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Direct Synthesis of Guanidines Using Di(imidazole-1-yl)methanimine

Yong-Qian Wu,* Sean K. Hamilton, Douglas E. Wilkinson, and Gregory S. Hamilton

Department of Research, Guilford Pharmaceuticals, Inc., Baltimore, Maryland 21224

wuy@guilfordpharm.com

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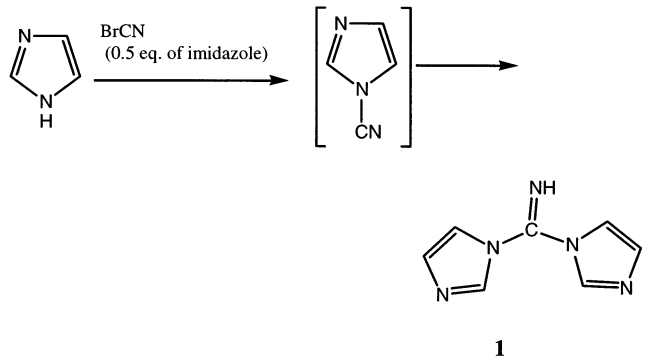
Abstract: A direct synthetic approach to guanidine compounds is reported here using di(imidazole-1-yl)methanimine and di(imidazole-1-yl)cyanomethanimine as guanylating reagents.

Many natural products and synthetic pharmaceuticals contain guanidine functional groups, which often play an essential role in their biological activity.[1] Consequently, there are a number of guanylating reagents in the literature and/or available from commercial sources such as 1,3-bis(*tert*-butoxycarbonyl)guanidine,[2] *N*,*N*′-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine,[3] and most recently di(benzotriazol-1-yl)methanimine.[4] A direct synthetic approach would have the advantage of quickly assembling the guanidine moiety from a diverse set of amines without manipulating protecting groups. Di(imidazole-1-yl)methanimine has been previously reported as a coupling reagent for the formation of phosphodiester bonds.[5] To this end, we report its new usage as a direct guanylating reagent, as well as its analogue, di(imidazole-1-yl)cyanomethanimine, for the synthesis of guanidines.

Di(imidazole-1-yl)methanimine **1** was synthesized readily by treating cyanogen bromide with imidazole on the basis of a modified literature procedure[5] (Scheme 1) in good yield (81%). Since **1** is a solid, it is of easy handling in the experiments.

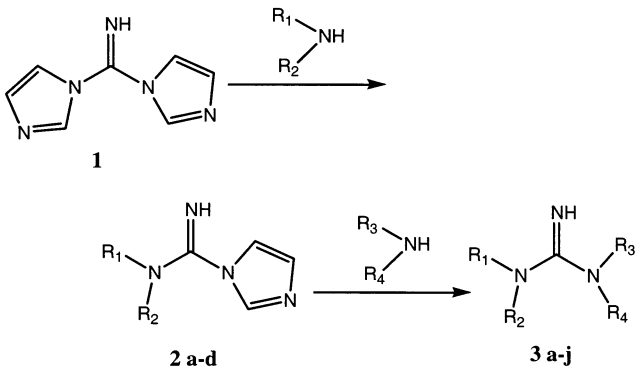
According to Scheme 2, the sequential condensation of **1** with two amines leads to the substituted guanidines directly. We have found that both primary and secondary aryl and alkylamines were effective for the first displacement of imidazole, affording compounds **2a**−**d** in the range of 66−82% yield (Table 1). The reactions were accomplished at room temperature within several hours, except secondary arylamine (**2b**), which needed to be heated to slightly above 40 °C. The side product generated was the water-soluble imidazole, which could be removed by successive washing with water and saturated NH_4Cl. The crude products were usually sufficiently pure to carry on to the next step. It is worth noting that compounds **2a**−**d** were obtained free from symmetrical guanidines, which could potentially result from further condensation of **2a**−**d**, even when excess amines were used. Apparently, the electrophilicity of the methanimine carbon in compounds **2a**−**d** is significantly decreased after the displacement of the first imidazole moiety. Consequently, the second imidazole displacement by amines for the formation of guandines **3a**−**j** could only take place at reaction temperatures above 60 °C in THF. A wide range of primary and secondary aryl and alkylamines were reacted with compounds **2a**−**d** and found to successfully displace the second imidazole group. The aqueous workup followed by silica gel purification (0−10% ethanol in ethyl acetate) afforded the pure guanidines in moderate to good yields (Table 1). Less nucleophilic amines such as aniline failed to react at refluxing THF as in the case of **3i**. At higher temperatures such as 90 °C in DMF, the imidazole group was eliminated to form phenylcyanamide, which trimerized readily[6] to give **4** as the major product with **3i** present as a minor product (Scheme 3). Interestingly, compound **3k** was readily obtained in good yield when 1,2-phenyldiamine was reacted with **1**. No cyanamide was observed in this case, and apparently the strong tendency toward cyclization

SCHEME 1



1

SCHEME 2



1 **2 a-d** **3 a-j**

$R_{1\text{-}4}$ = H, alkyl, and aryl

* Corresponding author. Phone: + 1-410-631-6823. Fax: + 1-410-631-6848.

(1) (a) *The Pharmacological Basis of Therapeutics*, 7th ed.; Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F., Eds.; Pergamon Press: New York, 1990; p 899. (b) Hu, L. Y.; Guo, J.; Magar, S. S.; Fischer, J. B.; Burke-Howie, K. J.; Durant, G. J. *J. Med. Chem.* **1997**, *40* (26), 4281−9.

(2) Koert, U. et al. *Tetrahedron* **1999**, *55* (10), 713.

(3) Lipton, M. *Tetrahedron Lett.* **1999**, *40*, 53.

(4) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V. *J. Org. Chem.* **2000**, *65*, 8080−8082.

(5) Ferris, J. P.; Huang, C. H.; Hagan, W. J. *Nucleosides Nucleotides* **1989**, *8* (3), 407−414.

(6) Arndt, F. *Ann. Chem.* **1911**, *384*, 322.

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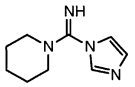
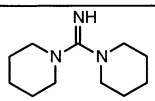
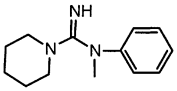
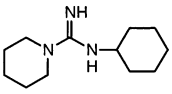
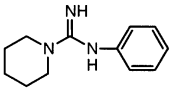
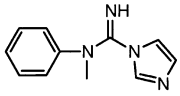
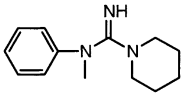
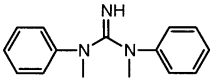
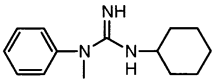
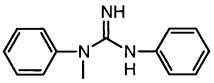
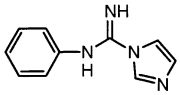
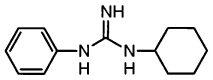
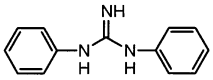
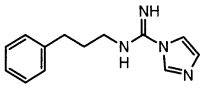
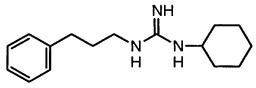
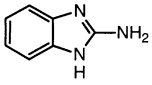
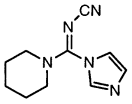
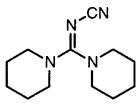
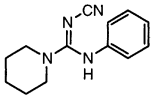
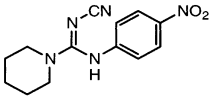
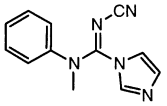
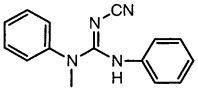
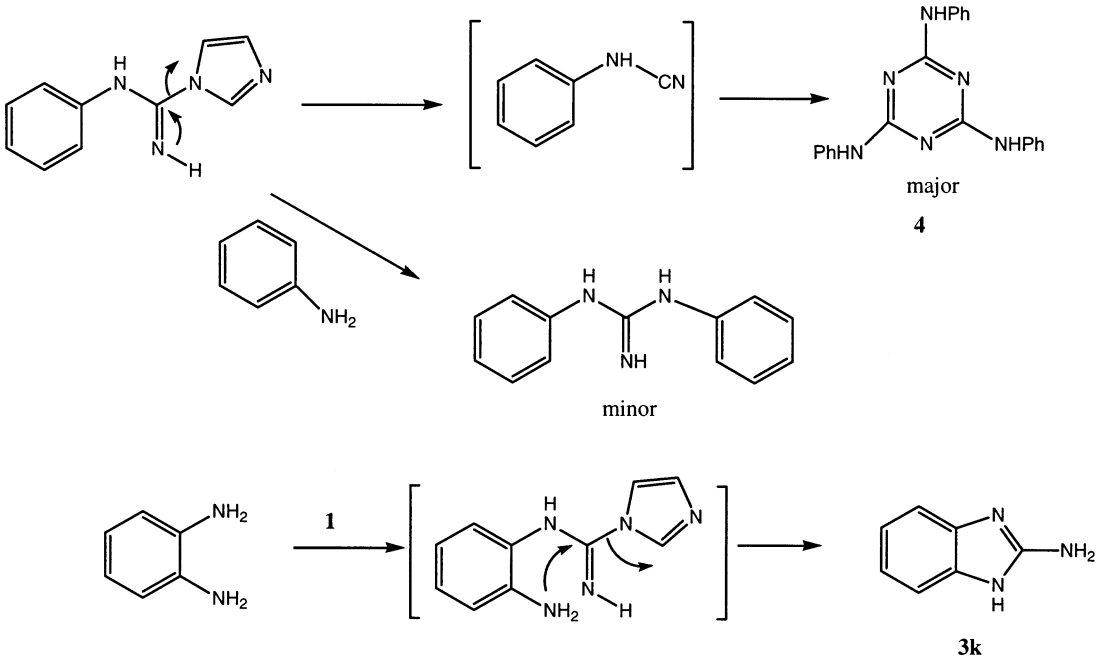
TABLE 1

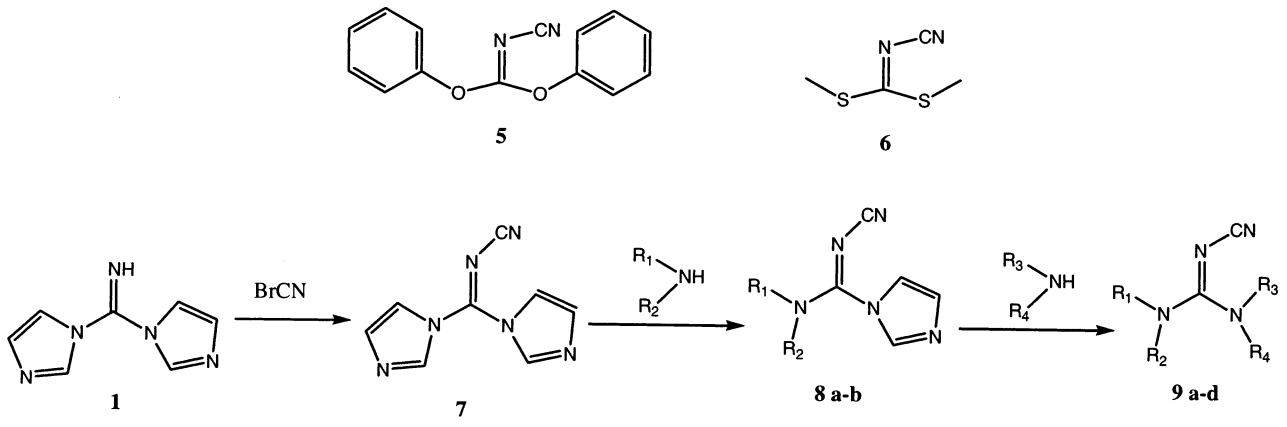
No	Products	Conditions Yield [a, b]	No	Products	Conditions Yield [a, b]
2a		THF, 6h, r.t., 69%	3a		THF, 12h, reflux, 53%
			3b		DMF, 12h 90°C, 76%
			3c		THF, 12h reflux, 81%
			3d		THF, 18h reflux, 51%
2b		THF, 6h, 40°C 82%	3b		THF, 12h reflux, 64%
			3e		DMF, 18h 90°C, 70%
			3f		THF, 12h reflux, 61%
			3g		DMF, 18h 90°C, 40%
2c		THF, 6h, r.t. 66%	3h		THF, 12h reflux, 74%
			3i		DMF, 12h 90°C, 15%
2d		THF, 6h, r.t. 73%	3j		THF, 12h reflux, 85%
			3k		THF, 12h reflux, 59%
8a		THF, 6h, r.t. 66%	9a		THF, 12h reflux, 82%
			9b		THF, 12h reflux, 70%
			9c		DMF, 10h 90°C, 0%
8b		THF, 6h, r.t. 64%	9d		DMF, 10h 90°C, 42%

[a] Isolated yield [b] Reaction conditions not optimized.

SCHEME 3



SCHEME 4



8a $R_1R_2 = (CH_2)_4$
8b $R_1 = CH_3$, $R_2 = Ph$

was the driving force for the second displacement of imidazole by an otherwise unreactive amine (Scheme 3). Overall, the guanidines synthesized were extremely diverse with every possible combination of aryl and alkyl substitutions, and more importantly, highly substituted guanidines (tri/tetra) could be obtained readily in a mild and efficient manner.

Next, we extended the same protocol to the preparation of cyanoguanidines. Cyanoguanidines are considered as bioisosteres of urea and thiourea functionalitites and often provide unique biological activities.[7] Therefore, they are as highly desired as guanidines in medicinal chemistry. Two cyanoguanalyting reagents are available commercially, namely, diphenyl cyanocarbonimidate **5** and dimethyl cyanodithioiminocarbonate **6** (Scheme 4). However, after the introduction of the first amines to these reagents, the conversion of isoureas or isothioureas to cyanoguanidines by aminolysis requires strenuous conditions, e.g., heating the reaction mixture in 2-propanol at 120 °C in a sealed bottle. In addition, less nucleophilic aromatic amines were extremely sluggish and pretreatment with trimethylaluminum was necessary.[8] Handling trimethylaluminum requires extreme cautions due to its flammable nature, and therefore the procedure may not be suitable for large-scale or process chemistry. We envisioned that di(imidazole-1-yl)cyanomethanimine might possess better reactivity than **5** and **6** because it contains a better leaving imidazole group. Furthermore, imidazole as a side product is environmentally safe and can be recyclable to the synthesis of **1**. Thus, di(imidazole-1-yl)-cyanomethanimine **7** was synthesized smoothly by cya-

(7) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem.* **1977**, *20* (7), 901−906.

(8) Atwal, K. S.; Ferrara, F. N.; Ahmed, S. Z. *Tetrahedron Lett.* **1994**, *35*, 8085−8088.

nation of **1** with BrCN (Scheme 4). Indeed, like **1**, **7** reacted readily with piperidine (an alkylamine) and *N*-methylaniline (an arylamine), to yield **8a** and **8b**, respectively. In turn, **8a** was converted to **9a**,**b** smoothly upon treatment with piperidine (an alkylamine) and aniline (an arylamine), respectively, in refluxing THF. Not surprisingly, no product was observed from the reaction of **8a** with *p*-nitroaniline, presumably due to the extremely poor nucleophilicity of the amine. In the case of **9d**, the reaction proceeded at elevated temperatures with moderate yield (Table 1).

In summary, we have found and successfully demonstrated the versatility of di(imidazole-1-yl)methanimine and its derivative di(imidazole-1-yl)cyanomethanimine as useful reagents for the synthesis of a wide variety of guanidines and cyanoguanidines, respectively. Their additional applications in the solid-phase synthesis, as well as in the formation of heterocyclic compounds,[9] are underway in this laboratory.

Experimental Section

General Methods. All commercially available starting materials and solvents were reagent grade. Anhydrous tetrahydrofuran (THF) and dimethylformamide (DMF) were used. Analytical thin-layer chromatography was carried out using precoated silica gel plates. Flash chromatography was performed using kieselgel 60 (230−400 mesh) silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz instrument. Chemical shifts are reported in parts per million (ppm). Mass spectral analyses were performed. Elemental analyses were determined and are within ±0.4% of the calculated values unless otherwise noted.

Di(imidazole-1-yl)methanimine (1). To a solution of imidazole (6.8 g, 100 mmol) in 500 mL of dichloromethane was added cyanogen bromide (3.7 g, 33 mmol) and the mixture heated at reflux temperature for 30 min. The mixture was cooled to rt, the white precipitate removed by filtration, and the filtrate concentrated to 50 mL and cooled to 0 °C for 2 days. The crystallized solid was filtered and washed with cold dichloromethane and dried to give 4.4 g (81%) of **1** as a white solid. ^{1}H NMR (DMSO-d_6): δ 7.13 (s, 1H); 7.58 (s, 1H); 8.10 (s, 1H); 10.24 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 119.3; 130.1; 137.8; 141.3.

Typical Procedure for the Preparation of Imidazole-1-carboximidamides 2 (2a as an Example). To a solution of **1** (322 mg, 2 mmol) in 5 mL of THF was added piperidine (204 mg, 2.4 mmol). After the mixture was allowed to stir at room temperature for several hours, TLC indicated that the reaction was completed. Then, 10 mL of water was added to the mixture, followed by extraction with CH_2Cl_2. The organic layer was washed successively with saturated NH_4Cl, water, and brine. After drying over $MgSO_4$, the organic solvent was removed to afford a crude product. Further purification by silica gel chromatography yielded the pure **2a** as a white solid (247 mg, 69%). ^{1}H NMR ($CDCl_3$): δ 8.22 (br, 1H); 8.10 (s, 1H); 7.49(s, 1H); 6.87 (s, 1H); 3.54 (m, 4H); 1.55 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 24.3; 26.5; 45.6; 117.2; 128.7; 136.5; 160.3. Anal. Calcd for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.43. Found: C, 60.52; H, 7.96; N, 31.58.

Typical Procedure for the Preparation of Guanidines 3 (3b as an Example). To a solution of **2a** (89 mg, 0.5 mmol) in 1.0 mL of DMF was added *N*-methylaniline (80 mg, 0.75 mmol). After the mixture was allowed to stir at 90 °C overnight, 5 mL of water was added, followed by extraction with CH_2Cl_2. The organic layer was washed successively with saturated NH_4Cl, water, and brine. After drying over $MgSO_4$, the organic solvent was removed to afford a crude product. Further purification by silica gel chromatography yielded the pure **3b** as a white solid (83 mg, 76%). ^{1}H NMR ($CDCl_3$): δ 7.23 (m, 4H); 7.06 (br, 1H); 7.02 (m, 1H); 3.33 (s, 3H); 3.26 (m, 4H); 1.53 (m, 2H); 1.44-(m, 4H). ^{13}C NMR ($CDCl_3$): δ 24.8; 25.8; 37.8; 45.3; 125.1; 126.8; 128.6; 146.2; 159.1. MS (*m*/*e*): 217 (M+). Anal. Calcd for $C_{13}H_{19}N_3$: C, 71.85; H, 8.81; N, 19.34. Found: C, 71.36; H, 8.86; N, 19.26.

Di(imidazole-1-yl)cyanomethanimine (7). To a mixture of **1** (0.3 g, 1.86 mmol) in THF (5 mL) was added CNBr (0.23 g, 2.23 mmol) followed by triethylamine (0.30 mL, 2.23 mmol). After the mixture was stirred at room temperature overnight, the solvent was evaporated and the yellow residue chromatographed using 2:1 hexanes−ethyl acetate to provide (0.22 g, 63%) **7** as a pale yellow solid. ^{1}H NMR (DMSO-d_6): δ 7.21(s, 1H); 7.61-(s, 1H); 8.09 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 118.3, 130.1, 137.6, 138.2, 144.2. Anal. Calcd for $C_8H_6N_6$: C, 51.61; H, 3.25; N, 45.14. Found: C, 51.43; H, 3.21; N, 45.24.

Typical Procedure for the Preparation of Imidazole-1-cyanocarboximidamides (8a as an Example). A solution of **7** (205 mg, 1.1 mmol) and piperidine (187 mg, 2.2 mmol) in THF was stirred at room temperature. After the reaction was complete as indicated by TLC, the solvent was evaporated and the residue subjected to column chromatography to afford **8a** as a solid (148 mg, 66% yield). ^{1}H NMR ($CDCl_3$): δ 1.57 (m, 6H); 3.57 (m, 4H); 6.87 (s, 1H); 7.49(s, 1H); 8.10 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 25.1; 26.2; 45.2; 117.7; 119.2; 128.3; 136.1; 161.2. Anal. Calcd for $C_{10}H_{13}N_5$: C, 59.10; H, 6.45; N, 34.46. Found: C, 58.92; H, 6.43; N 34.5.

Typical Procedure for the Preparation of Cyanoguanidines 9 (9b as an Example). A solution of **8a** (224 mg, 1.1 mmol) and aniline (205 mg, 2.2 mmol) in THF was refluxed for 12 h. After the reaction was completed as indicated by TLC, the solvent was evaporated and the residue subjected to column chromatography to afford **9b** as a solid (175 mg, 70% yield). ^{1}H NMR ($CDCl_3$): δ 1.42 (m, 4H); 1.55 (m, 2H); 3.54 (m, 4H); 6.99 (m, 2H); 7.32(m, 3H). ^{13}C NMR ($CDCl_3$): δ 25.1; 26.2; 44.2; 118.3, 119.2; 129.1; 129.4, 136.1; 162.3. Anal. Calcd for $C_{13}H_{16}N_4$: C, 68.39; H, 7.06; N 24.54. Found: C, 68.30; H, 6.99; N, 24.21.

JO0202381

(9) Wu, Y. Q.; Limburg, D.; Wilkinson, D. E.; Hamilton, G. S. *J. Heterocycl. Chem.*, submitted.