ORGANIC LETTERS

2011
Vol. 13, No. 17
4562–4565

Ti-amide Catalyzed Synthesis of Cyclic Guanidines from Di-/Triamines and Carbodiimides

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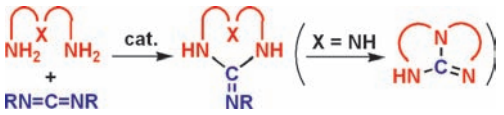
Received June 29, 2011

ABSTRACT



A titanacarborane monoamide catalyzed, one-step synthesis of mono/bicyclic guanidines from commercially available di/triamines and carbodiimides is reported. The reaction mechanism is also proposed.

A growing number of biologically and pharmaceutically relevant compounds incorporate the cyclic guanidine functionality.[1] Cyclic guanidines are also capable of catalyzing organic reactions[2] and exhibiting a variety of coordination modes and a range of donor properties leading to compatibility with a wide range of metal ions.[3] Therefore, their synthesis has been extensively explored. Generally, the known methods include (1) the reactions[4] of

(1) For examples, see: (a) *Guanidines 2: Further Explorations of the Biological and Chemical Significance of Guanidino Compounds*; Mori, A., Cohen, B. D., Koide, H., Eds.; Plenum Press: New York, 1987. (b) Greenhil, J. V.; Lue, P. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science: New York, 1993; Vol. 30, ch 5. (c) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919. (d) He, H.; Williamson, R. T.; Shen, B.; Graziani, E. I.; Yang, H. Y.; Sakya, S. M.; Petersen, P. J.; Carter, G. T. *J. Am. Chem. Soc.* **2002**, *124*, 9729. (e) Jackson, M. D.; Gould, S. J.; Zabriskie, T. M. *J. Org. Chem.* **2002**, *67*, 2934. (f) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. (g) Durant, G. J. *Chem. Soc. Rev.* **1985**, *14*, 375. (h) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377. (i) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339. (j) Heys, L.; Moore, C. G.; Murphy, P. J. *Chem. Soc. Rev.* **2000**, *29*, 57. (k) Berlinck, R. G. S. *Nat. Prod. Rep.* **2002**, *19*, 617.

(2) For examples, see: (a) Leow, D.; Tan, C.-H. *Synlett* **2010**, 1589. (b) Leow, D.; Tan, C.-H. *Chem.—Asian. J.* **2009**, *4*, 488. (c) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737. (d) Ma, T.; Fu, X.; Kee, C. W.; Zong, L.; Pan, Y.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 2828. (e) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286. (f) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (g) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832. (h) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245. (i) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

(3) For examples, see: (a) Coles, M. P. *Dalton Trans.* **2006**, 985. (b) Coles, M. P.; Sözerli, S. E.; Smith, J. D.; Hitchcock, P. B. *Organometallics* **2007**, *26*, 6691. (c) Dyer, P. W.; Fawcett, J.; Hanton, M. J. *Organometallics* **2008**, *27*, 5082. (d) Bailey, P. J.; Pace, S. *Coord. Chem. Rev.* **2001**, *214*, 91. (e) Chen, E. Y.-X.; Rodriguez-Delgado, A. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Oxford, 2007; Vol. 4.

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(8) For more examples, see: (a) Bycroft, B. W.; Cameron, D.; Croft, L. R.; Johnson, A. W. *Chem. Commun.* **1968**, 1301. (b) Obase, H.; Nakamizo, N.; Takai, H.; Teranishi, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3189. (c) Ishikawa, F.; Kosasayama, A.; Nakamura, S.; Konno, T. *Chem. Pharm. Bull.* **1978**, *26*, 3658.

10.1021/ol201752e
Published on Web 08/04/2011

amines with *S*,*S*-dimethyl-*N*-tosyliminodithiocarbonimidates,[4a] dimethyl cyanoimido-dithiocarbonates,[4b] isothiocyanates,[4c−e] or carbon disulfide;[4f] (2) cyclization of guanidino-alkynes;[5] (3) intramolecular alkylation of guanidines;[6] (4) reactions of unsaturated molecules with azridines,[7] and so forth.[8] Very recently, oxidative amination and radical cascade cyclization methods were also successfully applied to the synthesis of cyclic guanidines.[9] However, most of these routes require multistep operations or functionalization of precursors. Herein, we report a novel and direct method for the catalytic synthesis of cyclic guanidines from commercially available di/triamines and carbodiimides in one step.

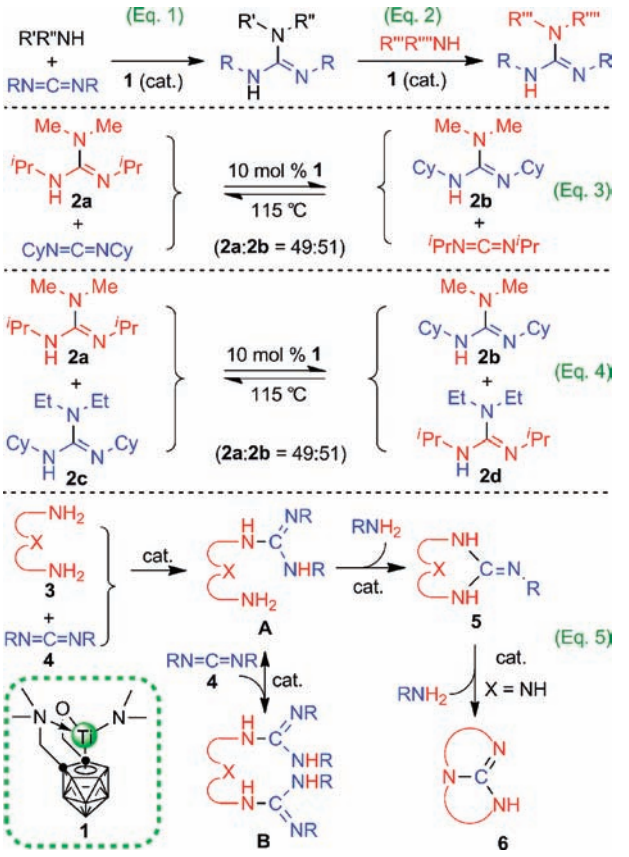
Recently, we reported a highly reactive titanacarborane monoamide $[\sigma{:}\eta^1{:}\eta^5\text{-}(OCH_2)(Me_2NCH_2)C_2B_9H_9]Ti\text{-}(NMe_2)$ (**1**),[10] which can be viewed as an isoelectronic/isostructral analogue of constrained-geometry lanthanide amide or a cationic group 4 metal amide.[11] This complex efficiently catalyzes the cascade hydroamination of cyanoalkynes to give isoindoles and isoquinolines,[12] the sequential C−N bond-forming reaction of propargylamines with nitriles to yield imidazoles,[12] and the [3 + 2] annulation of propargylamines with carbodiimides to produce 2-amino-imidazoles.[5d]

In addition, complex **1** acts as an elegant catalyst in the hydroamination of carbodiimides (Scheme 1, eq 1),[13] and it also shows a very high catalytic activity toward the transamination reaction of guanidines (Scheme 1, eq 2).[14]

These results and the group 4 metallacarborane mediated C−N bond cleavage of guanidinates[15] promote us to further explore the catalytic metathesis of guanidines with carbodiimides and that of two guanidines. After a C_6D_6 solution of guanidine **2a** (0.1 mmol), DCC (0.1 mmol), and **1** (0.01 mmol, 10 mol %) was heated at 115 °C for 24 h, the ^{1}H NMR indicated that an equilibrium between **2a** and **2b** (in a molar ratio of 49:51) was reached (Scheme 1, eq 3). Similarly, the NMR reaction of **2a** with **2c** in the presence of 10 mol % of **1** at 115 °C for 24 h resulted in another equilibrium of **2a**:**2b** (49:51) (Scheme 1, eq 4). In marked contrast, no metathesis reaction was observed in the absence of catalyst **1**.

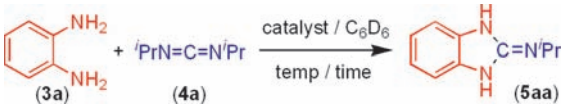
On the basis of the prevalence of olefin ring-closing metathesis (RCM) and the fact that **1** catalyzes both the hydroamination of carbodiimides (Scheme 1, eq 1) and the intermolecular metathesis of guanidines with amines/carbodiimides/guanidines (Scheme 1, eq 2/3/4), we envisaged

Scheme 1. Construction and Reconstruction of Guanidines Catalyzed by **1**



that a reaction of di/triamines with carbodiimides in the presence of **1** would serve as a new approach for the synthesis of cyclic guanidines (Scheme 1, eq 5), via the

Table 1. Effects of Metal Complexes in Reaction of **3a** with **4a**[a]



entry	catalyst	loading (mol %)	temp (°C)	time (h)	yield (%)
1	none	0	110	196	<10
2	**1**	5	110	196	60
3	**1**	10	110	196	>95
4	**1**	5	140	32	63
5	**1**	10	140	32	>95
6	$Ti(NMe_2)_4$	10	110	196	70
7	$Zr(NMe_2)_4$	10	110	196	20
8	$Hf(NMe_2)_4$	10	110	196	18
9	Cp_2TiMe_2	10	110	196	<10
10	Cp_2ZrMe_2	10	110	196	<10
11	Cp_2HfMe_2	10	110	196	<10

[a] NMR yield using ferrocene as the internal standard.

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(12) Shen, H.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 11473.

(13) Shen, H.; Chan, H.-S.; Xie, Z. *Organometallics* **2006**, *25*, 5515.

(14) Shen, H.; Xie, Z. *Organometallics* **2008**, *27*, 2685.

(15) Shen, H.; Chan, H.-S.; Xie, Z. *J. Am. Chem. Soc.* **2007**, *129*, 12934.

intermolecular hydroamination (**3**+**4** to **A**) and the intramolecular metathesis (**A**/**B** to **5**, **5** to **6**).

The model reaction of *o*-phenylenediamine (**3a**) with diisopropylcarbodiimide (**4a**) was initially examined (Table 1) in the presence of a catalytic ammount of **1** or commercially available complexes or commonly used catalysts.[16] In the absence of a catalyst, no expected product **5aa** was observed at 110 °C for 196 h (entry 1). However, addition of 10 mol % of **1** led to the formation of **5aa** in more than 95% NMR yield under the same conditions (entry 3). The reaction could also go to completion in 32 h at 140 °C (entry 5). A lower catalyst loading resulted in a lower yield (entries 2 and 4).

It is documented that carbodiimides react readily with highly nucleophilic cyclic aliphatic amines, in the absence of a catalyst, to generate the corresponding guanidines at high temperatures.[17] Thus, the substrate scope of this reaction was examined to see if the catalyst is necessary for different substrates (Table 2). The reaction of highly nucleophilic *N*,*N*′-dimethylethylenediamine **3j** proceeded very well in the absence of the catalyst (entry 9 vs 10), whereas reactions of correspondingly less nucleophilic amines (such as aromatic diamine **3a** and primary aliphatic diamine **3f**) do need the catalyst (entries 1−6). The diarylcarbodiimide showed a better reactivity than the dialkylcarbodiimide (entries 1/2 vs 3/4, 5/6 vs 7/8).

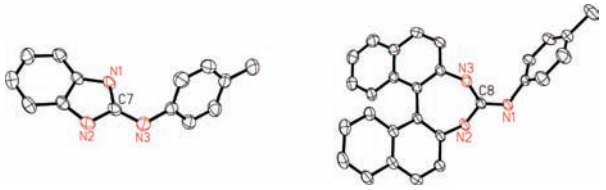


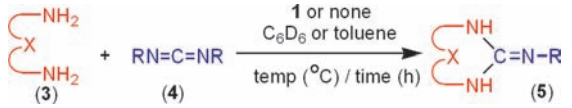
Figure 1. X-ray Structures for **5ac** and **5ec**.

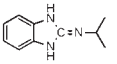
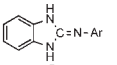
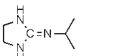
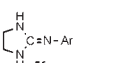
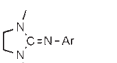
According to the above observations, more substrates were included except for the highly nucleophilic amines. A series of di- and triamines were examined, and the corresponding results were compiled in Table 3. Reactions of diamines afforded five- to seven-membered cyclic guanidines (entries 1−11). The reaction of *cis*-1,4-cyclohexadiamine **3i** gave the bridged cyclic guanidine **5ic** (entry 12). Triamines **3k**/**3l** reacted with carbodiimides to produce the bicyclic guanidines **6k**/**6l** (entries 13−15). The chiral cyclic guanidine (***S*-5ec**) was also prepared from the corresponding chiral amine (***S*-3e**) with the retention of the *ee* value (entry 7). All of those products were fully characterized. Compounds **5ac** and **5ec** were further confirmed by X-ray analyses (Figure 1).

(16) For examples, see: (a) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1153. (b) Lorber, C.; Choukroun, R.; Vendier, L. *Organometallics* **2004**, *23*, 1845. (c) Straub, B. F.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4632. (d) Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959. (e) Ong, T.-G.; O'Brien, J. S.; Korobkov, I.; Richeson, D. S. *Organometallics* **2006**, *25*, 4728.

(17) Thomas, E. W.; Nishizawa, E. E.; Zimmermann, D. C.; Williams, D. J. *J. Med. Chem.* **1989**, *32*, 228.

Table 2. Screening of Substrate Scope



entry	3	R (4)	cat. %	temp/ time	5[a]	yield (%)
1		^{i}Pr (**4a**)	0	140/ 32		<10[b]
2			10	140/ 32		>95[b] (95)[c]
3		4-tol (**4c**)	0	115/ 36		30[b]
4			10	115/ 36		>90[b] (81)[c]
5		^{i}Pr (**4a**)	0	140 /48		30[b]
6			10	140/ 48		>80[b] (70)[c]
7		4-tol (**4c**)	0	140/ 48		>90[a]
8			10	140/ 48		>90[b] (86)[c]
9		4-tol (**4c**)	0	115 /12		>95[b]
10			10	115/ 12		>90[b] (90)[c]

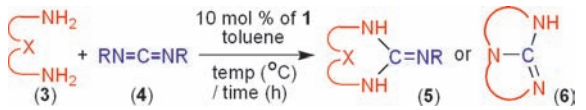
[a] Ar = 4-tol. [b] NMR yield using ferrocene as an internal standard. [c] Isolated yield (shown in parentheses).

Scheme 2. Synthesis and Conversion of the Intermediate **7aa**

Although these reactions were developed on the basis of the well-established construction and reconstruction of guanidines (Scheme 1), the mechanism was further investigated. To gain some insight for the pathway, attempts to separate the intermediate were made. Treatment of *o*-phenylenediamine (**3a**) with 1 equiv of diisopropylcarbodiimide (**4a**) at room temperature for 3 h, in the presence of 10 mol % of **1**, led to the isolation of the intermediate **7aa** in 59% yield (Scheme 2). Two parallel reactions (**7aa** in C_6D_6 vs **7aa** with 10 mol % of **1** in C_6D_6) were carried out at 140 °C, which were monitored by ^{1}H NMR using ferrocene as the internal standard. The experimental results showed that no obvious difference was observed and both of them resulted in the formation of **5aa** in more than 95% NMR yield in 30 h. This observation implies that the catalyst might not be involved in the cyclization step.

Due to the unique structure of **1** (the Ti atom is σ-bonded to only one amido group and strongly supported by the

Table 3. Synthesis of Cyclic Guanidines Catalyzed by **1**



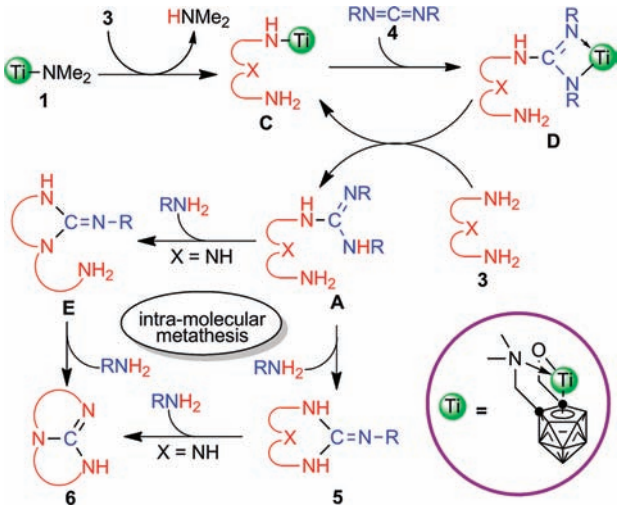
entry	**3**	R (**4**)	temp /time	product **5** or **6**[a]	yield (%)[b]
1	3a	Cy (**4b**)	140 /120	5ab	62
2	3b	4-tol (**4c**)	115 /12	5bc	71
3	3c	^{i}Pr (**4a**)	115 /8	5ca	95
4	3c	Cy (**4b**)	115 /8	5cb	94
5	3c	4-tol (**4c**)	115 /60	5cc	90
6	3d	4-tol (**4c**)	115 /12	5dc	77
7	S-3e	4-tol (**4c**)	140 /240	S-5ec	55[c]
8	*rac*-**3e**[d]	4-tol (**4c**)	140 /240	*rac*-**5ec**[d]	71
9	3g	^{i}Pr (**4a**)	140 /120	5ga	65
10	3g	4-tol (**4c**)	115 /48	5gc	80
11	3h	4-tol (**4c**)	115 /168	5hc	67
12	3i	4-tol (**4c**)	140 /480	5ic	73
13	3k	^{i}Pr (**4a**)	115 /168	6k	71
14	3k	4-tol (**4c**)	115 /240	6k	61
15	3l	4-tol (**4c**)	115 /240	6l	76

[a] Ar = 4-tol. [b] Isolated yield. [c] *ee* = 99%. [d] *rac* = racemic.

trianionic ligand $[\sigma{:}\eta^1{:}\eta^5\text{-}(OCH_2)(Me_2NCH_2)C_2B_9H_9]^{3-}$), the involvement of any titanium-imido (Ti=N) species can be ruled out.[5d,10,12−14] Given these experimental results and those of well-established reactions (Scheme 1), a possible reaction mechanism is proposed in Scheme 3. Amine exchange reaction between **1** and amine **3** affords **C** to enter the catalytic cycle.[5d,10,12−14] An intermolecular insertion of carbodiimide into Ti−N bond leads to the formation of **D**.[10,13,14] Acid−base reaction of **D** with **3** regenerates **C** to complete the catalytic cycle and releases amino-guanidine **A**.[13,14] Intramolecular metathesis of **A** produces the cyclic guanidine **5**.[18] If a triamine is used as the starting material (X = NH), sequential intramolecular metathesis results in the production of bicyclic guanidine **6** from **A** via **E** or **5**.[18]

(18) The intramolecular metathesis reaction of an amino-guanidine in the absence of a catalyst is supported by the parallel reactions of **7aa** (Scheme 2).

Scheme 3. Proposed Reaction Mechanism



In summary, we have developed a methodology for the synthesis of mono/bicyclic guanidines in good to excellent yields from di/triamines and carbodiimides, which is catalyzed by a titanium monoamide. A chiral guanidine can also be prepared with the retention of the *ee* value. The possible reaction mechanism, involving the Ti-catalyzed intermolecular hydroamination and intramolecular metathesis, is proposed as well.

Acknowledgment. This work was supported by grants from the Research Grants Council of the HKSAR (No. 404609), NSFC/RGC Joint Research Scheme (No. N_CUHK470/10), and CAS-Croucher Funding Scheme for Joint Laboratories.

Supporting Information Available. Experimental procedures, spectroscopic data, and X-ray data in CIF format for **5ac** and **5ec**. This material is available free of charge via the Internet at http://pubs.acs.org.