Efficient Synthesis of Polysubstituted Acylguanidines and Guanylureas

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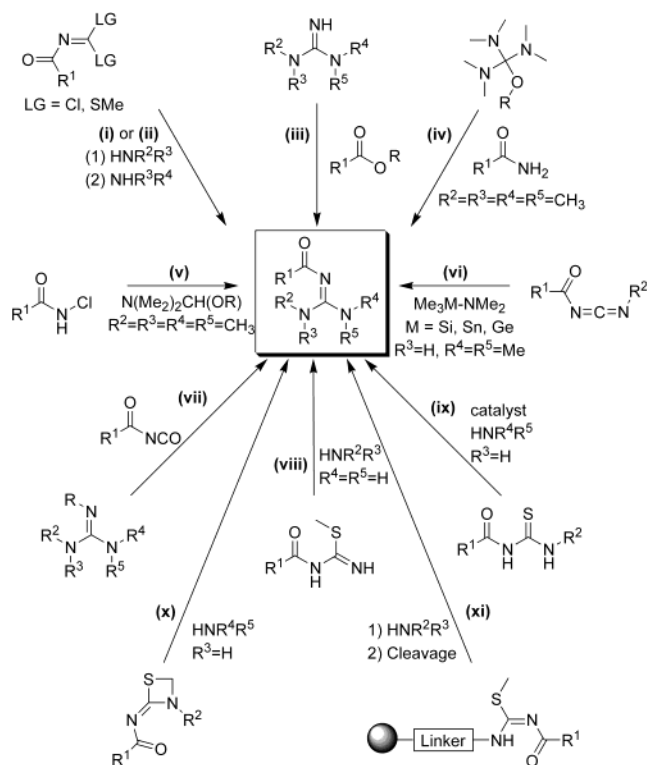*katritzky@chem.ufl.edu*

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(Benzotriazol-1-yl)carboximidamides were applied for the preparation of polysubstituted acylguanidines and guanylureas. The reaction sequence utilized mild conditions and gave high yields for final compounds and intermediates. The protocol developed allows for variation of the substituents at all positions of the products.

Introduction

Many natural and synthetic guanidines, including their acyl and carbamoyl derivatives, are of great interest because of their diverse biological activities.[1] Acylguanidines have found applications in the treatment of osteoporosis,[2] cardiac ischemia and reperfusion,[3] glaucoma,[3c] and as initropic drugs,[4] antihypertensive agents,[5] $\alpha_v\beta_3$ antagonists,[6a] diuretics,[6b] and thrombin inhibitors.[7] Their activity toward different receptors has been studied.[8] Acylguanidines have antifungal[9] and plant-protecting[10] properties.

Synthetic approaches to acylguanidines (Scheme 1) include (i) reactions of isocyanide dichlorides[11] with

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amines and (ii) reactions of dimethyl *N*-acyliminodithiocarbonates[12] with amines, which often form symmetrical byproducts, (iii) direct acylations of guanidines with esters,[9,13] (iv) treatment of hexamethyl(alkoxymethane)triamines with amides,[14] (v) reactions of *N*-chloroamides with tetramethyl(alkoxymethane)diamines[15] to give the

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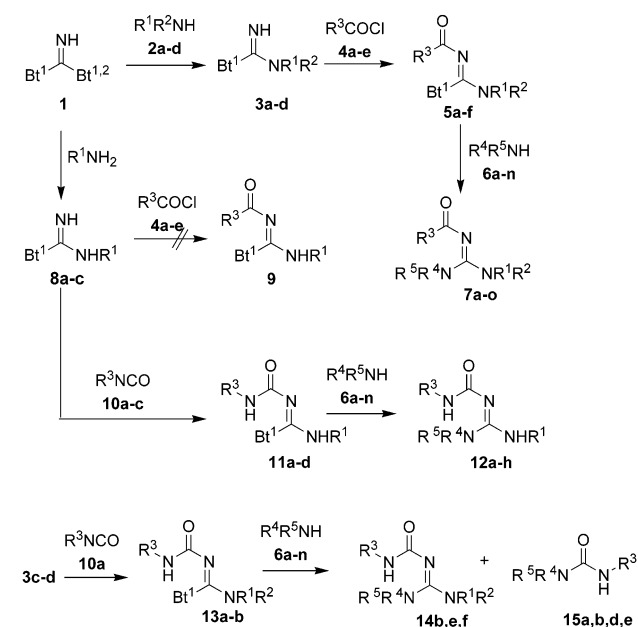
corresponding *N*-acyl-*N*,*N*,*N'*,*N'*-tetramethylguanidines, and (vi) additions to acylcarbodiimides of trimethylstannyl(germanyl or silyl)amines.[16] (vii) Reactions of pentasubstituted guanidines with acyl isocyanates or isothiocyanates provide tetrasubstituted acylguanidines via the formation of a four-membered [2 + 2] cycloadduct.[17] (viii) 1-Aroylisothioureas have been converted into acylguanidines upon reaction with a variety of amines,[18] and (xi) direct conversion of acylthioureas into acylguanidines has been carried out in the presence of a catalyst (HgCl$_2$,[19] 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), 2-chloro-1-methylpyridinium iodide,[19b] or Bi(NO$_3$)$_3$·5H$_2$O[20]). (x) Acyliminolthiazetidines (formed from the corresponding acylthioureas) afford acylguanidines in moderate to good yields with amines.[21] (xi) The combinatorial solid-supported preparation of acylguanidines has been developed with the utilization of solid-supported isothioureas.[22,23]

We[24a-c] and others[24d] have previously reported (benzotriazole-1-yl)carboximidamides **3** to be efficient reagents for the synthesis of polysubstituted guanidines in solution and on solid support.[25] Acyl(benzotriazolyl)carboximidamides **5** are also versatile intermediates for the synthesis of five-[26] and six-membered[27,24b] heterocycles. We now report the utilization of **5** and synthesis and utilization of **11** in the efficient preparation of polysubstituted acylguanidines and guanylureas, respectively.

Results and Discussion

(Benzotriazole-1-yl)carboximidamides **3a–d** and **8a–c** were prepared by a previously published procedure[24a,26a] from di(benzotriazolyl)methanimines **1**. The tautomeric equilibrium of monosubstituted (benzotriazole-1-yl)carboximidamides **8a–c** in chloroform was discussed previously,[24a] and all the present compounds showed spectra consistent with the discussion in and assignments of our previous investigation. Thus, according to both ^{1}H NMR and ^{13}C NMR data, aryl substituted compounds **8b,c**

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SCHEME 2

TABLE 1. Preparation of *N*-acyl(benzotriazole-1-yl)carboximidamides 5a–f and Aminocarbonyl(Benzotriazole-1-yl)carboximidamides 11a–d and 13a,b

entry	starting	product	R^1	R^2	R^3	yield (%)
1	**3a**	**5a**	−(CH$_2$)$_5$−		Ph	78
2	**3b**	**5b**	*i*-Pr	*i*-Pr	C$_2$H$_5$	75
3	**3b**	**5c**	*i*-Pr	*i*-Pr	Ph	76
4	**3c**	**5d**	−(CH$_2$)$_2$O(CH$_2$)$_2$−		4-MeOC$_6$H$_4$	69
5	**3c**	**5e**	−(CH$_2$)$_2$O(CH$_2$)$_2$−		2-Furoyl	64
6	**3c**	**5f**	−(CH$_2$)$_2$O(CH$_2$)$_2$−		4-Cl-C$_6$H$_4$	70
7	**3c**	**13a**	−(CH$_2$)$_2$O(CH$_2$)$_2$−		Ph	65
8	**3d**	**13b**	Bn	Bn	Ph	80
9	**8a**	**11a**	*n*-hexyl	H	Ph	86
10	**8b**	**11b**	Bn	H	4-MeOC$_6$H$_4$	76
11	**8c**	**11c**	*p*-tolyl	H	Ph	73
12	**8c**	**11d**	*p*-tolyl	H	4-Cl-C$_6$H$_4$	89

(R^1 = Ar or HetAr, R^2 = H) exist in chloroform solution predominantly as the ArN=C(NH$_2$)Bt form. Alkyl substituted analogue **8a** (R^1 = *n*-hexyl, R^2 = H) exists as a mixture of both tautomers with C$_6$H$_{13}$NHC(Bt)=NH dominating. Acylation of disubstituted (benzotriazole-1-yl)carboximidamides **3a–d** with acid chlorides **4a–e** gave the expected acyl derivatives **5a–f**. A similar reaction of monosubstituted (benzotriazole-1-yl)carboximidamides **8a–c** with acid chlorides gave complex reaction mixtures independent of the substrates used, and no desired products of type **9** (R^2 = H) were isolated.

Reactions of mono- and disubstituted compounds **3c,d** and **8a–c** with isocyanates **10a–c** gave the desired aminocarbonyl(benzotriazole-1-yl)carboximidamides **11a–d** and **13a,b** in excellent yields (Scheme 2, Table 1). All compounds **11** and **13** were obtained in the sole tautomeric form depicted in Scheme 1 due to the presence of the aminocarbonyl group. A single set of signals in both the ^{1}H and ^{13}C NMR supports this statement. Thus, ^{1}H NMR spectrum for *N*-[1*H*-benzotriazol-1-yl(4-toluidino)methylidene]-*N*-phenylurea **11c** in CDCl$_3$ solution showed two singlets for the NH protons near the carbonyl and tolyl groups at 11.05 and 9.24 ppm,

TABLE 2. Synthesis of *N*-Acyl Guanidines 7a−o

entry	starting compd	product	R^4	R^5	yield (%)
1	**5a**	**7a**	4-MeOC$_6$H$_4$	H	68
2	**5a**	**7b**	−(CH$_2$)$_2$O(CH$_2$)$_2$−		78
3	**5a**	**7c**	Ph	H	76
4	**5a**	**7d**	*n*-Bu	H	84
5	**5b**	**7e**	PhC$_2$H$_4$	H	51
6	**5b**	**7f**	PhCH$_2$	H	50
7	**5b**	**7g**	*i*-Bu	H	56
8	**5b**	**7h**	4-MeOC$_6$H$_4$CH$_2$	H	70
9	**5c**	**7i**	Ph	H	60
10	**5c**	**7j**	PhCH$_2$	H	78
11	**5d**	**7k**	−(CH$_2$)$_2$O(CH$_2$)$_2$−		84
12	**5e**	**7l**	PhC$_2$H$_4$	H	81
13	**5e**	**7m**	*p*-Tolyl	H	79
14	**5f**	**7n**	MeO$_2$CCH(Ph)	H	70
15	**5f**	**7o**	−(CH$_2$)$_4$−		78

TABLE 3. Synthesis of *N*-Carbamoylguanidines 12a−h and 14a−f

entry	starting compd	R^4	R^5	product and yield (%)	
1	**11a**	PhC$_2$H$_4$	H	**12a** (51)	
2	**11a**	4-MeOC$_6$H$_4$	H	**12b** (67)	
3	**11b**	−(CH$_2$)$_2$O(CH$_2$)$_2$−		**12c** (85)	
4	**11b**	*n*-Bu	H	**12d** (87)	
5	**11c**	PhCH$_2$	H	**12e** (60)	
6	**11c**	*n*-Bu	*n*-Bu	**12f** (58)	
7	**11d**	*n*-Bu	*n*-Bu	**12g** (70)	
8	**11d**	4-ClC$_6$H$_4$	H	**12h** (57)	
9	**13a**	4-MeOC$_6$H$_4$	H	**14a** (0)	**15a** (56)
10	**13a**	*n*-Bu	H	**14b** (43)	**15b** (46)
11	**13b**	4-MeOC$_6$H$_4$	H	**14c** (0)	**15a** (51)
12	**13b**	−(CH$_2$)$_2$O(CH$_2$)$_2$−		**14d** (0)	**15d** (72)
13	**13b**	4-MeOC$_6$H$_4$CH$_2$	H	**14e** (35)	**15e** (40)
14	**13b**	*n*-Bu	H	**14f** (31)	**15b** (46)

respectively. Similarly, the NH proton of the aminocarbonyl group for compound **11a** was found at 10.48 ppm; the NH proton near the *n*-hexyl moiety overlapped with some protons of the benzotriazolyl and tolyl moieties in the region of 7.30−7.64 ppm. All other signals are well resolved (when no overlapping is present), supporting the presence of a single tautomeric form.

The benzotriazole moiety in compounds **5a−f** was displaced by the action of amines **6a−n** in refluxing tetrahydrofuran (THF) (Scheme 2, Table 2) to form the desired *N*-acyl polysubstituted guanidines **7a−o**; the benzotriazole formed as a byproduct was removed from reaction mixtures by washing with a 10% aqueous solution of sodium hydroxide. We previously described reactions of acylated benzotriazolylcarboximidamides **5** with hydrazines for the preparation of 1,2,4-triazole ring systems.[26a] In some cases, the concurrent displacement of benzotriazole or the amino functionality was observed and 5-amino-1,2,4-triazoles or 5-benzotriazol-1-yl-1,2,4-triazoles or both were obtained. The amines now used for the preparation of the acylguanidines are less nucleophilic and, correspondingly, less reactive than hydrazines. In most cases, hydrazines displace the benzotriazolyl or amino group at room temperature, whereas displacement of benzotriazole with amines requires elevated temperature up to reflux in THF for 12−18 h. The only exception was the reaction of compound **5d** with pyrrolidine. In this case, a symmetrical product was the major product in a mixture containing the desired unsymmetrical acylguanidine as detected by ^{1}H and ^{13}C NMR spectroscopy; this mixture could not be separated because of the close nature of the polarity of the compounds. Reaction of **5d** with morpholine gave the desired *N*-acyl guanidine **7k** in 84% yield. Displacement of amino functionality was not detected in any other reaction.

Successful displacement of the benzotriazole moiety from compounds **5a−f** does not depend on the nature of the acyl group. All the acyl-substituted (benzotriazole-1-yl)carboximidamides gave the desired guanidines **7a−d,k−o** in good to excellent yields in reactions with primary and secondary alkylamines, anilines, and α-amino esters. However, hindered *N*-acyl *N*,*N*-di(isopropyl)-carboximidamides **5b,c** gave final guanidines **7e−h,j** only with primary alkylamines. No reaction was observed for **5b,c** with morpholine or dibenzylamine.

The reaction sequence now developed is suitable for the conversion of α-amino acids to corresponding α-gua-

nyl derivatives. Thus, *N*-[benzotriazol-1-yl(morpholin-4-yl)methylene]-4-chlorobenzamide **5f** reacted with L-phenylalanine methyl ester hydrochloride in the presence of triethylamine to afford the corresponding α-guanyl derivative **7n**. Because of the strong basicity of the guanidine moiety, compound **7n** was isolated partially as a hydrochloride (38%) and partially as hydrate (32%) from the same reaction mixture. The compositions of both derivatives were confirmed by combustion analysis and NMR spectroscopy.

Similarly, *N*-substituted and *N*,*N*-disubstituted *N*-aminocarbonyl(benzotriazole-1-yl)carboximidamides **11a−d** and **13a,b** were reacted with various amines **6a−n**. *N*-Monosubstituted (benzotriazol-1-yl)carboximidamides **11a−d** afforded the desired guanylureas **12a−h** (Scheme 2, Table 3). The benzotriazolyl moiety was displaced under conditions similar to those used for the reaction of compounds **5a−f** with amines: refluxing in THF with variable reaction times. Completion of the reaction was determined by thin-layer chromatography (TLC) analysis from the disappearance of starting material. The presence of the carbonyl group determines the configuration of the products obtained. According to both the ^{1}H and ^{13}C NMR, all compounds **12a−h**, independently of the nature of the substituents, were obtained in a single tautomeric form with the double-bonded C=N nitrogen bearing the carbonyl group. All well-resolved signals correspond to a single tautomeric form. The only exception was for compound **12g** (R^1 = *p*-tolyl, R^2 = H, R^3 = 4-Cl-C$_6$H$_4$, R^4 = R^5 = *n*-Bu), for which two sets of signals were observed in both the ^{1}H and ^{13}C NMR in the approximate ratio of 2 to 1. However, it was not possible to assign signals to the individual tautomeric forms.

Reactions of *N*,*N*-disubstituted *N*-aminocarbonyl(benzotriazol-1-yl)carboximidamides **13a,b** with amines **6a−n** gave the desired guanylureas **14a−f** in low yields or not at all. The major products in the reactions of **13a,b** with **6** are di- and trisubstituted ureas **15a,b,d,e** as a result of the nucleophilic attack of an amine on the aminocarbonyl group and displacement of the whole (benzotriazolyl)carboximidamide moiety. 1-(Benzotriazol-1-yl-dibenzylaminomethylene)-3-phenylurea **13b** in the reaction with 4-methoxybenzylamine gave the desired 1-[dibenzylamino-(4-methoxybenzylamino)methylene]-3-phenylurea **14e** in 35% yield along with 1-(4-methoxybenzyl)-3-phenylurea **15e** in 40% yield. Reactions of **13b** with

p-anisidine and morpholine afforded only the corresponding ureas **15a,d** in 51 and 72% yield, respectively: no products **14c,d** were isolated.

Conclusion

We have developed a simple and efficient procedure for the preparation of acylguanidines **7a−o** and guanylureas **12a−h**. All reaction steps of the sequence are carried out in mild conditions and provide products in good to excellent yields. The purification of intermediates and final products requires in most cases simple washing with a 10% aqueous solution of sodium hydroxide after each of two benzotriazole displacement steps and with water after the acylation step. However, reactions of **13a,b** with amines sometimes give the corresponding guanylureas **14b,e,f** together with substantial amount of the corresponding simple ureas **15b,e**. In other cases only the urea **15a,d** is formed.

Our method allows the introduction of a variety of amino group substituents for the preparation of asymmetrical *N*-acyl guanidines, which is difficult if not impossible for the synthesis based on isocyanide dichlorides,[11] dimethyl *N*-acyliminodithiocarbonates,[12] hexamethyl(alkoxymethane)triamines,[14] or tetramethyl(alkoxymethane)diamines;[15] moreover, the available diversity of these reagents is limited. Many previously described methods[16a,b,18−21] impose limits on the number of substituents in the *N*-acyl guanidine molecules that can be prepared, whereas the method presently described allows the preparation of diversely substituted *N*-acylguanidines and *N*-guanylureas with complete control. Benzotriazole formed as the only byproduct can be recovered and recycled.

Experimental Section

General Procedure for the Preparation of Compounds 5a−f. To a stirred solution of 1*H*-benzotriazol-1-ylcarboximidamide (0.011 mol) in chloroform (30 mL), the appropriate acid chloride (0.011 mol) was added at room temperature followed by the addition of triethylamine (0.011 mol). The reaction mixture was allowed to react overnight at room temperature. Completion of the reaction was monitored by TLC. Upon completion, the reaction mixture was washed twice with water and dried over magnesium sulfate, and the solvent was removed under reduced pressure. The desired *N*-acyl-1*H*-benzotriazol-1-ylcarboimidamides **5a,c−f** were purified by recrystallization from an appropriate solvent; compound **5b** was purified by gradient column chromatography (ethyl acetate/hexanes, from 5 to 50% ethyl acetate in 5% steps).

N-(1H-Benzotriazol-1-yl(piperidino)methylidene)benzamide (5a). White microcrystals were obtained from ethyl acetate: mp 148−149 °C. ^{1}H NMR: δ 1.80 (br s, 6H), 3.56−3.59 (m, 4H), 7.36−7.41 (m, 3H), 7.45−7.52 (m, 3H), 8.04−8.09 (m, 3H). ^{13}C NMR: δ 24.0, 25.7, 48.9, 110.9, 120.3, 124.9, 128.0, 129.2, 129.5, 132.1, 132.7, 135.7, 145.5, 147.3, 174.9. Anal. Calcd for $C_{19}H_{19}N_5O$: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.10; H, 5.55; N, 21.01.

General Procedure for the Preparation of Compounds 11a−d. To a solution of (benzotriazole-1-yl)carboximidamide (0.01 mol) in chloroform (10 mL) was added aryl isocyanate (0.01 mol) at room temperature with stirring. The reaction mixture was allowed to react at room temperature overnight. Completion of the reaction was monitored by TLC. Upon completion, the solvent was evaporated under reduced pressure, and the pure desired aminocarbonyl(benzotriazole-1-yl)-carboximidamides **11a−d** were obtained after purification:

11a was recrystallized from chloroform/hexanes; **11b** was purified by gradient column chromatography with ethyl acetate/hexanes, from 1:9 to 1:3; **11c** was purified by gradient column chromatography with ethyl acetate/hexanes, from 1:20 to 1:1; **11d** was used for the subsequent transformations without additional purification.

N-(1H-Benzotriazol-1-yl(hexylamino)methylidene)-N'-phenylurea (11a). White needles were obtained from chloroform/hexanes: mp 121−122 °C. ^{1}H NMR: δ 0.86 (t, $J = 6.7$ Hz, 3H), 1.24−1.43 (m, 6H), 1.65−1.75 (m, 2H), 3.65−3.68 (m, 2H), 7.09 (t, $J = 7.3$ Hz, 1H), 7.30−7.64 (m, 7H), 8.09−8.15 (m, 2H), 10.48 (br s, 1H). ^{13}C NMR: δ 13.8, 22.0, 25.9, 28.5, 30.8, 42.9, 112.7, 118.5, 119.6, 122.1, 125.2, 128.4, 129.1, 131.8, 140.0, 144.9, 146.9, 158.8. Anal. Calcd for $C_{20}H_{24}N_6O$: C, 65.91; H, 6.64; N, 23.06. Found: C, 65.79; H, 6.63; N, 22.74.

General Procedure for the Preparation of Compounds 13a,b. Benzotriazole-1-carboximidamide **3** (10 mmol) was dissolved in dry THF (100 mL), and phenyl isocyanate (1.10 mL, 10 mmol) was added under vigorous stirring. The resulting solution was allowed to react for 24 h at room temperature. After concentration of the reaction mixture, *N*-aminocarbonyl-(benzotriazol-1-yl)carboximidamides **13a,b** were obtained and recrystallized from methanol.

N-[1H-Benzotriazol-1-yl(morpholino)methylidene]-N'-phenylurea (13a). White prisms were obtained from ethanol: mp 158−160 °C (lit.[28] 158−160 °C). ^{1}H NMR (DMSO-d_6): δ 3.44−3.56 (m, 4H), 3.70−3.81 (m, 4H), 6.90 (t, $J = 7.2$ Hz, 1H), 7.16 (t, $J = 7.7$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.51 (t, $J = 7.6$ Hz, 1H), 7.67 (t, $J = 7.6$ Hz, 1H), 7.86 (d, $J = 8.2$ Hz, 1H), 8.18 (d, $J = 8.3$ Hz, 1H), 9.79 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 46.8, 65.6, 110.8, 118.5, 119.8, 122.2, 125.1, 128.4, 129.4, 132.4, 139.7, 144.5, 145.7, 157.7.

N-[1H-Benzotriazol-1-yl(dibenzylamino)methylidene]-N'-phenylurea (13b). White prisms were obtained from methanol: mp 136−138 °C (lit.[28] 215−217 °C). ^{1}H NMR (DMSO-d_6): δ 4.67 (s, 4H), 6.89 (t, $J = 7.1$ Hz, 1H), 7.14 (t, $J = 7.6$ Hz, 2H), 7.22−7.45 (m, 13H), 7.53−7.62 (m, 2H), 8.13 (d, $J = 8.2$ Hz, 1H), 10.05 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 52.0, 110.1, 118.9, 120.4, 123.2, 124.8, 128.0, 128.1, 128.7, 128.9, 129.3, 132.9, 135.1, 138.4, 145.2, 148.6, 157.3. Anal. Calcd for $C_{28}H_{24}N_6O$: C, 73.02; H, 5.25; N, 18.25. Found: C, 72.89; H, 5.27; N, 18.24.

General Procedure for the Preparation of Guanidines 7a−o. To a solution of *N*-acyl-1*H*-benzotriazol-1-ylcarboximidamide **5a−f** (3.0 mmol) in THF (25 mL), the amine of choice (3.0 mmol) was added with stirring. The reaction mixture was heated to reflux and kept at that temperature until the full conversion of starting materials (TLC control). Upon completion, the solvent was evaporated under reduced pressure; crude product was dissolved in chloroform, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. Desired guanidines were isolated by column chromatography (first ethyl acetate to remove impurities and methanol to elute guanidine) with additional recrystallization from ethyl acetate where applicable.

N-[(4-Methoxyanilino)(piperidino)methylidene]-benzamide (7a). Microcrystals were isolated as a carbonate salt: mp 77−79 °C. ^{1}H NMR: δ 1.58 (s, 6H), 3.48−3.50 (m, 4H), 3.78 (s, 3H), 6.84 (d, $J = 8.9$ Hz, 2H), 7.02 (d, $J = 8.9$ Hz, 2H), 7.38−7.46 (m, 3H), 8.24 (d, $J = 6.6$ Hz, 2H), 11.74 (br s, 1H). ^{13}C NMR: δ 24.3, 25.5, 47.8, 55.4, 114.5, 123.0, 127.8, 129.0, 131.1, 133.0, 138.5, 156.4, 160.0, 176.5. Anal. Calcd for $C_{21}H_{25}N_3O_5$: N, 10.52. Found: N, 10.83.

General Procedure for the Preparation of Guanylureas 12a−h. To a stirred solution of *N*-aminocarbonyl-1*H*-benzotriazol-1-ylcarboximidamides **11a−d** (0.54 mmol) in THF (10 mL) was added the amine of choice at room temperature. The reaction mixture was heated to reflux and allowed to react

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at this temperature overnight. Completion of the reaction was monitored by TLC. Upon completion, the solvent was evaporated and the obtained residue was dissolved in chloroform. The solution was washed twice with 10% aqueous NaOH and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. Desired guanylureas **12a**−**h** were obtained after purification by column chromatography: **12a** ethyl acetate/hexanes, 3:1 (silica gel); **12b** chloroform (basic alumina, 50−200 μm, Acros); **12c** gradient elution with ethyl acetate/hexanes, from 1:1 to pure ethyl acetate (silica gel); **12d** gradient elution with chloroform/methanol, from 1:1 to 5:1 (silica gel); **12e** chloroform/ethyl acetate, 20:1 (silica gel); **12f** gradient elution with ethyl acetate/hexanes, from 1:19 to 1:1 (basic alumina, 50−200 μm, Acros); **12g** gradient elution with ethyl acetate/hexanes, from 1:19 to 1:4 (silica gel); **12h** gradient elution with ethyl acetate/hexanes from 1:19 to 1:3 (silica gel).

***N*-[(Hexylamino)(phenethylamino)methylene]-*N*-phenylurea (12a)** White prisms were obtained from methanol: mp 90−92 °C. Broadening of signals and some doubling of signals are observed that are due to restricted rotation. Spectra appear as described. ^{1}H NMR: δ 0.67−0.87 (m, 3H), 1.20−1.39 (m, 6H), 1.41−1.52 (m, 2H), 2.70−2.91 (m, 2H), 2.90−3.20 (m, 2H), 3.30−3.52 (m, 2H), 4.20 (br s, 1H), 6.95 (t, $J = $ 7.4 Hz, 1H), 7.10−7.36 (m, 7H), 7.45 (d, $J = $ 7.7 Hz, 2H), 9.39 (br s, 1H). ^{13}C NMR: δ 14.0, 22.4, 26.5, 29.0, 31.3, 35.8, 41.0, 42.2, 118.7, 121.7, 121.8, 126.6, 128.6, 128.7, 138.4, 140.0, 158.9, 163.5. Anal. Calcd for $C_{22}H_{30}N_4O_3$: C, 72.10; H, 8.63; N, 15.29. Found: C, 72.22; H, 8.63; N, 15.35.

General Procedure for the Preparation of Compounds 14b,e,f and 15a,b,d,e. Compounds **14b,e,f** and **15a,b,d,e** were prepared starting from **13a,b** according to the procedure for the preparation of compounds **12a**−**h**.

***N*-[(Butylamino)(morpholino)methylidene]-*N*-phenylurea (14b).** White prisms were obtained from methanol (43%): mp 108−110 °C. ^{1}H NMR: δ 0.98 (t, $J = $ 7.3 Hz, 3H), 1.38−1.51 (m, 2H), 1.59−1.70 (m, 2H), 3.18−3.25 (m, 2H), 3.41 (t, $J = $ 4.7 Hz, 4H), 3.78 (t, $J = $ 4.6 Hz, 4H), 7.04 (t, $J = $ 7.3 Hz, 1H), 7.12 (br s, 1H), 7.28−7.34 (m, 2H), 7.49 (d, $J = $ 7.8 Hz, 2H), 9.05 (br s, 1H). ^{13}C NMR: δ 13.6, 19.9, 32.5, 45.4, 47.8, 66.5, 118.8, 122.3, 128.7, 139.6, 162.9, 164.7. Anal. Calcd for $C_{16}H_{24}N_4O_2$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.43; H, 8.12; N, 18.66.

***N*-(4-Methoxyphenyl)-*N*-phenylurea (15a).** White prisms were obtained from methanol: mp 199−201 °C (lit.[29] 196−197 °C). ^{1}H NMR (DMSO-d_6): δ 3.71 (s, 3H), 6.87 (d, $J = $ 9.0 Hz, 2H), 6.95 (t, $J = $ 7.3 Hz, 1H), 7.27 (t, $J = $ 7.8 Hz, 2H), 7.37 (d, $J = $ 8.9 Hz, 2H), 7.46 (d, $J = $ 7.8 Hz, 2H), 8.47 (br s, 1H), 8.58 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 55.1, 114.0, 118.1, 120.0, 121.6, 128.7, 132.7, 139.9, 152.7, 154.5.

Supporting Information Available: Descriptions of NMR data, elemental analysis (CHN) or high-resolution mass spectrometry (HRMS), and physical properties for compounds **5b**−**f**, **7b**−**o**, **11b**−**d**, **12b**−**h**, **14e,f**, and **15b,d,e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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