Use of allylic boranes in organic syntheses. Synthesis of an analog of the alkaloid flustrabromine

I. V. Zhun and A. V. Ignatenko

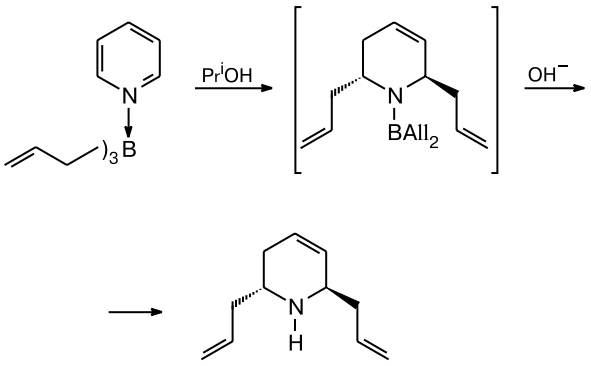
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: bor@ioc.ac.ru

The analog of the alkaloid flustrabromine containing no Br atom in position 6 was obtained in three steps. The key step involves reductive prenylation of 3-R-indole with triprenylborane.

Key words: allylboranes, triprenylborane, heterocycles, indole derivatives, flustrabromine, indolines, alkaloids.

β,γ-Unsaturated (allylic) derivatives of boron can easily add to compounds containing multiple carbon—carbon or carbon—heteroatom bonds and to some aromatic nitrogen heterocycles. Reductive allylation of nitrogen heterocycles with allylboranes[1] proceeds highly stereoselectively to give α-allylated and *trans*-α,α′-diallylated products in high yields[2] (Scheme 1).

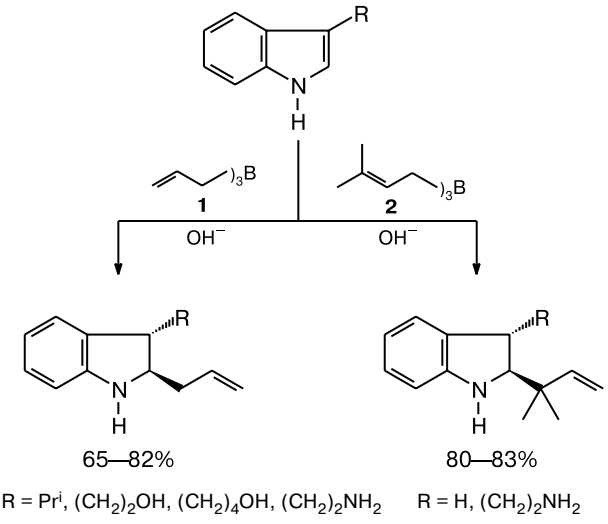
Scheme 1



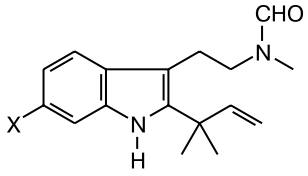
Apart from the reductive *trans*-2,5-diallylation of pyridine with triallyl-[3] and trimethallylboranes,[4] the allylboration of pyrrole,[5,6] indole,[6,7] quinolines,[8] isoquinoline,[9] and phenanthridine[8] was studied. It was found[10] that 3-substituted indoles in the presence of allylic boranes undergo reductive allylation, while the use of triprenylborane **2** in this reaction affords not easily accessible 2-(1,1-dimethylallyl)-3-R-2,3-dihydroindoles.

In the present work, the reductive prenylboration of 3-R-indole was a key step in the synthesis of debromoflustrabromine (**3a**), an analog of the alkaloid flustrabromine (**3b**) isolated from the Baltic bryozoan *Flustra foliacea*.[11]

Scheme 2



The synthesis was carried out in three steps. The reductive prenylboration of *N*(10)-methyltryptamine (**4**) prepared according to a known procedure[12] gave *trans*-2-(1,1-dimethylallyl)-2,3-dihydroindole **5** in 93% yield. The reaction at 120—130 °C was completed in 4.5 h.



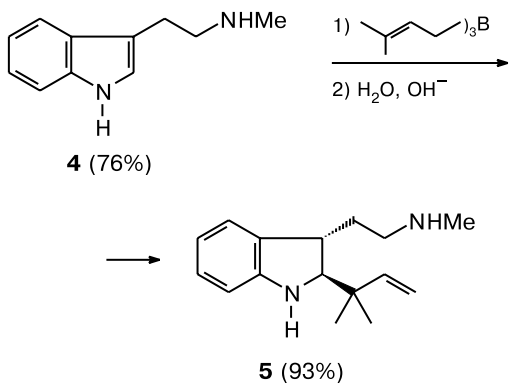
3

X = H (**a**), Br (**b**)

Compound **5** was converted into debromoflustrabromine by formylation with ethyl formate followed by

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 2126—2128, October, 2004.

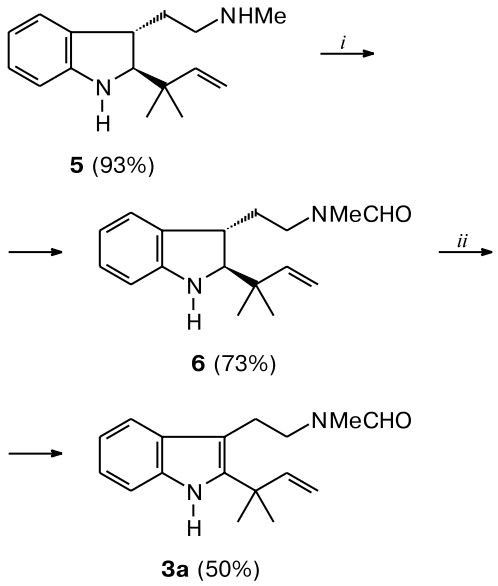
Scheme 3



Conditions: 120—130 °C, 4.5 h.

the oxidation (aromatization) of the resulting formamide **6** with tetrachloro-*p*-benzoquinone (chloranil).[13] The low yield at the final step is probably due to steric hindrances presented by the 1,1-dimethylallyl group.

Scheme 4



i. HCO_2Et, 100 °C, 1 h. *ii*. Chloranil, xylene, Δ, 9 h.

Thus, the reductive prenylboration of 3-R-indoles was successfully used in the synthesis of the analog of a natural compound containing a "reversed" prenyl group in position 2 of the indole ring.

Like flustrabromine **3b**, debromoflustrabromine **3a** is characterized by a double set of signals in the NMR spectra, which indicates the presence of two isomers of this compound. The spectra of the formamide **6** obtained also show a double set of signals. Apparently, the observed isomerism is due to the hindered rotation of the CO group about the C(O)—N bond.[11]

The recently[14] developed method of introducing a prenyl and "reversed" prenyl group involves generation of 3-chloroindolenines and prenylboration of the C=N double bond.

Experimental

All reactions with organoboron compounds were carried out in an atmosphere of dry argon. Solvents were purified before use according to standard procedures. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200P spectrometer; the chemical shifts are given on the δ scale with reference to $SiMe_4$. *N*(10)-Methyltryptamine **4** was prepared according to a known procedure.[12]

Tris(3-methylbut-2-enyl)borane (triprenylborane 2). Solutions of boron trifluoride etherate (20.06 g, 141 mmol) in 69 mL of ether and of 1-bromo-3-methylbut-2-ene (66.37 g, 445 mmol) in 36 mL of ether were added simultaneously for 2 h to stirred magnesium (12.43 g, 511 mmol) in 300 mL of ether. The mixture was refluxed for 1 h and left at room temperature for 1 day. The precipitate of the unreacted magnesium and the salts was separated and the product was extracted with hexane. The solvents were removed and the product was distilled *in vacuo*, b.p. 92—96 °C (1 Torr). Redistillation gave tris(3-methylbut-2-enyl)borane (15.72 g, 51%), b.p. 69—70 °C (1 Torr) (*cf.* Ref. 15: b.p. 68—70 °C (1 Torr)).

2-(1,1-Dimethylallyl)-3-(2-methylaminoethyl)indoline (5). A mixture of [2-(1*H*-indol-3-yl)ethyl](methyl)amine **4** [12] (0.58 g, 3.3 mmol) and triprenylborane (0.90 mL, 0.73 g, 3.3 mmol) was stirred at 120—130 °C for 4.5 h. The reaction mixture was cooled to ambient temperature and treated with 20% NaOH (2.2 mL). The organic layer was separated and the organic material was extracted from the aqueous layer with ether. The combined organic layer was washed with water, brine, and 1 *M* HCl. The acidic layer was washed with ether and alkalified with an alkali solution to pH 14. The organic layer was separated and the product was extracted from the aqueous layer with ether. The combined organic layer was dried over K_2CO_3. The solvent was removed to give indoline **5** (0.77 g, 94%), b.p. 149.5—152 °C (0.5 Torr). n^D_{20} 1.5555. Found (%): C, 78.16; H, 9.85; N, 11.35. $C_{16}H_{24}N_2$. Calculated (%): C, 78.64; H, 9.90; N, 11.46. ^1H NMR ($CDCl_3$), δ: 0.85 (s, 3 H, Me); 0.95 (s, 3 H, Me); 1.65—1.80 (m, 3 H, CH_2 + MeNH); 2.35 (s, 3 H, MeN); 2.50—2.70 (m, 2 H, C$\underline{H}_2$NHMe); 3.10—3.20 (m, 1 H, H(3)); 3.25 (d, 1 H, H(2), J = 5 Hz); 4.10 (br.s, 1 H, NH); 4.90—5.10 (m, 2 H, =CH_2); 5.65—5.85 (dd, H, =CH—, J = 18.2 Hz, J = 11.9 Hz); 6.45 (d, 1 H, Ar, J = 7.5 Hz); 6.60 (t, 1 H, Ar, J = 5.6 Hz); 7.95 (m, 2 H in Ar). ^{13}C NMR ($CDCl_3$), δ: 20.96 (Me); 22.20 (Me); 35.99 (CH_2); 36.74 (CH_2NH); 40.96 (C(3)); 41.32 (C_{quat}); 48.63 (CH_3NH); 71.2 (C(2)); 107.32 (CH, Ar); 112.36 (CH, Ar); 116.98 (=CH_2); 123.57 (CH, Ar); 127.02 (CH, Ar); 131.44 (C(3a)); 144.81 (=CH—); 150.25 (C(7a)).

2-(1,1-Dimethylallyl)-3-(2-methylformamidoethyl)indoline (6). A solution of indoline **5** (0.92 g, 3.76 mmol) in ethyl formate (5.0 mL, 61.9 mmol) in a sealed tube was heated in a boiling water bath for 1 h. The ethyl formate was removed and the residue was dissolved in ether and washed with 0.5 *M* HCl

(5×6 mL). The acidic layer was washed with ether and alkalified with an alkali solution to pH 14. The organic layer was separated and the organic material was extracted from the aqueous layer with ether (2×5 mL). The organic layer was washed with water (10 mL) and a solution of NaCl (2×10 mL) and concentrated to give compound **6** (0.75 g, 73%), b.p. 150—190 °C (0.008 Torr). Found (%): C, 74.22; H, 8.71; N, 10.21. $C_{17}H_{24}N_2O$. Calculated (%): C, 74.96; H, 8.88; N, 10.28. ^{1}H NMR ($CDCl_3$), δ: 1.05 (s, 6 H, 2 Me); 1.70—2.00 (m, 2 H, CH_2); 2.85 (s, 3 H, MeN); 3.10—3.50 (m, 4 H, $C\underline{H}_2NH_2$ + H(3) + H(2)); 4.53 (s, 0.36 H, NH of the minor stereomer); 4.62 (s, 0.64 H, NH of the major diastereomer); 5.00—5.20 (m, 2 H, $=CH_2$); 5.75—5.95 (m, H, =CH—); 6.5—6.85 (m, 2 H in Ar); 7.0—7.2 (m, 2 H in Ar); 8.00 (s, 0.35 H, CHO of the minor diastereomer); 8.05 (s, 0.65 H, CHO of the major diastereomer). ^{13}C NMR ($CDCl_3$), δ: 21.19 (Me); 21.30 (Me); 28.38 (MeNH); 32.61 (CH_2); 33.20 (CH_2); 34.35 (MeNH); 39.96 (C_{quat}); 40.25 (C_{quat}); 40.61 (CH_2NH); 40.77 (C(3)); 45.67 (CH_2NH); 70.34 (C(2)), 106.80, 106.90 (CH in Ar); 111.78, 111.99 (CH in Ar); 116.28 ($=CH_2$, *i*-Pren); 122.66, 122.92 (CH, Ar); 126.63, 126.85 (CH, Ar); 129.56, 130.15 (C(3a)); 143.91, 144.11 (=CH—); 149.97, 150.05 (C(7a)); 161.37, 161.56 (CHO).

***N*-2-[2-(1,1-Dimethylallyl)-1*H*-indol-3-yl]ethyl-*N*-methylformamide (debromoflustrabromine) (3a).** Indoline **6** (0.20 g, 0.73 mmol) and 2,3,5,6-tetrachlorobenzoquinone (chloranil) (0.18 g, 0.73 mmol) in 11 mL of *p*-xylene were refluxed for 8 h. The reaction mixture was cooled, washed with 20% NaOH (4×10 mL), water, brine, 2 *M* HCl (3×10 mL), and NaCl (3×5 mL), and concentrated to give pure (NMR data) debromoflustrabromine **3a** (0.10 g, 50%). For elemental analysis, compound **3a** was purified by chromatography on Flash silica gel (32—63 μm) with ether as an eluent; R_f 15—36%. Found (%): C, 75.31; H, 8.11; N, 10.41. $C_{17}H_{22}N_2O$. Calculated (%): C, 75.52; H, 8.20; N, 10.36. ^{1}H NMR ($CDCl_3$), δ: 1.40—1.70 (m, 6 H, 2 Me); 2.80—3.10 (m, 5 H, CH_3N + CH_2); 3.35—3.65 (m, 2 H, CH_2); 5.05—5.2 (m, 2 H, $=CH_2$); 6.0—6.2 (m, H, =CH—); 7.0—7.7 (m, 4 H, Ar); 7.90—8.10 (m, NH); 8.45 (s, 0.4 H, CHO of the minor isomer); 8.65 (s, 0.6 H, CHO of the major isomer). ^{13}C NMR ($CDCl_3$), δ: 22.42, 24.74 (CH_2); 27.51 (2 Me); 29.84, 34.79 (MeNH); 38.64, 38.69 (C_{quat}); 49.21, 50.00 (CH_2N); 106.28, 107.20 (C(3)); 110.42, 110.74 (CH, Ar); 111.44, 111.53 ($=CH_2$); 117.22, 117.84 (CH, Ar); 119.06, 119.12 (CH, Ar); 121.07, 121.21 (CH, Ar); 128.82, 129.20 (C(3a)); 134.19, 134.29 (C(2)); 139.90, 140.17 (C(7a)); 145.79 (=CH—); 162.26, 162.41 (CHO).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-32248) and the Foundation of the President of the Russian Federation (Program for Support of Leading Scientific Schools, Grant NSh-1917.2003.3).

References

1. Yu. N. Bubnov, E. A. Shagova, S. V. Evchenko, A. V. Ignatenko, and I. D. Gridnev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 2644 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1991, **40**, 2315 (Engl. Transl.)].
2. Yu. N. Bubnov, *Pure Appl. Chem.*, 1994, **66**, 235; Yu. N. Bubnov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1203 [*Russ. Chem. Bull.*, 1995, **44**, 1156 (Engl. Transl.)]; Yu. N. Bubnov, in *Advances in Boron Chemistry*, Ed. W. Siebert, *The Royal Society of Chemistry*, 1997, p. 123; Yu. N. Bubnov, E. V. Klimkina, I. V. Zhun, F. V. Pastukhov, and I. V. Yampolski, in *Contemporary Boron Chemistry*, Eds. M. Davidson, A. K. Hughes, T. B. Marder, and K. Wade, *The Royal Society of Chemistry*, Thomas Graham House, Cambridge, 2000, p. 446.
3. Yu. N. Bubnov, E. A. Shagova, S. V. Evchenko, and A. V. Ignatenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1994, 693 [*Russ. Chem. Bull.*, 1994, **43**, 645 (Engl. Transl.)]; Yu. N. Bubnov, E. V. Klimkina, A. V. Ignatenko, and I. D. Gridnev, *Tetrahedron Lett.,* 1996, **37**, 1317; Yu. N. Bubnov, E. V. Klimkina, A. V. Ignatenko, and I. D. Gridnev, *Tetrahedron Lett.*, 1997, **38**, 4631.
4. Yu. N. Bubnov, E. E. Demina, A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 627 [*Russ. Chem. Bull.*, 1997, **46**, 606 (Engl. Transl.)]; Yu. N. Bubnov, E. E. Demina, M. O. Dekaprilevich, and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1413 [*Russ. Chem. Bull.*, 1997, **46**, 1356 (Engl. Transl.)].
5. Yu. N. Bubnov, E. V. Klimkina, L. I. Lavrinovich, A. Yu. Zykov, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 1718 [*Russ. Chem. Bull.*, 1997, **48**, 1696 (Engl. Transl.)]; Yu. N. Bubnov, A. Yu. Zykov, L. I. Lavrinovich, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1329 [*Russ. Chem. Bull.*, 1993, **42**, 1271 (Engl. Transl.)].
6. Yu. N. Bubnov, L. I. Lavrinovich, A. Yu. Zykov, E. V. Klimkina, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1327 [*Russ. Chem. Bull.*, 1993, **42**, 1269 (Engl. Transl.)].
7. Yu. N. Bubnov, M. E. Gurskii, and T. V. Potapova, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 2807 [*Russ. Chem. Bull.*, 1996, **45**, 2665 (Engl. Transl.)].
8. Yu. N. Bubnov, S. V. Evchenko, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 2815 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 2239 (Engl. Transl.)].
9. Yu. N. Bubnov, S. V. Evchenko, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1325 [*Russ. Chem. Bull.*, 1993, **42**, 1268 (Engl. Transl.)]; Yu. N. Bubnov, E. V. Klimkina, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 1206 [*Russ. Chem. Bull.*, 1998, **47**, 1175 (Engl. Transl.)].
10. Yu. N. Bubnov, I. V. Zhun, E. V. Klimkina, A. V. Ignatenko, and Z. A. Starikova, *Eur. J. Org. Chem.*, 2000, 3323.
11. P. Wulf, J. S. Carle, and C. Christophersen, *J. Chem. Soc. Perkin Trans. 1*, 1981, 2895; C. Christophersen, *Acta Chem. Scand.*, 1981, **B39**, 517.
12. A. Alemany, E. Fernandez Alvarez, O. Nieto Lopez, and M. E. Rubio Herraez, *Bull. Soc. Chim. Fr.*, 1974, **12**, 2883.
13. A. P. Terent´ev, M. N. Preobrazhenskaya, A. S. Bobkov, and G. M. Sorokina, *Zh. Org. Khim.*, 1959, **29**, 2541 [*J. Gen. Chem. USSR*, 1959, **29** (Engl. Transl.)].
14. J. M. Schkeryants, J. C. G. Woo, P. P. Siliphaivanh, K. M. Depew, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 11964.
15. B. M. Mikhailov, V. N. Smirnov, and O. D. Ryazanova, *Dokl. Akad. Nauk*, 1972, **204**, 612 [*Dokl. Chem.*, 1972, **204** (Engl. Transl.)].

Received July 1, 2004;
in revised form October 14, 2004