A Versatile One-Pot Synthesis of 1,3-Substituted Guanidines from Carbamoyl Isothiocyanates

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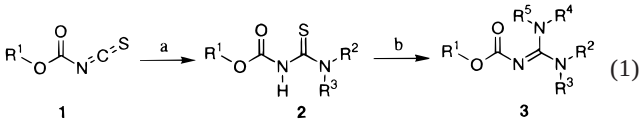
Recent advances have demonstrated the importance of the guanidine group in receptors capable of binding molecular anions.[1,2] The need for more complex receptors required a new protocol for creating highly substituted guanidines under mild conditions. Several new methods have been developed that use carbamate protection to reduce the basicity of guanidines, simplifying purification.[3−8] While these methods permit the mild guanidinylation of amines to form monosubstituted guanidines, most do not allow the formation of highly functionalized guanidines. Synthesis of multisubstituted guanidines has been accomplished primarily with unprotected isothiouronium salts[9] or imino carbonates[10] or using protocols requiring treatment with strong base.[11−13] We wished to take advantage of the benefits of carbamate-protected guanidines, but with a protocol that allowed the formation of 1,3-multisubstituted guanidines from two separate amines.

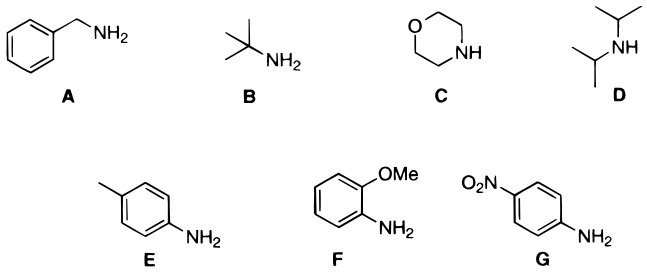
This procedure, shown in eq 1, exploits several advantages of carbamoyl isothiocyanates **1**. These reagents



(1)

a.) R^2R^3NH, CH_2Cl_2/THF; b.) R^4R^5NH, EDCI, CH_2Cl_2.

Table 1. Reaction of Ethoxycarbonyl Isothiocyanate with Various Amines To Form Thiourea 2 and Guanidine 3



amine	% yield of thiourea **2**	% yield of guanidine **3**						
		A	**B**	**C**	**D**	**E**	**F**	**G**
A	99	99	99	95	76	92	82	85
B	99	99	74	59	55	99	99	65
C	99	0	0	0	0	0	0	0
D	99	0	0	0	0	0	0	0
E	92	99	87	99	81	95	97	34
F	77	96	99	61	84	98	67	39
G	72	85	76	99	42	35	34	0

provide a protecting group throughout the synthesis, making purification trivial, without the later inclusion of a protection step. The carbamate increases the reactivity of the isothiocyanate, permitting formation of thiourea **2** even with hindered amines. A second amine can be coupled to the carbamoyl thiourea **2** using EDCI,[4] forming 1,3-disubstituted and 1,1,3-trisubstituted guanidines through either stepwise or one-pot synthesis.

To gauge the steric and electronic limitations of this procedure, amines of varying reactivity (**A**−**G**) were investigated for their ability to form protected thiourea **2** and guanidine **3**. The synthetic yields for this series of reactions with ethoxycarbonyl isothiocyanate and amines **A**−**G** are shown in Table 1. Formation of thiourea **2** proceeded in near quantitative yields for alkylamines (**A**−**D**), while aromatic amines (**E**−**G**) produced slightly lower yields. Each amine has a dual effect on guanidine synthesis: reactivity of the amine with various thioureas as well as coupling efficiency of the thiourea formed from that amine. Both showed a steric effect as yields decreased with bulkier substituents. Most noticeably, both thioureas formed from secondary amines (**2C** and **2D**) failed to form guanidines in detectable yields. It is unclear if this results from increased steric bulk limiting nucleophile attack or from the removal of a reactive proton. Trisubstituted guanidines can be formed, however, through the coupling of unencumbered thioureas with secondary amines, albeit in lower yields than with primary amines. Aromatic amines were also successful in both aspects of guanidinylation, with both phenylamine and the more sterically hindered 2-methoxyphenylamine producing guanidinium in good yields. The electronic nature of the 4-nitrophenylamine reduces the efficiency of the reaction of this amine to form guanidine as well as the coupling with the corresponding thiourea, producing lower yields in each case.

The generality of this procedure for other carbamoyl isothiocyanates allows synthetic flexibility in the final

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(13) Of notable exception is the method of Dodd and Wallace (Dodd, D.; Wallace, O. B. *Tetrahedron Lett.* **1998**, *39*, 5701−5704) which permits the solid-phase synthesis of *N*,*N*′-disubstituted guanidines.

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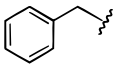
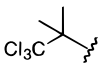
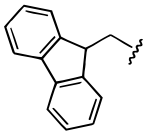
Table 2. Yields of Reaction Products for Various Protecting Groups ($R_2 = R_4 = Bn$, $R_3 = R_5 = H$)

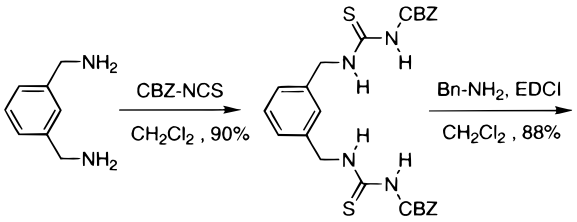
R^1	1	2	3
	Commercially Available	99	99
	80	97	99
	99	97	75
	64	97	Carbamate Cleavage
	90	95	Carbamate Cleavage

deprotection step. In addition to the ethyl carbamate employed above, benzyl carbamate (Cbz), 2,2,2-trichloro-1,1-dimethylethyl carbamate, fluorenylmethyl carbamate (Fmoc), and phenyl carbamate were investigated for their potential to participate in the guanidine synthesis as in eq 1. In each case, carbamoyl isothiocyanate **1** was converted to thiourea **2** with benzylamine and coupled with a second equivalent of benzylamine to form guanidine **3**. These yields are listed in Table 2.

While ethoxycarbonyl isothiocyanate was commercially available, all other carbamoyl isothiocyanates **1** were synthesized from the corresponding chloroformate and potassium thiocyanate. Several reports list acetonitrile or ethyl acetate as reaction solvents,[14−16] however yields of benzyloxycarbonyl isothiocyanate [**1**, $R^1 = Bn$] and fluorenylmethoxycarbonyl isothiocyanate [**1**, $R^1 = (C_{13}H_9)$-CH_2] were maximized using 20% acetonitrile/toluene, which reduced the production of alternate products formed by the ambident thiocyanate nucleophile.[17] Other carbamoyl isothiocyanates **1** were synthesized using this same procedure and are stable in the refrigerator for months. Reaction of carbamoyl isothiocyanate **1** with benzylamine to form thiourea **2** proved trivial, with high yields being observed in every case. Coupling of thiourea with amine was limited, however, by the stability of the carbamate under the reaction conditions. While benzyloxycarbonyl thiourea [**2**, $R_1 = Bn$] and 2,2,2-tricloro-1,1-dimethylethyl thiourea [**2**, $R_1 = Cl_3CC(CH_3)_2$] efficiently formed guanidine **3**, Fmoc and phenyl carbamate failed to produce guanidine in appreciable yields. In these cases the carbamates were not stable to the basic reaction conditions and resulted in protecting group cleavage. It appears that any carbamate capable of withstanding the coupling conditions will be applicable to this protocol.

An additional advantage of this method is the creation of multisubstituted guanidines using a one-pot synthesis. Highly reactive carbamoyl isothiocyanates reacted smoothly with equimolar amounts of amine to form thioureas in high yield and purity. Addition of a second amine, base, and the coupling reagent resulted in the formation of the protected guanidine **3**, without purification of the initial thiourea **2**. Dibenzylethoxycarbonylguanidine **3AA** was formed in 98% yield through a one-pot reaction starting from ethoxycarbonyl isothiocyanate, while asymmetric *N*-benzyl-*N′*-butyl-*N″*-ethoxycarbonylguanidine **3AB** was formed in 80% yield. It is recommended that carbamoylguanidines be purified prior to deprotection due to the polarity of the guanidinium product.

Synthetic difficulty increases with molecules containing more than one guanidine due to the accumulation of charge, making purification more challenging. Using this protocol, there are no highly polar or charged intermediates which may be formed using existing methods. The constant presence of a carbamoyl group in this protocol permits all intermediates to be purified through standard organic chromatography. As an example, bis-guanidine **5** (eq 2) was synthesized in a 79% overall yield from the two-step reaction of benzyloxycarbonyl isothiocyanate [**1**, $R^1 = Bn$] with xylylenediamine to form bis-carbamoyl thiourea **4**, and subsequent coupling with benzylamine.



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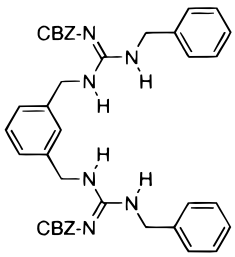

(2)

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Carbamoyl isothiocyanates are ideal starting materials for the synthesis of multisubstituted guanidines. The electron-withdrawing protecting groups reduce the basicity of guanidines, making them more easily handled through standard organic techniques. The coupling of amine to protected thiourea occurs under mild conditions and without producing unpleasant side products. The nature of these carbamoyl thioureas permits creation of disubstituted and trisubstituted guanidines, as well as aromatic guanidines. The success of this protocol in a one-pot synthesis of guanidines further underscores the ease and efficiency of this protocol.

Experimental Section

General Procedure for the Preparation of Carbamoyl Isothiocyanates (1). A saturated solution of potassium thiocyanate (40 g) in boiling ethanol (300 mL) was poured into 1.5 L of ethyl ether, forming a fine, white powder. The solid was collected by filtration and washed

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with 300 mL of ethyl ether, before being dried in vacuo over P_2O_5. Finely powdered potassium thiocyanate was isolated (33 g, 82%).

Alkyl chloroformate (20 mmol) was slowly added to a well-stirred suspension of freshly powdered potassium thiocyanate (10 g, 110 mmol) in 250 mL of 20% toluene/acetonitrile. After 2 days of stirring, no chloroformate was detectable by TLC (silica, 20% dichloromethane/hexanes). The reaction mixture was filtered through Celite, and the solid was washed twice with toluene (50 mL). Solvent was removed in vacuo with mild heating, before isolating the carbamoyl isothiocyanate by distillation or silica gel chromatography.

General Procedure for the Preparation of Carbamoyl Thioureas (2). A solution of carbamoyl isothiocyanate **1** (1.0 mmol) in 50 mL of dichloromethane was cooled to 0 °C before adding alkylamines **A**−**G** (1.0 mmol). The ice bath was removed, and the solution was stirred for 4 h under nitrogen. The solution was washed with 1% HCl, water, and brine and dried with Na_2SO_4. Solvent was removed under reduced pressure, yielding a white solid. As an alternative to extractive workup, the reaction mixture can be poured into 50 mL of pentane. The white solid that formed was collected by filtration and dried in vacuo.

General Procedure for the Preparation of Carbamoyl Guanidines (3). Carbamoyl thiourea **2** (1.0 mmol), alkylamines **A**−**G** (1.5 mmol), and diisopropylethylamine (1.0 mmol) were added to 10 mL of anhydrous dichloromethane and cooled to 0 °C. EDCI (1.5−2.0 mmol) was added, and the solution was stirred under nitrogen. After 1 h the ice bath was removed and the solution was stirred for an additional 10 h at room temperature. In cases where TLC indicated unreacted starting material, addition of more amine and EDCI resulted in increased yields. The reaction mixture was washed with 1% HCl, water, and brine and dried with Na_2SO_4. The residue that remained after removal of solvent under reduced pressure was purified by silica chromatography.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, HRMS, and elemental analyses for all compounds discussed herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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