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# Reformatsky Reaction of Methyl 1-Bromocyclobutane- and 1-Bromocycloheptanecarboxylates with Schiff Bases

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**Abstract**—Reformatsky reagents derived from methyl 1-bromocyclobutane- and 1-bromocycloheptanecarboxylates reacted with Schiff bases to give 2,3-diaryl-2-azaspiro[3.3]heptane-1-ones and 2,3-diaryl-2-azaspiro[3.6]decan-1-ones, respectively.

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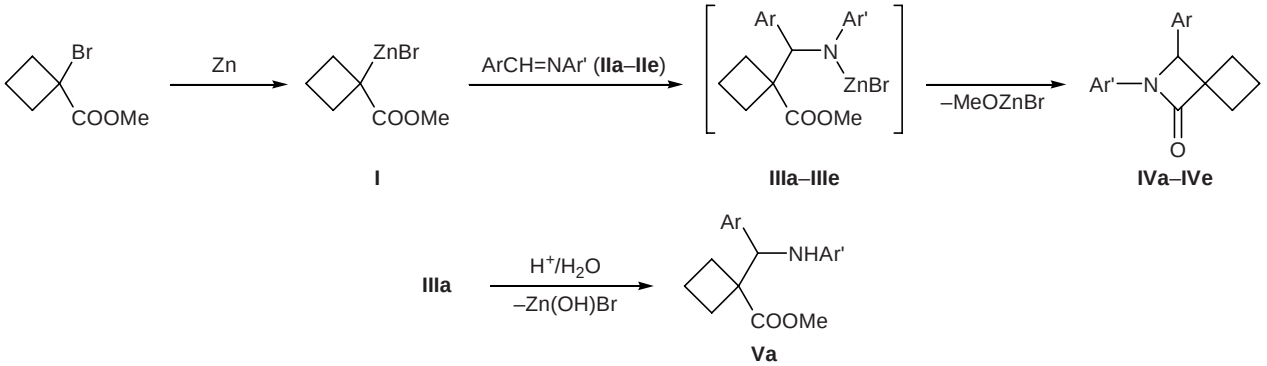
Compounds possessing a β-lactam fragment were shown to exhibit versatile biological activity [1]. We previously reported on reactions of methyl 1-bromocyclopentane- and 1-bromocyclohexanecarboxylates with zinc and Schiff bases, which led to the formation of spiro-β-lactams having tetra- and pentamethylene substituents [2]. The goal of the present work was to synthesize analogous spiro-β-lactams with tri- and hexamethylene fragments.

Reformatsky reagent **I** prepared from methyl 1-bromocyclobutanecarboxylate added at the C=N bond of Schiff bases **IIa**–**IIe** in toluene–ethyl acetate–HMPA (10:5:1, by volume) to give intermediates **IIIa**–**IIIe** which underwent spontaneous cyclization to 2,3-diaryl-2-azaspiro[3.3]heptan-1-ones **IVa**–**IVe** (Scheme 1). In the reaction of organozinc compound **I** with Schiff base **IIa** we also isolated methyl 1-[(4-bromophenyl)(phenylamino)methyl]cyclobutanecarboxylate (**Va**) as a result of hydrolysis of intermediate product **IIIa**.

Likewise, reactions of Schiff bases **IIa**–**IId** with organozinc derivative **VI** prepared from methyl 1-bromocycloheptanecarboxylate gave the corresponding spiro-fused β-lactams, 2,3-diaryl-2-azaspiro[3.6]decan-1-ones **VIIIa**–**VIIId** through intermediates **VIIa**–**VIId** (Scheme 2) Schiff base **IIe** failed to react with compound **VI** and was recovered from the reaction mixture.

The structure of compounds **IVa**–**IVe**, **Va**, and **VIIIa**–**VIIId** was proved by the data of elemental analysis and $^1$H NMR and IR spectroscopy. Compounds **IVa**–**IVe** and **VIIIa**–**VIIId** characteristically showed in the IR spectra an absorption band in the region 1725–1745 cm$^{-1}$ due to stretching vibrations of

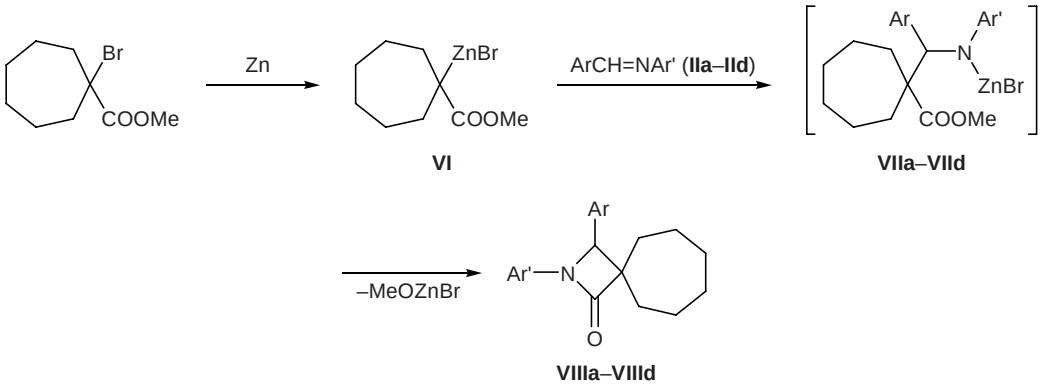
**Scheme 1.**




Ar = 4-BrC$_6$H$_4$, Ar′ = Ph (**a**), 4-BrC$_6$H$_4$ (**b**), 4-MeOC$_6$H$_4$ (**c**); Ar = 4-ClC$_6$H$_4$, Ar′ = 4-MeOC$_6$H$_4$ (**d**); Ar = 4-MeOC$_6$H$_4$, Ar′ = 4-MeOC$_6$H$_4$ (**e**).

† Deceased.

**Scheme 2.**




Ar = 4-$BrC_6H_4$, Ar′ = Ph (**a**), 4-$BrC_6H_4$ (**b**), 4-$MeOC_6H_4$ (**c**); Ar = 4-$ClC_6H_4$, Ar′ = 4-$MeOC_6H_4$ (**d**).

the lactam carbonyl group, while the spectrum of **Va** contained an ester carbonyl band at 1715 $cm^{-1}$. The C**H**Ar signal appeared in the $^1H$ NMR spectra at δ 4.52–4.72 ppm.

## EXPERIMENTAL

The IR spectra were obtained on a Specord 75IR spectrophotometer from samples dispersed in mineral oil. The $^1H$ NMR spectra were recorded from solutions in $CDCl_3$ on a Tesla BS-576A instrument (100 MHz); the chemical shifts were measured relative to hexamethyldisiloxane as internal reference.

**2,3-Diaryl-2-azaspiro[3.3]heptan-1-ones IVa–IVe (*general procedure*).** A mixture of 2 g of activated zinc powder, 15 mmol of methyl 1-bromocyclobutanecarboxylate, 10 mmol of Schiff base **IIa**–**IIe**, 10 ml of anhydrous toluene, 5 ml of anhydrous ethyl acetate, and 1 ml of HMPA was heated for 2 h under stirring. The mixture was cooled, treated with 5% acetic acid, and extracted with ethyl acetate. The extracts were dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was recrystallized from methanol–ethyl acetate (10:1).

**3-(4-Bromophenyl)-2-phenyl-2-azaspiro[3.3]heptan-1-one (IVa).** Yield 0.89 g (26%), mp 134–135°C. IR spectrum: ν 1735 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.40–2.70 m (6H, $CH_2$), 4.72 s (1H, CHN), 7.02 d and 7.42 d (2H each, 4-$BrC_6H_4$, *J* = 8.3 Hz), 7.12 s (5H, Ph). Found, %: C 63.29; H 4.78; Br 23.58; N 4.22. $C_{18}H_{16}BrNO$. Calculated, %: C 63.17; H 4.71; Br 23.35; N 4.09.

**2,3-Bis(4-bromophenyl)-2-azaspiro[3.3]heptan-1-one (IVb).** Yield 1.73 g (41%), mp 140–141°C. IR spectrum: ν 1740 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.40–2.70 m (6H, $CH_2$); 4.69 s (1H, CHN); 7.00 d, 7.02 d, 7.24 d, and 7.42 d (2H each, 4-$BrC_6H_4$, *J* = 8.3 Hz). Found, %: C 51.23; H 3.71; Br 38.08; N 3.22. $C_{18}H_{15}Br_2NO$. Calculated, %: C 51.34; H 3.59; Br 37.95; N 3.33.

**3-(4-Bromophenyl)-2-(4-methoxyphenyl)-2-azaspiro[3.3]heptan-1-one (IVc).** Yield 1.19 g (32%), mp 125–126°C. IR spectrum: ν 1740 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.40–2.70 m (6H, $CH_2$), 3.68 s (3H, MeO), 4.68 s (1H, CHN), 6.68 d and 7.04 d (2H each, 4-$MeOC_6\mathbf{H}_4$, *J* = 8.7 Hz), 7.10 d and 7.41 d (2H each, 4-$BrC_6H_4$, *J* = 8.3 Hz). Found, %: C 61.23; H 4.75; Br 21.67; N 3.83. $C_{19}H_{18}BrNO_2$. Calculated, %: C 61.30; H 4.87; Br 21.46; N 3.76.

**3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-azaspiro[3.3]heptan-1-one (IVd).** Yield 1.48 g (45%), mp 113–114°C. IR spectrum: ν 1745 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.41–2.71 m (6H, $CH_2$), 3.68 s (3H, MeO), 4.70 s (1H, CHN), 6.68 d and 7.04 d (2H each, 4-$MeOC_6\mathbf{H}_4$, *J* = 8.5 Hz), 7.13 d and 7.27 d (2H each, 4-$ClC_6H_4$, *J* = 8.3 Hz). Found, %: C 69.82; H 5.55; Cl 11.01; N 4.38. $C_{19}H_{18}ClNO_2$. Calculated, %: C 69.62; H 5.53; Cl 10.82; N 4.27.

**2,3-Bis(4-methoxyphenyl)-2-azaspiro[3.3]heptan-1-one (IVe).** Yield 1.10 g (34%), mp 153–154°C. IR spectrum: ν 1730 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.45–2.63 m (6H, $CH_2$); 3.67 s (3H, MeO); 3.74 s (3H, MeO); 4.67 s (1H, CHN); 6.66 d, 6.79 d, 7.04 d, and 7.13 d (2H each, 4-$MeOC_6\mathbf{H}_4$, *J* = 8.3 Hz). Found, %: C 74.43; H 6.71; N 4.22. $C_{20}H_{21}NO_3$. Calculated, %: C 74.28; H 6.55; N 4.33.

**Methyl 1-[(4-bromophenyl)(phenylamino)methyl]cyclobutanecarboxylate (Va)** was isolated in the reaction of organozinc compound **I** with Schiff base **IIa**. Yield 0.86 g (23%), mp 152–153°C. IR spectrum: ν 1715 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.02–

2.68 m (6H, $CH_2$); 3.58 s (1H, OMe); 4.52 s (1H, CHN); 4.70 br.s (1H, NH); 6.39 d, 6.51 t, and 6.99 t (5H, Ph, $J$ = 8 Hz); 7.07 d and 7.31 d (2H each, 4-$BrC_6H_4$, $J$ = 8.3 Hz). Found, %: C 60.80; H 5.48; Br 21.47; N 3.52. $C_{19}H_{20}BrNO_2$. Calculated, %: C 60.97; H 5.39; Br 21.35; N 3.74.

**2,3-Diaryl-2-azaspiro[3.6]decan-1-ones VIIIa–VIIId** were synthesized as described above for compounds **IVa–IVe** from methyl 1-bromocycloheptanecarboxylate.

**3-(4-Bromophenyl)-2-phenyl-2-azaspiro[3.6]decan-1-one (VIIIa).** Yield 1.27 g (33%), mp 137–138°C. IR spectrum: ν 1740 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 0.94–2.35 m (12H, $CH_2$), 4.70 s (1H, CHN), 7.02 d and 7.39 d (2H each, 4-$BrC_6H_4$, $J$ = 8.3 Hz), 7.17 s (5H, Ph). Found, %: C 65.82; H 5.71; Br 20.98; N 3.32. $C_{21}H_{22}BrNO$. Calculated, %: C 65.63; H 5.77; Br 20.79; N 3.64.

**2,3-Bis(4-bromophenyl)-2-azaspiro[3.6]decan-1-one (VIIIb).** Yield 1.49 g (32%), mp 110–111°C. IR spectrum: ν 1740 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.03–2.37 m (12H, $CH_2$); 4.67 s (1H, CHN); 6.99 d, 7.03 d, 7.26 d, and 7.45 d (2H each, 4-$BrC_6H_4$, $J$ = 8.3 Hz). Found, %: C 54.28; H 4.74; Br 34.27; N 3.20. $C_{21}H_{21}Br_2NO$. Calculated, %: C 54.45; H 4.57; Br 34.50; N 3.02.

**3-(4-Bromophenyl)-2-(4-methoxyphenyl)-2-azaspiro[3.6]decan-1-one (VIIIc).** Yield 2.32 g (56%), mp 105–106°C. IR spectrum: ν 1735 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.03–2.37 m (12H, $CH_2$), 3.68 s (3H, MeO), 4.67 s (1H, CHN), 6.69 d and 7.00 d (2H each, 4-$MeOC_6\mathbf{H}_4$, $J$ = 8.8 Hz), 7.10 d and 7.38 d (2H each, 4-$BrC_6H_4$, $J$ = 8.3 Hz). Found, %: C 63.52; H 5.75; Br 19.50; N 3.53. $C_{22}H_{24}BrNO_2$. Calculated, %: C 63.77; H 5.84; Br 19.28; N 3.38.

**3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-azaspiro[3.6]decan-1-one (VIIId).** Yield 1.89 g (51%), mp 114–115°C. IR spectrum: ν 1725 $cm^{-1}$ (C=O). $^1H$ NMR spectrum, δ, ppm: 1.03–2.30 m (12H, $CH_2$); 3.69 s (3H, MeO); 4.69 s (1H, CHN); 6.69 d ($J$ = 8.7 Hz) and 6.92–7.32 m (8H, 4-$MeOC_6\mathbf{H}_4$, 4-$ClC_6H_4$). Found, %: C 71.42; H 6.72; Cl 9.50; N 3.97. $C_{22}H_{24}ClNO_2$. Calculated, %: C 71.44; H 6.54; Cl 9.58; N 3.79.

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