ORGANIC LETTERS

2011
Vol. 13, No. 21
5804–5807

N-Bromosuccinimide Promoted One-Pot Synthesis of Guanidine: Scope and Mechanism

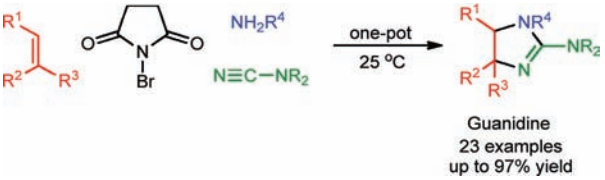
Ling Zhou, Jie Chen, Jing Zhou, and Ying-Yeung Yeung*

3 Science Drive 3, Department of Chemistry, National University of Singapore, Singapore 117543

chmyyy@nus.edu.sg

Received September 5, 2011

ABSTRACT



A novel electrophilic one-pot guanidine synthesis has been developed using an olefin, a cyanimide, an amine, and *N*-bromosuccinimide. A number of guanidine derivatives were prepared with good to excellent yields. An rTRTVI precursor was also prepared based on this useful process.

Guanidine is an important class of nitrogen-containing heterocyclic compounds, which is the fundamental unit of many natural products, biologically active molecules, and metal complexation ligands.[1] Due to its strong basicity, guanidine is also considered as an organic superbase that is useful in both stoichiometric and catalytic deprotonation processes.[2] Guanidine is also an attractive scaffold that is found in chiral auxiliaries[3] and chiral Brønsted base organocatalysts.[4]

Compared to other heterocyclic compounds' syntheses,[5] the synthetic methodologies for guanidine are limited to several representative approaches.[1i–k,3,4] Additionally, the demand for more environmentally benign processes has emerged in recent years due to the concern for sustainable development.[6] Herein we report a facile and efficient approach toward guanidine using a one-pot multicomponent strategy.

Recently, we have reported a novel electrophilic Br initiated cascade, which is applicable to the synthesis of aminoalkoxylation and imidazolines.[7] Indeed, we found that the same protocol can be applied to the construction of a guanidine skeleton.

Based on our previous study on the one-pot imidazoline synthesis,[7a] we modified the system by replacing the nitrile

(1) (a) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*, Vol. 1A; Padwa, A., Ed.; Pergamon Press: Oxford, UK, 1996; pp 1–60. (b) Rai, K. M. L.; Hassner, A. In *Comprehensive Heterocyclic Chemistry II*, Vol. 1A; Padwa, A., Ed.; Pergamon Press: Oxford, U.K., 1996; pp 61–96. (c) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*, Vol. 3; Katritsky, A. R., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; pp 77–220. (d) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919–954. (e) Berlinck, R. G. S.; Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516–550. (f) Nagasawa, K.; Hashimoto, Y. *Chem. Rec.* **2003**, *3*, 201–211. (g) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571–4624. (h) De Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1–23. (i) Suhs, T.; Koenig, B. *Mini Rev. Org. Chem.* **2006**, *3*, 315–331. (j) Sullivan, J. D.; Giles, R. L.; Looper, R. E. *Curr. Bioact. Compd.* **2009**, *5*, 39–78. (k) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237–243.

(2) (a) Kumamoto, T. In *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organoctalysts*; Ishikawa, I., Ed.; John Wiley & Sons Press: West Sussex, U.K., 2009; pp 295–313. (b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737–752.

(3) (a) Isobe, T.; Fukuda, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7770–7773. (b) Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7774–7778. (c) Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7779–7785. (d) Ishikawa, T.; Isobe, T. *Chem.—Eur. J.* **2002**, *8*, 552–557.

(4) Leow, D.; Tan, C.-H. *Chem.—Asian J.* **2009**, *4*, 488–507.

(5) (a) Kemp, J. E. In *Comprehensive Organic Synthesis*, Vol. 7; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; pp 469–513. (b) Booker-Milburn, K. I.; Guly, D. J.; Cox, B.; Procopiou, P. A. *Org,. Lett.* **2003**, *5*, 3313–3315. (c) Abe, T.; Takeda, H.; Miwa, Y.; Yamada, K.; Yamada, R.; Ishikura, M. *Helv. Chim. Acta* **2010**, *93*, 233–241.

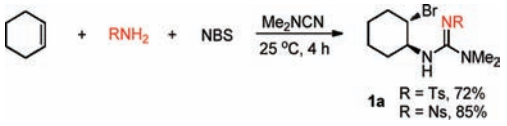
(6) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J., Jr.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411–420.

(7) (a) Zhou, L; Zhou, J.; Tan, C. K.; Chen, J.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2448–2451. (b) Zhou, L.; Tan, C. K.; Zhou, J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 10245–10247.

10.1021/ol202402y
Published on Web 10/11/2011

with a cyanimide partner. Thus, a mixture of *N*-bromosuccinimide (NBS), *p*-toluenesulfonamide ($TsNH_2$), cyclohexene, and *N*,*N*-dimethylcyanimide was reacted at 25 °C for 4 h and yielded guanidine **1a** (R = Ts) in 72% yield (Scheme 1). Replacing $TsNH_2$ with *p*-nitrobenzenesulfonamide ($NsNH_2$) allowed us to obtain the corresponding guanidine **1a** (R = Ns) in 85% yield.

Scheme 1. One-Pot Guanidine Synthesis

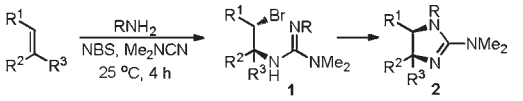


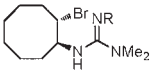
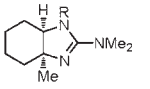
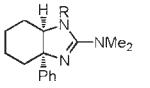
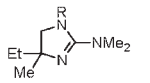
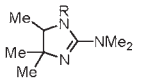
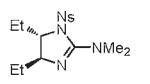
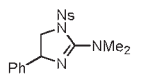
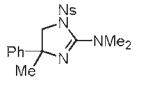
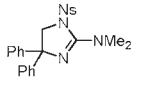
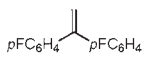
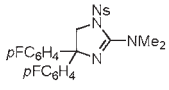
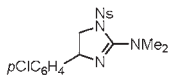
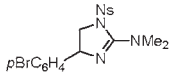
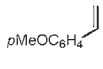
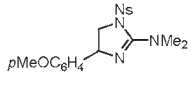
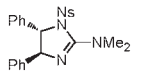
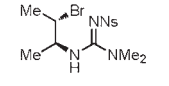
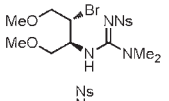
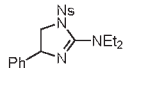
With this positive result in hand, various olefinic substrates were subjected to investigation. In general, good to excellent yields of the desired products were obtained (Table 1).[8] The reactions were also highly regioselective, with only Markovnikov-type products were isolated (Table 1, entries 2−5, 7−13). This reaction also worked well not only with the electron-rich olefins (Table 1, entries 8−9, 13) but also with the relatively electron-deficient olefins (Table 1, entries 10−12). The reaction also worked well with *N*,*N*-diethylcyanimide (Table 1, entry 17).

Potentially due to the high basicity of guanidine, most of the products were isolated as the corresponding cyclized products (Table 1, entries 2−14). For those reactions which yielded open-chain guanidines (e.g., Scheme 2, **1s**), the corresponding cyclized product (e.g., Scheme 2, **2s**) could easily be achieved by simply heating up the same pot of reaction mixture at 80 °C for 2 h. The structures of **1p**, **2c**, **2f**, **2k**, and **2s** were unambiguously confirmed by X-ray studies.[9]

In an effort toward the development of efficient and diversity-orientated approaches toward biologically important heterocycles in our laboratory,[7] we attempted to synthesize guanidine **6**, a key intermediate for the synthesis of rTRPVI inhibitor **7** which has been prepared by a multistep sequence.[10] Preliminary studies showed that **6**

Table 1. One-Pot Synthesis of Guanidines Using Various Olefins



entry[a]	substrate	product		yield (%)
1			**1b**	(R = Ts) 75 (R = Ns) 83
2			**2c**	(R = Ts) 90 (R = Ns) 90
3			**2d**	(R = Ts) 89 (R = Ns) 95
4[b]			**2e**	(R = Ts) 97 (R = Ns) 93
5			**2f**	(R = Ts) 80 (R = Ns) 85
6			**2g**	78
7			**2h**	90
8			**2i**	90
9			**2j**	85
10			**2k**	74
11			**2l**	95
12			**2m**	94
13			**2n**	62
14			**2o**	91
15[c]			**1p**	89
16			**1q**	62
17[d]			**1r**	85

[a] Reactions were carried out with olefin (0.6 mmol), NBS (0.6 mmol), and RNH_2 (0.5 mmol) in *N*,*N*-dimethylcyanimide (1 mL) at 25 °C for 4 h. The yields were isolated yields. [b] 1.0 mmol of olefin was used. [c] Excess *cis*-2-butene (gas) was used. [d] Et_2NCN was used instead of Me_2NCN.

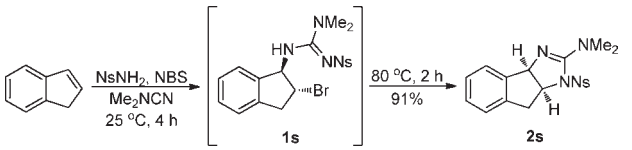
(8) General procedure: To a solution of *N*-bromosuccinimide (107 mg, 0.6 mmol) and sulfonamide (0.5 mmol) in dry *N*,*N*-dimethylcyanimide (1 mL) in the dark was added olefin (0.6 mmol). After stirring for 4 h at 25 °C, the reaction was quenched with saturated $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to yield the corresponding product.

(9) The details appear in the Supporting Information.

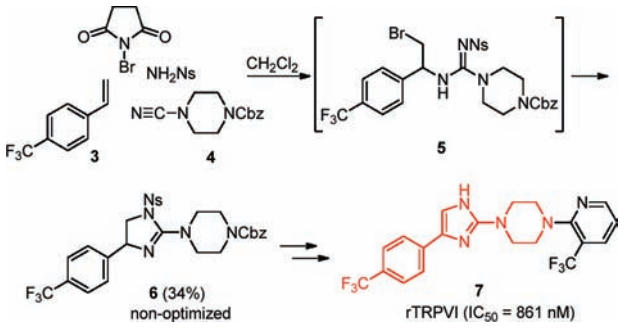
(10) Gore, V. K.; Ma, V. V.; Tamir, R.; Gavva, N. R.; Treanor, J. J. S.; Norman, M. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5825–5830.

(11) Promotors are typically required to activate the weakly electrophilic Br in NBS: (a) Schmid, G. H.; Garrat, D. G. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1977; Suppl. A, Part 2, p 725. (b) DeLaMare, P. B. D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, 2nd ed.; Elsevier: New York, 1982; pp 136−197. (c) Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, *28*, 207–291. For recent examples of electrophilic Br initiated cascades, see: (d) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899–7903. (e) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314. (f) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *Adv. Synth. Catal.* **2010**, *352*, 621–626.

Scheme 2. One-Pot Synthesis of **2s**



Scheme 3. Study towards the Synthesis of **7**

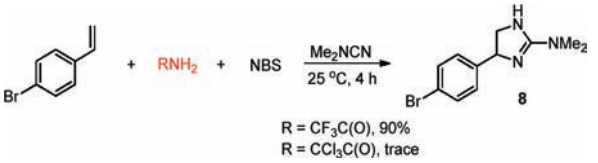


could readily be furnished by simply mixing *p*-trifluoromethylstyrene (**3**), $NsNH_2$, cyanimide **4**, and NBS in CH_2Cl_2 at 25 °C for 4 h (Scheme 3).

It is important to notice that the above-mentioned reactions proceeded smoothly *in the absence of any additional NBS activator*.[11] Moreover, the same phenomenon was observed in our previous reports on the imidazoline and the cyclic ether cascades;[7] this led us to probe the sole origin of the reactivity. We had suspected that the reaction might proceed through an autocatalytic process; i.e. the guanidine product might act as a Lewis base catalyst to promote the halogenation reaction.[12] However, this hypothesis was ruled out by using tetramethylguanidine as the catalyst, for which no improvement in reaction rate and yield was observed.[13] We have also investigated the importance of the acidity of the amide nucleophile using *p*-bromostyrene as the model substrate. Instead of $NsNH_2$, it was found that the use of trifluoroacetamide could afford the corresponding guanidine **8** in 90% yield.[14] However, the reaction was sluggish when using trichloroacetamide (Scheme 4).

Other than the above-mentioned studies, an important mechanistic clue was unearthed by the discovery of an intermediate (traced by TLC) that was detected consistently in each of the reactions. After extensive experimentations, it

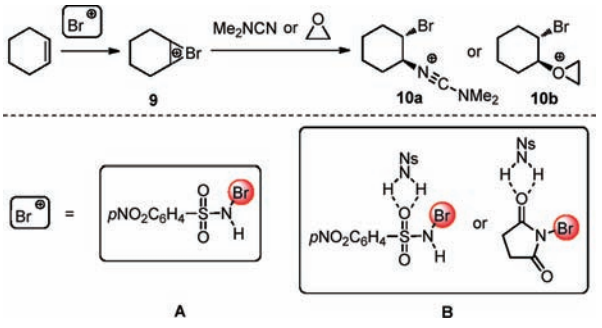
Scheme 4. Synthetic Studies toward **8** Using Acetamides



appears that the intermediate was formed by the Br exchange between RNH_2 (R = Ts, Ns) and NBS accompanied with the formation of succinimide. We have also conducted a ^1H NMR study on a 1:1 mixture of NBS and $NsNH_2$ (or $TsNH_2$) in CD_3CN.[9,15] A set of new signals was observed (7.04 ppm, singlet; 8.11 ppm, doublet; 8.41 ppm, doublet) accompanied by another new signal at 2.60 ppm which belongs to succinimide. Based on the calculation of the integration ratio, ca. 20% of NBS was consumed and ca. 20% of $NsNH_2$ (8.06, 8.35 ppm) was transformed to the new species (8.11, 8.41 ppm). The above results and observations suggest that the Br exchange afforded an intermediate which should be NsNHBr.

Based on these observations, it appears that (1) an amine nucleophilic partner, which contains acidic protons, is critical for the reaction and (2) RNHBr (R = Ts, Ns) may be an important intermediate.[16] Although the mechanism remains unclear, a possible pathway is that the *in situ* generated NsNHBr may act as a more reactive Br source in the formation of bromonium intermediate **9** (Scheme 3, Mode **A**). Subsequent trapping of **9** with a cyanimide (e.g., Me_2NCN) or a cyclic ether (e.g., ethylene oxide) can afford the cationic species **10a** or **10b**, respectively.

Scheme 5. Proposed Mechanism of the Br Activation



Finally, **10** can be captured by the amide to yield the desired products. On the other hand, we also spectulate that the halogen source (NBS or NsNHBr) may be activated by

(12) (a) Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A.; Redmond, J. M.; White, A. J. P. *Tetrahedron Lett*. **2007**, *48*, 5948–5952. (b) Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Tetrahedron Lett*. **2007**, *48*, 915–918.

(13) 10 mol% of tetramethylguanidine was added to the reaction using cyclohexene or styrene, for which the rate and yield were identical to those of the original reaction.

(14) The trifluoroacetyl group was not stable and was deprotected during the workup process. The same free guanidine **8** could be furnished by removing the Ns group of **2m**.

(15) Attempts to prepare pure TsNHBr or NsNHBr were unsuccessful. For related studies, see: (a) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc*. **2010**, *132*, 15474–15476. (b) Catino, A. J.; Nichols, J. M.; Forslund, R. E.; Doyle, M. P. *Org. Lett*. **2005**, *7*, 2787–2790.

(16) Cai, Y.; Liu, X.; Jiang, J.; Chen, W.; Lin, L.; Feng, X. *J. Am. Chem. Soc*. **2011**, *133*, 5636–5639.

the mildly acidic $NsNH_2$, potentially through the coordination of the carbonyl (or sulfonyl) oxygen (Scheme 5, Mode **B**). The failure in obtaining a good yield when NCS or NIS was employed suggests that the $NsNH_2$/NBS activation mode (either **A** or **B**) is highly specific.[17]

In summary, we have developed a general and efficient one-pot guanidine synthesis using an olefin, NBS, an amide, and a cyanimide. A wide range of guanidine derivatives can be synthesized using this methodology. The reaction can proceed smoothly in the absence of an additional NBS activator, in which the sole origin of the reactivity can be ascribed to the unique chemical pair, NBS and $NsNH_2$ (or $TsNH_2$). Research toward the exploration of reactions that are analogous to this methodology as well as the synthesis of bioactive guanidine derivatives is underway.

(17) The results were unsatisfactory when using NCS or NIS as the halogen source. The same phenomenon was also observed in our previous studies. For details, see ref 7.

Acknowledgment. We thank the financial support from the National University of Singapore (Grant No. 143-000-428-112). We also thank Prof. Scott E. Denmark (University of Illinois) for his valuable advice on this project.

Supporting Information Available. Experimental procedures and additional information. This material is available free of charge via the Internet at http://pubs.acs.org.