New synthesis of 9-methanesulfonyl-1,2,3,9a-tetrahydro- and 1,2,3,4-tetrahydrocarbazoles from *N*-methanesulfonyl-2-(cyclohex-1-enyl)aniline

Rail R. Gataullin,* Alexander M. Sotnikov, Ildus B. Abdrakhmanov and Genrikh A. Tolstikov

Institute of Organic Chemistry, Ufa Reseach Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. Fax: +7 3472 35 606; e-mail: chemorg@anrb.ru

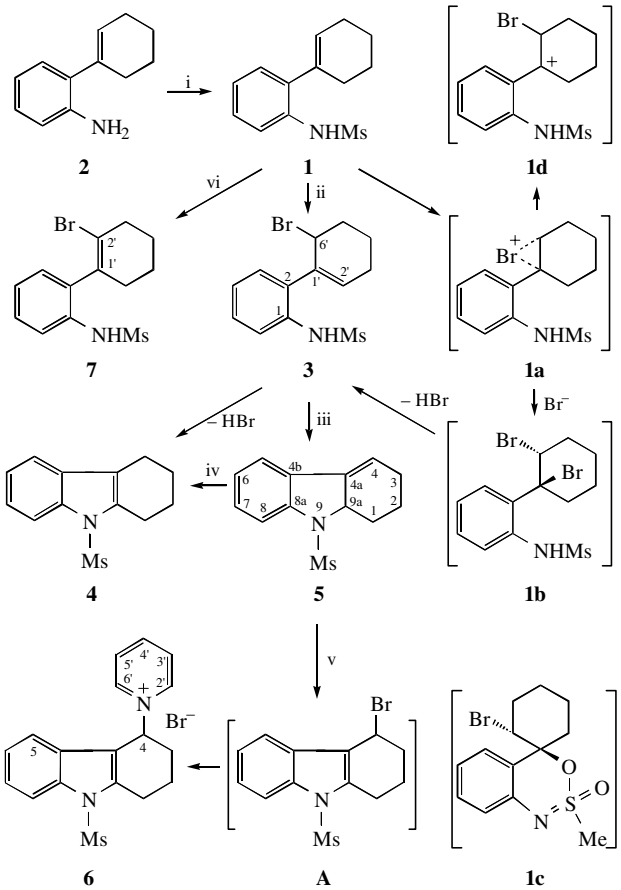
10.1070/MC2003v013n05ABEH001699

The reaction of N-methanesulfonyl-2-(cyclohex-1-en-1-yl)aniline with Br_2 in the presence of $NaHCO_3$ in MeCN results in *N*-methanesulfonyl-2-(6-bromocyclohex-1-en-1-yl)aniline, which was cyclised to 9-methanesulfonyl-1,2,3,4-tetrahydrocarbazole, and the effect of NH_3 leads to 9-methanesulfonyl-1,2,3,9a-tetrahydrocarbazole. The reaction of the latter with molecular bromine in the presence of pyridine results in 1-(9-methanesulfonyl-1,2,3,4-tetrahydro-4-carbazolyl)pyridinium bromide in a good yield.

Tetrahydrocarbazoles are used in the synthesis of alkaloids[1,2] or for medical purposes.[3] The production of these heterocycles was reviewed in the literature.[4,5] Here we propose a new method for the production of 1,2,3,9a- and 1,2,3,4-tetrahydrocarbazole *N*-mesylates from 2-(cyclohex-1-enyl)aniline *N*-mesylate **1**.

The interaction of amine **2**[6] with MsCl in pyridine gives amide **1**; its reaction with Br_2 in the presence of $NaHCO_3$ in MeCN leads to allyl bromide **3**.† Compound **3** transforms spontaneously to tetrahydrocarbazole **4**[7,8] within ~5 days at room temperature practically in a quantitative yield.‡ The interaction of bromide **3** with NH_3 in MeOH or MeCN yielded tetrahydrocarbazole **5**.§[,8] Earlier,[8] compound **5** was obtained in a mixture with isomer **4** using tributyltin hydride as a reagent for radical cyclization. This reagent cannot be used for medical purposes because of its toxicity and difficulties in the separation of by-products from a reaction mixture.[9] The treatment of compound **5** with an HBr solution leads to heterocycle **4**. A quaternary salt of **6**¶ was obtained from tetrahydrocarbazole **5** in the reaction with Br_2 in the presence of Py in MeCN in a 62.5% yield (Scheme 1). Probably, one of the key stages of this process is the formation of halide **A** with an extraordinarily mobile bromine atom (Scheme 1).

Probably, allyl bromide **3** is formed as a result of the *trans*-addition of Br_2 to sulfonyl amide **1** leading to dibromide **1b**. Compound **1b** underwent *trans*-elimination according to Zaitsev's



Scheme 1 *Reagents and conditions*: i, MsCl, Py, 20 °C; ii, Br_2, $NaHCO_3$, MeCN, 20 °C; iii, NH_3/H_2O, MeCN or MeOH; iv, HBr, CH_2Cl_2; v, Br_2, Py, 20 °C; vi, NBS, MeCN or CH_2Cl_2, 20 °C or NBS, $NaHCO_3$, MeCN or CH_2Cl_2, 20 °C.

† ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300.13 and 75.47 MHz, respectively (internal standard was TMS). IR spectra were recorded on a UR-20 spectrophotometer. Mass spectra were measured on a MX-1320 instrument (70 ev). Thin layer chromatography was carried out using Silufol UV 254 plates (Czech Republic) ($CHCl_3$ as an eluent).

N-*Methanesulfonyl-2-(cyclohex-1-en-1-yl)aniline* **1**. MsCl (1.71 g, 15 mmol) was added dropwise to a solution of compound **2**[6] (1.73 g, 10 mmol) in Py (20 ml) and stirred. The reaction mixture was allowed to stand for 18 h at room temperature, diluted with 2 ml of H_2O and stirred for 1 h; the solvent was evaporated in a vacuum. The residue was dissolved in 100 ml of CH_2Cl_2, washed with water (2×10 ml), 5% HCl solution, and then with water (10 ml). The organic phase was dried with $MgSO_4$. The solvent was removed in a vacuum; the residue was recrystallised from EtOH. The yield of sulfonylamide **1** was 2.28 g (93%), mp 89–90 °C (EtOH). Found (%): C, 61.83; H, 6.48; N, 5.22; S, 12.34. Calc. for $C_{13}H_{17}NO_2S$ (%): C, 62.12; H, 6.82; N, 5.57; S, 12.76.

N-*Methanesulfonyl-2-(6-bromocyclohex-1-en-1-yl)aniline* **3**. To a solution of sulfonylamide **1** (0.125 g, 0.5 mmol) and $NaHCO_3$ (0.42 g, 5 mmol) in 10 ml of MeCN a solution of Br_2 (0.08 g, 0.5 mmol) in 3 ml of the above solution was added with intense stirring. The reaction mixture was stirred for 3 h, the residue was filtered off, the solvent was evaporated in a vacuum. Transparent glassy compound **3** was obtained. The yield was 0.152 g (92%), amorphous mass, R_f 0.4 (C_6H_6–EtOAc, 4:1). ^{1}H NMR ($CDCl_3$) δ: 1.70–3.00 (m, 6H, $3CH_2$), 3.05 (s, 3H, Me), 4.99–5.03 (m, 1H, H-6′), 5.88 (ddd, 1H, H-2′, J_1 0.8 Hz, J_2 2.8 Hz, J_3 4.8 Hz), 6.90 (s, 1H, NH), 7.10–7.14 (m, 2H, Ar), 7.28–7.35 (m, 1H, Ar), 7.68 (dt, 1H, Ar, J_1 0.8 Hz, J_2 8.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.6, 25.0, 32.7 ($3CH_2$), 39.5 (Me), 53.5 (CH–Br), 118.0, 123.8, 128.6, 134.0 (C-6, C-4, C-3, C-5), 129.0 (C-2′), 131.4, 134.5, 135.2 (C-2, C-1, C-1′). Found (%): C, 46.93; H, 4.47; Br, 24.02; N, 3.90; S, 9.44. Calc. for $C_{13}H_{16}BrNO_2S$ (%): C, 47.28; H, 4.88; Br, 24.20; N, 4.24; S, 9.71.

‡ *9-Methanesulfonyl-1,2,3,4-tetrahydrocarbazole* **4**.

a. Amide **3** (0.16 g, 0.49 mmol) was left for 96 h at room temperature; resulting compound **4** was dissolved in CH_2Cl_2 (15 ml) and washed with 10% $NaHCO_3$ (15 ml). The organic phase was dried with Na_2SO_4, and the solvent was evaporated in a vacuum. The residue was subjected to silica gel column chromatography (0.5 g, CH_2Cl_2 as an eluent), which yielded 0.12 g (98%) of carbazole **4**.

b. A solution of AcBr (0.03 ml, 0.32 mmol) and (0.05 ml, 0.32 mmol) of H_2O in 1 ml of CH_2Cl_2 was added to a solution of **5** (0.04 g, 0.16 mmol) in 2 ml of CH_2Cl_2. After 72 h, the reaction mixture was diluted with 30 ml of CH_2Cl_2 and washed with 20 ml of a 10% $NaHCO_3$ solution. The organic phase was dried with Na_2SO_4; the solvent was evaporated in a vacuum. The yield of heterocycle **4** was 0.039 g (97.5%). R_f 0.75 (C_6H_6–EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ: 1.25–2.75 (m, 8H, $4CH_2$), 3.00 (s, 3H, Me), 7.15–8.20 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.9, 21.9, 23.0, 24.3 ($4CH_2$), 40.1 (Me), 113.6, 118.0, 123.2, 123.8 (C-8, C-5, C-6, C-7), 118.4, 130.2, 135.2, 135.8 (C-4a, C-4b, C-9a, C-8a). Found (%): C, 62.45; H, 6.03; N, 5.21; S, 12.59. Calc. for $C_{13}H_{15}NO_2S$ (%): C, 62.63; H, 6.06; N, 5.62; S, 12.86.

rule. In this process, the participation of the methane sulfonyl group is possible with the formation, for example, of **1c** because like reactions are known.[10] However, this supposition was not confirmed by the interaction of sulfonyl amide **1** with NBS, where the formation of cyclic **1c** can occur. In this case, only vinyl bromide **7**†† was obtained, which can be the stabilization product of carbocation **1d**.

The composition and structure of the compounds obtained were determined by NMR spectroscopy (two-dimensional HH-cosy, CH-corr) and JMOD and confirmed by elemental analysis. One-dimensional NOE studies show intramolecular Overhauser interaction between H-4, H-5 and H-4, H-2′,6′ as well as between H-5 and H-2′,6′, in the ^{1}H NMR spectrum of **6**. It was found that the saturation of the H-4 proton gives rise to an increase in the intensity of H-5 and H-2′,6′ bands by 5.4 and 17.0%, respectively. Similar irradiation of H-5 causes H-2′,6′ pattern intensity growth by 2.9%. These facts indicate the spatial proximity of the above protons.

§ *9-Methanesulfonyl-1,2,3,9a-tetrahydrocarbazole* **5**.[8]

a. 30 ml of a 1.5 N NH_3 solution in MeOH was added to 1.0 g (3.03 mmol) of **3** in 20 ml of MeOH. After 24 h, the solvent was evaporated in a vacuum; the residue was dissolved in 100 ml of CH_2Cl_2 and washed with H_2O (50 ml). The organic phase was dried with Na_2SO_4. The solvent was evaporated in a vacuum. Recrystallization from EtOH yielded 0.6 g (79%) of compound **5**, mp 106–108 °C (EtOH).

b. To a solution of sulfonylamide **1** (0.8 g, 3.1 mmol) and $NaHCO_3$ (2.52 g, 31 mmol) in 30 ml of MeCN a solution of Br_2 (0.5 g, 3.1 mmol) in 10 ml of the above solution was added with intense stirring. Then, the reaction mixture was stirred for 3 h, and the precipitate was filtered off. This process was carried out two times with the same quantities of amide **1** and bromine. The filtrates were combined and evaporated to a volume of ~20 ml. The addition of 30 ml of an aqueous 25% NH_3 solution resulted in carbazole **5** in 20–30 min, which was filtered off, washed with 10 ml of water and dried in a vacuum. The yield was 1.97 g (85%), mp 106–108 °C. ^{1}H NMR ($CDCl_3$) δ: 1.55–2.75 (m, 6H, 3CH_2), 2.90 (s, 3H, Me), 4.35 (dq, 1H, H-9a, J_1 3.6 Hz, J_2 10.0 Hz), 5.98 (q, 1H, H-4, J 3.6 Hz), 7.06 (dt, 1H, H-7, J_1 0.9 Hz, J_2 7.5 Hz), 7.23 (dd, 1H, H-6, J_1 7.5 Hz, J_2 8.1 Hz), 7.38 (d, 1H, H-8, J 7.5 Hz), 7.51 (dd, 1H, H-5, J_1 0.6 Hz, J_2 8.1 Hz). ^{13}C NMR ($CDCl_3$): 19.9, 24.4, 29.1 (3CH_2), 33.8 (Me), 64.7 (C-9a), 114.3 (C-8), 118.7 (C-6), 120.2 (C-5), 124.0 (C-4), 135.3 (C-7), 129.1, 129.3, 143.2 (C-4b, C-4a, C-8a). Found (%): C, 62.24; H, 5.81; N, 5.43; S, 12.43. Calc. for $C_{13}H_{15}NO_2S$ (%): C, 62.63; H, 6.06; N, 5.62; S, 12.86.

¶ *1-(9-Methanesulfonyl-1,2,3,4-tetrahydro-4-carbazolyl)pyridinium bromide* **6**. 0.96 g (5.9 mmol) of Br_2 in 10 ml of MeCN was added slowly to tetrahydrocarbazole **5** (1.47 g, 5.9 mmol) in 20 ml of MeCN and 1.5 g (18 mmol) of Py with intense stirring. After 1 h, the solvent was evaporated in a vacuum. The residue was dissolved in hot H_2O (10 ml), the solution was decanted and then cooled. The precipitated crystals of the quaternary salt of **7** were filtered off. The yield was 1.5 g (62.5%), mp 129–130 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.85–3.37 (m, 6H, 3CH_2), 3.52 (s, 3H, Me), 6.48 (t, 1H, H-4, J 4.7 Hz), 6.98 (d, 1H, H-5, J 7.7 Hz), 7.15 (t, 1H, H-6, J 7.7 Hz), 7.35 (dt, 1H, H-7, J_1 1.0 Hz, J_2 8.4 Hz), 7.95 (d, 1H, H-8, J 8.4 Hz), 8.18 (t, 2H, H-3′, H-5′, J 7.5 Hz), 8.70 (t, 1H, H-4′, J 7.7 Hz), 9.31 (dd, 2H, H-2′, H-6′, J_1 1.0 Hz, J_2 5.2 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 17.9, 23.4, 30.6 (3CH_2), 41.60 (Me), 63.9 (C-4), 109.9 (C-4a), 113.6 (C-8), 117.9 (C-5), 123.5 (C-6), 124.6 (C-7), 126.3 (C-4b), 128.2 (C-3′, C-5′), 135.4 (C-8a), 142.3 (C-9a), 143.9 (C-2′, C-6′), 146.3 (C-4′). Found (%): C, 52.91; H, 4.53; Br, 19.27; N, 6.41; S, 7.49. Calc. for $C_{18}H_{19}BrN_2O_2S$ (%): C, 53.08; H, 4.70; Br, 19.62; N, 6.88; S, 7.87.

†† N-*Methanesulfonyl-2-(2-bromocyclohex-1-en-1-yl)aniline* **7**. The mixture of mesilate **1** (0.25 g, 1 mmol) with NBS (0.53 g, 3 mmol) in 20 ml of CH_2Cl_2 was stirred in the presence of $NaHCO_3$ (1 g) for 4 h. Then, the reaction mixture was added to a 12% Na_2SO_3 solution (10 ml), stirred for 10 min and extracted with 50 ml of CH_2Cl_2. The organic phase was washed with water (10 ml) and dried over Na_2SO_4. The solvent was evaporated in a vacuum; the residue was recrystallised from ethanol, the yield of compound **7** was 0.3 g (91%), mp 148–150 °C (EtOH). IR (ν/cm^{-1}): 490, 514, 530 (C–Br), 3262 (NH). ^{1}H NMR ($CDCl_3$) δ: 1.75–1.95 (m, 4H, 2CH_2), 2.25–2.40 (m, 2H, CH_2), 2.60–2.80 (m, 2H, CH_2), 3.10 (s, 3H, SO_2Me), 6.40 (s, 1H, NH), 7.06 (dd, 1H, H-6, J_1 1.6 Hz, J_2 7.6 Hz), 7.15–7.35 (m, 2H, H-4, H-5), 7.60 (d, 1H, H-3, J 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 22.4, 24.4, 33.5, 36.2 (C-3′, C-4′, C-5′, C-6′), 39.9 (Me), 118.5, 124.8, 128.6, 128.7 (C-3, C-4, C-5, C-6), 131.6, 133.2, 133.6, 134.3 (C-1, C-1′, C-2, C-2′). Found (%): C, 46.84; H, 4.45; Br, 23.82; N, 3.81; S, 9.29. Calc. for $C_{13}H_{16}BrNO_2S$ (%): C, 47.28; H, 4.88; Br, 24.20; N, 4.24; S, 9.71.

References

1 J.-C. Gramain, H.-P. Husso and Y. Troin, *J. Org. Chem.*, 1985, **50**, 5517.
2 A. G. Mustafin, I. N. Khalilov, I. B. Abdrakhmanov and G. A. Tolstikov, *Khim. Prir. Soedin.*, 1989, 816 [*Chem. Nat. Compd*. (*Engl. Transl.*), 1989, 693].
3 N. I. Andreeva, G. A. Bogdanova, A. I. Bokanov, P. Yu. Ivanov, M. D. Mashkovski and V. I. Shvedov, *Khim.-Farm. Zh*., 1992, 4 (in Russian).
4 G. W. Gribble, *J. Chem, Soc., Perkin Trans. 1*, 2000, 1045.
5 *Comprehensive Organic Chemistry*, eds. D. Barton and W. D. Ollis, Pergamon Press, Oxford–New York–Toronto–Sydney–Paris–Frankfurt, 1979, p. 8.
6 R. R. Gataullin, I. S. Afon'kin, A. A. Fatykhov, L. V. Spirikhin and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim*., 2000, 118 (*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 122).
7 M. Kizil, C. Lampard and J. R. Murphy, *Tetrahedron Lett*., 1996, **37**, 2511.
8 J. A. Murphy, K. A. Scot, R. S. Sinclan and N. Lewis, *Tetrahedron Lett*., 1997, **38**, 7295.
9 B. Patro, M. C. Merret, S. D. Makin, J. A. Murphy and K. E. B. Parkes, *Tetrahedron Lett*., 2000, **41**, 421.
10 J. I. G. Cadogan, D. K. Cameron, I. Gosney, R. M. Highcock and S. F. Newlands, *J. Chem. Soc., Chem. Commun*., 1986, **10**, 766.

Received: 18th December 2002; Com. 02/2025