Volume 3, issue 1, (2016), pp. 19-26. **Research article**

Journal homepage: http://dergipark.ulakbim.gov.tr/jotcsa

e-ISSN: 2149-0120

SYNTHESIS OF GUANIDINES VIA REACTION OF AMINES WITH CARBODIIMIDES IN THE PRESENCE OF IONIC LIQUID

Foad Shaghayeghi Toosi*

**Pharmed Medical Industries, Eshtehard Industrial Zone, Iran.*

Abstract: Different ionic liquids (ILs) were synthesized and evaluated for the preparation of substituted guanidines from the reaction of amines and carbodiimides. 1-methylimidazolium tetrafluoroborate [HMIm]BF_4 was found to be the best ionic liquid for this reaction. This IL acted as a promoter for the addition of primary and secondary amines to carbodiimides. By this efficient approach, various guanidines were prepared in excellent yields.

Keywords: Guanylation, ionic liquids, carbodiimide.

Submitted: August 5, 2015. **Revised:** November 16, 2015. **Accepted:** January 11, 2016.

Cite this: Shaghayeghi Toosi F. SYNTHESIS OF GUANIDINES VIA REACTION OF AMINES WITH CARBODIIMIDES IN THE PRESENCE OF IONIC LIQUID. JOTCSA. 2016;3(1):19–26.

DOI: 10.18596/jotcsa.44903.

Correspondence to: Foad Shaghayeghi Toosi. E-mail: Foad.shaghayeghi@pharmed.co, tel:+98(26)37777620.

Introduction

The formations of C-C and C-N bonds are among the most important transformations in synthetic organic chemistry. Substituted guanidines possess a wide range of interesting and important biochemical and pharmaceutical properties. Moreover, guanidine derivatives have also been widely used as ligands for various metal complexes, including those of early transition metals and lanthanides [1]. As a result, the synthesis of guanidine has been intensively investigated. Among these, addition of amine N-H bonds to carbodiimides, providing a straightforward and atom-economical path to guanidines, is a typical one. Additionally, hydroamination of carbodiimides provides a direct approach to guanidines without the formation of any byproducts [2-7]. The guanylation of amines without catalyst requires harsh conditions [7]. However, very few catalysts have been used to promote the catalytic addition of amines to carbodiimides [8]. In the absence of a catalyst, aromatic amines do not react with diisopropylcarbodiimide to any detectable degree even with prolonged heating at 140 °C. The catalytic addition of primary aromatic amines to carbodiimides was reported by using titanium and vanadium imido complexes to yield the corresponding guanidines, but secondary amines could not be used in these reactions, because the catalytic process required the regeneration of a "M.N" imido moiety [9]. Rare earth metal amido complexes such as lanthanocene amides $(EBI)LnN(TMS)_2$ (EBI = ethylenebisindenyl, TMS = trimethylsilyl), cyclopentadienyl-free rare earth metal amido complexes such as $[(Me_3Si)_2N]_3Ln(l\text{-}Cl)Li(THF)_3$, $Ln[N(SiMe_3)_2]_3$ have found good catalytic activity for guanylation [2-7]. Recently, $Yb(OTf)_3$ [10], $AlMe_3$ [11], SmI_2 [12] and titanocarborane complexes [13] catalyzed guanylation of carbodiimides by amines. In fact, although various metal complexes and organometallic compounds have been reported, there is a clear lack of research investment in the field of carbodiimide activation and no metal free approach could be found in the literature, and in particular, the products were easily separated.

On the other hand, ionic liquids have recently received growing attention due to their tunable features for various chemical tasks and their advantages as reusable homogeneous catalysts, reaction media, and reagents with "green" aspects. Most importantly, their non-volatility, high thermal stability, and extraordinary solvent properties make them green solvents for the chemical industry [14]. These remarkable properties of ionic liquids (ILs) all serve to facilitate various chemical transformations when these are used as the reaction media [15]. Also, the high solubility of many organic and inorganic compounds in room temperature ionic liquids (RTILs) can, in principle, lead to enhanced rates and improved yields for reactions [15].

We are interested in contributing to this field by developing new catalysts, reactions, and targets. One aspect of our research involves the use of RTILs for novel reactions, without metal catalysts. The increasing number of structurally diverse guanidine compounds with biological relevancy highlights a need for new strategies to address the significant synthetic challenges associated with the introduction and manipulation of substituted guanidines. To the best of our knowledge, the metal-free guanylation of aromatic or secondary amines using conventional ionic liquids has not yet been reported. It would be a novel application of ionic liquids. In this paper, we wish to report the hydroamination reaction of amines and carbodiimides using the ionic liquid, [HMIm] [BF_4], as a green media which resulted in high yields of product (Scheme 1). Also, this transformation is carried out without the use of a catalyst.

Experimental Section

Preparation of different ionic liquids: The synthesis of all the ionic liquids has been carried out using similar method reported in the literature [16].

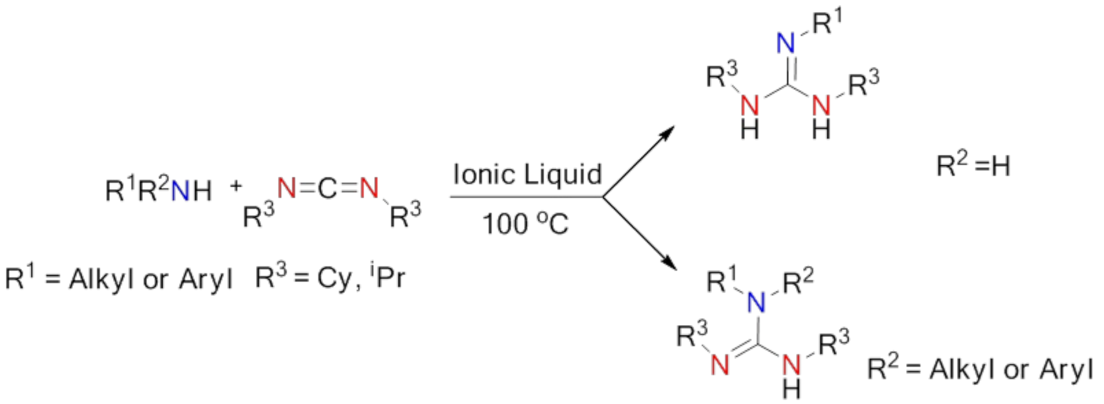
General procedure for the direct synthesis of guanidines using ionic liquid [HMIm][BF_4]: To a round bottom flask, ionic liquid (1.2 mmol, 0.204 g) was added to a mixture of N,N-diisopropylcarbodiimide (1 mmol, 0.126 g) and aniline (1 mmol, 0.93 g). The resulting mixture was stirred at room temperature until completion of the reaction. The reaction mixture was then hydrolyzed with a solution of Na_2CO_3. The product was separated as a white solid by filtration and vacuum-dried.

Results and Discussion

The guanylation of morpholine and diisopropylcarbodiimide was selected as the model for subsequent screening. Ionic liquids were used because of the recent rise in their application in organic transformation. Ionic liquid can also be synthesized with relative ease. In our study, we used a series of both protic and aprotic ionic liquids. As shown in Table 1, the reaction efficiency was significantly influenced by fine-tuning the cationic and anionic moieties of the ionic liquids. Among the different ILs examined as the promoter, the protic N-methyl-imidazolium ionic liquid with BF_4 as anion exhibited the highest reaction efficiency, as compared to the other ionic liquids. As summarized in Table 2, there are representative results obtained from [HMIm][BF_4]-mediated reactions among aromatic and aliphatic amines with carbodiimides at 100 ^oC. Aromatic amines with either electron withdrawing or electron–donating groups, all afforded their corresponding guanidine products in good isolated yields. In addition, aliphatic secondary amines could be also applied. At the end of the reaction, guanylation products were hydrolyzed with alkaline water and solid products were separated with filtration.

Table 1: Guanylation of morpholine and DCC by different ionic liquids at 100 °C.

Entry	Ionic Liquid	Time (h)	Yield (%)
1	N/A	12	N/A
2	$[HMIm][BF_4]$	6	89
3	$[HMIm][NO_3]$	12	10
4	[TMG][TFA]	12	10
5	[HMIm][TFA]	12	20
6	$[TMG][HSO_4]$	12	40
7	[TMG][Ac]	12	20



Scheme 1. Addition of amines to carbodiimides by ionic liquid.

Table 2: Reaction of amines with carbodiimides in the presence of Ionic Liquid.

Entry	Amine	R^3	Yield (%)[a]	Time (h)
1	Aniline	Cy	96	1
2	4-Methylaniline	Cy	94	1
3	4-Bromoaniline	Cy	96	0.5
4	4-Chloroaniline	Cy	96	1
5	4-Methoxyaniline	Cy	90	1
6	2-Nitroaniline	Cy	84	1
7	4-Nitroaniline	Cy	95	1
8	Benzylamine	Cy	80	3
9	Morpholine	Cy	89	6
10	Aniline	^{i}Pr	90	2
11	4-Chloroaniline	^{i}Pr	80	1
12	4-Bromoaniline	^{i}Pr	93	1
13	Morpholine	^{i}Pr	85	5

[a]Yields refer to isolated pure compounds.

Conclusion

In conclusion, we would like to emphasize that [HMIm][BF_4] as a catalyst offers a straightforward, atom-economic route to synthesis of N,N', N''- trisubstituted guanidines. [HMIm][BF_4] catalyzes the guanylation of carbodiimides without use of organometallic compounds or transition metal complexes.

References

[1] Mori A, Cohen BD, Lowenthal A, Japan Guanidino Compounds Research Association, editors. Guanidines: historical, biological, biochemical, and clinical aspects of the naturally occurring guanidino compounds. New York: Plenum Press; 1985. 479 p. ISSN: 978-0-306-41920-1.

[2] a)Wu Y-Q, Hamilton SK, Wilkinson DE, Hamilton GS. Direct Synthesis of Guanidines Using Di(imidazole-1-yl)methanimine. The Journal of Organic Chemistry. 2002 Oct;67(21):7553–6. DOI: 10.1021/jo0202381.
b) Evindar G, Batey RA. Copper- and Palladium-Catalyzed Intramolecular Aryl Guanidinylation: An Efficient Method for the Synthesis of 2-Aminobenzimidazoles †. Organic Letters. 2003 Jan;5(2):133–6. DOI: 10.1021/ol027061h.
c) Powell DA, Ramsden PD, Batey RA. Phase-Transfer-Catalyzed Alkylation of Guanidines by Alkyl Halides under Biphasic Conditions: A Convenient Protocol for the Synthesis of Highly Functionalized Guanidines. The Journal of Organic Chemistry. 2003 Mar;68(6):2300–9. DOI: 10.1021/jo0265535.

[3] Li J, Zhang Z, Fan E. Solid-phase synthesis of 1,5-substituted 2-(N-alkylamino)-imidazolidin-4-ones. Tetrahedron Letters. 2004 Feb;45(6):1267–9. DOI: 10.1016/j.tetlet.2003.11.127.

[4] Vaidyanathan G, Zalutsky MR. A New Route to Guanidines from Bromoalkanes. The Journal of Organic Chemistry. 1997 Jul;62(14):4867–9. DOI: 10.1021/jo9704164.

[5] Linton BR, Carr AJ, Orner BP, Hamilton AD. A Versatile One-Pot Synthesis of 1,3-Substituted Guanidines from Carbamoyl Isothiocyanates. The Journal of Organic Chemistry. 2000 Mar;65(5):1566–8. DOI: 10.1021/jo991458q.

[6] Feichtinger K, Zapf C, Sings HL, Goodman M. Diprotected Triflylguanidines: A New Class of Guanidinylation Reagents. The Journal of Organic Chemistry. 1998 Jun;63(12):3804–5.

[7] Tin MKT, Thirupathi N, Yap GPA, Richeson DS. Guanidinate anions and dianions. Reactions involving alkylguanidines, (RNH)2CNR (R = i-Pr or Cy), and metal amido complexes M(NMe2)5 (M = Ta or Nb). Journal of the Chemical Society, Dalton Transactions. 1999;(17):2947–51. DOI: 10.1039/a904072b.

[8] a) Zhang W-X, Hou Z. Catalytic addition of alkyne C–H, amine N–H, and phosphine P–H bonds to carbodiimides: an efficient route to propiolamidines, guanidines, and phosphaguanidines. Organic & Biomolecular Chemistry. 2008;6(10):1720. DOI: 10.1039/b800135a.
b) Zhang W-X, Nishiura M, Hou Z. Catalytic Addition of Amine N-H Bonds to Carbodiimides by Half-Sandwich Rare-Earth Metal Complexes: Efficient Synthesis of Substituted Guanidines through Amine Protonolysis of Rare-Earth Metal Guanidinates. Chemistry - A European Journal. 2007 May 7;13(14):4037–51. DOI: 10.1002/chem.200601383.
c) Zhang W-X, Nishiura M, Hou Z. Catalytic Addition of Secondary Amines to Carbodiimides by a Half-Sandwich Yttrium Complex: An Efficient Route to N,N′,N′′,N′′-Tetra¬substituted Guanidines. Synlett. 2006 May;2006(8):1213–6. DOI: 10.1055/s-2006-939081.

[9] a) Ong T-G, Yap GPA, Richeson DS. Catalytic Construction and Reconstruction of Guanidines: Ti-Mediated Guanylation of Amines and Transamination of Guanidines. Journal of the American Chemical Society. 2003 Jul;125(27):8100–1. DOI: 10.1021/ja035716j.
b) Montilla F, Pastor A, Galindo A. Guanylation of aromatic amines catalyzed by vanadium imido complexes. Journal of Organometallic Chemistry. 2004 Mar;689(6):993–6. DOI: 10.1016/j.jorganchem.2004.01.005. DOI: 10.1016/j.jorganchem.2004.01.005.

[10] Zhu X, Du Z, Xu F, Shen Q. Ytterbium Triflate: A Highly Active Catalyst for Addition of Amines to Carbodiimides to N , N ′, N ′′-Trisubstituted Guanidines. The Journal of Organic Chemistry. 2009 Aug 21;74(16):6347–9. DOI: 10.1021/jo900903t.

[11] Zhang W-X, Li D, Wang Z, Xi Z. Alkyl Aluminum-Catalyzed Addition of Amines to Carbodiimides: A Highly Efficient Route to Substituted Guanidines. Organometallics. 2009 Feb 9;28(3):882–7. DOI: 10.1021/om801035t.

[12] Du Z, Li W, Zhu X, Xu F, Shen Q. Divalent Lanthanide Complexes: Highly Active Precatalysts for the Addition of N−H and C−H Bonds to Carbodiimides. The Journal of Organic Chemistry. 2008 Nov 21;73(22):8966–72. DOI: 10.1021/jo801693z.

[13] Shen H, Chan H-S, Xie Z. Guanylation of Amines Catalyzed by a Half-Sandwich Titanacarborane Amide Complex. Organometallics. 2006 Nov;25(23):5515–7. DOI: 10.1021/om060811x.

[14] Wasserscheid P, Welton T. Ionic liquids in synthesis [Internet]. Weinheim: Wiley-VCH; 2003 [cited 2016 Jan 16]. ISBN: 978-3-527-60544-6 978-3-527-60070-0.

[15] Greaves TL, Drummond CJ. Protic Ionic Liquids: Properties and Applications. Chemical Reviews. 2008 Jan;108(1):206–37. DOI: 10.1021/cr068040u.

[16] a) Holbrey JD, Seddon KR. The phase behaviour of 1-alkyl-3-methylimidazolium tetrafluoroborates; ionic liquids and ionic liquid crystals. Journal of the Chemical Society, Dalton Transactions. 1999;(13):2133–40. DOI: 10.1039/a902818h.
b) Palimkar SS, Siddiqui SA, Daniel T, Lahoti RJ, Srinivasan KV. Ionic Liquid-Promoted Regiospecific Friedlander Annulation: Novel Synthesis of Quinolines and Fused Polycyclic Quinolines. The Journal of Organic Chemistry. 2003 Nov;68(24):9371–8. DOI: 10.1021/jo035153u.
c) Zhu A, Jiang T, Han B, Huang J, Zhang J, Ma X. Study on guanidine-based task-specific ionic liquids as catalysts for direct aldol reactions without solvent. New Journal of Chemistry. 2006;30(5):736. DOI: 10.1039/b600277c.
d) Cole AC, Jensen JL, Ntai I, Tran KLT, Weaver KJ, Forbes DC, et al. Novel Brønsted Acidic Ionic Liquids and Their Use as Dual Solvent−Catalysts. Journal of the American Chemical Society. 2002 May;124(21):5962–3. DOI: 10.1021/ja026290w.
e) Leng Y, Wang J, Zhu D, Ren X, Ge H, Shen L. Heteropolyanion-Based Ionic Liquids: Reaction-Induced Self-Separation Catalysts for Esterification. Angewandte Chemie. 2009 Jan;121(1):174–7. DOI: 10.1002/ange.200803567.

Türkçe öz ve anahtar kelimeler

İYONİK SIVI VARLIĞINDA KARBODİİMİDLERLE AMİNLERİN TEPKİMESİNDEN GUANİDİNLERİN SENTEZİ

Öz: Farklı iyonik sıvılar (IS) sentezlenmiş ve aminler ile karbodiimidler arasındaki reaksiyondan sübstitüe guanidinlerin hazırlanmasında değerlendirilmiştir. Bu reaksiyonlar sırasında 1-metilimidazolyum tetrafloroborat [HMIm]BF_4, en iyi iyonik sıvı olarak tespit edilmiştir. Bu IS, karbodiimidlere primer ve seconder aminlerin katılmasında bir destekçi olarak davranmaktadır. Bu etkili yaklaşım ile çeşitli guanidinler mükemmel verimlerle sentez edilmiştir.

Anahtar kelimeler: Guanillenme, iyonik sıvılar, karbodiimid.