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Synthesis of Mono- and Symmetrical Di-*N*-hydroxy- and *N*-Aminoguanidines

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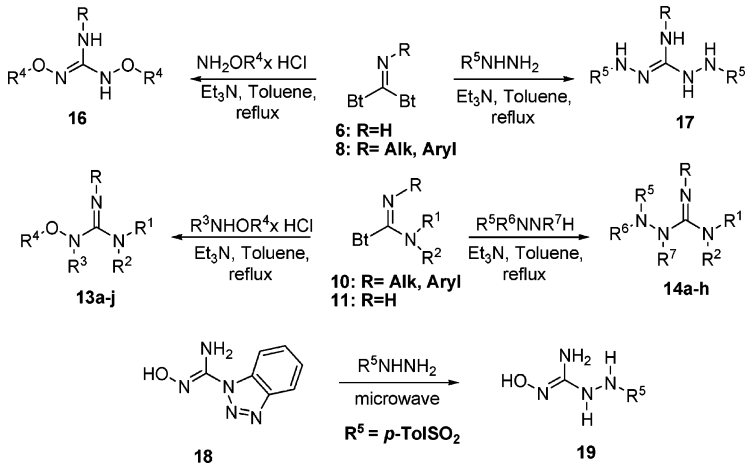


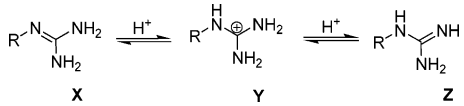
Novel mono- and symmetrical di-*N*-hydroxy- and *N*-aminoguanidines were readily prepared from the reaction of diverse hydroxylamines or hydrazines with reagent classes di(benzotriazol-1-yl)methanimine **6**, (bis-benzotriazol-1-yl-methylene)amines **8a**,**b**, benzotriazole-1-carboxamidines **10a**−**i**, benzotriazole-1-carboximidamides **11a**,**b**, and *N*′-hydroxy-1*H*-1,2,3-benzotriazole-1-carboximidamide **18**. The preparation is described for a variety of *N*-hydroxy- and *N*-aminoguanidines with different substitution patterns in good yields.

Introduction

Guanidines possess a wide range of interesting and important biochemical and pharmaceutical properties. Guanidines are strongly basic and are fully protonated under physiological conditions which is crucial for specific ligand−receptor interactions. Identification of guanidine metabolites has provided leads for drugs for the treatment of metabolic disorders, cancer, cardiovascular diseases, and diabetes.[1a] Guanidino-containing drugs such as MIBG and MGBG were shown several decades ago to have antitumor properties and have been subjected to intense preclinical and clinical evaluation.[1b]

The guanidine unit combines *p*-donor and π-acceptor nitrogens in an interesting manner. The symmetrical cation **Y** (Scheme 1) loses preferentially the most acidic proton, i.e., from the least basic nitrogen atom, so that if R is electron-withdrawing either mesomerically (R = CO, NO_2) or inductively (NR_2 or OR), the neutral species exists as **X** and not as the rival tautomer **Z**.[2] This generalization has been supported by crystal structures of cyanoguanidine, nitroguanidine, acylguanidines, and heterocyclic guanidines.[2,3a] Quantum-mechanical calculations on methyl- and ethylguanidines suggest small energy differences

SCHEME 1. Tautomerism of Guanidines



(1) (a) Katritzky, A. R.; Rogovoy, V. *Arkivoc* **2005**, (*iv*), 49. (b) Ekelund, S.; Nygren, P.; Larsson, R. *Biochem. Pharm.* **2001**, *61*, 1183.

(2) Bedford, G. R.; Taylor, P. J.; Webb, G. A. *Magn. Reson. Chem.* **1995**, *33*, 383.

(3) (a) Abou-Jneid, R.; Ghoulami, S.; Martin, M.; Dau, E. T. H.; Travert, N.; Al-Mourabit, A. *Org. Lett.* **2004**, *6*, 3933. (b) Norberg, J.; Foloppe, N.; Nilsson, L. *J. Chem. Theory Comput.* **2005**, *1*, 986.

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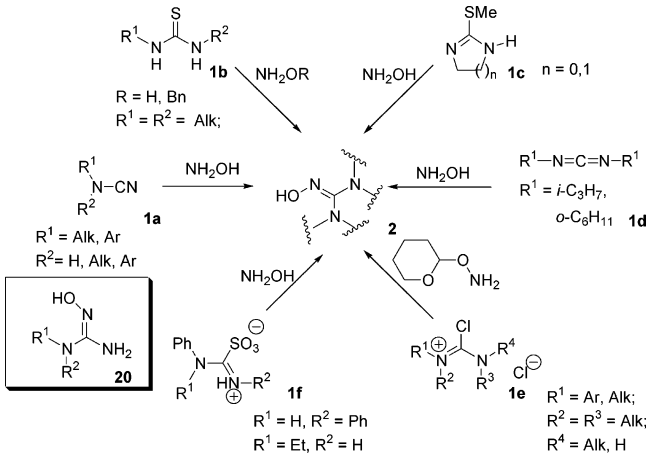
between **X** and **Z** when R is an alkyl group[3b] (see also the discussion of Scheme 4 below).

Syntheses of guanidines frequently utilizes thioureas, often with initial activation; however, in many cases the active intermediates are not described, characterized, isolated, or even defined.[1a] Isothioureas, particularly, *S*-methylisothioureas, are also well-developed guanylating agents due to their easy preparation and availability. Guanidines have also been successfully prepared from *N*-arylsulfonyl-*S*-methylisothioureas.[4a] Other guanylating reagents include carbodiimides,[4b] cyanoamides,[4c] pyrazole-1-carboximidamide,[4d,e] triflate guanidines,[4f] and benzotriazole and imidazole-containing reagents.[4g−j]

Recently, we reported a facile and efficient method for the preparation of *N*,*N*′,N″-trisubstituted guanidines by interaction of diverse amines with novel guanylating reagents (bis-benzotriazol-1-ylmethylene)amines and benzotriazole-1-carboxamidines.[4f] We have now expanded this methodology to include *N*-hydroxy- and *N*-aminoguanidines.

Functionalized guanidines[1a,5] are important structural elements in a variety of natural products[6a] and show interesting biological properties.[6b] In particular, *N*-hydroxyguanidines are electron-donor[6c] substrates for heme-containing enzymes such as nitric oxide synthases[7a,b] (NOS) and peroxidases.[8] Interest in *N*-hydroxyguanidines has grown since it was demonstrated that *N*-aryl-*N*′-hydroxyguanidines are reducing substrates for dopamine β-hydroxylase[9] and that *N*′-hydroxy-L-arginine (NOHA) is a key intermediate in the biosynthesis of nitric oxide (NO) from L-arginine.[10a−c] *N*-Hydroxyguanidines can act as antihypertensive agents[11] and scavengers of peroxynitrate (PN),[12] which is generated from the reaction of NO with superoxide anions; (PN) is generally considered to be more toxic than (NO) or superoxide.[13]

SCHEME 2. Literature Synthesis of *N*-Hydroxyguanidines 2



Aminoguanidines display both dopamine β-oxidase inhibition, and antihypertensive properties.[14a] Some substituted aminoguanidines inhibit nitric oxide synthase (NOS)[14b] and 2-ethylaminoguanidine displays high selectivity for iNOS compared with nNOS and eNOS isoform variations.[14b] Di- and trisubstituted aminoguanidines inhibit the formation of advanced nonenzymatic glycosylation of proteins[15a,b] and arylaminoguanidines are a novel class of 5-HT2aA receptor antagonists with enhanced activity.[16]

Common methods for the preparation of *N*-hydroxyguanidines **2** involve the reaction of electrophilic nitrogen rich species **1a**−**f** with hydroxylamine or its derivatives (Scheme 2). A popular approach to *N*-hydroxyguanidines **2** starts from primary amines through intermediate formation of the corresponding cyanamides **1a** (Scheme 2).[7a,11,17−19] However, only monosubstituted *N*-hydroxyguanidines of type **20** can be prepared by this method. Substituted thioureas **1b** react with hydroxylamine or *O*-benzylhydroxylamine in the presence of mercury(II) salts to form disubstituted *N*-hydroxyguanidines **2**.[20−22] Cyclic 1,3-ethylene- and 1,3-trimethylene-2-hydroxyguanidines **2** were synthesized by nucleophilic displacement of a thiomethyl group from **1c**.[23] Zinner et al.[24] reported the synthesis of tri- and tetrasubstituted **2** starting from the carbodiimides **1d**, but this

(4) (a) Kent, D. R.; Cody, W. L.; Doherty, A. M. *Tetrahedron Lett.* **1996**, *37*, 8711. (b) Molina, P.; Aller, E.; Lorenzo, A. *Synlett* **2003**, *5*, 714. (c) Reddy, N. L.; Fan, W.; Magar, S. S.; Perlman, M. E.; Yost, E.; Zhang, L.; Berlove, D.; Fischer, J. B.; Burke-Howie, K.; Wolcott, T.; Durant, G. J. *J. Med. Chem.* **1998**, *41*, 3298. (d) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497. (e) Zahariev, S.; Guarnaccia, C.; Lamba, D.; Cemažar, M.; Pongor, S. *Tetrahedron Lett.* **2004**, *45*, 9423. (f) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *363*, 3804. (g) Katritzky, A. R.; Khashab, N. M.; Bobrov, S. *Helv. Chim. Acta* **2005**, *88*, 1664. (h) Musiol, H. J.; Moroder, L. *Org. Lett.* **2001**, *3*, 3859. (i) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080. (j) Wu, Y. Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S. *J. Org. Chem.* **2002**, *67*, 7553.

(5) Wermann, K.; Walther, M.; Anders, E. *Arkivoc* **2002**, *5*, 24.

(6) (a) Byk, G.; Soto, J.; Mattler, C.; Frederic, M.; Scherman, D. *Biotechnol. Bioeng.* **1998**, *61*, 81. (b) Anselmi, C.; EtTorre, A.; Andreassi, M.; Centini, M.; Neri, P.; Stefano, A. D. *Biochem. Pharm.* **2002**, *63*, 437. (c) Southan, G. J.; Srinivasan, A. *Nitric Oxide* **1998**, *2*, 270.

(7) (a) Renodon-Corniere, A.; Dijols, S.; Perollier, C.; Lefevre-Groboillot, D.; Boucher, J.; Attias, A.; Sari, M.; Stuehr, D.; Mansuy, D. *J. Med. Chem.* **2002**, *45*, 944. (b) Jia, Q.; Cai, T.; Huang, M.; Li, H.; Xian, M.; Poulos, T. L.; Wang, P. G. *J. Med. Chem.* **2003**, *46*, 2271.

(8) Ricoux, R.; Boucher, J.; Mandon, D.; Frapart, Y. M.; Henry, Y.; Mansuy, D.; Mahy, J. *Eur. J. Biochem.* **2003**, *270*, 47.

(9) Slama, P.; Boucher, J.; Réglier, M. *Biochem. Biophys. Res. Commun.* **2004**, *316*, 1081.

(10) (a) Southan, G. J.; Srinivasan, A.; George, C.; Fales, H. M.; Keefer, L. K. *Chem. Commun.* **1998**, 1191. (b) Mansuy, D.; Boucher, J. *Free Radical Biol. Med.* **2004**, *37*, 1105. (c) Cho, J. Y.; Dutton, A.; Miller, T.; Houk, K. N.; Fukut, J. M. *Arch. Biochem. Biophys.* **2003**, *417*, 65.

(11) Bailey, D. M.; DeGrazia, C. G.; Lape, H. E.; Frering, R.; Fort, D.; Skulan, T. *J. Med. Chem.* **1973**, *16*, 151.

(12) Southan, G. J.; Salzman, A. L.; Szabo, C. *Free Radical Biol. Med.* **1998**, *25*, 914.

(13) Schubert, P.; Ogata, T.; Marchini, C.; Ferroni, S. *Mech. Aging Devel.* **2001**, *123*, 47.

(14) (a) Augstein, J.; Green, S. M.; Katritzky, A. R.; Monro, A. M. *J. Org. Chem.* **1964**, *29*, 5. (b) Wolff, D. J.; Gauld, D. S.; Neulander, M. J.; Southan, G. *J. Pharm. Exp. Therap.* **1997**, *283*, 265.

(15) (a) Cerami, A.; Wagle, D. R.; Ulrich, P. C. PCT Int. Appl. 96/40663, **1996**; *Chem. Abstr*. **1997**, *126*, 131465. (b) Ulrich, P.; Cerami, A. PCT Int. Appl. 92/19236, **1992**; *Chem. Abstr*. **1993**, *118*, 73676.

(16) Bryant, H. U.; Nelson, D. L.; Button, D.; Cole, H. W.; Baez, M. B.; Lucaites, L.; Wainscott, D. B.; Whitesitt, C.; Reel, J.; Simon, R.; Koppel, G. A. *Life Sci.* **1996**, *59*, 1259.

(17) Dijols, S.; Perollier, C.; Lefevre-Groboillot, D.; Pethe, S.; Attias, R.; Boucher, J.; Stuehr, D. J.; Mansuy, D. *J. Med. Chem.* **2001**, *44*, 3199.

(18) Xian, M.; Fujiwara, N.; Wen, Z.; Cai, T.; Kazuma, T.; Janczuk, A. J., Tang, X.; Telyatnikov, V. V.; Zhang, Y.; Chen, X.; Miyamoto, Y.; Taniguchi, N.; Wang, P. G. *Bioorg. Med. Chem.* **2002**, *10*, 3049.

(19) Cai, T.; Xian, M.; Wang, P. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1507.

(20) Li, H.; Shimizu, H.; Flinspach, M.; Jamal, J.; Yang, W.; Xian, M.; Cai, T.; Wen, E. Z.; Jia, Q.; Wang, P. G.; Poulos, T. L. *Biochemistry* **2002**, *41*, 13868.

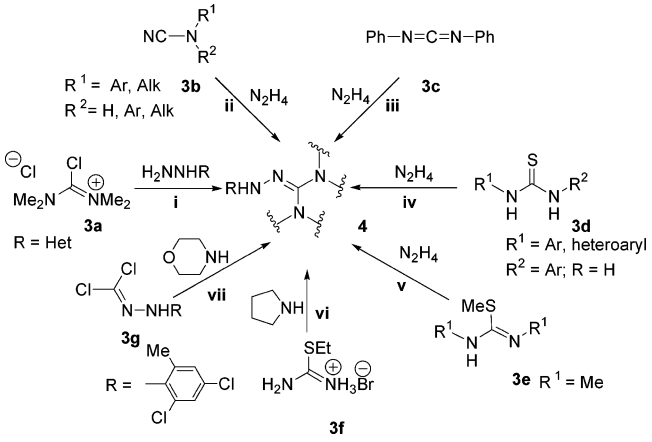
(21) Cherkofsky, S. C. US Patent 3867447, 1974; *Chem. Abstr*. **1974**, *81*, 37274.

(22) Moynihan, H. A.; Robera, S. M.; Weldon, H.; Allcock, G. H.; Anggard, E. E.; Warner, T. D. *J. Chem. Soc., Perkin Trans. 1* **1994**, *1*, 769.

(23) Belzecki, C.; Trojnar, J. *Tetrahedron Lett.* **1970**, *22*, 1879.

(24) Zinner, G.; Gross, H. *Chem. Ber.* **1972**, *105*, 1709.

SCHEME 3. Literature Syntheses of Substituted Aminoguanidines 4



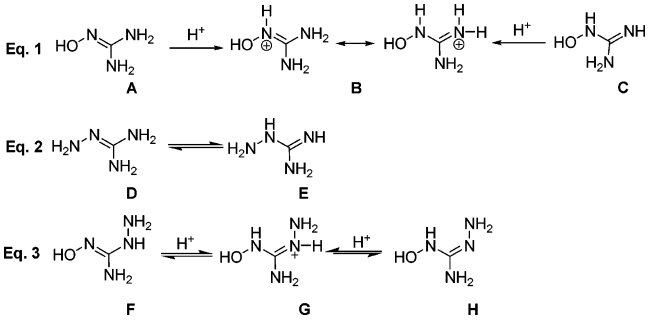
method suffers from long reaction times (3−5 days) and limited applicability. Acyclic trisubstituted and tetrasubstituted *N*-hydroxyguanidines have been prepared in moderate yields by use of chloroformamidinium chlorides **1e** generated from the corresponding ureas or thioureas.[25] A limited number of *N*-hydroxyguanidines **2** were synthesized by treatment of the corresponding aminoiminomethansulfonic acids **1f** with hydroxylamine hydrochloride and triethylamine.[26]

Syntheses of substituted aminoguanidines **4** include reactions of hydrazine or its derivatives with (i) Vilsmeier salt **3a**;[27] (ii) cyanamides **3b**;[28,29] (iii) diphenylcarbodiimide **3c**;[30] (iv) 1,3-disubstituted thioureas **3d** in the presence of PbO;[31,32] (v) 1,2,3-trimethylisothiourea **3e**[33] or *S*-alkyl thiourea salts.[34] The synthesis of substituted aminoguanidines **4** was also reported from *S*-ethylthiosemicarbazidium salt **3f**[3] or *N*-aminocarbonimidic dichloride **3g**[28,36] by the reaction with amines (routes vi and vii) (Scheme 3). All these methods were utilized for specific classes of aminoguanidines. But apparently, no method has been shown to be general for this class of compounds.

Tautomerism of hydroxyguanidines has recently been studied when these substrates are connected to nitrogen oxide synthase (NOS) in connection with the activity of each conformation.[37a−c] Most research groups prefer to depict *N*-hydroxyguanidines as structure **A** (eq 1, Scheme 4), but others use structure **C**; the common cation **B** is mesomeric.[37a] Spectral methods[37a] suggest that *N*-hydroxy-L-arginine exists in a tautomer of type **A** (eq 1, Scheme 4).

Aminoguanidines could exist in either structure **D** or **E** (eq 2, Scheme 4). *N*-Hydroxy-*N*-aminoguanidines which are 20−30 times more active than the hydroxyguanidines as inhibitors of ribonucleotide reductase from rat Novikoff tumors are little known.[38] ^{15}N NMR studies on *N*-hydroxy-*N*-aminoguanidines support expected structure for the conjugate acid of *N*-hydroxy-*N*-aminoguanidine **G** (eq 3, Scheme 4)[38] and that the deprotonated free base exists as structure **F** (eq 3, Scheme 4).[38]

SCHEME 4. Tautomerism of Hydroxyguanidines and Aminoguanidines



We now describe a general approach for the conversion of hydroxylamine or hydrazine derivatives into the corresponding *N*-hydroxy- or *N*-aminoguanidines utilizing benzotriazole containing reagents.

Results and Discussion

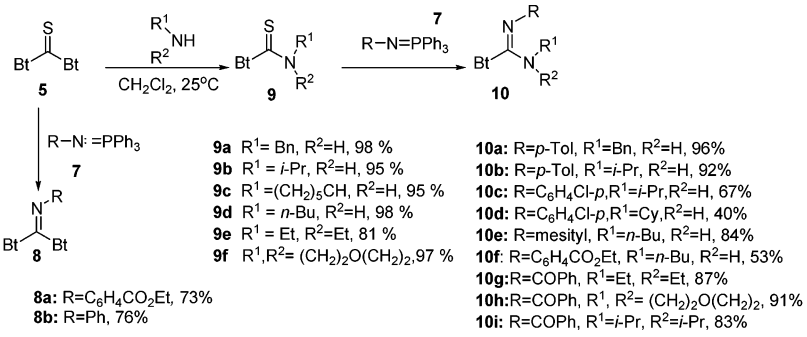
Recently, we have utilized bis-benzotriazol-1-ylmethanethione **5**[4f] and di(benzotriazol-1-yl)methanimine **6**[39] in the synthesis of substituted guanidines. Reaction of bis-benzotriazol-1-ylmethanethione **5** with triphenylphosphine ylides **7** gave symmetrical guanylation reagents **8** in 73−76% yields[4f] (Scheme 5). A simple one-step procedure for the preparation of **9** from bis-benzotriazol-1-ylmethanethione **5** in nearly quantitative yields has recently been developed in our group.[40] Refluxing **9** with triphenylphosphine ylides **7** afforded a new class of guanylation reagents **10** in 40−96% yields[4f] (Scheme 5).

We have also reported the synthesis of guanylating reagents **11a** and **11b**, which react with secondary amines in refluxing THF to give substituted guanidines **12** (Scheme 6).[39] In a continuation of this approach, we have now utilized reagents **6** and **8** in the synthesis of symmetrical dihydroxyguanidine **16** and diaminoguanidine **17**. Benzotriazole intermediates **10** and **11a**,**b** were used in the synthesis of mono-*N*-hydroxyguanidines **13a**−**j** and *N*-aminoguanidines **14a**−**h**.

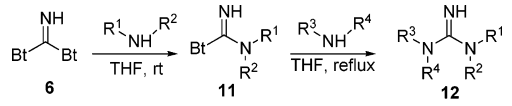
Preparation of Unsymmetrical *N*-Hydroxyguanidines 13a−**j.** *N*-Hydroxyguanidines **13a**−**j** were prepared in high yields by the reaction of **10a**,**b**,**d**,**e**,**g**,**h** and **11a**,**b** with hydroxylamine hydrochloride in refluxing toluene for 4−12 h in the presence of triethylamine (Scheme 7). The completion of the reaction was monitored by TLC. The white triethylamine hydrochloride salt was filtered from the reaction mixture. Concentration of the reaction mixture followed by a flash basic alumina column afforded **13a**−**j** in 22−87% yields (Scheme 7, Table 1). Ethyl acetate was used as an eluant to wash out the impurities followed by methanol to obtain the *N*-hydroxyguanidines as colorless oils. The highly basic nature of guanidines (pK_a = 12) causes

(25) Ziman, S. D. *J. Org. Chem.* **1976**, *41*, 3253.
(26) Miller, A. E.; Feeney, D. J.; Ma, Y.; Zarcone, L.; Aziz, M. A.; Magnuson, E. *Synth. Commun.* **1990**, *20*, 217.
(27) Guillot, N.; Viehe, H. G.; Tinant, B.; Declercq, J. P. *Tetrahedron* **1990**, *46*, 3897.
(28) Belzecki, C.; Hintze, B.; Kwiatkowska, K. *Bull. Acad. Pol. Sci.* **1970**, *18*, 375.
(29) Lieber, E.; Smith, G. B. L. *Chem. Rev.* **1938**, 213.
(30) Khorana, H. G. *Chem. Rev*. **1953**, *53*, 145.
(31) Kieslich, K. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 1058.
(32) Lakhan, R.; Sharma, B. P.; Shukla, B. N. *Farmaco* **2000**, *55*, 331.
(33) Henry, R. H.; Smith, G. B. L. *J. Am. Chem. Soc.* **1951**, *73*, 1858.
(34) Hunig, S.; Muller, F. *Liebigs Ann. Chem.* **1962**, *73*, 651.
(35) Lalezari, I.; Golgolab, H. *J. Heterocycl. Chem.* **1970**, *7*, 689.
(36) Moon, M. W. *J. Org. Chem.* **1972**, *37*, 2005.
(37) (a) Tierney, D. L.; Huang, H.; Martasek, P.; Masters, B. S. S.; Silverman, R. B.; Hoffman, B. M. *Biochem*istry **1999**, *38*, 3704. (b) Cho, K. B.; Gauld, J. W. *J. Phys. Chem. B* **2005**, *109*, 23706. (c) Cho, K. B.; Gauld, J. W. *J. Am. Chem. Soc*. **2004**, *126*, 10267.
(38) Tai, A. W.; Lien, E. J.; Moore, E. C.; Chung, Y.; Roberts, J. D. *J. Med. Chem*. **1983**, *26*, 1326.
(39) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080.
(40) Katritzky, A. R.; Ledoux, S.; Witek, R. M.; Nair, S. K. *J. Org. Chem.* **2004**, *69*, 2976.

SCHEME 5. Synthesis of Benzotriazole Intermediates 8 and 10



SCHEME 6. Synthesis of Benzotriazole Intermediates 11a,b and Substituted Guanidines 12



SCHEME 7. Preparation of Unsymmetrical *N*-Hydroxyguanidines 13a−j

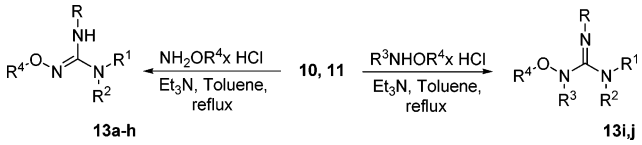


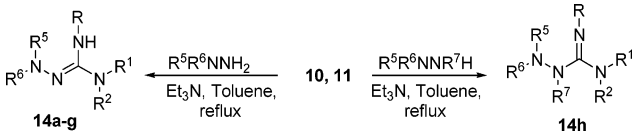
TABLE 1. Preparation of Unsymmetrical *N*-Hydroxyguanidines 13a−j

reactant	R	R1	R2	R3	R4	product	yield, %
10a	*p*-Tol	Bn	H	H	H	**13a**	80
10b	*p*-Tol	*i*-Pr	H	H	H	**13b**	72
10d	C_6H_4Cl-*p*	Cy	H	H	H	**13c**	56
10e	Mesityl	*n*-Bu	H	H	H	**13d**	87
10g	COPh	Et	Et	H	H	**13e**	71
10h	COPh	$(CH_2)_2O(CH_2)_2$		H	H	**13f**	74
10b	*p*-Tol	*i*-Pr	H	H	Bn	**13g**	41
11a	H	Bn	H	H	Me	**13h**	67
10a	*p*-Tol	Bn	H	Me	H	**13i**	53
11b	H	*n*-Bu	H	Me	Me	**13j**	22

difficulties in the isolation and characterization of these compounds. Structures **13a−j** were supported by elemental analysis, ^{1}H and ^{13}C NMR spectra. ^{1}H NMR spectra no longer showed distinctive signals in the range of 7.0−8.2 ppm corresponding to the benzotriazole group. The NH protons were difficult to detect in the spectra of **13c**,**e**,**f**,**h** mainly due their fast exchange rate between the three nitrogen atoms of guanidine. The dominant tautomeric structure from *N*-unsubstituted hydroxylamines has the double bond involving the hydroxylamine nitrogen (**13a−h**, Scheme 7). However, *N*-substituted hydroxylamines obviously form structures **13i**,**j** (Scheme 7).

Preparation of Unsymmetrical *N*-Aminoguanidines 14a−h. Reagents **10a−c**,**f**,**h** and **11b** were successfully employed in the synthesis of *N*-aminoguanidines **14a−h**. Refluxing corresponding **10** or **11** with 1.1 equiv of appropriate hydrazine in toluene for 3 h in the presence of 2 equiv of triethylamine afforded **14a−h** in yields of 30−91%, average 60% (Scheme 8, Table 2). The completion of the reaction was monitored by TLC. The benzotriazole generated as a side product was easily removed by flash chromatography on basic alumina with ethyl

SCHEME 8. Synthesis of *N*-Aminoguanidines 14a−h



acetate as an eluant. Products were isolated as oils using methanol as eluant. Novel **14a**,**b**,**d−h** were characterized by elemental analysis and ^{1}H and ^{13}C NMR spectra. Compound **14c** was not stable at room temperature and decomposed after 2 h. Similar to *N*-hydroxyguanidines, the NH protons were not visible in the ^{1}H spectra of **14a**,**d**,**e**,**h** probably because they are interchanging rapidly producing different tautomeric forms of **14**. The dominant tautomeric structure has the double bond involving the hydrazine nitrogen (R^7 = H) (**14a−g**, Scheme 8). However, if R^7 is different from H, then structure **14h** obviously forms (Scheme 8).

On the other hand, reacting **10i** with 2-hydrazinopyridine afforded a cyclic product **15** via a simple intramolecular condensation with the loss of one water molecule. Compound **15** was isolated as fluorescent white microcrystals in 93% yield (Scheme 9). A single example of a 1,3,5-substituted 1,2,4-triazole was reported in the literature.[41] Guanidynal hydroiodide was reacted with acetic acid and methyl iodide to give 3-methyl-5-amino-1,2,4-triazole in moderate yield.[41]

Preparation of Symmetrical Dihydroxyguanidine 16 and Diaminoguanidine 17. Syntheses of novel dihydroxyguanidine **16** and diaminoguanidine **17** were accomplished in high yields from the reaction of **6** and **8a** with 3 equiv of hydroxylamines hydrochloride or hydrazine derivatives in the presence of 3 equiv of triethylamine in refluxing toluene for 30−45 min (Scheme 10, Table 3). Reaction time for the preparation of *N*-hydroxy and *N*-aminoguanidines is significantly shorter than that for the preparation of guanidines due to enhancement of nucleophilicity by the α effect.[42]

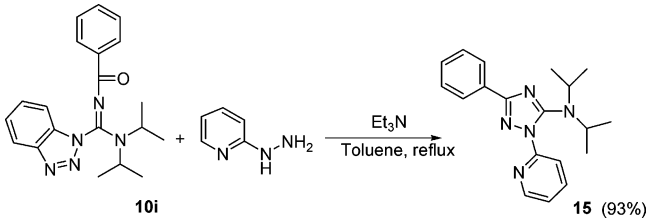
A novel guanylating reagent **18** was prepared from the reaction of 1 equiv di(benzotriazol-1-yl)methanimine **6** with 1.2 equiv of hydroxylamine in THF. The mixture was refluxed for 1 h and then washed with 10% sodium carbonate. Extracting the organic layer afforded **18** in 89% yield. Microwave reaction of **18** with a hydrazine derivative afforded compound *N*-hydroxy-*N*′-aminoguanidine **19** in 61% yield (Scheme 11). The structure of novel **19** was verified by ^{1}H and ^{13}C NMR spectra and high-resolution mass spectroscopy. Schiff bases of *N*-hydroxy-*N*′-aminoguanidines are often used as anticancer,

(41) Barascut, J. L.; Viallefont, P.; Daunis, J. *Bull. Soc. Chim. Fr.* **1975**, *7−8*, 1649.
(42) Grekov, V. *Russ. Chem. Rev.* **1978**, *47*, 631.

TABLE 2. Synthesis of *N*-Aminoguanidines 14a−h

reactant	R	R^1	R^2	R^5	R^6	R^7	product	yield, %
10b	*p*-Tol	*i*-Pr	H	H	H	H	**14a**	84
11b	H	*n*-Bu	H	C_6H_4OMe-*p*	H	H	**14b**	91
10c	C_6H_4Cl-*p*	*i*-Pr	H	SO_2Ph	H	H	**14c**	76
10a	*p*-Tol	Bn	H	Me	Me	H	**14d**	82
10f	$C_6H_4CO_2Et$	*n*-Bu	H	Me	Me	H	**14e**	84
10h	COPh	$(CH_2)_2O(CH_2)_2$		Me	Me	H	**14f**	71
11b	H	*n*-Bu	H	Me	Ph	H	**14g**	85
10c	C_6H_4Cl-*p*	*i*-Pr	H	Me	H	Me	**14h**	30

SCHEME 9. Synthesis of Substituted 1,2,4-Triazole 15

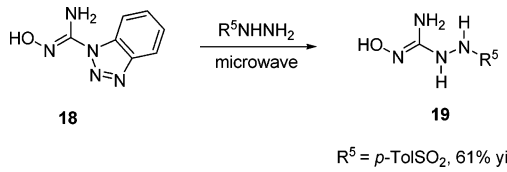


SCHEME 10. Syntheses of Dihydroxyguanidine 16 and Diaminoguanidine 17

TABLE 3. Syntheses of Dihydroxyguanidine 16 and Diaminoguanidine 17

reactant	R	R^4	R^5	product	yield, %
8a	$C_6H_4CO_2Et$	H		**16**	91
6	H		C_6H_4OMe-*p*	**17**	61

SCHEME 11. Synthesis of *N*-Hydroxy-*N*′-aminoguanidine 19



antibacterial, and antiviral agents[43a,b] and recently as electron acceptors for xanthine oxidase.[44]

Conclusion

An efficient and simple route to mono- and symmetrical di-*N*-hydroxy- and *N*-aminoguanidines has been developed using benzotriazole guanylating reagents. The procedure uses no aggressive reagents, occurs under mild reaction conditions, and allows ease of isolation of the products.

Experimental Section

General Procedure for the Preparation of Compounds 13a−j. To a solution of **10a**,**b**,**d**,**e**,**g**,**h** or **11a**,**b** (see Schemes 3 and 4) (1.70 mmol) in toluene (13 mL), was added 2.55 mmol of the hydroxylamine of choice followed by 2.55 mmol (0.4 mL) of triethylamine. The reaction mixture was heated under reflux until full conversion of starting materials (4−12 h). Upon completion, the solvent was evaporated under reduced pressure. The crude product was dissolved in dichloromethane, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The desired *N*-hydroxyguanidines were isolated by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **13a−j.**

***N*-Benzyl-*N*-hydroxy-*N*″-(4-methylphenyl)guanidine (13a):** oil (80%); ^{1}H NMR δ 7.31−7.21 (m, 5H), 7.13 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.68 (br s, 1H), 5.35 (br s, 1H), 4.37 (d, J = 5.8 Hz, 2H), 2.28 (s, 3H), 1.67 (br s, 1H); ^{13}C NMR δ 156.2, 155.6, 139.0, 135.6, 129.8, 128.6, 127.4, 127.3, 122.0, 44.2, 20.8. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.18; H, 6.46; N, 16.84.

General Procedure for the Preparation of Compounds 14a−h. To a solution of **10a−c**,**f**,**h** or **11b** (see Schemes 3 and 4) (0.68 mmol) in toluene (10 mL) was added 0.75 mmol of the hydrazine of choice followed by 1.36 mmol (0.25 mL) of triethylamine. The reaction mixture was heated under reflux until full conversion of starting materials (3 h). Upon completion, the solvent was evaporated under reduced pressure. The crude product was dissolved in dichloromethane, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The desired *N*-aminoguanidines were isolated by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **14a−h**.

***N*-Isopropyl-N′-(4-methylphenyl)-1-hydrazinecarboximidamide (14a):** oil (84%); ^{1}H NMR δ 7.78 (s, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 4.02−3.91 (m, 1H), 2.37 (s, 3H), 2.10 (s, 2H), 1.17 (d, J = 6.3 Hz, 6H); ^{13}C NMR δ 153.4, 139.7, 139.5, 130.9, 125.0, 45.6, 29.7, 23.1. Anal. Calcd for $C_{11}H_{18}N_4$: C, 64.05; H, 8.79; N, 27.16. Found: C, 63.98; H, 8.42; N, 27.01.

Preparation of *N*,*N*-Diisopropyl-5-phenyl-1-(2-pyridinyl)-1*H*-1,2,4-triazol-3-amine (15). To a solution of 0.15 g (0.43 mmol) of *N*-[1*H*-1,2,3-benzotriazol-1-yl(diisopropylamino)methylidene]-benzamide in 15 mL of toluene was added 0.14 g (1.3 mmol) of 2-hydrazinopyridine. The mixture was stirred for 5 min and then brought to reflux. After 2 h, the reaction was stopped and the solvent evaporated under vacuum. The crude product was washed with 10% Na_2CO_3 and then extracted with dichloromethane (3 × 20 mL). Evaporating the organic fraction followed by flash column chromatography on basic alumina afforded **15** (0.13 g, 93%).

***N*,*N*-Diisopropyl-5-phenyl-1-(2-pyridinyl)-1*H*-1,2,4-triazol-3-amine (15).** Recrystallized from EtOAc−hexanes to give white crystals (93%): mp 104−105 °C; ^{1}H NMR δ 8.30 (br d, J = 4.8 Hz, 1H), 7.72 (t d, J = 8.1 Hz, 2.0 Hz, 1H), 7.55−7.50 (m, 3H), 7.36−7.29 (m, 3H), 7.15 (dd, J = 7.5, 4.8 Hz, 1H), 4.17 (septet, J = 6.7 Hz, 2H), 1.37 (d, J = 6.9 Hz, 12H); ^{13}C NMR δ 163.1, 152.7, 151.3, 148.1, 138.2, 129.7, 129.2, 129.1, 127.9, 122.1, 118.2, 46.4, 20.7. Anal. Calcd for $C_{19}H_{23}N_5$: C, 71.00; H, 7.21; N, 21.79. Found: C, 71.32; H, 7.56; N, 21.98.

(43) (a) Tang, A.; Kien, E. J.; Lai, M. M. C. *J. Med. Chem.* **1985**, *28*, 1103. (b) Pignatello, R.; Panico, A.; Mazzone, P.; Pinizzotto, M. R.; Garozzo, A.; Fumeri, P. M. *Eur. J. Med. Chem.* **1994**, *29*, 781.

(44) Prusis, P.; Dambrova, M.; Andrianov, V.; Rozhkov, E.; Semenikhina, V.; Piskunova, I.; Ongwae, E.; Lundstedt, T.; Kalvinsh, I.; Wikberg, E. S. *J. Med. Chem.* **2004**, *47*, 3105.

General Procedure for the Preparation of Compounds 16 and 17. To a solution of **8a** or **6** (see Schemes 3 and 4) (0.6 mmol) in toluene (10 mL) was added 1.8 mmol of the hydroxylamine or hydrazine of choice followed by 1.8 mmol (0.3 mL) of triethylamine. The reaction mixture was heated under reflux until full conversion of starting materials (30−45 min). Upon completion, the solvent was evaporated under reduced pressure. The crude product was dissolved in dichloromethane, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The desired products were isolated by flash column chromatography on basic alumina (first ethyl acetate to remove impurities and methanol to elute guanidine) to give **16** and **17**.

Ethyl 4-{[(hydroxyamino)(hydroxyimino)methyl]amino}-benzoate (16): oil (90%); ^{1}H NMR δ 7.79 (d, J = 8.5 Hz, 2H), 6.57 (d, J = 8.5 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.99 (br s, 2H), 1.59 (br s, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 166.7, 150.7, 131.5, 123.0, 120.0, 113.7, 60.3, 14.4; HRMS calcd for $C_{10}H_{13}N_3O_4$ (M + 1) 240.2275, found 240.2280.

***N*-2-Bis(4-methoxyphenyl)-1-hydrazinecarboximidohydrazide (17):** oil (61%); ^{1}H NMR δ 7.66 (d, J = 8.9 Hz, 4H), 6.90 (d, J = 8.9 Hz, 4H), 3.81 (s, 4H), 1.50 (s, 6H); ^{13}C NMR δ 140.0, 130.6, 129.3, 128.2, 113.8, 29.7. Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 13.24. Found: C, 59.80; H, 6.46; N, 12.65.

Preparation of *N*′-Hydroxy-1*H*-1,2,3-benzotriazole-1-carboximidamide 18. To a solution of 2.0 g (7.6 mmol) of di(1*H*-1,2,3-benzotriazol-1-yl)methanamine in THF (30 mL) was added 0.43 g (9.12 mmol) of hydroxylamine hydrochloride followed by triethylamine (2.0 mL). The mixture was refluxed for 1 h and then left to cool at room temperature. The reaction mixture was washed with 10% Na_2CO_3, and extracted with dichloromethane (3 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate. Evaporating the solvent under reduced pressure afforded pure **18** (1.2 g, 89%).

General Procedure for the Preparation of Compound 19. To 0.56 mmol of *N*′-hydroxy-1*H*-1,2,3-benzotriazole-1-carboximidamide **18** was added 0.56 mmol of the hydrazine of choice. The mixture was microwaved neat for 5 min (*T*: 115 °C, power: 120 W). The reaction was then stopped, and the mixture washed with 10% Na_2CO_3 and extracted with dichloromethane (3 × 20 mL). Evaporating the organic fraction followed by flash column chromatography on basic alumina afforded **19**.

***N*′-Hydroxy-2-[(4-methylphenyl)sulfonyl]-1-hydrazinecarboximidamide (19):** oil (61%); ^{1}H NMR δ 7.38 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 2.32 (s, 3H), 1.55 (s, 1H); ^{13}C NMR δ 137.4, 133.9, 129.8, 129.7, 128.5, 21.0; HRMS (EI) calcd for $C_8H_{12}N_4O_3S$ (M + Na) 267.2598, found 267.2593.

Supporting Information Available: Characterization data for compounds **13b−j** and **14b,d−h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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