Diprotected Triflylguanidines: A New Class of Guanidinylation Reagents

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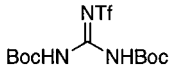
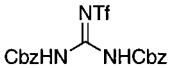
The guanidino group is an important structural component in many biologically active compounds.[1] Because of their strongly basic character, guanidines are fully protonated under physiological conditions. The positive charge thus imposed on the molecule forms the basis for specific interactions between ligand and receptor or enzyme and substrate, mediated by hydrogen bonds and/or electrostatic interactions. Consequently, synthetic procedures that allow the preparation of guanidines with high yield and under mild conditions are of great interest in medicinal chemistry. Typically, the synthesis of guanidines involves treatment of an amine with an electrophilic amidine species. The most commonly used reagents include derivatives of pyrazole-1-carboxamidine, *S*-alkylisothioureas, and protected thiourea derivatives, the latter mostly used in conjunction with mercury salts or Mukaiyama's reagent.[2−11]

We now wish to report *N*,*N*′-di-Boc-*N*″-triflylguanidine **1** and *N*,*N*′-di-Cbz-*N*″-triflylguanidine **2** as two examples of diprotected triflylguanidines, a new class of guanidinylation reagents. Both compounds are stable crystalline substances that allow the preparation of protected guanidines with exceptional ease and efficiency. The starting material guanidine hydrochloride is cheap and readily available in large quantities.



1



2

Reagent **1** is obtained in two steps from guanidine hydrochloride **3** in 51% overall yield (Scheme 1). Reaction of **3** with Boc-anhydride under strongly alkaline conditions produces intermediate **4**, which is easily converted to target compound **1** with triflic anhydride. In a similar sequence of reactions, the synthesis of reagent **2** commences with the conversion of guanidine hydrochloride to *N*,*N*′-di-Cbz-guanidine **5**. Contrary to the synthesis of reagent **1**, the final sulfonation step is carried out with sodium hydride as a base in place of triethylamine. Both **1** and **2** are stable, crystalline substances which have been stored at room temperature for at least three months with no apparent loss of activity; hence, these compounds should remain stable indefinitely if refrigerated.

Scheme 1

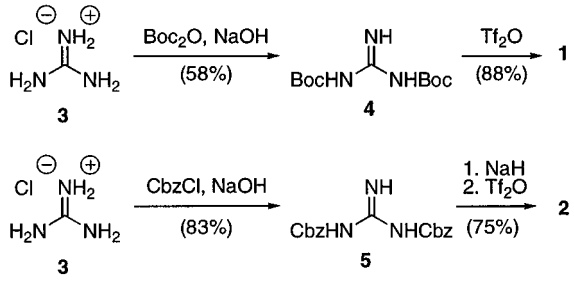
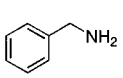
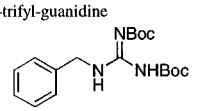
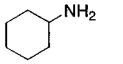
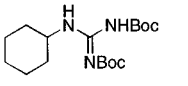
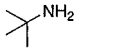
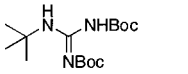
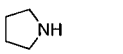
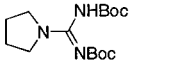
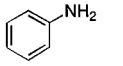
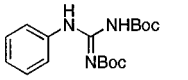
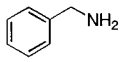
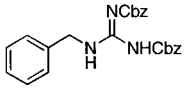
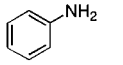
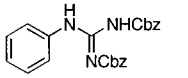


Table 1. Guanidinylation of Amines with Diprotected Triflyl-guanidines

Entry	Amine	Conditions	Product	Yield (%)[a,b]
Section I. Guanidinylations with N,N'-di-Boc-N"-trifyl-guanidine				
1		CH_2Cl_2 0.5 h, rt		100
2		CH_2Cl_2 1 h, rt		99
3		CH_2Cl_2 8 h, reflux		75
4		CH_2Cl_2 2 h, rt		96
5		CH_2Cl_2 24 h, rt		89
Section II. Guanidinylations with N,N'-di-Cbz-N"-trifyl-guanidine				
6		$CHCl_3$ 1 h, rt		94
7		$CHCl_3$ 1 h, rt		98

[a] Isolated yield after chromatography. [b] Diisopropylamine showed no reaction.

To investigate the scope and limitations of our new reagents, a series of structurally different amines was subjected to reaction with compounds **1** or **2**. The results are illustrated in Tables 1 and 2. Dichloromethane or chloroform was employed as a solvent in all examples. Although guanidinylations have been successfully carried out in polar solvents such as DMF or methanol (data not shown), the reactions proceed faster in nonpolar solvents. In a typical reaction (procedure A), a slight excess of the amine was added in one portion to a solution of either **1** or **2** and 1 equiv of triethylamine, and the course of the reaction was followed by TLC. After completion of the reaction, triethylamine and the byproduct triflic amide were removed during a simple aqueous workup procedure. Typically, the crude products obtained in this way were greater than 95% pure as evidenced by TLC and ^{1}H NMR. A different protocol (procedure B) was developed for the guanidinylation of N-α-protected ornithine derivatives (Table 2, entries 1 and 2) which are insoluble in dichloromethane. In this case the amino acids were first converted into soluble derivatives by silylation with methyl(trimethylsilyl)trifluoracetamide in refluxing dichloromethane under anhydrous conditions. The

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(5) Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977.
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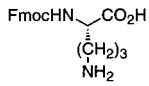
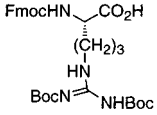
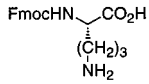
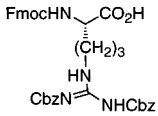
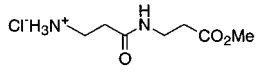
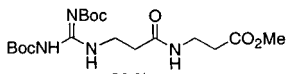
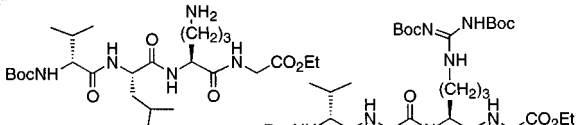
Table 2. Guanidinylation of Amino Acids and Peptides with Diprotected Triflyl-guanidines. All Reactions Performed in CH_2Cl_2 for 4 h at rt

Entry[a]	Amine	Product/Yield[b]
1[c]		 82%
2[c]		 85%
3[d]	 **6**	 86 % **7**
4[d]	 **8**	88 % **9**

[a] Isolated yield after chromatography. [b] Procedure B. [c] Procedure A.

guanidinylation was then achieved at room temperature without isolation of the silylated amino acid by adding a slight excess of either guanidine **1** or **2** and 1 equiv of triethylamine.

Several conclusions can be drawn from the results obtained. First, the guanidinylation of unhindered primary amines (Table 1, entries 1, 2) with reagent **1** is extremely facile, and very high yields were obtained in all cases investigated. Usually all starting material is consumed within several minutes at room temperature. Secondary (entry 4) and aromatic (entry 5) amines react somewhat slower, and the reactions take several hours to complete. However, the yields are also excellent. Difficulties are only observed with highly sterically hindered amines. *tert*-Butylamine (entry 3) reacts rather sluggishly at room temperature. However, a good yield is obtained in refluxing dichloromethane. Diisopropylamine as an example of a highly hindered amine shows no reaction even at elevated reaction temperatures (refluxing chloroform). Equally impressive are the results obtained with reagent **2** (entries 6 and 7, Table 1, entry 2, Table 2). Especially remarkable is the rapid reaction of aniline (entry 7, Table 1).

Two examples demonstrating the reactivity of reagent **1** with substrates of higher complexity are given in Table 2. Both the β-alanine dimer **6** and the tetrapeptide **8** could be guanidinylated in high yield and under mild conditions.

The guanidinylation of benzylamine was chosen as a model reaction to compare guanidine **1** with other reagents **10**−**12** described in the literature.[3,6,10,11] All reactions were carried out in 10 mM solution in the solvent recommended by the authors,[3,6,10,11] and the kinetics of product formation were followed by HPLC. The results and experimental

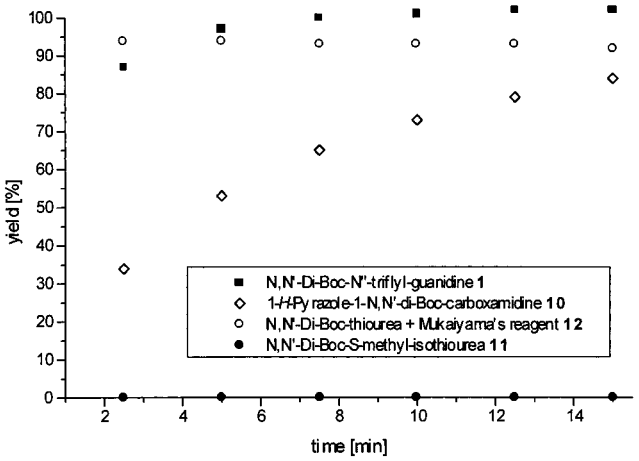
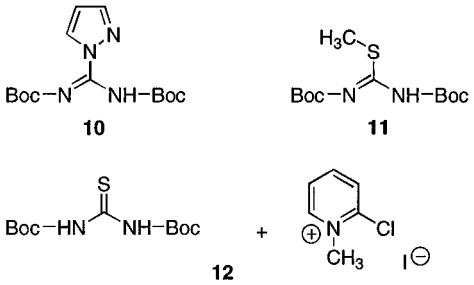


Figure 1. Comparison of different reagents using the guanidinylation of benzylamine as a model reaction. All data points constitute the average of two independent experiments. The yield of product was determined by HPLC using either biphenyl (reagents **10** and **12**) or phenanthrene (reagents **1** and **11**) as internal standards. Reactions with compounds **1**, **10,** and **11** were carried out at 10 mM solution at room temperature with a 1.5-fold excess benzylamine. In the experiment with reagent **12** the concentration of benzylamine was 10 mM and the concentration of reagent **12** was 20 mM. Attempts using a smaller excess of the reagents afforded much lower yields.

details are given in Figure 1. With both guanidine **1** and the combination of *N*,*N*′-di-Boc-thiourea and Mukaiyama's reagent[10] (reagent **12**), very rapid product formation was observed. The guanidinylation with pyrazole **10**[3,6] proceeded significantly slower, and isothiourea **11**[11] did not react to any extent under the conditions chosen. It should be noted that the concentrations used are chosen to show differences in reactivity and are not optimized for preparative purposes. At higher concentrations isothiourea **11** showed synthetically useful reaction rates.



In summary, both guanidine **1** and reagent combination **12** proved superior to the other reagents examined. Between these two alternatives, **12** seems to be superior in the guanidinylation of sterically hindered amines. However, experimental setup and product isolation with reagent **1** is much less demanding, making it the reagent of choice for most applications. We believe that our new reagents **1** and **2** will find widespread use in the synthesis of protected guanidines.

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Supporting Information Available: Typical experimental procedures and experimental data for all new compounds (6 pages).

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