Biguanidines, guanylureas and guanylthioureas

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Dedicated to Prof. Bruce E. Maryanoff and Prof. Cynthia A. Maryanoff in honor of their outstanding contributions to organic chemistry

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Abstract
Classical and more recent preparations of biguanidines, guanylureas and guanylthioureas are summarized, together with their biological activity and other applications. Biguanides are depicted in their most stable tautomeric form, modified where necessary from that in the literature.
Keywords: Biguanides, guanylureas, guanylthioureas, hypoglycemic agents, spasmolytic agents

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1. Introduction

Biguanidines are an interesting class of compounds with many known or potential applications. We were unable to locate any recent review of the synthesis and biological properties of the structurally related biguanidines 1, guanylureas 2 and guanylthioureas 3 (Figure 1). Consequently, we have now attempted to review both classical and more recent procedures for the preparation of biguanidines, guanylureas, and guanylthioureas together with their industrial applications.

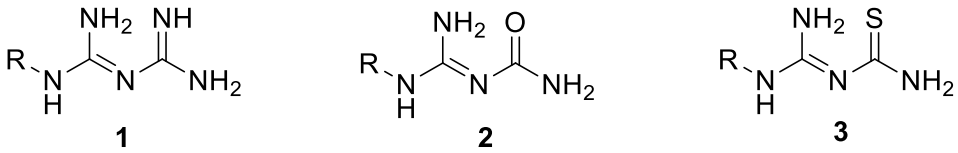


Figure 1

2. Biguanides

2.1 Structure of biguanides

In the literature, structures of biguanides continue to be commonly depicted as shown for **4**, which lead to a misleading perception. In fact, X-ray crystallographic analysis,[1] ^{15}N NMR spectroscopy,[2] molecular modeling[3] and tautomer stability studies[4] have confirmed that biguanides should be represented as **5** (Figure 2), where there is an absence of hydrogen on the bridging nitrogen. Hence, throughout this review we have represented biguanides according to form **5**, modifying the literature structures where necessary.

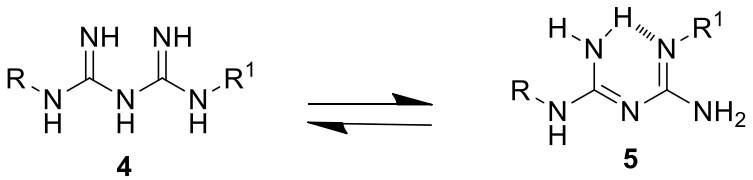
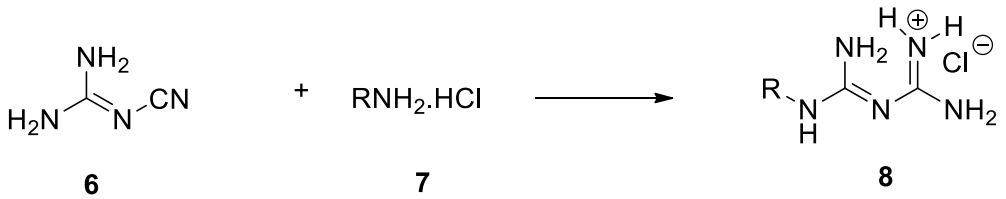


Figure 2

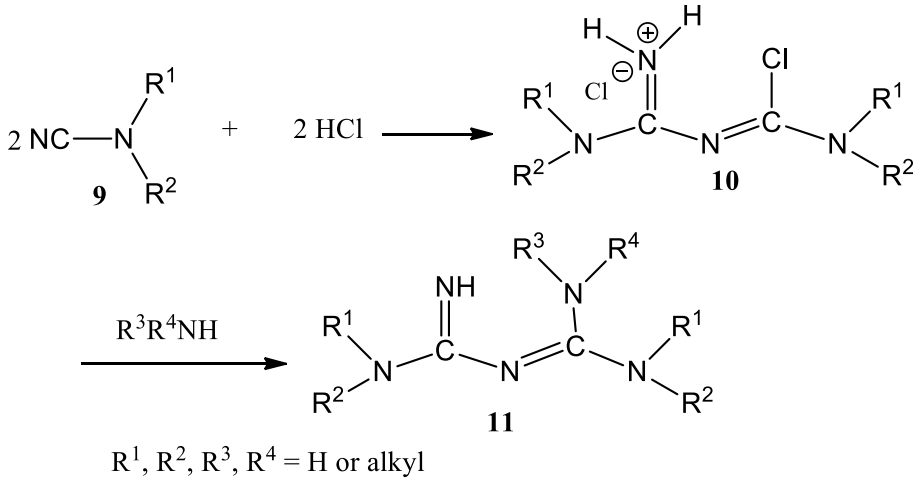
2.2 Methods of preparation

The synthesis most commonly utilized for substituted biguanidines **8** is the reaction of primary amine salts **7** with cyanoguanidine **6** (Scheme 1).



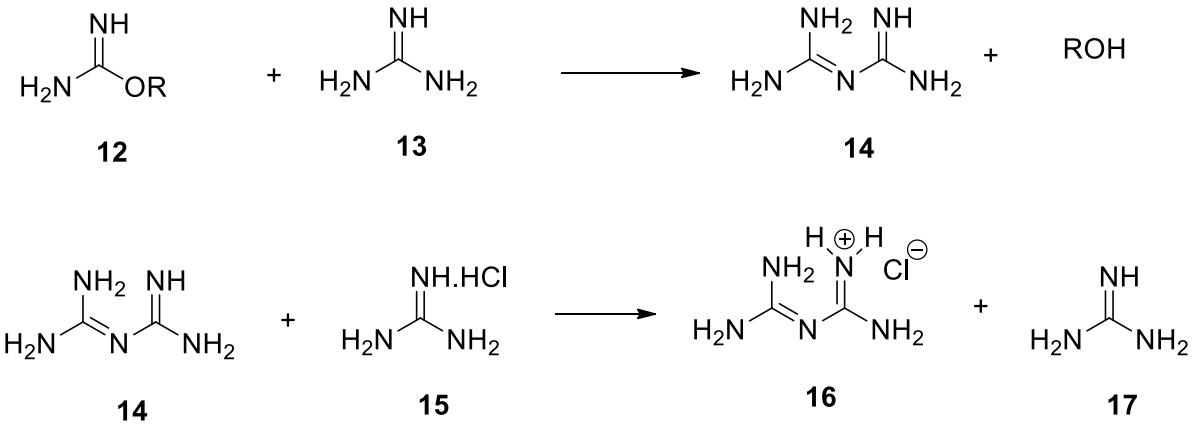
Scheme 1

Treatment of dialkylcyanamide **9** with hydrogen chloride at 60 ºC to 150 ºC gave alkylguanylchloroformamidine hydrochlorides **10**. Reaction these with aqueous ammonia or amines gave the corresponding biguanides **11** (Scheme 2).[5]



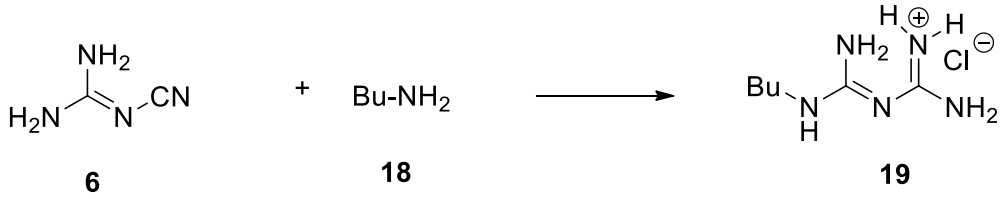
Scheme 2

In 1960 Priyadaranjan Ray reviewed complexes of biguanidines with metals, reporting preparations of biguanidines up to 1958.[6a] In 1968 Kurzer and Pitchfork reviewed the chemistry of biguanides.[6b] In 1960 Shirai and Sugino found that the biguanidine **16** can be obtained in good yield from O-alkylisoureas **12** and guanidine **13** in ethanol as solvent (Scheme 3).[7]



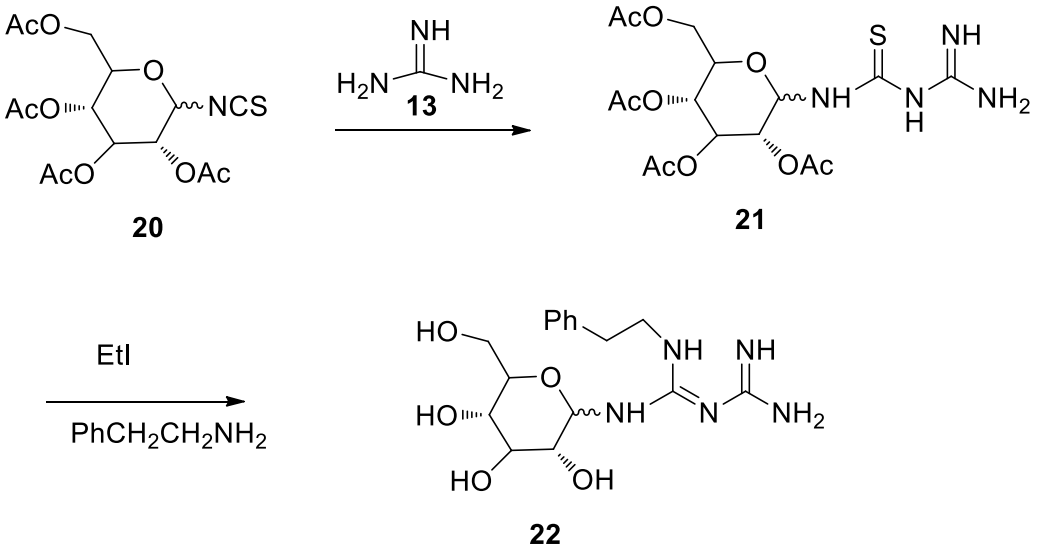
Scheme 3

Amines add to the cyanoguanidine **6** in the presence of $FeCl_3$ or $ZnCl_2$ under mild conditions: thus, cyanoguanidine **6** and butylamine **18** in the presence of $FeCl_3$ gave butylbiguanide **19** at 20 °C (Scheme 4).[8]



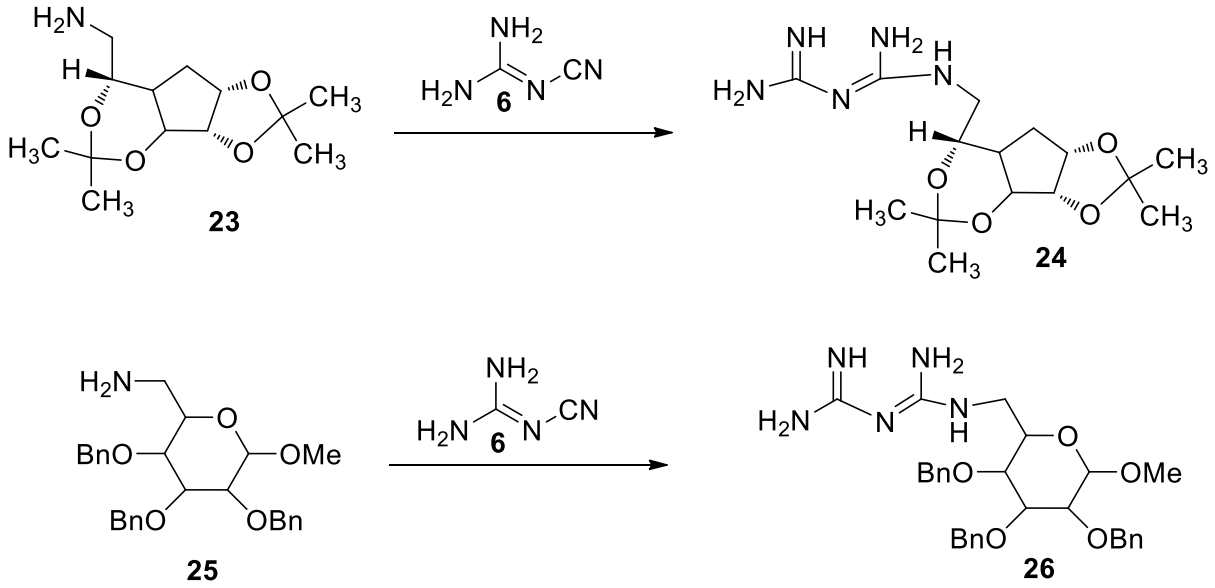
Scheme 4

A monosaccharide **22** containing the biguanide functionality had no hypoglycemic activity (Scheme 5) at the doses tested.[9] The isothiocyanate **20** was treated with guanidine **13** to afford **21**, which was then treated with ethyl iodide, followed by an excess of phenylethylamine to give **22** (a 7:3 mixture of β/α anomers).



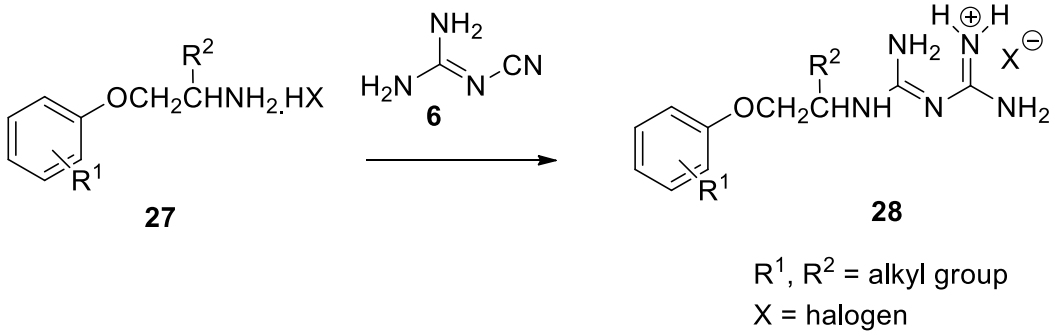
Scheme 5

Compounds **24** [6-biguanidino-1,2:3,5-bis-*O*-(1-methylethylidene)-6-deoxy-α-D-glucofuranose] and **26** [methyl 6-biguanidino-6-deoxy-2,3,4-*O*-tribenzyl-α-D-glucopyranoside] exhibit hypoglycemic activity close to that of Phenformin **63** and Metformin **64** (see Figure 5) as measured by the inhibition of rise of blood glucose levels, and were prepared as shown in Scheme 6.[9]



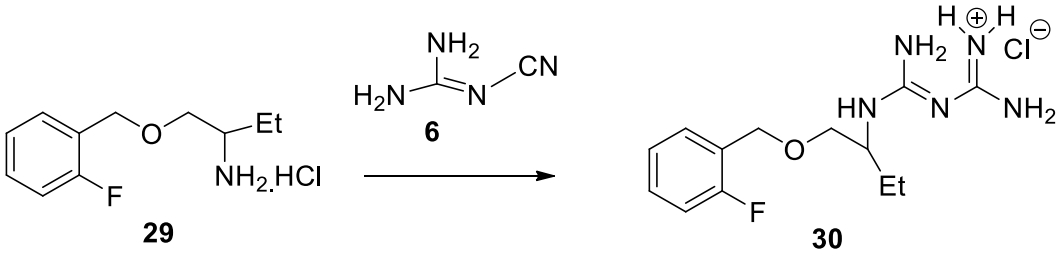
Scheme 6

A high-purity biguanide derivative **28** was prepared by treatment of the phenoxyalkylamine salt **27** with cyanoguanidine **6** in high yields (Scheme 7).[10]



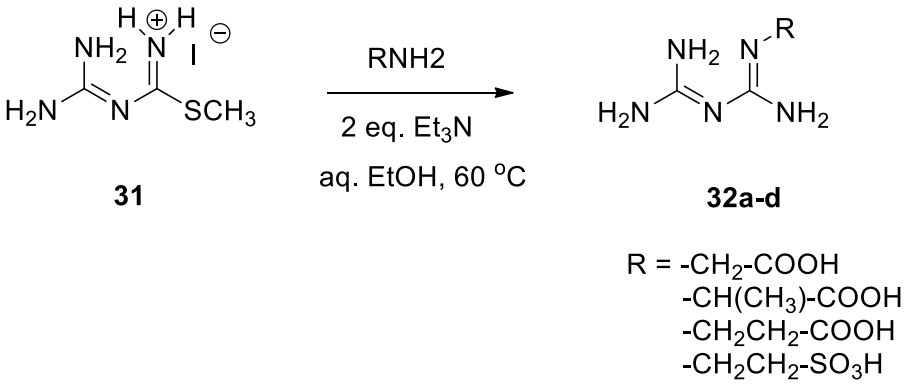
Scheme 7

The aryl-alkylamine hydrochlorides **29** and dicyandiamide **6** give the 1-aralkyl biguanides **30** at 120-150 °C. (Scheme 8).[11]



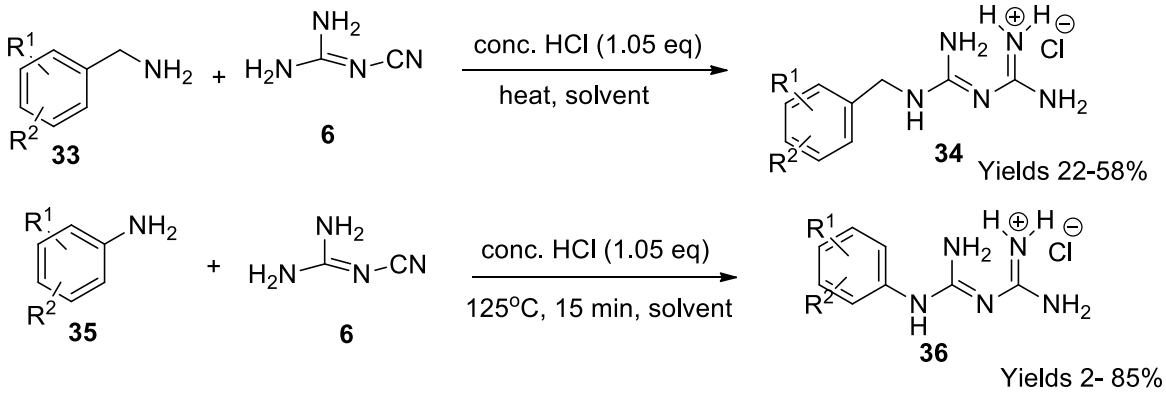
Scheme 8

The biguanide transfer reagent **31** converted glycine, β-alanine, 3-aminopropanoic acid, and taurine into the desired biguanide analogs **32a-d** (Scheme 9).[12]



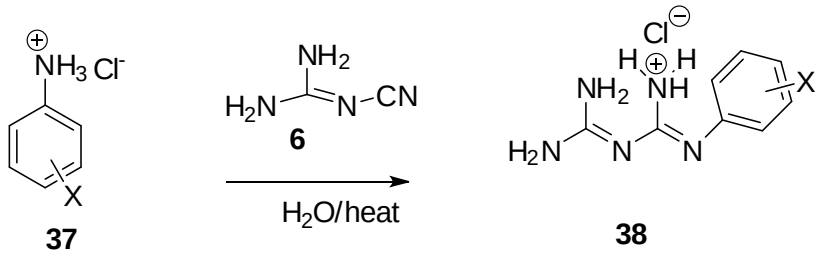
Scheme 9

Organ's group[13] produced an array of alkyl- and aryl- based biguanide compounds **34** and **36** using microwave irradiation, starting from the substituted benzylamine **33** and anilines **35** with dicyandiamide **6** in average yields of 40% (Scheme 10). These compounds showed significant inhibitory activity of dihydrofolate reductase (DHFR).



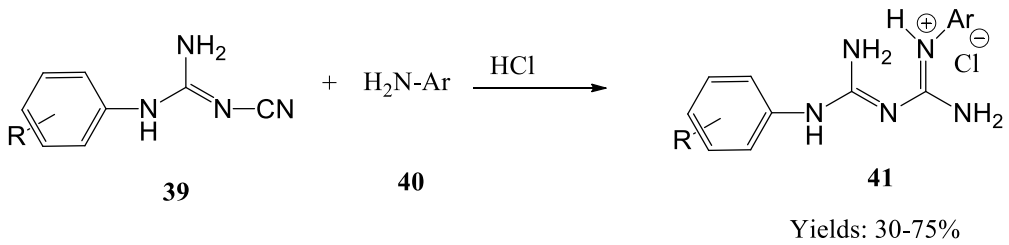
Scheme 10

LeBel and his group synthesized the mono-substituted aryl-biguanides **38** from **37** and dicyandiamide, **6**, by heating the mixture under reflux conditions for 12 h, in a modification of the method reported by Curd and Rose (Scheme 11).[1a]



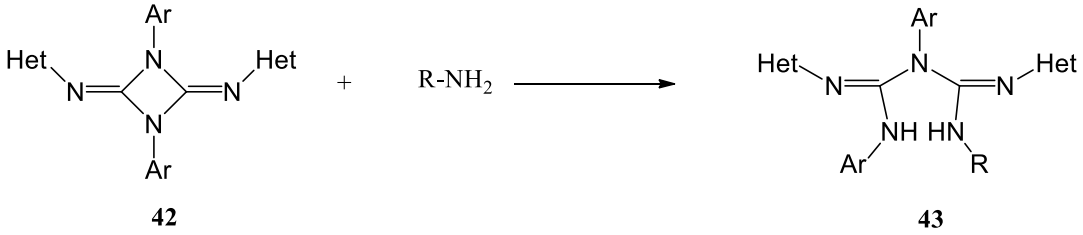
Scheme 11

Neelakantan synthesized the 1,5-diarylbiguanides **41** by using a one-pot procedure, from aniline derivatives **40** and phenylcyanoguanidine **39** at 100 °C (Scheme 12).[14]



Scheme 12

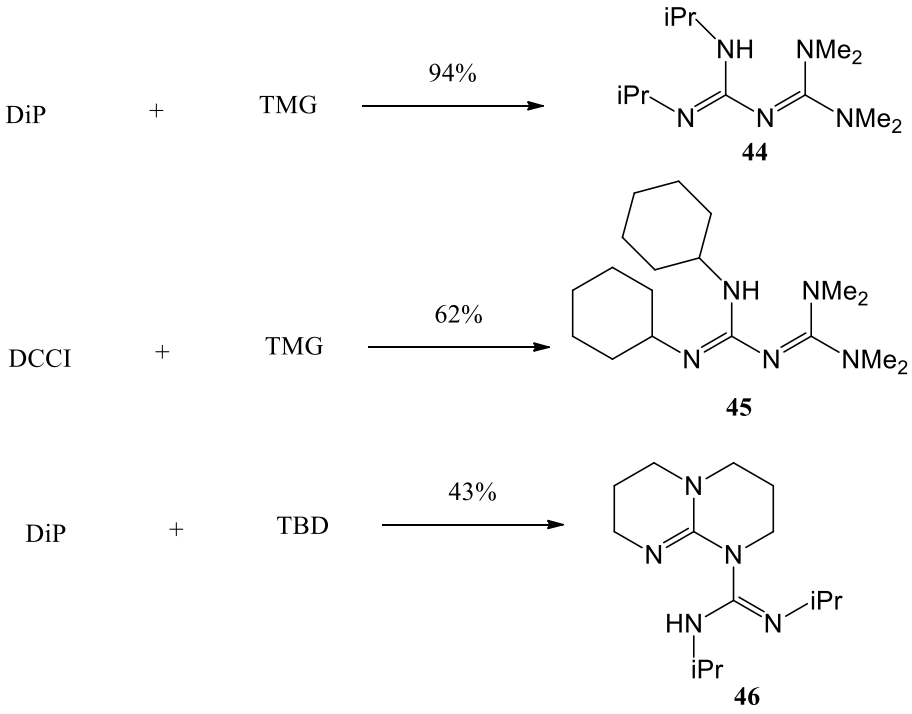
Molina *et al* synthesized the penta-substituted biguanides **43** by reacting 1,3-diaryl-2,4-*bis*-(heteroarylimino)-1,3-diazetidines **42** with primary amines in dry methylene chloride at room temperature in 47-96% yield (Scheme 13).[15]



42 **43**

Scheme 13

Gelbard *et al* synthesized *N*-alkylated biguanides **44**-**46** through addition of 1,1,3,3-tetramethylguanidine (TMG) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) to di-isopropylcarbodiimide (DiP) and dicyclohexylcarbodiimide (DCCI) as shown in Scheme 14.[16a]

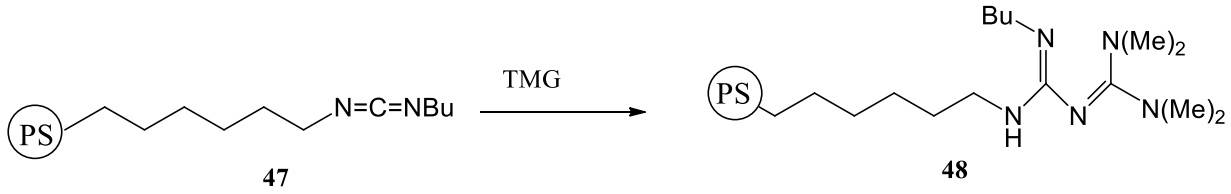


44 **45** **46**

Scheme 14

Gelbard *et al* also synthesized a polystyrene-supported biguanide **48** by the nucleophilic addition of 1,1,3,3-tetramethylguanidine (TMG) to the polymeric carbodiimide **47**. They showed

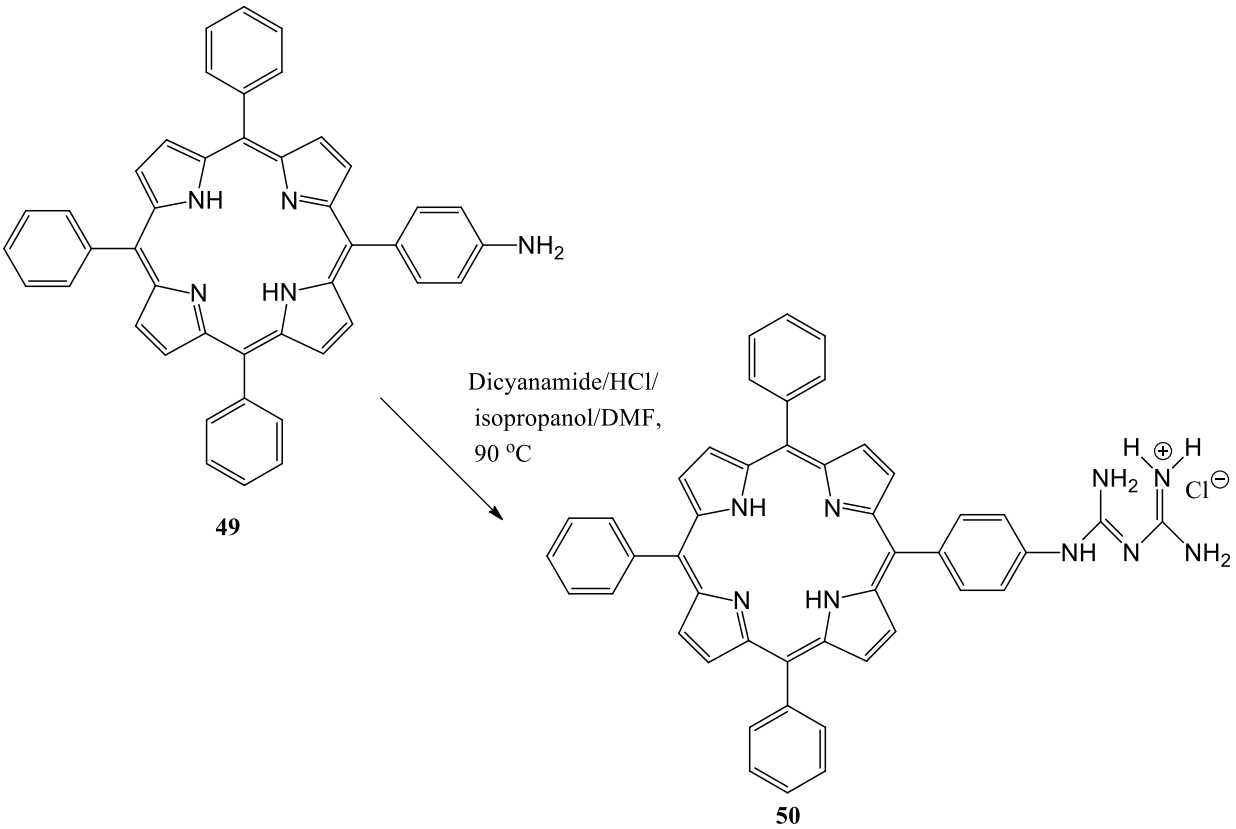
that the biguanide **48** was an excellent recyclable catalyst for the transesterification of triglycerides (Scheme 15).[16a,b]



47 **48**

Scheme 15

Vicente and coworkers synthesized the porphyrin derivative **50** containing a biguanidine unit by treatment of the mono-amino porphyrin **49** in dicyanamide in the presence of HCl and isopropanol at 90 ºC for 18 h (Scheme 16).[17] The fluorescence quantum yield determined for **50** is higher at low pH (<6) and showed low dark-toxicity toward human carcinoma HEp2 cells.

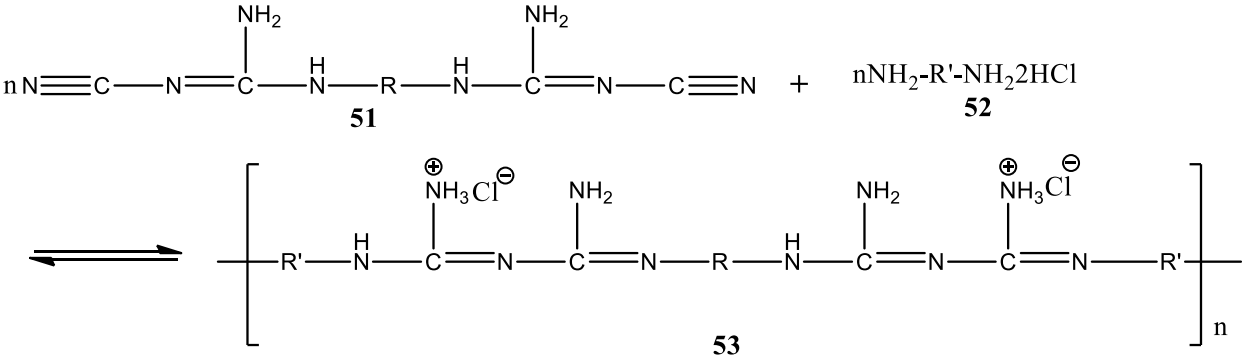


49 **50**

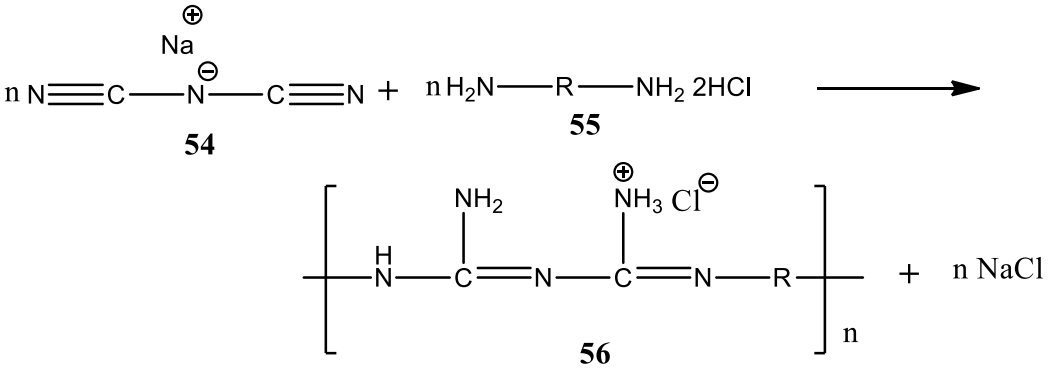
Scheme 16

A series of polymeric biguanide hydrochlorides **53**, **56**, **59** containing hexamethylene groups was synthesized by developing methods for melt- and solution- polymerization, based on the

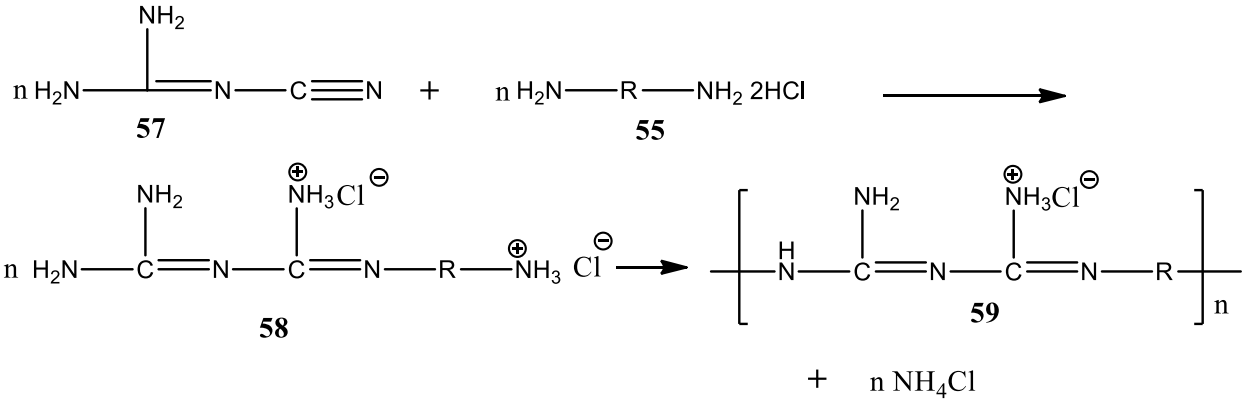
reaction of cyano groups with amine hydrochlorides (Schemes 17-19).[18] The polybiguanide salts in both aqueous and polar non-aqueous solutions showed typical solution viscosity features of polyelectrolytes. The polybiguanides readily formed colored complexes with copper ions.



Scheme 17. Melt polymerization.



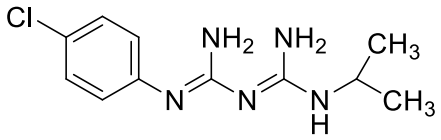
Scheme 18. Solution polymerization.



Scheme 19. Melt polymerization.

2.3 Biological properties of biguanides

2.3.1 Antimalarial activity. Malaria is an infectious disease causing enormous public health problems. The disease is caused by protozoan parasites of the genus *Plasmodium*. Biguanides possess antimalarial activity and (*N*-(4-chlorophenyl)-*N'*-(isopropyl)-imidodicarbonimidic diamide (Proguanil) **60** (Figure 3) has been used as an antimalarial drug.[19a-k]



60

Figure 3

Jensen *et al*. recently synthesized 34 analogs of the biguanide PS-15 (**61a**) and a prodrug of diaminotriazine WR-99210 (**62**). Several of them, such as **61b** (PS-33) and **61c** (PS-26), maintain or exceed the *in vivo* activity of PS-15 and do not require the use of highly regulated starting materials (Figure 4).[19*l*]

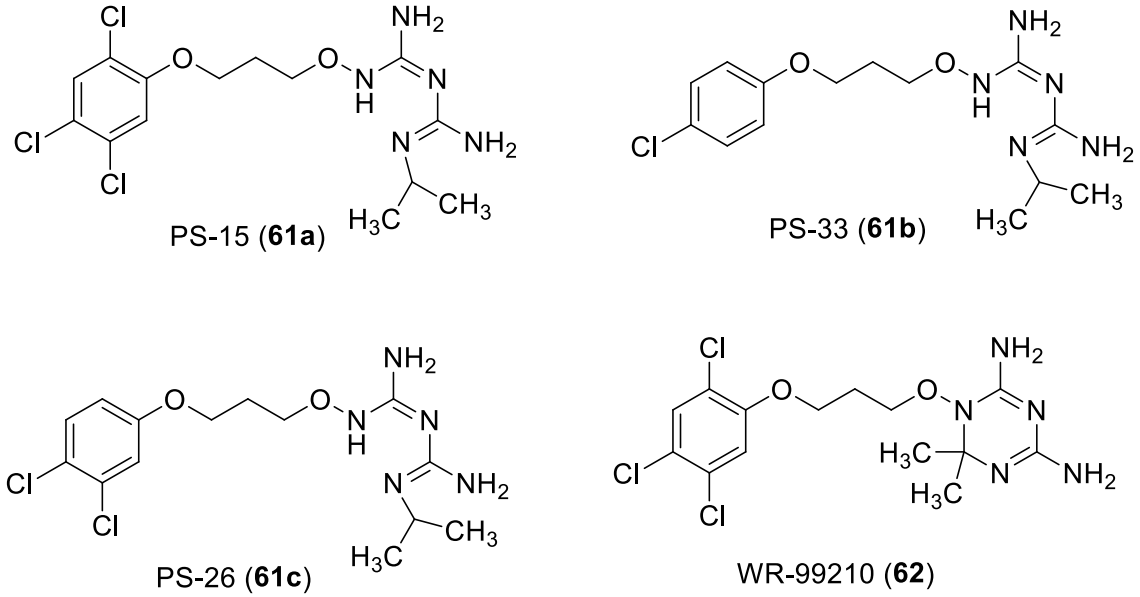


Figure 4

2.3.2 Hypoglycemic agents. Diabetes mellitus is one of the most serious public health problems and has a rapidly increasing incidence, especially in the West. Diabetes is an enormous economic burden in the industrialized world, accounting for huge healthcare costs.[20a,b] Biguanides are widely used for the treatment of Type 2 diabetes mellitus [*e.g.*, 1,1-dimethylbiguanide (metformin) **63**, and phenylethylbiguanide (phenformin) **64** (Figure 5)].[20c-e] Metformin **63** is a

potent anti-diabetic agent currently used as a first-line treatment for patients with type 2 diabetes.[20f] In 2003, Hundal and Inzucchi reviewed the role of metformin in the treatment of patients with Type 2 diabetes and described the benefits it provides over and above its effect on glucose levels alone.[21]

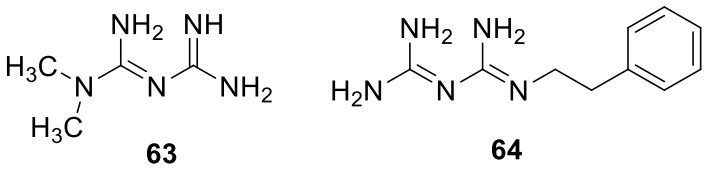
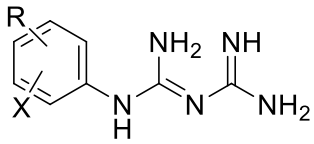


Figure 5

2.3.3 Antitumor activity. The antitumor activity of biguanides has been mentioned frequently since preliminary reports by Kundu *et al* in 1967 on pyrimidinodiguanidines as anticancer drugs.[22] Lugaro and co-workers found that mono- and di- substituted biguanidines exhibited antitumor activity.[23a-c] Sączewski and co-workers used biguanides in the synthesis of 2,4-diamino-1,3,5-triazine derivatives, which showed moderate to strong growth inhibition activity on various tumor panel cell lines between 0.148 and 56.2 μ*M* concentrations.[23d] Ghosh and co-workers have reported antitumor properties of boron complexes with hydroxy- biguanidine.[24]

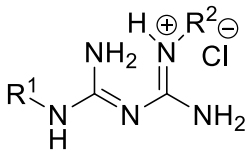
2.3.4 Spasmolytic agents. Diamond and co-workers found that 1-substituted phenyl biguanides **65** possess useful gastric anti-secretory and spasmolytic agents (Figure 6).[25]



R = alkyl group, X = halogen

Figure 6

2.3.5 Antiseptic properties. Tsubouchi and co-workers synthesized 1,5-disubstituted biguanidines **66**, and the bactericidal activity in 3,4-dichlorobenzyl derivatives was found to be high (Figure 7).[26]

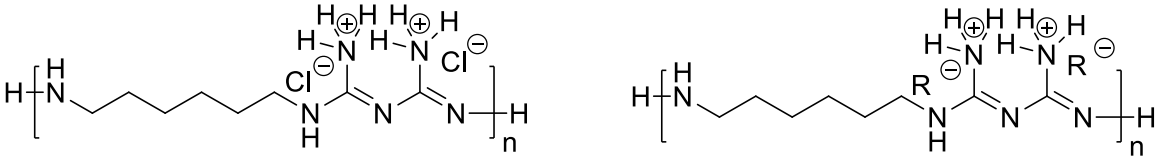


66

R^1 = aryl, aryl
R^2 = alkyl, aryl

Figure 7

Zhang's group synthesized the water-soluble polyhexamethylene biguanidine hydrochloride (PHBGC) **67** and the lipophilic polyhexamethylene biguanide stearate (PHBGS) **68**, and tested their antimicrobial activity (Figure 8).[27] The polymeric biguanides are effective in controlling both bacteria and fungi.



67 **68**

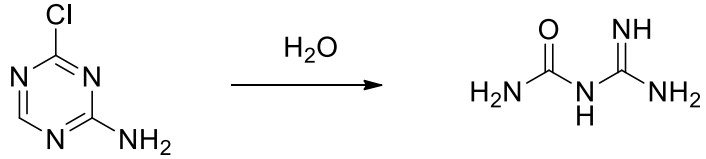
R = $CH_3(CH_2)_{16}COO$

Figure 8

3. Guanylureas

3.1 Methods of preparation

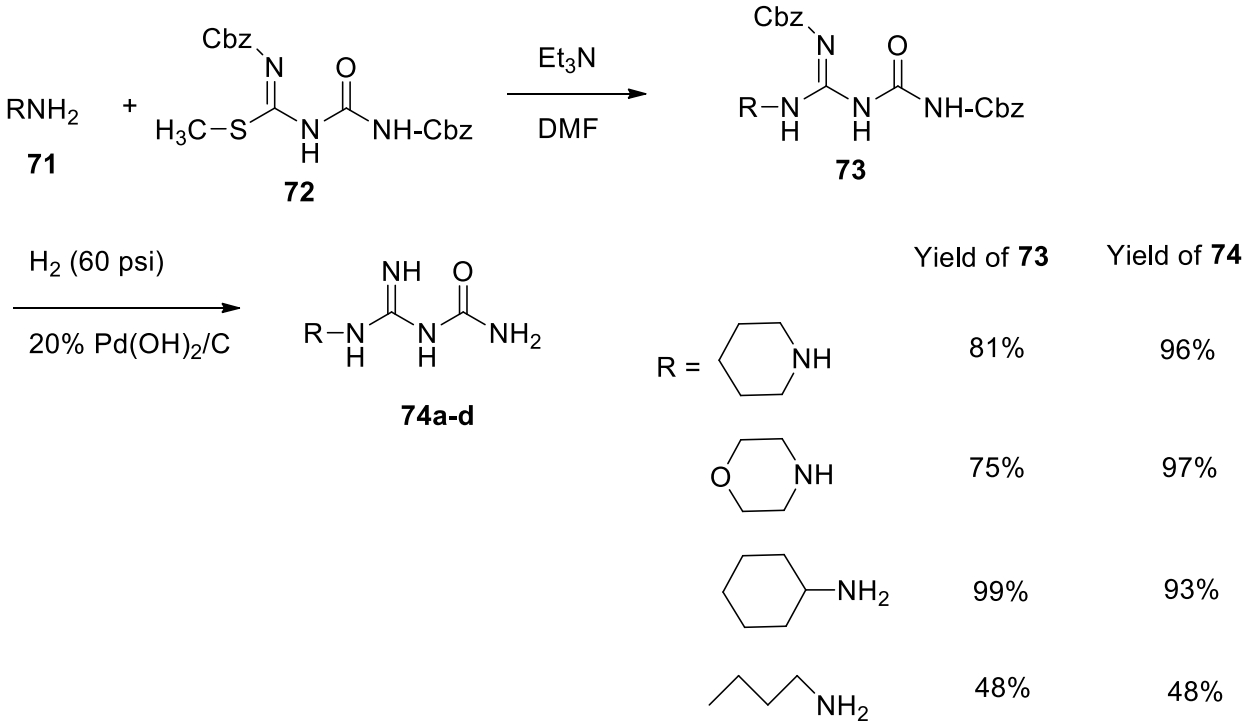
Treatment of 2-amino-4-chloro-1,3,5-triazine **69** with water gave guanylurea **70** (Scheme 20).[28]



69 **70**

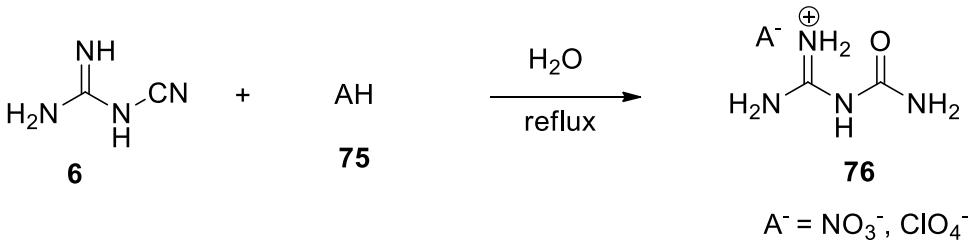
Scheme 20

The guanylurea derivatives **74** are also obtained by condensation of N-Cbz-ureido-N'-Cbz-S-methylisothiourea **72** with amines **71** in the presence of triethylamine in DMF at 20 °C, followed by hydrogenation (Scheme 21).[29]



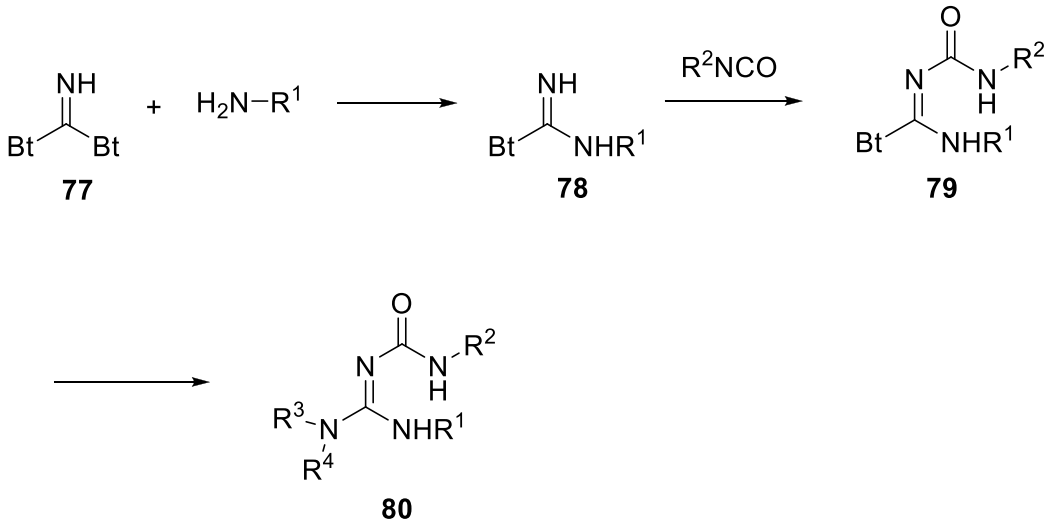
Scheme 21

Guanylurea nitrate (GUN) **76a** and guanylurea perchlorate (GUP) **76b** were prepared by hydrolysis of cyanoguanidine (CG) **6** with the corresponding concentrated acid in aqueous solution (Scheme 22).[30]



Scheme 22

Katritzky and his co-workers reported the synthesis of guanylureas **80** from (benzotriazol-1-yl)carboximidamides **78** by treatment of **78** with isocyanate followed by amines (Scheme 23).[31]



Scheme 23

3.2 Applications of guanylureas

Salts of protonated guanylurea with dinitramide **81**,[32] the nitrate **76a** and the perchlorate **76b** anions[30] (Figure 9) have been prepared for use as energetic materials.

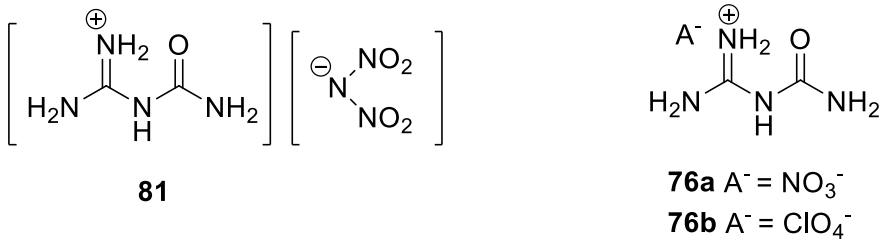
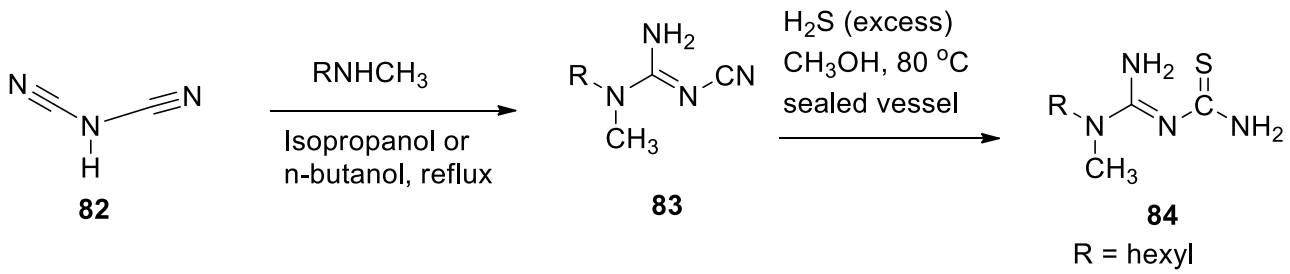


Figure 9

4. Guanylthioureas

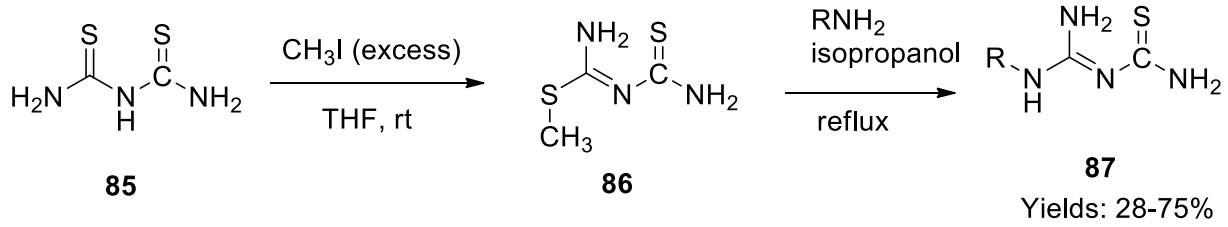
4.1 Methods of preparation

Mono-*N*-substituted guanylthioureas **84** are synthesized in two steps: (i) reaction of dicyanamide with an amine and (ii) treatment of the resulting cyanoguanidine **83** with hydrogen sulfide at 80ºC (Scheme 24).[33]



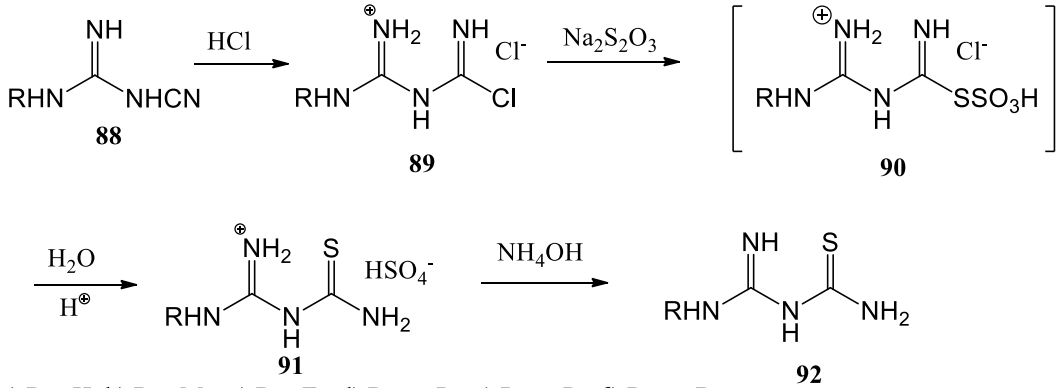
Scheme 24

Reiter and co-workers synthesized mono-*N*-substituted guanylthioureas, **87,** in 28-75% yields by mono-S-alkylation of dithiobiuret, **85,** to give the corresponding thio-uronium salt **86**, which was treated with amines to provide the desired mono- *N*-substituted guanylthioureas **87** (Scheme 25).[34]



Scheme 25

Tari and Gajary synthesized guanylthioureas **92** by reacting dicyandiamide derivatives, **88**, and sodium thiosulfate in acidic medium, followed by neutralization with a base (Scheme 26).[35] This reaction involves three steps: (a) the addition of two moles of hydrogen chloride to dicyandiamide, (b) addition of thiosulfuric acid to afford acidic hydrolysis of the product, and (c) release of the free guanylthiourea by treatment with ammonium hydroxide.



a) R = H, b) R = Me, c) R = Et, d) R = *n*-Pr, e) R = *i*-Pr, f) R = *n*-Bu

Scheme 26

4.2 Applications of guanylthioureas

Guanylthiourea derivatives have immuno-stimulant and tumor cell inhibitory activity[36] and can significantly inhibit dihydrofolate reductase (DHFR).[37] Guanylthiourea is introduced into the structure of ion-exchange/coordinating resins having a vinylbenzyl chloride/divinylbenzene matrix in order to detect metal cations.[38]

5. Conclusions

In this overview, we have attempted to summarize the classical and more recent preparation of biguanidines, guanylureas and guanylthioureas together with their applications. We have also modified the literature structures of biguanides to indicate the most stable tautomeric form where necessary.

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