Reactions of Aminoacetals with C-Nucleophiles as a New Method for the Synthesis of Di(het)arylmethane Derivatives with a Taurine Fragment

A. V. Smolobochkin\textsuperscript{a,\textdagger}, L. J. Yakhshilikova\textsuperscript{b}, D. D. Bekrenev\textsuperscript{b}, A. S. Gazizov\textsuperscript{a}, A. R. Burilov\textsuperscript{a}, and M. A. Pudovik\textsuperscript{a}

\textsuperscript{a} Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center, Russian Academy of Sciences, Kazan, 420088 Russia
\textsuperscript{b} Kazan National Research Technological University, Kazan, 420015 Russia

\textdagger}e-mail: smolobochkin@iopc.ru

Received November 11, 2021; revised December 14, 2021; accepted December 16, 2021

Abstract—Based on the acid-catalyzed reaction of functionalized aminoacetals with C-nucleophiles, a series of new diarylmethane derivatives with a taurine fragment were synthesized, the structure of which was established by NMR spectroscopy method.

Keywords: taurine, diarylmethanes, C-nucleophiles

DOI: 10.1134/S1070363222020049

Among a large number of synthetic and natural organic compounds, diarylmethane derivatives attract attention, which is due to their high biological activity and the use of a number of them as drugs, such as fendiline—an antianginal, hypotensive, antiarrhythmic, coronary dilating agent [1], antihistamine agent diphenhydramine [2] and methadone used as an analgesic, as well as in the treatment of drug dependence [3, 4]. Diarylmethane derivatives may be potential agents for the treatment of COVID-19 [5]. Diarylmethanes with two phenolic fragments have anti-inflammatory [6], antiviral [7, 8], antiproliferative [9], anti-HIV [10], anticancer [11], and antimicrobial [12] activity.

Taurine (2-aminoethanesulfonic acid), as a pharmacophore unit, is a part of taurocholic acid, which is involved into the fats emulsification [13–15], and the drug netobimine used in the treatment of helminthiases in animals [16, 17].

Combining two biologically active fragments in one molecule is a promising route for the synthesis of compounds with new pharmacological properties compared to the original structures. The synthesis of hybrid structures, including the taurine and diarylmethane fragments, seems to be relevant.

Previously, an original method was developed for the preparation of diarylmethane derivatives based on the acid-catalyzed reaction of 1-(3,3-diethoxybutyl)ureas with resorcinol and its derivatives [18]. Extending the boundaries of this method makes it possible to obtain previously unknown diarylmethane derivatives with a taurine fragment. The synthesis of starting acetals 3a–3e was carried out in several stages according to previously developed procedures [19]. The reaction of 2-chloroethanesulfonyl chloride 1 with amines in dichloromethane in the presence of trifluoroacetic acid at room temperature led to the formation of diarylmethane derivatives 4c and 4d (Scheme 1).

Phenols [4-chlororesorcinol, sesamol (1,3-benzo-dioxol-5-ol), 2-methylresorcinol] and heterocycles (antipyrine, 4-hydroxy-6-methyl-2H-pyran-2-one), which quite easily enter into electrophilic substitution reactions and show biological activity, were chosen as C-nucleophiles. The reactions of acetals 3e and 3d with 4-chlororesorcinol in chloroform in the presence of an excess of trifluoroacetic acid at room temperature led to the formation of diarylmethane derivatives 4c and 4d.
Compounds 5b, 5e, and 6a were obtained in a similar way by reacting acetals 3 with sesamol and 2-methylresorcinol, respectively. Compound 6a was isolated in only 12% yield, which is probably due to the formation of a large number of oligomers and polymers. Using 4-hydroxy-6-methyl-2H-pyran-2-one and antipyrine as nucleophiles, new representatives of dihetarylmethanes 7c and 8e were obtained. In conclusion, using the reactions of functionalized aminoacetals with C-nucleophiles, new di(het) arylmethane derivatives modified with a taurine fragment were synthesized. The proposed route for the synthesis of these compounds is simple and allows varying the substituents in both the taurine and diarylmethane moieties over a wide range.

**EXPERIMENTAL**

$^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker MSL 400 spectrometer (400 and 150 MHz) relative to residual proton signals of the deuterated solvent (CDCl$_3$, DMSO-$d_6$). IR spectra were recorded on a Bruker Tensor 27 spectrometer from KBr pellets. Elemental analysis was
2-chloroethanesulfonyl chloride and propan-1-amine (3b). Yield 5.36 g (87%).

Methyl 2-chloroethyl sulfone (3c). A solution of 3.2 mmol of propan-1-amine in 30 mL of chloroform was added to 3.2 mmol of 2-chloroethanesulfonyl chloride. The mixture was stirred for 72 h at room temperature, then the solvent was removed under reduced pressure. The residue was washed with 10 mL of diethyl ether. The resulting white powder was dried under reduced pressure.

2-[(3,3-Diethoxypropyl)amino]-N,N-diethylethane-1-sulfonamide (3a). Yield 5.77 g (93%).

4-[4,4-Diethoxybutyl]amino]-N-hexylethane-1-sulfonamide (3e). Yield 5.28 g (75%).

General procedure for the synthesis of aminoacetals 3a–3e. To a mixture of 3.64 g (20 mmol) of 2-chloroethanesulfonyl chloride and 6 mL of Et3N in 100 mL of methylene chloride was added 20 mmol of an amine under cooling (5–8°C). The reaction mixture was stirred at room temperature for 12 h, then washed with saturated aqueous sodium hydrogen carbonate solution (3×10 mL). The organic layer was separated and concentrated in vacuum. The resulting vinylsulfonamides 2a–2e were subjected without additional purification to theaza-Michael reaction with 20 mmol of aminoacetal (3,3-diethoxypropan-1-amine, 4,4-diethoxybutan-1-amine) in 30 mL of chloroform. The reaction mixture was refluxed for 25 h, after which the solvent was removed under reduced pressure. The reaction products were brown resinous substances.
trifluoroacetate (4d). Yield 0.30 g (29\%), mp 70–72°C. IR spectrum, ν, cm−1: 1503, 1685, 3035, 3275, 3157. 1H NMR spectrum (DMSO-d6), δ, ppm: 0.82–0.92 m (3H, CH3), 1.17–1.35 m (6H, CH2), 1.38–1.54 m (2H, CH2), 2.05–2.22 m (2H, CH2), 2.88–2.99 m (4H, CH2), 3.14–3.26 m (4H, CH2), 4.26–4.31 m (1H, CH), 6.48 s (2HAr), 6.91 s (2HAr). 13C NMR spectrum (DMSO-d6), δC, ppm: 14.33, 22.46, 26.18, 29.94, 30.01, 30.14, 31.26, 34.37, 42.85, 47.54, 48.58, 104.26, 109.68, 117.05 q (1JCF 295.9 Hz) 122.15, 128.88, 154.12, 154.78, 158.84 κ (2JCF 33.3 Hz). Found, %: C 48.39; H 5.60; Cl 10.79; N 4.16; S 5.12. C26H33Cl3F23N2O7S. Calculated, %: C 48.23; H 5.45; Cl 10.95; N 4.33; S 4.95.

3,3-Bis(6-hydroxybenzo[d][1,3]dioxol-5-yl)-N-[2-(pyrrolidin-1-ylsulfonyl)ethyl]propane-1-aminium trifluoroacetate (5b). Yield 0.66 g (68\%), mp 106–107°C. IR spectrum, ν, cm−1: 1504, 1682, 3076, 3136. 1H NMR spectrum (DMSO-d6), δ, ppm: 0.86–0.93 m (3H, CH3), 2.32–2.38 m (2H, CH2), 2.65–2.71 m (2H, CH2), 2.79–2.89 m (2H, CH2), 3.18–3.24 m (6H, CH2), 4.44 t (1H, CH, 3JHH 6.6 Hz), 5.85 d (4H, CH2, 3JHH 6.4 Hz), 6.43 s (2HAr), 6.66 s (2HAr). Found, %: C 49.77; H 4.99; N 4.76; S 5.41. C25H29F3N2O10S. Calculated, %: C 49.50; H 4.82; N 4.62; S 5.29.

N-[2-(N-Hexylsulfamoyl)ethyl]-4,4-bis(6-hydroxybenzo[d][1,3]dioxol-5-yl)butane-1-aminium trifluoroacetate (5e). Yield 0.64 g (59\%), mp 97–99°C. IR spectrum, ν, cm−1: 1503, 1680, 3076, 3132. 1H NMR spectrum (DMSO-d6), δ, ppm: 1.17 t (3H, CH3, 3JHH 6.8 Hz), 1.17–1.32 m (8H, CH2), 1.59–1.68 m (2H, CH2), 2.23–2.41 m (2H, CH2), 2.82–2.97 m (2H, CH2), 3.02–3.12 m (2H, CH2), 3.14–3.22 m (2H, CH2), 3.98–4.12 2H, CH2), 4.23 t (1H, CH, 3JHH 6.7 Hz), 4.34–4.52 m (2H, CH2), 5.84 d (4H, CH2, 3JHH 6.5 Hz), 6.38 s (2HAr), 6.68 c (2HAr). Found, %: C 51.89; H 5.56; N 4.40; S 5.12. C28H37F3N2O10S. Calculated, %: C 51.69; H 5.73; N 4.31; S 4.93.

N-[2-(N,N-Diethylsulfamoyl)ethyl]3,3-bis(2,4-dihydroxy-3-methylphenyl)propane-1-aminium trifluoroacetate (6a). Yield 0.11 g (12\%), mp 114–116°C. IR spectrum, ν, cm−1: 1503, 1682, 3056, 3274, 3148. 1H NMR spectrum (DMSO-d6), δ, ppm: 1.10 t (6H, CH3, 3JHH 7.0 Hz), 1.98 s (3H, CH3), 1.99–2.02 m (2H, CH2), 2.05–2.23 m (2H, CH2), 2.77–2.92 m (2H, CH2), 3.16–3.30 m (2H, CH2), 3.36–3.45 m (4H, CH2), 4.46 t (1H, CH, 3JHH 7.6 Hz), 6.32 d (2HAr, 3JHH 8.4 Hz), 6.73 d (2HAr, 3JHH 8.4 Hz). Found, %: C 51.60; H 5.89; N 4.89; S, 5.67. C25H35F3N2O8S. Calculated, %: C 51.72; H 6.08; N 4.82; S 5.52.

3,3-Bis(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-N-[2-(morpholin-4-ylsulfonyl)ethyl]propane-1-aminium trifluoroacetate (7e). Yield 0.46 g (48\%), mp 167–169°C. IR spectrum, ν, cm−1: 1504, 1676, 3059, 3089. 1H NMR spectrum (DMSO-d6), δ, ppm: 1.59–1.73 m (2H, CH2), 2.10 s (6H, CH3), 2.23–2.36 m (2H, CH2), 2.48–2.70 m (2H, CH2), 2.79–2.87 m (4H, CH2), 2.94–3.03 m (2H, CH2), 3.19–3.26 m (4H, CH2), 4.29 t (1H, CH, 3JHH 8.1 Hz), 5.88 s (2H, CH). Found, %: C 46.33; H 4.98; N 4.79; S 5.18. C22H29F3N2O11S. Calculated, %: C 46.15; H 4.88; N 4.68; S 5.36.

ACKNOWLEDGMENTS

The work was performed using the equipment of the Spectral Analytical Center of the Federal Research Center “Kazan Scientific Center of the Russian Academy of Sciences.”
CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Schäfer, N., Belz, G.G., Stauch, M., and Schneider, B., Deutsch Medizinische Wochenschrift, 2008, vol. 105, p. 1253. https://doi.org/10.1055/s-2008-1070851
2. Albert, K.S., Hallmark, M.R., Sakmar, E., Weidler, D.J., and Wagner, J.G., J. Pharmacokinet. Biopharm., 1975, vol. 3, p. 159. https://doi.org/10.1007/BF01067905
3. Ferrari, A., Coccia, C., Bertolini, A., and Sternieri, E., Pharmacol. Res., 2004, vol. 50, p. 551. https://doi.org/10.1016/j.phrs.2004.05.002
4. Hu, X., Chen, C.Z., Xu, M., Hu, Z., Guo, H., Itkin, Z., Shinn, P., Ivin, P., Leek, M., Liang, T.J., Shen, M., Zheng, W., and Hall, M.D., ACS Med. Chem. Lett., 2021, vol. 12, p. 1267. https://doi.org/10.1021/acsmedchemlett.1c00263
5. Cardinal, S., Paquet-Côté, P.-A., Azelmat, J., Bouchard, C., Grenier, D., and Voyer, N., Bioorg. Med. Chem., 2017, vol. 25, p. 2043. https://doi.org/10.1016/j.bmc.2017.01.050
6. Sumoto, K., Mibu, N., Yokomizo, K., and Uyeda, M., Chem. Pharm. Bull. (Tokyo), 2002, vol. 50, p. 298. https://doi.org/10.1248/cpb.50.298
7. Mibu, N., Yokomizo, K., Miyata, T., and Sumoto, K.J., Heterocycl. Chem., 2010, vol. 47, p. 1434. https://doi.org/10.1002/jhet.457
8. Pericherla, K., Shirazi, A.N., Kameshwara Rao, V., Tiwari, R.K., DaSilva, N., McCaffrey, K.T., Beni, Y.A., González-Sarrias, A., Seeram, N.P., Parang, K., and Kumar, A., Bioorg. Med. Chem. Lett., 2013, vol. 23, p. 5329. https://doi.org/10.1016/j.bmcl.2013.07.058
9. Chauthe, S.K., Bharate, S.B., Sabde, S., Mitra, D., Bhutani, K.K., and Singh, I.P., Bioorg. Med. Chem., 2010, vol. 18, p. 2029. https://doi.org/10.1016/j.bmcl.2010.01.023
10. Chauthe, S.K., Bharate, S.B., Periyasamy, G., Khanna, A., Bhutani, K.K., Mishra, P.D., and Singh, I.P., Bioorg. Med. Chem. Lett., 2012, vol. 22, p. 2251. https://doi.org/10.1016/j.bmcl.2012.01.089
11. Bouthenet, E., Oh, K.-B., Park, S., Nagi, N.K., Lee, H.-S., and Matthews, S.E., Bioorg. Med. Chem. Lett., 2011, vol. 21, p. 7142. https://doi.org/10.1016/j.bmcl.2011.09.072
12. Schuller-Levis, G.B. and Park, E., FEMS Microbiol. Lett., 2003, vol. 226, p. 195. https://doi.org/10.1016/S0378-1097(03)00611-6
13. Brosnan, J.T. and Brosnan, M.E., J. Nutr., 2006, vol. 136, p. 1636S. https://doi.org/10.1093/jn/136.6.1636S
14. Martinez-Valladares, M., Martín-Ramos, E., Esteban-Ballesteros, M., Balañá-Fouce, R., and Rojo-Vázquez, F.A., Parasite, 2021, vol. 28, p. 71. https://doi.org/10.1051/parasite/2021068
15. Gokbulut, C. and McKellar, Q.A., Vet. Parasitol., 2018, vol. 261, p. 27. https://doi.org/10.1016/j.vetpar.2018.08.002
16. Smolobochkin, A.V., Gazizov, A.S., Burilov, A.R., and Pudovik, M.A., J. Chem., 2019, p. 1. https://doi.org/10.1155/2019/34224319
17. Smolobochkin, A.V., Muravyeva, E.A., Vagapova, L.I., Knyazeva, I.R., Voronina, J.K., Burilov, A.R., Pudovik, M.A., Gildebrant, A.V., Sazykin, I.S., Sazykina, M.A., and Gazizov, A.S., Chem. Biodivers., 2019, vol. 16, p. e1800490. https://doi.org/10.1002/cbdv.201800490