Tetrahedron Letters 53 (2012) 5156–5158

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First iron-catalyzed guanylation of amines: a simple and highly efficient protocol to guanidines

Srinivas Pottabathula *, Beatriz Royo *

Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Av. da República, EAN, 2780-157 Oeiras, Portugal

ARTICLE INFO

Article history:
Received 24 May 2012
Revised 11 July 2012
Accepted 13 July 2012
Available online 20 July 2012

Keywords:
Iron catalyzed
Guanylation
Homogeneous catalysis
Amines
Guanidines

ABSTRACT

The first iron-catalyzed guanylation of amines is reported. Commercially available $Fe(OAc)_2$ acts as an excellent catalyst for the addition of amines to carbodiimides. The reaction is broadly applicable to a variety of primary, secondary, and heterocyclic amines, and tolerates a wide range of functionalities allowing the easy preparation of a large family of guanidines. The low price and low toxicity of the commercially available iron catalyst make this methodology highly attractive.

Guanidines are important classes of compounds that have found relevant applications in medicine as therapeutic agents suitable for the treatment of a wide spectrum of diseases.[1] Moreover, guanidine is a substructure of many important molecules with biological activity,[2] and also has extensive uses in organic chemistry as organic bases, and as ancillary ligands to various metals.[3] A convenient methodology for the preparation of guanidines is the catalytic addition of amine N–H bonds to carbodiimides, also known as guanylation reaction (Fig. 1). This methodology provides a waste-free process, being a convenient atom-economical approach to substituted guanidines.

Since the seminal publication of a titanium imido complex capable to effect the catalytic addition of primary aromatic amines to carbodiimides,[4] other catalytic systems including a vanadium imido,[5] half-sandwich lanthanide alkyls,[6] lanthanide amides and aryloxides,[7] $LiN(SiMe_3)_2$,[8] titaniocarborane amide,[9] and commercially available alkyl metals $ZnEt_2$,[10] $MgBu_2$,[10] LiBu,[10] AlR_3,[11] and $Zn(OTf)_2$[12] have been reported to catalyze the guanylation reaction extending the applicability of this reaction to secondary amines.

In recent years the search for cheap, readily available catalysts for efficient chemical transformations has been responsible for the resurgence of catalytic systems based on iron metal.[13] Indeed, in the last decade iron catalysis has emerged as a challenging area for the development of alternative more sustainable methods.[14]

Following our interest in developing new iron-based catalytic systems,[15,16] we decided to explore the catalytic activity of iron

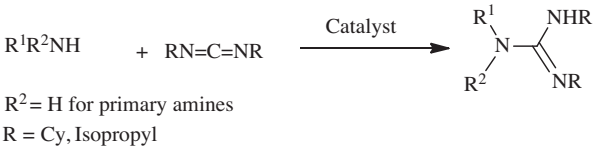


Figure 1. Catalytic addition of primary and secondary amines to carbodiimides.

complexes in the guanylation reaction. Herein, we report for the first time the efficient addition of amines to carbodiimides using a convenient iron catalyst, $Fe(OAc)_2$, with excellent functional group tolerance and broad scope. An attractive feature of this Fe-catalytic system is its operational simplicity, since the reaction can be performed with analytical grade solvents in air without special precautions.

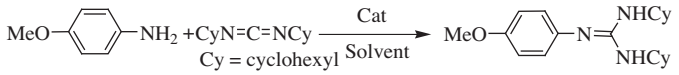
We first investigated the reaction of *p*-anisidine with *N,N′*-dicyclohexylcarbodiimide as a model system to identify and optimize potential catalysts and reaction conditions. We found that in the presence of 5 mol% of iron(II)acetate the reaction took place in toluene at 120 °C affording quantitative yield (97%) of the corresponding guanidine in 2 h (Table 1, entry 1).

Iron(II)triflate also afforded quantitative conversion under similar conditions (Table 1, entry 2). We also tested the catalytic activity of the well-defined cyclopentadienyl-NHC iron complex (Cp^*-NHC)Fe(CO)I ($Cp^* = \eta^5$-C_5Me_4; NHC^{Me} = N-heterocyclic carbene) recently prepared by us.[15,16] This complex displayed good catalytic activity affording quantitative yield of the corresponding guanidine derivative, although longer reaction times were needed

* Tel.: +351 214469754; fax: +351 214411277.
E-mail address: broyo@itqb.unl.pt (B. Royo).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.065

Table 1
Catalytic addition of *p*-anisidine to *N,N′*-dicyclohexylcarbodiimide with iron catalysts[a]



Entry	Catalyst (mol %)	Solvent	T (°C)	Yield[b] (%)
1	$Fe(OAc)_2$ (5)	Toluene	120	97
2	$Fe(OTf)_2$ (5)	Toluene	120	95
3	$(Cp^*–NHC)Fe(CO)I$	Toluene	120	96[c]
4	$FeCl_2$ (5)	Toluene	120	24
5	$FeCl_3$ (5)	Toluene	120	12
6	$Fe_3(CO)_{12}$ (5)	Toluene	120	65
7	$Fe(OAc)_2$ (5)	THF	80	0
8	$Fe(OAc)_2$ (5)	benzene	80	0
9	$Fe(OAc)_2$ (5)	DMF	120	0
10	$Fe(OAc)_2$ (5)	DMSO	120	0
11	$Fe(OAc)_2$ (5)	Toluene	100	0
12	$Fe(OAc)_2$ (2)	Toluene	120	97
13	Without catalyst	Toluene	120	0

[a] Reaction conditions: aniline (1 mmol), *N,N′*-dicyclohexylcarbodiimide (1.2 mmol), solvent (2 mL), 2 h.
[b] Yield of isolated product.
[c] 5 mol % of Catalyst was used, 5 h of reaction.

to complete the reaction (5 h, Table 1, entry 3). Other iron sources such as iron(II) and iron(III) chlorides showed some activity but gave significantly lower yields (24% and 12% yield, respectively; Table 1, entries 4 and 5). The iron(0) carbonyl $Fe_3(CO)_{12}$ showed a moderate activity affording 65% of the corresponding guanidine under similar conditions (Table 1, entry 6). From the above results, $Fe(OAc)_2$ was selected as the best catalyst choice because of its high reactivity, availability, and easy handling.

After screening the reaction conditions, toluene was found to be the most suitable solvent for this reaction. The appropriate selection of solvent and temperature was crucial for the reaction to proceed efficiently. No reaction occurred in the presence of other solvents such as THF, benzene, DMF, and DMSO (Table 1, entries 7–10, respectively). The reaction temperature revealed to be a determinant parameter. If the temperature is lowered to 100 °C, no reaction occurred even after being reacted for several hours (Table 1, entry 11). We observed that the amount of catalyst could be reduced to 2 mol % without noticeable detrimental effects in the isolated yields (Table 1, entry 12). As expected, the reaction did not occur in the absence of catalyst (Table 1, entry 13).

With the optimized conditions in hand, $Fe(OAc)_2$ (2 mol %) in toluene (2 mL) at 120 °C, we explored the scope and limitations of $Fe(OAc)_2$ in the catalytic addition of a variety of primary aromatic amines bearing different functional groups (Tables 2 and 3). As illustrated in Table 2, the Fe-catalyzed guanylation displayed remarkable functional group tolerance; many functionalities, such as -halogens (F, Cl, Br, I), $–NO_2$, –CN, –COMe, –COOEt, –OMe, and –Me, were unaffected under the reaction conditions used (Table 2, entries 1–17). In all cases excellent yields (>90% isolated yield) were obtained, and no difference was detected for electron-withdrawing or electron-donating groups under the described reaction conditions. For the *ortho* and *meta*-substituted anilines a slight increase in the temperature (130 °C) and time (2–2.5 h) were applied to improve the yields of the corresponding guanidines (Table 2, entries 18–25).

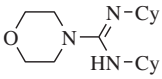
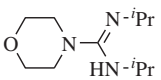
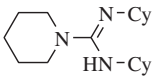
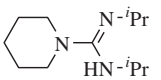
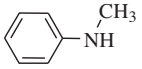
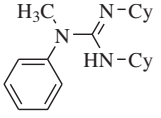
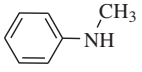
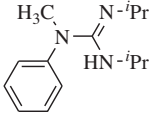
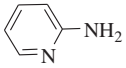
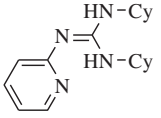
The reaction also worked well with *N,N′*-diisopropylcarbodiimide (Table 2, entries 1–27). Different *p*-, *o*, *m*-substituted electron-rich and electron-deficient anilines were also added conveniently to *N,N′*-diisopropylcarbodiimide in excellent yields. The addition reaction between the sterically hindered 2,4,6-trimethylaniline and *N,N′*-dicyclohexylcarbodiimide or *N,N′*-diisopropylcarbodiimide also afforded high yield of the corresponding guanidines (Table 2, entries 26 and 27, respectively). We have also explored

Table 2
$Fe(OAc)_2$-catalyzed addition of aromatic primary amines to RN = C = NR[a]

Entry	$ArNH_2$	Carbodiimide	Time (h)	*T* (°C)	Yield[b] (%)
1	$C_6H_5NH_2$	CyN = C = NCy	2	120	94
2	4-OMe-$C_6H_4NH_2$	CyN = C = NCy	2	120	97
3	4-OMe-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	1.5	120	97
4	4-Me-$C_6H_4NH_2$	CyN = C = NCy	2	120	96
5	4-NO_2-$C_6H_4NH_2$	CyN = C = NCy	1.5	120	95
6	4-NO_2-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	1.5	120	93
7	4-F-$C_6H_4NH_2$	CyN = C = NCy	1.5	120	96
8	4-F-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	1.5	120	94
9	4-Cl-$C_6H_4NH_2$	CyN = C = NCy	1.5	120	94
10	4-Cl-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	1.5	120	96
11	4-Br-$C_6H_4NH_2$	CyN = C = NCy	1.5	120	94
12	4-I-$C_6H_4NH_2$	CyN = C = NCy	1.5	120	93
13	4-I-$C_5H_4NH_2$	^{i}PrN = C = N^{i}Pr	1.5	120	95
14	4-CN-$C_6H_4NH_2$	CyN = C = NCy	1.5	120	94
15	4-CN-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	1.5	120	93
16	4-COMe-$C_6H_4NH_2$	CyN = C = NCy	1.5	120	91
17	4-COOMe-$C_6H_4NH_2$	CyN = C = NCy	1.5	120	90
18	2-Me-$C_6H_4NH_2$	CyN = C = 8NCy	2	130	92
19	2-OMe-$C_6H_4NH_2$	CyN = C = NCy	2	130	93
20	2-OMe-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	2	130	91
21	2-NO_2-$C_6H_4NH_2$	CyN = C = NCy	2.5	130	91
22	2-NO_2-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	2	130	90
23	2-I-$C_6H_4NH_2$	CyN = C = NCy	2.5	130	89
24	3-Me-$C_6H_4NH_2$	CyN = C = NCy	2.5	130	91
25	3-Me-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	2	130	90
26	2,4,6-$(Me)_3$-$C_6H_4NH_2$	CyN = C = NCy	3	130	90
27	2,4,6-$(Me)_3$-$C_6H_4NH_2$	^{i}PrN = C = N^{i}Pr	3	130	88

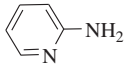
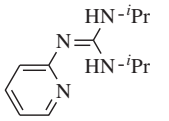
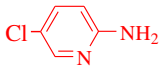
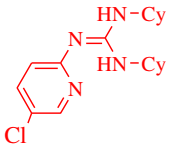
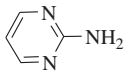
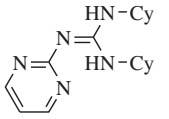
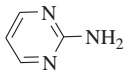
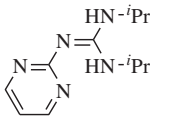
[a] Reaction conditions: aromatic amine (1 mmol), carbodiimide (1.2 mmol), $Fe(OAc)_2$ (2 mol %), and toluene (2 mL).
[b] Yield of isolated product.

Table 3
$Fe(OAc)_2$-catalyzed guanylation with heteroaryl and secondary amines[a]

Entry	Amine	Carbodiimide	Product	Yield[b] (%)
1		CyN = C = NCy		96
2		^{i}PrN = C = N^{i}Pr		97
3		CyN = C = NCy		78[c]
4		^{i}PrN = C = N^{i}Pr		82[c]
5		CyN = C = NCy		60
6		^{i}PrN = C = N^{i}Pr		68
7		CyN = C = NCy		95

(*continued on next page*)

Table 3 (*continued*)

Entry	Amine	Carbodiimide	Product	Yield[b] (%)
8		^{i}PrN = C = N^{i}Pr		92
9		CyN = C = NCy		95
10		CyN = C = NCy		96
11		^{i}PrN = C = N^{i}Pr		94

[a] Reaction conditions: amine (1 mmol), carbodiimide (1.2 mmol), $Fe(OAc)_2$ (5 mol %), and toluene (2 mL) at 140 °C for 5 h.
[b] Yield of isolated product.
[c] Reaction performed in a pressure tube.

the addition reaction of the asymmetrical carbodiimide 1-*tert*-butyl-3-ethylcarbodiimide. Its reaction with 4-methoxyaniline gave 55% yield of the corresponding guanidine after 5 h of reaction at 130 °C.

Notably, the iron catalytic system demonstrated excellent performance with more challenging substrates such as secondary cyclic and heterocyclic amines. These results are summarized in Table 3. All substrates are fully converted into the corresponding guanidines essentially in quantitative yields (Table 3, entries 1–4 and 7–11). The less basic amino-heterocyclic 2-amino-5-chloropyridine was also fully converted to the corresponding guanidine (Table 3, entry 9). However, the addition of N-methylaniline to *N*,*N*′-dicyclohexyl- and *N*,*N*′-diisopropyl-carbodiimide gave lower yields of the corresponding guianidines (Table 3, entries 5 and 6).

In conclusion, we have demonstrated that $Fe(OAc)_2$ is a versatile and efficient catalyst for the guanylation of amines. The main features of this catalyst are: (i) its low price and availability; (ii) its lower toxicity compared to other aluminum-, lithium, and lanthanide-based catalysts used for this reaction; (iii) its tolerance to air and moisture; (iv) its high efficiency, broad application, and its tolerance to many functional groups. In addition, remarkable advantages of this protocol include high isolated yields, clean reactions, and easy work-up.

Acknowledgments

The authors thank FCT of Portugal for financial support, POCI 2010, and FEDER through project PTDC/QUI-QUI/110349/2009. S.P. thanks FCT for grant SFRH/BDP/68720/2010. We thank FCT for REDE/1504/REM/2005 and REDE/1517/RMN/2005. The authors thank João M.S. Cardoso (from our group at ITQB) for preparation of the iron complex (Cp*-NHC)Fe(CO)I.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.065.

References and notes

1. (a) Guilman, A.; Gododman, L. S.; Rall, T. W. *The Pharmacological Basis of Therapeutics*, 7th Ed.; Pergamon Press: New York, 1990. pp 899; (b) Manimala, J. C.; Anslyn, E. V. *Eur. J. Org. Chem.* **2002**, *67*, 3909–3922; (c) Rodriguez, F.; Rozas, I.; Ortega, J. E.; Erdozain, A. M.; Meana, J. J.; Callado, L. F. *J. Med. Chem.* **2009**, *52*, 601–609; (d) Katritzky, A. R.; Rogovoy, B. V. *Arkivoc* **2005**, 49–87.
2. (a) Mori, A.; Cohen, B. D.; Lowenthal, A. *Guanidines: Historical, Biological, Biochemical and Clinical Aspects of the Naturally Occurring Guanidino Compounds, Ed*; Plenum Press: New York, 1985; (b) More, A.; Cohen, B. D.; Koide, H. *Further Explorations of the Biological and Clinical Significance of Guanidino Compounds, Ed*; Plenum Press: New York, 1987.
3. (a) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, *5*, 737–753; (b) Kovacevik, B.; Maksic, Z. B. *Org. Lett.* **2001**, *3*, 1523–1526; (c) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 552–557; (d) Bailey, P. J.; Pace, S. *Coord. Chem. Rev.* **2001**, *214*, 91–141; (e) Berry, J. F.; Cotton, F. A.; Ibragimov, S. A.; Murillo, C. A.; Wang, X. *Inorg. Chem.* **2005**, *44*, 6129–6137.
4. Ong, T.-G.; Yap, G. P. A.; Richeson, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 8100–8101.
5. (a) Montilla, F.; del Rio, D.; Pastor, A.; Galindo, A. *Organometallics* **2006**, *25*, 4996–5002; (b) Montilla, F.; Pastor, A.; Galindo, A. J. *Organomet. Chem.* **2004**, *689*, 993–996.
6. (a) Zhang, W. X.; Nishiura, M.; Hou, Z. *J. Am. Chem. Soc.* **2005**, *127*, 16788–16789; (b) Zhang, W. X.; Nishiura, M.; Hou, Z. *Chem. Eur. J.* **2007**, *13*, 4037–4051; (c) Zhang, W. X.; Nishiura, M.; Hou, Z. *Synlett* **2006**, 1213–1216.
7. (a) Li, Q.; Wang, S.; Zhou, S.; Yang, G.; Zhu, X.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 6763–6767; (b) Zhou, S. L.; Wang, S.; Yang, G.; Li, Q.; Zhang, L.; Yao, Z.; Zhou, Z.; Song, H. *Organometallics* **2007**, *26*, 3755–3761; (c) Cao, Y.; Du, Z.; Li, W.; Zhang, Y.; Xu, F.; Shen, Q. *Inorg. Chem.* **2011**, *50*, 3729–3737.
8. Ong, T. G.; ÓBrien, J. S.; Korobkov, I.; Richeson, D. S. *Organometallics* **2006**, *25*, 4728–4730.
9. Shen, H.; Chan, H. S.; Xie, Z. W. *Organometallics* **2006**, *25*, 5515–5517.
10. Alonso-Moreno, C.; Carrillo-Hermosilla, F.; Garcés, A.; Otero, A.; López-Solera, I.; Rodríguez, A. M.; Antiñolo, A. *Organometallics* **2010**, *29*, 2789–2795.
11. Zhang, W. X.; Li, D.; Wang, Z.; Xi, Z. *Organometallics* **2009**, *28*, 882–887.
12. Li, D.; Guang, J.; Zhang, W.-X.; Wang, Y.; Xi, Z. *Org. Biomol. Chem.* **2010**, *8*, 1816–1820.
13. (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254; (b) Plietker, B. *Iron Catalysis in Organic Chemistry, Ed*; Wiley-VCH: Weinheim, 2008.
14. Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317–3321.
15. Kandepi, V. V. K. M.; Cardoso, J. M. S.; Peris, E.; Royo, B. *Organometallics* **2010**, *29*, 2777–2782.
16. Cardoso, J. M. S.; Royo, B. *Chem. Commun.* **2012**, *48*, 4944–4946.