3-aminopropane (1.0 g, 10 mmol) dissolved in dichloromethane (25 mL). The solution was allowed to stir at 25 °C for 18 h. The solvent was removed *in vacuo* an the product was purified by flash chromatography (hexane, ethyl acetate, 3:1) to yield a yellow oil (2.34 g, 89.1 %): ^1H NMR (300 MHz, $CDCl_3$) δ 10.78 (br, 1 H), 9.22 (br, 1 H), 7.73 (d, J=7.2 Hz, 2 H), 7.51 (t, J=7.5 Hz, 1 H), 7.38 (t, J= 7.2 Hz, 2 H), 3.71 (q, J= 6.5 Hz, 2 H), 3.34 (t, J= 6.6 Hz, 2 H), 1.90 (p, J= 6.7 Hz, 2 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 179.6, 166.8, 133.2, 131.4, 128.7, 127.3, 48.8, 42.7, 27.2; HRMS CI$^+$ m/z calcd. for $C_{11}H_{14}N_5OS$ (M+H$^+$) 264.0919, obsd. 264.0915.

***N*-[3-(azido)propyl] thiourea (16).** To 2 N NaOH (20 mL) at 100 °C was added **24** (501 mg, 1.93 mmol) dissolved in 2 mL MeOH. The solution was allowed to stir for 30 min. It was then cooled to 0 °C and acidified with 1 M HCl. The suspension was neutralized with conc. NH_4OH and the extracted with ethyl acetate (EtOAc, 4 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and washed to yield a yellow residue (74.4 mg, 24.2%) that was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (t, *J*=6.6 Hz, 2 H), 3.18 (t, *J*= 6.3 Hz, 2 H), 1.73 (pentet, *J*= 6.8 Hz, 2 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.6, 49.0, 37.7, 29.2; HRMS CI^+ *m/z* calcd. for $C_4H_{10}N_5S$ $(M+H^+)$ 160.0657, obsd. 160.0665.

α-bromo-α′-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-*m*-xylene (17). Potassium phthalimide (5.28 g, 28.5 mmol) was added portionwise over 4 hours to α,α-dibromo-*m*-xylene (10.0 g, 37.9 mmol) in acetone (100 mL) with stirring. The mixture was heated to reflux for 18 h. The mixture was allowed to cool to room temperature and concentrated *in vacuo*. The remaining solid was taken up in dichloromethane (100 mL) and water (100 mL). The layers were separated and the organic layer was washed with water (3 x 50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (hexanes/ethyl acetate, 9:1, followed by hexanes/ethyl acetate, 3:1) to elute unreacted α,α-dibromo-*m*-xylene (4.30 g, 43.0%) and 5.20 g (55.3%) of the product as a white solid: mp 130-132 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (m, 2 H), 7.65 (m, 2 H), 7.41 (s, 1 H), 7.33 (m, 1 H), 7.25 (m, 2 H), 4.78 (s, 2 H), 4.41 (s, 2 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.8, 138.1, 136.8, 133.9, 131.9, 129.1, 128.6, 128.5, 123.3, 41.1, 33.1; HRMS-CI^+ *m/z* calcd. for $C_{16}H_{13}NO_2Br$ $(M+H^+)$ 330.0130, obsd. 330.0126.

***N*,*N*′-bis-(*tert*-butyloxycarbonyl)-1-methyl-2-thiourea (18).**[37] 1-methyl-2-thiourea (676 mg, 7.50 mmol) was dissolved in dry THF (150 mL) under N_2 and cooled to 0 °C. Sodium hydride (811 mg, 33.8 mmol) was added in one portion with stirring. The ice bath was removed after 5 min and the mixture was allowed to stir for 10 min. The mixture was recooled to 0 °C and di-*tert*-butyldicarbonate (3.60 g, 16.5 mmol) was added neat. The mixture was allowed to stir at 0 °C for 30 min and then at 25 °C for 3 h. The excess sodium hydride was quenched with satd. $NaHCO_3$ (10 mL). The reaction mixture was poured into water (250 mL) and extracted with ethyl acetate (3 x 75 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated to a yellow liquid. The liquid was purified by flash chromatography (hexanes/ethyl acetate, 3:1) to yield a yellow oil containing a mixture of the mono and bis-*tert*-butyloxycarbonyl protected products. On drying under high vacuum the product precipitated as yellow crystals which were collected by filtration and washed with hexanes. The process was repeated until no more crystals formed upon drying: Final yield: 4.09 g, 42.3 %; mp 87-88 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.10 (br, 1 H), 3.54 (s, 3 H), 1.51 (s, 9 H), 1.47

(s, 9 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 181.1, 154.3, 150.1, 85.4, 82.3, 37.2, 28.0, 27.9; HRMS-CI$^+$ *m/z* calcd. for $C_{12}H_{23}N_2O_4S$ (M+H$^+$) 291.1379, obsd. 291.1370.

General protocol for the synthesis of carbamic acid, alkyl-[[[(1,1-dimethylethoxy)carbonyl]imino](thio)methyl]-,1,1-dimethlethyl ester monomers. *N,N′*-bis-(*tert*-butyloxycarbonyl)thiourea (1 equiv.) was dissolved in dry THF (150 mL) with stirring under argon. The solution was cooled to 0 °C and NaH (1.2 equiv.) was added. The reaction was allowed to stir for five minutes at 0 °C and ten minutes at 25 °C. The mixture was recooled and the alkyl bromide (1 equiv.) was added. The cloudy solution was allowed to stir at 0 °C for 30 minutes and at 25 °C for 18 h. The reaction was carefully quenched with saturated aq. $NaHCO_3$ (10 mL) and poured into water (200 mL). The product was extracted into ethyl acetate (3 x 75 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography (hexanes/ethyl acetate, 9:1).

Carbamic acid, [3-(azido)propyl][[[(1,1-dimethylethoxy)carbonyl]imino](thio)methyl]-,1,1-dimethlethyl ester (19). 16 (478 mg, 3.01 mmol) was dissolved in dry THF (150 mL) with stirring under argon. The solution was cooled to 0 °C and sodium hydride (325 mg, 13.5 mmol) was added. The reaction was allowed to stir for five minutes at 0 °C and ten minutes at 25 °C. The mixture was recooled and *N,N′*-bis-*tert*-butyloxycarbonylthiourea (1.96g, 9 mmol) was added. The cloudy solution was allowed to stir at 0 °C for 30 minutes and at 25 °C for 18 h. The reaction was carefully quenched with $NaHCO_3$ (10 mL) and poured into water (200 mL). The product was extracted into ethyl acetate (3 x 75 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to a yellow oil which was purified by flash chromatography (hexanes/ethyl acetate 3:1) to yield a yellow liquid (1.00 g, 92.6%): ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (t, *J*=7.5 Hz, 2 H), 3.28 (t, *J*=6.6 Hz, 2 H), 1.89 (p, *J*=6.6 Hz, 2 H), 1.46 (s, 9 H), 1.42 (s, 9 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 184.2, 148.7, 146.6, 85.0, 83.8, 47.9, 42.1, 29.9, 27.2; HRMS CI$^+$ *m/z* calcd. for $C_{14}H_{26}N_5O_4S$ (M+H$^+$) 360.1706, obsd. 360.1700.

Carbamic acid, [3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)propyl][[[(1,1-dimethylethoxy)-carbonyl]imino](thio)methyl]-,1,1-dimethlethyl ester (20). Prepared according to the procedure above using *N*-(3-bromopropyl)phthalimide (582 mg, 2.17 mmol). The product was isolated as a white amorphous solid (283 mg, 33.7 %): ^1H NMR (300 MHz, CD_3OD) δ 7.77 (m, 2 H), 7.66 (m, 2 H), 3.76 (t, *J*=6.8 Hz, 2 H), 3.34 (t, *J*=6.8 Hz, 2 H), 2.18 (p, *J*=6.8 Hz, 2 H), 1.45 (s, 18 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 177.7, 168.0, 150.2, 149.6, 133.9, 131.8, 123.1, 83.9, 81.7, 36.5, 31.4, 29.7, 27.8; HRMS CI$^+$ *m/z* calcd. for $C_{22}H_{30}N_3O_6S$ (M+H$^+$) 464.1855, obsd. 464.1847.

Carbamic acid, [*N*-*m*-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)xylylenediamine][[[(1,1-dimethylethoxy)carbonyl]imino](thio)methyl]-,1,1-dimethlethyl ester (21). Prepared according to the procedure above using **17** (820 mg, 2.48 mmol). The product was isolated as a white foam (1.20g, 92.4%): mp 49-51 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.79 (m, 2 H), 7.65 (m, 2 H), 7.43 (s, 1 H), 7.25 (m, 3 H), 4.79 (s, 2 H), 4.21 (s, 2 H), 1.52 (s, 9 H), 1.46 (s, 9 H); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ 169.8, 167.6, 160.4, 150.4, 136.4, 136.2, 133.7, 131.8, 129.7, 129.0, 128.5, 127.4, 123.1, 83.0, 80.6, 41.1, 35.4, 27.8; HRMS CI$^+$ *m/z* calcd. for $C_{27}H_{32}N_3O_6S$ (M+H$^+$) 526.2012, obsd. 526.1998.

General procedure for the formation Carbamic acid, alkyl-[[[(1,1-dimethylethoxy)carbonyl]imino][(2,4-dinitrophenyl)thio]methyl]-,1,1-dimethlethyl ester monomers.[37] The *N*-alkyl-*N*,*N*′-bis-*tert*-butyloxycarbonyl-thiourea monomer (1 equiv.) was dissolved in acetonitrile (25 mL) and dichloromethane (5 mL), if needed. Potassium carbonate (5 equiv.) and 2,4-dinitro-flourobenzene (1.2 equiv.) were added with stirring at room temperature. After 18 h the solvent was removed *in vacuo* and the resulting red solid was taken up in water (50 mL) and DCM (50 mL). The organic layer was washed with water (3 x 25 mL) and the combined aqueous layers were extracted with DCM (3 x 25 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure to yield a yellow foam.

Carbamic acid, methyl-[[[(1,1-dimethylethoxy)carbonyl]imino][(2,4-dinitrophenyl)thio]methyl]-, 1,1-dimethlethyl ester (13). Prepared following the procedure above with **18** (65.3 mg, 0.225 mmol). The product was purified by flash chromatography (hexanes/ethyl acetate, 3:1) to yield a pale yellow solid (80.7 mg, 78.7%): mp 134-135 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.94 (d, *J*=2.1 Hz, 1 H), 8.33 (dd, *J*= 6.3 Hz, 2.4 Hz, 1 H), 7.77 (d, *J*= 8.7 Hz, 1 H), 3.28 (s, 3 H), 1.36 (d, *J*=2.4 Hz, 18 H); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ 157.3, 152.6, 152.1, 146.5, 146.0, 139.6, 133.5, 126.7, 120.8, 84.3, 83.3, 36.5, 27.7; HRMS-CI$^+$ *m/z* calcd. for $C_{18}H_{25}N_4O_8S$ (M+H$^+$) 457.1393, obsd. 457.1407.

Carbamic acid, [3-(azido)propyl][[[(1,1-dimethylethoxy)carbonyl]imino][(2,4-dinitrophenyl)-thio]methyl]-,1,1-dimethlethyl ester (22). Prepared following the procedure above with **19** (1.00 g, 2.79 mmol). The product was purified by flash chromatography (hexanes/ethyl acetate; 9:1, then hexanes/ethyl acetate; 3:1) to yield a yellow oil (571 mg, 48.8%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.87 (s, 1 H), 8.30 (dd, *J*= 8.9 Hz and 2.6 Hz, 1 H), 7.78 (d, *J*= 9.0 Hz), 3.80 (t, *J*= 7.1 Hz, 2 H), 3.34 (t, *J*= 6.5 Hz, 2 H), 1.91 (quintet, *J*= 8.8 Hz, 2 H), 1.32 (s, 9 H), 1.28 (s, 9 H); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ 160.3, 156.9, 151.6, 133.5, 130.4, 126.6, 122.2, 120.6, 120.0, 84.3, 83.0, 48.8, 47.1, 27.7, 27.5, 27.5; HRMS CI$^+$ *m/z* calcd. for $C_{20}H_{28}N_7O_8S$ (M+H$^+$) 526.1720, obsd. 526.1728.

Carbamic acid, [*N*-*m*-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)xylylenediamine][[[(1,1-dimethylethoxy)carbonyl]imino][(2,4-dinitrophenyl)thio]methyl]-,1,1-dimethlethyl ester (23). Prepared following the procedure above with **21** (565 mg, 1.08 mmol). The product was purified by flash chromatography (hexanes/ethyl acetate, 9:1, then hexanes/ethyl acetate, 3:1) to yield a yellow oil (252 mg, 33.8%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.15 (d, *J*=2.4 Hz, 1 H), 8.80 (d, *J*= 2.7 Hz, 1 H), 8.38 (dd, 1 H), 7.81 (m, 2 H), 7.68 (m, 2 H), 7.21 (m, 4 H), 4.74 (s, 2 H), 4.15 (s, 2 H), 1.50 (s, 9 H), 1.36 (s, 9 H); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ 167.9, 148.3, 146.0, 140.2, 137.9, 136.8, 135.7, 134.1, 132.0, 130.7, 129.6, 129.0, 128.6, 128.2, 127.9, 123.4, 121.0, 120.0, 86.1, 82.7, 46.6, 37.0, 28.0, 27.23; HRMS CI$^+$ *m/z* calcd. for $C_{33}H_{34}N_5O_{10}S$ (M+H$^+$) 692.2026, obsd. 692.2031.

General protocol for the preparation of benzoylthioureas. The amine (1 equiv.) was dissolved in dichloromethane (25 mL) and cooled to 0 °C. Benzoyl isothiocyanate (1.1 equiv.) was added dropwise and the solution was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the product was purified by flash chromatography (hexanes/ethyl acetate, 3:1).

(*N*-Benzoyl-*N*′-propyl) thiourea (24). Prepared by the above method with propyl amine (1.8 mL, 22 mmol). The product was isolated as a white crystalline solid (4.1 g, 98%): mp 125 °C; ^{1}H NMR (300 MHz, CD$_3$OD) δ 7.91 (d, *J*=7.2 Hz, 2 H), 7.67 (m, 1 H), 7.52 (m, 2 H), 3.65 (t, *J*= 7.2 Hz, 2 H), 1.72 (q, *J*= 7.3 Hz, 2 H), 1.01 (t, *J*= 7.4 Hz, 3 H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 180.0, 168.1, 132.9, 132.2, 128.5, 128.4, 46.4, 21.0, 11.3; HRMS CI$^+$ *m/z* calcd. for $C_{11}H_{15}N_2OS$ (M+H$^+$) 223.0905, obsd. 223.0904

[*N*-benzoy-*N*′-[3-[(9-fluorenylmethyloxycarbonyl)amino]propyl]] thiourea (25). Prepared by the above method with mono-Fmoc-1,3-diaminopropane hydrochloride (627mg, 1.88 mmol) and *N*,*N*′-diisopropylethylamine (327 μL, 1.88 mmol). The product was isolated as a white solid (728 mg, 84.4%): mp 139-140 °C; NMR (300 MHz, CDCl$_3$) δ 9.21 (br, 1 H), 7.80 (br, 1 H), 7.79 (m, 4 H), 7.85 (m, 3 H), 7.40 (m, 6 H), 5.37 (t, *J*= 6.2 Hz, 1 H), 4.39 (d, *J*= 6.9 Hz, 2 H), 4.20 (t, *J*= 6.9 Hz, 1 H), 3.79 (q, *J*= 6.2 Hz, 2 H), 3.29 (q, *J*= 6.1 Hz, 2 H), 1.89 (t, *J*= 6.3 Hz, 2 H); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ 180.1, 166.8, 156.5, 143.8, 141.1, 133.3, 131.5, 128.8, 127.5, 127.4, 126.9, 125.0, 119.8, 66.5, 47.1, 42.5, 37.8, 28.7; HRMS CI$^+$ *m/z* calcd. for $C_{26}H_{26}N_3O_3S$ (M+H$^+$) 460.1695, obsd. 460.1705.

[*N*-[(3-azido)propyl]-*N*′(9-fluorenylmethyloxycarbonyl)] thiourea (27). 3-azapropylamine (395 mg, 3.92 mmol) was dissolved in DCM (25 mL) and cooled to 0 °C. Fmoc-isothiocyanate (1.00 g, 3.56 mmol) was added dropwise and the solution was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the product was purified by flash chromatography (hexanes/ethyl acetate, 9:1, then hexanes/ethyl acetate, 3:1) to yield a white foam (1.25 g, 91.6 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (br, 1 H), 9.27 (br, 1 H), 7.74 (d, *J*=7.5 Hz, 2 H), 7.57 (d, *J*= 7.5 Hz, 2 H), 7.40 (t, *J*= 7.4, 2 H), 7.31 (t, *J*= 7.2 Hz, 2 H), 4.39 (d, *J*= 6.9 Hz, 2 H), 4.19 (t, *J*= 6.9 Hz, 1 H), 3.76 (q, *J*= 6.5 Hz, 2 H), 3.37 (t, *J*= 6.6 Hz, 2 H), 1.93 (pentet, *J*= 6.8 Hz, 2 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.2, 152.6, 142.7, 140.9, 127.7, 126.9, 124.7, 119.9, 68.0, 48.8, 46.1, 42.5, 27.3; HRMS CI$^+$ *m/z* calcd. for $C_{19}H_{20}N_5O_2S$ (M+H$^+$) 382.1338 obsd. 382.1332.

General protocols for solid phase synthesis: Protecting group removal (10 mL of each solvent was used for 100 mg resin): Fmoc was removed with 20% piperidine in DMF for 20 min. at room temperature followed by washing with DMF (1 min), DCM (1 min), MeOH (1 min), and DCM (2 x 1 min). Azide was reduced with triphenylphosphine (10 equiv.) in THF (9 mL) and water (1 mL) for 18 h at room temperature followed by washing with THF (1 x 1 min), DCM (1 min), MeOH (1 min), and DCM (2 x 1 min).

Normal wash sequence: DCM (1 x 1 min), MeOH (1 x 1 min), DCM (2 x 1 min)

Cleavage from the resin: All resins were shrunk in MeOH and dried under high vacuum for at least 4 h prior to cleavage. Wang resins were cleaved with 90% TFA and 10% ethanedithiol for 2 h at room temperature. 2-chloro-trityl resins were cleaved with 5% TFA and 5% triisopropylsilane (TIS) in dichloromethane for 2 h at room temperature. The cleavage solution was removed by filtration. The resin was washed with alternating DCM and MeOH and the filtrate was concentrated *in vacuo*.

Method A:

L-Phenylalanine, *N*-[4-[3-(*N*-benzyl)imino-5-phenyl-2,4-diazapent-1-yl]benzoyl] (4). Fmoc-Phe-Wang resin (300 mg, 0.153 mmol amine) was deprotected normally with 20% piperidine in DMF. 4-((9-flourenylmethyloxycarbonyl)aminomethyl)benzoic acid (10 equiv.), and 1-hydroxybenzotriazole hydrate (HOBT, 10 equiv.) were added in DMF (10 mL) followed by diisopropylcarbodiimide (DIC, 10 equiv.) and the resin was spun at room temperature for 24 h followed by a normal wash sequence. The resulting resin (2) was deprotected normally with 20% piperidine in DMF. Benzyl isothiocyanate (203 µL, 1.53 mmol) was added in DCM and the resin was spun at 25 °C for 48 h. The resulting resin (3) was filtered and washed normally and the reaction was judged complete by the ninhydrin test. 2-Chloro-1-methylpyridinium iodide (390 mg, 1.53 mmol) and *N,N′*-diisopropylethylamine (133 µL, 0.76 mmol) were added in DCM and the resin was spun at 25 °C for 2 h. The resin was filtered and washed with DCM (2x). Fresh 2-chloro-1-methylpyridinium iodide (390 mg, 1.53 mmol) and *N,N′*-diisopropylethylamine (133 µL, 0.76 mmol) were added in DCM and the resin was spun at 25 °C for 2 h. The resin was washed as before and the alkylation process was repeated once more. Benzylamine (250 µL, 2.30 mmol), 2-chloro-1-methylpyridinium iodide (195 mg, 0.76 mmol), and *N,N′*-diisopropylethylamine (266 µL, 1.53 mmol) were added in DCM. The resin was spun at 25 °C for 18 h. The product was cleaved from the resin with 10% ethanedithiol in TFA for 2 h at 25 °C and purified by repeated reversed phase FPLC to yield 47 mg (59%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (m, 1 H), 8.14 (br, 1 H), 7.72 (d, *J*=8.2 Hz, 4 H), 7.25 (m, 14 H), 7.15 (t, *J*= 7.5 Hz, 1 H), 6.53 (q, *J*= 6.3 Hz, 1 H), 4.71 (br, 2 H), 4.67 (br, 2 H), 4.55 (m, 1 H), 4.24 (dd, *J*= 6.0 Hz, 18 Hz, 2 H), 3.18 (dd, *J*= 6.3 Hz, 14.7 Hz, 1 H), 3.06 (t, *J*= 11.7 Hz, 1 H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 173.3, 165.9, 158.1, 144.4, 140.8, 138.4, 132.6, 132.4, 129.1, 128.2, 128.2, 128.1, 127.2, 126.9, 126.8, 126.6, 126.5, 126.2, 54.4, 43.0, 42.7, 36.4; HRMS CI$^+$ *m/z* calcd. for $C_{32}H_{33}N_4O_3$ (M^+) 521.2553, obsd. 521.2541.

Method B:

L-Phenylalanine, *N*-[4-[3-(*N*-benzyl)imino-2,4-diazahep-1-yl]benzoyl] (11). Fmoc-Phe-Wang resin (300 mg, 0.153 mmol amine) was deprotected normally. α-Bromo-*p*-toluic acid (329 mg, 1.53 mmol) and 1-hydroxybenzotriazole hydrate (207 mg, 1.53 mmol) were added in DMF followed by 1,3-diisopropylcarbodiimide (240 μL, 1.53 mmol) and the suspension was spun at 25 °C for 24 h. The resin was filtered and washed (DMF, DCM, MeOH, DCM x 2) and the reaction was judged compete by the ninhydrin test. Sodium azide (650 mg, 10.0 mmol) in DMSO was added and the mixture was spun at 50 °C for 48 h. The resin was filtered and washed (H_2O, DMF, DCM, dry THF, DCM x 2). Benzyl isothiocyanate (203 μL, 1.53 mmol) in dry THF was added and the mixture was spun at 25 °C for 15 min. Triphenylphosphine (1.40 g, 5.36 mmol) was added and the suspension was spun at 25 °C for 4 h. The resin was filtered and washed with alternating dry THF and DCM washed (three each). Propylamine (126 μL, 1.53 mmol) in DMSO was added and the mixture was spun at 25 °C for 18 h. The resin was filtered and washed (DMF, DCM, MeOH, DCM x 2, MeOH) and pumped dry under high vacuum for 4 h. The oligomer was cleaved with a mixture of TFA (9 mL) and ethanedithiol (1 mL) for 2 h and the resin was washed with TFA, DCM, MeOH, DCM, and MeOH. The filtrate was concentrated to a cloudy oil which was purified by reversed phase FPLC and lyophilized to yield a white powder (40.4 mg, 54.6%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.63 (d, *J*= 7.2 Hz, 2 H), 7.19 (m, 12 H), 4.72 (t, *J*= 6.0 Hz, 1 H), 4.48 (d, *J*=10.2 Hz, 2 H), 3.35 (m, 1 H), 3.20 (t, *J*= 7.2 Hz), 3.13 (m, 1 H), 1.54 (p, *J*= 7.4 Hz, 2 H), 0.79 (t, *J*= 7.5 Hz, 3 H); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ 177.4, 168.6, 156.1, 141.5, 139.4, 137.7, 135.2, 131.2, 130.6, 129.9, 129.2, 129.0, 128.6, 128.0, 127.4, 57.4, 45.6, 45.2, 44.5, 39.0, 23.3, 11.2; HRMS CI$^+$ *m/z* calcd. for $C_{28}H_{33}N_4O_3$ (M^+) 473.2553, obsd. 473.2535.

L-Phenylalanine, *N*-[4-[3,9-di-(*N*-benzyl)imino-2,4,8,10-tetraazatridec-1-yl]benzoyl] (12). Prepared by the above method with Fmoc-Phe-Wang resin (250 mg, 0.127 mmol amine) using 1-azido-3-aminopropane (127 mg, 1.27 mmol) for the first monomer. Following the first coupling, the resin was washed (DMF, DCM, dry THF, DCM x 2). Benzyl isothiocyanate (203 μL, 1.53 mmol) was added in dry THF and spun for 15 min at room temperature. Triphenylphosphine (1.40 g, 5.36 mmol) was added and the resin was spun at 25 °C for 4 h. The resin was filtered and washed with alternating dry THF and DCM (3 x each). Propylamine (126 μL, 1.53 mmol) was added in DMSO and the resin was spun at 25 °C for 18 h. The product was cleaved with 10% ethane dithiol in TFA for 2 h at room temperature and purified by cation exchange and RP FPLC. The product was identified by HRMS but could not be adequately purified for NMR. HRMS FAB$^+$ *m/z* calcd. for $C_{39}H_{48}N_7O_3$ (M+H$^+$) 662.3819, obsd. 662.3815.

Method C:

General procedure for the solid phase synthesis of guanidiniums using Sanger's reagent. The resin was deprotected if necessary. To the resin (free amine) was added the carbamic acid, alkyl-[[[(1,1-dimethylethoxy)carbonyl]imino][(2,4-dinitrophenyl)thio]methyl]-,1,1-dimethlethyl ester monomers (2 equiv.) and *N,N′*-diisopropylethylamine (2 equiv) in THF (15 mL). The resulting blood red mixture was allowed to spin at room temperature for 18 h. The red solution was removed by filtration and the resin was washed with THF, DCM, MeOH, and DCM (2x). Following a negative ninhydrin test, the resin was either deprotected or cleaved as necessary.

2-aza-4,5-dihydro-5-oxo-4-(phenylmethyl)-1-methyl-1*H*-imidazol and 2-(methyl)aza-4,5-dihydro-5-oxo-4-(phenylmethyl)-1-methylimidazol (14). Prepared by the above method using Fmoc-Phe-Wang resin (863 mg, 0.751 mmol amine) and **13** (685 mg, 1.50 mmol). Following cleavage with TFA, the yellow filtrate was concentrated *in vacuo* and dried under high vacuum to a yellow oil which was purified by reverse phase FPLC (25 mM aq. NH_4Ac to CH_3CN) to yield 23.3 mg (27.5%) of a mixture of isomers: ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (m, 5 H), 6.63 (br, 3 H), 4.35 (t, *J*= 5.3 Hz, 1 H), 3.19 (dd, 1 H), 3.05 (dd, 1 H), 2.90 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) 173.9, 158.2, 134.5, 129.5, 128.6 127.4, 60.5, 37.4, 25.3; HRMS-CI$^+$ *m/z* calcd. for $C_{11}H_{14}N_3O$ (M+H$^+$) 204.1137, obsd. 204.1139.

L-Phenylalanine, *N*-[4-[3-imino-2,4-diazapent-1-yl]benzoyl] (15). Prepared by the above method using *p*-Fmoc-aminomethylbenzyl-Phe-Wang resin (prepared as in **2**, 0.51 mmol amine) and **13** (1.16 g, 2.55 mmol). Following cleavage with TFA, the product was purified by RP-FPLC and lyophilized three times to yield 152 mg (84.2%) of a white powder: ^1H NMR (300 MHz, CD_3OD) δ 7.70 (d, *J*=8.1 Hz, 2 H), 7.33 (d, *J*= 7.8 Hz, 2 H), 7.19 (m, 5 H), 4.78 (t, *J*=4.2 Hz, 1 H), 4.44 (s, 2 H), 3.33 (m, 1 H), 3.10 (m, 1 H), 2.83 (s, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD) δ 176.7, 167.9, 157.8, 141.0, 138.8, 129.9, 128.5, 128.1, 127.9, 127.4, 126.7, 57.0, 44.7, 38.4, 27.7; HRMS CI$^+$ *m/z* calcd. for $C_{19}H_{23}N_4O_3$ (M+H$^+$) 355.1770, obsd. 355.1765.

Method D:

General protocol for the solid phase synthesis of guanidinium linked oligomers with EDC. The resin was deproteced if necessary. To the resin (free amine) was added the benzoylthiourea or Fmoc-thiourea (3 equiv.) and EDC (3 equiv.) in dry DMF (10 mL). The reaction was spun at room temperature for 18 h (benzoyl monomers) or 48 h (Fmoc monomers). The resin was filtered and washed (DMF, DCM, MeOH, DCM (2x). The resin was either deprotected or prepared for cleavage as necessary. Following cleavage, the protected oligomer was taken up in 6 N HCl (15 mL) and stirred at 100 °C for 24-48h.[34b] The solution was allowed to cool to room temperature and was then extracted with ether (3 x 25 mL). The aqueous layer was lyophilized and purified by reversed phase and/or cation exchange FPLC.

Benzoic acid, 4-(3-imino-2,4-diazahep-1-yl)-, hydrochloride (28). Prepared by the above solid phase protocol using 4-aminomethylbenzoyl-2-chloro-trityl resin (150 mg, 0.15 mmol amine) and **24**. The product was cleaved with TFA (5%) and TIS (5%) in DCM (10 mL) for 2 h at room temperature. The resin was filtered and washed with alternating dichloromethane and THF (3 x each). The solvent was removed *in vacuo* and the resulting yellow oil was purified by flash chromatography (DCM/NH_3 saturated MeOH, 8:2) to yield a yellow oil which was used without further purification: HRMS CI$^+$ *m/z* calcd. for $C_{19}H_{22}N_3O_3$ (M+H$^+$) 340.1661, obsd. 340.1663.

The benzoyl group was removed as described above to yield a white powder (40.7 mg, 83.6%): ^{1}H NMR (300 MHz, D_2O) δ 7.85 (d, *J*= 8.4 Hz, 2 H), 7.28 (d, *J*= 8.4 Hz, 2 H), 4.37 (s, 2 H), 3.01 (t, *J*= 7.1 Hz, 2 H), 1.38 (pentet, 2 H), 0.69 (t, *J*= 7.4 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, D_2O) δ 172.0, 157.5, 143.8, 131.7, 131.0, 128.4, 45.7, 44.6, 23.1, 11.9; HRMS CI$^+$ *m/z* calcd. for $C_{12}H_{18}N_3O_2$ (M+H$^+$) 236.1399, obsd. 236.1385.

Benzoic acid, 4-(3,9-diimino-2,4,8,10-tetraazatridec-1-yl)-, dihydrochloride (29). Prepared by the above solid phase protocol using 4-aminomethylbenzoyl-2-chloro-trityl resin (186 mg, 0.186 mmol amine). Benzoylthiourea **25** was used for the first coupling and benzoylthiourea **24** was used for the second coupling. The product was cleaved with TFA (5%) and TIS (5%) in DCM (10 mL) for 2 h at room temperature. The resin was filtered and washed with alternating dichloromethane and THF (3 x each). The solvent was removed *in vacuo* to yield a yellow oil which was used without further purification: HRMS CI$^+$ *m/z* calcd. for $C_{30}H_{35}N_6O_4$ (M+H$^+$) 543.2720, obsd. 543.2707.

The benzoyl groups were removed as described above to yield a white powder (44.0 mg, 58.3%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 (d, *J*= 8.1 Hz, 2 H), 7.18 (d, *J*= 8.4 Hz, 2 H), 4.35 (s, 2 H), 3.16 (q, *J*=6.0, 2 H), 3.02 (t, *J*= 7.5 Hz, 2 H), 1.67 (t, *J*= 6.0 Hz, 2 H), 1.46 (sextet, *J*= 7.4 Hz, 2 H), 0.85 (t, *J*= 7.2 Hz, 3 H);

$^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 167.1, 156.1, 155.9, 142.7, 129.8, 129.5, 127.2, 43.6, 42.5, 38.3, 38.2, 28.3, 21.9, 11.1; HRMS FAB$^+$ *m/z* calcd. for $C_{16}H_{27}N_6O_2$ (M+H$^+$) 335.2195, obsd. 335.2190.

Benzoic acid, 4-(3,9,15,21-tetraimino-2,4,8,10,14,16,20,22-octaazapentacos-1-yl)-, tetrahydrochloride (30). Prepared by the above solid phase protocol using 4-aminomethylbenzoyl-2-chloro-trityl resin (100 mg, 0.100 mmol amine). Benzoylthiourea **25** was used for the first three couplings. Benzoylthiourea **24** was used for the final coupling. The product was cleaved with TFA (5%) and TIS (5%) in DCM (10 mL) for 2 h at room temperature. The resin was filtered and washed with alternating DCM and THF (3 x each). The solvent was removed *in vacuo* and the resulting yellow oil was purified by flash chromatography (DCM/NH_3 saturated MeOH, 8:2) to yield a yellow oil which was used without further purification: HRMS FAB$^+$ *m/z* calcd. for $C_{52}H_{61}N_{12}O_6$ (M+H$^+$) 949.4837, obsd. 949.4886.

The benzoyl groups were removed as described above to yield 17.6 mg (26.0% overall yield) of a white powder: ^1H NMR (300 MHz, DMSO-d_6) δ 7.79 (d, *J*= 8.1 Hz, 2 H), 7.22 (d, *J*= 8.1 Hz, 2 H), 4.37 (s, 2 H), 3.16 (br, 12 H), 3.04 (br, 2 H), 1.68 (m, 6 H), 1.48 (q, *J*= 7.0 Hz, 2 H), 0.86 (t, *J*= 6.8 Hz, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 175.6, 171.2, 156.2, 156.1, 139.1, 137.6, 129.1, 126.0, 43.6, 42.4, 38.5, 27.7, 23.9, 21.9, 11.1; HRMS FAB$^+$ *m/z* calcd. for $C_{24}H_{45}N_{12}O_2$ (M+H$^+$) 533.3788, obsd. 533.3797.

Benzoic acid, 4-(14-azido-3,9-diimino-2,4,8,10-tetraazatetradec-1-yl) (31). Prepared by the above solid phase protocol using 4-aminomethylbenzoyl-2-chloro-trityl resin (100 mg, 0.100 mmol amine). Fmoc-thiourea **27** was used for the both couplings. Prior to cleavage the guanidiniums were deprotected with 20% piperidine in DMF for 20 min. The product was cleaved with TFA (5%) and TIS (5%) in DCM (10 mL) for 2 h at room temperature. The resin was filtered and washed with alternating DCM and THF (3 x each). The solvent was removed *in vacuo* to yield a tan powder that was purified by cation exchange FPLC to yield a white powder (12.7 mg, 13.0%): ^1H NMR (300 MHz, DMSO-d_6) δ 7.78 (d, *J*=7.8 Hz, 2 H), 7.20 (d, *J*= 8.1 Hz, 2 H), 4.37 (s, 2 H), 3.40 (t, *J*= 6.6 Hz, 2 H), 3.16 (m, 6 H), 1.74 (s, 2 H), 1.68 (s, 2 H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 175.5, 156.4, 156.3, 139.0, 138.0, 129.1, 125.9, 48.1, 43.5, 38.5, 38.1, 27.7, 24.4, 22.5; HRMS FAB$^+$ *m/z* calcd. for $C_{16}H_{26}N_9O_2$ (M+H$^+$) 376.2209, obsd. 376.2217.

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