A New Route to Guanidines from Bromoalkanes

Ganesan Vaidyanathan* and Michael R. Zalutsky

Box 3808, Department of Radiology, Duke University Medical Center, Durham, North Carolina 27710

Received March 6, 1997[⊗]

Traditionally, guanidines have been prepared by the treatment of ammonia or an amine with cyanamide[1] or *S*-alkylisothiouronium salts.[2] Subsequent studies mainly have focused on the search for better guanylating agents of amines. Applications of reagents such as aminoiminomethanesulfonic acid,[3] 1*H*-pyrazole-1-carboxamidine hydrochloride,[4] and benzotriazole-1-carboxamidinium tosylate[5] have been reported. In the last few years, a number of carbamate-protected reagents such as N^1, N^2-bis(*tert*-butyloxy/benzyloxycarbonyl)thiourea, N^1,N^2-bis-(*tert*-butyloxy/benzyloxycarbonyl)-*S*-methylisothiourea, as well as 1*H*-pyrazole-1-[N^1,N^2-bis(*tert*-butyloxy/benzyloxycarbonyl)]carboxamidine and its dimethyl substituted derivative have been developed.[6] Additionally, the usefulness of sulfonyl-protected 2-methyl-2-thiopseudourea in the conversion of amines to guanidines has been demonstrated,[7] and conditions for utilizing carbamate derivatives have been improved and applied to the synthesis of various compounds.[8] Excellent yields of protected guanidines often have been obtained using these reagents and purification by chromatography has been facile due to the less polar nature of protected guanidines. Guanidines can be easily generated from these derivatives in excellent yields by simple treatment with hydrochloric acid or trifluoroacetic acid.[6a,8a]

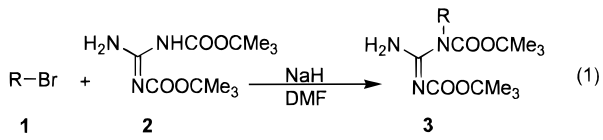
Whereas most methods for guanidine preparation involve guanylation of ammonia or an amine, conversion of nitriles[9] and alcohols under Mitsunobu conditions[10, 11] has been reported. In light of these reports, a protocol for the direct conversion of a bromoalkane to a protected guanidine using N^1,N^2-bis(*tert*-butyloxycarbonyl)guanidine (**2**) would be advantageous.

Our interest in this synthetic route relates to the development of radiolabeled derivatives of (*m*-iodobenzyl)guanidine (MIBG), an agent used in the diagnosis and treatment of neuroendocrine tumors.[12,13] In this connection, we wanted to prepare 2-(guanidinomethyl)-6-nitrobenzoic acid, which could be synthesized from commercially available 2-methyl-6-nitrobenzoic acid. Following benzylic bromination, the desired guanidine could be prepared by a number of methods.[10,14] However, these routes involved several additional synthetic transformations, and encouraged by the alkylation of the monosodium salt of N^1,N^2-bis(*tert*-butyloxycarbonyl)hydrazine,[15,16] we investigated the conversion of a number of bromoalkanes to the corresponding protected guanidines by treatment with the sodium salt of **2** (Na-**2**).

Results and Discussion

The results obtained from the guanylation of bromoalkanes (eq 1) are summarized in Table 1. Although our main interest was in the preparation of benzylguanidine derivatives, the general applicability of the reaction was investigated using some aliphatic and heterocyclic compounds. The conditions were mild, and the reactions often were clean.

While **1a** was converted to **3a**, **1b** failed to react. In contrast, the yield of guanidine derivatives from both primary and secondary alcohols under Mitsunobu conditions was more than 95%.[10] Although a dual mechanistic pathway has been proposed for Mitsunobu reaction,[17] the final step involves the S_N2 substitution of a nucleophile on the alkoxyphosphonium intermediate resulting in the inversion of configuration at carbon in asymmetric alcohols. Such inversion has been observed in the conversion of 2-butanol to the guanidine derivative.[10] It is believed that an S_N2 mechanism most likely is involved in the conversion of **1** to **3** (eq 1). Thus, it is not clear why



2-bromobutane failed to yield any substitution product. Being a secondary halide, 2-bromobutane should be susceptible to undergoing elimination in the presence of a base. To investigate this possibility, the reaction was conducted using **1c**. Again, no substitution product **3c** was obtained; however, a product identical in TLC (hexane) and NMR to commercially available *trans*-β-methylstyrene was isolated in almost quantitative yield. This suggests that, under these reaction conditions, secondary bromides undergo elimination rather than substitution.

* To whom correspondence should be addressed. Tel.: (919) 684-7811. Fax: (919) 684-7122. E-mail: g405@acpub.duke.edu.

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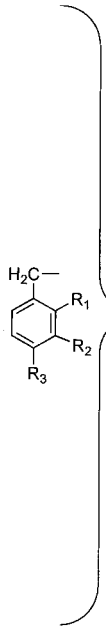
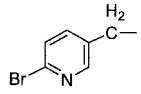
S0022-3263(97)00416-7 CCC: $14.00

Table 1. Conversion of Bromoalkanes 1 to the Corresponding Protected Guanidines 3

Entry	R	R_1	R_2	R_3	Yield of **3** (%)[a]
a	*n*-butyl	---	---	---	45
b	*sec*-butyl	---	---	---	*b*
c		---	---	---	*c*
d		H	H	H	70
e		H	F	H	66
f		H	I	H	80
g		H	NO_2	H	73
h		H	H	O-CO-Ph	31[d]
i		H	H	COOH	70[e]
j		H	H	COOR[f]	70
k		COOR[f]	NO_2	H	35
l		$SiMe_3$	H	COOR[f]	48[g]
m		I	H	COOR[f]	56[g]
n		Me	H	H	80
o		H	Me	H	56
p		H	H	Me	85
q		H	OMe	H	73
r		---	---	---	100

[a] Yields of pure products isolated by chromatography; reaction scale varied from 0.2 to 5.0 mmol. [b] No **3b** was isolated; most of **2** was recovered. [c] See discussion. [d] Yield based on the recovered starting material (~20%); a considerable amount unknown product was also isolated. [e] Two equiv of NaH was used. [f] R = $-CH_2-CH_2SiMe_3$. [g] Overnight stirring was required for completion of reaction.

Except in the case of **1h** and **1i**, TLC of reaction mixtures with arylalkyl substrates indicated a single species corresponding to that of **3** with little or no byproduct. In the cases of **3k** and **3l**, where the reactions were run on a small scale (0.2 mmol), lower yields may be due to loss during workup.

In the case of **1h**, side reactions in addition to the expected substitution are possible. Substitution can occur at the desired benzylic carbon and/or at the ester carbonyl carbon. Although the NH_2 of **3h** is not very acidic, it can be potentially alkylated with **1h**. However, the spectral (NMR, IR, and MS) data of the major byproduct do not match those expected for the byproducts from the above possibilities. Yet another possibility is a product formed from the reaction of a small amount of dibromo impurity present in **1h** (see Experimental Section) and 2 equiv of **2**, but neither the spectral data nor the mass amount are consistent with this explanation.

With **1i**, the acid functionality could be deprotonated with Na-**2**. With 1 equiv of base, not only does this not yield (or at least decrease the amount of) the desired product but could result in polymeric product(s) by the self-condensation (intermolecular) of the conjugate base of **1i** (Na-**1i**). The reaction was conducted using both 1 and 2 equiv of base. In both cases, the starting material was completely consumed within 1 h. When 1 equivalent of base was used, more than 50% of **2** was recovered; a substantial amount of a solid insoluble even in DMSO was isolated. The remainder was a mixture of two components—**3i** (minor) and an unidentified compound. Performing the reaction with 2 equiv of base resulted in **3i** as the major product. While no DMSO-insoluble product was formed, the amount of the unidentified compound was minimal; about 25% of **2** was recovered. The byproducts may be oligomers of **1i**. Proton abstraction by Na-**2** from **1i** is faster than the desired reaction, which in turn is faster than the polymerization of Na-**1i**.

In conclusion, a new method for the efficient preparation of guanidines starting from bromoalkanes under facile conditions has been developed. In the case of secondary bromides, elimination rather than substitution is the preferred mode of reaction. For arylalkyl substrates, the electron-withdrawing/donating nature or position of the ring substituent does not seem to have any significant influence on the reaction.

Experimental Section

General Methods. Bromoalkanes **1a**−**g,i,n**−**q** and other starting materials were obtained from Aldrich and were used as such. Silylation-grade DMF (Pierce, Rockford, IL) was used without any further purification for all reactions. The compound **1h** was obtained by the benzylic bromination of *p*-tolyl benzoate. Although chromatographically homogeneous, NMR indicated the presence of a small amount (about 10%) of dibromo derivative. The compound **1i** was prepared from α-bromo-*p*-toluic acid by the carbodiimide-mediated esterification. The substrates **1k** and **1m** were prepared from 2-methyl-6-nitrobenzoic acid and 3-iodo-4-methylbenzoic acid, respectively, by esterification followed by benzylic bromination. A three-step synthesis (BuLi-mediated silylation, esterification, and benzylic bromination) was used for the preparation of **1l** from 3-bromo-4-methylbenzoic acid. For the preparation of **1r**, 2-bromo-5-methylpyridine was brominated using NBS/benzoyl peroxide. Most of the above intermediates were used for the subsequent reaction without extensive purification.

Typical Reaction Procedure for the Conversion of 1 to 3. To a suspension of 24 mg (1 mmol) of sodium hydride in 5 mL of dry DMF was added 259 mg (1 mmole) of **2**.[10] The suspension turned to a clear solution after 5 min of stirring at room temperature. To this solution was added dropwise a solution of 1 mmol of the **1** in 2 mL of DMF, and the reaction mixture was stirred at room temperature until TLC indicated the complete consumption of **1** (usually 1 h). The reaction mixture was partitioned between water and ethyl acetate, and the pure product was isolated by silica gel chromatography (column or preparative plate) using ethyl acetate/hexane mixtures.

***N*¹,*N*²-Bis(*tert*-butyloxycarbonyl)-*N*¹-*n*-butylguanidine (3a):** 1:3 ethyl acetate:hexane, R_f 0.55; oil; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.8 Hz), 1.24−1.40 (m, 2H), 1.5 (s, 9H), 1.52 (s, 9H), 1.46−1.62 (m, 2H), 3.9 (t, 2H, J = 10.8 Hz), 9.30 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{15}H_{30}N_3O_4$ (MH^+) 316.2236, found 316.2229. Anal. Calcd for $C_{15}H_{29}N_3O_4$: C, 57.12; H, 9.27; N, 13.32. Found: C, 57.16, H, 9.34; N, 13.26.

***N*¹-Benzyl-*N*¹,*N*²-bis(*tert*-butyloxycarbonyl)guanidine (3d):** 1:3 ethyl acetate:hexane, R_f 0.80); white crystals; mp 84 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.49 (s, 9H), 5.19 (s, 2H), 7.23−7.29 (m, 5H) 9.40 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{18}H_{28}N_3O_4$ (MH^+) 350.2080, found 350.2069. Anal. Calcd for $C_{18}H_{27}N_3O_4$: C, 61.87; H, 7.79; N, 12.03. Found: C, 62.44; H, 7.69; N, 11.63.

***N*¹,*N*²-Bis(*tert*-butyloxycarbonyl)-*N*¹-(3-fluorobenzyl)guanidine (3e):** 1:4 ethyl acetate:hexane, R_f 0.39; white crystals; mp 102 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 1.49 (s, 9H), 5.17 (s, 2H), 6.85−7.10 (m, 3H), 7.20−7.30 (m, 1H), 9.30

(br s, 1H), 9.45 (br s, 1H); HRMS (FAB$^+$) calcd for $C_{18}H_{27}FN_3O_4$ (MH^+) 368.1986, found 368.1993. Anal. Calcd for $C_{18}H_{26}FN_3O_4$: C, 58.84; H, 7.13; N, 11.44. Found: C, 58.98; H, 7.23; N, 11.42.

***N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)-*N*^{1}-(3-iodobenzyl)-guanidine (3f):** 3:17 ethyl acetate:hexane, R_f 0.60; white granular solid; mp 135 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 1.50 (s, 9H), 5.11 (s, 2H), 6.98−7.08 (m, 1H), 7.20−7.24 (m, 1H), 7.50−7.70 (m, 2H), 9.23 (br s, 1H), 9.42 (br s, 1H); HRMS (FAB$^+$) calcd for $C_{18}H_{27}IN_3O_4$ (MH^+) 476.1046, found 476.1055. Anal. Calcd for $C_{18}H_{26}IN_3O_4$: C, 45.48; H, 5.51; N, 8.84. Found: C, 45.27; H, 5.49; N, 8.56.

***N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)-*N*^{1}-(3-nitrobenzyl)-guanidine (3g):** 1:4 ethyl acetate:hexane, R_f 0.25; pale yellow solid; mp 119 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.49 (s, 9H), 5.24 (s, 2H), 7.44−7.52 (m, 1H), 7.63−7.66 (m, 1H), 8.10−8.15 (m, 1H), 8.20−8.22 (m, 1H), 9.30 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{18}H_{27}IN_4O_6$ (MH^+) 395.1931, found 395.1936. Anal. Calcd for $C_{18}H_{26}N_4O_6$: C, 54.80; H, 6.65; N, 14.21. Found: C, 54.70; H, 6.61; N, 14.27.

***N*^{1}-[4-(Benzoyloxy)benzyl]-*N*^{1},*N*^{2}-bis(*tert*-butyloxycarbonyl)guanidine (3h):** 1:4 ethyl acetate:hexane, R_f 0.39; white crystals; mp 146 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 1.50 (s, 9H), 5.20 (s, 2H), 7.15 (d, 2H, J = 8.4 Hz), 7.26−7.38 (m, 2H), 7.48−7.56 (m, 2H), 7.60−7.69 (m, 1H), 8.20 (d, 2H, J = 8.4 Hz), 9.35 (br s, 1H), 9.45 (br s, 1H); HRMS (FAB$^+$) calcd for $C_{25}H_{32}N_3O_6$ (MH^+) 470.2291, found 470.2307. Anal. Calcd for $C_{25}H_{31}N_3O_6$: C, 63.94; H, 6.66; N, 8.95. Found: C, 63.85; H, 6.63; N, 8.89.

4-[[*N*^{1},*N*^{2}-bis(*tert*-butyloxycarbonyl)guanidino]methyl]benzoic acid (3i): 1:50:50 acetic acid:ethyl acetate:hexane, R_f 0.41; white crystals (ethyl acetate/hexane); mp 165−67 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.48 (s, 9H), 5.24 (s, 2H), 7.28 (d, 2H, J = 8.8 Hz), 8.01 (d, 2H, J = 8.8 Hz), 9.38 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{19}H_{28}N_3O_6$ (MH^+) 394.1977, found 394.1981. Anal. Calcd for $C_{19}H_{27}N_3O_6$: C, 58.00; H, 6.92; N, 10.68. Found: C, 57.91; H, 6.99; N, 10.68.

2-(Trimethylsilyl)ethyl 4-[[*N*^{1},*N*^{2}-bis(*tert*-butyloxycarbonyl)guanidino]methyl]benzoate (3j): 3:17 ethyl acetate:hexane, R_f 0.32; oil; ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 1.13 (t, 2H, J = 8.8 Hz), 1.29 (s, 9H), 1.48 (s, 9H), 4.43 (t, 2H, J = 8.8 Hz), 5.23 (s, 2H), 7.27 (d, 2H, J = 8.1 Hz), 7.97 (d, 2H, J = 8.1 Hz), 9.35 (br s, 1H), 9.45 (br s, 1H); HRMS (FAB$^+$) calcd for $C_{24}H_{40}N_3O_6Si$ (MH^+) 494.2686, found 494.2689. Anal. Calcd for $C_{24}H_{39}N_3O_6Si$: C, 58.39; H, 7.96; N, 8.51. Found: C, 58.37; H, 7.95; N, 8.32.

2-(Trimethylsilyl)ethyl 2-[[*N*^{1},*N*^{2}-bis(*tert*-butyloxycarbonyl)guanidino]methyl]-6-nitrobenzoate (3k): 2:3 ethyl acetate:hexane, R_f 0.56; pale yellow crystals; mp 123 °C; ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 1.11 (t, 2H, J = 11.0 Hz), 1.28 (s, 9H), 1.46 (s, 9H), 4.43 (t, 2H, J = 11.0 Hz), 5.32 (s, 2H), 7.42 (d, 1H, J = 11.8 Hz), 7.50−7.58 (m, 1H), 8.00 (d, 1H, J = 11.8 Hz), 9.35 (br s, 1H), 9.52 (br s, 1H); HRMS (FAB$^+$) calcd for $C_{24}H_{39}N_4O_8Si$ (MH^+) 539.2537, found 539.2538. Anal. Calcd for $C_{24}H_{38}N_4O_8Si$: C, 53.51; H, 7.11; N, 10.41. Found: C, 53.47; H, 7.15; N, 10.35.

2-(Trimethylsilyl)ethyl 4-[[*N*^{1},*N*^{2}-bis(*tert*-butyloxycarbonyl)guanidino]methyl]-3-(trimethylsilyl)benzoate (3l): 1:9 ethyl acetate:hexane, R_f 0.34; oil; ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 0.40 (s, 9H), 1.14 (t, 2H, J = 11.2 Hz), 1.26 (s, 9H), 1.41 (s, 9H), 4.41 (t, 2H, J = 11.2 Hz), 5.37 (s, 2H), 7.05 (d, 1H, J = 8.9 Hz), 7.95 (d, 1H, J = 8.9 Hz), 8.18 (s, 1H), 9.45 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{27}H_{48}N_3O_6Si_2$ (MH^+) 566.3082, found 566.3069. Anal. Calcd for $C_{27}H_{47}N_3O_6Si_2$: C, 57.31; H, 8.37; N, 7.42. Found: C, 57.23; H, 8.33; N, 7.28.

2-(Trimethylsilyl)ethyl 4-[[*N*^{1},*N*^{2}-bis(*tert*-butyloxycarbonyl)guanidino]methyl]-3-iodobenzoate (3m): 1:9 ethyl acetate:hexane, R_f 0.24; white crystals; mp 55−56 °C; ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 1.14 (t, 2H, J = 6.6 Hz), 1.25 (s, 9H), 1.47 (s, 9H), 4.41 (t, 2H, J = 6.6 Hz), 5.22 (s, 2H), 7.05 (d, 1H, J = 8.5 Hz), 7.95 (d, 1H, J = 8.5 Hz), 8.45 (s, 1H), 9.45 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{24}H_{39}IN_3O_6Si$ (MH^+) 620.1653, found 620.1649. Anal. Calcd for $C_{24}H_{38}IN_3O_6Si$: C, 46.53; H, 6.18; N, 6.78. Found: C, 46.66; H, 6.25; N, 6.76.

***N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)-*N*^{1}-(2-methylbenzyl)guanidine (3n):** 1:19 ethyl acetate:hexane, R_f 0.18; white crystals; mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9H), 1.46 (s, 9H), 2.29 (s, 3H), 5.18 (s, 2H), 6.95−7.20 (m, 4H), 9.45 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{19}H_{30}N_3O_4$ (MH^+); 364.2236, found 364.2226. Anal. Calcd for $C_{19}H_{29}N_3O_4$: C, 62.79; H, 8.04; N, 11.56. Found: C, 62.81; H, 8.02; N, 11.63.

***N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)-*N*^{1}-(3-methylbenzyl)guanidine (3o):** 1:9 ethyl acetate:hexane, R_f 0.27; white crystals; mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.49 (s, 9H), 2.32 (s, 3H), 5.14 (s, 2H), 7.04−7.20 (m, 4H), 9.40 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{19}H_{30}N_3O_4$ (MH^+) 364.2236, found 364.2241. Anal. Calcd for $C_{19}H_{29}N_3O_4$: C, 62.79; H, 8.04; N, 11.56. Found: C, 63.40; H, 7.98; N, 11.13.

***N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)-*N*^{1}-(4-methylbenzyl)guanidine (3p):** 1:9 ethyl acetate:hexane, R_f 0.2; white crystals; mp 138−139 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.48 (s, 9H), 2.32 (s, 3H), 5.13 (s, 2H), 7.19 (m, 4H), 9.40 (br s, 2H). HRMS (FAB$^+$) calcd for $C_{19}H_{30}N_3O_4$ (MH^+) 364.2236, found 364.2226. Anal. Calcd for $C_{19}H_{29}N_3O_4$: C, 62.79; H, 8.04; N, 11.56. Found: C, 62.63; H, 7.97; N, 11.43.

***N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)-*N*^{1}-(3-methoxybenzyl)guanidine (3q):** 1:9 ethyl acetate:hexane, R_f 0.08; white crystals; mp 79−80 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.48 (s, 9H), 3.79 (s, 3H), 5.15 (s, 2H), 6.81 (m, 3H), 7.23 (t, 1H, J = 8.0), 9.42 (br s, 2H); HRMS (FAB$^+$) calcd for $C_{19}H_{30}N_3O_5$ (MH^+) 380.2185, found 380.2184. Anal. Calcd for $C_{19}H_{29}N_3O_4$: C, 60.14; H, 7.70; N, 11.07. Found: C, 60.08; H, 7.69; N, 11.10.

5-[[*N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)guanidino]methyl]-2-bromopyridine (3r): 1:3 ethyl acetate:hexane, R_f 0.29; pale yellow powder; mp 147 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.49 (s, 9H), 5.11 (s, 2H), 7.45 (d, 1H, J = 10.0 Hz), 7.64 (d, 1H, J = 10.0 Hz), 8.36 (s, 1H), 9.20 (br s, 1H), 9.44 (br s, 1H); HRMS (FAB$^+$) calcd for $C_{17}H_{26}BrN_4O_4$ (MH^+) 429.1137, found 429.1138. Anal. Calcd for $C_{17}H_{25}BrN_4O_4$: C, 47.56; H, 6.02; N, 13.05. Found: C, 47.83; H, 6.07; N, 13.13.

Acknowledgment. This work is supported by grants (CA 60066 and CA 42324) from the National Institutes of Health. The authors thank Donna J. Affleck and Jean Li for their excellent technical assistance.

JO9704164