This article was downloaded by: [East Carolina University]
On: 28 July 2013, At: 11:06
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Convenient Preparation of Bicyclic Guanidines

Sergei Usachev [a] & Alexei Gridnev [a]

[a] Institute of Chemical Physics of the Russian Academy of Sciences, Moscow, Russian Federation

Accepted author version posted online: 30 Jun 2011.Published online: 16 Jun 2011.

To cite this article: Sergei Usachev & Alexei Gridnev (2011) Convenient Preparation of Bicyclic Guanidines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:24, 3683-3688, DOI: 10.1080/00397911.2010.519848

To link to this article: http://dx.doi.org/10.1080/00397911.2010.519848

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

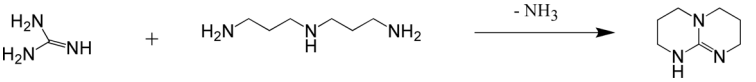
Synthetic Communications®, 41: 3683–3688, 2011
Copyright © Taylor & Francis Group, LLC
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.519848

Taylor & Francis
Taylor & Francis Group

CONVENIENT PREPARATION OF BICYCLIC GUANIDINES

Sergei Usachev and Alexei Gridnev
Institute of Chemical Physics of the Russian Academy of Sciences, Moscow, Russian Federation

GRAPHICAL ABSTRACT



Abstract *New synthesis of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was developed from inexpensive and nontoxic chemicals. Guanidine, cyanamide, or their derivatives are heated with bis (3-aminopropyl)amine and a strong acid at 140–180°C for 7–9 h to form TBD in 95–97% yield.*

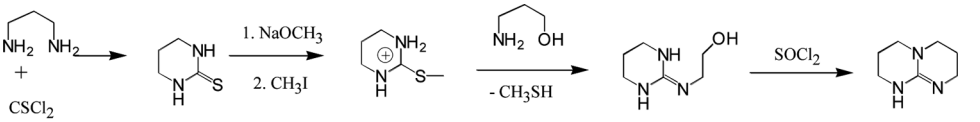
Keywords Bicyclic guanidine; guanidine; synthesis; TBD

Downloaded by [East Carolina University] at 11:06 28 July 2013

INTRODUCTION

Cyclic guanidines are known for their outstanding basicity,[1,2] which makes them good catalysts in a number of reactions.[3–10] Solid-phase-supported guanidines have also been employed.[11] However, cyclic guanidines are not readily available. We were able to find only 1,5,7-triazabicyclo[4.4.o]dec-5-ene (TBD), not other bicyclic guanidines, in a few catalogs, and it cost about \$1/g. Cost is a major obstacle to wide usage of cyclic guanidines.

One of the straightforward and, most likely, most reliable synthesis of TBD can be found in Ref. 12. The reaction (1) from this reference, is given.

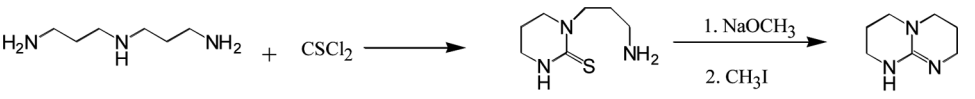


(1)

This reaction scheme can be simplified to Eq. (2) if corresponding triamine is taken instead of propylenediamine.[13]

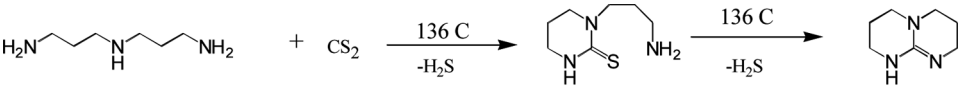
Received August 23, 2010.

Address correspondence to Alexei Gridnev, Institute of Chemical Physics of the Russian Academy of Sciences, 4 Kosygin St., Moscow, Russian Federation. E-mail: aagridnev@gmail.com



(2)

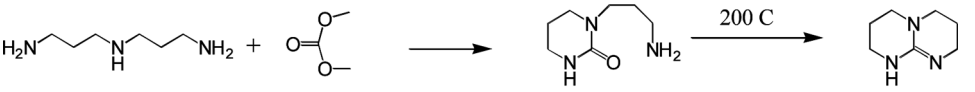
Despite good yields, toxic intermediates (thiophosgene and mercaptane), make this synthetic route not very convenient. Another synthesis of TBD[14] suggests carbon disulfide to replace thiophosgene; however, the hydrogen sulfide that forms in the reaction is still quite toxic [Eq. (3)]:



(3)

The authors claimed yields of ~80%. We tried to reproduce this synthesis and obtained mostly polyureas with at most ~40% of TBD yield. Moreover, TBD was contaminated with a substantial amount (>40%) of impurities, which were difficult to remove. Perhaps because of these difficulties other authors[15] used higher temperatures and different solvents for the reaction (3).

Recent patents[16,17] suggest using cyclic urea derivatives at elevated temperatures or dehydrating agents such as orthosilicates (4):

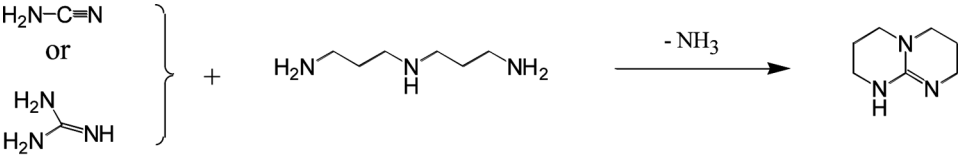


(4)

Another reported interesting approach to the synthesis of TBD is hydrogenation of bis(β-cyanoethyl)amine.[18]

RESULTS AND DISCUSSION

We found that TBD can be made easily and in good yields using a number of cyanamide and guanidine salts in one step (5):

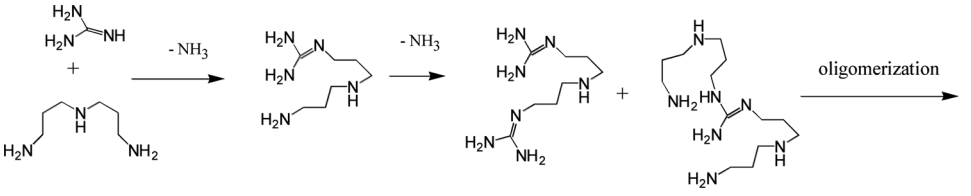


(5)

Downloaded by [East Carolina University] at 11:06 28 July 2013

Addition of acids (HCl, TsOH, MsOH, and HBr) is essential in up to 1 equivalent of the amount of triamine. Without acids the yield of TBD was ~50%, while under the same conditions in the presence of acids >90% yields are typical. The best temperature for reaction (5) is >130 °C. Below this temperature, the reaction is slow. We did not try to find the high-temperature limit because at 150–170 °C very good yields of pure TBD can be reached.

Apparently, formation of a TBD starts with a substitution of a nitrogen atom in guanidine with a nitrogen atom from the triamine followed by a number of further substitutions with formation both TBD and oligomeric products (6):



(6)

The major driving force for the reactions (6) is constant removal of volatile amines from the reaction mixture. It could be ammonia (guanidine) or dimethylamine (tetramethylguanidine). In neutral form, the oligomers are relatively stable. However, protonated oligomers become labile. In the presence of acids, a number of cross-substitution reactions occur, leading to the most stable product, which is TBD salt.

In first-approximation reaction (5) follows first-order kinetics (Fig. 1). Most likely, first and second substitution are faster than the third substitution, which leads to a cyclic product because the secondary amino group is involved instead of primary

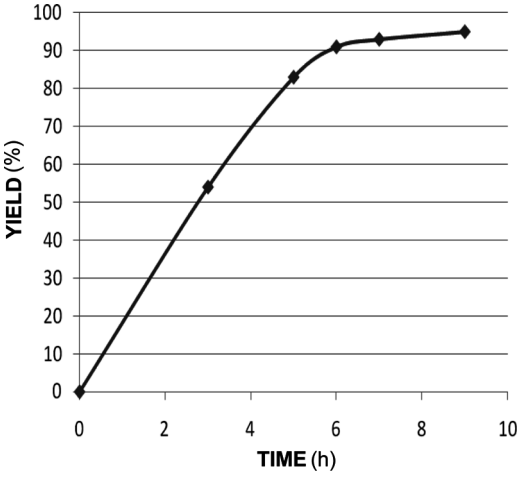


Figure 1. Kinetics of TBD synthesis at 155 °C followed by NMR. Equimolar amounts of guanidine hydrochloride and bis(3-aminopropyl)amine, no solvent.

Downloaded by [East Carolina University] at 11:06 28 July 2013

ones. Most of TBD is obtained in the first 4–5 h of heating. Then the reaction slows down. Reaction (5) can be easily monitored by ammonia evolution. We obtained almost quantitative yields at 7–9 h. However, even at 9 h, evolution of ammonia continues. Inert solvents, for example, triglyme, do not improve the rate of the reaction much and make isolatiotion of TBD challenging.

TBD salts are liquid at $>120\,^{\circ}C$ and can be potentially used as ionic liquids. Free TBD can be easily obtained from its salts by treatment with sodium or potassium hydroxides or alkoholates.

CONCLUSIONS

Condensation of guanidine and cyanamide with bis(3-aminopropyl)amine is a simple and technologically convenient synthesis of TBD. We believe that bis(3-aminopropyl)amine can be replaced with other triemines so that other cyclic guanidines, such as 1,4,6-triazabicyclo[3.3.0]oct-4-ene (TBO), can be made utilizing the same principle, condensation in the presence of strong acids under elevated temperatures. A noteworthy advance of our synthesis is the vability to reach >95% purity of TBD in one step without any additional purification. For comparison, few samples of commercial TBD available for us were found to be less than 80% pure.

In organic synthesis, condensation with amines may lead to oligomers rather than to a cyclic product. Previously,[19] we reported synthesis of imidazoles via condensation of amines with dialdehydes. It was shown that addition of strong acids drastically improved yields of imidazoles versus polyimines. One may conclude that acidification could be a general approach to suppress formation of polyimines when more thermodynamically stable products are desired.

Instead of guanidine and cyanamide, their derivatives can be used for synthesis of TBD, such as tertramethylguanidine or dicyandiamide, at 75–85% yields, although no optimization was attempted. In the case of cyanamide, the first step in reaction (5) is addition of the triamine to the triple bond with formation of guanidine. One may conclude that all guanidine moiety–containing structures can produce cyclic guanidine according to reaction (5). However, melamine was found to be inert. This indicates the importance of good basicity of the ''guanidine'' component in the reaction.

EXPERIMENTAL

Guanidine carbonate, guanidine hydrochloride (ReaKhim), hydrobromic acid (ReaKhim), MsOH (methanesulfonic acid), and TsOH (p-toluenesulfonic acid, both Acros), and triglyme (Aldrich) were used as received. Bis(3-aminopropyl)amine (Acros) was vacuum distilled prior to use. NMR spectra were recorded using a Jeol 400-MHz instrument.

Guanidine hydrochloride (9.5 g, 0.1 mol) and 13.1 g of bis(3-aminopropyl) amine (0.1 mol) in were heated at $155\,^{\circ}C$ a 100-mL round-bottom flask with slow agitation. After dissolution of guanidine (~20 min), gaseous ammonia started to form. After 7–9 h, the reaction mixture was chilled to 60–70 °C, and 30 ml of methanol was added.

After homogenization, 0.1 mol of $NaOCH_3$ solution in methanol was added. The mixture was evaporated under reduced pressure to remove most of the

Downloaded by [East Carolina University] at 11:06 28 July 2013

methanol. Then 30 ml of methylene chloride was added. Sodium chloride was filtered off, and methylene chloride solution was evaporated, first in a rotary evaporator, then under high vacuum (<5 Torr for 1–3 h) at 90 °C. Yield: 12.9 g (93%) of slightly yellow/off-white soft solid material. ^{1}H NMR (D_2O, 400 MHz, 25 °C) δ 3.207 (t, 4H, $^1J = 6.0$ Hz); 3.270 (t, 4H, $^1J = 6.0$ Hz); 1.959 (p, 4H, $^1J = 6.0$ Hz). Estimated purity is 95–97% as calculated by comparison of TBD resonance at 1.96 ppm versus impurity signals at 1.84 and 1.7 ppm.

In the case of experiments where TsOH or MsOH acids were used, the acids were added slowly after guanidine carbonate or cyanamide have been mixed with triamine. Guanidine hydrobride was made by slow addition of aquavious hydrobromic acid to guanidine carbonate followed by evaporation under vacuum.

Downloaded by [East Carolina University] at 11:06 28 July 2013

REFERENCES

1. Kiesewetter, M. K.; Scholten, M. D.; Kirn, N.; Weber, R. L.; Hedrick, J. L.; Waymouth, R. M. Cyclic guanidine organic catalysts: What is magic about triazabicyclodecene? *J. Org. Chem.* **2009**, *74*, 9490–9496
2. Kaljurand, I.; Kuett, A.; Soovaeli, L.; Rodima, T.; Maeemets, V.; Leito, I.; Koppel, I. A. Extension of the self-consistent spectrophotometric basicity scale in acetonitrile to a full span of 28 pKa units: Unification of different basicity scales. *J. Org. Chem.* **2005**, *70*, 1019–1028.
3. Pahadi, N. K.; Ube, H.; Terada, M. Aza-Henry reaction of ketimines catalyzed by guanidine and phosphazene bases. *Tetrahedron Lett.* **2007**, *48*, 8700–8703.
4. Yu, K. M. K.; Curcic, I.; Gabriel, J.; Morganstewart, H.; Tsang, S. C. Catalytic coupling of CO_2 with epoxide over supported and unsupported amines. *J. Phys. Chem. A* **2010**, *114*, 3863–3872.
5. Mahe, O.; Frath, D.; Dez, I.; Marsais, F.; Levacher, V.; Briere, J.-F. TBD-organocatalysed synthesis of pyrazolines. *Org. Biomol. Chem.* **2009**, *7*, 3648–3651.
6. Ren, W. M.; Liu, Z. W.; Wen, Y. Q.; Zhang, R.; Lu, X. B. Mechanistic aspects of the copolymerization of CO_2 with epoxides using a thermally stable single-site cobalt(III) catalyst. *J. Am. Chem. Soc.* **2009**, *131*, 11509–11518.
7. Li, J.; Wen, P.; Luo, C. Manufacture of biodiesel from cottonseed oil by organic catalysis. *Faming Zhuanli Shenqing Gongkai Shuomingshu* **2009**, CN 101469272.
8. Williams, D. B. G.; Sibiya, M. S.; van Heerden, P. S.; Kirk, M.; Harris, R. Verkade super-base-catalyzed transesterification of propylene carbon.ate with methanol to co-produce dimethyl carbonate and propylene glycol. *J. Mol. Catal. A: Chem.* **2009**, *304*, 147–152.
9. Schmid, G. Organic light-emitting devices employing metal complexes with guanidinate ligands and phosphorescent metal complexes with guanidinate ligands. *PCT Int. Appl.* WO patent 2009039845, 2009.
10. Ye, W.; Xu, J.; Tan, C. T.; Tan, C. H. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)–catalyzed Michael reactions. *Tetrahedron Lett.* **2005**, *46*, 6875–6878.
11. Sartori, G.; Maggi, R.; Sartorio, R. Organic transformations through supported guanidines. *New Devel. Catal. Res.* **2005**, 129–160.
12. McKay, A. F.; Kreling, M. E. Preparation and chemistry of Δ8-hexahydro-1,4,8-pyrimidazole, Δ9–1,5,9-triazabicyclo [4.4.0] decene, and Δ9–1,4,9-triazabicyclo[5.3.0]decene. *Can. J. Chem.* **1957**, *35*, 1438–1445.
13. Schmidtchen, F. P. Synthesis of symmetrically substituted bicyclic guanidines. *Chem. Ber.* **1980**, *113*, 2175–2182.

14. A'Court, R. Process for preparation of bicyclic guanias catalysts for chemical reactions. *Eur. Patent Appl.* EP 198680, 1986.
15. Minch, B. A.; Hickenboth, C. R.; Karabin, R. F.; Zawacky, S. R.; Hockswender, T. R.; McCollum, G. J. Manufacture of bicyclic guanidines via cyclic thiourea. U.S. patent 20090286978, 2009.
16. Boyd, D. W.; Eswarakrishnan, V.; Hickenboth, C. R.; Karabin, R. F.; McCollum, G. J.; Minch, B. A.; Moriarity, T. C.; Zawacky, S. R. Method for producing bicyclic guanidines by use of a cyclic urea. U.S. patent 20090281314, 2009.
17. Minch, B. A.; Hickenboth, C. R.; Karabin, R. F.; Zawacky, S. R.; McCollum, G. J. Method for producing bicyclic guanidines by use of a cyclic urea. U.S. patent 20090281313, 2009.
18. Cheng, X.; Liu, F. A facile synthesis of intermediate of the bicyclic organic bases DBU and TBD. *Synth. Commun.* **1993**, *23*, 3191–3194.
19. Gridnev, A. A.; Mihaltseva, I. M. Synthesis of 1-alkylimidazoles. *Synth. Commun.* **1994**, *24*, 1547–1551.

Downloaded by [East Carolina University] at 11:06 28 July 2013