ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 10, pp. 1486–1489. © Pleiades Publishing, Inc., 2006.
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Reformatsky Reaction of Methyl 1-Bromocycloalkane-1-carboxylates with Phenyl- and Benzoylhydrazones Derived from Aromatic Aldehydes

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Received September 21, 2005

Abstract—Reformatsky reagents obtained from methyl 1-bromocyclohexane- and 1-bromocyclopentane-1-carboxylates reacted with aromatic aldehyde phenyl- and benzoylhydrazones to give 3-aryl-2-phenylamino-2-azaspiro[3.5]nonan-, 3-aryl-2-phenylamino-2-azaspiro[3.4]octan-, 3-aryl-2-benzoylamino-2-azaspiro[3.5]-nonan-, and 3-aryl-2-benzoylamino-2-azaspiro[3.4]octan-1-ones, respectively. The reaction of furan-2-carbaldehyde phenylhydrazone with methyl 1-bromocyclohexane-1-carboxylate and zinc led to the formation of 4-(2-furyl)-2-phenyl-2,3-diazaspiro[4.5]decan-1-one.

DOI: 10.1134/S1070428006100150

We previously found that Reformatsky compounds derived from methyl 1-bromocycloalkane-1-carboxylates add at the C=N bond of Schiff bases and that the subsequent cyclization leads to the corresponding spiro-fused β-lactams [1]. While continuing these studies, we examined reactions of Reformatsky reagents **III** and **IV** derived from methyl 1-bromocyclohexane-1-carboxylate (**I**) and 1-bromocyclopentane-1-carboxylate (**II**), respectively, with aromatic aldehyde phenyl- and benzoylhydrazones. Nucleophiles **III** and **IV** were found to successfully add across the C=N bond of the hydrazones in benzene–ethyl acetate–HMPA (5:5:1). The reactions involved 2 equiv of compound **III** or **IV**, and intermediate **Va**–**Vc** or **VI** thus formed could undergo intramolecular nucleophilic attack by both nitrogen atoms on the ester carbonyl carbon atom. The main path of stabilization of compounds **Va**–**Vc** and **VI** was cyclization to spiro-fused β-lactams **VIIa**–**VIIc** and **VIII**, whose hydrolysis led to the formation of 3-aryl-2-phenylamino-2-azaspiro[3.5]nonan-1-ones **IXa**–**IXc** and 3-(4-bromophenyl)-2-phenylamino-2-azaspiro[3.4]octan-1-one (**X**), respectively (Scheme 1).

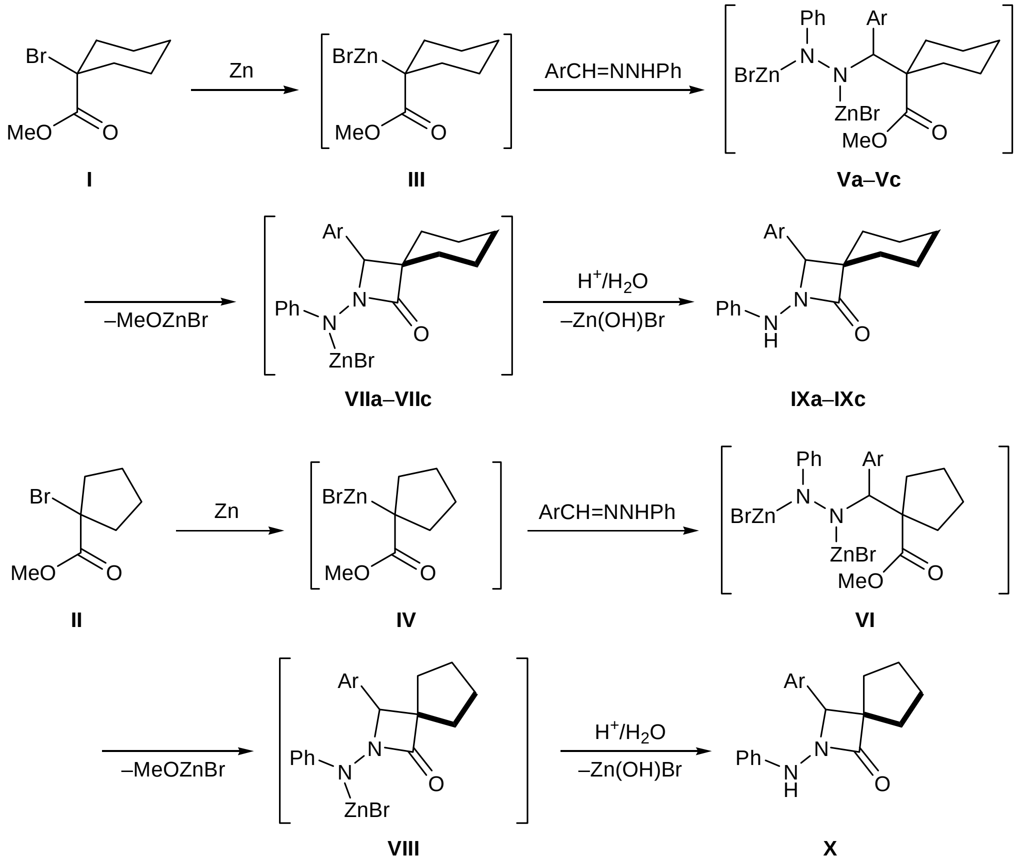
The structure of compounds **IXa**–**IXc** and **X** was proved by their analytical data and IR and ^{1}H NMR spectra. The IR spectra of **IXa**–**IXc** and **X** contained absorption bands belonging to stretching vibrations of the lactam carbonyl group (1750–1755 cm^{-1}) and N–H bond (3280–3285 cm^{-1}). In the ^{1}H NMR spectra of these compounds we observed singlets from ArC**H** protons at δ 4.05–4.10 (**IXa**–**IXc**) and 4.25 ppm (**X**), and signals from the NH proton were located at δ 8.20–8.32 ppm.

Reformatsky reagents **III** and **IV** reacted in a similar way with benzoylhydrazones; in this case, the products were 3-aryl-2-benzoylamino-2-azaspiro[3.5]-nonan-1-ones **XIa**–**XIc** and 3-aryl-2-benzoylamino-2-azaspiro[3.4]octan-1-ones **XIIa** and **XIIb**, respectively (Scheme 2). Compounds **XIa**–**XIc**, **XIIa**, and **XIIb** showed in the IR spectra two carbonyl absorption bands at 1670–1675 (amide) and 1785–1795 cm^{-1} (lactam); stretching vibrations of the N–H bond gave rise to absorption in the region 3230–3280 cm^{-1}. Their ^{1}H NMR spectra contained signals from the ArC**H** protons as singlets at δ 4.96–5.13 ppm and NH proton signals at δ 10.85–10.95 ppm.

By treatment of Reformatsky reagent **III** with furan-2-carbaldehyde phenylhydrazone we obtained compound **XV** (Scheme 3). The carbonyl absorption band in the IR spectrum of **III** was located at 1660 cm^{-1}, and NH stretching vibrations appeared at 3225 cm^{-1}. The doublet at δ 4.48 ppm in the ^{1}H NMR spectrum of **XV** was assigned to the CH proton in the pyrazole ring, and the doublet at δ 6.48 ppm, to the vicinal NH proton.

Presumably, the different direction of the intramolecular cyclization of intermediate **XIII** is governed by intramolecular coordination between the furan oxy-

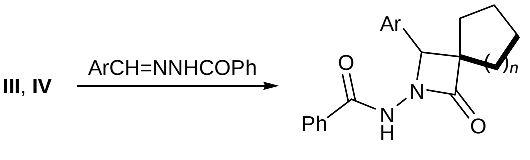
Scheme 1.



V, **VII**, **IX**, Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**); **VI**, **VIII**, **X**, Ar = 4-BrC_6H_4.

gen atom and zinc. As a result, nucleophilic attack on the ester carbonyl carbon atom occurs with participation of the N–Ph nitrogen atom. Hydrolysis of intermediate cyclization product **XIV** yields 4-(2-furyl)-2-phenyl-2,3-diazaspiro[4.5]decan-1-one (**XV**).

Scheme 2.



XIa–**XIc**, **XIIa**, **XIIb**

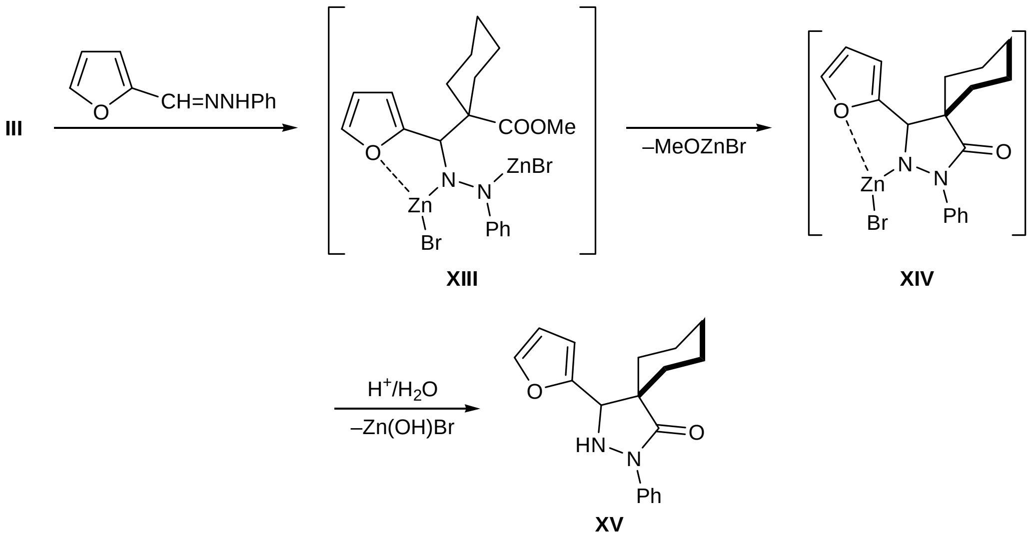
Ar = 4-BrC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 2-$MeOC_6H_4$ (**c**);
XI, $n = 2$; **XII**, $n = 1$.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrophotometer from samples dispersed in mineral oil. The ^1H NMR spectra were measured from solutions in DMSO-d_6–CCl_4 (1:3) on a Bruker DRX-500 instrument (500 MHz) relative to tetramethylsilane as internal reference.

3-Aryl-2-phenylamino-2-azaspiro[3.5]nonan-1-ones IXa–IXc and 3-(4-bromophenyl)-2-phenylamino-2-azaspiro[3.4]octan-1-one (X) (*general procedure*). A solution of 0.02 mol of methyl 1-bromocyclohexane-1-carboxylate (**I**) or methyl 1-bromocyclopentane-1-carboxylate in 10 ml of anhydrous benzene was added dropwise under stirring to a mixture of 2 g of metallic zinc (prepared as fine turnings), a catalytic amount of mercury(II) chloride, 10 ml of anhydrous diethyl ether, 10 ml of anhydrous benzene, 2 ml of HMPA, and 0.01 mol of the corresponding substituted benzaldehyde phenylhydrazone. The mixture was heated for 2 h under reflux, cooled, separated from zinc by decanting, and treated with 5% aqueous acetic acid. The organic phase was separated, and the aqueous phase was extracted with two portions of diethyl ether. The extracts were combined with the organic phase and dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was recrystallized from ethyl acetate.

Scheme 3.



3-Phenyl-2-phenylamino-2-azaspiro[3.5]nonan-1-one (IXa). Yield 1.13 g (37%), mp 163–164°C. IR spectrum, ν, cm^{-1}: 1750 (C=O), 3285 (N–H). ^{1}H NMR spectrum, δ, ppm: 0.70–1.96 m [10H, (CH$_2$)$_5$]; 4.05 s (1H, CHN); 6.74 t, 6.82 d, 7.16 t, 7.30 t, 7.32 d, and 7.38 t (10H, H$_{arom}$, $J \approx 8$ Hz); 8.20 s (1H, NH). Found, %: C 78.52; H 7.11; N 9.02. $C_{20}H_{22}N_2O$. Calculated, %: C 78.40; H 7.24; N 9.14.

3-(4-Bromophenyl)-2-phenylamino-2-azaspiro-[3.5]nonan-1-one (IXb). Yield 1.66 g (43%), mp 215–216°C. IR spectrum, ν, cm^{-1}: 1755 (C=O), 3280 (N–H). ^{1}H NMR spectrum, δ, ppm: 0.70–1.95 m [10H, (CH$_2$)$_5$]; 4.08 s (1H, CHN); 6.73 t, 6.81 d, 7.15 t, 7.26 d, and 7.53 d (9H, H$_{arom}$, $J \approx 8$ Hz); 8.22 s (1H, NH). Found, %: C 62.48; H 5.61; N 7.13. $C_{20}H_{21}BrN_2O$. Calculated, %: C 62.34; H 5.49; N 7.27.

3-(4-Methoxyphenyl)-2-phenylamino-2-azaspiro-[3.5]nonan-1-one (IXc). Yield 1.18 g (35%), mp 181–182°C. IR spectrum, ν, cm^{-1}: 1745 (C=O), 3295 (N–H). ^{1}H NMR spectrum, δ, ppm: 0.65–1.90 m [10H, (CH$_2$)$_5$]; 3.77 s (3H, MeO); 4.10 s (1H, CHN); 6.76 t, 6.84 d, 6.97 d, 7.19 t, and 7.24 d (9H, H$_{arom}$, $J \approx 8$ Hz); 8.32 s (1H, NH). Found, %: C 74.69; H 7.03; N 8.51. $C_{21}H_{24}N_2O_2$. Calculated, %: C 74.97; H 7.19; N 8.33.

3-(4-Bromophenyl)-2-phenylamino-2-azaspiro-[3.4]octan-1-one (X). Yield 1.71 g (46%), mp 180–182°C. IR spectrum, ν, cm^{-1}: 1750 (C=O), 3230 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.20–2.15 m [8H, (CH$_2$)$_4$]; 4.25 s (1H, CHN); 6.75 t, 6.79 d, 7.15 t, 7.20 d, and 7.54 d (9H, H$_{arom}$, $J \approx 8$ Hz); 8.24 s (1H, NH). Found, %: C 61.63; H 5.02; N 7.42. $C_{19}H_{19}BrN_2O$. Calculated, %: C 61.46; H 5.16; N 7.54.

3-Aryl-2-benzoylamino-2-azaspiro[3.5]nonan-1-ones XIa–XIc and 3-aryl-2-benzoylamino-2-aza-spiro[3.4]octan-1-ones XIIa and XIIb were synthesized following an analogous procedure with the use of the corresponding benzoylhydrazone.

2-Benzoylamino-3-(4-bromophenyl)-2-azaspiro-[3.5]nonan-1-one (XIa). Yield 2.48 g (60%), mp 258–259°C. IR spectrum, ν, cm^{-1}: 1670, 1795 (C=O); 3250 (N–H). ^{1}H NMR spectrum, δ, ppm: 0.97–2.03 m [10H, (CH$_2$)$_5$]; 4.96 s (1H, CHN); 7.46 d, 7.50 t, 7.59 t, 7.60 d, and 7.83 d (9H, H$_{arom}$, $J \approx 8$ Hz); 10.85 s (1H, NH). Found, %: C 61.31; H 4.98; N 6.55. $C_{21}H_{21}BrN_2O_2$. Calculated, %: C 61.03; H 5.12; N 6.78.

2-Benzoylamino-3-(4-chlorophenyl)-2-azaspiro-[3.5]nonan-1-one (XIb). Yield 1.92 g (52%), mp 254–256°C. IR spectrum, ν, cm^{-1}: 1675, 1795 (C=O); 3230 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.00–2.05 m [10H, (CH$_2$)$_5$], 5.02 s (1H, CHN), 7.45–7.66 m and 7.86 d (9H, H$_{arom}$, $J \approx 8$ Hz), 10.95 s (1H, NH). Found, %: C 68.49; H 5.78; N 7.45. $C_{21}H_{21}ClN_2O_2$. Calculated, %: C 68.38; H 5.74; N 7.59.

2-Benzoylamino-3-(2-methoxyphenyl)-2-aza-spiro[3.4]nonan-1-one (XIc). Yield 2.98 g (82%), mp 239–240°C. IR spectrum, ν, cm^{-1}: 1650, 1770 (C=O); 3340 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.05–2.20 m [10H, (CH$_2$)$_5$], 3.79 s (3H, MeO), 5.09 s (1H, CHN), 6.78–7.90 m (9H, H$_{arom}$), 10.68 s (1H, NH). Found, %: C 72.32; H 6.78; N 7.87. $C_{22}H_{24}N_2O_3$. Calculated, %: C 72.50; H 6.64; N 7.69.

2-Benzoylamino-3-(4-bromophenyl)-2-azaspiro-[3.4]octan-1-one (XIIa). Yield 2.23 g (56%), mp 236–237°C. IR spectrum, ν, cm^{-1}: 1675, 1785 (C=O); 3260

(N–H). ^{1}H NMR spectrum, δ, ppm: 1.03–2.01 m [8H, $(CH_2)_4$], 5.08 s (1H, CHN), 7.45–7.64 m and 7.84 d (9H, H_{arom}, $J \approx 8$ Hz), 10.90 s (1H, NH). Found, %: C 60.34; H 4.89; N 6.91. $C_{20}H_{19}BrN_2O_2$. Calculated, %: C 60.16; H 4.80; N 7.02.

2-Benzoylamino-3-(4-chlorophenyl)-2-azaspiro-[3.4]octan-1-one (XIIb). Yield 1.7 g (48%), mp 222–223°C. IR spectrum, ν, cm^{-1}: 1675, 1795 (C=O); 3280 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.05–2.05 m [8H, $(CH_2)_4$], 5.04 s (1H, CHN), 7.46–7.66 m and 7.80 d (9H, H_{arom}, $J \approx 8$ Hz), 10.93 s (1H, NH). Found, %: C 67.84; H 5.58; N 7.76. $C_{20}H_{19}ClN_2O_2$. Calculated, %: C 67.70; H 5.40; N 7.89.

4-(2-Furyl)-2-phenyl-2,3-diazaspiro[4.5]decan-1-one (XV) was synthesized following a similar procedure from furan-2-carbaldehyde phenylhydrazone and methyl 1-bromocyclohexane-1-carboxylate. Yield 0.71 g (24%), mp 153–154°C (from methanol). IR spectrum, ν, cm^{-1}: 1660 (C=O), 3225 (N–H). ^{1}H NMR spectrum, δ, ppm: 1.06–1.92 m [10H, $(CH_2)_5$]; 4.48 d (1H, CHN, $J \approx 10$ Hz); 6.48 d (1H, NH, $J \approx 10$ Hz); 6.28 d (1H, $J \approx 3.5$ Hz), 6.32 d (1H, $J \approx 3.5$ Hz), and 7.42 d (1H, $J \approx 1.5$ Hz) (C_4H_3O); 7.04 t, 7.30 t, and 7.87 d (5H, C_6H_5, $J \approx 8$ Hz). Found, %: C 72.77; H 6.62; N 9.58. $C_{18}N_{20}N_2O_2$. Calculated, %: C 72.95; H 6.80; N 9.45.

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 04-03-96036, 04-03-97505).

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