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Solid Phase Synthesis of Guanidines

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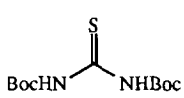
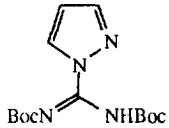
ABSTRACT: A comparison of guanylating agents **1** and **2** was performed on a series of primary, secondary and aromatic amines in solution and on solid phase resins. Thiourea **1** performed well in solution and on solid supported primary and secondary amines. Pyrazole **2** performed well in each case, except one aniline which failed to react. © 1997 Published by Elsevier Science Ltd.

As part of a solid phase combinatorial library synthesis program we desired to convert a variety of primary and secondary amines and anilines to their corresponding guanidine derivatives. The Rathke guanidine synthesis and its variants are the most common and reliable methods for converting amines to guanidines. The classic form of this reaction used S-methylisothiouronium salts to convert amines to guanidinium salts in high yield.[1] A number of other reagents also yield guanidines from amines, including, cyanamide,[2] O-methylisourea hydrogen sulfate, 2-ethyl-2-thiopseudo hydrobromide and 3,5-dimethylpyrazole-1-carboxamidine nitrate.[3] Unfortunately, these reagents have been reported to lack sufficient reactivity for solid phase peptide synthesis.[4] Since our combinatorial library strategy required the use of a solid support and neutral to mildly basic reaction conditions, we conducted a preliminary study on the reactivity of N,N'- bis-Boc-thiourea **1**[5] and N,N' -bis-Boc-1-guanylpyrazole **2**[6] with a selected set of primary and secondary amines and anilines in solution and on solid phase, as reported herein.



1



2

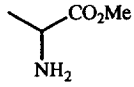
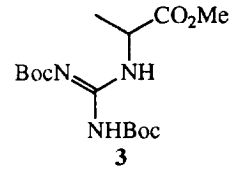
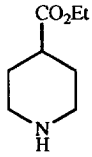
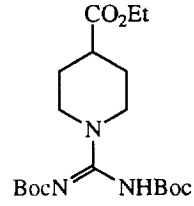
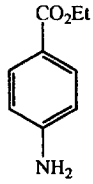
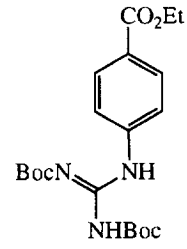
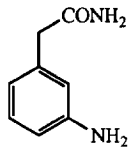
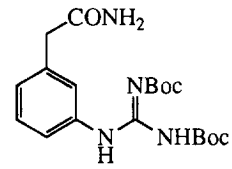
Methyl 2-aminopropanoate and ethyl isonipecotate were treated with thiourea **1** at room temp for 72 h in DCE. The N,N' bis-Boc-guanyl derivatives **3** and **4** were obtained in 86% and 95% respectively (Table 1). Similarly, treatment of ethyl isonipecotate with guanylpyrazole **2** gave guanyl product **4** in 91% isolated yield. Addition of thiourea **1** to ethyl 4-aminobenzoate did not result in the isolation of any N,N' bis-Boc guanyl product. If thiourea **1** was activated with mercuric chloride, **5** could be obtained in 84% yield. When the more reactive guanylpyrazole **2** was added to ethyl 4-aminobenzoate, **5** was obtained in 64% yield without any secondary activation. Similarly, treatment of 3-aminophenylacetamide with guanylpyrazole **2** gave **6** in 66% yield.

Fmoc 4-(aminomethyl)benzoic acid and Fmoc isonipecotic acid were both attached to Wang resin with HOBT/DICDI in DCE/DMF. Fmoc 4-aminobenzoic acid and Fmoc 3-aminophenylacetic acid were both attached to Rink Amide AM resin in the same manner. A sample of each resin was treated with a 50% mixture of TFA:DCM for 4 h(Wang) or 95% TFA:DCM for 1 h (Rink Amide AM) to determine the loadings of the amino acids: 0.36 meq/g, 0.59 meq/g, 0.54 meq/g and 0.46 meq/g respectively. The Fmoc protecting groups were then removed by treating the resins with 50% piperidine in DMF. The resins were then washed and dried. Examination of the resins by FTIR indicated the Fmoc groups were removed.

Treatment of Wang resin bound 4-(aminomethyl)benzoic acid **7** and isonipecotic acid **8** with thiourea **1** followed by treatment of the resin with 50% mixture of TFA:DCM gave the guanyl TFA salts **11** and **12** in 87% and 97% isolated yields (Table 2). Similarly, treatment of **7** and **8** with guanylpyrazole **2** gave **11** and **12** in 86% and 99% isolated yields.

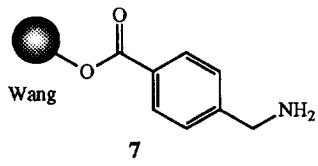
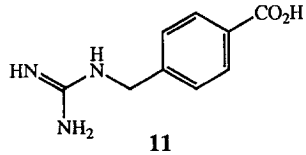
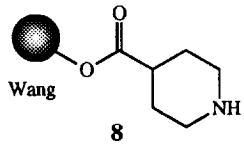
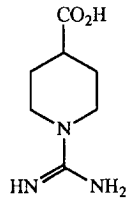
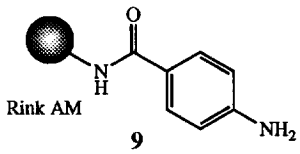
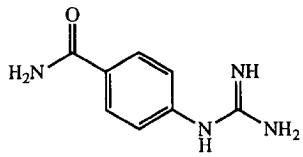
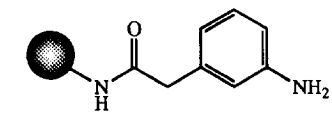
The resin bound anilines, **9** and **10** proved to be less reactive. When **9** was exposed to thiourea **1** in the presence of $HgCl_2$ for 3 days, the guanyl product **13** was isolated in 40% yield. Treatment of **9** with pyrazole **2** also afforded **13** in 72% yield. The mercury activated thiourea performed better in solution than in the presence of a solid phase. The pyrazole performed well in solution or on solid phase. Resin **10**, by comparison, did not yield any guanyl products upon prolonged exposure to either thiourea **1** or pyrazole **2**, even though pyrazole **2** had provided product from the solution study. Further studies on correlating solution and solid phase reactivities are in progress.

Table 1. Solution Phase N,N' bis-Boc Guanidine Synthesis.

Amine	Guanylating Agent	Conditions	Yield (%)	Product
	**1**	i	86	 **3**
	**1**	i	95	 **4**
	2	ii	91	
	**1**	i	NR	 **5**
	1	iii	84	
	2	ii	64	
	**2**	ii	66	 **6**

i) 1.5 eq each of **1**, DIPEA and DICDI in 1:5 DMF:DCE.
ii) 1 eq. of **2** in DCE.
iii) 1 eq. of **1**, 1.1 eq. of $HgCl_2$, 1 eq. of DIPEA, DMF/DCE

Table 2. Solid Phase Guanidine Synthesis.

Resin Bound Amine	Guanylating Agent	Conditions	Yield (%)	Product
 Wang **7**	**1**	i	87%	 TFA salt **11**
	2	ii	86%	
 Wang **8**	**1**	i	97%	 TFA salt **12**
	2	ii	99%	
 Rink AM **9**	**1**	iii	40%	 TFA salt **13**
	2	ii	72%	
 Rink AM **10**	**1**	i	NR	
	2	ii, iv	NR	

i) 2 eq. of **1** and DICDI, DCE.
ii) 2 eq. **2**, DCE.
iii) 1 eq. of **1**, 1.2 eq. of $HgCl_2$, DMF/DCE.
iv) 4 eq. of **2**, DCE.

Experimental

All solvents were anhydrous and were obtained from the Aldrich Chemical Co. in Sure/Seal™ bottles and were used as is. FMOC Rink Amide AM resin was purchased from Peptides International and Wang resin from Nova BioChem. All resins were rinsed with the following sequence after each reaction: DCM, MeOH, DMF, MeOH, DCM, MeOH and DCM. Rink Amide AM and Fmoc protected amines were deprotected by 4 h exposure to 50% piperidine in DMF followed by the rinse sequence and drying in a N_2 atmosphere. Product cleavage from Rink Amide AM was done in 95 : 5 trifluoroacetic acid(TFA) : dichloromethane(DCM) for 1 h; cleavage from Wang resin was done in 1 : 1 TFA : DCM for 4 h. ^{1}HNMR spectra were taken on a Varian Unity+ 400 MHz instrument and mass spectra were acquired on a VG Platform (APCI probe) by Fissons Instruments. The solid phase reactions were followed by FTIR using a NicPlan FTIR microscope from SpectraTech. All reactions were conducted at ambient temperature unless noted. All compounds were purified by radial chromatography or crystallization unless otherwise noted. All purified products were a single spot by tlc with elution in hexanes, 1:1 hexanes : ethyl acetate, and 1 : 9 methanol : ethyl acetate. Compounds **1** and **2** were prepared according to the published procedures.

Solution Phase:

Methyl 2-(N,N'-bis-BOC-guanyl)-propanoate **3**: *Procedure A*: To a stirred solution of methyl 2-aminopropanoate (10 mmol, 1.396 g) in DMF (2 mL) and dichloroethane (DCE) (10 mL) under nitrogen was added **1** (15 mmol, 4.14 g) and diisopropylcarbodiimide (DICDI) (15 mmol, 1.89 g). After stirring 72 h, ethyl acetate (48 mL) was added and the resultant solution was washed with H_2O (3X, 30 mL) and with brine (2X, 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness in vacuo. The sticky yellow residue was triturated with 1:1 hexanes:MTBE three times to remove residual **1** and N,N'-diisopropylthiourea. The residue was dried to a glassy, yellow gum to yield **3** (2.96 g, 86%); ^{1}H NMR($CDCl_3$) δ 11.41 (bs, 1 H), 8.89 (bd, 1 H), 4.85 (m, 1 H, J = 11 Hz), 3.74 (s, 3 H), 1.51 (s, 9 H), 1.49 (s, 9 H), 1.47 (d, 3 H, J = 11 Hz); MS (APCI); *m/z* (%) = 346 (M+H, 100), 345 (M^+, 30).

Ethyl 1-(N,N'-bis-BOC-guanyl)-isonipecotate **4**: prepared according to Procedure A, ethyl isonipecotate (10 mmol) and **1** gave **4** in 95% yield; ^{1}H NMR($CDCl_3$) δ 10.16 (bs, 1 H), 4.15 (q, 2 H, *J* = 7 Hz), 4.06 (m, 2 H), 3.08 (t of d, 2 H, *J* = 11 Hz, *J* = 3 Hz), 2.52 (m, 1 H), 1.94 (m, 2 H), 1.82 (m, 2 H), 1.49 (s, 9 H), 1.46 (s, 9 H), 1.24 (t, 3 H, *J* = 7 Hz); MS (APCI); *m/z* (%) = 400 (M+H, 100), 399 (M^+, 25). *Procedure B*: To a solution of ethyl isonipecotate (252 mg, 1.6 mmol) in DCE (1 mL) was added **2** (497 mg, 1.6 mmol). After stirring 3 days, the reaction was eluted on a flash chromatography column with diethyl ether to give **4** in 91% yield.

Ethyl 4-(N,N'-bis-BOC-guanyl)-benzoate **5**: mercury(II) chloride (5.5 mmoles, 1.49 g) was added to the solution of ethyl 4-aminobenzoate (5 mmol, 0.76 g), and **1** (5 mmol, 1.38 g) in DCE (5 mL) and DMF (5 mL); a slight exotherm occurred and the reaction became opaque. Following 40 h stirring, the reaction was filtered through Celite to remove HgS and the filtrate was concentrated to dryness. Purification gave **5** (1.65 g, 84%); ^{1}H NMR ($CDCl_3$) δ 11.30 (bs, 1 H), 7.89 (d, 2 H, *J* = 9 Hz), 6.66 (d, 2 H, *J* = 9 Hz), 4.32 (q, 2 H, *J* = 7 Hz), 1.51 (s, 9 H), 1.49 (s, 9 H), 1.48, (t, 3 H, *J* = 7 Hz); MS (APCI); *m/z* (%) = 394 (M+H, 100), 393 (M^+, 18). Prepared according to Procedure B, ethyl 4-aminobenzoate (1.4 mmol, 211 mg) and **2** (1.4 mmol, 434 mg) in DCE (1 mL) and DMF (1 mL) was stirred for 72 h. Purification yielded **5** (352 mg, 64%).

3-N,N'-bis-BOC-guanylphenylacetamide **6**: A solution of 3-aminophenylacetamide (66 μmol, 9.9 mg) and **2** (66 μmol, 20.4 mg) in DCE (1 mL) and DMF (2 mL) was stirred for 11 days at 60°C. Purification granted **6** (17 mg, 66%); ^{1}H NMR (acetone-d_6) δ 9.60 (bs, 1 H), 8.36 (s, 1 H), 7.78 (d, 2 H), 7.7-7.4 (m, 2 H), 7.38-7.02 (m 2 H), 6.55 (s, 1 H), 3.0 (d, 2 H), 1.55 (s, 9 H) 1.53 (s, 9 H); MS (APCI); *m/z* (%) = 393 (M+H, 100), 392 (M^+, 23).

Solid Phase:

Wang FMOC 4-aminomethylbenzoate ester **7**: To a mixture of Wang resin (10 g, 6 mmol), Fmoc 4-aminomethylbenzoate (17.92 g, 48 mmol), DICDI (6.06 g, 48 mmol), N-hydroxy-benzotriazole (HOBT) (6.49 , 48 mmol) in DCM (80 mL) and DMF (20 mL) was added DIPEA

(2.32 g, 18 mmol). The mixture was agitated for 64 h, collected on a glass frit and rinsed with the wash solvents (100 mL each). Drying in an N_2 atmosphere gave **7** (0.36 meq/g by cleavage).

Wang FMOC isonipecotate ester **8**: In a similar reaction to **7**, Wang resin (10 g, 6 mmol) was combined with FMOC isonipecotic acid (16.86 g, 48 mmol) to give **8** (0.59 meq/g by cleavage).

Rink Amide AM FMOC 4-aminobenzoate amide **9**: In a manner similar to **7**, Rink Amide AM (1.07 g, 0.57 mmol, 0.54 meq/g) was reacted with FMOC 4-aminobenzoic acid (0.83 g, 4.6 mmol) to give **9** (0.54 meq/g).

Rink Amide AM FMOC 3-aminophenylacetate amide **10**: In the same manner as **9**, Rink Amide AM (6.24 g, 2.93 mmol, 0.47 meq/g) was combined with FMOC 3-aminophenylacetic acid (4.38 g, 11.7 mmol) to yield **10** (0.46 meq/g by cleavage).

4-Guanylmethylbenzoic acid, trifluoroacetic acid salt **11**: *Procedure C:* to the mixture of resin **7** (70 mg, 25 μmol) and **1** (14 mg, 50 μmol) was added DICDI (6 mg, 50 μmol) in DCE (8 mL). After 9 days of agitation, the resin was washed with 10 mL of each rinse solvent. Drying, cleavage and purification gave **11** (6.7 mg, 87%) as the TFA salt ^{1}H NMR(DMSO-d_6) δ 12.5 (bs, 2 H), 8.45 (bs, 2 H), 8.20 (bs, 1 H), 7.86 (d, 2 H, J = 8 Hz), 7.33 (d, 2 H, J = 8 Hz), 3.81 (d, 2 H); MS (APCI); *m/z* (%) = 194 (M+H, 89), 193 (M^+, 17), for free base. *Procedure D:* to the mixture of **7** (85 mg, 31 μmol) and DCE (8 mL) was added **2** (19 mg, 62 μmol). After agitation for 9 days, the resin was washed with 10 mL of each rinse solvent. Drying, cleavage and purification gave **11** (8.6 mg, 86%).

N-guanylisonipecotic acid, trifluoroacetic acid salt **12**: prepared according to procedure C, resin **8** (100 mg, 59 μmol) was combined with **1** (1.5 eq) and reacted for 4 days. After the same workup, cleavage and purification, **12** (9 mg, 97%) was obtained. ^{1}H NMR(DMSO-d_6) δ 12.5 (bs, 2 H), 8.45 (bs, 2 H), 8.20 (bs, 1 H), 3.19 (m, 2 H), 2.89 (m, 2 H), 2.53 (m, 1 H), 1.93 (m, 2 H), 1.64 (m, 4 H); MS (APCI); *m/z* (%) = 422 (100), 172 (M+H, 27), 171(M^+, 8), for free base. Prepared

according to procedure D, resin **8** (54.4 mg, 32 μmol) was combined with **2** (2 eq) and reacted for 10 days. After workup, cleavage and purification, **12** (8 mg, 72%) was obtained.

4-Guanylphenylcarboxamide, trifluoroacetic acid salt **13**: prepared according to procedure C, resin **9** (63 mg, 34 μmol), **1** (11 mg, 41 μmol) in DCE (4 mL) and DMF (4 mL) was added mercury(II) chloride (19 mg, 41μmol) and the resulting mixture was agitated for three days. The usual workup and purification gave **13** (4.0 mg, 40%) ^{1}H NMR(DMSO-d_6) δ 12.5 (bs, 2 H), 10.01 (s, 1 H), 8.44 (bs, 2 H), 8.21 (bs, 1 H), 7.90 (d, 2 H, *J* = 8 Hz), 7.26 (d, 2 H, *J* = 8 Hz), MS (APCI); *m/z* (%) = 179(M+H, 15), 178 (M^+, 100), for free base. Prepared according to procedure D, resin **9** (70 mg, 38 μmol) and **2** (24 mg, 76 μmol) in DCE (8 mL) was agitated for 3 days. Workup, cleavage and purification yielded **13** (8 mg, 72%).

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[1] Rathke, B. *Chem. Ber.*, **1881**, *14*, 1774. Rathke, B. *Chem. Ber.*, **1884**, *17*, 297.

[2] Schow, S. "Cyanamide" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 1408-1410.

[3] Other reagents for the synthesis of guanidines include; Palmer, D. C. "S-Methylisothiourea" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 3523-3525. Cheon, S. H. "S-Methylisothiosemicarbazide" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 3522-3523. Campopiano, O. "Thiourea" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 4885-4886. "Thiourea Dioxide" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 4886-4888. Garratt, P. J. "Diphenyl Cyanocarbonimidate" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 2205-2207. Palmer, D. C. "O-Methylisourea" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 3525-3526. Bernatowicz, M. S. "1*H*-Pyrazole-1-carboxamidine Hydrochloride" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 4343-4344. Miller, A., Palmer, D. C. "Aminoiminomethanesulfonic Acid" *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. Ed., Wiley, Sussex UK, 1996, Vol p 176-178.

[4] Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497-2502. Tian, Z.; Roeske, R. W. *Int. J. Peptide Protein Res.* **1991**, *37*, 425-429.

[5] Iwanowicz, E. J.; Poss, M. A.; Lin, J. *Syn. Commun.* **1993**, *23*(10), 1443-1445. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*(48), 7677-7680. Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z.*Tetrahedron Lett.* **1992**, *33*(40), 5933-5936. Verdini, A. S.; Lucietto, P.; Fossati, G.; Giordani, C. *Tetrahedron Lett.* **1992**, *33*(43), 6541-6542.

[6] Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*(21), 3389-3392. Wu, Y.; Matsueda, G. R.; Bernatowicz, M. S. *Synthetic Commun.* **1993**, *23*(21), 3055-3060. Drake, B.; Patek, M. LeBel, M. *Synthesis* **1994**, *6*, 579-582.

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