ISSN 1070-4280, Russian Journal of Organic Chemistry, 2016, Vol. 52, No. 9, pp. 1304–1307. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © A.V. Smolobochkin, E.A. Anikina, A.S. Gazizov, A.R. Burilov, M.A. Pudovik, 2016, published in Zhurnal Organicheskoi Khimii, 2016, Vol. 52, No. 9, pp. 1316–1319.

Synthesis of 1-(Arenesulfonyl)-2-arylpyrrolidines by Reaction of *N*-(4,4-Diethoxybutyl)-4-methylbenzenesulfonamide with Phenols

A. V. Smolobochkin[a], E. A. Anikina[b], A. S. Gazizov[a],* A. R. Burilov[a], and M. A. Pudovik[a]

[a] *Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, ul. Arbuzova 8, Kazan, 420088 Tatarstan, Russia*
**e-mail: agazizov@iopc.ru*

[b] *Kazan National Research Technological University, ul. Karla Marksa 68, Kazan, 420015 Tatarstan, Russia*

Received June 2, 2016

Abstract—New 1-(arenesulfonyl)-2-arylpyrrolidines were synthesized by reactions of several phenols with *N*-(4,4-diethoxybutyl)-4-methylbenzenesulfonamide in the presence of trifluoroacetic acid.

DOI: 10.1134/S1070428016090086

Over the past decades, 1-(arenesulfonyl)-2-arylpyrrolidines have been the subjects of extensive studies. Such a keen interest in these compounds is determined by broad spectrum of their biological activity [1–6]. The most common procedure for the synthesis of 1-(arenesulfonyl)-2-arylpyrrolidines is based on intramolecular cyclization of aryl-substituted unsaturated compounds containing a sulfonamide group [7–16]. Disadvantages of this approach include the use of expensive catalysts and reagents, harsh reaction conditions, and laborious preparation of starting compounds. Development of a new efficient and accessible method for the synthesis of 1-(arenesulfonyl)-2-arylpyrrolidines is an important problem.

We have previously shown that polyhydric phenols react with (4,4-diethoxybutyl)ureas in chloroform in the presence of trifluoroacetic acid to give 2-arylpyrrolidines with a carboxamide moiety on the nitrogen atom [17–19]. Taking into account similar steric and electronic characteristic of carboxamide and sulfonamide groups, we presumed that analogous reaction of phenols with *N*-(4,4-diethoxybutil)sulfonamides should lead to the formation of 1-(arenesulfonyl)-2-arylpyrrolidines.

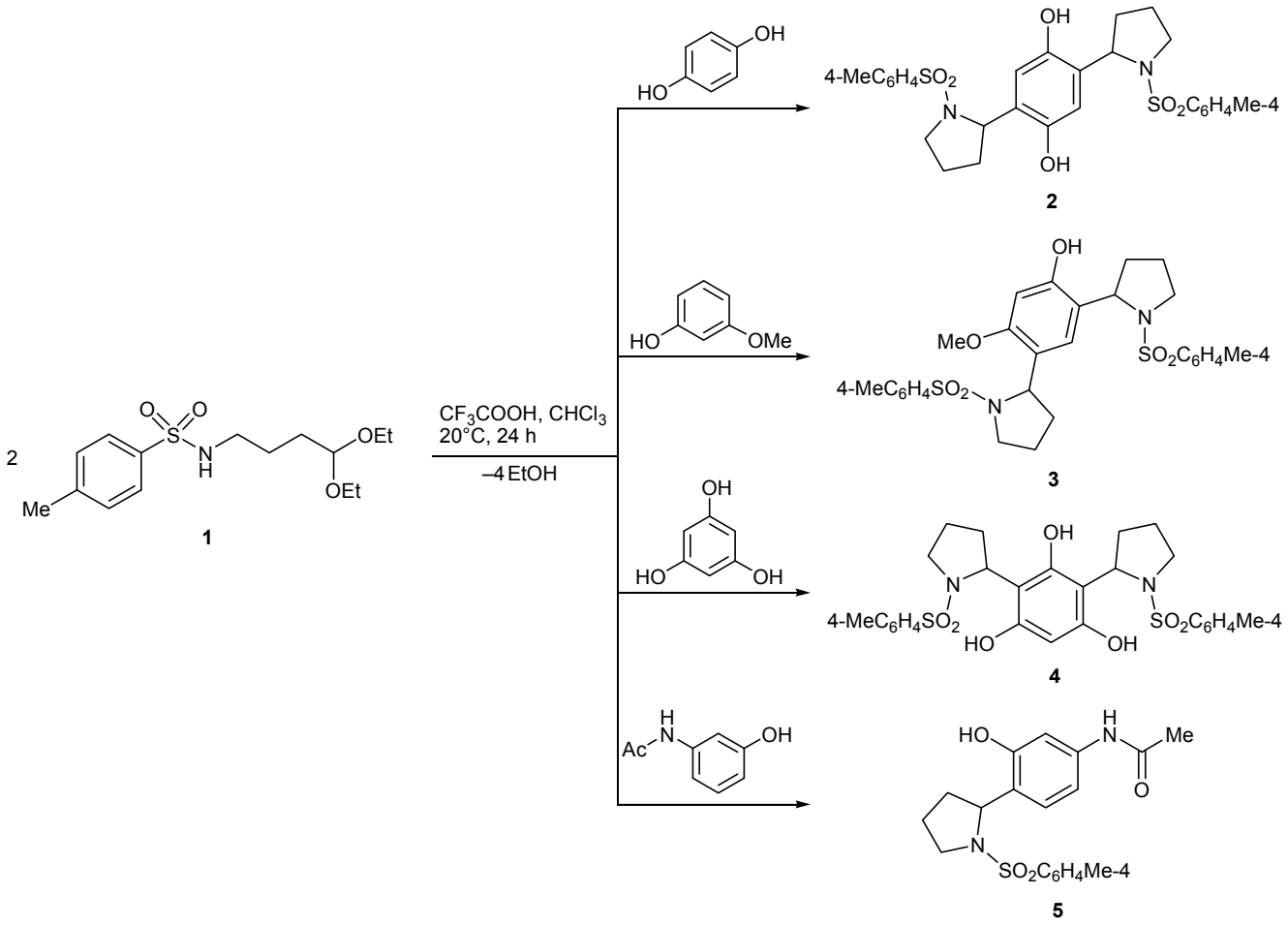
N-(4,4-Diethoxybutyl)-4-methylbenzenesulfonamide (**1**) was synthesized by reaction of 4-methylbenzenesulfonyl chloride with 4-aminobutanal diethyl acetal in the presence of triethylamine. The reaction of hydroquinone with 2 equiv of **1** in chloroform containing trifluoroacetic acid led to the formation of new heterocyclic compound **2** (Scheme 1). According to the ^{1}H NMR data, compound **2** was formed as two diastereoisomers, but we succeeded in isolating only one pure stereoisomer in a poor yield (9%). Presumably, the low yield of the product is related to both low reactivity of hydroquinone and its easy oxidation.

Further experiments showed that acetal **1** reacted with 3-methoxyphenol at a ratio of 2:1 in chloroform in the presence of trifluoroacetic acid to produce 67% of pyrrolidine derivative **3** which was a 1:1.3 mixture of diastereoisomers (according to spectral data).

The reaction of *N*-(4,4-diethoxybutyl)-4-methylbenzenesulfonamide (**1**) with phenols possessing three reactive centers was expected to afford a product containing three 1-(arenesulfonyl)pyrrolidine fragments. However, phloroglucinol reacted with acetal **1** in a way similar to hydroquinone and 3-methoxyphenol with formation of bis-pyrrolidine **4** which was isolated as a mixture of diastereoisomers. Unfortunately, we failed to determine their ratio by ^{1}H NMR due to strong signal overlap.

Unlike the above reactions, only one position of the aromatic ring of *N*-(3-hydroxyphenyl)acetamide was substituted in the reaction with *N*-(4,4-diethoxybutyl)-4-methylbenzenesulfonamide (**1**). Compound **5** was isolated in 61% yield. The reasons for the observed

Scheme 1.



difference in the reactivities of *N*-(3-hydroxyphenyl)-acetamide and other phenols still remain unclear.

Thus, *N*-(4,4-diethoxybutyl)-4-methylbenzenesulfonamide reacts with some phenols, namely hydroquinone, 3-methoxyphenol, phloroglucinol, and *N*-(3-hydroxyphenyl)acetamide, to give 1-arenesulfonyl-2-arylpyrrolidine derivatives.

EXPERIMENTAL

The IR spectra were recorded in the range 400–3600 cm^{-1} on a UR-20 spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were measured on a Bruker MSL 400 instrument at 400 MHz, and the ^{13}C NMR spectra were taken on a Bruker Avance 600 spectrometer at 150 MHz; the chemical shifts were determined relative to the residual proton and carbon signals of the deuterated solvent. The elemental analyses were obtained using a Carlo Erba EA 1108 analyzer. The melting points were measured in glass capillaries on a Stuart SMP 10 melting point apparatus. Solvents were purified according to standard procedures [20].

***N*-(4,4-Diethoxybutyl)-4-methylbenzenesulfonamide (1).** 4,4-Diethoxybutan-1-amine, 3.4 g (20 mmol), was added on cooling (5–8°C) to a mixture of 3.8 g (20 mmol) of 4-methylbenzenesulfonyl chloride and 3.5 mL of triethylamine. The mixture was stirred for 12 h at room temperature and washed with a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic phase was separated, and methylene chloride was removed under reduced pressure. Yield 6.2 g (98%). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.19 t (6H, CH_3, J = 7.1 Hz), 1.54–1.64 m (4H, CH_2), 2.44 s (3H, CH_3), 2.94–3.01 m (2H, CH_2), 3.42–3.51 m (2H, CH_2), 3.58–3.66 m (2H, CH_2), 4.42 t (1H, CH, J = 5.1 Hz), 4.88 br.s (1H, NH), 7.31 d (2H, H_{arom}, J = 8.0 Hz), 7.76 d (2H, H_{arom}, J = 8.2 Hz).

2,5-Bis[1-(4-methylbenzenesulfonyl)pyrrolidin-2-yl]benzene-1,4-diol (2). Trifluoroacetic acid, 0.27 g (0.16 mmol), was added to a mixture of 0.51 g (0.16 mmol) of *N*-(4,4-diethoxybutyl)-4-methylben-

zenesulfonamide, 10 mL of anhydrous chloroform, and 0.09 g (0.80 mmol) of hydroquinone. The mixture was stirred for 24 h at room temperature, and the precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure. Yield 0.08 g (9%), mp <250°C (from EtOH). IR spectrum, ν, cm^{-1}: 3451 (O–H), 1598 (C=C_{arom}), 1154 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.49–1.57 m (2H, CH_2), 1.58–1.72 m (6H, CH_2), 2.42 s (6H, CH_3), 3.47–3.55 m (4H, CH_2), 4.80–4.85 m (2H, CH), 6.79 s (2H, H_{arom}), 7.46 d (4H, H_{arom}, J = 8.1 Hz), 7.70 d (4H, H_{arom}, J = 8.2 Hz), 8.83 s (2H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.48, 23.10, 33.83, 49.76, 58.80, 113.98, 126.25, 130.37, 130.99, 135.53, 141.27, 144.66. Found, %: C 60.71; H 5.65; N 4.93; S 11.66. $C_{28}H_{32}N_2O_6S_2$. Calculated, %: C 60.41; H 5.79; N 5.03; S 11.52.

5-Methoxy-2,4-bis[1-(4-methylbenzenesulfonyl)-pyrrolidin-2-yl]phenol (3). Yield 0.3 g (67%), mp 149–151°C (from EtOH); mixture of diastereoisomers at a ratio of 1:1.3. IR spectrum, ν, cm^{-1}: 3479 (O–H), 3445, 1597 (C=C_{arom}), 1153 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: minor isomer: 1.53–2.11 m (6H, CH_2), 2.37–2.57 m (2H, CH_2), 2.43 s (6H, CH_3), 3.21–3.36 m (1H, CH_2), 3.37–3.45 m (1H, CH_2), 3.46–3.63 m (2H, CH_2), 3.65 s (3H, OCH_3), 4.55–4.66 m (2H, CH), 6.36 s (1H, H_{arom}), 7.07 s (1H, H_{arom}),7.23–7.42 m (4H, H_{arom}), 7.63–7.81 m (4H, H_{arom}); major isomer: 1.53–2.11 m (6H, CH_2), 2.37–2.57 m (2H, CH_2), 2.43 s (6H, CH_3), 3.21–3.36 m (1H, CH_2), 3.37–3.45 m (1H, CH_2), 3.46–3.63 m (2H, CH_2), 3.72 s (3H, OCH_3), 4.91–4.97 m (2H, CH), 6.39 s (1H, H_{arom}), 7.17 s (1H, H_{arom}), 7.23–7.42 m (4H, H_{arom}), 7.63–7.81 m (4H, H_{arom}). Found, %: C 59.89; H 6.17; N 5.13; S 11.19. $C_{29}H_{34}N_2O_6S_2$. Calculated, %: C 61.03; H 6.00; N 4.91; S 11.24.

2,4-Bis[1-(4-methylbenzenesulfonyl)pyrrolidin-2-yl]benzene-1,3,5-triol (4). Yield 0.17 g (48%), mp 196–197°C (from EtOH); mixture of diastereoisomers. IR spectrum, ν, cm^{-1}: 3479 (O–H), 3445, 1597 (C=C_{arom}), 1153 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: isomer **4a**: 11.23–1.35 m (2H, CH_2), 1.76–2.00 m (6H, CH_2), 2.39 s (3H, CH_3), 3.42–3.52 m (2H, CH_2), 3.51–3.62 m (2H, CH_2), 4.88–4.99 m (2H, CH), 7.33–7.42 m (5H, H_{arom}), 7.60–7.77 m (4H, H_{arom}); isomer **4b**: 1.23–1.35 m (2H, CH_2), 1.76–2.00 m (6H, CH_2), 2.40 s (3H, CH_3), 3.42–3.52 m (2H, CH_2), 3.51–3.62 m (2H, CH_2), 4.88–4.99 m (2H, CH), 7.33–7.42 m (5H, H_{arom}), 7.60–7.77 m (4H, H_{arom}). Found, %: C 58.91; H 5.53; N 5.06; S 19.44. $C_{28}H_{32}N_2O_7S_2$. Calculated, %: C 58.72; H 5.63; N 4.89; S 19.56.

***N*-{3-Hydroxy-4-[1-(4-methylbenzenesulfonyl)-pyrrolidin-2-yl]phenyl}acetamide (5).** Yield 0.15 g (61%), mp <250°C (from EtOH). IR spectrum, ν, cm^{-1}: 3413 (O–H), 3396, 1597 (C=C_{arom}), 1151 (SO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.46–1.54 m (1H, CH_2), 1.46–1.54 m (1H, CH_2), 1.55–1.73 m (3H, CH_2), 2.02 s (3H, CH_3), 2.42 s (3H, CH_3), 3.18–3.27 m (1H, CH_2), 3.52–3.59 m (1H, CH_2), 4.80–4.87 m (1H, CH), 6.85 d (1H, H_{arom}, J = 8.1 Hz), 7.12 d (1H, H_{arom}, J = 8.4 Hz), 7.31 s (1H, H_{arom}), 7.46 d (2H, H_{arom}, J = 8.3 Hz), 7.70 d (1H, H_{arom}, J = 8.2 Hz), 9.53 s (1H, NH), 9.77 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.49, 23.80, 24.47, 34.00, 49.66, 58.74, 106.53, 109.97, 125.07, 127.31, 127.71, 130.33, 134.87, 139.28, 143.75, 153.99, 168.53. Found, %: C 61.19; H 5.80; N 7.71; S 8.56. $C_{19}H_{22}N_2O_4S$. Calculated, %: C 60.94; H 5.92; N 7.48; S 8.56.

This study was performed under financial support by the Russian Science Foundation (project no. 16-13-10023).

REFERENCES

1. Noguchi, T., Tanaka, N., Nishimata, T., Goto, R., Hayakawa, M., Sugidachi, A., Ogawa, T., Asai, F., and Fujimoto, K., *Chem. Pharm. Bull*., 2007, vol. 55, p. 1494.
2. Guo, T., Gu, H., Hobbs, D.W., Rokosz, L.L., Stauffer, T.M., Jacob, B., and Clader, J.W., *Bioorg. Med. Chem. Lett*., 2007, vol. 17, p. 3010.
3. Noguchi, T., Tanaka, N., Nishimata, T., Goto, R., Hayakawa, M., Sugidachi, A., Ogawa, T., Asai, F., Matsui, Y., and Fujimoto, K., *Chem. Pharm. Bull*., 2006, vol. 54, p. 163.
4. Vincent, M. and Jürgen, W., US Patent Appl. no. US2003212066, 2013.
5. Vincent, M., Eric, V., and Jürgen, W., US Patent no. 6284785, 2001; *Chem. Abstr*., 2002, vol. 137, no. 201289.
6. Cheng, X.-C., Wang, Q., Fang, H., Tang, W., and Xu, W.-F., *Bioorg. Med. Chem*., 2008, vol. 16, p. 7932.
7. Nambu, H., Anilkumar, G., Matsugi, M., and Kita, Y., *Tetrahedron*, 2003, vol. 59, p. 77.
8. Yin, Y. and Zhao, G., *J. Fluorine Chem*., 2007, vol. 128, p. 40.
9. Schlummer, B. and Hartwig, J.F., *Org. Lett*., 2002, vol. 4, p. 1471.
10. Xu, T., Qiu, S., and Liu, G., *J. Organomet. Chem*., 2011, vol. 696, p. 46.
11. Tamaru, Y., Hojo, M., Kawamura, S., and Yoshida, Z., *J. Org. Chem*., 1986, vol. 51, p. 4089.

12. Leger, P.R., Murphy, R.A., Pushkarskaya, E., and Sarpong, R., *Eur. J. Chem*., 2015, vol. 21, p. 4377.
13. Cui, Z., Yu, H.-J., Yang, R.-F., Gao, W.-Y., Feng, C.-G., and Lin, G.-Q., *J. Am. Chem. Soc*., 2011, vol. 133, p. 12394.
14. Meguro, M. and Yamamoto, Y., *Tetrahedron Lett*., 1998, vol. 39, p. 5421.
15. Scarborough, C.C. and Stahl, S.S., *Org. Lett*., 2006, vol. 8, p. 3251.
16. Yin, Y., Zhou, H., Sun, G., and Liu, X., *J. Heterocycl. Chem*., 2015, vol. 52, p. 1337.
17. Gazizov, A.S., Smolobochkin, A.V., Voronina, J.K., Burilov, A.R., and Pudovik, M.A., *Synth. Commun*., 2015, vol. 45, p. 1215.
18. Gazizov, A.S., Smolobochkin, A.V., Voronina, J.K., Burilov, A.R., and Pudovik, M.A., *Tetrahedron*, 2015, vol. 71, p. 445.
19. Smolobochkin, A.V., Gazizov, A.S., Burilov, A.R., and Pudovik, M.A., *Russ. J. Org. Chem*., 2015, vol. 51, p. 1261.
20. Gordon, A.J. and Ford, R.A., *The Chemist's Companion*, New York: Wiley, 1972.