Russian Journal of Organic Chemistry, Vol. 40, No. 6, 2004, pp. 834–836. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 6, 2004, pp. 873–875.

Reformatsky Reaction of Methyl α-Bromoisobutyrate with Schiff Bases Derived from Salicylaldehyde and 2-Hydroxynaphthalene-1-carbaldehyde

V. V. Shchepin, D. V. Fotin, and M. I. Vakhrin

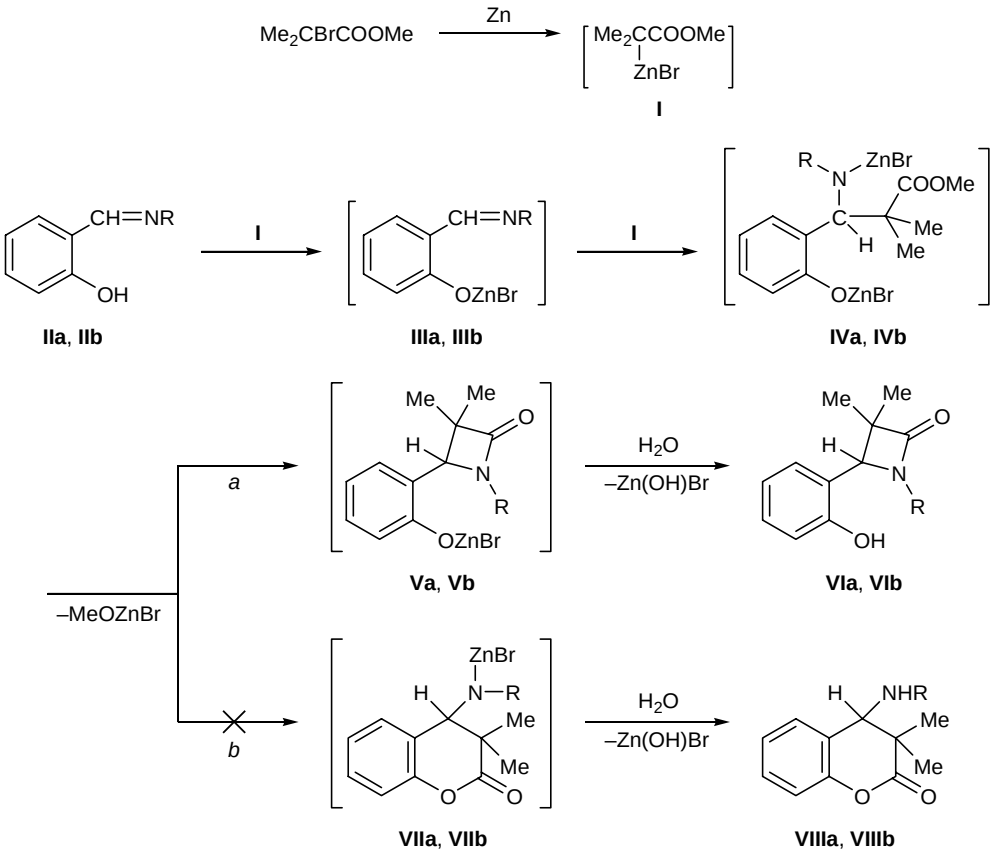
Perm State University, ul. Bukireva 15, Perm, 614990 Russia
e-mail: koh@psu.ru

Received November 15, 2002

Abstract—Reformatsky reaction of methyl α-bromoisobutyrate with Schiff bases derived from salicylaldehyde and its analogs gives the corresponding 1,4-disubstituted 3,3-dimethylazetidin-2-ones.

Reformatsky reaction with Schiff bases has been well documented [1–3]. This reaction underlies a general procedure for the synthesis of β-lactams (azetidin-2-ones). However, we have found no published data on Reformatsky reaction with Schiff bases derived from salicylaldehyde. This may be due to some difficulties in carrying out such reactions, arising from the presence of hydroxy group in the aromatic ring of the

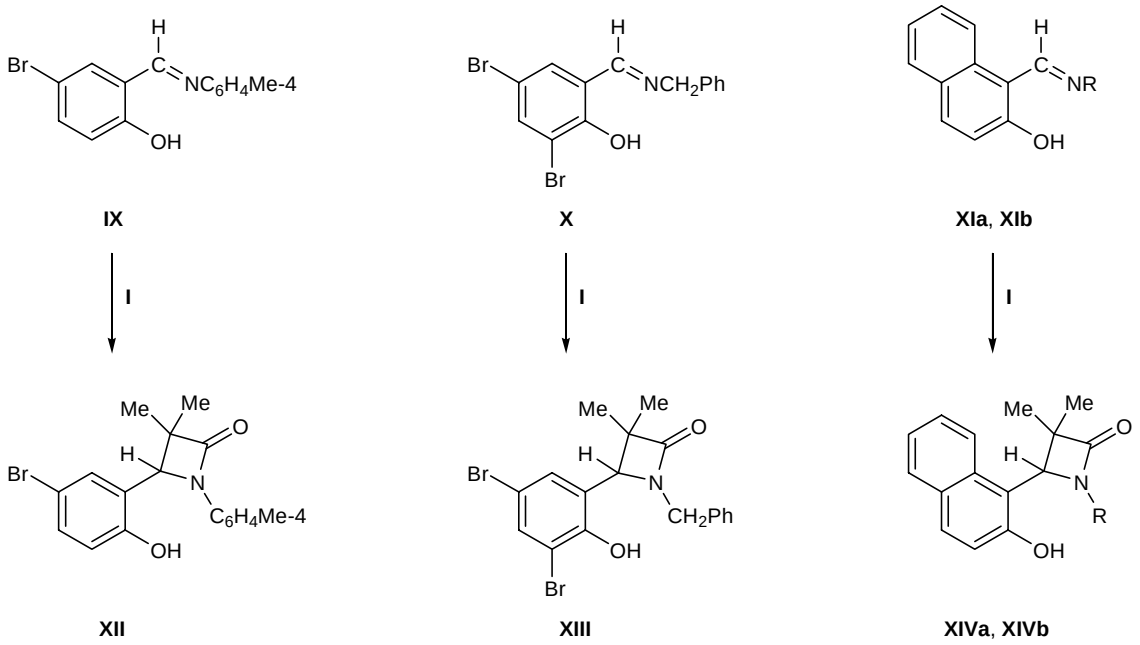
Scheme 1.



II–**VI**, R = Ph (**a**), 4-BrC_6H_4 (**b**).

1070-4280/04/4006-0834

Scheme 2.



XI, **XIV**, R = Ph (**a**), 4-MeC_6H_4 (**b**).

Schiff base, as well as from the reduced electrophilicity of the C=N carbon atom. In fact, we failed to effect the reaction under standard conditions in diethyl ether–benzene. The process successfully occurred only in a mixture of diethyl ether, benzene, hexamethylphosphoramide (HMPA), and tetrahydrofuran (THF).

Presumably, just that system ensures the nucleophilicity of Reformatsky reagent **I** to be sufficient to add at the C=N bond of intermediate **III**. In addition, intermediates **III** and **IV** do not separate from the solution. Theoretically, two reaction paths are possible (Scheme 1). Path *a* involves intermediate **IV** and leads to formation of lactam **VI**, while path *b* yields lactone **VIII** through intermediate **VII**. Our experiments showed that only path *a* is operative. As a result, N-substituted 4-(2-hydroxyphenyl)-3,3-dimethylazetidin-2-ones **VIa** and **VIb** were obtained. Likewise, Reformatsky reactions of methyl α-bromoisobutyrate with Schiff bases **IX**–**XI** afforded the corresponding β-lactams **XII**, **XIII**, **XIVa**, and **XIVb** (Scheme 2).

The structure of the products was proved by the IR and ^{1}H NMR spectra. In the IR spectra we observed a characteristic carbonyl absorption band 1720–1730 cm^{-1}. Absorption of the hydroxy group was weakly expressed; for example, the IR spectra of compounds **VIb** and **XIII** contained broad absorption bands at about 3170 and 3220 cm^{-1}, respectively.

In the ^{1}H NMR spectra, signals at δ 0.70–1.01, 1.30–1.58, and 4.43–5.69 ppm belong to protons of the geminal methyl groups and 4-H, respectively. Compounds **XIVa** and **XIVb** give rise to a double set of the above signals. Presumably, these compounds exist as two relatively stable conformers due to restricted rotation about the C^4–C_{arom} bond. The rotamer ratio is 40:60.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer. The ^{1}H NMR spectra of compounds **VIa**, **VIb**, **XII**, **XIII**, and **XIVa** were obtained on an RYa-2310 instrument (60 MHz) from solutions in $CDCl_3$ and DMSO-d_6 using HMDS as internal reference. The ^{1}H NMR spectrum of **XIVb** was measured on a Bruker DRX-500 spectrometer (500 MHz) from a solution in CCl_4–DMSO-d_6 (3:1) using TMS as internal reference.

1,4-Disubstituted 3,3-dimethylazetidin-2-ones VIa, VIb, XII, XIII, XIVa, and XIVb (*general procedure***).** Methyl α-bromoisobutyrate, 5.06 g (0.028 mol), was added to a mixture of 4 g (0.0615 mol) of zinc (prepared as fine turnings), 3 g (0.007 mol) of the corresponding Schiff base, 15 ml of diethyl ether, 7 ml of benzene, and 7 ml of HMPA. The mixture was heated until a reaction started, and the reaction then

occurred spontaneously. When the reaction was complete, 6 ml of THF was added, and the mixture was heated for 30 min under reflux. The mixture was cooled, treated with 10% acetic acid, and extracted with diethyl ether. The extract was dried over sodium sulfate, the solvent was distilled off, and the residue was recrystallized twice from methanol.

4-(2-Hydroxyphenyl)-3,3-dimethyl-1-phenylazetidin-2-one (VIa). Yield 44%, mp 153–154°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.83 s and 1.50 s (6H, 2Me), 5.10 s (1H, CHN), 6.70–7.40 m (9H, 2-HOC_6**H**$_4$, C_6H_5), 7.50 s (1H, OH). Found, %: C 76.51; H 5.98. $C_{17}H_{17}NO_2$. Calculated, %: C 76.67; H 6.06.

1-(4-Bromophenyl)-4-(2-hydroxyphenyl)-3,3-dimethylazetidin-2-one (VIb). Yield 61%, mp 248–250°C. ^{1}H NMR spectrum ($CDCl_3$–DMSO-d_6, 3:1), δ, ppm: 0.77 s and 1.46 s (6H, 2Me), 5.04s (1H, CHN), 6.70–7.40 m (8H, 2-HOC_6**H**$_4$, 4-BrC_6H_4), 9.34 s (1H, OH). Found, %: C 59.02; H 4.30. $C_{17}H_{16}BrNO_2$. Calculated, %: C 59.15; H 4.38.

4-(5-Bromo-2-hydroxyphenyl)-3,3-dimethyl-1-(4-methylphenyl)azetidin-2-one (XII). Yield 39%, mp 176–178°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.71 s and 1.33 s (6H, 2Me), 2.18 s (3H, 4-**Me**C_6H_4), 5.03 s (1H, CHN), 6.70–7.40 m (7H, C_6H_3, C_6H_4), 10.18 s (1H, OH). Found, %: C 60.06; H 4.68. $C_{18}H_{18}BrNO_2$. Calculated, %: C 60.18; H 4.77.

1-Benzyl-4-(3,5-dibromo-2-hydroxyphenyl)-3,3-dimethylazetidin-2-one (XIII). Yield 47%, mp 207–208°C. ^{1}H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 0.70 s and 1.30 s (6H, 2Me), 3.93 d and 4.80 d (2H, C**H**$_2$Ph, J = 16 Hz), 4.43 s (1H, CHN), 7.07 d and 7.48 d (2H, C_6H_2), 7.20 s (5H, C_6H_5), 8.67 br.s (1H, OH). Found, %: C 49.10; H 3.81. $C_{18}H_{17}Br_2NO_2$. Calculated, %: C 49.23; H 3.90.

4-(2-Hydroxy-1-naphthyl)-3,3-dimethyl-1-phenylazetidin-2-one (XIVa). Yield 54%, mp 201–203°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 s, 0.97 s, 1.50 s, 1.56 s (6H, 2Me); 5.53 s, 5.80 s (1H, CHN); 6.90–8.10 m (11H, $C_{10}H_6$, C_6H_5); 9.36 s, 9.76 s (1H, OH). Found, %: C 79.30; H 5.94. $C_{21}H_{19}NO_2$. Calculated, %: C 79.47; H 6.03.

4-(2-Hydroxy-1-naphthyl)-3,3-dimethyl-1-(4-methylphenyl)azetidin-2-one (XIVb). Yield 39%, mp 190–192°C. ^{1}H NMR spectrum (CCl_4–DMSO-d_6), δ, ppm: 0.95 s, 1.01 s, 1.58 s, 1.64 s (6H, 2Me); 2.22 s (3H, 4-**Me**C_6H_4); 5.50 s, 5.69 s (1H, CHN); 6.90–8.05 m (10H, $C_{10}H_6$, C_6H_4); 9.40 s, 9.75 s (1H, OH). Found, %: C 79.33; H 6.28. $C_{21}H_{19}NO_2$. Calculated, %: C 79.49; H 6.37.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 04-03-96036).

REFERENCES

1. Gaudemar, M., *Organomet. Chem. Rev*., 1972, vol. 8, p. 183.
2. Furstner, A., *Synthesis*, 1989, no. 8, p. 571.
3. Kuznetsov, V.V. and Prostikov, N.S., *Khim. Geterotsikl. Soedin*., 1990, no. 1, p. 5.