ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 7, pp. 1641–1644. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © V.B. Sokolov, A.Yu. Aksinenko, T.A. Epishina, T.V. Goreva, 2017, published in Zhurnal Obshchei Khimii, 2017, Vol. 87, No. 7, pp. 1214–1217.

LETTERS TO THE EDITOR

Reactions of Carbazole with Dimethyl Alkanedisulfonates

V. B. Sokolov, A. Yu. Aksinenko*, T. A. Epishina, and T. V. Goreva

Institute of Physiologically Active Substances, Russian Academy of Sciences, Severnyi proezd 1, Chernogolovka, 142432 Russia
**e-mail: alaks@ipac.ac.ru*

Received April 19, 2017

Abstract—Reaction of carbazole with dimethyl alkanedisulfonates in the presence of sodium hydride resulted in the formation of three main products: 2-(9*H*-carbazol-9-yl)alkylmethanesulfonates, 1,2-di-(9*H*-carbazol-9-yl)alkanes, and 9-alkenyl-9*H*-carbazoles.

Keywords: carbazole, dimethyl alkanedisulfonates, alkylation, conjugates, olefination, sodium hydride

DOI: 10.1134/S1070363217070337

N-Substituted derivatives of carbazoles are a promising class of biologically active compounds, among which substances have been found showing antimicrobial [1], antifungal [2], antitumor [3], antioxidant [4], anti-inflammatory [5], and neuroprotective properties [6–12]. In this regard, the development of preparative methods for the functionalization of carbazoles at the NH function seems to be one of the promising and relevant areas of medical chemistry.

A prerequisite for this study was the data on the synthesis of three types of *N*-substituted carbazoles: 2-(9*H*-carbazol-9-yl)ethylmethanesulfonate obtained by alkylation of carbazole with 2-iodoethanol and subsequent mesylation of the resulting 2-(9*H*-carbazol-9-yl)ethanol [13], 1,2-di-(9*H*-carbazol-9-yl)ethane synthesized by alkylating carbazole with dibromoethane [14], and 9-vinyl-9*H*-carbazole obtained by alkylating carbazole with vinyl bromide [15]. The aim of the present work was to study the synthetic possibilities of the reaction of available carbazole and dimethyl alkanedisulfonates to obtain *N*-substituted carbazole derivatives of the three above-mentioned structural types, including promising synthetic blocks.

We found that carbazole **1** in the presence of sodium hydride reacted with dimethyl alkanedisulfonates **2a** and **2b** to form three reaction products:

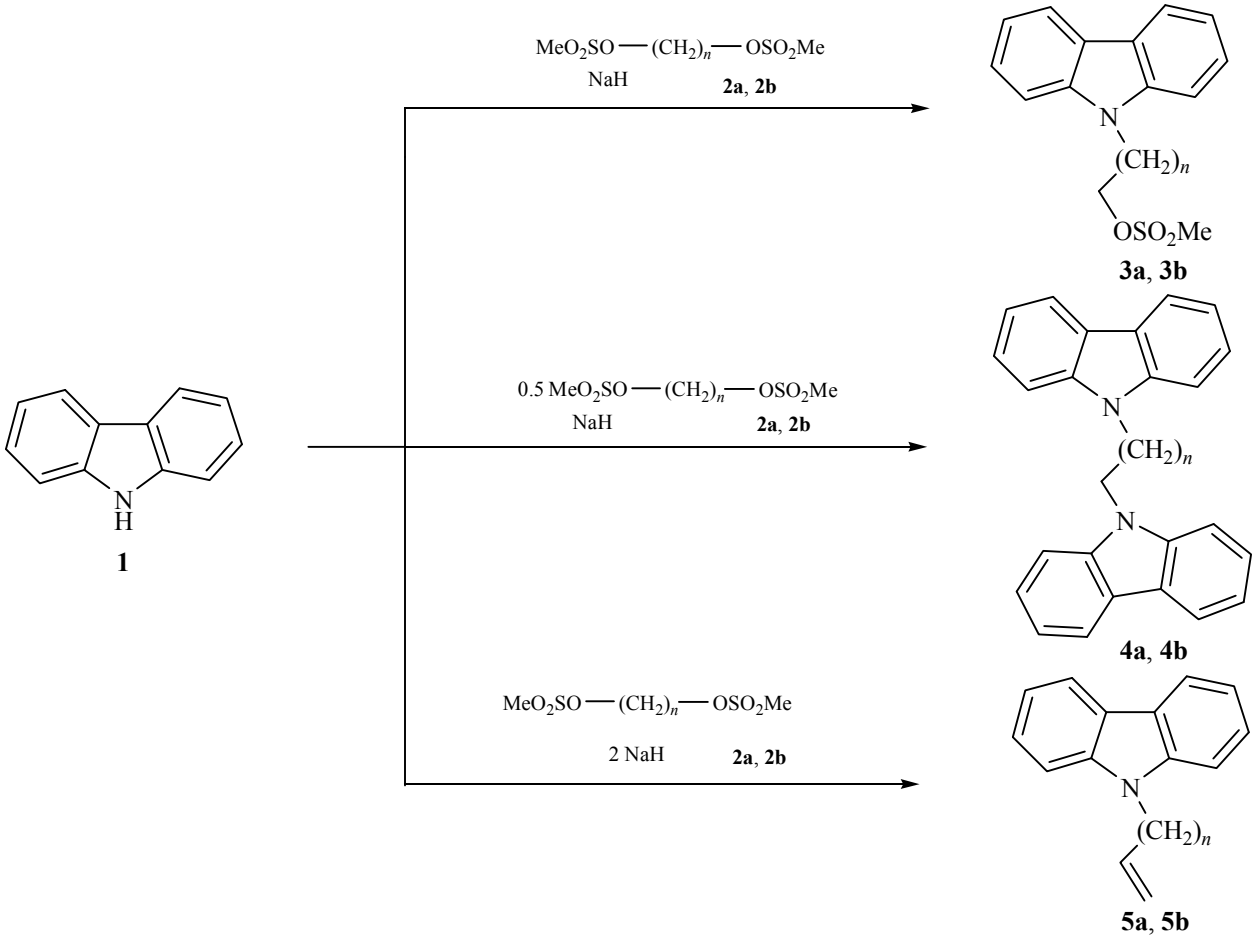
2-(9*H*-carbazol-9-yl)ethylmethanesulfonates **3a** and **3b**, 1,2-di-(9*H*-carbazol-9-yl)alkanes **4a** and **4b**, 9-alkenyl-9*H*-carbazoles **5a** and **5b**; depending on the stoichiometric ratio of the reagents and the reaction conditions, each of three products can be obtained and isolated as the main substance (Scheme 1). Thus, when carrying out the reaction in THF with an equimolar ratio of the reagents, carbazoles **3a** and **3b** formed predominantly. When using a double excess of carbazole **1** and sodium hydride, carbazoles **4a** and **4b** were obtained in high yields. The reaction of equimolar amounts of carbazole **1** and dimethyl alkanedisulfonates **2a** and **2b** at boiling in the presence of a twofold excess of sodium hydride led to the formation of *N*-vinyl- and *N*-allylcarbazoles **5a** and **5b**.

Compounds **3**–**5** were crystalline substances whose composition and structure were confirmed by elemental analysis and NMR spectroscopy methods. In the ^{1}H NMR spectra of compounds **3**–**5** there were characteristic signals of aromatic protons of the carbazole ring in the range of 7.1–8.1 ppm. The spectra of compounds **3a** and **3b** contained the signals of methanesulfonic group at 2.4–2.7 ppm. The signals of the ethylene spacer in the spectra of compounds **4a** and **4b** were observed in the range of 2.43–4.92 ppm. In the NMR spectra of compounds **5a a**nd **5b** there were the signals of vinyl protons at 4.8–7.2 ppm.

The structure of compound **3a** was also confirmed by chemical transformations. Thus, carbazole **3a** reacted with 3,5-dimethylaminoadamantane **6** in isopropanol under reflux to produce carbazole and amino-adamantane conjugate **7** (Scheme 2). The ^{1}H NMR spectrum contained a superposition of the signals of carbazole and adamantane fragments.

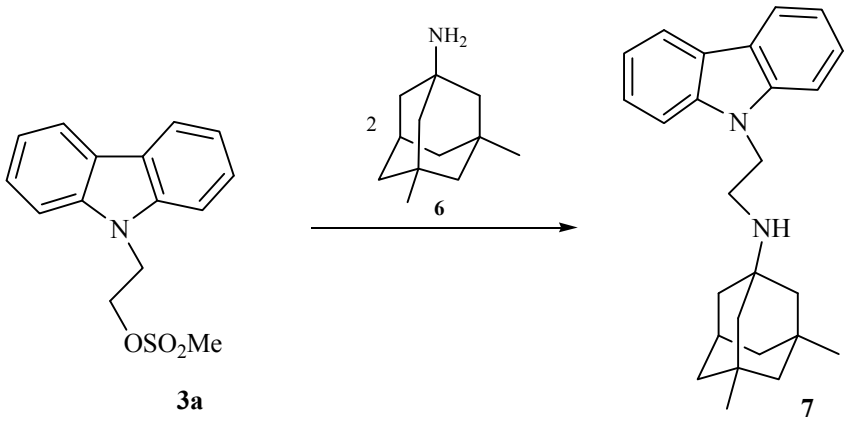
In conclusion, an original approach towards the synthesis of *N*-substituted carbazoles of three structural

Scheme 1.



n = 0 (**a**), 1 (**b**).

Scheme 2.



types by reacting carbazole and dimethyl alkanedisulfonates in the presence of sodium hydride was developed.

Dimethyl alkanedisulfonates **2a** and **2b** were prepared according to the procedure described in [16]; carbazole **1** was purchased from Aldrich.

2-(9*H*-Carbazol-9-yl)ethylmethanesulfonate (3a). A mixture of 1.1 mmol of NaH and 1 mmol of carbazole **1** in 20 mL of THF was stirred for 1 h, then 0.1 mmol of dimethyl sulfonate **2a** was added, and the mixture was stirred for 2 h at 20°C. After the reaction completed the mixture was poured into 100 mL of

water, the precipitate formed was filtered off and recrystallized from ethanol. Yield 0.24 g (83%), mp 162–164°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.48 s (3H, CH_3SO_2O), 4.46–4.72 m (4H, CH_2), 7.14–7.32 m (2H, CH_{Ar}), 7.36–7.52 m (4H, CH_{Ar}), 8.07 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.6 Гц). Found, %: C 62.41; H 5.45; N 4.71. $C_{15}H_{15}NO_3S$. Calculated, %: C 62.26; H 5.23; N 4.84.

2-(9*H*-Carbazol-9-yl)propylmethanesulfonate (3b) was prepared similarly. Yield 0.24 g (79%), mp 107–109°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.19 q (2H, CH_2, $^3J_{HH}$ = 5.8), 2.67 s (3H, CH_3SO_2O), 3.27 t (2H, CH_2, $^3J_{HH}$ = 5.8), 3.46 t (2H, CH_2, $^3J_{HH}$ = 5.8), 7.44–7.64 m (4H, CH_{Ar}), 7.71–7.87 m (4H, CH_{Ar}). Found, %: C 63.17; H 5.86; N 4.43. $C_{16}H_{17}NO_3S$. Calculated, %: C 63.34; H 5.65; N 4.62.

1,2-Di-(9*H*-carbazol-9-yl)ethane (4a). To a solution of 1 mmol of carbazole **1** in 20 mL of THF was added 1.1 mmol of NaH. The reaction mixture was stirred for 1 h, then 0.05 mmol of dimethyl sulfonate **2a** was added and stirring was continued for 2 h at 20°C. After the reaction completed the mixture was poured into 100 mL of H_2O. The precipitate formed was filtered off and recrystallized from ethanol. Yield 0.27 g (75%), mp 300°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.92 s (4H, CH_2), 7.01–7.14 m (4H, CH_{Ar}), 7.18–7.27 m (8H, CH_{Ar}), 8.01 d (4H, CH_{Ar}, $^3J_{HH}$ = 7.8). Found, %: C 86.86; H 5.75; N 7.98. $C_{26}H_{20}N_2$. Calculated, %: C 86.65; H 5.59; N 7.77.

1,2-Di-(9*H*-carbazol-9-yl)propane (4b) was prepared similarly. Yield 0.27 g (72%), mp 181–183°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.43 q (2H, CH_2, $^3J_{HH}$ = 7.3), 4.32 t (4H, CH_2, $^3J_{HH}$ = 7.3), 7.10–7.30 m (8H, CH_{Ar}) 7.39 t (4H, CH_{Ar}, $^3J_{HH}$ = 7.6), 8.10 d (4H, CH_{Ar}, $^3J_{HH}$ = 7.6). Found, %: C 86.38; H 6.11; N 7.31. $C_{27}H_{22}N_2$. Calculated, %: C 86.60; H 5.92; N 7.48.

8-Vinyl-9*H*-carbazole (5a). To a solution of 1 mmol of carbazole **1** in 20 mL of THF was added 2.1 mmol of NaH. The reaction mixture was stirred for 1 h, then 0.1 mmol of dimethyl sulfonate **2a** was added and the mixture was stirred for 8 h at 60°C. After the reaction completed the mixture was poured into 100 mL of H_2O. The formed precipitate was filtered off and recrystallized from ethanol. Yield 0.14 g (73%), mp 101–103°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 5.16 d (1H, CH_2=, $^3J_{HH}$ = 9.0), 5.55 d (1H, CH_2=, $^3J_{HH}$ = 16.2), 7.18–7.38 m (3H, CH_{Ar} + CH=), 7.48 t (2H, CH_{Ar}, $^3J_{HH}$ = 7.6), 7.67 d (2H, CH_{Ar}, $^3J_{HH}$ = 8.2), 8.08 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.6). Found, %: C 86.79; H 5.91; N 7.06. $C_{14}H_{11}N$. Calculated, %: C 87.01; H 5.74; N 7.25.

8-(Propen-2-yl)-9*H*-carbazole (5b) was prepared similarly. Yield 0.14 g (68%), mp 71–72°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.83 d.t (2H, CH_2, $^3J_{HH}$ = 4.9, $^4J_{HH}$ = 1.5), 4.98 d.d.t (1H, CH_2=, $^3J_{HH}$ = 17.1, $^2J_{HH}$ = 1.5, $^4J_{HH}$ = 1.5), 5.11 d.d.t (1H, CH_2=, $^3J_{HH}$ = 10.4, $^2J_{HH}$ = $^4J_{HH}$ = 1.5), 5.93 d.d.d (1H, CH=, $^3J_{HH}$ = 17.1, $^3J_{HH}$ = 10.4, $^3J_{HH}$ = 4.9), 7.10–7.27 m (2H, CH_{Ar}), 7.28–7.52 m (4H, CH_{Ar}), 8.08 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.6). Found, %: C 86.74; H 6.48; N 6.53. $C_{15}H_{13}N$. Calculated, %: C 86.92; H 6.32; N 6.76.

***N*-[2-(9*H*-Carbazol-9-yl)ethyl]-3,5-dimethyladamantyl-1-amine (7)**. A solution of 0.01 mmol of ethyl methanesulfonate **3a** and 0.02 mmol of 3,5-dimethyladamantane-1-amine **6** in 10 mL of isopropanol was refluxed for 8 h, then poured into 100 mL of H_2O. The precipitate formed was filtered off and recrystallized from ethanol. Yield 0.31 g (83%), mp 178–180°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.77 s (6H, CH_3), 0.96–1.09 m (2H, CH_2), 1.09–1.26 m (9H, CH_2 + NH), 1.30–1.42 m (2H, CH_2), 1.99–2.12 m (1H, CH), 3.01 t (2H, CH_2, $^3J_{HH}$ = 7.0), 4.36 t (2H, CH_2, $^3J_{HH}$ = 7.0), 7.16–7.31 m (2H, CH_{Ar}), 7.40–7.53 m (4H, CH_{Ar}), 8.08 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.6). Found, %: C 83.61; H 8.84; N 7.33. $C_{26}H_{32}N_2$. Calculated, %: C 83.82; H 8.66; N 7.52.

^{1}H NMR spectra were recorded on a Bruker DPX 200 spectrometer, reference $SiMe_4$. Melting points were determined in a glass capillary.

ACKNOWLEDGMENTS

This work was supported by the Russian Science Foundation (project no. 14-23-00160).

REFERENCES

1. Yaqub, G., Hannan, A., Akbar, E., Usman, M., Hamid, A., Sadiq, Z., and Iqbal, M., *J. Chem*., 2013, ID 818739. doi 10.1155/2013/ 818739
2. Thevissen, K., Marchand, A., Chaltin, P., Meert, E.M.K., and Cammue, B.P.A., *Curr. Med. Chem*., 2009, vol. 16, no. 17, p. 2205. doi 10.2174/092986709788612701
3. Giraud, F., Bourhis, M., Nauton, L., Théry, V., Herfindal, L., Døskeland, S.O., Anizon, F., and Moreau, P., *Bioorg. Chem*., 2014, vol. 57, p. 108. doi 10.1016/ j.bioorg.2014.09.004
4. Guillonneau, C., Pierre, A., Charton, Y., Guilbard, N., Berthier, L.K., Leonce, S., Michael, A., Bisagni, E., and

Atassi, G., *J. Med. Chem*., 1999, vol. 42, no. 12, p. 2191. doi 10.1021/jm981093m

5. Bandgar, B.P., Adsul, L.K., Chavan, H.V., Jalde, S.S., Shringare, S.N., Shaikh, R., Meshram, R.J., Gacche, R.N., and Masand, V., *Bioorg. Med. Chem. Lett*., 2012, vol. 22, no. 18, p. 5839. doi 10.1016/j.bmcl.2012.07.080
6. Zhu, D., Chen, M., Li, M., Luo, B., Zhao, Y., Huang, P., Xue, F., Rapposelli, S., Pi, R., and Wen, S., *Eur. J. Med. Chem*., 2013, vol. 68, p. 81. doi 10.1016/j.ejmech.2013.07.029
7. Yoon, H.J., Kong, S.-Y., Park, M.-H., Cho, Y., Kim, S.-E., Shin, J.-Y., Jung, S., Lee, J., Farhanullah, Kim, H.-J., and Lee, J., *Bioorg. Med. Chem*., 2013, vol. 21, no. 22, p. 7165. doi 10.1016/j.bmc.2013.08.066
8. MacMillan, K. S., Naidoo, J., Liang, J., Melito, L., Williams, N.S., Morlock, L., Huntington, P.J., Estill, S.J., Longgood, J., Becker, G.L., McKnight, S.L., Pieper, A.A., De Brabander, J.K., and Ready, J.M., *J. Am. Chem. Soc*., 2011, vol. 133, no. 5, p. 1428. doi 10.1021/ja108211m
9. Bachurin, S.O., Shevtzova, E.P., Lermontova, N.N., Serkova, T.P., and Ramsay, R.R., *Neuro Toxicol*., 1996, vol. 17, nos. 3–4, p. 897.
10. RF Patent 2608737, 2016.
11. Sokolov, V.B., Aksinenko, A.Yu., Goreva, T.V., Epishina, T.A., Grigor'ev, V.V., Gabrel'yan, A.V., Vinogradova, D.V., Dubova, L.G., Shevtsov, P.N., Shevtsova, E.F., and Bachurin, S.O., *Russ. Chem. Bull*., 2016, vol. 65, no. 5, p. 1346. doi 10.1007/s11172-016-1460-6
12. Sokolov, V.B., Aksinenko, A.Yu., Goreva, T.V., Epishina, T.A., Dubova, L.G., Dubrovskaya, E.S., Klochkov, S.G., Shevtsov, P.N., Shevtsova, E.F., and Bachurin, S.O., *Russ. Chem. Bull*., 2016, vol. 65, no. 9, p. 2306. doi 10.1007/s11172-016-1582-x
13. Kim, Y.J., Ryu, J.-H., Cheon, Y.J., Lim, H.J., and Jeon, R., *Bioorg. Med. Chem. Lett*., 2007, vol. 17, no. 12, p. 3317. doi 10.1016/j.bmcl.2007.04.005
14. Narkhede, H.P., *Int. J. Chem. Sci.*, 2014, vol. 12, no. 2, p. 551.
15. Lebedev, A.Y., Izmer, V.V., Kazyul'kin, D.N., Beletskaya, I.P., and Voskoboynikov, A.Z., *Org. Lett*., 2002, vol. 4, no. 4, p. 623. doi 10.1021/ol0172370
16. Poldy, J., Peakal, R., and Barrow, R.A., *Tetrahedron. Lett*., 2008, vol. 49, no. 15, p. 2446. doi 10.1016/j.tetlet.2008.02.037