Solid-Phase Synthesis of Guanidinium Derivatives from Thiourea and Isothiourea Functionalities

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Guanidinium-based compounds are biologically, medicinally, and pharmaceutically vital molecules. Due to their ability to form H-bond interactions, charge pairing, and cation-π interactions, guanidinium groups also perform key roles in supramolecular chemistry. They are found in nature in numerous forms and can be synthesized using different methods. Solid-phase synthesis permits the preparation of synthetically challenging molecules and can be used for the synthesis of combinatorial libraries of lead molecules. A brief survey of methods for the synthesis of guanidiniums from thiourea and isothiourea using different reagents is discussed.

Introduction

Guanidines are basic molecules (pK_a of their conjugate acids around 12.5) with the capacity to form intermolecular contacts mediated by H-bonding interactions.[1] The guanidinium moiety interacts with functional groups present in enzymes or receptors on the basis of hydrogen bonds and electrostatic interactions. Thus, they are useful pharmacophores in medicinal chemistry.[2] They are also studied for their ability to form intermolecular associations in supramolecular chemistry. There are many ways to synthesize guanidiniums in the solid phase;[3−21] converting thiourea and isothiourea moieties into guanidiniums is one of the most popular methods.

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Arginine, a naturally occurring amino acid with a guanidinium moiety, is found in numerous enzyme active sites and cell recognition motifs. Horseradish peroxidase,[22] fumarate reductase,[23] creatine kinase,[24] and malate dehydrogenase,[25] are just a few enzymes that have arginine-containing active sites. Integrins are a family of transmembrane cell-surface receptors that are involved in cell-cell and cell-matrix adhesion processes. The tripeptide sequence RGD (Arg-Gly-Asp) is a common cell-recognition motif responsible for the binding of the integrin receptors.[26] This sequence has been used as a lead for developing different integrin antagonists.[27]

Nonpeptide cyclic cyanoguanidines are used as HIV-1 protease inhibitors,[28] while carbocyclic guanidino analogs are used as influenza neuraminidase inhibitors.[29] Guanidinium-based molecules are also extensively used as cardiovascular drugs,[30] antihistamines,[31] anti-inflammatory agents,[32,33] antidiabetic drugs,[34] antibacterial and anti-

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Dr. Anslyn received his B. S. degree in Chemistry from California State University Northridge in 1983. He received his Ph.D. from the California Institute of Technology in 1987, and was a National Science Foundation Postdoctoral Fellow at Columbia University. In 1989, he started an independent research career at The University of Texas at Austin, and was promoted to Associate Professor, then Full Professor, and recently was named University Distinguished Teaching Professor. His research is concerned with the design of receptors for sensing and catalytic purposes. In specific, guanidinium functional groups play a major role in many of his group's designs.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

fungal drugs,[35] antiprotozoal and other antiparasitic drugs,[36,37] anthelmintics,[38] antineoplastic and antiviral drugs,[39] and central nervous system drugs. Guanidinium-containing molecules are also used as inhibitors of neuronal Na^+ channels.[40,41] Ptilomycalin, a guanidine-containing molecule is a Na^+, K^+, or Ca^{2+} ATPase inhibitor. It competitively interacts with ATP at its binding sites. Thus, it has become a tool for clarifying the ATP binding site in these enzymes.[42] Gabexate, yet another guanidino compound, is a proteinase enzyme inhibitor that reduces insulin degradation and is useful in suppressing the progress of acute pancreatitis.[43] Guanidinium derivatives are also used as histamine H_3-receptor antagonists.[44] Oligonucleotides incorporating 4-guanidino-2-pyrimidinone nucleobases have been designed to mimic the double hydrogen bond donor pattern of protonated cytosines in parallel triple helices.[45]

Guanidiniums are widely used for molecular recognition purposes in supramolecular chemistry. Host compounds containing guanidiniums have been synthesized to sense aromatic carboxylate anions,[46] phosphodiesters,[47] underivatized amino acids,[48] and dinucleotides,[49] among others.

Guanidinium-containing compounds such as guanidinoacetic acid are used as artificial sweeteners.[50] The cyclic dipeptide composed of L-phenylalanine and L-norarginine catalyzes the enantioselective Strecker synthesis of (*S*)-phenylglycine derivatives from *N*-substituted aldimines and hydrogen cyanide.[51] Modified guanidines are also used as potential chiral superbases.[52,53]

Due to the utility of the guanidinium group in drugs, supramolecular structures, and sweeteners, scientists are working on the synthesis of guanidiniums through solid-phase combinatorial chemistry.[54] Combinatorial solid-phase synthesis is gaining momentum throughout the pharmaceutical industry as a powerful tool for preparing libraries of drug-like organic molecules.[55]

The advances in solid-phase synthesis allow chemists to make guanidinium oligomers and other synthetically challenging compounds containing guanidine moieties in a short period of time. There are many methods known to synthesize guanidine moieties.[56] The solid-phase synthesis of guanidines mainly focuses on three different approaches, namely the formation of resin-bound carbodiimides and their reaction with amines,[57–58] the solid-phase synthesis involving electrophiles in solution, and the reaction of supported thioureas with amines.[59] This Microreview summarizes the literature reports on the solid-phase synthesis of guanidiniums from thiourea and isothiourea.

Discussion

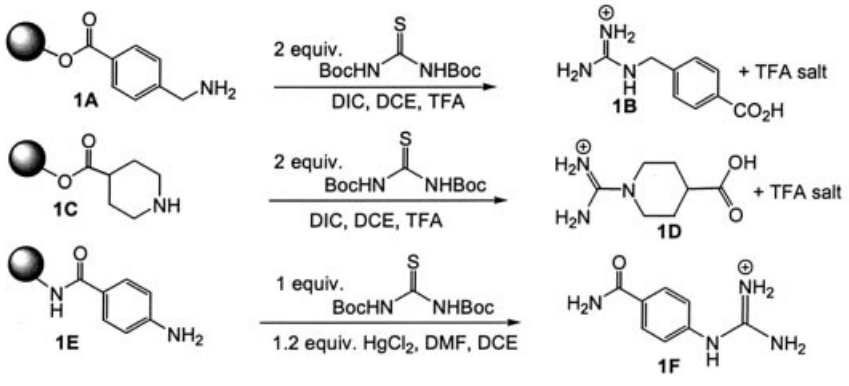
Guanidiniums from Thiourea

The attachment of thiourea groups to a solid phase is used as a precursor of guanidinium groups, as well as peptidomimetics,[60] a quencher,[61] thiazolylhydantoines,[62] and a precursor to 2-aminothiazole rings.[63] The thiourea moiety is converted into guanidinium functionalities in the presence of different coupling reagents: *N*,*N*-diisopropylcarbodiimide (DIC), mercury(II) chloride ($HgCl_2$), mercury(II) oxide (HgO), 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 2,4-dinitrofluorobenzene (Sanger's reagent), and triphenylphosphane dichloride.

DIC Coupling

Combinatorial Library Synthesis

As part of a combinatorial library synthesis, Roskamp and co-workers have reported the conversion of a variety of primary and secondary amines and anilines into their corresponding guanidiniums (Scheme 1).[64] Wang resins that were preloaded with Fmoc 4-(aminomethyl)benzoic acid (**1A**) or Fmoc isonipecotic acid (**1C**) in dichloroethane (DCE)/DMF, were allowed to react with two equivalents of Boc-protected thiourea and DIC to give the corresponding guanidiniums **1B** and **1D** after cleavage of the protecting groups. The product was cleaved from the resin with TFA. Preloaded Rink amide AM resin **1E** was also guanylated with Boc-protected thiourea and $HgCl_2$ in DCE/DMF to yield **1F** after cleavage and deprotection.



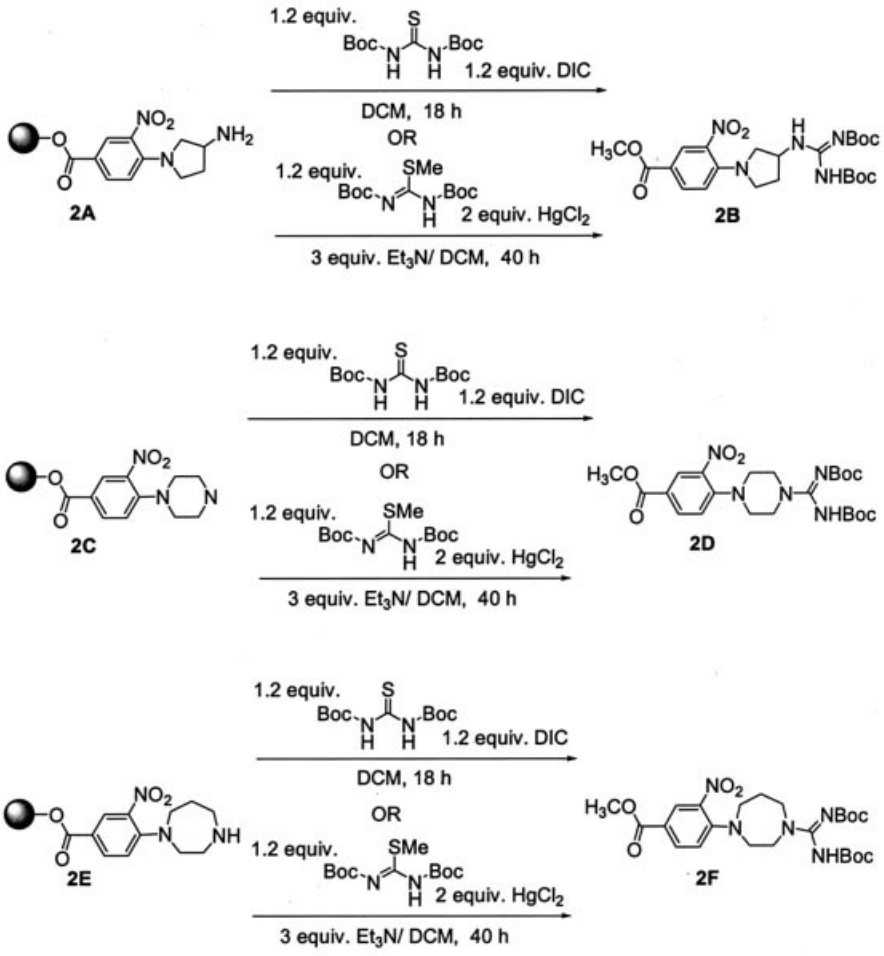
Scheme 1. A combinatorial library synthesis of mono-substituted guanidiniums

Use of a Soluble Polymer Support

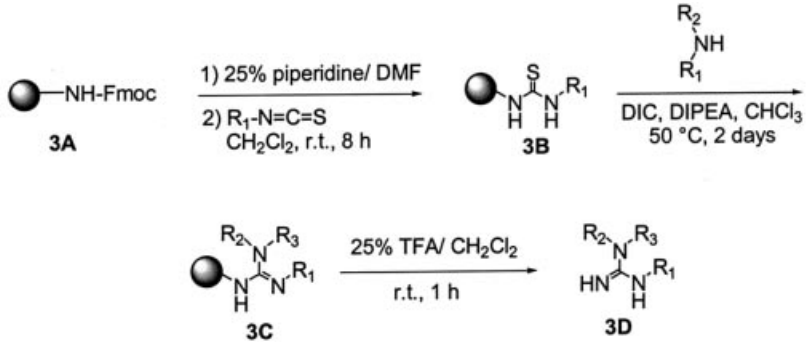
Sun and co-workers have reported a liquid-phase combinatorial synthesis of guanidines by the use of a soluble polymer support to generate libraries (Scheme 2).[65] The resin of choice was poly(ethylene glycol). The guanidines **2B**, **2D**, and **2F** were formed by coupling primary (**2A**) and secondary (**2C** and **2E**) amines with thiourea in the presence of DIC or *S*-methylisothiourea in the presence of $HgCl_2$. Only one of the guanidine amino groups was substituted.

Rink Amide Resin as an Amine Component

Portlock and co-workers have reported the synthesis of disubstituted guanidines through DIC coupling (Scheme 3).[66] The commercially available Rink amide resin



Scheme 2. Combinatorial library synthesis using a soluble polymer support



Scheme 3. Guanidinium synthesis using the Rink amide resin as an amine component

3A was deprotected, and was then allowed to undergo addition to isothiocyanate to form the thiourea **3B**. The thiourea was then converted into a guanidine **3C** with DIC coupling in the presence of a disubstituted amine and a base. The product was then cleaved from the resin under Rink resin cleavage conditions (25% TFA in CH_2Cl_2) to yield **3D**. Under these conditions, aromatic isothiocyanates and aliphatic amines were the most suitable substrates for guanylation.

Indole Resin as the Solid Support

Roskamp and co-workers have reported the synthesis of guanidiniums using an indole resin as the solid support (Scheme 4).[67] The indole resin **4A** was synthesized from indole-3-carboxaldehyde. The resin was then reductively aminated using a primary amine and $Me_4NBH(OAc)_3$ followed by treatment with $NaBH_3CN$ in methanol to yield **4B**. Compound **4B** was then guanylated under DIC coupling conditions with thiourea. The product was liberated from the resin in the presence of TFA to yield **4C**.

2-Aminoimidazolone Rings

The 2-aminoimidazolone ring is a derivative of guanidine and a core structure in many drug substances.[68] Few methods have been developed to synthesize 2-aminoimidazolones.[69,70] Wilson and co-workers have reported the synthesis of trisubstituted 2-aminoimidazolones based on an intramolecular cyclization between a δ-guanidinium nitrogen atom and an amide carbonyl group under acidic conditions, as depicted in Scheme 5.[68] The aminomethyl Rink resin **5A** was used to form the amide functionality **5B** through reaction with an amino acid using general peptide coupling to form the resin bound α-amino amide moiety. Reaction of **5B** with an isothiourea derivative gave the thiourea **5C**. The guanylation of **5C** with an amine in the presence of DIC and diisopropylethylamine (DIPEA) gave the corresponding resin-bound guanidine **5D**. The product **5E** could then be cleaved from the resin with 10% acetic acid.

$HgCl_2$ Coupling

Oligonucleotide Analogs

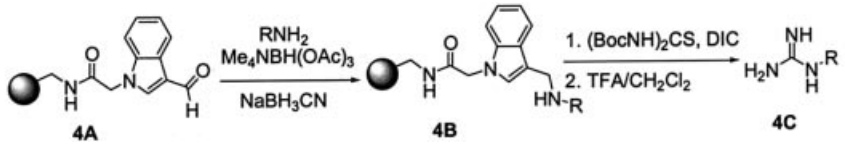
Molecules that are oligonucleotide analogs could be used for arresting cellular processes at the transcriptional and translational levels through recognition and binding to complementary RNA or DNA.[71−73] Replacing the phosphate backbone with positively charged guanidinium groups[74] increases the binding of these analogs and makes them resistant to nucleases.[75] The positively charged guanidinium might also give rise to cell membrane permeability by electrostatic attraction of the oligonucleoside to the negatively charged phosphate groups on the cell surface.[76]

Bruice and co-workers have reported the synthesis of deoxynucleotide guanidine oligomers (Scheme 6).[76] At first, the resin **6A** was loaded with protected and modified nucleotide **6B** in the presence of $HgCl_2$ in DMF to create guanidine **6C**. The 3′-amino group was then deprotected in 20% piperidine and was coupled with **3B** in the presence of $HgCl_2$ and triethylamine (TEA) in DMF to yield **6D**. This deprotection/coupling cycle was repeated seven more times. The product **6E** was cleaved from the resin with 3% trifluoroacetic acid (TFA). The guanidine was then deprotected with cadmium metal in acetic acid to yield **6F**. This synthesis was done on both 2-(2-aminoethoxy)ethanol 2-chlorotrityl resin or on Rink peptide amide resin loaded with a 3′-aminothymidyl nucleoside.

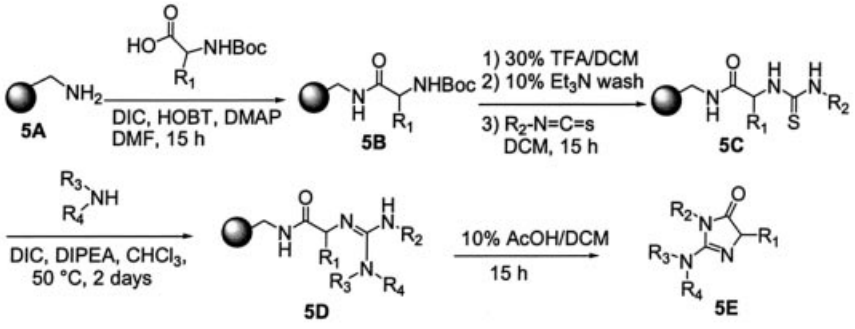
HgO Coupling

T2* Linker as an Amine Component

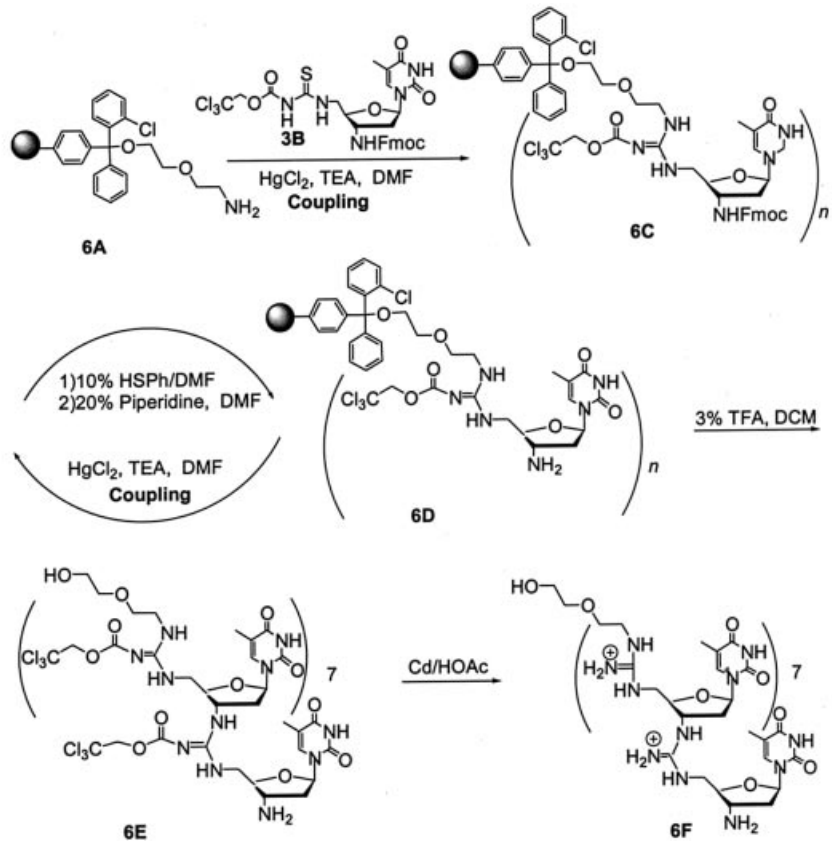
Brase and co-workers have reported the use of a traceless linker in guanidinium synthesis (Scheme 7).[57] At first, a



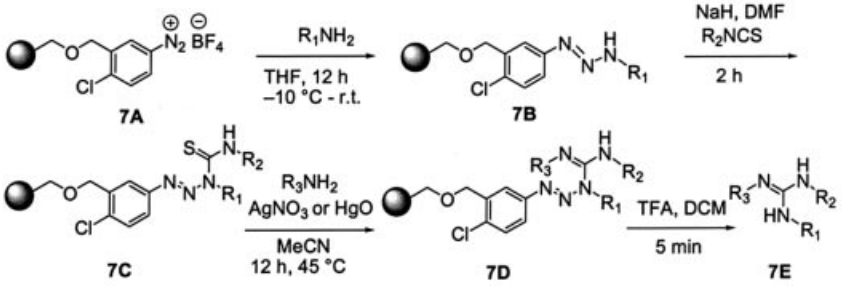
Scheme 4. Guandinium synthesis using an indole resin as the solid support



Scheme 5. Solid-phase synthesis of 2-aminoimidalonone ring



Scheme 6. Synthesis of oligonucleotide analogs



Scheme 7. Synthesis of guanidine using T2* diazonium resin

primary amine is attached to the T2* diazonium resin **7A** to yield **7B**, which was then deprotonated and converted into thiourea **7C**. The guanylation of **7C** with ammonia, or primary and secondary amines resulted in a variety of trisubstituted guanidines **7D**. The guanidines were then liberated from the resin with the use of TFA to yield **7E**.

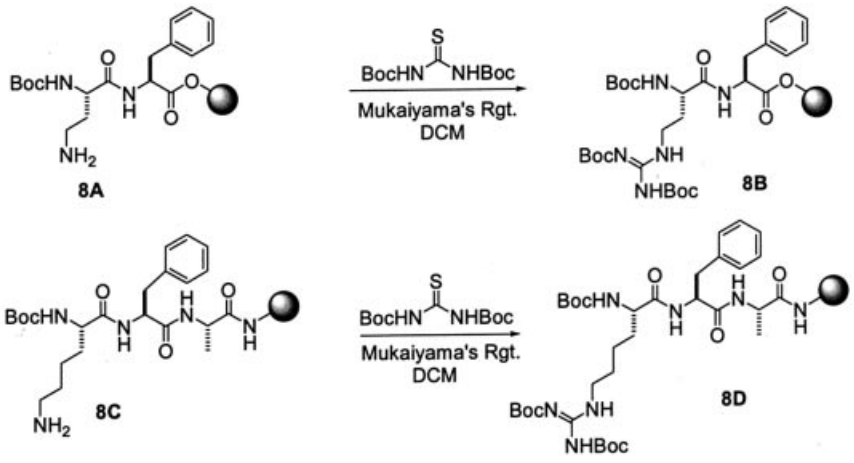
Mukaiyama's Reagent

Guanidinium-Based Catalysts

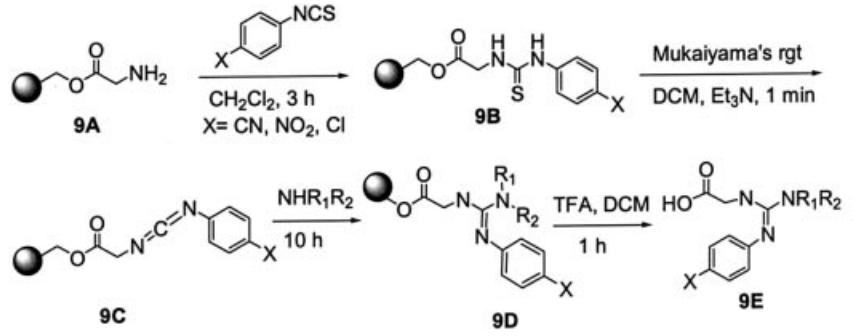
Lipton and co-workers reported the solid-phase synthesis of a guanidine that catalyzes the enantioselective Strecker synthesis of (*S*)-phenylglycine derivatives from *N*-substituted aldimines and hydrogen cyanide. The Boc-protected thiourea and resin-supported complex amines under Mukaiyama's coupling conditions were converted into guanidines (Scheme 8).[77] For example, the dipeptide-preloaded Merrifield resin **8A** and Rink resin **8C** were converted into guanidiniums **8B** and **8D**, respectively.

Guanidinocarboxylic Acids

Burgess and co-workers have reported the synthesis of substituted guanidinocarboxylic acids that can mimic an artificial sweetener (Scheme 9).[78] The isothiocyanate shown was reacted with Wang resin **9A** to give the thiourea **9B**. The treatment of **9B** with Mukaiyama's reagent in the presence of a base resulted in the formation of carbodiimide intermediate **9C**, which was readily converted into the guanidine **9D** upon treatment with another amine. The guanidine was then cleaved from the resin using TFA to yield **9E**.



Scheme 8. Synthesis of a guanidinium based catalyst

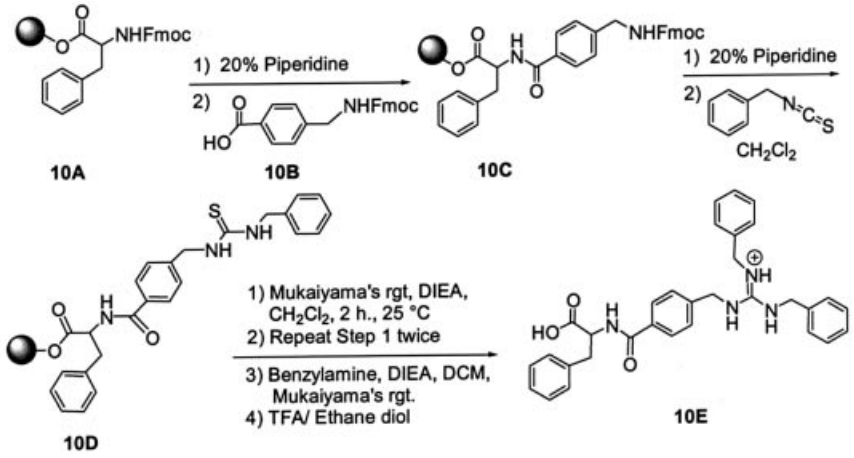


Scheme 9. Synthesis of guanidinocarboxylic acid as an artificial sweetener

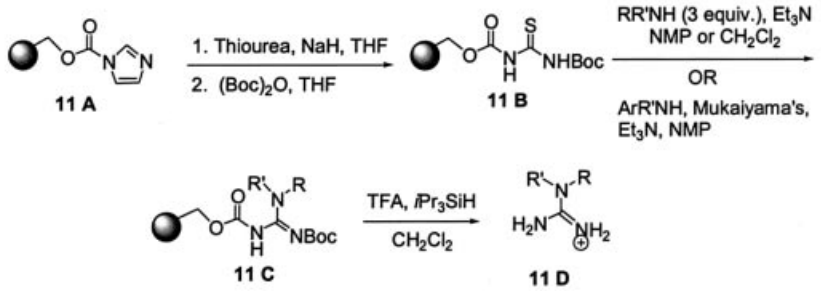
Anslyn and co-workers have reported the synthesis of another guanidinocarboxylic acid (Scheme 10).[80] At first, the linker **10B** was attached to NH_2-Phe-Wang resin **10A** to yield **10C**. The thiourea **10D** was formed by reaction of **10C** with benzyl isothiocyanate. The guanidinium **10E** was formed by coupling of the thiourea **10D** with Mukaiyama's reagent, followed by treatment with an amine and resin cleavage with TFA.

A Sulfonamide-Based Linker as Precursor

Josey and co-workers have reported the synthesis of a solid-phase linker for creating a guanidinium moiety de-



Scheme 10. Synthesis of a guanidinocarboxylic acid for molecular recognition purposes



Scheme 11. Synthesis of guanidinium with sulfonamide-based linker as a precursor

rived from primary, secondary or arylamines (Scheme 11).[81] The carbonylimidazole resin **11A** was prepared from Wang resin by treatment with thiourea in the presence of sodium hydride to give the resin-bound thiourea, which was then Boc protected to give **11B**. Primary and secondary amines reacted very well with this resin-bound thiourea in the presence of *N*-methylpyrolidinone (NMP) to give the guanidine **11C**. For arylamines, the thiourea needed to be activated with Mukaiyama's reagent. The guanidinium **11D** was then cleaved from the resin with TFA.

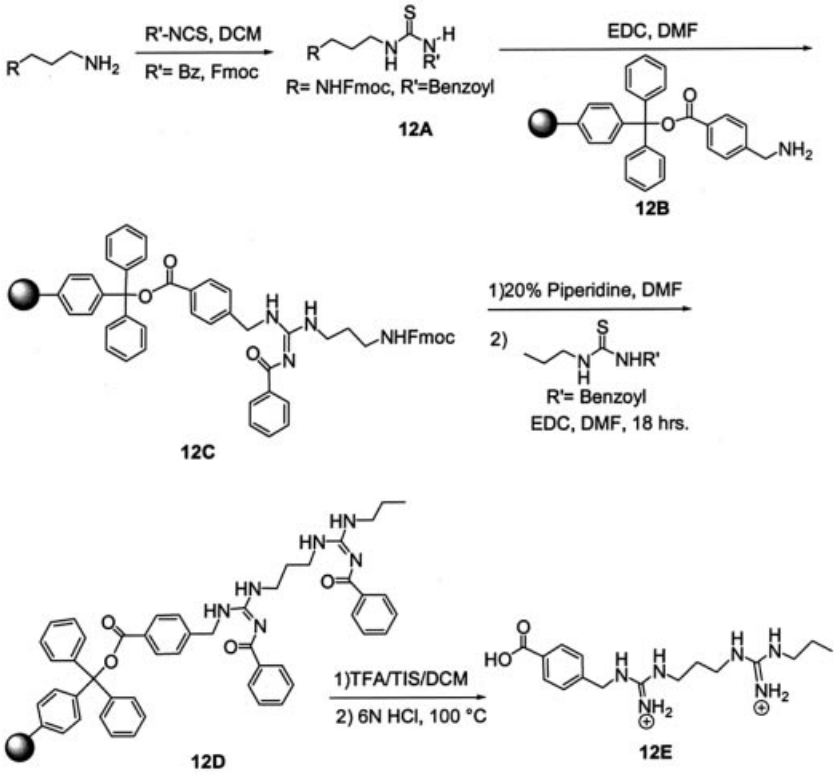
EDC Coupling

Guanidinium Oligomers

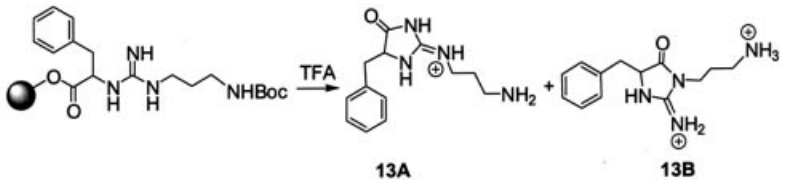
Oligomers of guanidiniums have been developed due to their biological activity, hydrogen bonding capabilities, stability, and positive-charge integrity over a wide pH range.[77] Anslyn and co-workers have reported the synthesis of guanidinium oligomers through EDC coupling (Scheme 12).[80] The EDC coupling of the protected thiourea **12A** with a preloaded chlorotrityl resin and an amine **12B** yielded the guanidine **12C**. The thiourea was prepared from protected isothiocyanates and primary amines. In the case of the thiourea containing another primary amine, it was coupled with another thiourea in the presence of EDC to form a second guanidine **12D**. The product **12E** was then liberated from the resin with TFA.

In strong acids such as TFA, a guanidinium nitrogen δ to an ester or amide carbonyl was cyclized via an Edman-like degradation (Scheme 13) to yield a cyclized amide **13A** and **13B**.[80]

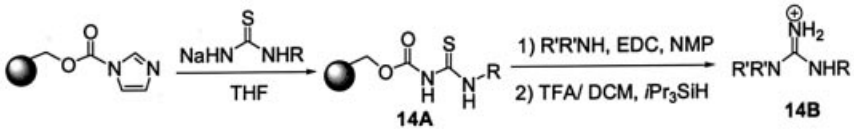
Mixed acyl/alkyl bis-substituted guanidines **14B** can also be made by EDC coupling (Scheme 14), as reported by Josey and co-workers.[81]



Scheme 12. Synthesis of guanidinium oligomers



Scheme 13. Synthesis of cyclized guanidiniums



Scheme 14. Guanidinium synthesis using carbonylimidazole resin

Acyl Thiocyanate Resin as a Precursor

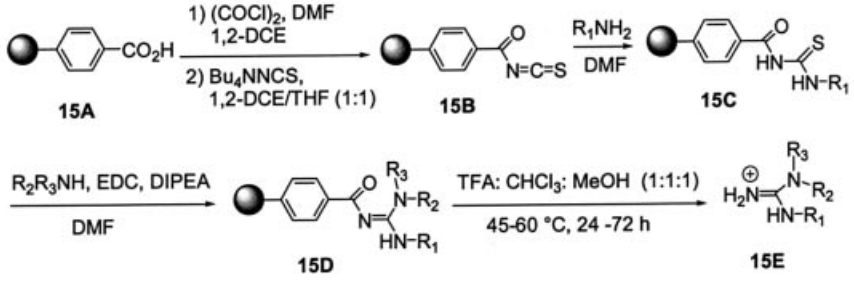
Wilson and co-workers have reported the solid-phase synthesis of mono- and disubstituted guanidines based on a novel acyl isothiocyanate resin (Scheme 15).[82] The reaction of carboxypolystyrene **15A** with oxalyl chloride in DMF and 1,2-dichloroethane (1,2-DCE) gave the acyl chloride, which was then allowed to react with tetrabutylammonium thiocyanate in THF and 1,2-DCE to give the acyl isothiocyanate resin **15B**. This resin was reacted with a variety of amines to give the thiourea **15C**. The guanidine **15D** was formed upon treatment of thiourea with EDC and DIPEA with a primary or secondary amine in DMF. The product **15E** was then easily cleaved from the resin with TFA.

Sanger's Reagent

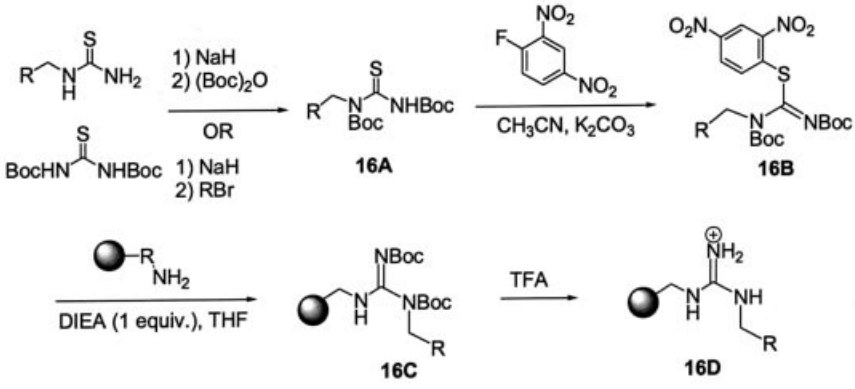
Guanidiniums on solid support could also be created through the use of Sanger's reagent (Scheme 16).[80] At first, the thiourea was protected with a Boc group, and a variety of R groups were added to give **16A**. This thiourea, upon reaction with Sanger's reagent, yielded the strongly activated thiourea **16B**, which was readily reacted with resin-bound amines to give the corresponding guanidine **16C**. The product **16D** could be cleaved from the resin with TFA.

Triphenylphosphane Dichloride

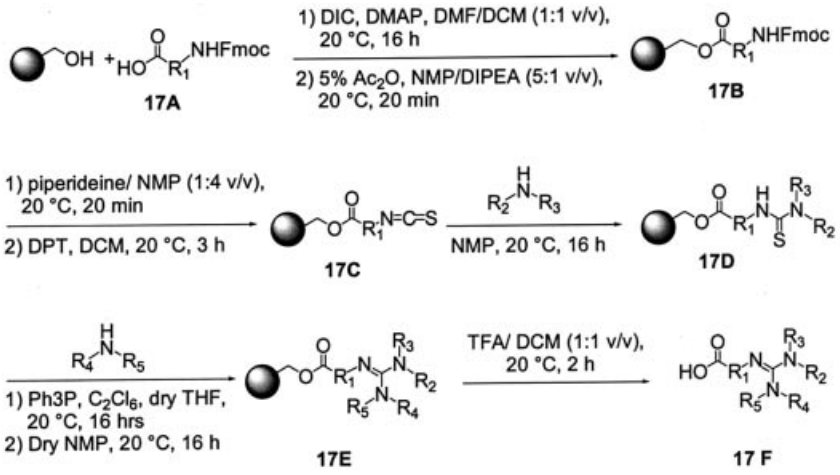
Jones and co-workers have shown that a thiourea can be readily desulfurized by treating it with triphenylphosphane



Scheme 15. Guanidinium synthesis using an acyl thiocyanate resin as a precursor



Scheme 16. Solid phase synthesis of guanidiniums using Sanger's reagent



Scheme 17. Guanidinium synthesis using triphenylphosphane dichloride

dichloride, which can then be easily converted into guanidines (Scheme 17).[83] The Wang resin was first loaded with Fmoc-protected amino acid **17A** by DIC peptide coupling. The Fmoc group was then deprotected and the amine was reacted with di-(2-pyridyl)thionocarbonate (DPT) to yield the isothiocyanate **17C**. The isothiocyanate was then converted into the thiourea **17D** by nucleophilic addition with a range of primary alkyl, secondary alkyl, and arylamines. Desulfurization of the thiourea **17D** was achieved by adding a fresh solution of triphenylphosphane dichloride prepared from triphenylphosphane and hexachloroethane in dry THF. The resulting carbodiimide was then readily converted into the guanidine **17E** by addition of primary alkyl, secondary alkyl, or arylamines. The cleavage of the *N*,*N*′,*N*′′- substituted guanidines **17F** from the solid support was accomplished by treatment with 50% TFA in DCM.

Guanidiniums from Isothiourea

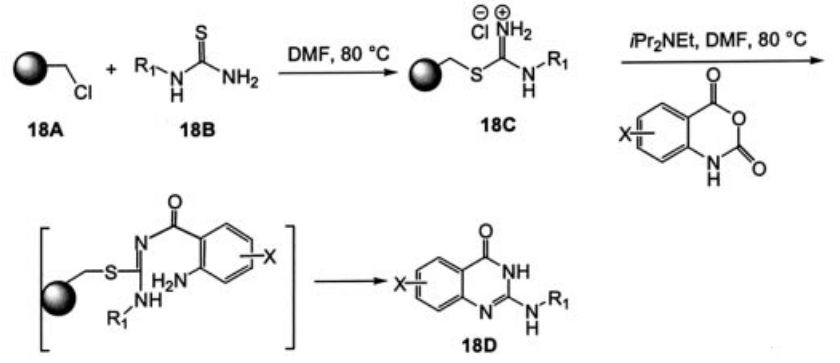
Solid-phase immobilization of isothiourea is used for the synthesis of ribonucleic acid analogs,[84][85] as well as precursors for guanidiniums. Resin-bound isothiourea is widely used as the precursor for 4(3*H*)-quinazolinone, pyrimidines, *N*-acyl-*N*′-carbamoylguanidines, parallel synthesis of guanidines, and other guanidiniums.

4(3*H*)-Quinazolinone

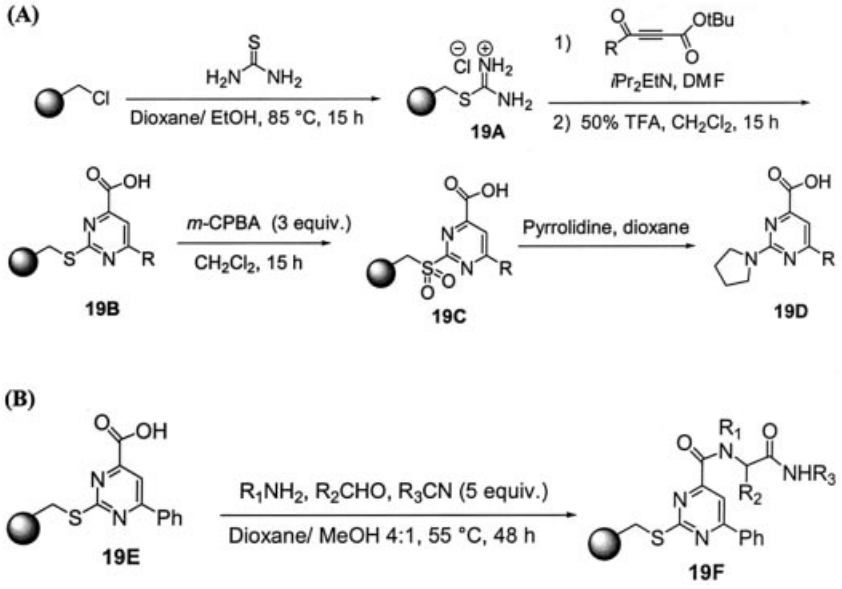
4(3*H*)-Quinazolinone has anticonvulsant,[86] antihypertensive,[87] antidiabetic,[88] anti-tumor,[89] antimicrobial,[90] and antihistaminic[92] activities. Yang and co-workers have reported the synthesis of 2-amino-4(3*H*)-quinazolinones on a solid phase (Scheme 18).[91] The reaction of chloromethylated polystyrene resin **18A** with thiourea **18B** resulted in the polymer-bound isothiourea **18C**, which was then allowed to react with isatoic anhydride and DIEA to give the 2-amino-4(3*H*)-quinazolinone **18D** after cleavage and intramolecular cyclization.

Pyrimidines

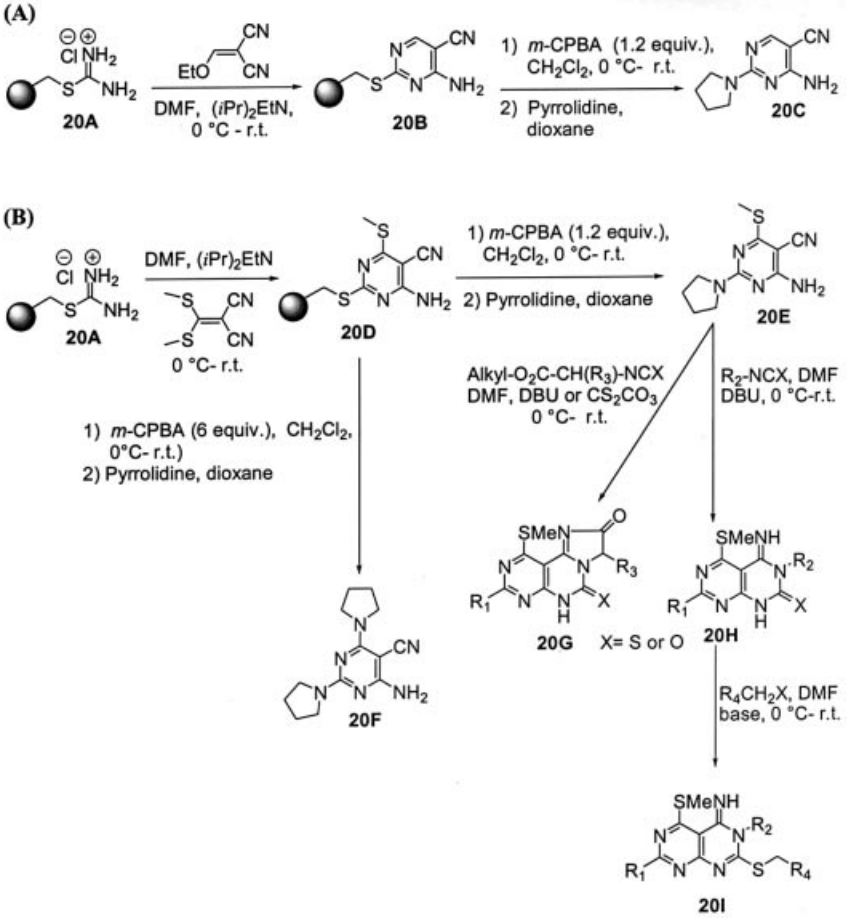
Pyrimidines and other nitrogen heterocycles are common pharmacophores[92] and are of high biological interest.[93] Pyrimidine derivatives are used as antiallergic,[94] antitumor,[95] antipyretic, anti-inflammatory,[96] and antiparasitic agents.[97] Obrecht and co-workers have reported a versatile cyclocondensation reaction of acetylenic ketones with a polymer-bound isothiourea.[98] These reactions formed



Scheme 18. Solid phase synthesis of 4(3*H*)-quinazolinone



Scheme 19. (A) Pyrimidine synthesis using an acetylenic ketone; (B) an Ugi four-component reaction



Scheme 20. (A) Synthesis of a pyrimidine precursor; (B) synthesis of tri- and tetrasubstituted pyrimidines

polymer-bound 2-(alkylthio)-4,6-disubstituted pyrimidines **19D** by the displacement reaction of the 2-sulfonyl group of pyrimidines with various nucleophiles (Scheme 19A).[98] The reaction of thiourea in dioxane/EtOH (4:1) with Merrifield resin gave the resin-bound thiouronium salt **19A**. This was then condensed with acetylenic ketones in DMF and diisopropylethylamine (DIEA) to give the corresponding resin-bound pyrimidinecarboxylic acids **19B** after cleavage

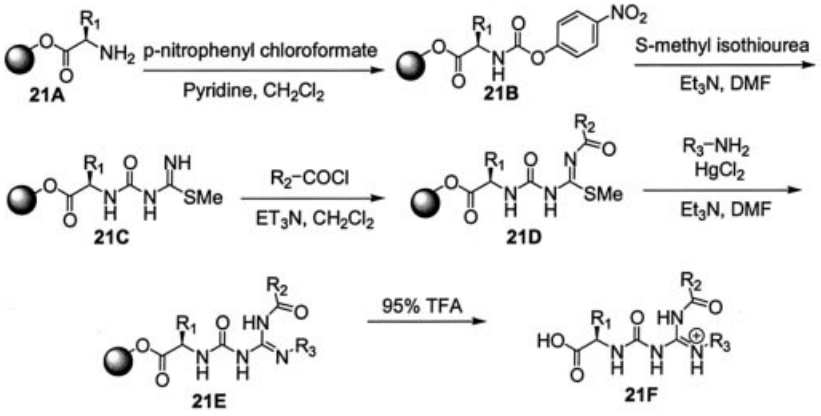
of the *tert*-butyl esters with 50% TFA in DCM. In order to cleave the product from the resin, the 2-alkylthio group was converted into the corresponding sulfone **19C** with 3-chloroperbenzoic acid in DCM, which was subsequently cleaved with various amine nucleophiles.

Prior to the resin cleavage, some of the carboxylic acid **19E** underwent an Ugi four-component reaction, where a carboxylic acid, an amine, an aldehyde, and an isocyanide formed an α-(acylamino) amide **19F** (Scheme 19B).[98] The product was then liberated as described above.

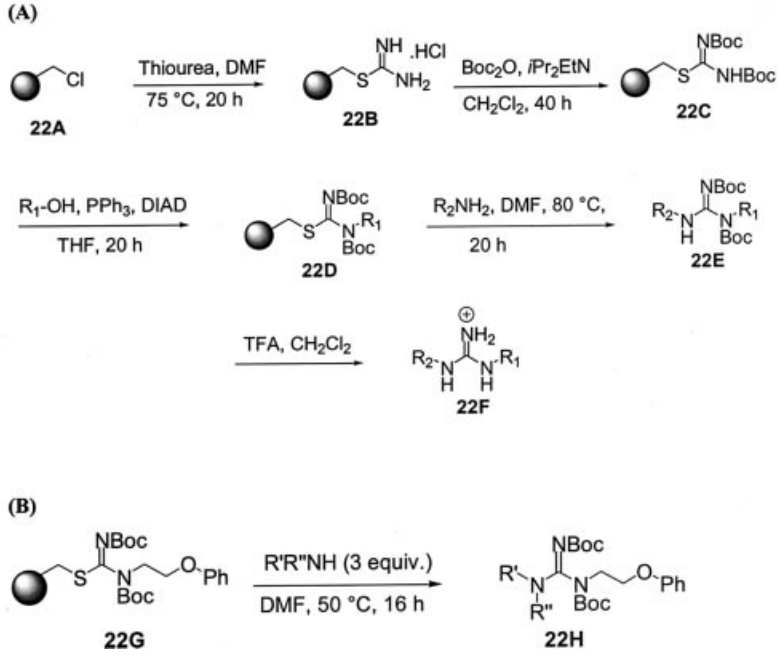
Masquelin and co-workers have reported the synthesis of 2,4,5-tri- and 2,4,5,6-tetrasubstituted pyrimidines and their conversions into condensed heterocycles (Schemes 20A and B).[99] The resin-bound thiouronium salt **20A** was reacted with (ethoxymethylidene)malononitrile or [bis (methylthio)-methylidene]malononitrile in DMF in the presence of DIEA to give the corresponding resin-bound (alkylthio)pyrimidines **20B** and **20D**. The pyrimidine derivatives could be oxidized with *meta*-chloroperbenzoic acid (*m*-CPBA) and reacted with pyrrolidine to form the derivatives **20C**, **20E**, and **20F**. The product was cleaved from the resin with an amine base to give the corresponding substituted pyrimidines. The compound **20E** was converted into the condensed heterocycles **20G** and **20H** by reaction with a thiocyanate or amide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Further, the thiourea-containing **20H** was converted into **20I** in the presence of an alkyl halide.

N-Acyl-N′-carbamoylguanidines

Amino acids that were immobilized on polystyrene-Wang or Rink resin **21A** were allowed to react with *p*-nitrophenyl chloroformate to give an activated urethane (**21B**, Scheme 21).[100] The urethane was then displaced by *S*-methyl isothiourea to yield **21C**. *N*-acylation of the isothiourea with an acid chloride activated **21C** to yield **21D**, allowing conversion into the guanidinium **21E** by displacing the thiomethyl group in the presence of $HgCl_2$ with a prim-



Scheme 21. Synthesis of *N*-Acyl-*N*′-carbamoylguanidines



Scheme 22. (A) Parallel synthesis of guanidiniums

ary amine. The product was liberated in the presence of TFA to give **21F**.

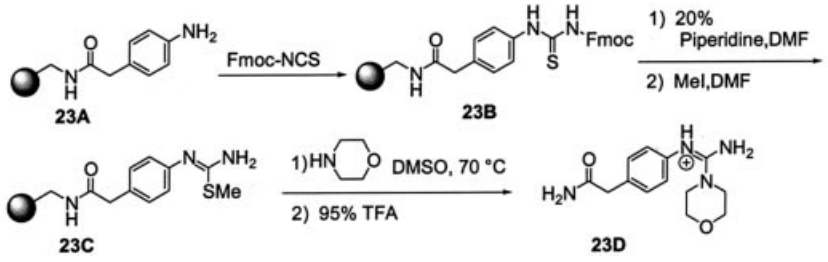
Parallel Synthesis

Dodd and co-workers have reported the parallel synthesis of mono-*N*-alkylated guanidines and *N*,*N*′-bisalkylated guanidines from resin-bound *N*,*N*′-bis Boc thiopseudourea as the masked guanidine scaffold (Scheme 22A).[101] Treatment of Merrifield resin **22A** with excess thiourea gave the resin-bound thiouronium salt **22B**, which was then Boc protected to give **22C**. Reaction of this protected thiopseudourea with alcohol in the presence of triphenylphosphane and diisopropyl azodicarboxylate (DIAD) gave **22D** in a Mitsunobu reaction. The guanidinium **22F** was then obtained by guanylation of **22D** with an amine to form **22E**, followed by deprotection with TFA.

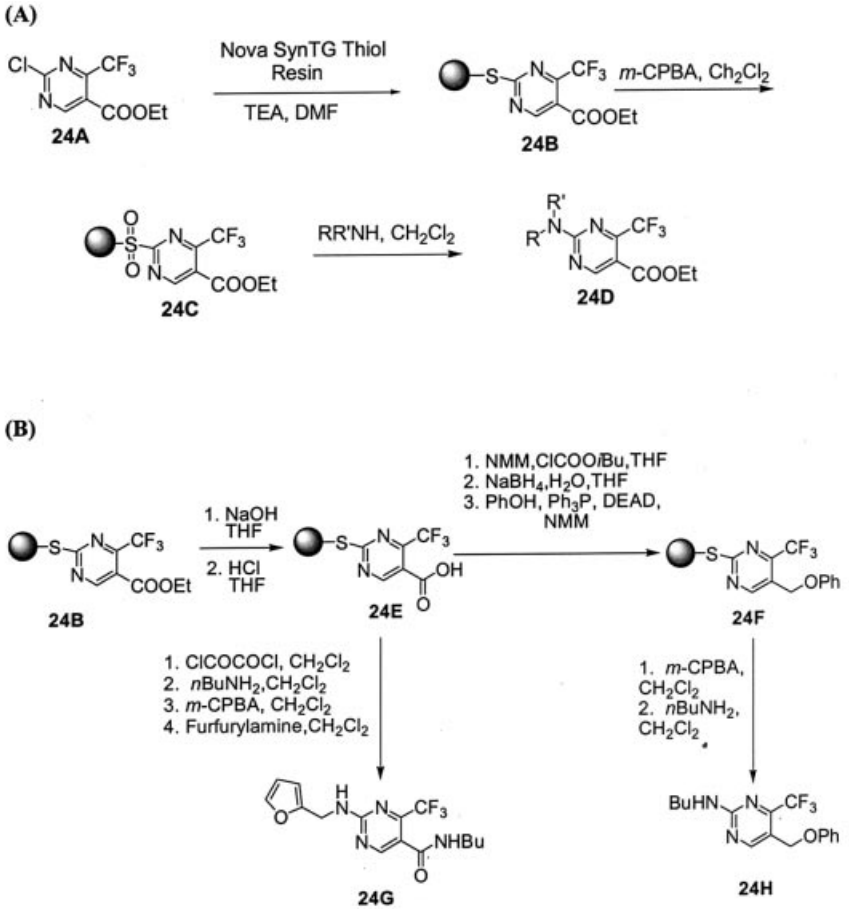
Coupling of a secondary amine to certain protected thiopseudoureas such as **22G** also gave guanidinium **22H** (Scheme 22B).[101]

Disubstituted Guanidines from Methyl Isothiourea

Flygare and co-workers have reported the synthesis of disubstituted guanidines from methyl isothiourea with morpholine, piperidine, and *N*-methylphenethylamine (Scheme 23).[102] The amino acid was attached to the Rink amide methylbenzhydrylamine (MBHA) resin through HOBt/2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) coupling to yield



Scheme 23. Disubstituted guanidinium from methyl isothiourea



Scheme 24. (A) Guanidinium synthesis by incorporating a traceless linker; (B) functionalized pyrimidines using a traceless linker

23A, which was then treated with Fmoc-thiocyanate to give the protected thiourea **23B**. After deprotection, the thiourea was converted into the methyl isothiourea **23C** by treatment with MeI. The aforementioned amines were then reacted with **23C** to give the corresponding guanidine, such as **23D**, after cleavage from the resin in 95% TFA.

Incorporation of a Traceless Linker

Suto and co-workers have reported the solid-phase synthesis of guanidiniums without using a functionalized resin (Scheme 24A).[103] This method prevented the presence of an undesired functionality in the product. The 2-chloro-4-trifluoromethyl pyrimidine-5-carboxylate **24A** was attached to the polyethylene glycol resin to form the isothiourea **24B**. The thiourea was then converted into the sulfone **24C** by treatment with excess *m*-CPBA. The sulfone **24C** was readily converted into **24D** by reaction with 1,3-pyrimidine substituted with an amine at the 2-position.

The resin-bound isothiourea from the above reaction also underwent reactions such as saponification, conversion into the acid chloride, reduction to the alcohol, and Mitsonobu couplings to give various functionalized and substituted 1,3-pyrimidines (Scheme 24B).[103]

Conclusion

In the past couple of decades, the interest of guanidinium groups in biological, pharmaceutical, and supramolecular applications has been ignited. They are valuable precursors of numerous medicinally important molecules and are assets in biological research. The chemical properties of the guanidinium moiety as well as its ability to form H-bonds, charge pairing, and cation-π interactions opens up a large number of possibilities in molecular recognition. As we learn on a daily basis that many biologically active compounds contain this moiety, the synthetic creation of it is in great demand. In laboratories, solid-phase chemistry has flourished into a chemist's companion in making synthetically challenging molecules. Due to the use of solid-phase combinatorial chemistry to develop potentially lead compounds, pharmaceutical companies are racing to find affordable yet faster ways to synthesize this moiety. The use of thiourea and isothiourea as precursors is of clear importance. As described herein, these expedient precursors can be utilized in the presence of diverse reagents and coupling agents.

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