Direct Guanylation of Amino Groups by Cyanamide in Water: Catalytic Generation and Activation of Unsubstituted Carbodiimide by Scandium(III) Triflate

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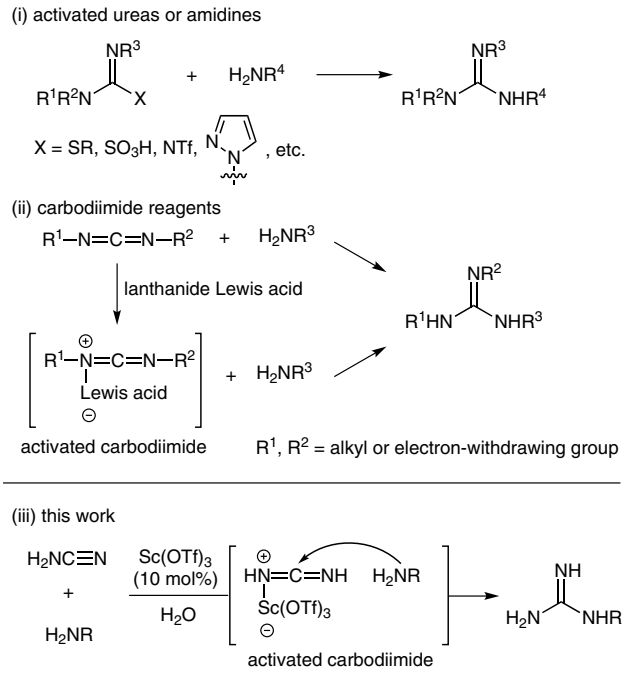
Abstract: Guanylation proceeded efficiently upon treatment of the various amines with cyanamide in the presence of catalytic amounts of scandium(III) triflate under mild conditions. The method did not require the guanylation reagents to be preactivated, and the reaction proceeded efficiently in water. The method, therefore, has practical utility for substrates that dissolve only in aqueous solutions, for example, peptides or pharmacologically important compounds.

Key words: guanylation, $Sc(OTf)_3$, cyanamide, activated carbodiimide

Guanidine moieties are found in the arginine groups of peptides as well as in many biologically active natural products and pharmacologically important compounds, such as the drugs Relenza or famotidine.[1] Guanidine groups play a variety of pivotal roles in biological processes. The transformation of an amino group to the corresponding guanidino group has been shown to improve the biological activity of a compound by, for example, increasing the cationic charge on the molecule and enhancing the cell permeability.[2] The development of a method for preparing guanidine groups from a variety of amines would constitute an important advance in synthetic organic chemistry.[3]

A large number of reactive reagents have been identified for efficiently transforming amines into guanidines. These reagents may be categorized into two groups (Scheme 1). The first group belongs to the urea- or amidine-based reagents, which contain good leaving groups[4–8] that are nucleophilically substituted by the amino groups. This group includes, for instances, chloroformamidines,[4] pyrazole-1-carboxamidines,[5] aminomethanesulfonic acids,[6] thioureas, and isothioureas,[7] or triurethanes and triflyldiurethanes.[8] The second group belongs to the activated carbodiimide derivatives.[9] These moieties are prepared in advance for addition reactions with amines under mild conditions. In most cases, carbodiimides, which are substituted by, for example, a carbamate or bulky alkyl group, are used to accelerate the nucleophilic addition of the amines and to stabilize the carbodiimides. Recently, lanthanide complexes were reported to accelerate the amino addition reaction to these carbodiimides. Wang and co-workers reported that ytterbium amide, $[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$, efficiently catalyzed the amine addition to the alkyl-substituted carbodiimides.[10] Shen and co-workers showed that the simple $Yb(OTf)_3$ catalyzed the addition of amines.[11] On the other hand, Looper and co-workers recently succeeded in generating a TMS-substituted carbodiimide in situ by the treatment of Cbz-substituted cyanamide with stoichiometric amounts of TMSCl, which was subsequently guanylated with various amine molecules in a one-pot process.[12]



Scheme 1 Guanylation of amino groups

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In pursuit of an efficient guanylation protocol that could be performed in aqueous media, we found that lanthanide carbodiimide complexes may be generated directly from the simplest unsubstituted cyanamide in the presence of lanthanide triflates in water, which smoothly reacted with a variety of amine nucleophiles. Based on this observation, we developed a protocol for the direct guanylation of various amines by mixing with cyanamide and catalytic amounts of scandium triflate [$Sc(OTf)_3$]. This reaction is the simplest protocol reported thus far and is the first reaction applicable to various water-soluble amine substrates and guanidine products, that is, biologically active natural products or peptides.

Guanidine derivatives have traditionally been prepared from unsubstituted cyanamide and the corresponding amines by heating the compounds in the presence of highly concentrated hydrochloric acid at 180 °C.[13,14] These protocols required harsh strongly acidic conditions, and the amines became protonated, which weakened the nucleophilicity. In most cases, excess amounts of cyanamide were required. The use of a Lewis acid in an aprotic organic solvent, for example, TMSOTf or $AlCl_3$ in dichrolomethane, can improve the efficiency of the protocol and require milder conditions.[15,16] Based on these procedures, we further optimized the Lewis acid catalysts, especially those based on lanthanide complexes,[17] toward efficiently catalyzing the guanylation reaction in water. In most cases, the starting amines and the guanylation products, which displayed biological activities, were only soluble in aqueous media.

The reaction was optimized using aniline **1a** as the model amino substrate. Cyanamide (1.2 equiv) was heated to 100 °C in the presence of various Lewis acids (10 mol%) in water (Table 1). Although $Nd(OTf)_3$ was nearly inactive as a catalyst (Table 1, entry 1), the guanylation reaction proceeded in about a 10–20% yield in the presence of $Zn(OTf)_2$, $Cu(OTf)_3$, AgOTf, $InCl_3$, $La(OTf)_3$, and $Tm(OTf)_3$ (Table 1, entries 2–7). The use of $Y(OTf)_3$ moderately accelerated the reaction, and the corresponding guanidine **2a** was obtained in a 43% yield (Table 1, entry 8). We were then gratified to find that the reaction efficiently proceeded in the presence of $In(OTf)_3$ or $Yb(OTf)_3$ (82% or 81% yields, respectively, Table 1, entries 9 and 10), and the guanidine **2a** was obtained in 95% yield in the presence of $Sc(OTf)_3$ as a Lewis acid catalyst (Table 1, entry 11). Although the reaction proceeded even at reduced catalyst loading levels (Table 1, entries 12 and 13), a longer time was required for the reaction to reach completion: more than four days. The use of 10 mol% catalyst was determined to be optimal.

The protocol was then applied to a wide range of amino-containing substrates (Table 2).[18] The reaction with aniline-containing substrates **1b**–**e** bearing electron-donating groups (Table 2, entries 1 and 2) and electron-withdrawing substituents (Table 2, entries 3 and 4) efficiently provided the corresponding guanidine derivatives **2b**–**e** in 63–88% yields. The heteroaromatic aniline nitrogen atoms also participated in the guanylation reaction. The quinoline derivative **1f** gave the guanidine **2f** in a 57% yield (Table 2, entry 5), and the indole substrate **1g** quantitatively provided **2g** through the selective reaction of an anilino nitrogen in the presence of an indole N1 nitrogen (Table 2, entry 6). It should be noted that in a traditional guanylation reaction of **1g** with cyanamide in aqueous hydrochloric solution, both aromatic nitrogen atoms were guanylated and other byproducts derived from a Friedel–Crafts-type reaction were obtained. The traditional reaction therefore provided the desired guanidine **2g** in less than a 10% yield. The reaction of the thiazole derivative **1h** (Table 2, entry 7), which could not react at all with the cyanamide under traditional conditions, provided the guanidine **2h** by new protocol, albeit in 31% yield. This result highlights the efficiency of the Lewis acid catalyzed reaction developed here.

Aliphatic amines were found to be amenable to the reaction. The linear primary amine **1i**, the heteroaromatic benzylamine **1j**, the protected amino acid **1k**, the secondary benzylic amine **1l**, and the cyclic amine **1m** efficiently participated in the aqueous guanylation reaction without any difficulties, providing **2i**–**m** in moderate to excellent

Table 1 Optimization of the Lewis Acid Catalyzed Guanylation in Water[a]

1a **2a**

Entry	Lewis acid	Yield (%)
1	$Nd(OTf)_3$	5
2	$Zn(OTf)_2$	9
3	$Cu(OTf)_2$	10
4	AgOTf	12
5	$InCl_3$	16
6	$La(OTf)_3$	19
7	$Tm(OTf)_3$	24
8	$Y(OTf)_3$	43
9	$In(OTf)_3$	82
10	$Yb(OTf)_3$	81
11	$Sc(OTf)_3$	95
12[b]	$Sc(OTf)_3$	66
13[c]	$Sc(OTf)_3$	34

[a] The reaction was performed by treating aniline with 1.2 equiv cyanamide at 100 °C for 12 h in H_2O.
[b] Conditions: 5 mol% $Sc(OTf)_3$ were used.
[c] Conditions: 2 mol% $Sc(OTf)_3$ were used.

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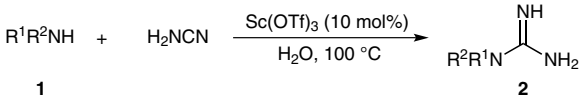
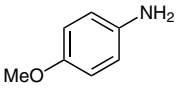
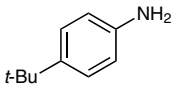
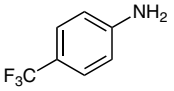
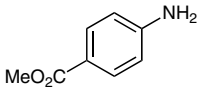
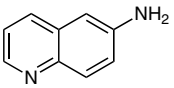
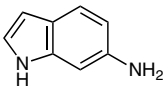
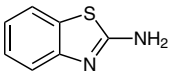
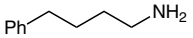
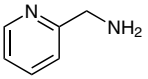
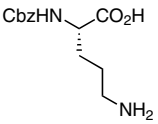
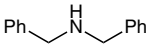
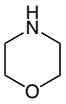
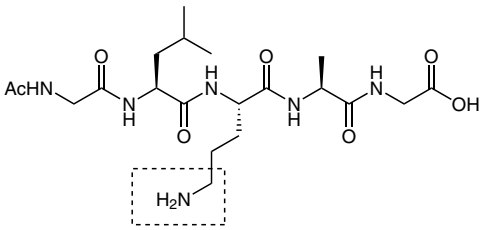
Table 2 $Sc(OTf)_3$-Catalyzed Aqueous Guanylation[a]



Entry	R^1R^2NH		Product	Time (d)	Yield (%)
1	**1b**		**2b**	2	80
2	**1c**		**2c**	2	67[b]
3	**1d**		**2d**	1	88
4	**1e**		**2e**	2	63[c]
5	**1f**		**2f**	2	57[b]
6	**1g**		**2g**	1	quant.
7	**1h**		**2h**	3	31[b]
8	**1i**		**2i**	1	68[b]
9	**1j**		**2j**	1	56
10	**1k**		**2k**	1	68
11	**1l**		**2l**	2	46[b]
12	**1m**		**2m**	3	83
13	**1n**		**2n**	2	56

[a] The reaction was performed by treating the amines with 1.2 equiv cyanamide and 10 mol% $Sc(OTf)_3$ at 100 °C in H_2O.
[b] H_2O–1,4-dioxane (1:1) mixture was used as solvent.
[c] Total yield of the ester **2e** (46%) and its hydrolyzed compound (17%).

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yields (Table 2, entries 8–12). The present aqueous protocol enabled the direct conversion of ornithine into a peptide structure **1n** to the corresponding arginine peptide **2n**. The peptide **1n** was smoothly transformed to the peptide **2n** by a reaction with cyanamide over two days, providing a 56% yield without epimerization under mild conditions (Table 2, entry 13).

Insights into the reaction mechanism of our $Sc(OTf)_3$-catalyzed reaction were obtained by heating the cyanamide with stoichiometric amounts of $Sc(OTf)_3$ at 100 °C in deuterated water under the conditions reported in Tables 1 and 2. The product development was directly monitored by ^{13}C NMR (Figure 1). After 12 hours, the ^{13}C signal at δ = 162 ppm, which appeared to be derived from a carbodiimide derivative, possibly in complex with a scandium triflate, was clearly observed with disappearance of the cyanamide carbon signal at δ = 118 ppm. Treatment of the mixture with aniline **1a** quantitatively provided the guanylated product **2a**. Hence, the present $Sc(OTf)_3$-catalyzed reaction involved the in situ generation of a reactive metalated carbodiimide species that reacted smoothly with various amino derivatives. Lanthanide metal complexes, such as ytterbium amides or ytterbium triflate, can accelerate the addition reactions of carbodiimides and amines.[10–12] $Sc(OTf)_3$ was found to activate the process examined here, suggesting a mechanism underlying the high reactivity of our catalyzed reaction. We found that cyanamide could be activated in situ to form reactive carbodiimides in the presence of catalytic amounts of $Sc(OTf)_3$, which reacted directly with various amino derivatives. The procedure developed here removed the need to preactivate the guanylation reagents, as required in other guanylation methods.

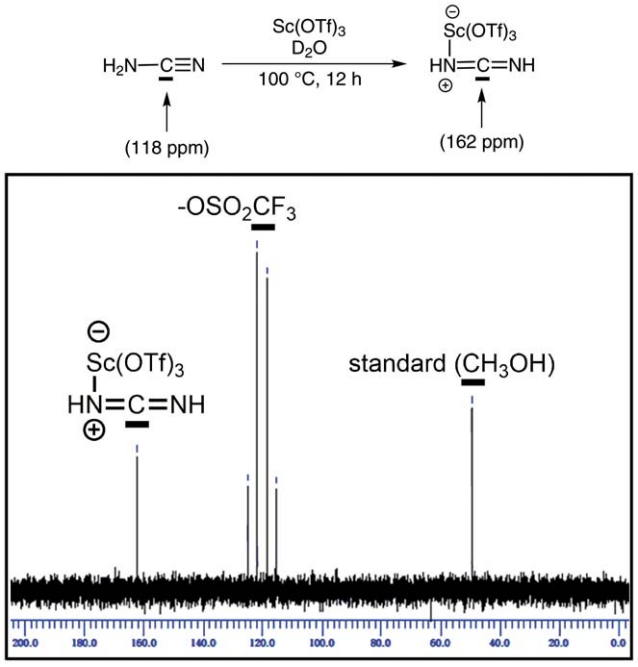

Figure 1 ^{13}C NMR spectrum of the cyanamide after treatment with $Sc(OTf)_3$ at 100 °C in deuterated water (MeOH was used as the internal standard).

In conclusion, we developed a direct method for guanylating amino groups via a reaction with cyanamide in water. The reaction was efficiently catalyzed by $Sc(OTf)_3$ under mild conditions. The activated carbodiimides, which were, in most cases, prepared independently from substituted cyanamide derivatives, were in fact generated by the treatment of cyanamide with catalytic amounts of $Sc(OTf)_3$. Metal–carbodiimide complex readily reacted with a variety of amines in water to provide various guanidine derivatives in good yields. The lanthanide triflate-catalyzed conditions developed here enabled the reactions of previously intransigent substrates that could not be dissolved in organic solvents. These approaches enabled efficient guanylation reactions in water. An ornithine group in an unprotected peptide could be efficiently transformed into an arginine congener. The simple procedure, which involved mixing substrates with $Sc(OTf)_3$ in water, easily yielded the isolated products after removing the catalyst by silica gel pad. The application of this method to the synthesis of guanidine-containing natural products and pharmacologically important compounds is currently in progress in our laboratories.

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(18) **General Procedure for the Guanylation of Amines: Preparation of *N*-(*p*-Methoxyphenyl)guanidine (2b)**
To a solution of *p*-methoxyaniline (**1b**, 61.6 mg, 0.50 μmol) and cyanamide (25.2 mg, 0.60 μmol) in H_2O (2.5 mL) was added $Sc(OTf)_3$ (24.6 mg, 50 nmol) at r.t. After the solution was stirred at 100 °C for 2 d, the resulting mixture was washed with $CHCl_3$ (3 × 10 mL). The aqueous layer was concentrated in vacuo, and the residue was purified by filtering through silica gel pad ($CHCl_3$–MeOH, 20:1) to give **2b** as a purple solid (66.1 mg, 80%). IR (neat): 3353, 2158, 1673, 1513, 1244, 1028 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.10 (d, *J* = 9.1 Hz, 2 H), 6.91 (d, *J* = 9.1 Hz, 2 H), 3.72 (s, 3 H). ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 164.8, 160.9, 128.9, 128.1, 116.2, 56.0. ESI-MS: *m/z* calcd for $C_8H_{11}N_3O$ $[M + H]^+$: 166.1; found: 166.1.

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