Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 562–565

An efficient stereoselective synthesis of 1-iodo- or 1-phenyl selenenyl-2-aryl-3-azabicyclo[3.1.0]hexane via electrophilic cyclization of benzyl-2-arylmethylidenecyclopropylmethyl-amines

Weijun Fu[a] and Xian Huang[a,b,*]

[a]*Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, PR China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China*

Received 26 July 2007; revised 7 November 2007; accepted 13 November 2007
Available online 17 November 2007

Abstract—The reaction of benzyl-2-arylmethylidenecyclopropylmethyl-amine **1** with iodine in the presence of potassium carbonate or PhSeBr stereoselectively gives ring-closure product 1-iodo-2-aryl-3-azabicyclo[3.1.0]hexane or 1-phenylselenenyl-2-aryl-3-azabicyclo[3.1.0]hexane in good yields at room temperature. A plausible reaction mechanism has been proposed.

3-Azabicyclo[3.1.0]hexanes are important structural motifs frequently found in pharmacologically interesting structures. They are present in a large number of biological active compounds, which exhibit activity against a broad range of Grampositive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA) and Staphylococcus epidermidis (MRSE) and vancomycin-resistant Enteroccocus faecium (VRE).[1] The current approach toward 3-azabicyclo[3.1.0]hexanes mainly involves rhodium(II) acetate-mediated cyclopropanation of an N-protected pyrroline with ethyl diazoacetate.[2] This method is obviously limited to small-scale synthesis because of the expensive catalytic system. Thus, a general and practical method to prepare 3-azabicyclo[3.1.0]hexanes is still required.

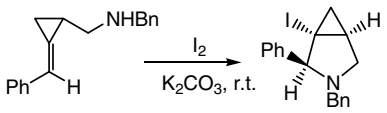
Methylenecyclopropanes (MCPs), highly strained but readily accessible molecules, have been proven to be useful synthetic intermediates because the relief of ring strain provides a potent thermodynamic driving force.[3] In the past several years, a number of methods for construction of complex and interesting organic molecules from MCPs have been developed.[4] The electrophilic cyclization of methylenecyclopropanes has been well documented.[5] Recently, we have found cyclizations of cyclopropylideneacetic acids and cyclopropylidene alcohols to afford 5,6-dihydro-2*H*-pyran-2-ones or dihydropyrans in good yields under different reaction conditions.[6] In our continual efforts on the application of MCPs in organic synthesis, we wish to report our recent studies on the reaction of benzyl-2-arylmethylidene-cyclopropylmethyl-amine **1**[7] with iodine or PhSeBr to give the corresponding 1-iodo-2-aryl-3-azabicyclo-[3.1.0]hexanes **2** or 1-phenylselenenyl-2-aryl-3-azabicyclo[3.1.0]hexanes **3** in good yields under mild conditions.

At the first attempt, we conducted the reaction of benzyl-2-benzylidenecyclo-propylmethyl-amine **1a** (1 mmol) with iodine (1.5 equiv) in THF at room temperature in the presence of potassium carbonate (1.7 equiv).[8] The desired product **2a** was obtained in 63% yield with excellent stereoselectivity (Table 1, entry 1). With this encouraging result, a systematic study was undertaken to screen various solvents for the cyclization process. The results are summarized in Table 1. We found that the ring-closure reactions promoted by iodine proceeded smoothly at room temperature to give the corresponding *trans*-1-iodo-2-phenyl-3-azabicyclo[3.1.0]hexane (**2a**) in moderate to good yields in all cases (Table 1, entries 1–5). In CH_3CN, this reaction proceeded

Keywords: Benzyl-2-arylmethylidenecyclopropylmethyl-amine; Ring-closure; 1-Iodo-2-aryl-3-azabicyclo[3.1.0]hexane; 1-Phenylselenenyl-2-aryl-3-azabicyclo-[3.1.0] hexane.
* Corresponding author. Fax: +86 571 88807077; e-mail: huangx@mail.hz.zj.cn

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.068

Table 1. Reaction of MCPs *E*-**1a** with iodine in a variety of solvents



1a **2a**

Entry	Solvent	Time (h)	Yield of **2a**[a] (%)
1	THF	4	63
2	DMF	24	51
3	CH_3CN	2	88
4	CH_2Cl_2	24	45
5	MeC_6H_5	24	56

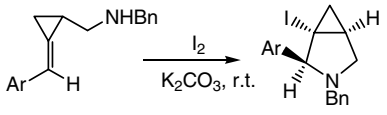
[a] Isolated yields, I_2 (1.5 equiv), K_2CO_3 (1.7 equiv).

efficiently to give **2a** in 88% yield for 2 h (Table 1, entry 3). Therefore, the reaction conditions chosen to carry out this reaction were in CH_3CN with iodine (1.5 equiv) and K_2CO_3 (1.7 equiv) at room temperature.

Then, we carried out the electrophilic cyclization of a variety of benzyl-2-arylmethylidenecyclopropylmethylamines *E*-**1** with iodine under the optimized conditions. The results are summarized in Table 2. It is obvious that both electron-donating and electron-withdrawing substituents on the benzene ring of **1** can be applied to afford 3-azabicyclo[3.1.0]hexanes **2** in fairly good yields. For MCPs *E*-**1**, *trans*-1-iodo-2-aryl-3-azabicyclo[3.1.0]hexanes **2** were obtained stereoselectively in all cases within 2 h (Table 2, entries 1–7). The cis isomers were not detected in the crude products. The configuration of **2b** was determined by X-ray diffraction. The X-ray crystal structure of **2b** is shown in Figure 1.[9]

Moreover, we examined a similar electrophilic cyclization reaction of benzyl-2-benzylidenecyclopropylmethylamine **1a** with PhSeBr. We found that the corresponding cyclization product **3a** was obtained in 89% yield when the reaction was carried out at room temperature in CH_2Cl_2 with 1.2 equiv of PhSeBr.[10] Then, the scope of this reaction was investigated. Some typical results are summarized in Table 3. From Table 3, it can be concluded that in the presence of 1.2 equiv of PhSeBr, this reaction proceeded efficiently to give the cyclization

Table 2. Iodocyclization of benzyl-2-arylmethylidenecyclopropylmethyl-amines **1**



1 **2**

Entry	Ar	Time (h)	Yield[a] (%)
1	C_6H_5(**1a**)	2	**2a**, 88
2	*p*-$CH_3C_6H_4$(**1b**)	2	**2b**, 92
3	*p*-$CH_3OC_6H_4$(**1c**)	2	**2c**, 89
4	*p*-BrC_6H_4(**1d**)	2	**2d**, 85
5	*p*-ClC_6H_4(**1e**)	2	**2e**, 91
6	*o*-$CH_3OC_6H_4$(**1f**)	2	**2f**, 78
7	*o*-BrC_6H_4(**1g**)	2	**2g**, 75

[a] Isolated yields based on MCPs **1**.

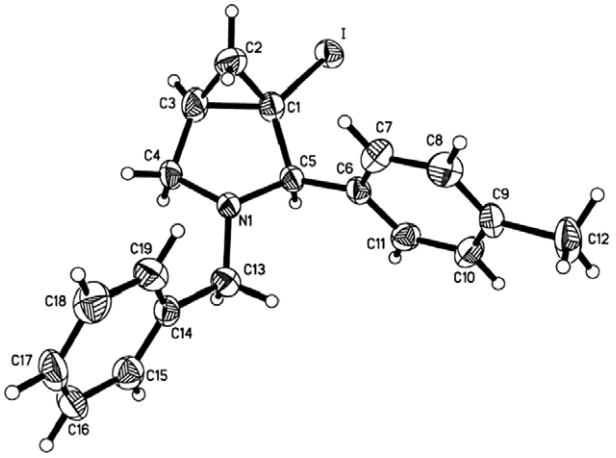
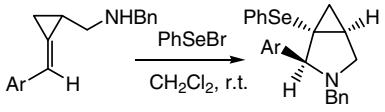


Figure 1. The crystal structure of **2b**.

Table 3. Reactions of benzyl-2-arylmethylidene cyclopropylmethylamines **1** with PhSeCl in CH_2Cl_2



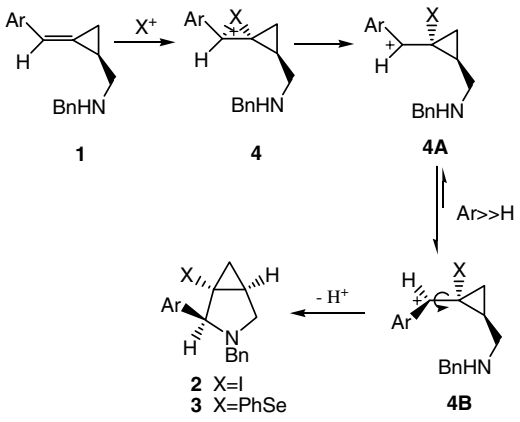
1 **3**

Entry	Ar	Time (h)	Yields[a] (%)
1	C_6H_5(**1a**)	1	**3a**, 85
2	*p*-$CH_3OC_6H_4$(**1c**)	1	**3b**, 76
3	*p*-BrC_6H_4(**1d**)	1	**3c**, 80
4	*o*-$CH_3OC_6H_4$(**1f**)	1	**3d**, 72
5	*o*-BrC_6H_4(**1g**)	1	**3e**, 77

[a] Isolated yields based on MCPs **1**.

products **3** in good yields in all cases. For MCPs **1**, *trans*-1-phenylselenenyl-2-aryl-3-azabicyclo[3.1.0]hexanes **3** were formed exclusively (Table 3, entries 1–5).[11]

Based on the above results, a plausible mechanism for this electrophilic cyclization reaction of MCPs **1** with iodine in the presence of K_2CO_3 and PhSeBr is depicted in Scheme 1. The addition of I^+ or $PhSe^+$ to the double bond of MCPs **1** would form the bridged intermediate



1 **4** **4A** **4B**

Scheme 1.

cation **4**. The intermediate cation **4** would open up to generate a carbocation **4A**, which is stabilized by the cyclopropyl and aryl rings.[12] Due to the steric hindrance of groups Ar and H, **4A** would adopt conformation **4B** by the rotation of bond C_4–C_5, in which the bulkier group Ar is trans to the I or PhSe group.[13] Then, the subsequent intramolecular nucleophilic attack of the NH group would lead to the stereoselective formation of cyclization product **2** or **3**.

In conclusion, we have developed a highly stereoselective iodocyclization and selenidocyclization reaction of MCPs **1** with iodine in the presence of K_2CO_3 or PhSeBr, leading to the formation of 1-iodo-2-aryl-3-azabicyclo[3.1.0]hexanes **2** or 1-phenylselenenyl-2-aryl-3-azabicyclo[3.1.0]hexanes **3** in good yields under mild conditions. The stereoselectivity may be controlled by the steric effects of the substituent group of the C=C bond. As the easy availability of starting materials, the convenient operation and the usefulness of the products, the reaction may have potential utilities in organic synthesis.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (20332060, 20472072) and Academic Foundation of Zhejiang Province.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.068.

References and notes

1. Renslo, A. R.; Jaishankar, P.; Venkatachalam, R.; Hackbarth, C.; Lopez, S.; Patel, D. V.; Gordeev, M. F. *J. Med. Chem.* **2005**, *48*, 5009.
2. Brighty, K. E.; Castaldi, M. J. *Synlett* **1996**, 1097.
3. Synthesis of MCPs: (a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. Recent reviews of MCPs: (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213; (c) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *2*, 111.
4. (a) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015; (b) Itazaki, M.; Nishihara, Y.; Osakada, K. *J. Org. Chem.* **2002**, *67*, 6889; (c) Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2661; (d) Nakamura, I.; Siriwardana, A. I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3445; (e) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270; (f) Shi, M.; Chen, Y. *J. Org. Chem.* **2004**, *69*, 426; (g) Bessmertnykh, A. G.; Blinov, K. A.; Grishin, Y. K.; Donskaya, N. A.; Tveritinova, E. V.; Yueva, N. M.; Beletskaya, I. P. *J. Org. Chem.* **1997**, *62*, 6069; (h) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6458; (i) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298; (j) Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203.
5. For brief investigations of halo lactonization of MCPs see: (a) Ettlinger, M. G. *J. Am. Chem. Soc.* **1952**, *74*, 5805; (b) Meinwald, J.; Wheeler, J. W.; Nimetz, A. A.; Liu, J. S. *J. Org. Chem.* **1965**, *30*, 1038; (c) Herriott, A. W.; Jones, W. M. *Tetrahedron Lett.* **1967**, 2387; (d) Wichmann, J.; Adam, G. *Eur. J. Org. Chem.* **1999**, 3131; (e) Goldschmidt, Z.; Finkel, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 45.
6. (a) Huang, X.; Zhou, H. W. *Org. Lett.* **2002**, *4*, 4419; (b) Huang, X.; Zhou, H. W.; Chen, W. L. *J. Org. Chem.* **2004**, *69*, 839; (c) Fu, W. J.; Huang, X.; Lin, Y. *Synlett* **2007**, 321.
7. Synthesis of methylenecyclopropanols and their mesyl intermediates: (a) Shao, L.-X.; Li, Y.-X.; Shi, M. *Chem. Eur. J.* **2007**, *13*, 862; (b) Okuma, K.; Tanaka, Y.; Yoshihira, K.; Ezaki, A.; Koda, G.; Otha, H.; Hara, K.; Kashimura, S. *J. Org. Chem.* **1993**, *58*, 5915; (c) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1993**, *58*, 5037; (d) Corre, M. L.; Hercouet, A.; Bessieres, B. *J. Org. Chem.* **1994**, *59*, 5483. *General procedure for the synthesis of* **1**: To a solution of 20 mmol of *E*-methylenecyclopropylcarbinol, 30 mmol of methanesulfonyl chloride in 50 mL CH_2Cl_2 was added 60 mmol of triethylamine. After stirring at room temperature for 1 h, the reaction was quenched with 50 mL of water. Then the organic phase was washed with 1 M HCl, saturated $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the residues without any further purification were dissolved in 30 mL of DMSO with an external ice bath. Catalytic amount of NaI was added. To the above mixture was then added 60 mmol of phenylmethanamine. The mixture was stirred at room temperature over night. After the reaction was complete, the reaction was quenched with 50 mL of water and extracted with ether. The combined organic layers were then washed with saturated brine and dried over anhydrous $MgSO_4$. After filtration and removal of the solvent in vacuo, the residues were purified with flash chromatography (silica/petroleum ether–ethyl acetate 4:1 v/v) to afford **1**. Selected spectrum data of **1d**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.42 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.33–7.31 (m, 4H), 7.26–7.23 (m, 1H), 6.70 (d, $J = 1.2$ Hz, 1H), 3.84 (dd, $J = 13.6$, 8.8 Hz, 2H), 2.74–2.64 (m, 2H), 1.80–1.62 (m, 1H), 1.63 (br, 1H), 1.61–1.57 (m, 1H), 1.18–1.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 140.2, 136.7, 131.5, 128.6, 128.4, 128.1, 128.0, 126.9, 120.5, 117.4, 53.6, 52.2, 13.7, 10.0; MS (EI): *m*/*z* (%) = 329 (10, [M^+ (^{81}Br)], 327 (10, [M^+ (^{79}Br)], 91 (100); IR (KBr): 3027, 2923, 1487, 1453, 1102 cm^{-1}.
8. (a) Wang, B. Y.; Huang, J. W.; Liu, L. P.; Shi, M. *Synlett* **2005**, 421; (b) Ma, S.; Wu, S. *Tetrahedron Lett.* **2001**, *42*, 4075; (c) Ma, S.; Wu, S. *Chin. J. Chem.* **2001**, *19*, 1280; (d) Ma, S.; Shi, Z. *Chem. Commun.* **2002**, *540*, and references cited therein.
9. *General procedure for the synthesis of* **2a–g**: To a solution of **1** (1 mmol) in 8 mL CH_3CN was added I_2 (1.5 mmol), and K_2CO_3 (1.7 mmol) and the resulting mixture were stirred at room temperature for 2 h. The reaction mixture was then diluted with ethyl acetate, washed with saturated $Na_2S_2O_3$ solution, dried (Mg_2SO_4), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1) to afford **2a–g**. Selected spectrum data of **2a**: Solid; mp 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.56–7.58 (m, 2H), 7.36–7.44 (m, 3H), 7.21–7.32 (m, 5H), 3.95 (s, 1H), 3.80 (d, $J = 12$ Hz, 1H), 3.16 (d, $J = 12$ Hz, 1H), 2.98 (d, $J = 8.8$ Hz, 1H), 2.65 (dd, $J = 8.8$ Hz, $J = 3.6$ Hz, 1H), 1.72–1.82 (m, 2H), 0.86–0.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.6, 138.5, 128.5, 128.3, 128.2,

128.1, 128.0, 126.9, 75.9, 56.2, 52.6, 25.7, 16.3, 9.9; MS (EI): m/z (%) = 375 (31, [M^+]); IR (KBr) 2918, 2795, 1598, 1450, 699 cm^{-1}. CCDC-666438 contains the supplementary crystallographic data for **2b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10. Chen, G. F.; Fu, C. L.; Ma, S. *Tetrahedron* **2006**, *62*, 4444.
11. *General procedure for the synthesis of* **3a–e**: To a solution of **1** (1 mmol) in 8 mL CH_2Cl_2 was added PhSeBr (1.2 mmol) and the resulting mixture was stirred at room temperature for 1 h. The mixture was then evaporated directly and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1) to afford **3a–e**. Selected spectrum data of **3a**: Solid; mp 95–96 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.52 (d, J = 6.4, 2H), 7.20–7.33 (m, 8H), 7.07–7.85 (m, 5H), 3.80 (s, 1H), 3.75 (d, J = 13.2 Hz, 1H), 3.07–3.12 (m, 2H), 2.53–2.56 (m, 1H), 1.75–1.78 (m, 2H), 0.78–0.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.4, 138.8, 131.7, 130.5, 128.7, 128.5, 128.3, 128.2, 128.1, 127.6, 126.8, 126.4, 72.8, 59.5, 53.2, 32.6, 25.7, 14.3; MS (EI): m/z (%) = 405 (25, [M^+]); IR (neat) 2923, 1493, 734, 699 cm^{-1}.
12. Kozhushkov, S.; Fiebig, T.; Galland, B.; Ruasse, M. F.; Xavier, P.; Apeloig, Y.; de Meijere, A. *J. Org. Chem.* **2002**, *67*, 4100.
13. Ma, S.; Lu, L. H. *J. Org. Chem.* **2005**, *70*, 7629.