Facile and Efficient Guanylation of Amines Using Thioureas and Mukaiyama's Reagent

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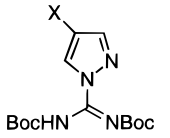
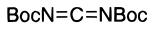
With the growing importance of peptides and peptidomimetics in a variety of disciplines, the need for efficient methods of synthesizing guanidines has increased, resulting in the recent development of several new reagents for the guanylation of amines.[1−5] During a recent solid phase synthesis of a guanidine-containing cyclic dipeptide,[6] we were confronted with the need for an efficient method for the guanylation of resin-bound amines. Initial studies led to the development of 4-nitro-1*H*-pyrazole-1-*N*,*N*′-bis(*tert*-butoxycarbonyl)carboxamidine (**1a**),[7] a more electrophilic variant of the literature reagent 1*H*-pyrazole-1-[*N*,*N*′-bis(*tert*-butoxycarbonyl)]carboxamidine (**1b**).[4] Dissatisfaction with the need for multiple equivalents of **1** to completely guanylate resin-bound amines led to a reexamination of the fastest and



1a X=NO_2
1b X=H



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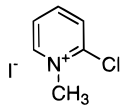

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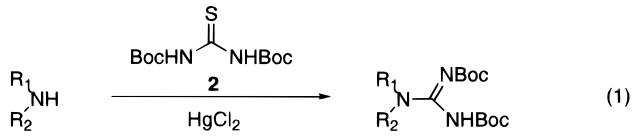
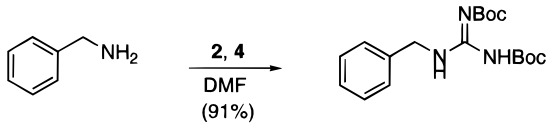
most efficient of the literature methods, treatment of amines with a *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea (**2**) and mercuric chloride (eq 1).[5a] Although, owing to the formation of insoluble mercuric sulfide precipitate, this reaction is not applicable to solid phase guanylation, it provides the basis for the development of improved reagents.



(1)

It has been suggested that the remarkable facility of the reaction shown in eq 1 results from the formation of *N*,*N*′-bis(*tert*-butoxycarbonyl)carbodiimide (**3**), a highly electrophilic intermediate.[5a] Operating on this assumption, other reagents known to promote formation of carbodiimides from thioureas were examined as replacements for mercuric chloride. Of the various candidates, Mukaiyama's reagent (**4**)[8] proved attractive since it is known to be compatible with amines. In the event, treatment of *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea (**2**) with **4** in the presence of benzylamine resulted in the rapid and complete consumption of amine and formation of the desired *N*,*N*′-bis(*tert*-butoxycarbonyl)guanidine (**5**) in 91% yield (eq 2).



(2)

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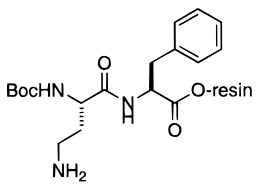
A representative sample of amines was subjected to reaction with **2** and **4** under a variety of conditions (Table 1). From these data, several conclusions can be reached. First, primary and unhindered secondary amines can generally be guanylated in high (>80%) yield using a slight excess of reagent in anhydrous DMF (entries 1−4). Second, for hindered or unreactive amines (entries 7 and 8) the use of methylene chloride as solvent can provide a substantial increase in yield over reactions run in DMF (entries 5 and 6). The effect of solvent on yield most likely results from the instability of the carbodiimide intermediate **3**: when nucleophilic attack by an amine is slow, a competitive decomposition of the carbodiimide leads to loss of reagent and thus lower yield. Support for this view comes from the recovery of unreacted amine in entries 5 and 6. When methylene chloride is used as solvent instead, the reactions are heterogeneous owing to the sparing solubility of **4**; it is believed that this results in a slower production of **3** and, consequently, its more efficient consumption by less reactive amines.

The guanylation of resin-bound amines under these conditions was also examined. The side-chain amino functionality of two peptides, **6** and **7**, bound to the



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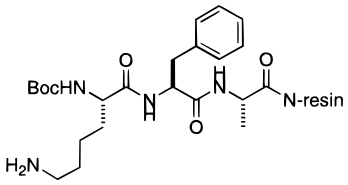

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Merrifield[9] and Rink[10] resins, respectively, were guanylated using three different reagents: **1a**, **1b**, and our new conditions. Reactions were monitored by the loss of amine, as judged by qualitative and quantitative ninhydrin assays.[11] As with other slowly reacting amines, reactions using **2** and **4** were found to improve markedly when methylene chloride was used as solvent. When DMF was used, **4** had to be repeatedly added in portions over 3 h to effect complete reaction. In contrast, guanylation in methylene chloride resulted in complete consumption of amine in 3 h using 3 equiv of reagent. Although the reaction was heterogeneous, washing the resin with DMF removed the precipitate, permitting the successful isolation of guanylated peptide. Reactions

(1) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497. See refs 3−6 for earlier methods.
(2) Kim, K.; Lin, Y.-T.; Mosher, H. S. *Tetrahedron Lett.* **1988**, *29*, 3183.
(3) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389.
(4) Drake, B.; Patek, M.; Lebl, M. *Synthesis* **1994**, 579.
(5) (a) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677. (b) Su, W. *Synth. Commun.* **1996**, *26*, 407.
(6) Kowalski, J. A.; Lipton, M. A. *Tetrahedron Lett.* **1996**, *37*, 5839−5840.
(7) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *Tetrahedron Lett.* **1997**, in press.
(8) Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 575.
(9) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149−2154.
(10) Rink, H. *Tetrahedron Lett.*. **1987**, *28*, 3787−3790.
(11) Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147.

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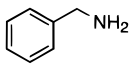
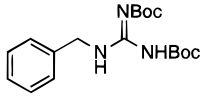
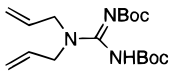
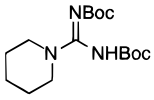
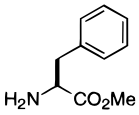
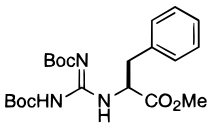
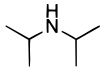
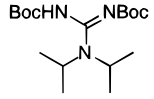
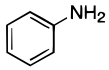
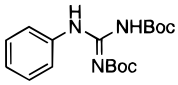
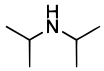
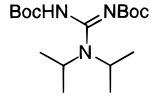
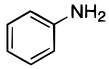
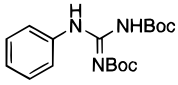
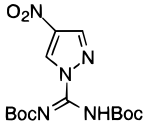
Table 1. Conversion of Various Amines to Guanidines Using Mukaiyama's Reagent

Entry	Substrate	Solvent	Product	Yield, %[a]
1		DMF	 **(5)**	91
2		DMF	 **(6)**	86
3		DMF	 **(7)**	57
4		DMF	 **(8)**	85
5		DMF	 **(9)**	21[b]
6		DMF	 **(10)**	34[b]
7		CH_2Cl_2	 **(9)**	71
8		CH_2Cl_2	 **(10)**	92
9		DMF	 **(11)**	43

[a] Isolated yield after chromatography [b] Unreacted starting material recovered.

using **1a** and **1b** were substantially less efficient, **1a** requiring 4 equiv of reagent and 24 h to completely consume amine, and **1b** failing to completely guanylate the amine after 3 days even when 8 equiv were used.

In conclusion, the use of thioureas and **4** to for the guanylation of amines would appear to have several advantages over existing methods. Like methods employing mercuric chloride,[5] these new conditions afford high yields of guanidines, even relatively unreactive ones. In addition, we believe that this new guanylation reaction represents the best method for guanylating resin-bound amines. Moreover, the use of **4** instead of mercuric chloride eliminates the environmental hazard of heavy metal waste without appreciable loss of yield or reactivity. It is anticipated that this new method will find wide application in the synthesis of protected guanidines.

Experimental Section

Guanylation of Primary and Unhindered Secondary Amines (General Procedure). To a solution of amine (40 μL, 0.366 mmol, 1 equiv) in anhydrous DMF (120 μL) were added *N,N′*-bis(*tert*-butoxycarbonyl)thiourea (121 mg, 0.439 mmol, 1.2 equiv) and triethylamine (113 μL, 0.806 mmol, 2.2 equiv). A suspension of Mukaiyama's reagent (112 mg, 0.439 mmol, 1.2 equiv) in anhydrous DMF (240 μL) was added dropwise via syringe to the reaction mixture and the reaction allowed to stir at 25 °C. When the reaction had reached completion as judged by TLC, the reaction was diluted with water (360 μL) and extracted with diethyl ether (3 × 360 μL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford the crude guanidine. The guanidines were purified by flash chromatography.

Guanylation of Hindered and Unreactive Amines (General Procedure). To a solution of amine (12 μL, 0.132 mmol, 1 equiv), *N,N′*-bis(*tert*-butoxycarbonyl)thiourea (44 mg, 0.158 mmol, 1.2 equiv), and triethylamine (41 μL, 0.290 mmol, 2.2 equiv) in CH_2Cl_2 (1.3 mL) was added Mukaiyama's reagent (40 mg, 0.158 mmol, 1.2 equiv). The reaction was allowed to stir at 25 °C until completion, as judged by TLC. Upon completion, the reaction was evaporated, and the residue redissolved in diethyl ether (2 mL) and washed with water (2 mL). The organic layer was dried ($MgSO_4$), the solvent removed *in vacuo*, and the product purified by flash chromatography.

***N,N′*-Bis(*tert*-butoxycarbonyl)-*N″*-benzylguanidine (5):**[4] mp = 126−127 °C; ^{1}H-NMR($CDCl_3$, 200 Hz): δ 8.61 (br s, 1H), 7.32 (m, 5H), 4.64 (d, J = 5.1, 2H), 1.52 (s, 9H), 1.48 (s, 9H); ^{13}C-NMR($CDCl_3$, 50 MHz): δ 163.9, 156.5, 153.6, 137.6, 129.2, 128.3, 128.1, 83.7, 80.0, 45.6, 28.8, 28.5; IR (KBr): 1741.4, 1654.0, 1625.7, 1559.8 cm^{-1}.

***N,N′*-Bis(*tert*-butoxycarbonyl)-*N″,N″*-diallylguanidine (6):** mp = 74−75 °C; ^{1}H-NMR($CDCl_3$, 200 Hz): δ 5.71−5.87 (m, 2H), 5.16−5.18 (m, 2H), 5.22−5.26 (m, 2H), 4.03 (d, J = 5.9, 4H), 1.48 (s, 18H); ^{13}C-NMR($CDCl_3$, 50 MHz): δ 163.0, 155.5, 151.3, 133.3, 119.0, 82.3, 79.9, 50.9, 28.6; IR (KBr): 1746.4, 1683.3,

1642.4, 1581.5, 1500.0 cm^{-1}. Anal. Calcd for $C_{17}H_{29}N_3O_4$: C, 60.15; H, 8.61; N, 12.38. Found: C, 60.47; H, 8.90; N, 12.42.

1-[*N*,*N*′-Bis(*tert*-butoxycarbonyl)carboxamidino]-piperidine (7): mp = 111−113 °C; ^{1}H-NMR($CDCl_3$, 200Hz): δ 3.49 (br s, 4H), 1.61 (br s, 6H), 1.47 (s, 18H); ^{13}C-NMR($CDCl_3$, 50 MHz): δ 155.5, 46.5, 28.6, 28.5, 26.2, 24.8; IR (NaCl): 1744.7, 1653.0, 1628.5, 1611.5 cm^{-1}. Anal. Calcd for $C_{16}H_{29}N_3O_4$: C, 58.69; H, 8.93; N, 12.83. Found: C, 58.89; H, 9.14; N, 12.66.

Methyl (*S*)-2-[*N*,*N*′-Bis(*tert*-butoxycarbonyl)guanidino]-3-phenylpropionate (8): ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 8.77 (br d, J = 7.4, 1H), 7.13−7.33 (m, 5H), 5.03−5.13 (m, 1H), 3.70 (s, 3H), 3.15 (dd, J = 7.41, 6.22, 1H), 3.25 (dd, J = 8.06, 5.78, 1H), 1.48 (s, 9H), 1.49 (s, 9H); ^{13}C-NMR($CDCl_3$, 50 MHz): δ 172.1, 163.8, 155.9, 153.2, 136.3, 129.9, 129.0, 127.6, 83.7, 79.8, 55.1, 52.8, 38.5, 28.8, 28.5; IR (KBr): 1746.8, 1725.5, 1639.7, 1617.1 cm^{-1}. $[\alpha]^{25}_D$ +35.7° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{31}N_3O_6$: C, 59.84; H, 7.41; N, 9.97. Found: C, 60.05; H, 7.65; N, 10.22.

***N*,*N*′-Bis(*tert*-butoxycarbonyl)-*N*″,*N*″-diisopropylguanidine (9):**[5a,b] mp = 104−105 °C; ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 8.28 (br s, 1H), 3.85−3.90 (m, 2H), 1.47 (s, 18H), 1.34 (s, 6H), 1.30 (s, 6H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 162.3, 152.1, 151.9, 81.8, 78.1, 48.9, 28.8, 28.6, 21.3; IR (KBr): 1743.8, 1654.9, 1602.8 cm^{-1}.

***N*,*N*′-Bis(*tert*-butoxycarbonyl)-*N*″-phenylguanidine (10):**[3,4] mp = 134−136 °C; ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 7.59−7.63 (m, 2H), 7.26−7.36 (m, 2H), 7.07−7.15 (m, 1H), 1.54 (s, 9H), 1.51 (s, 9H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 164.1, 154.0, 153.8, 137.3, 128.4, 125.2, 122.6, 84.2, 80.1, 28.7, 28.6; IR (KBr): 1727.1, 1637.7, 1597.9, 1562.1 cm^{-1}.

2-Nitropyrazole-1-*N*,*N*′-bis(*tert*-butoxycarbonyl)carboxamidine (11): mp = 51−53 °C; ^{1}H-NMR ($CDCl_3$, 200 Hz): δ 9.04 (s, 1H), 8.17 (s, 1H), 1.45−1.55 (m, 18H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 156.6, 149.3, 138.5, 137.6, 128.0, 84.9, 83.0, 77.7, 28.5; IR (NaCl): 1774.9, 1717.7, 1686.6, 1553.5, 1505.9 cm^{-1}. Anal. Calcd for $C_{14}H_{21}N_5O_6$: C, 47.32; H, 5.96; N, 19.71. Found: C, 47.51; H, 6.15; N, 19.86.

Guanylation of Resin-Bound Amines (General Procedure). A suspension of resin (50 mg, 23 μmol of amine, 1 equiv) in CH_2Cl_2 (0.75 mL) was treated with triethylamine (13 μL, 92 μmol, 4.0 equiv) and *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea (19 mg, 69 μmol, 3.0 equiv) and the resulting mixture shaken. After 15 min, Mukaiyama's reagent (18 mg, 69 μmol, 3.0 equiv) was added and the reaction allowed to shake for 3 h. The reaction was judged complete by ninhydrin assay.[11]

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