Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 1399–1402
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

A facile synthesis of imino-protected cyclic guanidine derivatives from diamines

Jian Hai Yuan, Xiao Xiao Yang *, Hao Lin, De Xin Wang

Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

Received 19 April 2011
Available online 12 October 2011

Abstract

A convenient one-step synthesis of five-membered or six-membered imino-protected cyclic guanidine *via* an intramolecular ring-closure reaction of alkyl diamine (**2a**–**2g**) with 1, 3-diamino-protected methylisothiourea (**1a** and **1b**) was established and investigated. Amino guanidine such as 3-(2-aminoethyl)-1, 2-dibenzyloxycarbonylguanidine (**4a**) has been proved to be the intermediate of the reaction *via* utilizing mono-protected diamine as starting material. The intramolecular ring closure of **4a** results in 2-benzyloxycarbonyliminoimidazolidine (**3a**). This new one-step synthesis has advantages of simple condition, easy workup procedure and reasonable yield.

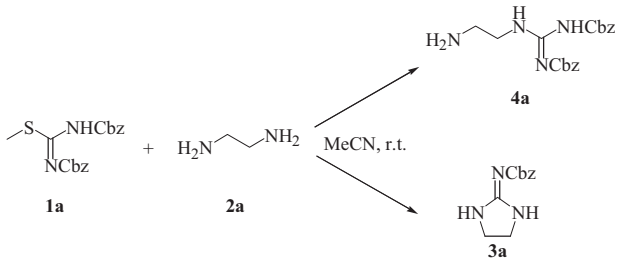
Keywords: Intramolecular cyclization; 1, 4-Nucleophilic addition; Alkyldiamines; Cyclic guanidine

The guanidine group is a very important alkalinous pharmacophore. A variety of molecules with diverse structure containing single or multiple guanidine units have been isolated from microorganisms or natural plants, many of which possess antimicrobial or cytotoxic activity [1,2]. Therefore, incorporation and derivation of guanidino group in certain compound may benefit their bioactivity. Generally, the typical synthesis of guanidine-containing compounds involves treatment of an amine with an electrophilic guanidinylating reagent [3]. Several guanidinylating reagents have been employed frequently such as pyrazole-1-carboxamidine, *S*-alkylisothiourea and protected thiourea derivatives [4–7]. Cyclic guanidines synthesis was reported by Rapport by reacting diamines with *S*, *S*-dimethyl-*N*-tosyliminodithiocarbonimidate [8], which turned out to be an alternative way to the classical method of reacting cyanogen bromide with diamines to afford five-membered 2-iminoimidazolidine and six-membered 3, 4, 5, 6-tetrahydropyrimidine rings [9].

Recently, in the context of developing peptidomimetic inhibitors in our ongoing research, we need to synthesize series of aminoalkyl guanidine. Initially, referred to reported method for synthesis aminoalkylguanidine [7], we attempt to synthesize 1-(3-aminopropyl)-2, 3-dibenzoxycarbonylguanidine (**4a**) by treating bis(benzyloxy-carbonyl)-2-methylisothiourea (**1a**) [10] ethylenediamine (**2a**). However, an unexpected compound was found as the only product of the reaction. By analyzing mass spectrum and NMR data, the product turned out to be 2-benzyloxycarbonyliminoimidazolidine (**3a**) which has been reported by Rapoport [11] with 3.7% yield using benzyl chloroformate (Cbz-Cl) and 2-iminoimidazolidine as reaction materials (Scheme 1). This result inspired us to develop

* Corresponding author.
E-mail address: yangxx@imm.ac.cn (X.X. Yang).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2011.07.008



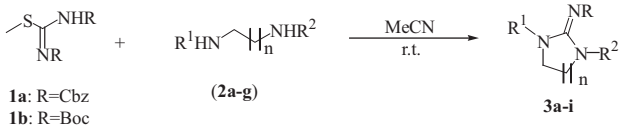
Scheme 1. Reaction of *N*-Cbz protected methylisothiourea and ethylenediamine.

a simple and convenient synthetic method of compound **3a** and then try to apply it to prepare other substituted five-membered or six-membered cyclic guanidine derivatives.

We introduced two guanidinylating reagents **1a** and **1b** to react with aliphatic diamine **2a–g** at ambient temperature to afford corresponding 2-alkyloxycarbonyliminoimidazolidine derivatives **3a–i** (Table 1) [12]. The yields ranged from moderate to high depending on the structure of the aliphatic diamine. For diamine with two primary amino (ethylenediamine **2a** and 1, 3-propylenediamine **2e**), the reaction condition was mild, and usually the product **3a** and **3e** could be precipitated gradually during reaction (acetonitrile as solvent) with high yield. However, for diamines with single or two secondary amino groups (Table 1, entry 3, 7–9), the yields were improved while the reaction time being extended or the reaction proceeding at 70 °C. We found that *tert*-butoxycarbonyl (Boc)-protected group was less beneficial for this reaction than benzyloxycarbonyl(Cbz)-protected group (entry 8, 9). For example, compound **3h** was obtained with lower yield than **3a** *via* treating the same diamine **2a** with compound **1b** and **1a** respectively. For the synthesis of **3h** and **3i**, our findings are generally correspondent with the results of Botta's group [7], in which **3h** was obtained by heating 1-(2-aminoethyl)-2, 3-di-Boc-guanidine and **3i** by reacting **2e** with 1-(trifluoromethanesulfonyl)-2, 3-di-Boc-guanidine in tetrahydrofuran. However, under our reaction condition, cyclic guanidine **3h** was obtained directly as the major product rather than *via* separable linear form intermediate.

The mechanism of the labile property of guanidinylethylamine **4a** was proposed and shown in Scheme 2. We presumed that two 1, 4-nucleophilic addition-elimination occurred subsequently when compound **1a** was treated with

Table 1
Results and yields of the synthesis of imino-protected cyclic guanidine derivatives.[a]



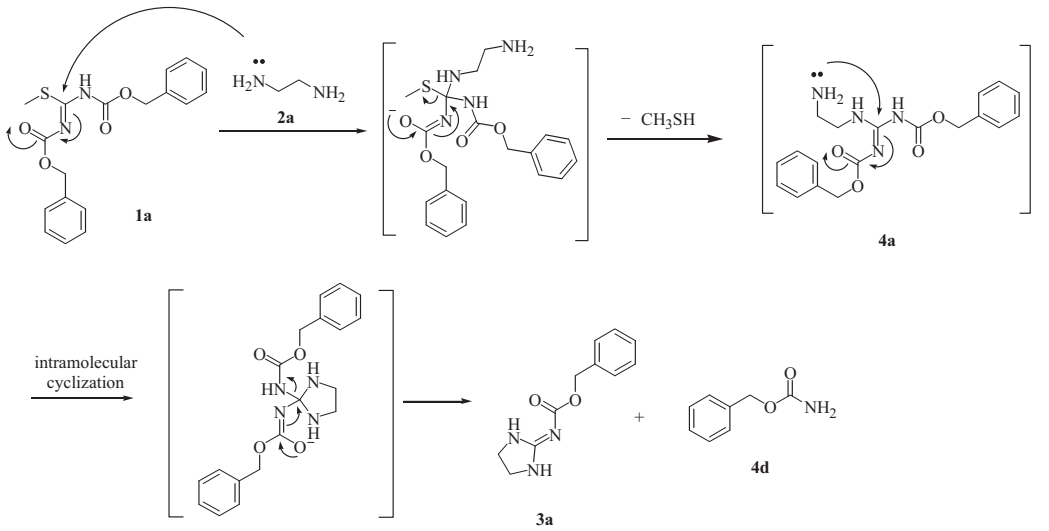
1a: R=Cbz
1b: R=Boc

(**2a-g**)

3a-i

Entry	Diamine **2**	*n*	R^1	R^2	Compound **1**	R	Product **3**	Yield (%)	Mp (°C)
1	**a**	1	H	H	**a**	Cbz	**a**	91	180–182
2	**b**	1	H	CH_3	**a**	Cbz	**b**	73	55–57
3	**c**	1	H	CH_2CH_3	**a**	Cbz	**c**	58, 79[b]	52–54
4	**d**	1	CH_3	CH_3	**a**	Cbz	**d**	70	–[c]
5	**e**	2	H	H	**a**	Cbz	**e**	90	192–194
6	**f**	2	H	CH_3	**a**	Cbz	**f**	72	39–41
7	**g**	2	CH_3	CH_3	**a**	Cbz	**g**	56, 76[b]	56–58
8	**a**	1	H	H	**b**	Boc	**h**	54, 86[b]	205[d]
9	**e**	2	H	H	**b**	Boc	**i**	57, 89[b]	176[d]

[a] Reaction condition: 1 mmol of diamine was reacted with 0.5 mmol of compound **1** in MeCN at ambient temperature.
[b] The yields were improved by heating at 70 °C for 2 h after stirring for 2 h at room temperature.
[c] The compound was achieved as colourless oil.
[d] The compound decomposed at this temperature.

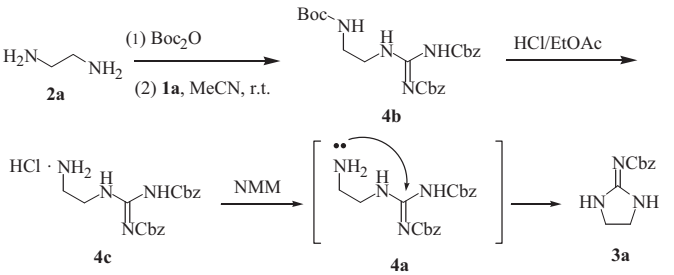


Scheme 2. Proposed mechanism for the synthesis of cyclic imino-protected guanidine derivatives 3.

diamine **2a**. Firstly, an intermolecular reaction took place between **1a** and diamine **2a**, and one methanethiol left during this process, and then another 1, 4-nucleophilic addition-elimination proceeded intramolecularly, in which **3a** was afforded by losing one benzyl carbamate.

To confirm this mechanism, firstly, **4c** (the hydrochloride of linear molecule **4a**) was prepared *via* reacting ethylenediamine with Boc_2O, then guanidinylating by compound **1a** and finally removing Boc with hydrochloride saturated ethyl acetate. Thereafter, **4c** was stirred with 1 equiv. *N*-methylmorpholine (NMM) in THF at room temperature. As **4a** was forming, its free amino group immediately attacked the quaternary electrophilic carbon atom of enamine bond to afford **3a** as the target product (Scheme 3). The benzyl carbamate **4d** generated as byproduct has also been confirmed not only by HPLC *via* co-injection crude product with standard benzyl carbamate (Fig. 1), but also by ^{1}H NMR and HRMS after separation. Thus these results provided solid evidence of the mechanism which indicates the linear molecule **4a** with a free amino was labile and the linear molecule **4a** could be the intermediate of the reaction.

In conclusion, we developed a simple and novel method for the synthesis of 2-iminoimidazolidine and 2(1*H*)-iminotetrahydropyrimidine derivatives. Compared to the classical method reported [7], the reaction condition of our method was facile and mild, and it was easily operated with moderate to high yields. Furthermore, the mechanism of this reaction was illustrated and testified by preparing **4c** and then treating **4c** with NMM to afford **3a**. The result that **4c** could be transformed to product **3a** when its amino was liberated by NMM strongly supported the mechanism we proposed. In addition, all compounds we synthesized in this paper were characterized by HRMS(ESI) and ^{1}H NMR, data are included in supporting information.



Scheme 3. The proof of the proposed mechanism.

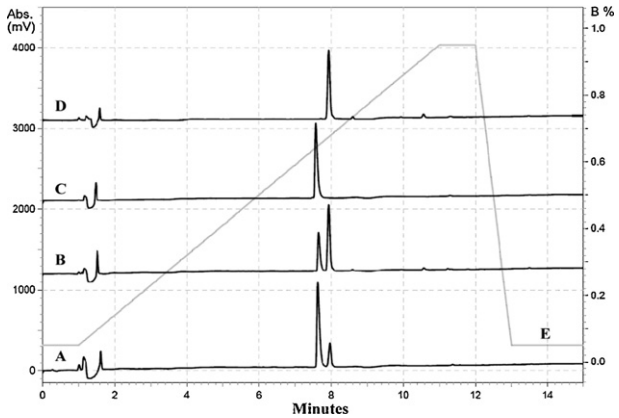


Fig. 1. HPLC co-injection of crude product with benzyl carbamate standard: crude product (A), crude product mix with benzyl carbamate standard (B), compound **3a** (C), benzyl carbamate standard (D), gradient of solvent B (E) [13].

Acknowledgments

We thank Project 81001366 supported by NSFC and basic scientific research foundation of Institute of Materia Medica (No. 2009CHX07) for financial support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2011.07.008.

References

[1] G.C. Harbour, A.A. Tymiak, K.L. Rinehart Jr., et al. J. Am. Chem. Soc. 103 (1981) 5604.
[2] C. Yuan, R.M. Williams, J. Am. Chem. Soc. 119 (1997) 11777.
[3] K. Feichtinger, H.L. Sings, T.J. Baker, et al. J. Org. Chem. 63 (1998) 8432.
[4] M.A. Poss, E. Iwanowicz, J.A. Reld, et al. Tetrahedron Lett. 33 (1992) 5933.
[5] D.R. Kent, W.L. Cody, A.M. Doherty, Tetrahedron Lett. 37 (1996) 8711.
[6] R.J. Bergeron, J.S. McManis, J. Org. Chem. 52 (1987) 1700.
[7] (a) D. Castagnolo, F. Raffi, G. Giorgi, et al. Eur. J. Org. Chem. 3 (2009) 334;
(b) F. Manetti, D. Castagnolo, F. Raffi, et al. J. Med. Chem. 52 (2009) 7376.
[8] J.V. Rodricks, H. Rapoport, J. Org. Chem. 36 (1971) 46.
[9] B. Adcock, A. Lawson, D.H. Miles, J. Chem. Soc. (1961) 5120.
[10] X. Wang, J. Thottathil, Tetrahedron: Asymmetry 11 (2000) 3665.
[11] K. Matsumoto, H. Rapoport, J. Org. Chem. 33 (1968) 552.
[12] General procedure for the synthesis of cyclic imino-protected guanidine derivatives (**3**): To a solution of 1 mmol alkyldiamine in MeCN, 0.5 mmol compound **1a** or **1b** in MeCN was added dropwise and stirred at ambient temperature for the appropriate amount of time as indicated in Table 1. The progress of the reaction was monitored by TLC. After completion, compound **3a** and **3e** could be precipitated from MeCN as pure products upon TLC examination. Other compound could be obtained via the following procedure: MeCN was removed in vacuo after reaction was completed, and EtOAc was added to take up the residue. The EtOAc solution was transferred to separation funnel, and then washed with water and brine each for 3 times subsequently. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica column chromatograph using 1% MeOH/DCM as eluent. Characterization of 2-benzoxycarbonyliminoimidazolidine (**3a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 2H, N*H*), 7.28-7.38 (m, 5H, Ph-*H*), 5.15 (s, 2H, Ph-CH_2-O), 3.62 (s, 4H, –CH_2CH_2–); MS (ESI): *m/z* 220.1527 $[M+H]^+$, 439.2047 $[2M+H]^+$; HRMS (ESI): calcd. for $C_{11}H_{14}N_3O_2$ $[M+H]^+$ 220.1065, found 220.1081.
[13] HPLC conditions: solvent A: water with 0.1%TFA; solvent B: acetonitrile with 0.1%TFA; column: Chromasil C18 reverse-phase, 4.6 × 15 cm, 5 μm; gradient: linear from 5% B to 95% B over 10 min, then 95% B for 1 min, and 5% B for 2 min. Wavelength used for detection: 214 nm.