Russian Journal of Organic Chemistry, Vol. 37, No. 9, 2001, pp. 1330–1334. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 9, 2001, pp. 1395–1399.

Synthesis of Aryloxy-Substituted 1,2,5-Thiadiazoles by the Ullmann Reaction

E. I. Strunskaya, Z. A. Bredikhina, N. M. Azancheev, and A. A. Bredikhin

Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences, ul. Arbuzova 8, Kazan, 420088 Tatarstan, Russia

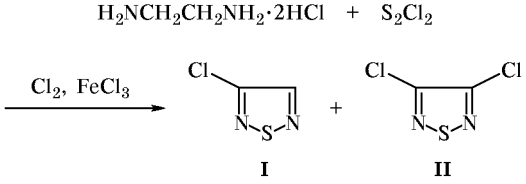
Received July 19, 2000

Abstract—3-Aryloxy-1,2,5-thiadiazoles were synthesized by the Ullmann reaction either from 3-chloro-1,2,5-thiadiazoles and phenols having donor substituents or from 3-hydroxy-1,2,5-thiadiazoles and chlorobenzenes containing acceptor substituents.

Substituted 1,2,5-thiadiazoles are known to exhibit a wide spectrum of biological activity [1]. In addition to pronounced herbicide activity, 1,2,5-thiadiazole derivatives were found to be efficient muscarine receptor agonists [2], as well as inhibitors of HIV-1 replication [3]. For example, 1-(1,1-dimethylethylamino)-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)-2-propanol (Timolol) is one of the most important medicines for treatment of glaucoma [4, 5]. The review articles on the chemistry of 1,2,5-thiadiazole [6] dealt mainly with the methods of building up the 1,2,5-thiadiazole ring, whereas its chemical modifications were covered to a lesser extent. However, this problem often arises while creating screening databases and libraries.

The present communication reports on the synthesis of a series of 3-aryloxy-1,2,5-thiadiazoles most of which contain a morpholino group in the 4-position of the heteroring. The starting compounds were 3-chloro- and 3,4-dichloro-1,2,5-thiadiazoles **I** and **II**. They were obtained by chlorination of a mixture of sulfur(I) chloride and ethylenediamine dihydrochloride with chlorine in the presence of $FeCl_3$ as catalyst [7] (Scheme 1). 3-Chloro-4-morpholino-1,2,5-thiadiazole (**III**) was prepared from dichloro derivative **II** by the procedure described in [5].

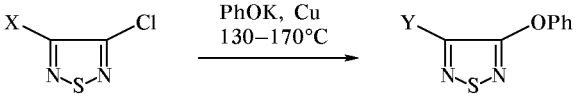
Scheme 1.



I **II**

Our attempts to obtain aryloxy-substituted 1,2,5-thiadiazoles from phenols and 3-chloro-4-morpholino-1,2,5-thiadiazole (**III**) under the conditions reported in [5] for the synthesis of analogous alkyloxy derivatives (*t*-BuOK/*t*-BuOH, 100°C) were unsuccessful. In all cases 3-hydroxy-4-morpholino-1,2,5-thiadiazole (**IV**) was isolated. A general method for preparation of diaryl ethers is based on the Ullmann reaction of phenoxides with aryl halides in the presence of a catalyst [8]. By reaction of chlorothiadiazoles **I** and **II** with potassium phenoxide under severe conditions (130–190°C, 2–10 h, no solvent) we succeeded in obtaining 3-phenoxy- and 3,4-diphenoxy-1,2,5-thiadiazoles **V** and **VI** in satisfactory yields (Scheme 2).

Scheme 2.



I, II **V, VI**

I, X = H; **II**, X = Cl; **V**, Y = H; **VI**, Y = OPh.

With 3-chloro-4-morpholino-1,2,5-thiadiazole (**III**) as an example, we performed the Ullmann reaction with a series of substituted phenols and isolated a set of 3-aryloxy-4-morpholino-1,2,5-thiadiazoles **VII**–**XV** (Scheme 3). The reaction conditions and the yields and properties of compounds **V**–**XV** are collected in Table 1. It should be emphasized that the conditions given therein were not optimized (all products were synthesized under standard conditions). Moreover, the yields refer to the isolated products, i.e., they also reflect the efficiency of purification procedure (e.g.,

1070-4280/01/3709-1330 $25.00 © 2001 MAIK "Nauka / Interperiodica"

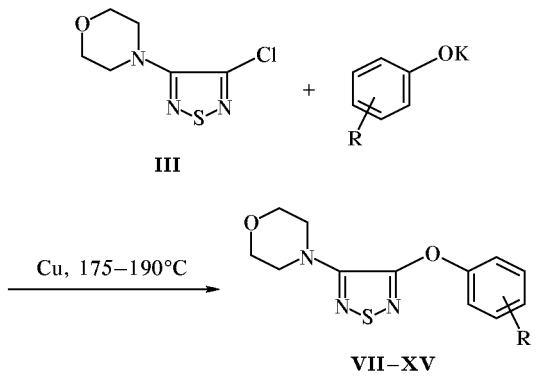
Table 1. Reaction conditions and yields, physical properties, and ^{1}H NMR spectral parameters of thiadiazoles **V**–**XVII**

Comp. no.	Reaction conditions		Yield, %	bp, °C (*p*, mm)	n_D^{20}	mp, °C (solvent)	^{1}H NMR spectrum,[a] δ, ppm (*J*, Hz)
	temp., °C	time, h					
V	130	10	54	128–130 (10)	1.5915	–	7.34 br.s (5H, H_{arom}), 7.95 s (1H, 4-H in Ht)
VI	170	2	55	–	–	106–107 (80% EtOH)	7.18 br.s (10H, H_{arom})
VII	180–190	2	53	132–134 (0.005)	1.5944	–	3.32–3.50 m (4H, CH_2NCH_2), 3.59–3.75 m (4H, CH_2OCH_2), 7.06 br.s (5H, H_{arom})
VIII	180–190	2	56	128–129 (0.005)	1.5870	–	2.16 s (3H, CH_3), 3.40–3.60 m (4H, CH_2NCH_2), 3.69–3.83 m (4H, CH_2O-CH_2), 7.06 br.s (4H, H_{arom})
IX	180–190	2	53	150–152 (0.005)	–	107–108 (80% EtOH)	2.12 s (6H, $2CH_3$), 3.51–3.63 m (4H, CH_2NCH_2), 3.69–3.82 m (4H, CH_2O-CH_2), 6.91 br.s (3H, H_{arom})
X	170–180	2	56	140–142 (0.003)	1.5862		3.29 d (2H, CH_2, allyl, 7.0), 3.45–3.56 m (4H, CH_2NCH_2), 3.63–3.76 m (4H, CH_2OCH_2), 4.75–5.05 m (2H, CH_2, allyl), 5.50–6.30 m (1H, CH, allyl), 7.10 br.s (4H, H_{arom})
XI	170–180	2	53	155–160 (0.008)	1.5920		3.35–3.49 m (4H, CH_2NCH_2), 3.60–3.73 m (4H, CH_2OCH_2), 3.70 s (3H, OCH_3), 6.46–7.16 m (4H, H_{arom})
XII	180–190	2	50			83–84 (90% EtOH)	3.43–3.56 m (4H, CH_2NCH_2), 3.70–3.83 m (4H, CH_2OCH_2), 6.83–7.52 m (4H, H_{arom})
XIII	180–190	2	80			67–68 (80% EtOH)	2.36 s (3H, CH_3), 3.42–3.60 m (4H, CH_2N-CH), 3.67–3.85 m (4H, CH_2OCH_2), 7.01 s (4H, H_{arom})
XIV	170–180	2	63	155–160 (0.015)		52–53 (100% EtOH)	3.40–3.56 m (4H, CH_2NCH_2), 3.66–3.83 m (4H, CH_2OCH_2), 3.83 s (3H, OCH_3), 6.62–7.07 m (4H, H_{arom})
XV	180–190	2	53	140–143 (0.02)		69–70 (100% EtOH)	3.38–3.52 m (4H, CH_2NCH_2), 3.65–3.80 m (4H, CH_2OCH_2), 6.92–7.38 m (4H, H_{arom})
XVI	150	20	52			145–146 (80% EtOH)	3.50–3.65 m (4H, CH_2NCH_2), 3.76–3.92 m (4H, CH_2OCH_2), 7.35–8.38 m (4H, H_{arom})
XVII	150	20	53	145–150 (0.004)		87–88 (80% EtOH)	3.50–3.65 m (4H, CH_2NCH_2), 3.76–3.92 m (4H, CH_2OCH_2), 7.42–8.26 m (3H, H_{arom})

[a] The ^{1}H NMR spectra of compounds **VII**–**XV** were recorded in CCl_4, and of **V**, **VI**, **XVI**, and **XVII**, in $CDCl_3$.

the ease of crystallization). Nevertheless we can speak about a weak effect of the steric factor on the reaction course. *ortho*-Substituted phenols do not fall out of the general series, and even 2,6-dimethylphenol turned out to be an effective reagent. By contrast, electronic effect of the substituent in the benzene ring was essential. Phenols with strongly acceptor substituents, such as NO_2 and CF_3 groups, failed to react with compound **III** despite wide variation of the reaction conditions. Therefore, the corresponding 1,2,5-thiadiazolyl ethers were synthesized by the reverse mode of the Ullmann reaction, i.e., 3-hydroxy-4-morpholino-

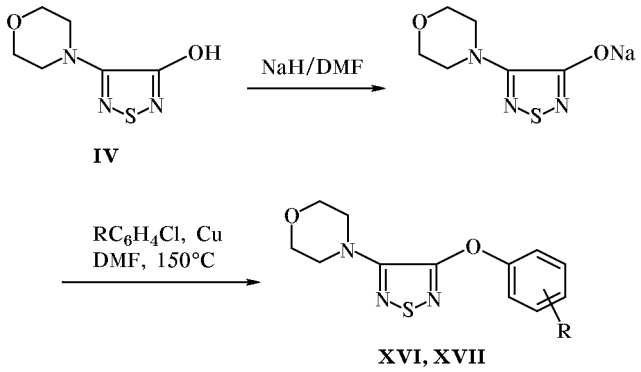
Scheme 3.



VII, R = H; **VIII**, R = 2-Me; **IX**, R = 2,6-Me_2; **X**, R = 2-allyl; **XI**, R = 3-OMe; **XII**, R = 3-Br; **XIII**, R = 4-Me; **XIV**, R = 4-OMe; **XV**, R = 4-Br.

1,2,5-thiadiazole sodium salt (**IV**) was used as nucleophile while the substrate was an appropriately substituted phenyl chloride (Scheme 4).

Scheme 4.



XVI, R = 4-NO_2; **XVII**, R = 4-CF_3-2-NO_2.

Thus the Ullmann reaction provides an efficient procedure for preparation of aryloxy-substituted 1,2,5-thiadiazoles. Here, the heterocyclic component should be used as the corresponding halogen derivative in reactions with phenols or as hydroxy derivative in reactions with aryl halides having electron-acceptor groups.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in mineral oil (or in film for liquid samples). The NMR spectra were obtained on Varian T-60 (^{1}H, 60 MHz) and Bruker MSL-400 spectrometers (^{13}C, 100.6 MHz) using $CDCl_3$ and CCl_4 as solvents and TMS as internal reference.

The IR spectra of compounds **V**–**XVII** contained the following absorption bands, ν, cm^{-1}: 1050–1130 (C–O), 1450–1500 (Ht), 1450–1600 (Ar).

3-Chloro- and 3,4-dichloro-1,2,5-thiadiazoles I and II. Sulfur(I) chloride, 165 ml (1.8 mol), was added to 450 ml of DMF and 1 g of iron powder, and the mixture was saturated with chlorine at 20°C. Ethylenediamine dihydrochloride, 134 g (1 mol), was added to the mixture at 30–40°C, and 830 g (11.7 mol) of chlorine was passed through the mixture at 57–59°C. The mixture was cooled to 20°C and 600 ml of water was added. The products were separated by azeotropic distillation with water at 75–110°C, the distillate was treated with methylene chloride, and the extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was separated by fractional distillation through a column to isolate 5 g of 3-chloro-1,2,5-thiadiazole (**I**), bp 123–124°C, n_D^{20} 1.5379 (published data: bp 124°C [9], n_D^{20} 1.5379 [10]), and 115.7 g (74%) of 3,4-dichloro-1,2,5-thiadiazole (**II**), bp 156–158°C, n_D^{20} 1.5620 (published data [9]: bp 155°C).

4-Morpholino-3-phenoxy-1,2,5-thiadiazole (VII). Potassium phenoxide was prepared from 1.18 g (12.6 mmol) of phenol and 0.65 g (11.6 mmol) of powdered KOH in 25 ml of toluene with removal of water by azeotropic distillation through a Dean–Stark trap. Copper powder, 0.02 g (0.3 mmol), and thiadiazole **III**, 2 g (9.7 mmol), were added to the resulting potassium phenoxide, and the mixture was heated for 2 h at 180–190°C. The mixture was diluted with 20 ml of water and extracted with ether. The extract was washed with 10% solutions of NaOH and $NaHCO_3$ and with water to neutral reaction, dried over Na_2SO_4, and evaporated. The viscous residue was distilled under reduced pressure.

3-Aryloxy-4-morpholino-1,2,5-thiadiazoles V, VI, and VIII–XV were synthesized by a similar procedure. In the synthesis of compound **VII** a double amount of potassium phenoxide was used. The reaction conditions and yields, physical constants, and ^{1}H and ^{13}C NMR spectra of the products are given in Tables 1 and 2.

4-Morpholino-3-(4-nitrophenoxy)-1,2,5-thiadiazole (XVI). A solution of 1.12 g (6 mmol) of thiadiazole **IV** in 4 ml of DMF was added dropwise to a suspension of 0.15 g (6 mmol) of sodium hydride in 2 ml of DMF, stirred in an inert atmosphere. The mixture was heated for 0.5 h at 70–80°C, 0.04 g (0.6 mmol) of copper powder and 0.95 g (6 mmol) of 4-nitrochlorobenzene were added, and the mixture was stirred for 20 h at 150°C. The solvent was distilled off under reduced pressure, 50 ml of water was

Table 2. ^{13}C NMR spectra of thiadiazoles **V**–**XVII**[a]

Comp. no.	H_2CN	H_2CO	C^3, C^4	C(R)	Ar		
					HC	RC	OC
V			164.07, 139.46		119.91, 125.47, 129.77		154.56
VI			151.08		120.10, 125.74, 129.87		154.53
VII	48.61	66.68	152.21, 151.11		120.51, 125.63, 129.96		154.90
VIII	48.46	66.54	152.31, 150.45	16.60	121.10, 125.87, 127.34, 131.55	129.55	153.27
IX	48.61	66.66	152.05, 149.86	16.94	126.17, 129.25	130.30	152.11
X	48.67	66.75	152.53, 150.70	34.99, 116.65, 136.30	121.58, 126.16, 128.02, 131.08	131.61	153.10
XI	48.62	66.62	151.93, 151.14	55.54	106.67, 111.40, 112.49, 130.18		155.84, 161.25
XII	48.69	66.67	151.46, 151.02		119.12, 124.00, 128.86, 130.92	123.17	155.34
XIII	48.62	66.72	152.55, 150.96	21.26	120.38, 130.42	135.03	152.77
XIV	48.62	66.66	152.86, 150.75	55.66	114.92, 121.64		148.43, 157.47
XV	48.67	66.65	151.66, 150.96		122.24, 133.04	118.68	153.84
XVI	48.30	66.50	151.06, 150.32		120.24, 125.74	145.02	158.90
XVII	48.34	66.53	150.34, 150.13	124.08	123.76, 124.80, 131.45	128.97, 141.53	149.56

[a] The ^{13}C NMR spectra of compounds **VII**–**XV** were recorded in CCl_4, and of **V**, **VI**, **XVI**, and **XVII**, in $CDCl_3$.

Table 3. Elemental analyses of thiadiazoles **V**–**XVII**

Comp. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
V	53.64	3.28	15.82	$C_8H_6N_2OS$	53.93	3.37	15.73
VI	62.02	3.54	10.30	$C_{14}H_{10}N_2O_2S$	62.22	3.70	10.37
VII	54.61	4.83	16.01	$C_{12}H_{13}N_3O_2S$	54.75	4.94	15.97
VIII	56.39	5.34	14.99	$C_{13}H_{15}N_3O_2S$	65.31	5.41	15.16
IX	58.16	5.82	14.38	$C_{14}H_{17}N_3O_2S$	57.73	5.84	14.43
X	59.55	5.72	13.90	$C_{15}H_{17}N_3O_2S$	59.40	5.61	13.86
XI	53.18	5.21	14.23	$C_{13}H_{15}N_3O_2S$	53.24	5.12	14.33
XII	42.27	3.41	12.12	$C_{12}H_{12}BrN_3O_2S$	42.11	3.51	12.28
XIII	56.42	5.14	15.50	$C_{13}H_{15}N_3O_2S$	56.31	5.41	16.16
XIV	53.18	5.29	15.08	$C_{13}H_{15}N_3O_3S$	53.24	5.12	14.33
XV	42.18	3.48	12.24	$C_{12}H_{12}BrN_3O_2S$	42.11	3.51	12.28
XVI	76.82	3.62	18.23	$C_{12}H_{12}N_4O_4S$	76.75	3.89	18.18
XVII	41.57	3.08	14.63	$C_{13}H_{11}F_3N_4O_4S$	41.49	2.92	14.89

added to the residue, and the mixture was treated with methylene chloride. The combined organic extracts were washed with 10% solutions of NaOH and $NaHCO_3$ and with water to neutral reaction, dried over Na_2SO_4, and evaporated. The residue was purified by recrystallization from EtOH–H_2O (4:1).

4-Morpholino-3-(2-nitro-4-trifluoromethylphenoxy)-1,2,5-thiadiazole (XVII) was synthesized by a similar procedure. The reaction conditions and the properties of compound **XVII** are given in Tables 1 and 2. Table 3 contains the analytical data for the newly synthesized compounds.

REFERENCES

1. Yoon, S., Cho, J., and Kim, K., *J. Chem. Soc., Perkin Trans. 1*, 1998, no. 1, pp. 109–116.
2. Mitch, S.H., Brown, T.J., Bumaster, F.P., Calligaro, D.O., Dieckman, D., Merrit, L., Peters, S.C., Quimby, S.J., Shannon, H.E., Shipley, L.A., Ward, J.S., Hansen, K., Olesen, P.H., Sauerberg, P., Seardown, M.J., Swedberg, M.J.V., Suzdak, P., and Greenwood, B., *J. Med. Chem.*, 1997, vol. 40, no. 4, pp. 538–546; Periyasamy, S., Messer, W.S., Roknich, S., Sauerberg, P., and Hoss, W., *Brain Res.*, 1995, vol. 693, nos. 1–2, pp. 118–123; *Chem. Abstr.*, 1995, vol. 123, no. 275207b.
3. Hanasaki, Y., Watanabe, H., Katsuura, K., Takayama, H., Shirakawa, S., Yamaguchi, K., Sakai, S., Ijichi, K., Fujiwara, M., Konno, K., Yokota, T., Shigeta, S., and Baba, M., *J. Med. Chem.*, 1995, vol. 38, no. 12, pp. 2038–2040.
4. Sorensen, S.J. and Abel, S.R., *Ann. Pharmacother.*, 1996, vol. 30, pp. 43–54; *Chem. Abstr.*, 1996, vol. 124, no. 219106b.
5. Weinstock, L.M., Mulvey, D.M., and Tull, R., *J. Org. Chem.*, 1976, vol. 41, no. 19, pp. 3121–3123.
6. Weinstock, L.M. and Pollak, P.I., *Adv. Heterocycl. Chem.*, 1968, vol. 9, pp. 107–163; Weinstock, L.M. and Shinkai, I., *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R. and Rees, C.W., Eds., Oxford: Pergamon, 1996, vol. 6, pp. 513–528; Carmack, M., *Sulfur Rep.*, 1995, vol. 16, no. 2, pp. 299–342.
7. GDR Patent no. 271425, 1989; *Chem. Abstr.*, 1990, vol. 112, no. 158259g.
8. Weingarten, H., *J. Org. Chem.*, 1964, vol. 29, no. 4, pp. 977–978.
9. Weinstock, L.M., Davis, P., Handelsman, V., and Tull, R., *J. Org. Chem.*, 1967, vol. 32, no. 9, pp. 2823–2829.
10. Appel, R., Lundehn, J.-R., and Labnann, E., *Chem. Ber.*, 1976, vol. 107, no. 7, pp. 2442–2455.