Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2018, **28**, 366–368

Mendeleev Communications

Synthesis of 3,5-dimethyl-1-boraadamantane and its transformation into 3,5-dimethyl-1-azaadamantane

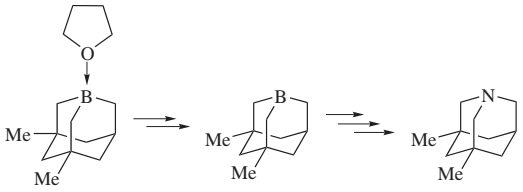
Mikhail E. Gurskii,[a] Galina D. Kolomnikova,[b] Sergey V. Baranin*[a] and Yurii N. Bubnov[a,b]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: svbar@ioc.ac.ru*

[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

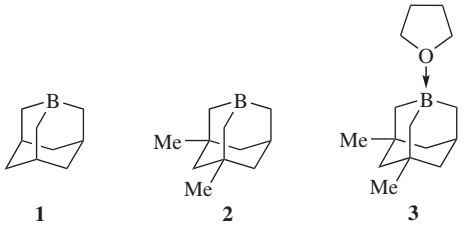
DOI: 10.1016/j.mencom.2018.07.008

The first synthesis of 3,5-dimethyl-1-boraadamantane from its easily available tetrahydrofuran adduct comprised sequential treatment with BuLi, AcCl, $(Cy_2BH)_2$ and heating. The compound was converted into its electronic 'antagonist', namely, 3,5-dimethyl-1-azaadamantane.



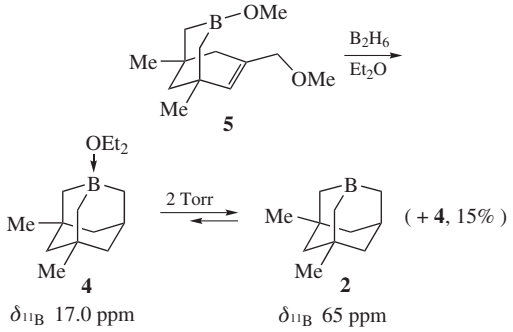
1-Boraadamantane **1** and its 2- and 3-alkyl derivatives with sp^2-hybridized boron atom are unique three-dimensional trialkylboranes and fundamentally differ from their complexes with four-coordinated boron atom. Although many of 1-boraadamantane complexes,[1–3] for instance, those with amines, pyridine[2] or α-amino acid esters[4] are air-stable, many important reactions and physicochemical studies should be conducted with 'free' 1-boraadamantanes that are sensitive to oxygen and moisture.

The parent compound **1** as a free Lewis acid was obtained *via* hydroboration of 7-methylidene-3-methoxy-3-borabicyclo-[3.3.1]nonane[5] or 3-methoxy-7-methoxymethyl-3-borabicyclo-[3.3.1]non-6-ene[6] with diborane in diethyl ether. Complex of 1-boraadamantane with Et_2O formed firstly completely loses the ether molecule upon double sublimation *in vacuo*.[5,6] 2-Alkyl-1-boraadamantanes are available on removal of the trimethylamine ligand from the corresponding complexes by treatment with $Et_2O{\cdot}BF_3$; the resulting labile ether complex readily yields the corresponding free adamantane under reduced pressure.[1] Borane **1** is a crystalline solid, whereas all its alkyl derivatives known to date are liquids or very hard crystallizing substances.[1,2] Recently, we synthesized free 3-methyl-1-boraadamantane (bp 49–51 °C/2 Torr) and established its structural parameters by gas electron diffraction.[3]



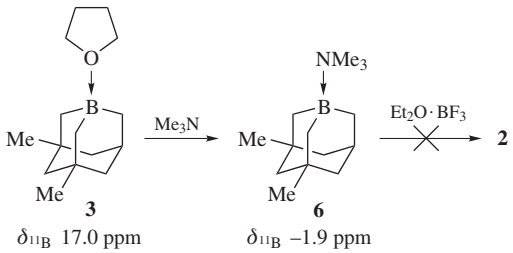
1 **2** **3**

Here, we report the first synthesis of 3,5-dimethyl-1-boraadamantane **2** from an easily available tetrahydrofuran adduct **3**[7] and its further transformation into 3,5-dimethyl-1-azaadamantane. We found that the ether complex **4** obtained by hydroboration of bicyclic compound **5**[8] in diethyl ether does not dissociate completely *in vacuo*. Even after several distillations of compound **4** (at 2 Torr), only ~85% of the ether can be removed (according to ^{11}B and ^1H NMR spectral data) (Scheme 1).



Scheme 1

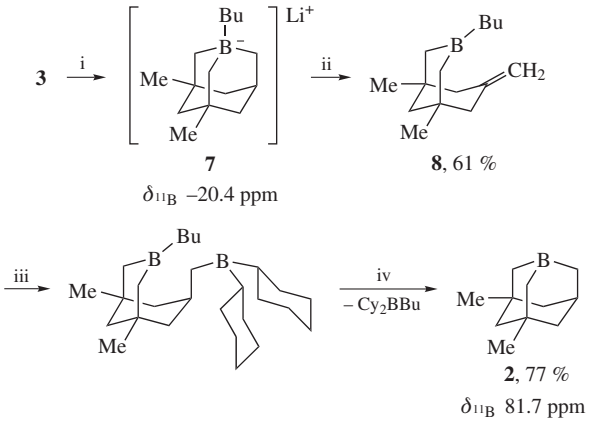
We also revealed that the amine ligand in adduct **6** is not removed under the action of $Et_2O{\cdot}BF_3$ (Scheme 2).



Scheme 2

For this reason, to access borane **2** we applied an alternative synthetic route, which was previously used for the preparation of 3-methyl-1-boraadamantane[3] (Scheme 3). The 3,5-dimethyl-1-boradamantane ate-complex **7** obtained by treatment of complex **3** with BuLi reacted with acetyl chloride[9] to form 3-butyl-1,5-dimethyl-7-methylene-3-borabicyclo[3.3.1]nonane **8**, which was

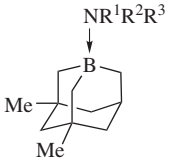
© 2018 Mendeleev Communications. Published by ELSEVIER B.V. on behalf of the N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences.



Scheme 3 *Reagents and conditions*: i, BuLi; ii, AcCl; iii, $(Cy_2BH)_2$ (0.5 equiv.), pentane; iv, Δ.

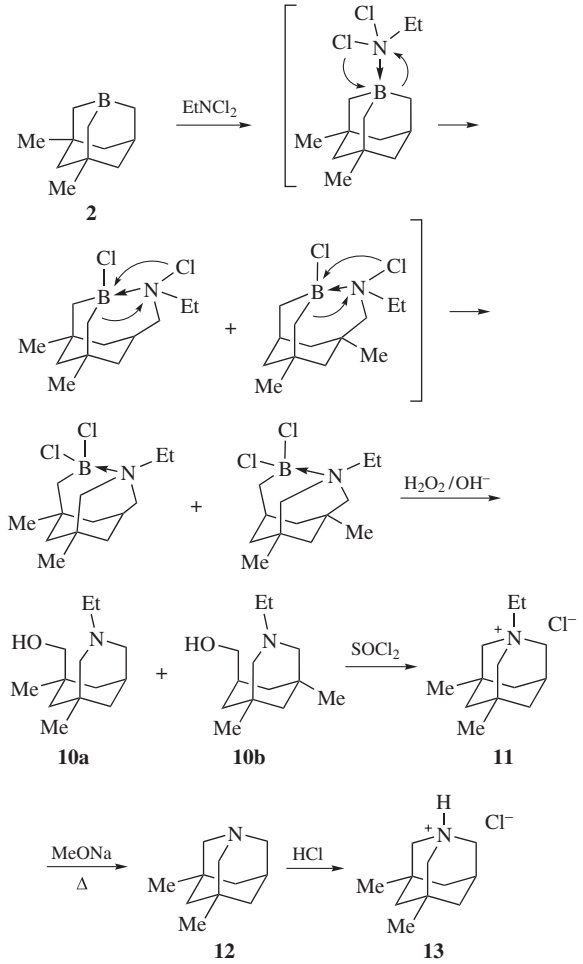
isolated by vacuum distillation. Hydroboration of compound **8** with tetracyclohexyldiborane[10] in pentane at 0 °C, and further refluxing the reaction mixture for 3 h to complete the reaction resulted in product **2** isolated by distillation (bp 56–57 °C/1 Torr). Its structure was confirmed by ^{1}H, ^{13}C and ^{11}B NMR spectroscopy, as well as by elemental analysis.†

1-Boraadamantanes are useful starting substances for the synthesis of cyclic and cage compounds, as well as a number of their amino analogues – the potential objects for pharmacological studies.[1,2] By treatment of compound **2** with three amines, we obtained complexes **9a–c**, including an adduct with 1,3-dimethyl-1-aminoadamantane **9a** (trade names: memantine, akatinol memantine, abixa, mema, noogeron[11–15]). Memantine, an antagonist of the *N*-methyl-D-aspartate receptor (NMDA-antagonist), is used in the treatment of the Alzheimer's and Parkinson's diseases, and is also being clinically tested as a possible therapy for attention deficit and hyperactivity disorder (ADHD), HIV-associated dementia, nystagmus and multiple sclerosis.[11–15]



9a $NR^1R^2R^3$ = 1-amino-3,5-dimethyladamantane
9b $NR^1R^2R^3$ = 1-aminoadamantane
9c $NR^1R^2R^3$ = isoquinoline

The significant achievement in the chemistry of cage boranes is the development on their basis of two best for today synthetic routes to 1-azaadamantanes, the electronic 'antagonists' of boraadamantanes.[16–18] The transformation of 1-boraadamantane **2** into its 1-aza analogue (Scheme 4) was performed according to the previously developed technique.[16,17] Treatment of compound **2** with *N*,*N*-dichloroethylamine[19] followed by oxidation (H_2O_2, OH^-) resulted in a mixture of two amino alcohols **10a**,**b** which under the action of thionyl chloride would cyclize to form the only product, 3,5-dimethyl-1-ethyl-1-azoniaadamantane chloride **11**. The quaternary salt **11** was transformed into 1,3-dimethyl-1-azadamantane **12** by the Hoffmann degradation according to the known method.[17] Compound **12** was isolated as a colourless oil (bp 58–59 °C/2 Torr). The corresponding hydrochloride **13** appeared as colourless crystals and was characterized by ^{1}H and ^{13}C NMR spectra.‡



Scheme 4

In summary, the first synthesis of 3,5-dimethyl-1-boraadamantane was developed and its further transformation into its electronic 'antagonist', 3,5-dimethyl-1-azaadamantane, was successfully performed.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.008.

† *3,5-Dimethyl-1-boraadamantane* **2**. A solution of compound **8** (11.95 g, 0.065 mol) in pentane (20 ml) was added dropwise to the suspension of tetracyclohexyldiborane[10] in (11.57 g) in pentane (50 ml) at ~0 °C. The mixture was slowly warmed to room temperature and stirred for 1 h, dissolution of the hydroborating agent was observed. The reaction mixture was then refluxed for 3 h. Distillation (water bath, 70 °C) gave 6.37 g (60%) of borane **2** as a colourless, extremely sensitive to air oxygen substance, bp 55–57 °C (1 Torr). ^{1}H NMR (600.13 MHz, $CDCl_3$) δ: 1.07 (s, 6H, Me), 1.04 and 1.34 (dd, 2H, 4-H$_{syn}$ and 4-H$_{anti}$, $^2J_{AB}$ 12.7 Hz), 1.18 and 1.40 (dd, 4H, 6,10-H$_{syn}$ and 6,10-H$_{anti}$, $^2J_{AB}$ 13.3 Hz), 1.38 (br. s, 4H, 2,9-H), 1.54 (d, 2H, 8-H, $^2J_{AB}$ 5.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 33.7 (Me), 37.1 (br. s, C^8), 42.3 (C^{6,10}), 45.5 (br., C^{2,9}), 48.7 (C^{3,5}), 52.5 (C^4). ^{11}B NMR (64.21 MHz, $CDCl_3$) δ: 81.7. Found (%): C, 81.09; H, 12.08; B, 6.11. Calc. for $C_{11}H_{19}B$ (%): C, 81.51; H, 11.82; B, 6.67.

‡ *Reaction of 3,5-dimethyl-1-boraadamantane* **2** *with* N,N-*dichloroethylamine*. Compound **2** (8.31 g, 51.3 mmol) in CH_2Cl_2 (15 ml) was added dropwise to a solution of dichloroethylamine[19] (5.85 g, 51.3 mmol) in CH_2Cl_2 (10 ml) at –70 °C. The mixture was stirred for an additional 1 h with cooling and left overnight. The solvent was removed *in vacuo* and diethyl ether (40 ml) was added to the residue, which then, with ice-cooling, was treated successively with NaOH (6.2 g, 0.155 mol) in water (50 ml) and 30% H_2O_2 (15 ml). After boiling for 2 h, distillation of the residue gave 4.9 g (46%) of a mixture of azabicyclic compounds **10a**,**b**, bp 124–126 °C (2 Torr).

3,5-Dimethyl-1-ethyl-1-azoniaadamantane chloride **11**. Thionyl chloride (3.5 ml) in benzene (5 ml) was carefully added to a solution of amino alcohols **10a**,**b** (3.43 g, 16.0 mmol) in benzene (10 ml) at 0–5 °C (a strong warming up of the reaction mixture was observed). The mixture was

References

1 Yu. N. Bubnov, M. E. Gurskii and I. D. Gridnev, in *Comprehensive Heterocyclic Chemistry II*, eds. A. R. Katritzky, Ch. W. Rees and E. F. V. Scriven, Pergamon, Oxford, 1996, vol. 8, pp. 889–931.

2 Yu. N. Bubnov, M. E. Gurskii and S. Yu. Erdyakov, in *Comprehensive Heterocyclic Chemistry III*, eds. A. R. Katrizky, Ch. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Amsterdam, 2008, vol. 12, pp. 573–633.

3 Yu. V. Vishnevskiy, M. A. Abaev, A. N. Rykov, M. E. Gurskii, P. A. Belyakov, S. Yu. Erdyakov, Yu. N. Bubnov and N. W. Mitzel, *Chem. Eur. J*., 2012, **18**, 10585.

4 C. E. Wagner, M. L. Mohler, G. S. Kang, D. D. Miller, E. E. Geisert, Y.-A. Chang, E. B. Fleischer and K. J. Shea, *J. Med. Chem*., 2003, **46**, 2823.

5 B. M. Mikhailov and V. N. Smirnov, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1972, **21**, 1622 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1972, 1672).

refluxed for 30 min, the supernatant was decanted from the precipitated oil, which crystallized after several washes with hexane and cooling. The substance is very hygroscopic and decomposes above 250 °C. Yield 2.28 g (61%). ^{1}H NMR (200.13 MHz, CD_3OD) δ: 1.16 (s, 6H, Me), 1.14–1.45 (m, 10H), 2.15 (br.s, 1H, C^7H), 3.04–3.34 (series of overlapping multiplets of CH_2N bicyclic and ethyl group protons). ^{13}C NMR (CD_3OD) δ: 6.6 (*Me*CH_2), 27.7 (Me), 28.4 (C^7), 30.6 ($C^{3,5}$), 42.3 ($C^{6,10}$), 48.6 (C^4), 63.4 (C^8), 73.7 ($C^{2,9}$). Found (%): C, 66.91; H, 9.98; Cl, 14.81; N; 6.03. Calc. for $C_{13}H_{24}ClN$ (%): C, 67.95; H, 10.53; Cl, 15.43; N; 6.10.

3,5-Dimethyl-1-azaadamantane **12**. According to published procedure,[17] from salt **11** (1 g), product **12** (0.42 g, 68%) was obtained as a colourless oil, bp 60–62 °C (20 Torr). All physicochemical data were close to those[18] of the authentic sample. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 0.68 (s, 6H, Me), 1.29 (m, 2H, 4-H), 1.40–1.61 (AB spectrum, 4H, 6,10-H, $^2J_{AB}$ 11.8 Hz), 1.75 (br.s, 1H, 7-H), 2.57–2.73 (AB spectrum, 4H, 2,9-H, $^2J_{AB}$ 12.6 Hz), 2.89 (s, 2H, 8-H). ^{13}C NMR ($CDCl_3$) δ: 27.7 (Me), 28.2 (C^7), 28.7 ($C^{3,5}$), 42.7 ($C^{6,10}$), 50.5 (C^4), 57.2 (C^8), 64.3 ($C^{2,9}$).

6 B. M. Mikhailov, T. K. Baryshnikova, V. G. Kiselev and A. S. Shashkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1979, **28**, 2361 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1979, 2544).

7 B. M. Mikhailov, T. V. Potapova and A. S. Shashkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1979, **28**, 2533 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1979, 2724).

8 B. M. Mikhailov, V. N. Smirnov and V. A. Kasparov, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1976, **25**, 2148 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1976, 2302).

9 B. M. Mikhailov, M. E. Gursky, T. V. Potapova and A. S. Shashkov, *J. Organomet. Chem*., 1980, **201**, 81.

10 R. Köster, G. Griaznov, W. Larbig and P. Binger, *Liebigs Ann. Chem*., 1964, **672**, 1.

11 D. M. Robinson and G. M. Keating, *Drugs*, 2006, **66**, 1515.

12 J. M. Rabey, P. Nissipeatu and A. D. Korczyn, *J. Neural Thansm. Park. Dis. Dement. Sect*., 1992, **4**, 277.

13 A. Heidrich, M. Rösler and P. Reiderer, *Fortschr. Neurol. Psychiatr*., 1997, **65**, 108.

14 J. Corbett, *Curr. Neurol. Neurosci. Rep*., 2007, **7**, 395.

15 P. Villoslada, G. Arrondo, J. Sepulcre, M. Alegre and J. Artieda, *Neurology*, 2009, **72**, 1630.

16 B. M. Mikhailov, E. A. Shagova and M. Yu. Etinger, *J. Organomet. Chem*., 1981, **220**, 1.

17 B. M. Mikhailov and E. A. Shagova, *J. Organomet. Chem*., 1983, **258**, 131.

18 (*a*) Yu. N. Bubnov, M. E. Gurskii and D. G. Pershin, *Mendeleev Commun*., 1994, **4**, 43; (*b*) Yu. N. Bubnov, M. E. Gurskii, D. G. Pershin, K. A. Lyssenko and M. Yu. Antipin, *Russ. Chem. Bull*., 1998, **47**, 1771 (*Izv. Akad. Nauk, Ser. Khim*., 1998, 1818).

19 L. K. Jackson, G. N. R. Smart and G. F. Wright, *J. Am. Chem. Soc*., 1947, **69**, 1539.

Received: 16th February 2018; Com. 18/5484