Russian Journal of General Chemistry, Vol. 75, No. 4, 2005, pp. 590–592. Translated from Zhurnal Obshchei Khimii, Vol. 75, No. 4, 2005, pp. 629–631.

Reaction with Azomethines or Azines of Reformatsky Reagents Prepared from Methyl 1-Bromocycloalkanoates and Zinc

N. F. Kirillov and V. V. Shchepin

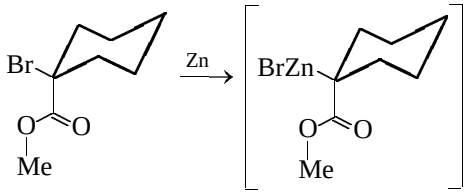
Perm State University, Perm, Russia

Received November 18, 2004

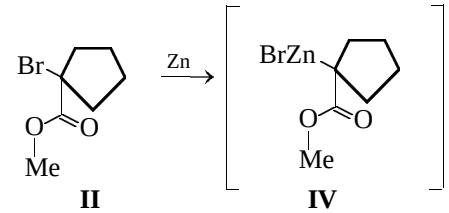
Abstract—Reformatsky reagents prepared from methyl 1-bromocycloalkanoates and zinc react with azomethines or azines to give 2,3-diaryl-2-azaspiro[3.5]nonan-1-ones, 2,3-diaryl-2-azaspiro[3.4]octan-1-ones or 2,2'-bis(3-aryl-1-oxo-2-azaspiro[3.5]nonanes), respectively.

The reaction of classical Reformatsky reagents with imines, resulting in formation of β-lactams, viz. azetidin-2-ones, has been reported [1, 2]. It is known that compounds containing a β-lactam fragment exhibit diverse biological activity [3, 4]. Therefore, in the present work we set ourselves the aim to develop a new method for preparing β-lactams with a spiro carbon atom.

To this end, we have studied the reaction with azomethines derived from aromatic aldehydes of Reformatsky reagents **III** and **IV** prepared from methyl 1-bromocyclohexanecarboxylic (**I**) and 1-bromocyclopentanecarboxylic (**II**) acids and zinc. It was found that the above nucleophilic agents are successfully added to the azomethine C=N bond in a benzene–ethyl acetate–HMPA mixture (10 : 5 : 1).

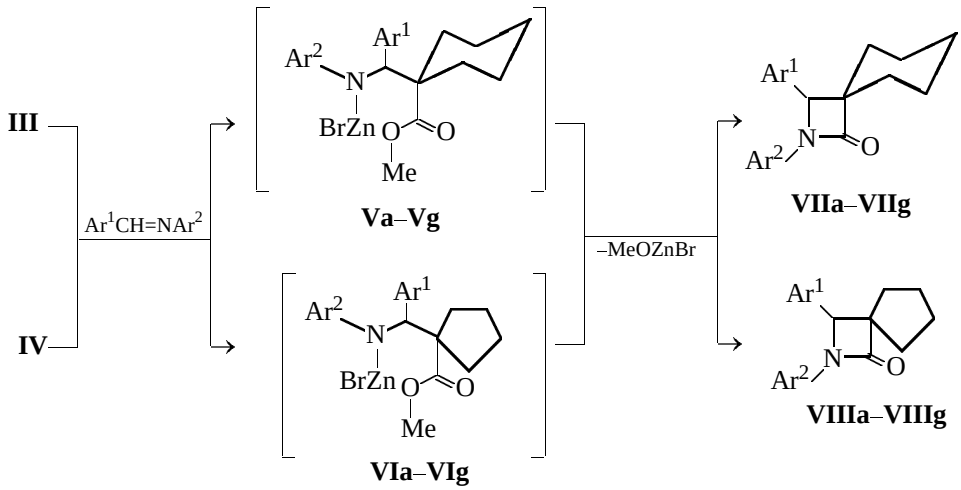


I **III**



II **IV**

Intermediates **V** and **VI** under these conditions spontaneously polymerize to give 2,3-diaryl-2-aza-



Va–**Vg**

VIa–**VIg**

VIIa–**VIIg**

VIIIa–**VIIIg**

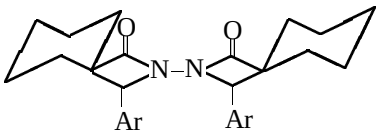
V–**VIII**, Ar^1 = 4-BrC_6H_4, Ar^2 = Ph (**a**), 4-BrC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 1-naphthyl (**d**); Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-$MeOC_6H_4$ (**e**), Ar^2 = 4-BrC_6H_4 (**f**); Ar^1 = 1-thienyl, Ar^2 = 4-BrC_6H_4 (**g**).

1070-3632/05/7504-0590

spiro[3.5]nonan-1-ones (**VIIa**–**VIIg**) or 2,3-diaryl-2-azaspiro[3.4]octan-1-ones (**VIIIa**–**VIIIg**) in high yields (see table).

The composition and structure of compounds **VIIa**–**VIIg** and **VIIIa**–**VIIIg** were comfirmed by their elemental analyses and ^{1}H NMR and IR spectra. The IR spectra contain a characteristic absorption band of the amide carbonyl group at 1730–1765 cm^{-1}. The ^{1}H NMR spectra display a characteristic methine proton signal at 4.47–5.58 ppm.

Then we have studied the reaction of reagent **III** with azines. It was found that the reaction occurs in a benzene : ether : HMPA mixture (10 : 5 : 1) by the same scheme and provides, of a number of possible reaction products, 2,2'-bis(3-aryl-1-oxo-2-azaspiro[3.5]nonanes) **IXa**, **IXb** (see Experimental).



IXa, IXb

IX, Ar = Ph (**a**), 4-BrC_6H_4 (**b**).

The IR spectra of compounds **IXa**, **IXb** contain two characteristic bands due to stretching vibrations of amide carbonyls at 1750 and 1775–1790 cm^{-1}. The ^{1}H NMR spectra show methine proton signals at 4.68–4.72 ppm.

Yields, constants, IR and ^{1}H NMR spectra, and elemental analyses of 2,3-diaryl-2-azaspiro[3.5]nonan-1-ones **VIIa**–**VIIg** and 2,3-diaryl-2-azaspiro[3.4]octan-1-ones **VIIIa**–**VIIIg**

Comp. no.	Yield, %	mp, °C	IR spectrum, $\nu(CO_{lact})$, cm^{-1}	^{1}H NMR spectrum, δ, ppm
VIIa	82	142–143	1730	1.05–2.05 m [10H, $(CH_2)_5$], 4.86 s (1H, CHN), 6.98–7.26 m, 7.48 d (9H, 4BrC_6H_4, Ph, *J* ~8 Hz)
VIIb	78	148–149	1755	1.05–2.06 m [10H, $(CH_2)_5$], 4.89 s (1H, CHN), 7.13 d, 7.20 d, 7.36 d, 7.48 d (8H, 4-BrC_6H_4, 4-BrC_6H_4, *J* ~8 Hz)
VIIc	95	132–134	1730	1.05–2.05 m [10H, $(CH_2)_5$], 4.81 s (1H, CHN), 3.72 s, 6.77 d, 7.12 d, 7.20 d, 7.47 d (11H, 4-BrC_6H_4, 4-MeOC_6H_4, *J* ~8 Hz)
VIId	76	193–195	1740	1.11–2.17 m [10H, $(CH_2)_5$], 5.33 s (1H, CHN), 7.23 d, 7.29 d, 7.37 t, 7.38 d, 7.53 t, 7.57 t, 7.69 d, 7.86 d, 8.27 d (11H, 4-BrC_6H_4, 1-naphthyl, *J* ~8 Hz)
VIIe	82	121–122	1730	1.02–2.00 m [10H, $(CH_2)_5$], 4.74 s (1H, CHN), 3.72 s, 3.78 s, 6.75 d, 6.85 d, 7.12 d, 7.16 d (14H, 4-MeOC_6H_4, 4-MeOC_6H_4, *J* ~8 Hz)
VIIf	52	102–103	1765	1.03–2.03 m [10H, $(CH_2)_5$], 4.80 s (1H, CHN), 3.78 s, 6.86 d, 7.14 d, 7.16 d, 7.34 d (11H, 4-MeOC_6H_4, 4-BrC_6H_4, *J* ~8 Hz)
VIIg	43	90–91	1750	1.18–2.04 m [10H, $(CH_2)_5$], 5.15 s (1H, CHN), 7.02 m, 7.36 d (3H, 2-thienyl, *J* ~4.5 Hz), 7.18 d, 7.3 d (4H, 4-BrC_6H_4, *J* ~8 Hz)
VIIIa	68	129–130	1740	1.10–1.85 m [8H, $(CH_2)_4$], 5.02 s (1H, CHN), 7.01 t, 7.15–7.25 m, 7.49 d (9H, 4-BrC_6H_4, Ph, *J* ~8 Hz)
VIIIb	52	131–132	1750	1.11–2.20 m [8H, $(CH_2)_4$], 5.04 s (1H, CHN), 7.14 d, 7.17 d, 7.36 d, 7.50 d (8H, 4-BrC_6H_4, 4-BrC_6H_4, *J* ~8 Hz)
VIIIc	82	118–119	1730	1.10–2.15 m [8H, $(CH_2)_4$], 4.97 s (1H, CHN), 3.71 s, 6.77 d, 7.13 d, 7.16 d, 7.48 d (8H, 4-BrC_6H_4, 4-MeOC_6H_4, *J* ~8 Hz)
VIIId	81	180–181	1750	1.31–2.32 m [8H, $(CH_2)_4$], 5.48 s (1H, CHN), 7.20 d, 7.29 d, 7.38 t, 7.40 d, 7.52 t, 7.57 t, 7.69 d, 7.89 d, 8.27 d (11H, 4-BrC_6H_4, 1-naphthyl, *J* ~8 Hz)
VIIIe	84	160–161	1725	1.15–2.15 m [8H, $(CH_2)_4$], 4.87 s (1H, CHN), 3.72 s, 3.78 s, 6.75 d, 6.86 d, 7.11 d, 7.14 d (14H, 4-MeOC_6H_4, 4-MeOC_6H_4, *J* ~8 Hz)
VIIIf	80	146–147	1740	1.17–2.15 m [8H, $(CH_2)_4$], 4.94 s (1H, CHN), 3.79 s, 6.87 d, 7.12 d, 7.14 d, 7.34 d (11H, 4-MeOC_6H_4, 4-BrC_6H_4, *J* ~8 Hz)
VIIIg	44	109–110	1750	1.35–2.13 m [8H, $(CH_2)_4$], 5.29 s (1H, CHN), 7.01 m, 7.36 d (3H, 2-thienyl, *J* 4.5 Hz), 7.20 d, 7.36 d (4H, 4-BrC_6H_4, *J* ~8 Hz)

Table (Contd.)

Compound no.	Found, %				Formula	Calculated, %			
	C	H	Br	N		C	H	Br	N
VIIa	64.65	5.34	21.41	3.83	$C_{20}H_{20}BrNO$	64.87	5.44	21.58	3.78
VIIb	53.61	4.18	35.41	3.00	$C_{20}H_{19}Br_2NO$	53.48	4.26	35.58	3.12
VIIc	62.86	5.48	20.19	3.57	$C_{21}H_{22}BrNO_2$	63.01	5.54	19.96	3.50
VIId	68.39	5.34	19.28	3.48	$C_{24}H_{22}BrNO$	65.58	5.28	19.01	3.33
VIIe	75.06	7.03	–	4.08	$C_{22}H_{25}NO_3$	75.19	7.17	–	3.99
VIIf	63.26	5.68	19.76	3.34	$C_{21}H_{22}BrNO_2$	63.01	5.54	19.96	3.50
VIIg	57.61	4.75	21.37	3.84	$C_{18}H_{18}BrNOS$	57.45	4.82	21.23	3.72
VIIIa	63.97	5.18	22.21	3.80	$C_{19}H_{18}BrNO$	64.06	5.09	22.43	3.93
VIIIb	52.65	3.78	36.61	3.34	$C_{19}H_{17}Br_2NO$	52.44	3.94	36.74	3.22
VIIIc	61.96	5.25	20.84	3.78	$C_{20}H_{20}BrNO_2$	62.19	5.21	20.68	3.63
VIIId	68.17	5.03	19.48	3.51	$C_{23}H_{20}BrNO$	67.99	4.96	19.67	3.45
VIIIe	74.61	6.98	–	4.31	$C_{21}H_{23}NO_3$	74.75	6.87	–	4.15
VIIIf	62.02	5.34	20.91	3.51	$C_{20}H_{20}BrNO_2$	62.19	5.21	20.68	3.63
VIIIg	56.25	4.30	21.97	3.98	$C_{17}H_{16}BrNOS$	56.36	4.45	22.05	3.87

EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrophotometer in mineral oil. The ^{1}H NMR spectra of solutions of compounds in DMSO-d_6–CCl_4 (1 : 3) were recorded on a Bruker DRX-500 spectrometer (500 MHz) against internal TMS.

2,3-Diaryl-2-azaspiro[3.5]nonan-1-ones VIIa–VIIg or 2,3-diaryl-2-azaspiro[3.4]octan-1-ones VIIIa–VIIIg. A mixture of 2 g of activated and grinded zinc, 0.02 mol of compound **I** or **II**, 0.01 mol of azomethine, 10 ml of benzene, 5 ml of ethyl acetate, and 1 ml of HMPA were heated with stirring for 2 h, cooled, and hydrolyzed with 5% acetic acid. The reaction products were extracted with benzene, the extracts were dried with anhydrous Na_2SO_4, the solvents were distilled off, and the residues were recrystallized from methanol.

2,2'-Bis(3-aryl-1-oxo-2-azaspiro[3.5]nonanes) IXa, IXb were prepared from 3 g of activated and grinded zinc, 0.03 mol of compound **I**, 0.01 mol of azine, 20 ml of benzene, 10 ml of ether, and 2 ml of HMPA by the above-described procedure.

2,2'-Bis(3-phenyl-1-oxo-2-azaspiro[3.5]nonane) (IXa). Yield 52%, mp 155- 156°C. ^{1}H NMR spectrum, δ, ppm: 0.82–1.83 m [20H, $(CH_2)_5$], 4.86 s (2H, CHN), 7.30–7.38 m (10H, Ph). IR spectrum, ν, cm^{-1}: 1750, 1772 (C=O). Found, %: C 78,69; H 7.40; N 6.68. $C_{28}H_{32}N_2O_2$. Calculated, %: C 78.47; H 7.53; N 6.54.

2,2'-Bis[3-(4-bromophenyl)-1-oxo-2-azaspiro-[3.5]nonane] (IXb). Yield 45%, mp 220–222°C. ^{1}H NMR spectrum, δ, ppm: 0.84–1.85 m [20H, $(CH_2)_5$, 4.72 s (2H, CHN), 7.32 d 7.59 d (8H, 4-BrC_6H_4). IR spectrum, ν, cm^{-1}: 1750, 1790 (C=O). Found, %: C 57.49; H 5.02; N 4.89. $C_{28}H_{30}Br_2N_2O_2$. Calculated, %: C 57.35; H 5.16; N 4.78.

ACKNOWLEDGMENTS

The study was financially supported by the Russian Foundation for Basic Research (project no. 04-03-96036).

REFERENCES

1. Furstner, A., *Synthesis*, 1989, no. 8, p. 571.
2. Kuznetsov, V.V. and Prostakov, N.S., *Khim. Geterotsikl. Soedin.*, 1990, no. 1, p. 5.
3. Ordizola, J.M., Cossio, F.P., and Polomo, C.S., *Chem. Commun.*, 1988, no. 12, p. 86.
4. Romanova, N.N., *Khim.-Farm. Zh.*, 1990, vol. 24, no. 1, p. 19.
5. Komatsu, M., Yamamoto, S., Okahiro, Y., and Agawa, T., *Heterocycles*, 1985, vol. 23, no. 3, p. 677.