Di(benzotriazol-1-yl)methanimine: A New Reagent for the Synthesis of Tri- and Tetrasubstituted Guanidines

Alan R. Katritzky,* Boris V. Rogovoy, Christophe Chassaing,‡ and Vladimir Vvedensky

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

katritzky@chem.ufl.edu

Received April 27, 2000

Introduction

Polysubstituted guanidine functionality occurs as the key component for the expression of the biological activity in numerous natural compounds. The wide range of biological activities found for guanidines has motivated the development of many reagents for their preparation. One class of reagents achieves guanylation by the addition of a nucleophilic amine onto a cyanamide,[1] or a carbodiimide.[2−6a] The carbodiimide is often prepared in situ from precursors such as oxidized or heavy metal-coordinated *N*,*N*′-dialkylthioureas,[2,3] *N*,*N*′-diprotected thioureas,[4] *N*-protected-*S*-alkyl isothioureas,[5] or aminoiminosulfonic acid.[6b,c] A second group of methods is based on the displacement of a leaving group X from a reagent of type $R_2NC(:NR)X$, where X can be the benzotriazole group of benzotriazole-1-carboxamidinium tosylate,[7] the pyrazole moiety of 1*H*-pyrazole-1-carboxamidine,[8] or of its *N*,*N*′-diprotected derivatives[9] or *N*-triflylamine from *N*,*N*′-diprotected triflylguanidines.[10] Additionally, triurethane-protected guanidines were used for a Mitsunobu conversion of alcohols into substituted guanidines.[11] These procedures have allowed the synthesis of numerous *N*-alkyl- and *N*-aryl-substituted guanidines. However, the potential diversity of the final products is limited by the two component nature of the condensations, along with the frequent need to use protecting groups. For this reason, we have developed a new guanylating reagent, which allows access to polysubstituted guanidines bearing up to four different groups. We now describe the use of di(benzotriazol-1-yl)methanimine **1** for the synthesis of tri- and tetrasubstituted guanidines.

Results and Discussion

Starting material **1** was obtained from the reaction of benzotriazole with cyanogen bromide according to an already described procedure[12] as a mixture of di(1*H*-benzotriazol-1-yl)methanimine **1** and 1*H*-benzotriazol-1-yl(2*H*-benzotriazol-2-yl)methanimine **1′** in overall 60−65% yield. The displacement of the first benzotriazole moiety was effected by the addition of an amine of choice to a solution of the mixture of isomers **1**+**1′** in THF. Compounds **2a**−**f** were each obtained as pure Bt[1] isomers, probably as a consequence of the preferential displacement of the Bt[2] group in the **1′** isomer. Theoretically, *N*-monosubstituted carboximidamides can exist in two tautomeric forms **2a**−**c** and **2′a**−**c**. In $CDCl_3$ solution we found that the *N*-phenyl derivative exists solely as the **2′a** tautomer, the *N*-amyl derivative as the pure **2b** tautomer, and the *N*-benzyl derivative as a mixture of **2c** and **2′c** tautomers in approximately equal concentrations, results which conform with those reported previously.[13,14]

The synthesis of compounds **2a**−**f** succeeded at room temperature even for hindered diisopropylamine (compound **2f**). The benzotriazole generated as a side product was easily removed by concentration of the mixture, dilution with CH_2Cl_2, and washing with 10% aqueous Na_2CO_3. The purification protocol is significantly simpler than those of the previous methods, which involve the use of a heavy metal;[2,3] furthermore, tedious filtrations and washing procedures are avoided and the environmentally safe side product benzotriazole can be recycled into compound **1**. This procedure provides 1*H*-benzotriazole-1-carboximidamides **2a**−**f** as pure products without the need of further purification (Scheme 1). Six diverse amines gave yields in the range of 68−80% (Table 1).

The fact that compounds **2a**−**f** could be obtained without contamination by side products resulting from self-condensation or condensation of a second equivalent of amine underlines the chemospecificity of the reaction. Introduction of the first amine into compound **1** evidently lowers the electrophilicity of the methanimine carbon sufficiently to prevent further condensation; indeed attempted condensation of **2a**−**c** with a second amine failed under the above conditions. However, a diverse range of aromatic and aliphatic primary and secondary amines in refluxing THF successfully displaced the remaining benzotriazole group in **2d**−**f** and gave the *N*,*N*,*N*′-trisubstituted guanidines **3′a**,**b**,**c**,**e**,**f**,**g** (this tautomeric form is preferred in $CDCl_3$ solution) or its *N*,*N*,*N*′,*N*′-tetrasubstituted analogue **3d** in fair to good yields (Scheme 1, Table 2). Repeating the purification protocol used for the preparation of **2a**−**f** gave the analytically pure guanidines **3a**−**g**. However, it is important that a secondary amine is utilized at the first stage of the reaction. If the

‡ Present address: Intervet GesmbH, Research Pharmaceuticals Chemistry, Althanstrasse 14, A-1090 Vienna, Austria.

(1) Rowley, G. L.; Greenleaf, A. L.; Kenyon, G. L. *J. Am. Chem. Soc.* **1971**, *93*, 5542.
(2) Ramadas, K.; Srinivasan, N. *Tetrahedron Lett.* **1995**, *36*, 2841.
(3) Ramadas, K.; Janarthanan, N.; Pritha, R. *Synlett* **1997**, 1053.
(4) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677.
(5) Kent, D. R.; Cody, W. L.; Doherty, A. M. *Tetrahedron Lett.* **1996**, *37*, 8711.
(6) (a) Arzeno, H. B.; Bingenheimer, W.; Morgans, D. L., Jr. *Synth. Commun.* **1990**, *20*, 3433. (b) Marianoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. *J. Org. Chem.* **1986**, *51*, 1882. (c) Miller, A. E.; Bischoff, J. J. *Synthesis* **1986**, 777.
(7) Katritzky, A. R.; Parris, R. L.; Allin, S. M.; Steel, P. J. *Synth. Commun.* **1995**, *25*, 1173.
(8) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497.
(9) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389.
(10) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804.
(11) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432.
(12) Thambidurai, S.; Jeyasubramanian, K.; Ramalingam, S. K. *Polyhedron* **1996**, *15*, 4011.
(13) Katritzky, A. R.; Brzezinski, J. Z.; Lam, J. N. *Rev. Roum. Chim.* **1991**, *36*, 573.
(14) Hafelinger, G. *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; John Wiley and Sons: London, 1975; p 53.

10.1021/jo0006526 CCC: $19.00
Published on Web 10/21/2000

Scheme 1

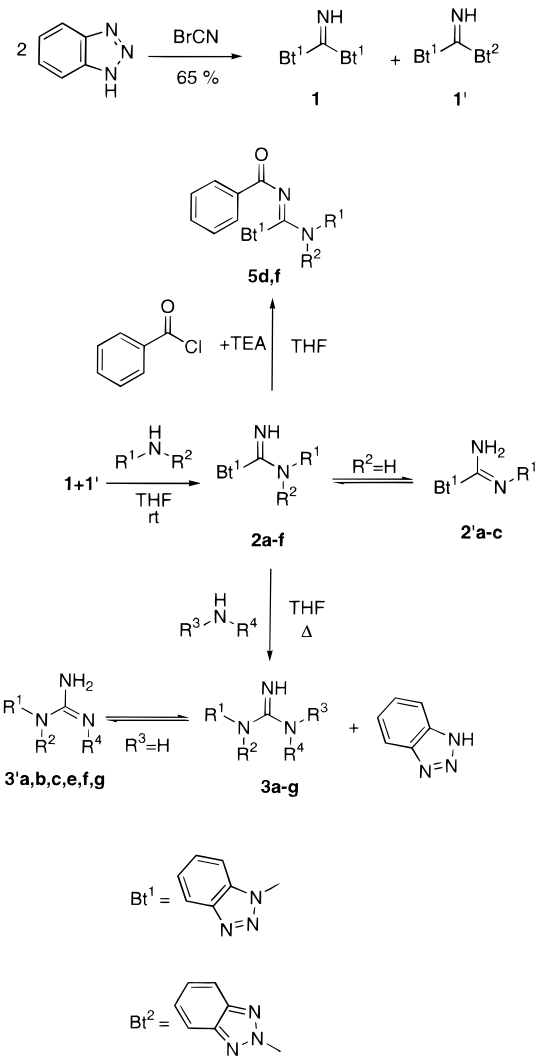

Table 1. Preparation of Benzotriazole-1-carboximidamides 2a-f

2	R^1	R^2	yield (%)
a	H	C_6H_5	80
b	H	*n*-C_5H_{11}	74
c	H	$CH_2C_6H_5$	68
d	-$(CH_2)_4$-		71
e	-$(CH_2)_2O(CH_2)_2$-		68
f	$CH(CH_3)_2$	$CH(CH_3)_2$	68

Table 2. Preparation of Guanidines 3a-g

3	R^1	R^2	R^3	R^4	reaction time (h)	yield (%)
a	-$(CH_2)_2O(CH_2)_2$-		C_6H_5	H	10	64
b	-$(CH_2)_2O(CH_2)_2$-		4-$CH_3C_6H_4$	H	12	74
c	-$(CH_2)_2O(CH_2)_2$-		$C_6H_5CH_2$	H	12	71
d	-$(CH_2)_2O(CH_2)_2$-		C_6H_5	CH_3	18	85
e	-$(CH_2)_4$-		C_6H_5	H	12	68
f	-$(CH_2)_4$-		4-$CH_3OC_6H_4$	H	17	60
g	$CH(CH_3)_2$	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	H	15	48

displacement of the first Bt group is by a primary amine, the reaction stops at the stage RNHC(:NH)Bt, and it is difficult to displace the second Bt group.

Tetrasubstituted guanidine **3d** was prepared using extended reaction times in yields comparable to most of the trisubstituted derivatives. Reaction of **2f** with 4-methoxyaniline yielded the desired guanidine **3′g** on using an extended reaction time, but attempted condensations of **2f** with amylamine and *N*-methylaniline gave exclusively *N*,*N*-bis(1-methylethyl)cyanamide as result of the loss of benzotriazole.

Conclusion

In summary we have developed the use of di(benzotriazolyl)methanimines **1,1′** as a new guanidinylating reagent for the general synthesis of trisubstituted and tetrasubstituted guanidines. The sequential condensation of two amines with **1,1′** is insensitive to electronic and steric effects allowing the use of a wide diversity of amines. Previously, good methods were available for the preparation of mono and disubstituted guanidines.[7,8] However, the synthesis of tri- and tetrasubstituted derivatives usually required the use of oxidizers.[3] It is now possible, with our new method, to obtain nonprotected tri- and tetrasubstituted guanidines in high yields under neutral and mild conditions using an easy purification protocol.

Experimental Section

General Methods. Melting points were determined using a capillary melting point apparatus equipped with a digital thermometer. ^{1}H and ^{13}C NMR spectra were collected on a 300 MHz NMR spectrometer (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Tetrahydrofuran (THF) was distilled under nitrogen immediately before use from sodium/benzophenone. Column chromatography was conducted with silica gel grade 230−400 mesh (compounds **2b**,**f**). The chromatographic technique used was flash chromatography as described by Still[15] with hexanes and ethyl acetate gradients unless otherwise stated. All other reagents were reagent grade and were used without purification.

Di(1*H*-benzotriazol-1-yl)methanimine (1) and 1*H*-Benzotriazol-1-yl(2*H*-benzotriazol-2-yl)methanimine (1′), Mixture of Isomers. Benzotriazole (5.9 g, 0.05 mol) was dissolved in ethanol (100 mL). To this solution kept at 0 °C was added cyanogen bromide (2.5 g, 0.025 mol) in acetone (10 mL) followed by a 10% solution of NaOH (0.025 mol). The white precipitate was filtered off and washed with ice cold ethanol and recrystallized from benzene to give pure white microneedles, mp 162−163 °C. Yield 62%. ^{1}H NMR δ 7.44−7.76 (m, 6H), 7.85−7.95 (m, 6H), 8.08 (d, J = 9.0 Hz, 1H), 8.30−8.39 (m, 8H), 11.77 (s, 2H), ^{13}C NMR δ 110.9, 112.3, 114.0, 120.0, 120.4, 121.2, 125.6, 125.8, 126.6, 127.3, 129.8, 130.7, 131.9, 132.1, 132.2, 140.9, 142.9, 144.9,146.1. Anal. Calcd for $C_{13}H_9N_7$: C, 59.31; H, 3.45; N, 37.24. Found: C, 59.43; H, 3.25; N, 37.27.

General Procedure for the Preparation of Benzotriazole-1-carboximidamides 2. Di(1,2,3-benzotriazol-1-yl)methanimine **1** (2 mmol) was dissolved under an inert atmosphere in dry THF (20 mL). The appropriate amines (2 mmol, 1 equiv) were added dropwise, and the resulting mixtures were allowed to react until complete conversion of **1**, as monitored by TLC. The mixtures were then concentrated under vacuum and dissolved in CH_2Cl_2 (20 mL). The organic layers were washed twice with aqueous 10% Na_2CO_3 and dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford compounds **2, 2′** in analytical purity. For compound **2f** heating to 50 °C is required.

***N*-(Benzyl)benzotriazole-1-carboximidamide (2c) and *N*′-(benzyl)benzotriazole-1-carboximidamide (2′c), mixture of tautomers (1:1):** colorless needles, mp 97−98 °C (hexanes). For **2c**: ^{1}H NMR δ 4.56 (d, J = 6.2 Hz, 2H), 6.38 (br s, 1H), 7.13 (br s, 1H), 7.30−7.57 (m, 7H), 8.09 (d, J = 8.3 Hz, 1H), 8.50 (d, J = 8.1 Hz, 1H); for **2′c**: ^{1}H NMR δ 4.60 (s, 2H), 5.68 (br s, 2H), 7.30−7.57 (m, 7H), 8.08 (d, J = 8.3 Hz, 1H), 8.53 (d, J = 8.1 Hz, 1H); ^{13}C NMR (**2c** + **2′c**) δ 45.3, 50.8, 115.4, 119.6, 119.7, 125.0, 125.1, 126.8, 127.2, 127.3, 128.0, 128.5, 128.9,

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

129.0, 129.2, 129.3, 131.2, 139.9, 146.5, 146.6. Anal. Calcd for $C_{14}H_{13}N_5$: C, 66.92; H, 5.21; N, 27.87. Found: C, 67.32; H, 5.29; N, 27.65.

***N,N*-Bis(1-methylethyl)benzotriazole-1-carboximidamide (2f):** white needles, mp 86−87 °C; ^{1}H NMR δ 1.38 (d, J = 6.9 Hz, 12H), 3.51−3.61 (m, 2H), 7.43 (t, J = 7.8 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 20.9, 48.7, 110.9, 120.0, 124.6, 128.6, 132.4, 145.4, 149.3. This compound was characterized as the benzoyl derivative; see next compound.

General Procedure for the Preparation of Acyl Derivatives of 1*H*-Benzotriazole-1-carboximidamides (5d,f). Appropriate compound **2** (1 equiv) was dissolved in chloroform, and acyl chloride (1 equiv) was added followed by addition of triethylamine (1 equiv). The mixture was allowed to react for 2−4 h at ambient temperature. The completion of the reaction was monitored by TLC. The chloroform solution was then washed with water to remove triethylamine hydrochloride. The chloroform layer was separated, dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate/hexanes: 1/1 as an eluent.

***N*-[1*H*-Benzotriazol-1-yl(diisopropylamino)methylidene]-benzamide (5f):** white prisms; mp 116−117 °C; ^{1}H NMR δ 1.53 (d, J = 6.7 Hz, 12H), 3.73−3.80 (m, 2H), 7.32−7.40 (m, 5H), 7.45−7.50 (m, 1H), 7.97−7.99 (m, 2H), 8.05−8.08 (m, 1H); ^{13}C NMR δ 20.7, 50.20, 110.1, 120.4, 124.6, 128.0, 128.8, 129.4, 131.9, 132.9, 135.9, 145.0, 145.8, 173.8. Anal. Calcd for $C_{20}H_{23}N_5O$: C, 68.74; H, 6.63; N, 20.04. Found: C, 68.97; H, 6.86; N, 20.20.

General Procedure for the Preparation of Compounds 3, 3′. Benzotriazole-1-carboximidamides **2** (500 mg, 2 mmol) were dissolved in dry THF (20 mL) under an argon atmosphere, and the appropriate amines (2 mmol) were added to the solution. The resulting mixtures were then refluxed until complete conversion of **2,** as monitored by TLC. After concentration under reduced pressure, the obtained residues were dissolved in CH_2Cl_2 (20 mL). The organic layers were washed twice with aqueous 5% Na_2CO_3 and dried ($MgSO_4$), and the solvent was removed under vacuum to afford guanidines **3** as pure products.

***N*`-Phenyltetrahydro-1*H*-pyrrole-1-carboximidamide (3′e):** light brown oil; ^{1}H NMR δ 1.82−1.90 (m, 4H), 3.30−3.39 (m, 4H), 3.67 (br s, 2H), 6.66−6.77 (m, 3H), 7.12−7.27 (m, 2H);^{13}C NMR δ 25.5, 50.3, 114.9, 117.8, 118.3, 129.1, 146.3. HRMS (EI) Calcd for $C_{11}H_{16}N_3$ (M + 1): 190.1344. Found: 190.1337.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, HRMS and CHN analysis for compounds **2′a**, **2b**, **2d**, **2e**, **3′a**, **3′b**, **3c**, **3d**, **3′f**, **3′g**, and **5d.** This material is available free of charge via the Internet at http://pubs.acs.org.

JO0006526