Chemistry of Heterocyclic Compounds, Vol. 38, No. 10, 2002

N-SILYLATION OF 2,4,6-TRIALKYL-2,4,6,8-TETRAAZABICYCLO-[3.3.0]OCTANE-3,7-DIONES

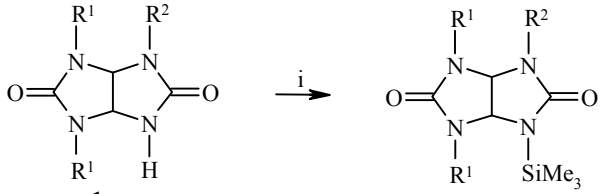
K. Yu. Chegaev, A. N. Kravchenko, O. V. Lebedev, Yu. A. Strelenko, and P. A. Belyakov

N-Trimethylsilyl derivatives of 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones have been prepared for the first time and the electrophilic substitution reaction of the trimethylsilyl group has been studied.

Keywords: 2,4,6-trialkyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones, silylation, electrophilic substitution, nuclear Overhauser effect.

The silylation of 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones (TABOD) has not been reported in the literature. The trimethylsilyl derivatives of TABOD attracted our attention most particularly because, on the basis of data obtained by the QSAR method, these compounds had been shown to be potentially promising psychotropically active materials [1]. On the other hand, they are of interest both from a practical and from a theoretical viewpoint as novel, chiral species.

The silylation reaction was studied for the case of the tri-N-alkyl-substituted TABOD **1a-c**, whose synthesis has been described by us previously [2]. Trimethylchlorosilane was chosen as the most readily available silylating agent. We have studied the effect of different proton acceptors (pyridine, triethylamine, and hexamethyldisilazane) and solvents (CH_2Cl_2, $CHCl_3$, and acetone) on the yield. The optimum yields of the trimethylsilyl derivatives of TABOD **2a-c** (85-93%) are achieved with hexamethyldisilazane and CH_2Cl_2.



1a–c **2a–c**

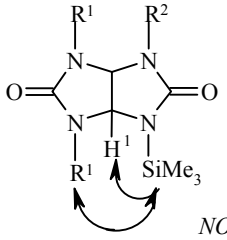
1, **2 a** $R^1 = R^2 = Me$; **b** $R^1 = Me$, $R^2 = Et$; **c** $R^1 = Et$, $R^2 = Me$
i = CH_2Cl_2; Me_3SiCl; $(Me_3Si)_2NH$; ~20°C, 1 h

An example has been reported in the literature for the formation of O-derivatives of TABOD in alkylation reactions [3]. We have shown that the silylation of **1a-c** occurs not at an oxygen but at the nitrogen atom. The structure of the synthesized compounds **2a-c** was proved by experimental NOE measurement [4]. The signal for the trimethylsilyl protons was saturated and changes in the intensity of the signals for the central H^1 proton and the protons of the substituent R^1 (Scheme 1) were observed. As a result it was shown that the trimethylsilyl group is situated on the nitrogen atom.

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913, Russia; e-mail: mnn@cacr.ioc.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1417-1420, October, 2002. Original article submitted January 14, 2000; revision submitted November 12, 2001.

 0009-3122/02/3810-1250$27.00

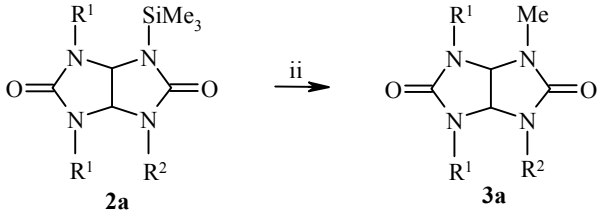
Scheme 1



The ^{1}H NMR spectra fully confirm the structure of the compounds **2a-c** obtained. The protons of the $SiMe_3$ groups appear as singlets with chemical shifts of 0.38 (**2a**), 0.08 (**2b**), and 0.02 (**2c**) ppm. Due to their nonequivalence, the methine protons form an AB system with the following constants, δ, ppm, *J* (Hz): for compound **2a** δ_A 4.95 and δ_B 5.05, J_{AB} = 8.01; for compound **2b** δ_A 4.85 and δ_B 4.91, J_{AB} = 7.82; for compound **2c** δ_A 4.88 and δ_B 5.96, J_{AB} = 7.85. The N-methyl groups protons appear in the spectrum of compound **2a** as three singlets with chemical shifts 2.71, 2.80, and 3.00 ppm; in the spectrum of compound **2b** as two singlets at 2.55 and 2.71 ppm; in the spectrum of compound **2c** as one singlet at 2.52 ppm. Due to the diastereotopic nature of the methylene protons of the ethyl groups they form an AMX_3 spectroscopic system. Hence, the ^{1}H NMR spectrum (δ, ppm; *J*, Hz) of compound **2b** shows a triplet (δ 0.90, $J_{AX} = J_{AM}$ = 6.40) and a doublet of sextets (δ 2.95 and 3.20, $J_{AM} = 2J_{AX}$ = 12.80). The spectrum of compound **2c** shows two AMX_3 systems with the following parameters: A'M'X'$_3$ triplet ($\delta_{X'}$ 0.81, $J_{A'X'} = J_{A'M'}$ = 7.11) and doublet of sextets ($\delta_{A'}$ 2.71, $\delta_{M'}$ 2.95, $J_{A'M'} = 2J_{A'X'}$ = 14.22) and A"M"X"$_3$ triplet ($\delta_{X"}$ -0.92, $J_{A"X"} = J_{A"M"}$ = 7.11) and doublet of sextets ($\delta_{A"}$ 3.20, $\delta_{M"}$ 3.32, $J_{A"M"} = 2J_{A"X"}$ = 14.22).

Hence we have synthesized for the first time the 4,6,8-trimethyl-2-trimethylsilyl-2,4,6,8-tetraazabicyclo-[3.3.0]octane-3,7-dione (**2a**), 4-ethyl-6,8-dimethyl-2-trimethylsilyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (**2b**), and 6,8-diethyl-4-methyl-2-trimethylsilyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (**2c**) which are novel, chiral species and show interest in connection with the problem of preparing optically pure biologically active materials.

From a chemical viewpoint, the greatest interest is in the electrophilic substitution reaction of the trimethylsilyl group. In a study of the desilylation of compounds **2a-c** it was found that they are stable in methanol but readily protodesilylated in an acidic medium (pH 3). This behavior can be incorporated when carrying out biological experiments on animals to reveal psychotropic activity. The electrophilic substitution of the trimethylsilyl group for an alkyl was studied for the example of the best known representative of this class of compound which is the 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (mebicar) [5]:



2a **3a**

$R^1 = R^2$ = Me. ii = MeI, $AgClO_4$, ~20°C, 2 h

The physicochemical properties of compound **3a** correspond to data in [6]. Hence we have shown the basis for the introduction of an alkyl substituent at the nitrogen atoms in TABOD and this opens up novel synthetic possibilities for varying the substituent and for broadening out this class of compound.

EXPERIMENTAL

^{1}H NMR spectra of compound solutions were measured on a Bruker AM 300 (300 MHz) instrument using $CDCl_3$. Calibration was carried out using the signal for the residual protons of the solvent at 7.27 ppm. ^{29}Si NMR spectra were recorded using selective polarization transfer from the protons. TLC was carried out on Silufol UV-254 plates and $CHCl_3$–MeOH (10:1).

Preparation of Compounds 2a-c. Each of compound **1a-c** (8.15 mmol) was dissolved in CH_2Cl_2 (15 ml). $(Me_3Si)_2NH$ (2 ml, 1.54 g, 9.5 mmol) was added followed by trimethylchlorosilane (1.35 ml, 1.15 g, 10.6 mmol) dropwise with stirring. The reaction product was stirred at room temperature for a further 1 h and the NH_4Cl precipitate was filtered off. The filtrate was evaporated in vacuo and the product was washed with ether and dried in a desiccator over NaOH.

4,6,8-Trimethyl-2-trimethylsilyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (2a). Yield 93%; mp 55°C (decomp.), R_f 0.64. ^{29}Si NMR spectrum, δ, ppm: 9.90 (s, SiMe). Found, %: C 46.75; H 7.94; N 21.93. $C_{10}H_{20}N_4O_2Si$. Calculated, %: C 46.88; H 7.81; N 21.88.

4-Ethyl-6,8-dimethyl-2-trimethylsilyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (2b). Yield 91%; mp 58°C (decomp.), R_f 0.72. Found, %: C 48.82; H 8.23; N 20.83. $C_{11}H_{22}N_4O_2Si$. Calculated, %: C 48.89; H 8.15; N 20.74.

6,8-Diethyl-4-methyl-2-trimethylsilyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (2c). Yield 85%; mp 52°C (decomp.), R_f 0.81. Found, %: C 50.63; H 8.52; N 19.87. $C_{12}H_{24}N_4O_2Si$. Calculated, %: C 50.70; H 8.45; N 19.72.

Preparation of Compound 3a. Compound **2a** (1 g, 3.9 mmol) was dissolved in CH_3I (5 ml). $AgClO_4$ (0.9 g, 4.3 mmol) was added with stirring. The reaction mixture was left at room temperature for 2 h and then diluted with MeOH (10 ml). The precipitated AgI was filtered off, the filtrate evaporated, and the product was washed with Et_2O to give compound **3a** (0.41 g, 53%); mp 230-232°C (mp 231-232°C in [6]), R_f 0.54.

REFERENCES

1. I. V. Svitan'ko, I. L. Zyryanov, M. I. Kumskov, L. I. Khmel'nitskii, L. I. Suvorova, A. N. Kravchenko, T. B. Markova, O. V. Lebedev, G. A. Orekhova, and S. V. Belova, *Mendeleev Commun.*, No. 2, 49 (1995).
2. A. N. Kravchenko, O. V. Lebedev, and E. Yu. Maksareva, *Mendeleev Commun.*, No. 1, 27 (2000).
3. L. I. Suvorova, L. V. Epishina, O. V. Lebedev, L. I. Khmel'nitskii, and S. S. Novikov in *O-Alkyl Derivatives of Saturated Condensed Bisureas* [in Russian], Summary Documents. II Moscow Conference for Chemistry and Technology, D. I. Mendeleev VKO, Moscow (1979), p. 50.
4. L. Birkofer, A. Ritter, and H. Kuhlthau, *Chem. Ber.*, **97**, 934 (1964).
5. M. D. Mashkovskii, *Medicinal Compounds* [in Russian], Meditsina, Moscow (1993), p. 99.
6. J. Nematolahi and R. Ketcham, *J. Org. Chem.*, **28**, 2378 (1963).