Zinc catalyzed Guanylation reaction of Amines with Carbodiimides/Isocyanate leading to Guanidines/Urea derivatives formation

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Abstract. We report the highly chemo-selective catalytic addition of N–H bonds from various aromatic amines to carbodiimides and isocyanates using (Ar-BIAO)ZnCl₂ complexes [Ar-BIAO = *N*-(aryl)imino-acenapthenone, Ar = 2,6-Me₂C₆H₃ (**1**), 2,4,6 Me₃C₆H₂ (**2**), 2,6-ⁱPr₂C₆H₃ (**3**)] as the pre-catalyst to prepare guanidine and urea derivatives in 55–90% yield. The complex **3** showed higher catalytic activity than analogous complexes **1** and **2** under similar reaction conditions. The catalytic guanylation of N–H bonds with heterocumulenes displays a broad substrate scope. The amines having electron donating groups underwent higher conversion than the amines having electron withdrawing groups to afford corresponding guanidine or urea derivatives. A possible mechanism involving penta-coordinated zinc transition state for the catalytic reaction is presented.

Keywords. Carbodiimide; isocyanate; guanidine; urea; Zn catalyst; guanylation.

1. Introduction

Guanidine, and the substituted guanidine derivatives are an important class of compounds present in biologically and pharmaceutically active molecules. They have received considerable attention due to their electronic and variable static effects.¹ Today, Guanidine derivatives are utilized for many purposes as they can serve as building blocks in various pharmaceutical and natural products.² Guanidine derivatives have found extensive applications in medicinal chemistry due to their ability to interact with functional groups present in enzymes or receptors through hydrogen bonds and electrostatic interactions. They are extensively used in medicine as therapeutic agents suitable for the treatment of various diseases and are also involved in antidiabetic, antibacterial, antihistaminic, anti-inflammatory and cardiovascular activity. These molecules can also act as organic bases, and catalyze various organic transformations.³ Guanidines are also used as ancillary ligands in the preparation of a variety of metal complexes including those of main group, transition and lanthanide metals.⁴ Many synthetic procedures have been explored for the preparation of guanidines. The most convenient and relevant route is the catalytic addition of amine N–H bonds to carbodiimides, also known as guanylation reaction.^{5–7}

The un-catalyzed guanylation of amines with carbodiimides is not a viable process due to requirement of harsh conditions.^{6d} Thus, analyzing various metal catalysts for guanylation reactions has received much interest. Metal complexes such as LiN(SiMe₃)₂,⁸ lanthanide amides and triflets,⁹ titanacarborane amides,¹⁰ metal alkyls such as half sandwich lanthanide alkyl complex¹¹ have been utilized for the synthesis of guanidines. In addition, commercially available alkyl metal complexes ZnEt₂, MgBu₂, *n*-BuLi, and AlR₃ have also been explored to be efficient catalysts for this reaction.¹²

Recently, we have reported the synthesis and structural details of various zinc complexes with bi-dentate *N*-(aryl)imino-acenapthenone (Ar-BIAO) ligand, where Ar-BIAO ligand contains conjugated exocyclic carbonyl and imine groups (scheme 1 and figure 1).¹³ We have observed from their molecular structures that a bidentate ligation from the Ar-BIAO ligands occur in each case through lone pairs of nitrogen and oxygen atoms and, by changing the steric crowding on the Ar-BIAO ligand, the nuclearity of the zinc complexes can be changed. In continuation with this project, we found that these zinc complexes are extremely active as pre-catalyst for the guanylation reaction between carbodiimides and amines. Herein we report the reactivity of zinc complexes as pre-catalyst for the reaction of a number of amines with different carbodiimides and isocyanates to synthesize various guanidine and urea derivatives.

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Scheme 1. Synthesis of zinc catalysts **1–3**.¹³

Figure 1. The molecular structure of zinc catalyst **3**.¹³

2. Experimental

2.1 General Information

All manipulations of air-sensitive materials were performed under inert atmosphere and in flame-dried Schlenk-type glassware, either on a dual manifold Schlenk line interfaced with a high vacuum (10^{-4} Torr) line, or in an argon-filled MBRAUN glove box. Hydrocarbon solvents (toluene and *n*-hexane) were distilled under nitrogen from LiAlH_4 and stored in the glove box. ^1H NMR (400 MHz) and $^{13}\text{C}\{^1\text{H}\}$ (100 MHz), spectra were recorded on a BRUKER AVANCE III-400 spectrometer. All amines, *N*, *N'*-di-cyclohexylcarbodiimide, *N*, *N'*-di-*tert*-butylcarbodiimide and phenylisocyanate were purchased from either Sigma Aldrich or Alfa Aesar. Amines were distilled over CaH_2 prior to use. Zinc complexes **1–3** were synthesized according to the published procedure.¹³ NMR solvent (CDCl_3) was purchased from Alfa Aesar and distilled over molecular sieves.

2.1a Typical procedure for guanylation reactions: Zinc complex catalyzed guanylation reactions were carried out by using the standard protocol mentioned hereunder. In the glove-box, the chosen pre-catalyst (0.1 mmol) was loaded into a Schlenk tube in 5 mL

toluene, and subsequently, the amine (1 mmol, 1 equiv) followed by the carbodiimides (1 mmol, 1 equiv) were added to the Schlenk tube. The mixture was stirred in an oil bath at the desired temperature (90°C). After 12 h, the solvent was evaporated under vacuum and the residue was dissolved in hexane and kept under stirring for 6 h. The solvent was evaporated to get the white solid product. The yield was calculated from the weight of the compound obtained.

2.1b Characterization of the products A–O (see table 2): The data for **A** is already described in the literature.¹⁴ The ^1H and ^{13}C NMR spectral data for guanidine (**B–K**) and urea derivatives (**M–O**) are given in the Supporting Information. The ^1H and ^{13}C NMR spectra for guanidine and urea derivatives **B–O** are given in the Supporting Information.

3. Results and Discussion

In this study, we describe the catalytic addition of N–H bonds from various amines to *N,N'*-dicyclohexylcarbodiimides and isocyanates with zinc complexes **1–3** as the pre-catalyst. Catalytic experiments were carried out using 10 mol% of zinc complex and equimolar amounts of either carbodiimides or isocyanate and amines which were added to a solution of the catalyst with suitable solvent under an inert atmosphere. Initially we employed mesitylamine (2,4,6- $\text{Me}_3\text{C}_5\text{H}_2\text{NH}_2$) and *N,N'*-dicyclohexylcarbodiimide (DCC) as model substrates to explore and optimize their catalytic reaction. When 10 mol% of zinc catalyst **1** was employed as Lewis acid catalyst at 90°C , we were pleased to find that the desired guanidine product **A** was obtained in good yield (table 1, entry 1). Then, other zinc catalysts were examined as Lewis acids in the reaction. The experimental results indicated among these three zinc complexes **1–3**, complex **3** exhibited best catalytic activity to the desired guanidine **A** in 81% yield (table 1, compare entry 3 with entries 1–2). When a zinc bromide complex **2*** (MesBIAOZnBr_2)¹³ was used as pre-catalyst, only 76% yield was isolated (table 1, entry 7). We also examined the solvent effect into the reaction and observed that toluene could be the better combination than tetrahydrofuran and dichloromethane (table 1, entries 3–5). It should be noted when only zinc dichloride was used as catalyst, no product was detected (table 1, entry 6). Further raising the temperature from 90°C to 110°C was not beneficial to the reaction as no increase in yield was observed (table 1, entry 8). The aliphatic amines were not suitable for this catalytic reaction due to their lower boiling points.

Table 1. Optimization of catalytic reaction between DCC and mesityl amine.

Entry	Amine	Carbodiimide	Catalyst	Solvent	Time (h)	T (°C)	Yield (%) ^a
1	Mesityl amine	DCC	1	Toluene	12	90	75
2	Mesityl amine	DCC	2	Toluene	12	90	78
3	Mesityl amine	DCC	3	Toluene	12	90	81
4	Mesityl amine	DCC	3	THF	12	60	70
5	Mesityl amine	DCC	3	CH ₂ Cl ₂	12	25	65
6	Mesityl amine	DCC	ZnCl₂	Toluene	12	90	0
7	Mesityl amine	DCC	2*	Toluene	12	90	76
8	Mesityl amine	DCC	3	Toluene	12	110	81
9	Mesityl amine	DCC	–	Toluene	24	90	0

^aIsolated yields.

After screening the reaction conditions, it can be concluded that the optimized reaction should be performed using the catalyst of 10 mol% complex **3** at 90°C using toluene as the solvent. The reaction mixture in each case was kept under stirring condition at elevated temperature for 12 h for carbodiimides and at room temperature for 1 h in case of isocyanates and the respective guanidine or urea products were isolated. The isolated products were analysed through ¹H and ¹³C NMR spectroscopy and yields were calculated after isolation of pure products (table 2). Under optimized reaction condition we found that a series of amines had undergone the N-H addition reaction smoothly with two different carbodiimides to give corresponding guanidine derivatives in moderate yield. The reaction of unsubstituted aniline with DCC gave 95% yield (table 2, entry 1). The anilines having nitro group in *ortho*-, or in *para*- position were tested for the N-H addition reaction and the yield of 85% and 75% of the respective guanidines were observed (table 2, entries 2 and 3); however substantial decrease in the yield (53%) was noticed when *m*-nitroaniline was used as the substrate due to greater extent of deactivating nature of the nitro group at *m*-position of the aniline. However, the aniline moieties were further deactivated when a halide group (F, Cl, I) was attached to the phenyl ring as 55–57% yield of respective urea derivative were obtained (table 2, entries 5–8). The mesityl and 2,6-dimethyl aniline having electron donating effect from the methyl groups were observed to show no significant increase in the yield (table 2, entries 9–10). However, no guanylation product was observed when DippNH₂ was used as the amine substrate probably due to enhanced steric

hindrance of DippNH₂ which restricted the approach of the bulky carbodiimide (DCC) towards itself (table 2, entry 11). When we reacted N,N'-di-*tert*-butylcarbodiimide with aniline, we obtained corresponding guanidine in good yield 75% (entry 12). To extend the scope of the reaction, we treated phenyl isocyanate with *tert*-butylamine and pyrrolidine under room temperature using the zinc pre-catalyst **3**. Recently, we have utilized a titanium complex imidazolin-2-iminato titanium amido complexes [(Im^{Dipp}N)Ti(NMe₂)₃] for the catalytic addition of amines with carbodiimide or phenyl isocyanate.¹⁵ In both the cases, we obtained excellent yield of the corresponding urea derivatives (table 2, entry 13 and 14). However, the DippNH₂ gave slightly reduced yield of the respective urea due to bulky size of the aniline moiety (table 2, entry 15). Thus we observed that, zinc pre-catalyst **3** can smoothly catalyse the guanylation reaction of a number of anilines with DCC at a slightly elevated temperature; however the reaction with phenyl isocyanate with amines required room temperature only.

A possible mechanism for zinc complex **3** catalyzed guanylation of amines to carbodiimides is proposed in scheme 2. In the first step, carbodiimido nitrogen should react with zinc complex **3** which is a Lewis acid catalyst through the lone pair of nitrogen to generate penta-coordinated zinc intermediate **I** where zinc can bear the negative charge and the second nitrogen of the carbodiimido moiety bears positive charge. The nucleophilic addition of an amine to **I** would afford another penta-coordinated zinc intermediate **II**. Finally, intramolecular proton transfer of **II** readily led to regenerate pre-catalyst **3** and release the free guanidine. Similar mechanistic cycles are known in literature.¹⁶

Table 2. Catalytic formation of guanidine and urea derivatives using **3** as pre-catalyst^a.

Entry	Amine	Carbodiimide/Isocyanate	Product	Yield (%) ^b
1		CyN=C=NCy		95
2		CyN=C=NCy		85
3		CyN=C=NCy		75
4		CyN=C=NCy		53
5		CyN=C=NCy		57
6		CyN=C=NCy		53
7		CyN=C=NCy		57

Table 2. *Continue.*

Entry	Amine	Carbodiimide/Isocyanate	Product	Yield (%) ^b
8		CyN=C=NCy	(I)	55
9		CyN=C=NCy	(A)	81
10		CyN=C=NCy	(J)	52
11		CyN=C=NCy	(K)	0
12		tBuN=C=NtBu	(L)	75
13		PhN=C=O ^c	(M)	88
14		PhN=C=O ^c	(N)	95
15		PhN=C=O ^c	(O)	79

^aAll compounds were characterized by ¹H and ¹³C NMR spectroscopy using CDCl₃ as NMR solvent. ^bYields were calculated from isolated pure products. ^cRoom temperature.

Scheme 2. Most plausible mechanism for the catalytic addition of N-H bond to carbodiimide using zinc pre-catalyst **3**.

4. Conclusions

In summary, we have presented the highly chemoselective catalytic addition of N-H bonds from various aromatic amines to carbodiimides and isocyanate using a zinc pre-catalyst supported by *N*-(aryl)iminoacacenaphthone ligand. The zinc complex **3** was proved to be efficient pre-catalyst for the conversion of aromatic amines to the corresponding guanidines *via* guanylation reaction with carbodiimides at elevated temperature in 55–95% yield. Complex **3** was also a potent catalyst for the conversion of isocyanate to corresponding urea in excellent yield when amines were reacted with isocyanate at room temperature. A possible mechanism involving five coordinated zinc intermediate is proposed for the guanylation reaction.

Supplementary Information (SI)

The ^1H and ^{13}C NMR spectral data for guanidine (**B-K**) and urea derivatives (**M-O**) are given in the Supporting Information. The ^1H and ^{13}C NMR spectra for guanidine and urea derivatives **B-P** are given in the Supporting Information, available at www.ias.ac.in/chemsci.

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