Recent developments in guanylating agents

Alan R. Katritzky*[,±] and Boris V. Rogovoy[§]

[±]*Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, P. O. Box 177200, Gainesville, FL 32611-7200*
[§] *Department of Pharmaceutical Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854*
E-mail: katritzky@chem.ufl.edu

Dedicated to Professor Nikolai Zefirov on the occasion of his 70th birthday

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Abstract

Guanidines are important molecules with a wide range of interesting properties. In this overview we summarize recent advances in the development of guanylating reagents which we define as compounds forming a guanidine structure by a chemical transformation. We cover important classes of guanylating agents developed in the last two decades and representative examples are reported.

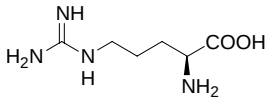
Keywords: Guanidine, guanidines, guanylating agent, guanylation, synthesis, preparation

Contents

1. Introduction

Guanidines possess great biochemical and pharmaceutical importance. Guanidine itself is a strong base (pKa of conjugated acid is 12.5) as are substituted guanidines.[1a] Guanidine was first prepared by Strecker in 1861 by oxidizing guanine. The biological role, chemical and biochemical properties of natural and synthetic guanidine derivatives have been outlined.[1b] The

natural amino acid, L-arginine **1**, is often found at active (or catalytic) sites in proteins and enzymes; it is critical for the normal function of living organisms.[2]



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Many natural guanidines have been isolated and tested for biological activity. The isolation, structural identification and synthesis of naturally occurring guanidines have been reviewed by Berlinck.[3a-d] The isolation and synthesis of guanidine metabolites from *Ptilocaulis spiculifer* has also been summarized.[3e] Isolation of guanidine compounds as metabolites provides leads for the prevention of metabolic disorders and helps the prognosis of cancer, cardiovascular diseases, diabetes etc.[3f] Recent examples of synthetic, biologically-active guanidines include antimicrobial activity,[4a,b] thrombin inhibitors,[5] Na^+/H^+ exchanger (NHE) inhibitors,[6a,b] transport for the delivery of anti-cancer agents,[7a,b] anti-influenza agents.[7d]

Figure 1 shows a few examples of superpotent sweeteners with the guanidine core structure;[8a] which have attracted a great deal of recent interest.[8b-e]

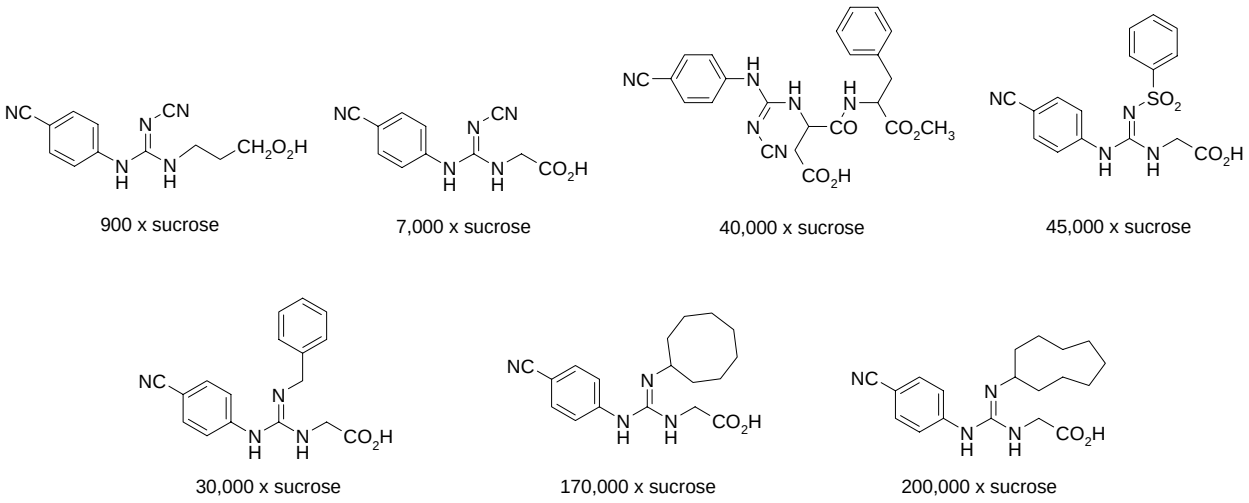


Figure 1. Superpotent guanidine sweeteners.

Guanidines are also known as useful basic catalysts.[1a,9] Several reports describe the synthesis of chiral guanidines and their use in asymmetric synthesis.[10a-c]

An excellent review of preparative methods for guanidines was prepared by Anslyn et al.,[11a] and others have emphasized solid phase synthesis.[11b,c]

Their wide importance has prompted the investigation of new approaches to guanidine derivatives. In this overview we summarize recent advances in the development of guanylating reagents (i.e. compounds which form the guanidine structure by a chemical transformation) for guanidine synthesis. Functionalizations of pre-existing guanidine cores, e.g., by alkylation, arylation or acylation are not covered. We do not attempt to catalog exhaustively the enormous

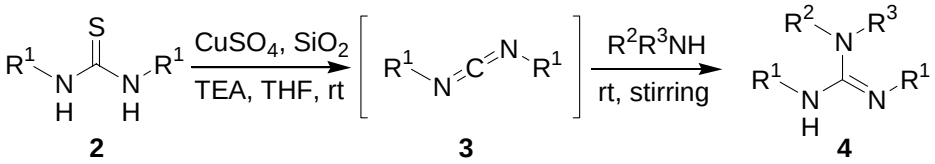
range of synthetic guanidine derivatives, but limit our review to reports describing the discovery of guanylating reagents, and investigations of reaction conditions (time, temperature, catalysis etc.) undertaken to improve the yields of guanidines. Reports of the preparation of guanidine compounds by previously developed methods (such as the synthesis of guanidine natural products and oligomers) are also outside the scope of this report.

2. Reagents for the preparation of guanidines

2.1. Thioureas

Thioureas are common reagents for the synthesis of guanidines. Usually the conversion of a thiourea into a guanidine requires initial activation. However, in many cases the characterization, isolation or even definition of active intermediates is not described.

Scheme 1 presents the conversion of thioureas **2** into guanidines **4** in a suitable solvent (THF, acetonitrile, or chloroform) containing copper sulphate – silica gel in the presence of tertiary amines.[12] The formation of the intermediate carbodiimide **3** (non-isolable under these conditions) proceeds quickly and the overall reaction time is short (Table 1). The presence of a tertiary amine, e.g., triethylamine, accelerates the desulfurization. The procedure allows the preparation a very wide range of di-, tri- and tetra-substituted guanidines.

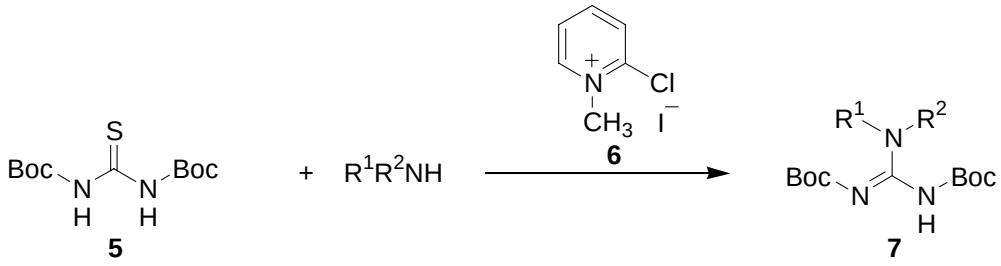


Scheme 1

Table 1. One pot desulfurization of thioureas and reaction with an amine by the procedure of Scheme 1

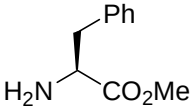
Entry	R^1	R^2	R^3	Reaction time, min	Yield, %
1	Ph	CH_3	H	50	78
2	Ph	CH_3	CH_3	55	75
3	Ph	C_6H_{11}	H	50	85
4	Ph	C_2H_5	C_2H_5	50	90
5	Ph	$PhCH_2$	H	50	80
6	Ph	*n*-Bu	H	45	75
7	*o*-Tolyl	C_2H_4OH	H	55	75
8	Ph	H	H	50	90
9	*o*-Tolyl	H	H	50	85
10	C_6H_{11}	H	H	60	86
11	n-Bu	H	H	50	80

Electron withdrawing substituents in the thiourea fragment also accelerate the reaction. Many recent synthetic approaches utilize protected thioureas, containing electron withdrawing protecting groups which can be removed by standard methods. Thus, di-Boc protected thiourea **5** is converted into guanidines **7** by amines in the presence of 1-methyl-2-chloropyridinium iodide[13] **6** (Mukaiyama's reagent, Scheme 2, Table 2) as follows: (i) primary and unhindered secondary amines are guanylated in high (>80%) yield using a slight excess of reagent in anhydrous DMF (entries 1-4); (ii) for hindered or unreactive amines, methylene chloride provides a substantial increase in yield (entries 7 and 8) over reactions run in DMF (entries 5 and 7). The effect of solvent on yield probably results from the instability of the carbodiimide intermediates. When nucleophilic attack by an amine is slow, competitive decomposition of the carbodiimide occurs. In methylene chloride, the reactions are heterogeneous owing to sparing solubility of the di-Boc protected thiourea; it is believed that this results in slower production of the di-Boc carbodiimide and consequently, more efficient consumption of the thioureum by less reactive amines. The guanylation of resin-bound amines under these conditions was also examined.

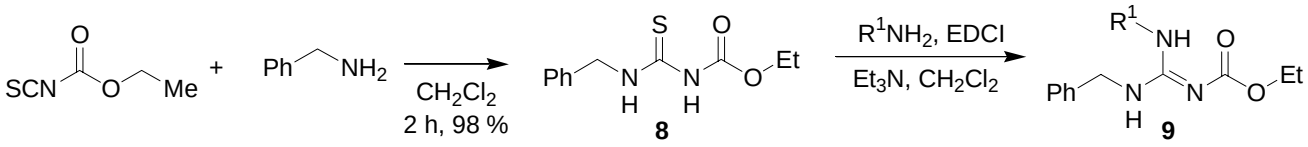


Scheme 2

Table 2. Preparation of guanidines from thioureas promoted by Mukaiyama's reagent (Scheme 2)

Entry	R^1R^2NH	Solvent	Product yield, %
1	$PhCH_2NH_2$	DMF	91
2	Diallylamine	DMF	86
3	Piperidine	DMF	57
4		DMF	85
5	Diisopropylamine	DMF	21
6	Diisopropylamine	CH_2Cl_2	71
7	Aniline	DMF	34
8	Aniline	CH_2Cl_2	92
9	4-Nitropyrazole	DMF	43

Ethoxycarbonyl substituted thioureas **8** are prepared using the corresponding isothiocyanate (Scheme 3). Guanidines **9** are prepared by displacement of sulfur in the presence of ethyl-3-aminopropyl carbodiimide hydrochloride (EDCI)[14] in 48 h without the formation of any major side products. The guanidines obtained *via* EDCI coupling (Table 3) were easily purified by flash chromatography. Deprotection can be achieved by the treatment with Me_3SiBr.

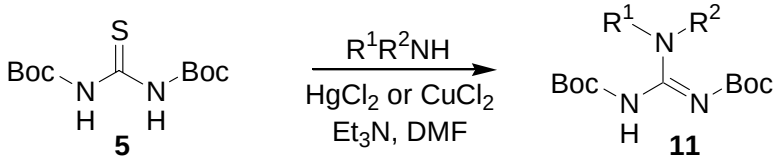


Scheme 3

Table 3. One pot preparation of guanidines by EDCI desulfurization and reaction of with amines (of Scheme 3)

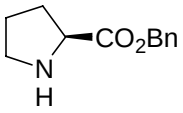
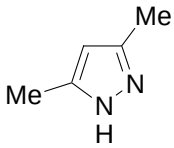
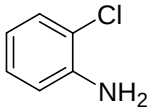
Entry	R^1NH_2	Yield, %	Entry	R^1NH_2	Yield, %
1	Benzylamine	80	6	2-Methylbenzylamine	80
2	4-Aminobenzylamine	83	7	Aniline	87
3	4-Nitrobenzylamine	88	8	*i*-Propylamine	85
4	4-Methoxybenzylamine	85	9	*t*-Butylamine	83
5	2,4-Dimethoxybenzylamine	78			

Amines can be converted into guanidines **11** by the reaction di-Boc thiourea **5**[15] in the presence of mercuric chloride or copper(II) chloride in the presence of triethylamine (Scheme 4). The influence of the desulphurizing agent is shown in Table 4.

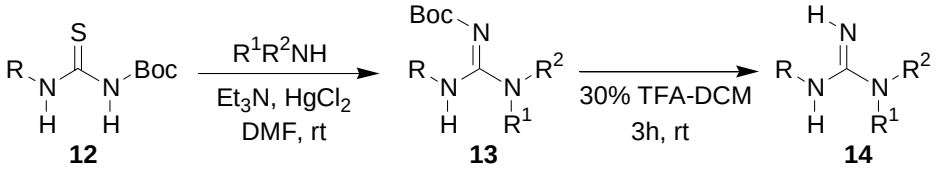


Scheme 4

Table 4. Preparation of guanidines in the presence of copper or mercuric salts (see Scheme 4)

Entry	Amine	Metal Salt	Conditions	Yield, %
1		$HgCl_2$	0 °C, 20 min	90
		$CuCl_2$	0 °C, 0.5 h, rt, 0.5 h	62
2		$HgCl_2$	60 °C, 2 h	87
3	$CF_3CH_2NH_2$	$HgCl_2$	rt, 1 h	89
		None	60 °C, 4 h	0
4		$HgCl_2$	rt, 2 h	78
		$HgCl_2$	rt, 20 h	92
		none	60 °C, 6 h	0
5	$((CH_3)_2CH)_2NH$	$HgCl_2$	0 °C, 0.5 h	90

N-Boc-*N'*-alkyl or aryl thioureas **12** reacted smoothly with an aryl or alkyl amine in the presence of $HgCl_2$[16a] (Scheme 5). The *N*- boc-*N'*,*N''*-disubstituted guanidine products **13** are easily deprotected, as shown in Scheme 5, providing an efficient route to *N*,*N'*-disubstituted guanidines**14**, which compares favorably with other methods (Table 5). For an adaptation to solid phase synthesis see ref 16[b].



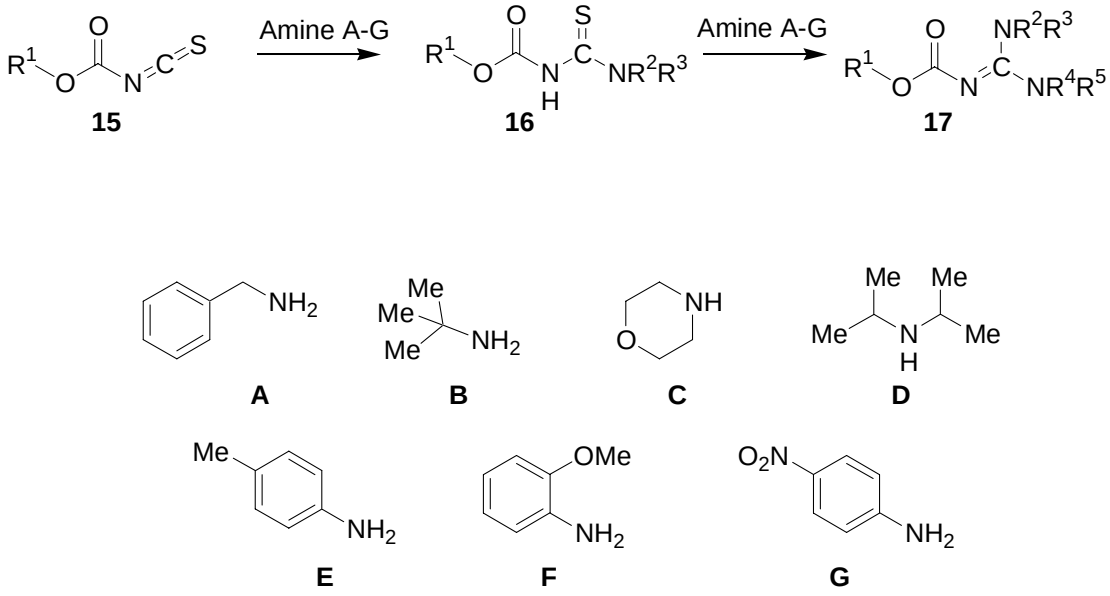
Scheme 5

Table 5. Synthesis of protected guanidines in the presence of $HgCl_2$ (see Scheme 5)

Entry	X	R	R^1R^2NH	Yield, %
1	Boc	Cyclohexyl	2-Tetrahydroisoquinoline	63
2	Boc	Cyclohexyl	Aniline	70
3	Boc	4-Nitrophenyl	4-Methoxyaniline	85
4	CH_3CO	Cyclohexyl	2-Tetrahydroisoquinoline	75
5	PhCO	Cyclohexyl	2-Tetrahydroisoquinoline	75
6	$PhCH_2CO$	Cyclohexyl	2-Tetrahydroisoquinoline	67
7	Ts	Cyclohexyl	2-Tetrahydroisoquinoline	83(41[a])
8	CN	Cyclohexyl	2-Tetrahydroisoquinoline	61[a]

[a] Overall yield for the two steps: formation of thiourea and in situ conversion into a guanidine derivative.

Carbamoyl isothiocyanates **15** possess several advantages for the preparation of thioureas[17] (Scheme 6, Table 6): These reagents provide a protecting group throughout the synthesis, facilitating purification, and they show increased reactivity over alkyl isothiocyanates, forming thioureas even with hindered amines. A second amine can be coupled to the carbamoyl thiourea **16** using EDCI, forming 1,3-disubstituted and 1,1,3-trisubstituted guanidines **17** through either a stepwise or one-pot synthesis. To gauge the steric and electronic limitations of this procedure, amines of varying reactivity (**A**-**G**) were investigated for their ability to form protected thiourea and guanidine; yields for reactions of ethoxycarbonyl isothiocyanate are shown in Table 6. This procedure is general for other carbamoyl isothiocyanates (ethyl carbamate, benzyl carbamate (Cbz), 2,2,2-trichloro-1,1-dimethylethyl carbamate, fluorenylmethyl carbamate (Fmoc), and phenyl carbamate) which allows synthetic flexibility in the deprotection.

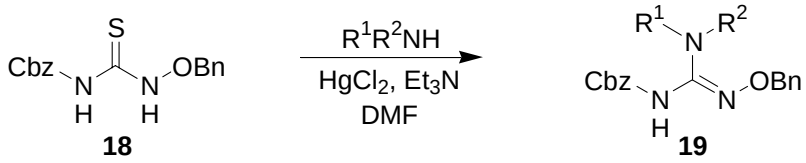


Scheme 6

Table 6. Synthesis of protected thioures **16** and guanidines **17** (see Scheme 6)

		% Yield of guanidine **17**						
Amine	% Yield of thiourea **16**	**A**	**B**	**C**	**D**	**E**	**F**	**G**
A	99	99	99	95	76	92	82	85
B	99	99	74	59	55	99	99	65
C	99	0	0	0	0	0	0	0
D	99	0	0	0	0	0	0	0
E	92	99	87	99	81	95	97	34
F	77	96	99	61	84	98	67	39
G	72	85	76	99	42	35	34	0

N-Hydroxyguanidines **19** were prepared from 1-benzyloxy-3-Cbz-thiourea **18**[18] (Scheme 7, Table 7). The Cbz strategy was chosen because cleavage of the Cbz and benzyl groups could be accomplished simultaneously. The solvent of choice was DMF; mercuric chloride provided efficient desulphurization.

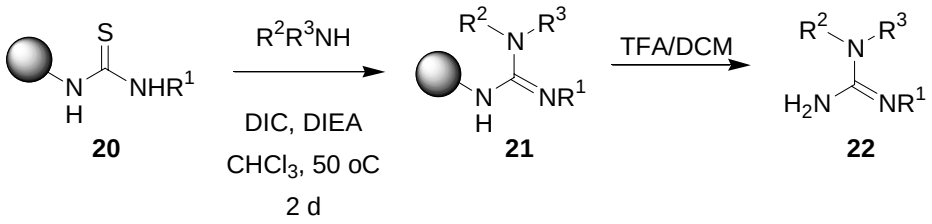


Scheme 7

Table 7. Synthesis of hydroxyguanidines in the presence of $HgCl_2$ (see Scheme 7)

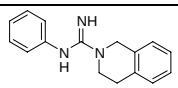
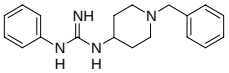
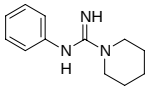
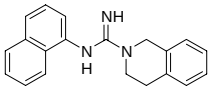
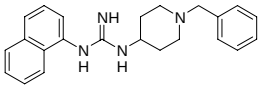
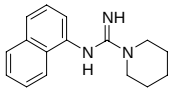
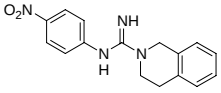
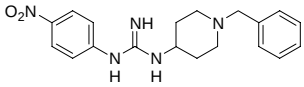
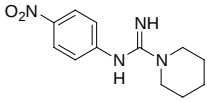
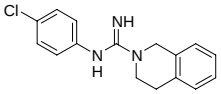
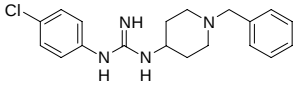
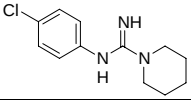
Entry	Amine	Reaction time, h	Yield, %
1	Benzyl amine	7	47
2	2-Aminocarbonylaziridine	9	34
3	Aniline	7.5	54
4	Diisopropylamine	9	34
5	3-Hydroxypropylamine	7	35
6	Aminoadamantane	10.5	67

The desulphurization of a thiourea to a carbodiimide and subsequent reaction with an amine was applied to solid phase synthesis.[19] The thiourea **20** was treated with an amine (5 equiv.) at 50°C in $CHCl_3$ in the presence of DIC (diisopropylcarbodiimide) (5 equiv.) and DIEA (5 equiv.) to give the resin bound guanidine **21**. The disubstituted guanidine **22** was then cleaved under mild Rink resin cleavage conditions (25% TFA/CH_2Cl_2 at room temperature) (Scheme 8, Table 8).

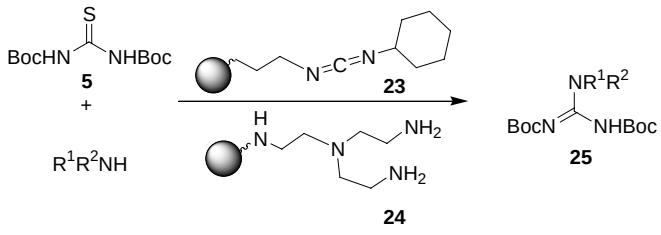


Scheme 8

Table 8. Conversion of thioureas to guanidines on solid phase (of Scheme 8)

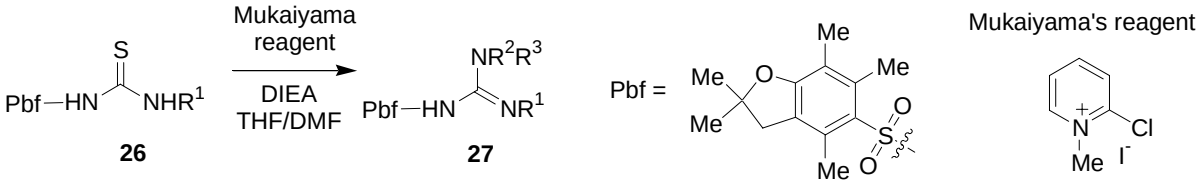
Entry	Product	Yield, %	Purity
1		71	70
2		77	54
3		70	56
4		95	86
5		98	91
6		89	75
7		87	90
8		95	85
9		96	95
10		100	83
11		99	83
12		88	83

The approach of Scheme 9 combines the advantages of traditional solution phase chemistry with the application of polymeric reagents.[20] The desired compounds are obtained in a high throughput manner without additional purification, and in satisfactory purity. No base is required.



Scheme 9

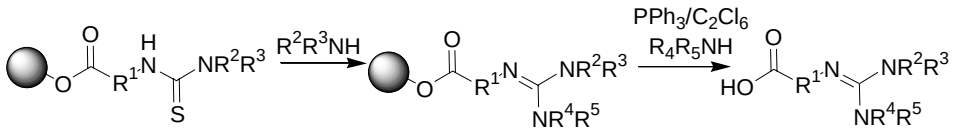
The use of TFA-cleavable Pbf-group protection/activation is an advantageous alternative for the synthesis of guanidines[21a] (Scheme 10). Primary or secondary amines, including *tert*-butylamine and diisopropylamine, in the presence of Mukaiyama's reagent, give guanidines **27** in high yields at room temperature and in 12-18 h. The high efficiency of Mukaiyama's reagent in promoting the guanidinylating reaction contrasts with its role in sulfamoylthiourea based systems. The transformation also succeeds with EDCI in place of Mukaiyama's reagent. No heavy metal salt or excessive heating was needed.



26 **27**

Scheme 10

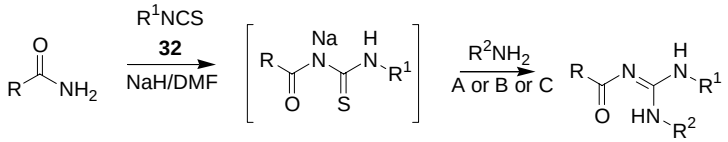
Solid phase strategy for the preparation of guanidines **30** has also applied triphenylphosphine dichloride as a desulphurizing agent.[21b] The immobilised thiourea **28** was treated with triphenylphosphine dichloride freshly prepared from triphenylphosphine with hexachloroethane in THF. The use of base proved to be detrimental.



28 **29** **30**

Scheme 11

The preparation of *N*,*N'*-disubstituted acylguanidines from primary amides **31,** isothiocyanates **32** and amines [21b] has utilized three alternative one pot procedures: $HgCl_2$, EDCI and Mukaiyama's reagent; each showed comparable yields of guanidines.



31 **33** **34**

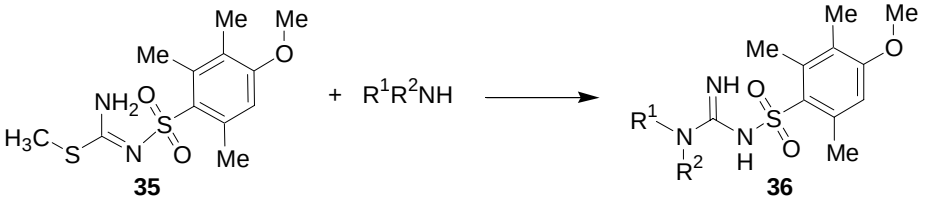
A = $HgCl_2$
B = EDCI, DMAP, Et_3N
C = 2-Chloro-1-methylpyridinium Iodide

Scheme 12

2.2. Isothioureas

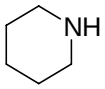
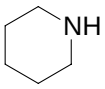
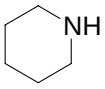
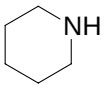
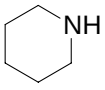
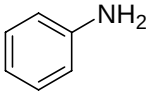
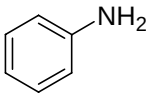
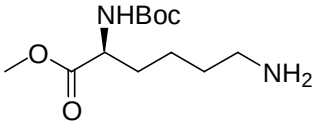
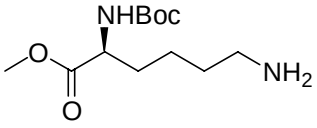
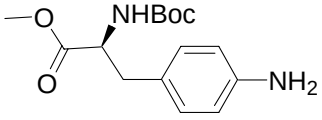
As well as thioureas, isothioureas, particularly *S*-methylisothioureas, are well developed as guanylating agents due to their easy preparation and availability.

Guanidines have been successfully prepared from *N*-arylsulfonyl *S*-methylisothioureas.[22] The Mtr-reagent **35** (Mtr is 4-methoxy-2,3,6-trimethylphenylsulfonyl) reacted with piperidine or aniline in the presence of triethylamine and $Hg(ClO_4)_2$ in refluxing THF (or toluene) to produce mono Mtr-protected guanidines **36** in moderate to good yields (Schemes 13, Table 10). Higher yields were obtained when the reactions were carried out in refluxing THF in the presence of triethylamine and mercuric perchlorate.

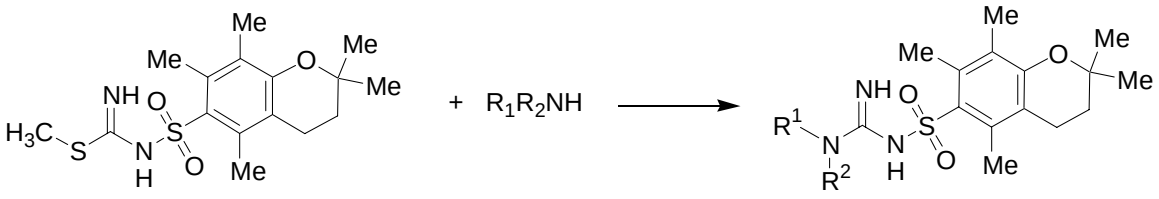


Scheme 13

Table 10. Synthesis of Mtr-protected guanidines **36** (of Scheme 13)

Entry	R^1R^2NH	Conditions	Yield, %
1		$HgCl_2$ (1.1 eq.), THF, Δ	42
2		$HgCl_2$ (1.1 eq.), Et_3N (2 eq.), toluene, Δ	37
3		$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), toluene, Δ	62
4		$AgClO_4$ (1.1 eq.), Et_3N (2 eq.), toluene, Δ	46
5		$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), THF, Δ	80
6		$HgCl_2$ (1.1 eq.), Et_3N (2 eq.), toluene, Δ	>20
7		$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), toluene, Δ	47
8		$HgCl_2$ (1.1 eq.), Et_3N (1.5 eq.), THF, Δ	51
9		$AgClO_4$ (1.1 eq.), Et_3N (2 eq.), toluene, Δ	71
10		$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), THF, Δ	93

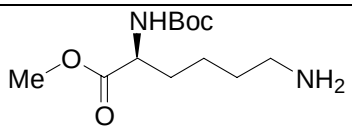
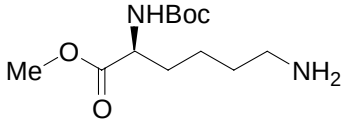
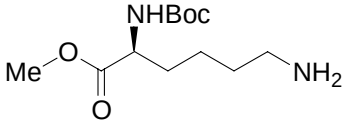
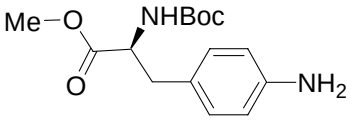
Reagents **35** and **37** (Schemes 13,14) were evaluated with several substrates to determine optimal conditions (Tables 10, 11). The reagents were reacted with Boc-Lys-OMe.HC1 and Boc-*p*-aminophenylalanine-OMe. The protected lysine ester (Table 11, Entries 1-3) has a primary aliphatic amine side chain but appears to react with **35** and **37** less readily and in lower yield, than the other substrates. The Boc-*p*-aminophenylalanine-OMe substrate reacts efficiently with both reagents in high yield to produce the target guanylated amino acids (Entry 4). These results indicate that arylsulfonyl isothioureas react with the less nucleophilic electron deficient amines more readily than the more basic primary aliphatic amines.



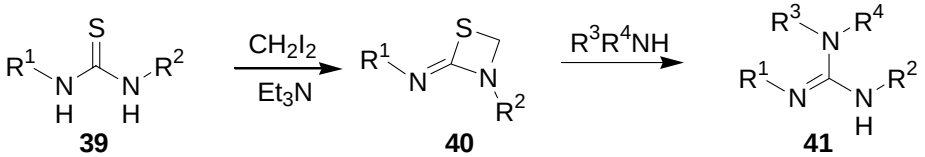
37

Scheme 14

Table 11. Synthesis of Pbf-protected guanidines **36** by procedure of Scheme 14

Entry	R^1R^2NH	Conditions	Yield, %
1		$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), toluene, Δ, 16 h	24
2		$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), THF, Δ, 48 h	35
3		$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), THF, Δ, 60 h	41
4		$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), THF, Δ, 60 h	93
5	CF_3CH_2-	$Hg(ClO_4)_2$ (1.1 eq.), Et_3N (2 eq.), neat, Δ, 16 h	72

The relatively easy activation of thioureas **39** as thiazetidines **40** provides tri- and tetra-substituted guanidines **41** [23] (Scheme 15, Table 12) in good to excellent yields.



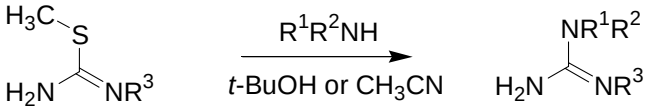
39 **40** **41**

Scheme 15

Table 12. Synthesis of polysubstituted guanidines *via* thiazetidine derivatives **40** (of Scheme 15)

Entry	R^1	R^2	R^3	R^4	Yield,%
1	2,4-Cl_2-C_6H_3-CO	4-Cl-C_6H_4	$PhCH_2$	H	92
2	2,4-Cl_2-C_6H_3-CO	4-Cl-C_6H_4	CH_3	H	68
3	2,4-Cl_2-C_6H_3-CO	4-Cl-C_6H_4	*n*-C_3H_7	H	90
4	2,4-Cl_2-C_6H_3-CO	4-Cl-C_6H_4	*i*-C_3H_7	H	89
5	2,4-Cl_2-C_6H_3-CO	4-Cl-C_6H_4	CH_3	CH_3	80
6	2,4-Cl_2-C_6H_3-CO	4-Cl-C_6H_4	$(EtO)_2CHCH_2$	H	58
7	4-CH_3-C_6H_4-CO	Ph	CH_3	CH_3	99
8	4-CH_3-C_6H_4-CO	Ph	$(CH_2)_5$		76
9	4-CH_3-C_6H_4-CO	Ph	$(CH_2)_2O(CH_2)_2$		88

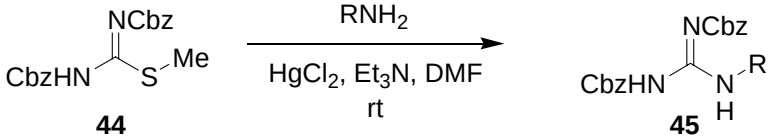
Reactions of S-methylisothioureas **42** [24] with various cyclic amines in refluxing tert-butyl alcohol gave almost a hundred salts of guanidine (Table 13, See Supplemental Materials) in fair to good yields (Scheme 16), accommodating phenyl substituents ranging from strongly electron withdrawing to strongly electron donating, as well as those with bulky substituents in the *ortho*-position. Either the isothiourea or the amine should be in the form of a soluble salt to achieve the satisfactory reaction rates.



42 **43**

Scheme 16

Mild and efficient promotion by mercuric chloride converts di-Cbz-isothioureas **44** into protected guanidines **45**[25] (Scheme 17, Table 14). Free and Cbz-protected guanidinoacids **47** were prepared similarly (Scheme 18, Table 15) from **44** and **46** by *in situ* carboxyl protection with trimethylsilyl chloride at the first stage of the reaction.[26] Simple crystallization after work up provided pure materials. The utility of generating a protected guanidine was established further by converting Gly-Gly to α-(bisbenzyloxycarbonyl)guanidinoacetylglycine.

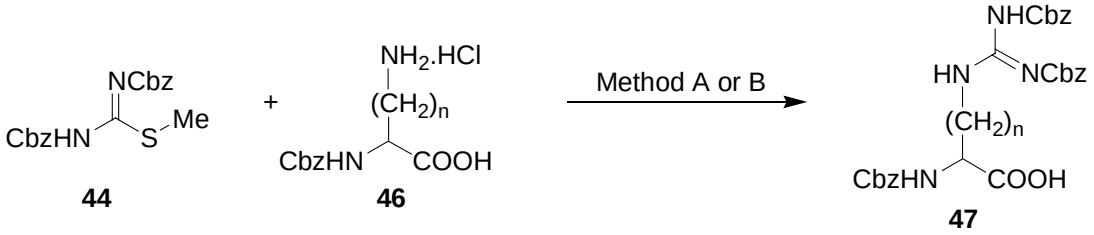


44 **45**

Scheme 17

Table 14. Synthesis of Cbz-substituted guanidines in the presence of $HgCl_2$ (of Scheme 17)

Entry	RNH_2	Yield, %
1	Ethyl 3-aminobutyrate hydrochloride	92
2	Benzylamine	75
3	4-Bromoaniline	83
4	*m*-Nitroaniline	58
5	3-Amino-4chlorobenzoic acid	56
6	3′-Aminoacetophenone	89
7	3-Aminobenzyl alcohol	92

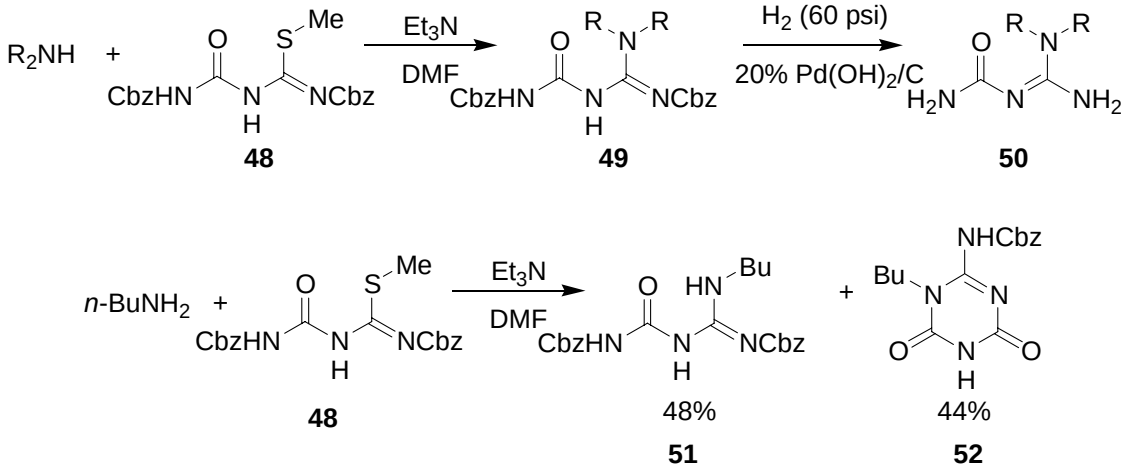


Scheme 18

Table 15. Synthesis of Cbz-substituted guanidines in the presence of $HgCl_2$ (of Scheme 18)

Entry	Amino acid	Method	Molar ratio Amino acid/reagent	Yield, %
1	N^{α}-Cbz-L-Orn.HCl	A	1:1.25	87
2	N^{α}-Cbz-L-Lys.HCl	A	1:1.1	62
3	H_2NCH_2COOH	B	1.2:1	97
4	$(S)PhCH_2CH(NH_2)COOH$	B	1.2:1	84
5	$H_2N(CH_2)_2COOH$	B	1.2:1	92
6a	$H_2N(CH_2)_3COOH$	B	1.2:1	92
6b	$H_2N(CH_2)_3COOH.HCl$	A	1.2:1	92
7	$H_2N(CH_2)_4COOH$	B	1.2:1	91
8	$H_2N(CH_2)_5COOH$	B	1.2:1	80
9	$HCl.p\text{-}NH_2CH_2C_6H_4COOH$	A	1.2:1	97
10	Gly-Gly	B	1.2:1	69

Guanidinoureas **49** and **50** were obtained by condensation of *N*-Cbz-ureido-*N*`-Cbz-*S*-methylisothiourea **48** [27] with amines in the presence of triethyl amine in DMF at 20 °C (Scheme 19. Table 16). In the reaction with butylamine, a triazinedione by-product **52** formed, but all the other cases gave exclusively guanidine compounds.

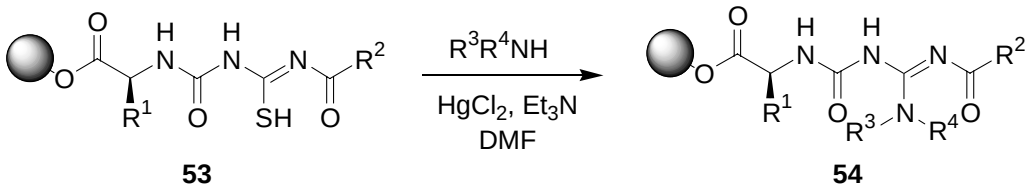


Scheme 19

Table 16. Synthesis of guanylureas **50**

Entry	Amine	Yield of protected product, %	Yield of final product, %
1	Piperidine	81	96
2	Morpholine	75	97
3	*c*-Hexylamine	99	93
4	*n*-Butylamine	48	99

A library of acylguanidinoureas has been reported.[28a] Isothioureas **53** were carbamoylated by a resin bound reagent, then acylated. Susequent aminolysis of the thiomethyl group in the presence of mercuric chloride led to **54** which were cleaved to give the guanidine library (Scheme 20, Table 17).

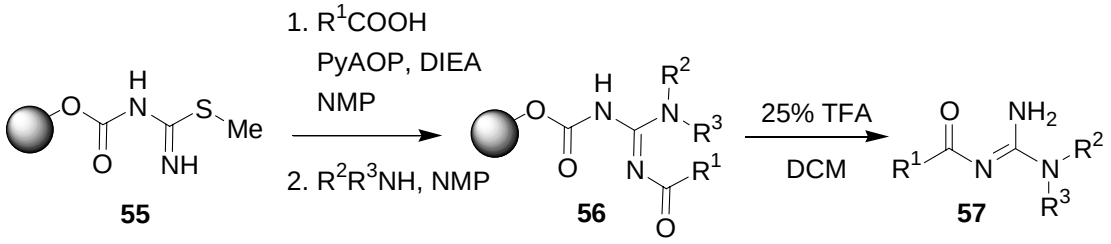


Scheme 20

Table 17. Solid phase synthesis of guanylureas **54** (of Scheme 20)

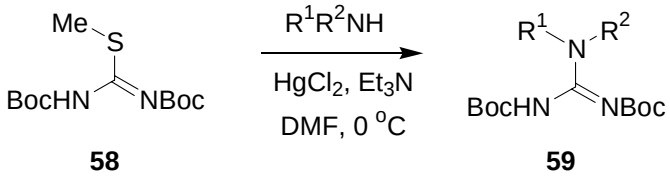
Entry	R^1	R^2	R^3	R^4	Yield,%	Purity
1	H	PhCH:CH	Benzyl	H	55	72-95
2	CH_3	*c*-Hexyl	Benzyl	H	49	72-95
3	*i*-Butyl	$PhCH_2$	2-Benzothiazolyl	H	83	72-95
4	H	Ph	*n*-Butyl	H	91	85
5	H	*c*-Propyl	$2\text{-}CH_3OC_6H_4CH_2$	H	86	95
6	H	$2\text{-}NO_2C_6H_4$	*i*-Propyl	*i*-Propyl	76	90
7	H	$2\text{-}CH_3OC_6H_4$	$\text{-}(CH_2)_4\text{-}$		47	95
8	*i*-Butyl	$PhOCH_2$	Benzyl	H	85	95
9	*i*-Butyl	$3\text{-}BrC_6H_4$	Benzyl	H	76	88
10	*i*-Butyl	4-pyridyl	$\text{-}(CH_2)_4\text{-}$		59	95
11	Benzyl	c-Hexyl	Benzyl	H	93	57
12	Benzyl	$2\text{-}NO_2C_6H_4$	$\text{-}(CH_2)_4\text{-}$		57	97
13	Benzyl	*c*-Propyl	Benzyl	H	93	99
14	4-Aminobutyl	$PhOCH_2$	Benzyl	H	92	92
15	4-Aminobutyl	$4\text{-}CH_3OC_6H_4CH_2$	$2\text{-}CF_3C_6H_4$	H	53	94

Another solid support approach for acyl guanidine synthesis utilizes resin bound *S*-methylthioureas **55**.[28b] Displacements of the methylthio group with ammonia, primary or secondary amines and aniline all proceeded cleanly at room temperature to give **56** which we than cleaved to **57**.



Scheme 21

Commercially available di-Boc-*S*-methylisothiourea **58** reacted with amines in the presence of mercuric chloride at 0-20 °C affording, after simple work up, the guanylated products **59** in goods yields[29] (Scheme 22). The results, summarized in Table 18, illustrate the broad application of the reagent. Since the synthesis is equally successful with aliphatic and aromatic amines. Sterically hindered amines react well as do anilines with electron donating groups. Electron deficient anilines react slowly to afford the guanylated product in acceptable yields.



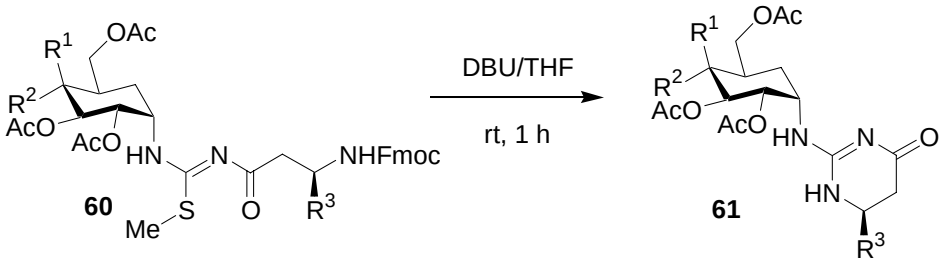
58 **59**

Scheme 22

Table 18. Preparation of guanidines **59**

Entry	R^1	R^2	Yield, %
1	*i*-Pr	i-Pr	77
2	Ph	H	89
3	3-$HOCH_2C_6H_4$	H	89
4	3-$NO_2C_6H_4$	H	68
5	4-HOC_6H_4	H	87
6	2-NO_2-4-HOC_6H_4	H	87
7	*o*-Phenylenediamine	H, H	80

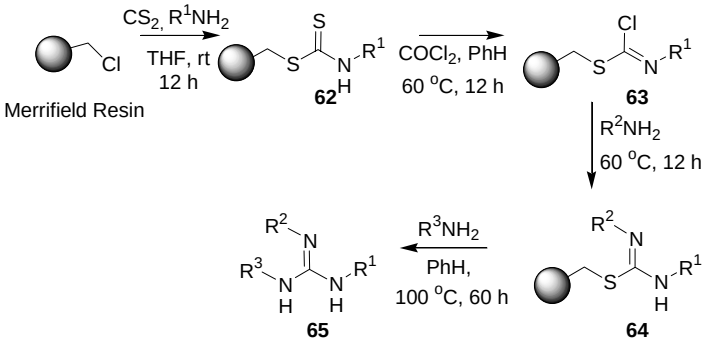
Guanidinoglycosides **61** were prepared by the intramolecular cyclization of β-amino *N*-Fmoc-protected acyl isothioureas **60** (Scheme 23). A catalytic amount of DBU (0.7% equiv) is optimal for converting these isothioureas into guanidinoglycosides (35-66%) within an hour.



60 **61**

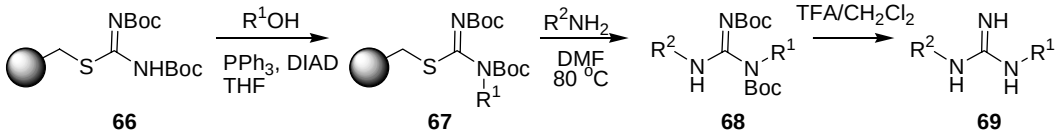
Scheme 23

S-Linked isothioureas **64** were formed *via* bis-electrophilic chlorothioformimines **63,** as key intermediates.[31] Dithiocarbamates were prepared from amines, carbon disulfide and benzyl chloride. Benzyl chloride was chosen for this study because it mimics the Merrifield resin. The dithiocarbamates **62** are quantitatively converted into the corresponding chlorothioformimines **63** by treatment at 60 °C with phosgene in toluene for 12 h. The first amine converts chlorothioformimines **63** into the isothiourea **64** without double addition. The second substitution to give **65** was effected at 100 °C, with an excess of a third amine, optimally in toluene. The reported reaction sequence is well adapted for SPS since it allows, in a four-step process, the addition of three primary amines under reaction conditions compatible with a wide variety of functional groups (Scheme 24). Moreover since the reaction conditions are suitable for automation and high-throughput synthesis, it appears possible to prepare large libraries of guanidines by this traceless linker strategy.



Scheme 24

S-Linked isothioureas **66** as a masked guanidine scaffold allow the parallel synthesis of mono and dialkylated guanidines in high yield and purity[32] (Scheme 25, Table 19). This procedure allows a high level of diversity using parallel array or combinatorial synthesis. The initial Mitsunobu step allows the use of either primary or secondary alcohols to generate **67** with the first point of diversity. Subsequent treatment of the resin bound *N*-alkyl isothioureas **67** with ammonia or primary amines liberates traceless guanidines **68** with a second point of diversity.



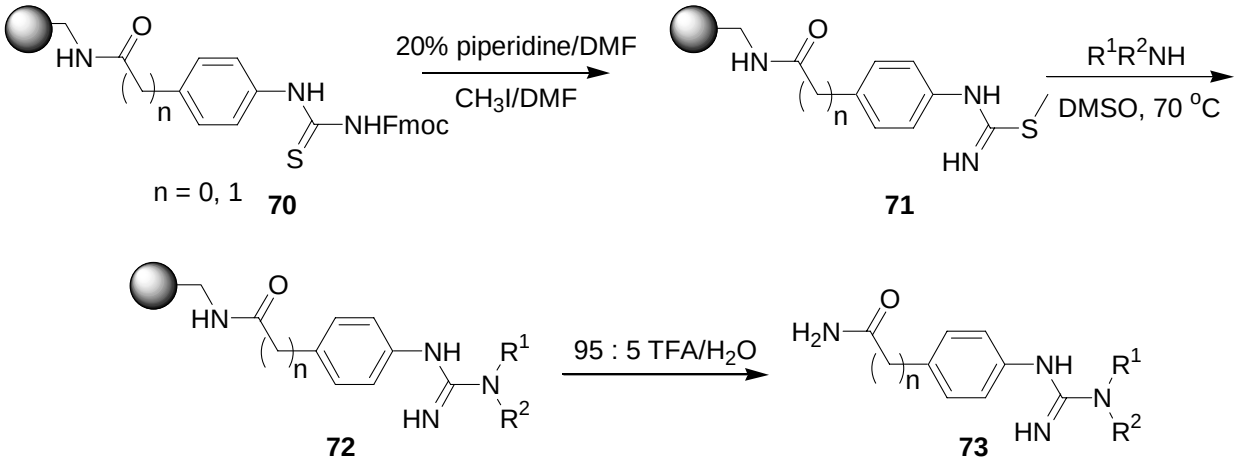
Scheme 25

Table 19. Traceless solid phase synthesis of guanidines via S-linked isothioureas (of Scheme 25)

Entry	R^1OH	R^2NH_2	Purity of DiBoc, %	Yield of DiBoc, %
1	$PhCH_2OH$	NH_3	95	88
2	$PhOCH_2CH_2OH$	NH_3	95	100
3	$BocNH(CH_2)_3OH$	NH_3	95	88
4	$PhCHC(CH_3)CH_2OH$	NH_3	95	95
5	$(CH_3)_2CCHCH_2OH$	NH_3	100	95
6	$(CH_3)_2CHCH_2C(CH_3)OH$	NH_3	90	85
7	$(CH_3)_2CCH(CH_2)_2C(CH_3)OH$	NH_3	86	85
8	$PhOCH_2CH_2OH$	$PhCH_2NH_2$	*	90
9	$PhOCH_2CH_2OH$	*c*-propylamine	*	92
10	$PhOCH_2CH_2OH$	$(CH_3)_2CH(CH_2)_2NH_2$	*	92
11	$PhOCH_2CH_2OH$	$BocNH(CH_2)_3NH_2$	*	96
12	$PhOCH_2CH_2OH$	$2\text{-}MeOC_6H_4NH_2$	*	0

* - Purity of compound was not determined.

Another combinatorial synthesis of guanidines utilizes resin bound thiourea **70**, which after conversion into the isothiourea **71** by treatment with iodomethane, reacted with primary or secondary amines to give polymer supported guanidines **72**. Cleavage provided access to a variety of guanidines **73**[33] (Scheme 26, Table 20).

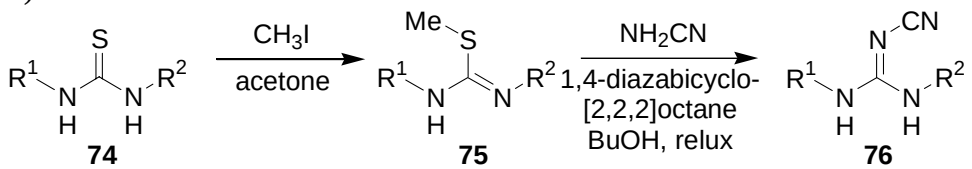


Scheme 26

Table 20. Synthesis of guanidines via resin-bound isothioureas (of Scheme 26)

Entry	n	R^1R^2NH	Purity, %	Yield, %
1	0	Morpholine	73	77
2	0	Piperidine	80	89
3	0	*N*-Methyl-*N*-phenethylamine	82	73
4	0	4-Methoxyphenethylamine	40	64
5	0	*n*-Butylamine	44	64
6	1	Morpholine	88	95
7	1	Piperidine	92	95
8	1	*N*-Methyl-*N*-phenethylamine	89	93
9	1	4-Methoxyphenethylamine	79	72
10	1	*n*-Butylamine	82	83

Cyanoguanidines **76** were obtained in high yields by the reaction of substituted isothioureas **75** with cyanamide[34] in boiling butanol in the presence of 1,4-diazabicyclo[2.2.2]octane (Scheme 27, Table 21).

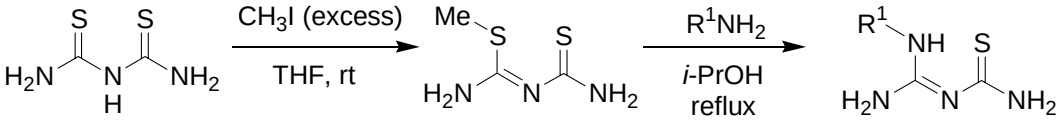


Scheme 27

Table 21. Synthesis of cyanoguanidines **76** in the presence of 1,4-diazabicyclo[2.2.2]octane (see Scheme 27)

Entry	R^1	R^2	Yield, %
1	Ph	Ph	68
2	Ph	Me	70
3	Ph	Allyl	77
4	Ph	*c*-Hexyl	77
5	*c*-Hexyl	Me	73
6	*c*-Hexyl	Allyl	76
7	*c*-Hexyl	*c*-Hexyl	73
8	Bn	Ph	67
9	Bn	Me	73
10	Bn	*c*-Hexyl	69
11	Bu	Ph	74
12	Bu	*c*-Hexyl	70

Readily available dithiobiuret **77** and amines in refluxing isopropanol[35] provide a convenient method for the preparation of mono *N*-substituted guanylthioureas **79** in moderate to very good yields (Scheme 28, Table 22).



77 **78** **79**

Scheme 28

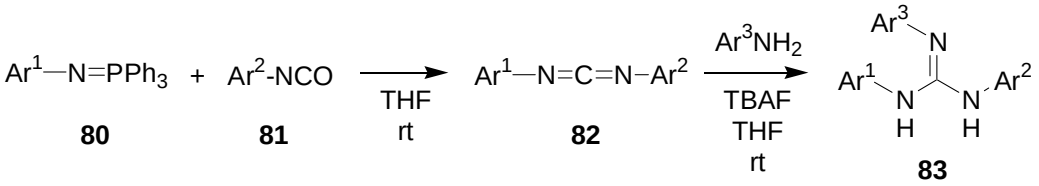
Table 22. Synthesis of guanylthioutreas from dithiobiuret **78** by method of Scheme 28

Entry	R^1	Yield, %	Entry	R^1	Yield, %
1	Ethyl	34	6	2-(Acetylamino)ethyl	56
2	c-Pr	57	7	2-(*t*-Boc-amino)ethyl	75
3	*n*-Pentyl	68	8	Benzyl	75
4	*n*-Hexyl	75	9	3-Pyridylmethyl	58
5	2-(Ethoxy)ethyl	73	10	Phenyl	28

2.3. Carbodiimides and cyanamides

N-Aryliminophosphoranes **80** were converted into N^1,N^2,N^3-triarylguanidines **83** in good yields by reaction with isocyanates **81** followed by treatment of the intermediate N^1,N^2-diarylcarbodiimides **82** with aromatic amines in the presence of TBAF.[36] The presence of one equiv of TBAF is essential and the reaction takes place at room temperature within 10 min to

give the desired guanidine (Scheme 29). As the commercially available THF solution of TBAF containes ca. 5 wt% water, it was pretreated with anhydrous $MgSO_4$.

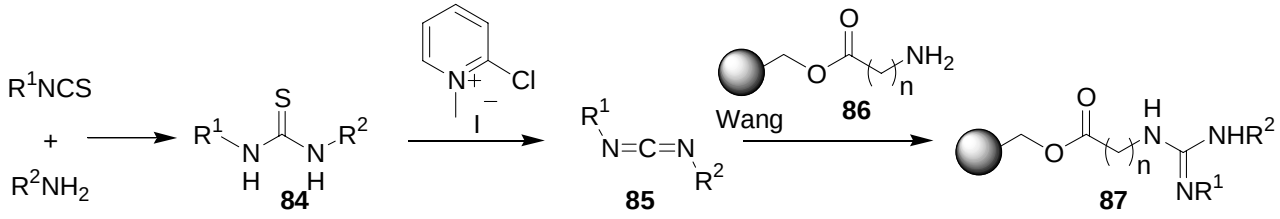


Scheme 29

Table 23. Synthesis of carbodiimides **82** and guanidines **83** (Scheme 29)

Entry	Ar^1	Ar^2	Ar^3	Yield, %
1	2-BrC_6H_4	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	73
2	4-$CH_3C_6H_4$	2-BrC_6H_4	4-$CH_3OC_6H_4$	80
3	2-BrC_6H_4	4-$CH_3C_6H_4$	4-ClC_6H_4	75
4	4-$CH_3C_6H_4$	2-BrC_6H_4	4-$NO_2C_6H_4$	67
5	C_6H_5	2-BrC_6H_4	4-$NO_2C_6H_4$	52
6	2-pyridyl	4-$CH_3C_6H_4$	2-pyridyl	18

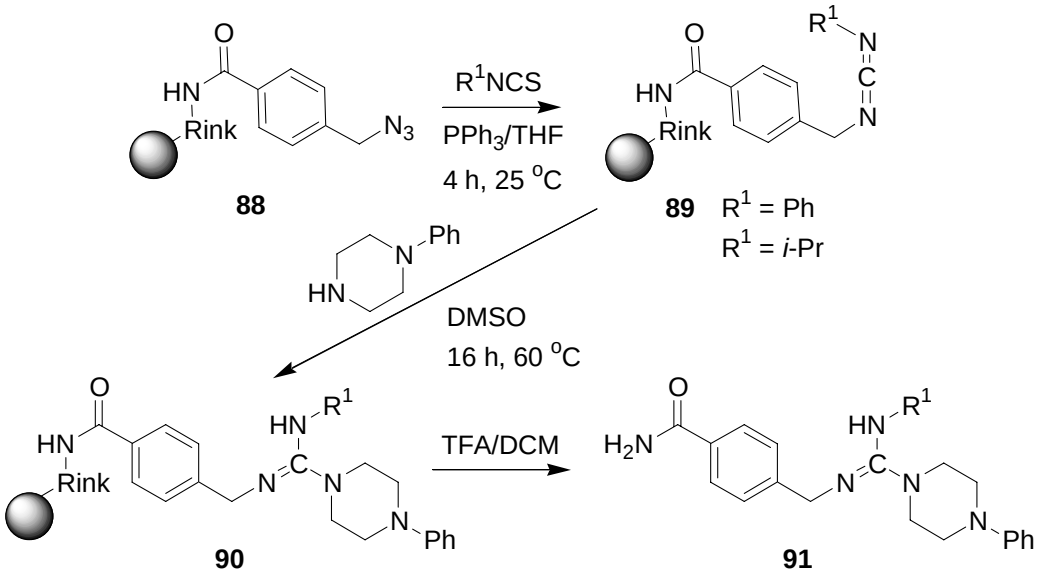
Guanidinoacetic acids were prepared as outlined in Scheme 30 on solid support *via* treatment of anchored amines with intermediate solution-generated carbodiimides **85**.[37] This particular protocol is extremely practical. Conversion of thioureas **84** to carbodiimides **85** on treatment with Mukaiyama's reagent (2-chloro-1-methypyridinium iodide) is almost instantaneous at room temperature though brief sonication was desirable to accelerate solubilization of the reagent. The carbodiimides are very nonpolar and are generally isolated by extraction into hexanes and filtration through a short silica *plug* using the same solvent. Reaction times for addition of the carbodiimides **85** to Wang-supported glycine or alanine **86** varied, but the transformation was conveniently monitored *via* the ninhydrin test.



Scheme 30

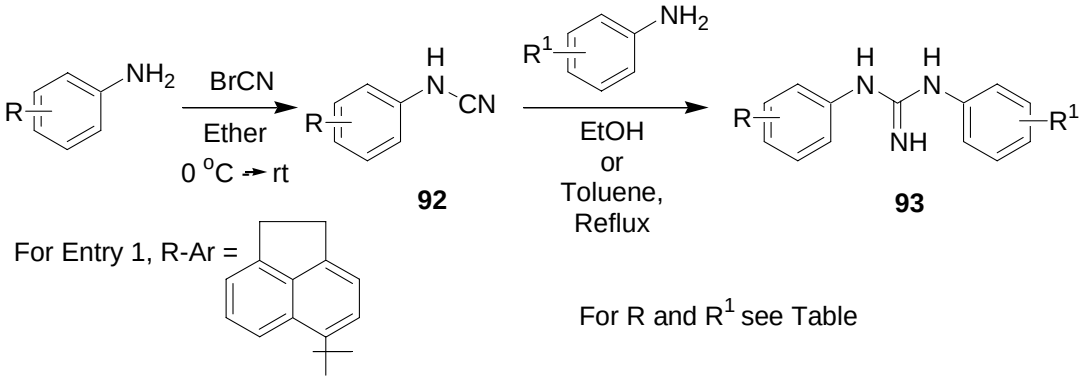
Another approach *via* carbodiimides involves their preparation on solid support followed by the reaction with amines to furnish resin bound guanidines[38] (Scheme 31). The sequence commenced with coupling of the *p*-bromomethyl benzoic acid to a primary amine of a Rink-extended macrocrown. The *p*-bromomethylbenzamide obtained underwent nucleophilic

displacement with azide to afford the α-azido-*p*-toluamide **88**. Treatment with triphenylphosphine and phenyl isothiocyanate provided the carbodiimide **89**, presumably *via* an *in situ* Staudinger reaction, to generate the intermediate iminophosphorane and subsequent aza-Wittig coupling with the isothiocyanate. Reaction of the carbodiimide with *N*-phenylpiperazine yielded a polymer-bound guanidine **90**, which was cleaved with TFA/$H_2$0 (95:5) to afford **91**.



Scheme 31

Cyanamides serve as suitable starting materials for the preparation of guanidines: a recent example describes the formation of **92** *in situ* and immediate reaction with excess of amine[39] to yield **93** (Scheme 32, Table 24).



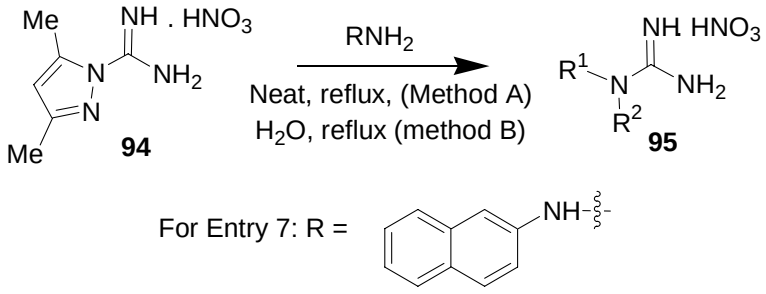
Scheme 32

Table 24. Synthesis of diarylguanidines **93** by method of Scheme 32

Entry	R	R_1	Yield, %[b]	Entry	R	R_1	Yield, %[b]
1	See Scheme	s-C_4H_9	50	9	*n*-C_6H_{13}	*n*-C_6H_{13}	68
2	CH_3	CH_3	20	10	C_6H_5	C_6H_5	8
3	C_2H_5	C_2H_5	38	11	OC_6H_5	OC_6H_5	38
4	*i*-C_3H_7	i-C_3H_7	27	12	SC_6H_5	SC_6H_5	14
5	*s*-C_4H_9	s-C_4H_9	32	13	$OCH_2C_6H_5$	*t*-C_4H_9	53
6	*t*-C_4H_9	t-C_4H_9	40	14	$OCH_2C_6H_5$	*n*-C_4H_9	44
7	*n*-C_4H_9	n-C_4H_9	20	15	*n*-OC_4H_9	$(CH_2)_4$-OH	67
8	*n*-OC_4H_9	n-OC_4H_9	27	16	$(CH_2)_4$-OH	$(CH_2)_4$-OH	79

2.4. Pyrazole-1-carboximidamides

Pyrazole-1-carboximidamides **94** are now frequently used for the preparation of guanidines **95**. The reaction of 2,4-dimethylpyrazole-1-carboximidamide with amines was considered in 1953 as abnormal because the initial desire was to substitute an NH_2 group in analogy to ureas and related compounds[40a] (Scheme 33). The guanidines prepared are listed in Table 25. For related work see references 40[b,c].

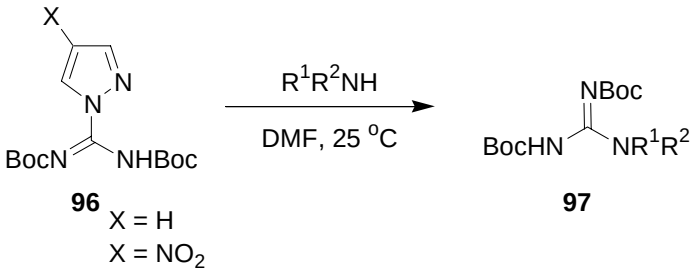


Scheme 33

Table 25. Synthesis of guanidines from 2,4-dimethylpyrazole-1-carboximidamide nitrate (Scheme 33)

Entry	R^1	R^2	Method	Yield, %
1	PhCONH	H	B	66
2	$PhCH_2$	H	B	63
3	-$(CH_2)_2O(CH_2)_2$-		A	50
4	PhCH2CH2	H	B	75
5	-$(CH_2)_5$-		B	68
6	-$(CH_2)_4$-		A	92
7	See Scheme	H	B	67
8	4-$CH_3C_6H_4SO_2NH$	H	B	16

A recent investigation showed that the presence of electron withdrawing groups in the pyrazole ring and/or on one or both of the carboximidamide nitrogens can be advantageous for the yield of guanidines and allow milder reaction conditions. Thus, di-Boc-4-nitropyrazole-1-carboximidamide **96** has been used for the preparation of protected guanidines **97** [41] (Scheme 34). A 4-nitro group in the pyrazole ring facilitates the reaction and gives higher yields (Table 26)

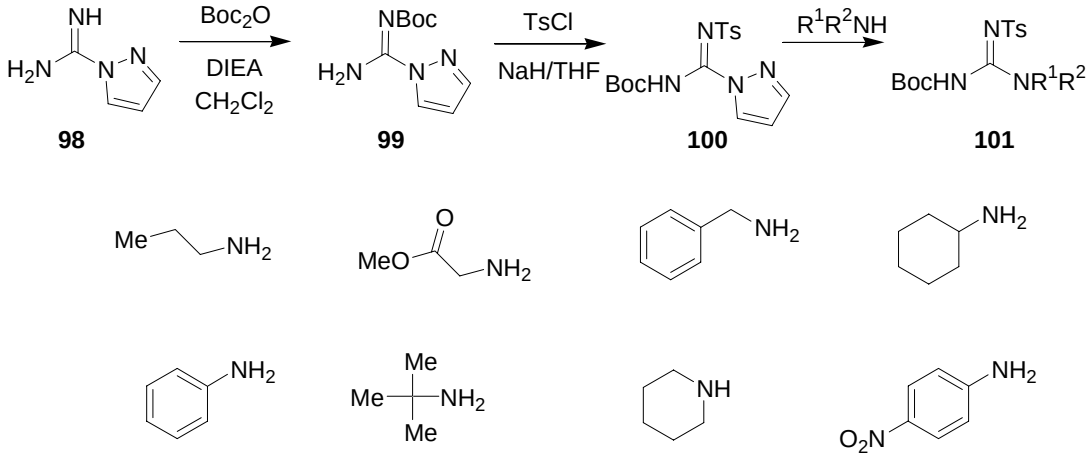


Scheme 34

Table 26. Synthesis of guanidines from di-Boc-4-nitropyrazole-1- carboximidamide **97** (Scheme 34)

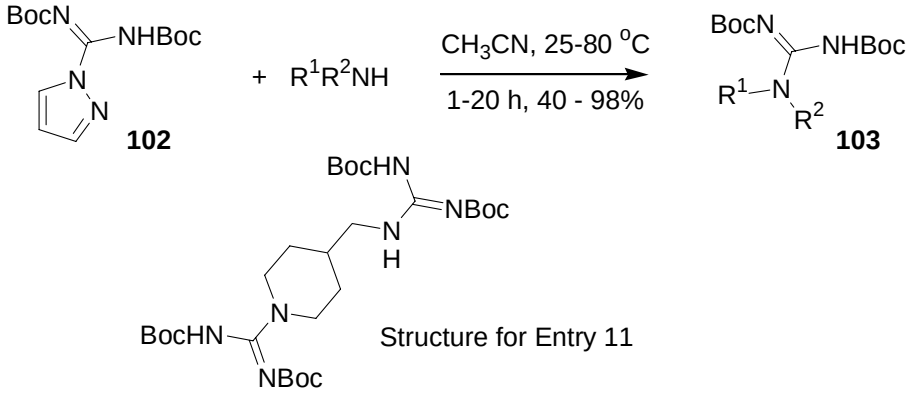
Entry	R^1R^2NH	X = H, Yield, %	X = NO_2, Yield, %
1	Benzylamine	80	94
2	Piperidine	70	82
3	Aniline	11	78
4	Diisopropylamine	<5	64

The use of *N*-Boc-*N'*-tosylpyrazole-1-carboximidamide **100** is very efficient for the preparation of guanidines **101** and for coupling to peptides[42] (Scheme 34). This reagent was also used for coupling with peptides in solution and on solid supports.



Scheme 34

The reactions of a variety of amines with di-Boc-pyrazole-1-carboximidamide **102** have also been examined[43] (Scheme 35, Table 27). In adidition to the guanylation of simple amines, several amino acids were converted into guanidino acids. Amino acids have a low solubility in many organic solvents, but reaction can be achieved in water, or aqueous acetonitrile to give satisfactory results.

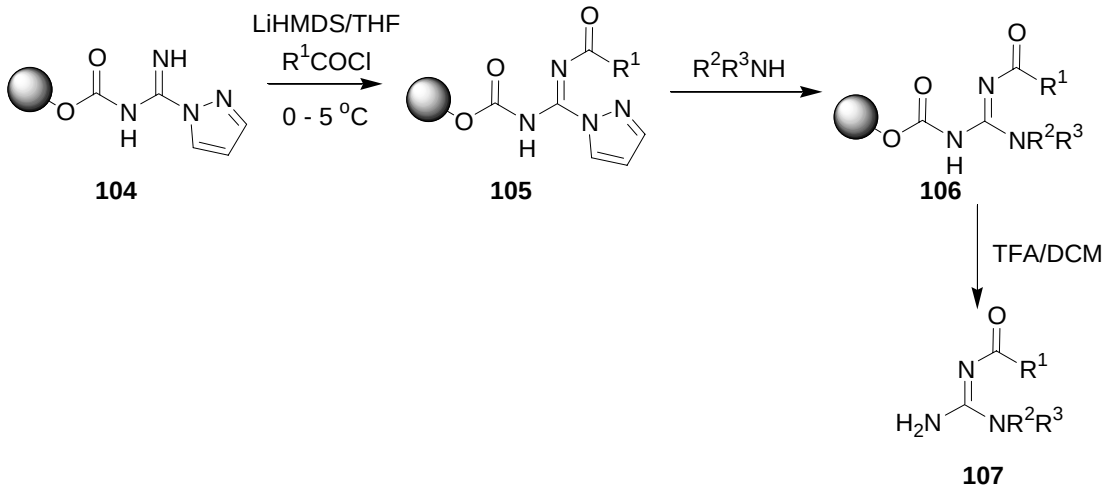


Scheme 35

Table 27. Synthesis of guanidines from di-Boc-pyrazole-1-carboximidamide (Scheme 35)

Entry	R^1	R^2	Yield, %
1	Bu	H	90
2	*t*-Bu	H	93
3	*c*-Hex	H	96
4	Bn	H	91
5	Allyl	H	98
6	Ph	H	71
7	4-$MeOC_6H_4$	H	71
8	4-$NO_2C_6H_4$	H	5
9	-$(CH_2)_5$-		92
10	-$(CH_2)_2O(CH_2)_2$-		86
11	-$(CH2)_2CH(CH_2NH_2)(CH_2)_2$-		67
12	Gly	H	71
13	*β*-Ala	H	38
14	3-Aminobutyric acid	H	70
15	6-Aminocaproic acid	H	76
16	Pro		73
17	Fmoc-Lys	H	57
18	Cbz-Orn	H	70
19	β-Ala-OMe	H	89

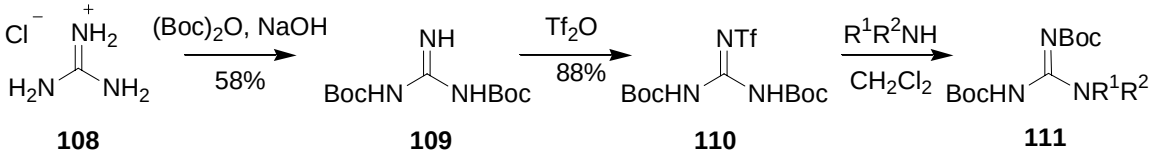
Pyrazole-1-carboximidamide connected to a solid support by an oxycarbonyl linker **104** can be acylated to **105** and thus becomes a potent reagent for the generation of guanidines **106** on solid supports[44] (Scheme 36) by utilizing electronically diverse acylating agents and amines. Guanidine derivatives from nitroanilines were obtained in good yields for a range of acylated derivatives of pyrazole-1-carboximidamide.



Scheme 36

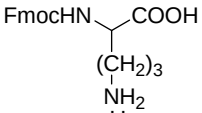
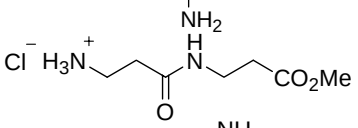
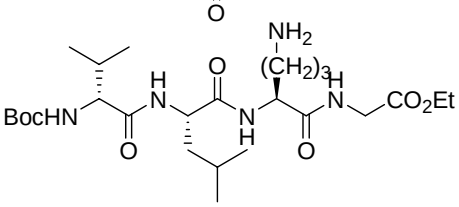
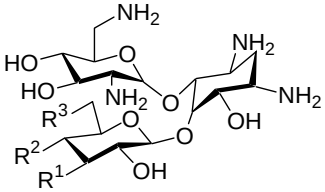
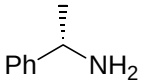
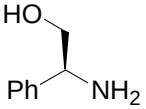
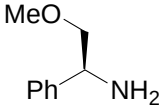
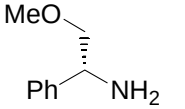
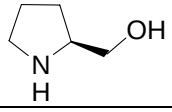
2.5. Triflyl guanidines

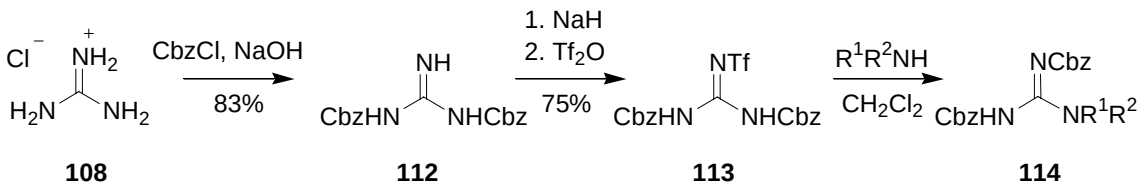
Triflyl guanidines, first reported in 1998, are becoming popular reagents for the preparation of guanidines.[45] Di-Boc-triflylguanidine **110** and di –Cbz-triflylguanidine **113** are efficiently converted by various primary amines into guanidines **111**, **114**.[45-47] (Schemes 37, 38, Tables 28, 29).



Scheme 37

Table 28. Synthesis of guanidines from di-Boc-triflylguanidine **110** (Scheme 37)

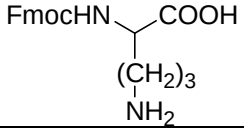
Entry	R^1R^2NH	Conditions	Yield, %	Ref.
1	Benzylamine	CH_2Cl_2, 0.5 h, rt	100	45
2	Cyclohexylamine	CH_2Cl_2, 1.0 h, rt	99	45
3	*t*-Butylamine	CH_2Cl_2, 8.0 h, reflux	75	45
4	4-Pyrrolidine	CH_2Cl_2, 2.0 h, rt	96	45
5	Aniline	CH_2Cl_2, 24 h, rt	89	45
6		CH_2Cl_2, 4 h, rt	82	45
7		CH_2Cl_2, 4 h, rt	85	45
8		CH_2Cl_2, 4 h, rt	88	45
9	$CH_3(CH_2)_4NH_2$	CH_2Cl_2, 1 h, rt	98	45
10	Piperidine	$CHCl_3$, 20 h, rt	85	45
11	Morpholine	-	86	45
12	Piperazine	-	100	45
13	Monoethanolamine	CH_2Cl_2, 2 h, rt	100	45
14		H_2O, Dioxane CH_3CN	22-49	46
15		CH_2Cl_2	42	47
16		CH_2Cl_2	21	47
17		CH_2Cl_2	38	47
18		CH_2Cl_2	39	47
19		CH_2Cl_2	42	47



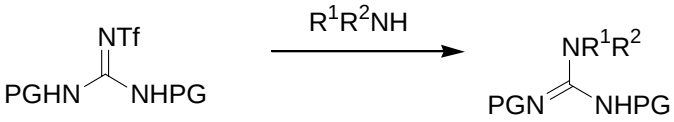
108 **112** **113** **114**

Scheme 38

Table 29. Synthesis of guanidines from di-Cbz-triflylguanidine **113** (Scheme 38)

Entry	R^1R^2NH	Conditions	Yield, %
1	Benzylamine	CH_2Cl_2, 1.0 h, rt	94
2	Aniline	CH_2Cl_2, 1 h, rt	98
3		CH_2Cl_2, 4 h, rt	85

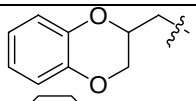
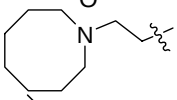
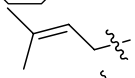
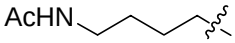
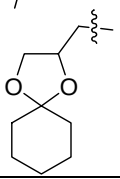
Primary and secondary amines were also converted into guanidines **116** by triflylguanidines **115**[48] (Scheme 39, Table 30).



115 **116**

Scheme 39

Table 30. Conversion of secondary amines into guanidines by di-protected triflylguanidine **115 (**Scheme 39)

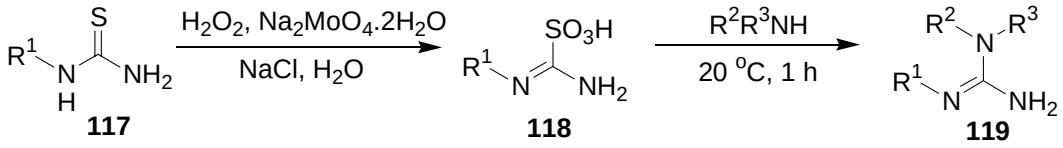
Entry	PG	R^1	R^2	Yield, %
1	Boc		H	100
2	Boc		H	88
3	Boc			49
4	Cbz		H	95

2.6. Aminoiminomethane-sulfonic and -sulfinic acids

Aminoiminosulfonic and -sulfinic acids, prepared by the oxidation of thioureas, are useful reagents for the synthesis of guanidines.

Marianoff and coworkers described a practical two-step procedure based on thioureas **117** oxidized with H_2O_2.[49] A high yield of pure sulfonic acid **118** was obtained rapidly in a short reaction time when the reaction was run as a slurry in water. The rate of reaction was dependent on the concentration of catalyst (Na_2MoO_4) employed. In general, the sulfonic acid derivatives are stable at room temperature and are the preferred intermediates. The oxidation products were isolated by filtration and air-dried for use in the displacement reaction (Scheme 40, Table 31).

The second step of the sequence, displacement of the oxidized sulfur with amine nucleophiles, to give **119** was carried out under mild conditions (Scheme 40). Yields of the displacement reactions are reported in Table 32.



Scheme 40

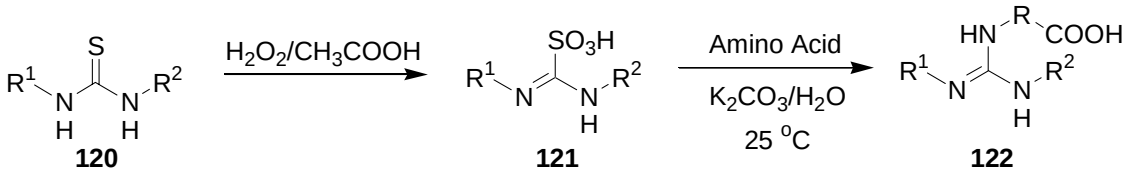
Table 31. Oxidation of thioureas **117** to sulfonic acid **118**

Entry	R^1	Yield, %
1	Ph	86
2	*n*-Pr	56
3	2-$CH_3C_6H_4$	83
4	4-FC_6H_4	76

Table 32. Synthesis of guanidines **119** from thiourea derived sulfonic acid **118**.

Entry	R^1	R^2	R^3	Yield, %
1	Ph	*t*-Butyl	H	99
2	Ph	*i*-Butyl	H	56
3	Ph	*sec*-Butyl	H	50
4	Ph	Ph	H	99
5	Ph	4-$CH_3OC_6H_4$	H	77
6	*n*-Pr	*sec*-Butyl	H	62
7	Ph	c-Hexyl	H	72
8	Ph	4-ClC_6H_4	H	50
9	Ph	2-CH_3-4-$CH_3OC_6H_4$	H	51
10	Ph	4-$NO_2C_6H_4$	H	84
11	*n*-Pr	*i*-Butyl	H	23
12	*n*-Pr	*n*-Butyl	H	60
13	Ph	-$(CH_2)_4$-		73
14	Ph	-$(CH_2)_2O(CH_2)_2$-		79

Similar investigation on the use of aminoiminomethansulfonic acids **121** has been described for the conversion of amino acids into a guanidino acids **122** [50] (Scheme 41, Table 33). This method is advantageous for the preparation of di- and tri-substituted guanidine acids due to their synthesis from isothiouronium compounds.

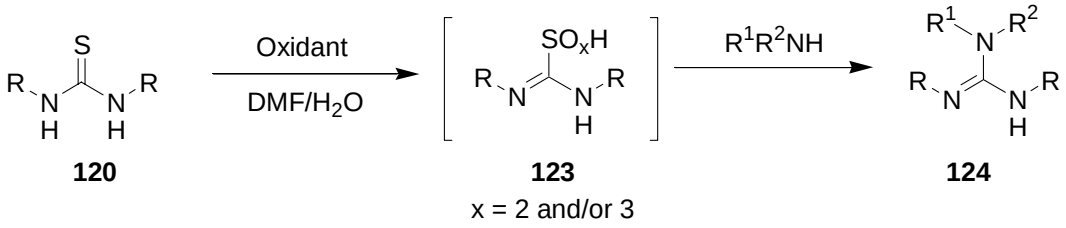


Scheme 41

Table 33. Synthesis of guanidines **122** *via* oxidized thioureas **121**

Entry	Amino Acid	R^1	R^2	Yield, %
1	3-Aminopropanoic Acid	H	H	75
2	DL-Alanine	H	H	5
3	p-Aminobenzoic Acid	H	H	80
4	4-Aminobutanoic Acid	H	H	50
5	5-Aminopentanoic Acid	H	H	55
6	Glycine	H	H	80
7	L-Iisoleucine	H	H	5
8	L-Leucine	H	H	-[a]
9	DL-Methionine	H	H	60
10	L-Phenylalanine	H	H	45
11	L-Proline	H	H	-[a]
12	DL-Serine	H	H	50
13	DL-Valine	H	H	55
14	3-Aminopropanoic Acid	H	Ph	70
15	*p*-Aminobenzoic Acid	H	Ph	65
16	4-Aminobutanoic Acid	H	Ph	0
17	Glycine	H	Ph	85
18	L-Leucine	H	Ph	0
19	3-Aminopropanoic Acid	Ph	Ph	25
20	p-Aminobenzoic Acid	Ph	Ph	25
21	Glycine	Ph	Ph	35

Continued optimization of the protocol for guanidine preparation led to use of the oxidized product without isolation[51] (Scheme 42). Oxidizing agents are compared in Table 32 and the oxidation rate for aliphatic derivatives was improved by addition of a catalytic amount of triethyl amine. The guanidines **124** were obtained by treatment with amines in water with short reaction times, excellent conversion, and simple isolation. However, trisubstituted thioureas resisted the oxidation.



Scheme 42

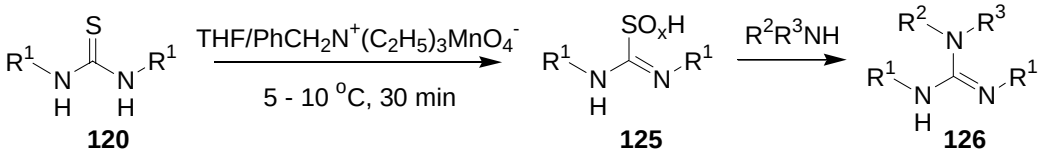
Table 34. Synthesis of guanidines **124** *via* nonisolatable intermediate oxidized thioureas **123**

Entry	R	R^1	R^2	$NaIO_4$ Yield, %	$NaClO_2$ Yield, %
1	Ph	H	H	76	80
2	*o*-Tolyl	H	H	80	76
3	C_6H_{11}	H	H	72	67
4	Ph	$-(CH_2)_2O(CH_2)_2-$		75	72
5	Ph	H	C_6H_{11}	84	81
6	Ph	H	Benzyl	68	65
7	Ph	Et	Et	76	80
8	Ph	H	Et	75	72
9	Ph	C_6H_{11}	C_6H_{11}	60	55

In a recent, one-pot procedure, quaternary ammonium permanganate in the presence of amine showed advantages over other oxidizing agents for thioureas **120**[52] (Scheme 43, Table 33).

Table 35. Synthesis of guanidines from oxidation of thioureas by quaternary ammonium permanganate (Scheme 43)

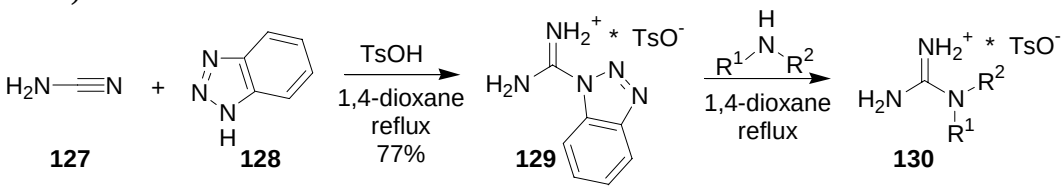
Entry	R^1	R^2	R^3	Yield, %
1	Ph	*c*-C_6H_{11}	H	92
2	Ph	Ethyl	Ethyl	95
3	Ph	H	H	90
4	Ph	Benzyl	H	87
5	Ph	*n*-Bu	H	86
6	*o*-Tolyl	H	H	82
7	Ph	*c*-C_6H_{11}	*c*-C_6H_{11}	82
8	Ph	*i*-Propyl	*i*-Propyl	78
9	Ph	$-(CH_2)_2O(CH_2)_2-$		89
10	2,6-Diethylphenyl	$-(CH_2)_2O(CH_2)_2-$		95



Scheme 43

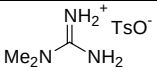
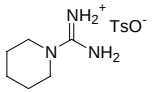
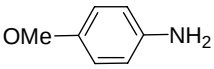
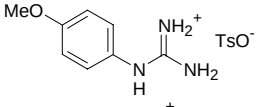
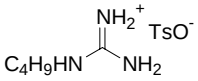
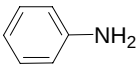
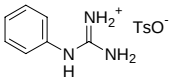
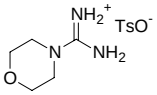
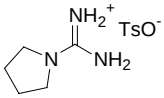
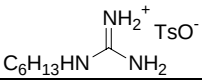
2.7. Benzotriazole and imidazole-activated reagents

Benzotriazole-1-carboxamidinium tosylate **129**[53] prepared from benzotriazole **128** with cyanamide **127** in refluxing 1,4-dioxane in the presence of *p*-TsOH, is an efficient general reagent for the synthesis of mono and disubstituted guanidines **130**. Reactions are conveniently carried out using equimolar amine in (i) DMF-diisopropylethylamine at room temperature, (ii) acetonitrile or (iii) the absence of solvent. Product isolation is facile as the precipitated guanidine can be filtered from the ether soluble benzotriazole by-poduct when DMF is used. The product precipitates during the reaction, while in the absence of solvent product can be isolated chromatographically. Under mild conditions, benzotriazole-1-carboxamidinium tosylate gives guanidines in moderate to good yields and offers advantages over previous procedures (Scheme 44, Table 36).

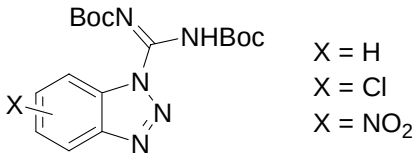


Scheme 44

Table 36. Synthesis of guanidines from benzotriazole-1-carboxamidinium tosylate

Entry	Amine	Guanidine	Yield, %
1	Me_2NH		69
2			84
3			68
4	$C_4H_9NH_2$		55
5			68
6			86
7			71
8	$C_6H_{13}NH_2$		67

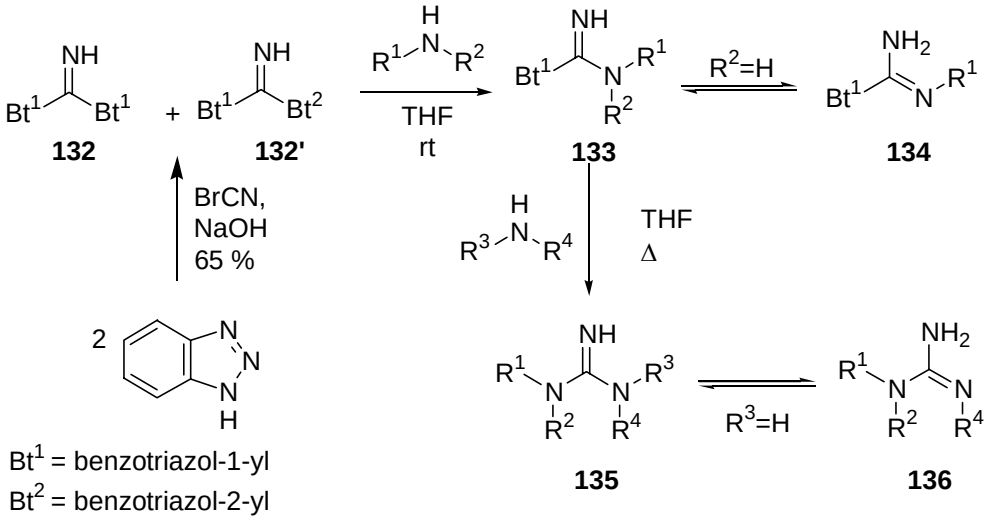
Modification of benzotriazole-1-carboxamidine by introducing electron withdrawing groups, Boc on both nitrogens of the amidine moiety and nitro or chloro group in benzotriazole to give **131**, enhanced the ability of the benzotriazole moiety as a leaving group[54] (Scheme 45).



131

Scheme 45

Di(benzotriazolyl)carboximidamide **132** has been developed as a new guanylating agent, for the synthesis of tri- **136** and tetra-substituted guanidines **135**.[55] The sequential condensation of two amines with di(benzotriazolyl)carboximidamide is insensitive to electronic and steric effects allowing the use of a wide variety of amines and guanidines as free bases. The products were obtained in high yields under neutral and mild conditions using an easy purification protocol (Scheme 46, Tables 37, 38).



Scheme 46

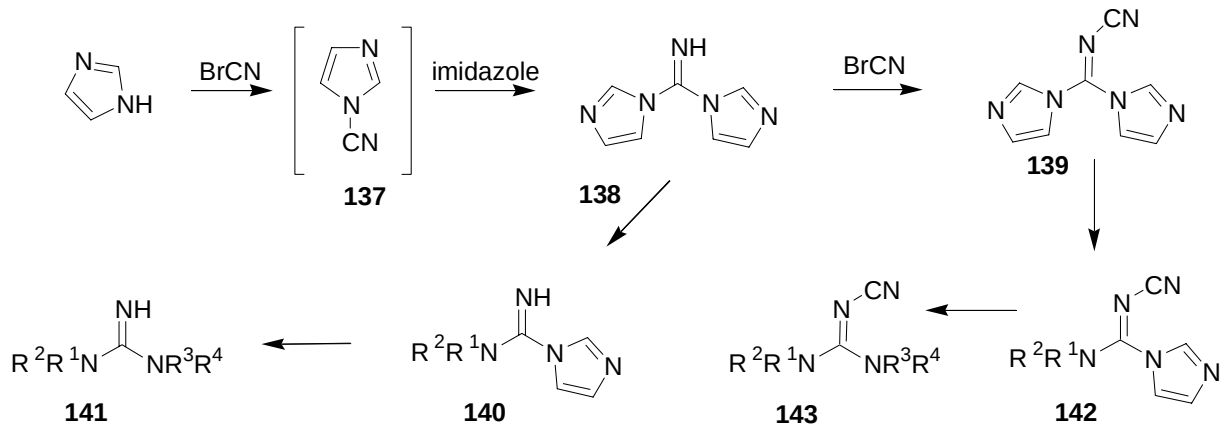
Table 37. Preparation of benzotriazole-1-carboximidamides **133** (of Scheme 46)

Entry	R^1	R^2	Yield, (%)
1	H	C_6H_5	80
2	H	*n*-C_5H_{11}	74
3	H	$CH_2C_6H_5$	68
4	-$(CH_2)_4$-		71
5	-$(CH_2)_2O(CH_2)_2$-		68
6	$CH(CH_3)_2$	$CH(CH_3)_2$	68

Table 38. Preparation of guanidines **135** (of Scheme 46)

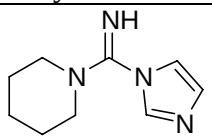
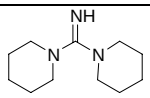
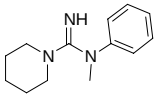
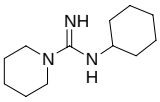
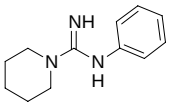
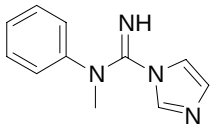
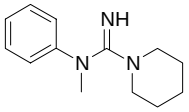
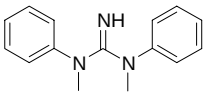
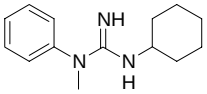
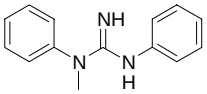
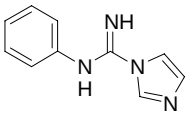
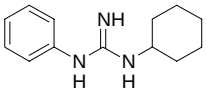
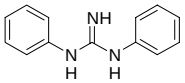
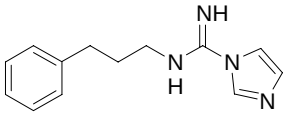
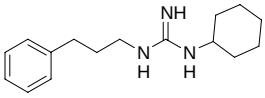
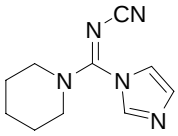
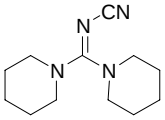
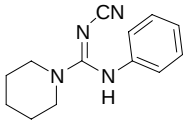
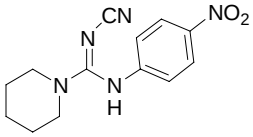
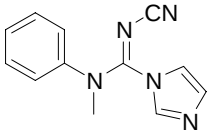
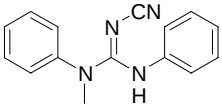
Entry	R^1	R^2	R^3	R^4	Reaction time (h)	Yield (%)
1	$-(CH_2)_2O(CH_2)_2-$		C_6H_5	H	10	64
2	$-(CH_2)_2O(CH_2)_2-$		4-$CH_3C_6H_4$	H	12	74
3	$-(CH_2)_2O(CH_2)_2-$		$C_6H_5CH_2$	H	12	71
4	$-(CH_2)_2O(CH_2)_2-$		C_6H_5	CH_3	18	85
5	$-(CH_2)_4-$		C_6H_5	H	12	68
6	$-(CH_2)_4-$		4-$CH_3OC_6H_4$	H	17	60
7	$CH(CH_3)_2$	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	H	15	48

Analogous to the di(benzotriazolyl)carboximidamide reagent **132**, di(imidazol-1-yl)carboximidamide **138** was later synthesized by treatment of cyanogens bromide with imidazole.[56] Reagent **138** can also be converted into substituted guanidines **141** by sequential displacement of imidazole moieties with amines. Further, through its *N*-cyano derivative **139** it provides an access to substituted cyanoguanidines **143** (Scheme 47, Table 38).

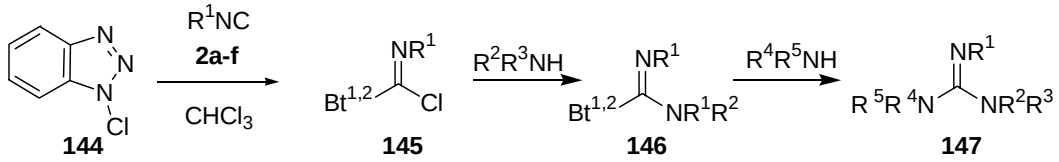


Scheme 47

Table 39. Preparation of Guanidines 141 and cyanoguanidines **143** (of Scheme 47)

No	Imidazol-1-yl carboximidamide	Guanidine	Yield, %
1			53
			76
			81
			51
2			64
			70
			
			
3			74
			90
4			85
5			82
			70
			0
			42

Benzotriazolylcarboximidoyl chlorides **145** (stable, odorless and convenient to handle) also allow the preparation of unsymmetrical guanidines[57] (Scheme 48).



Scheme 48

3. Conclusions

We have attempted to summarize recent advances in guanidine synthesis from the point of view of guanylating agents.

Supplementary information is available

4. References

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Biographical sketch

Alan Katritzky has taught, researched, consulted and published on heterocyclic chemistry, synthetic methods, and QSPR, first in the UK and since 1980 at the University of Florida where he is Kenan Professor of Chemistry and Director of the Center for Heterocyclic Compounds.

Dr. Rogovoy was born January 18th, 1973. He received his MS degree in 1995 in Chemical Engineering at Ukrainian State University for Chemical Engineering, Dnepropetrovsk, Ukraine and PhD degree in 2002 at the University of Tartu, Tartu, Estonia. In 1998 Dr. Rogovoy joined the Center for Heterocyclic Compounds at the University of Florida. In 2003 he joined the Department of Pharmaceutical Chemistry in School of Pharmacy in Rutgers University where he was involved in a development of prodrug systems for the site-specific release and activation of anticancer drugs and improvement of therapeutic effectiveness of anticancer agents with reduced systemic toxicity. In November of 2004, Dr. Rogovoy obtained a position of Senior Research Scientist at ChemDiv Inc, San Diego, CA. His research interests include heterocyclic synthesis, combinatorial synthesis in solution and solid support, development of efficient synthetic approaches.