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Reformatsky Reaction with N-Substituted 6-Bromo-2-oxochromene-3-carboxamides

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Abstract—Reformatsky reactions of ethyl α-bromopropionate, methyl α-bromobutyrate, and methyl α-bromoisobutyrate with N-substituted 6-bromo-2-oxochromene-3-carboxamides in the system diethyl ether–benzene–HMPA give *N*-benzyl-6-bromo-4-(1-alkoxycarbonylalkyl)-2-oxochroman-3-carboxamides, while in the system diethyl ether–benzene–HMPA–THF, 3-R^1-1-R^2-1-R^3-9-bromo-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]-pyridine-2,4,5-triones are obtained.

In continuation of our studies on functionalization of heterocyclic compounds with zinc intermediates [1], in the present work we examined Reformatsky reactions of α-bromopropionic, α-bromobutyric, and α-bromoisobutyric acid esters with *N*-benzyl-, *N*-(4-methylphenyl)-, and *N*-(4-methoxyphenyl)-6-bromo-2-oxochromene-3-carboxamides **Ia**–**Ic**. The results showed that bromozinc compounds derived from the above esters reacted with substrates **Ia**–**Ic** in a regioselective fashion, giving rise to intermediate **II** via attack on the electrophilic C^4 atom.

When the reaction was carried out in the system diethyl ether–benzene–HMPA (2:1:1), the subsequent hydrolysis afforded *N*-benzyl-6-bromo-4-(1-alkoxycarbonylalkyl)-2-oxochroman-3-carboxamides **IIIa** and **IIIb**. Addition of THF to the reaction mixture, followed by heating under reflux for 0.5 h, resulted in cyclization of bromozinc intermediates **IIa** and **IIb** to tricyclic structures **IVa**–**IVe**. Hydrolysis of the latter afforded 3-R^1-1-R^2-1-R^3-9-bromo-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones **Va**–**Ve** as final products (Scheme 1). The structure of compounds **IIIa**, **IIIb**, and **Va**–**Ve** was proved by the elemental analyses and IR and ^{1}H NMR spectra.

The IR spectra of **Va**–**Ve** contained characteristic absorption bands due to stretching vibrations of the imide carbonyl groups (1695 and 1730 cm^{-1}) and lactone carbonyl (1770–1780 cm^{-1}). In the ^{1}H NMR spectra of these compounds, a doublet at δ 4.30–4.53 ppm (J = 6 Hz) was present, which belongs to 4a-H (CHC=O).

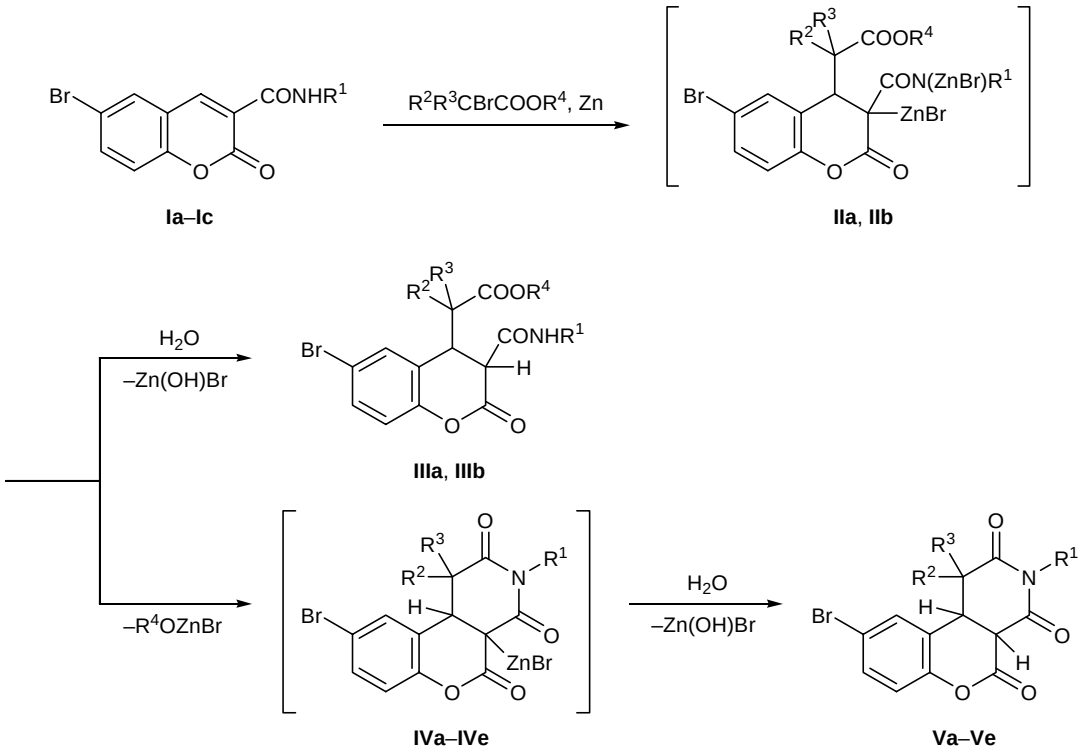
EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured from solutions in $CDCl_3$ or DMSO-d_6 on an RYa-2310 instrument (60 MHz) using HMDS as internal reference.

***N*-Benzyl-6-bromo-4-(1-ethoxycarbonylethyl)-2-oxochroman-3-carboxamide (IIIa).** Ethyl α-bromopropionate, 4.67 g (0.028 mol), was added to a mixture of 4 g (0.007 mol) of metallic zinc prepared as fine turnings, 2 g (0.007 mol) of *N*-benzyl-6-bromo-2-oxochromene-3-carboxamide, 15 ml of diethyl ether, 7 ml of benzene, and 7 ml of HMPA. The mixture was heated to initiate the reaction and was then heated for 30 min (after the addition of the bromo derivative was complete). The mixture was hydrolyzed with 10% acetic acid and extracted with ether. The extract was dried over sodium sulfate, the solvent was distilled off, and the residue was twice recrystallized from methanol. Yield 58%, mp 111–112°C. IR spectrum, ν, cm^{-1}: 1650, 1735, 1790 (C=O); 3350 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 d (3H, CH_3), 1.14 t (3H, $OCH_2C\mathbf{H}_3$), 2.40–2.80 m (1H, C**H**CH_3), ~3.75 m (2H, 3-H, 4-H), 4.08 q (2H, O**C**$\mathbf{H}_2CH_3$), 4.30 d (2H, C$\mathbf{H}_2$Ph), 7.05–7.50 m (9H, Ph, C_6H_3Br, NH). Found, %: C 57.28; H 4.73; N 3.20. $C_{22}H_{22}BrNO_5$. Calculated, %: C 57.40; H 4.82; N 3.04.

***N*-Benzyl-6-bromo-4-(1-methoxycarbonyl-1-methylethyl)-2-oxochroman-3-carboxamide (IIIb)** was synthesized in a similar way using 5.06 g (0.028 mol) of methyl α-bromoisobutyrate. Yield 85%,

Scheme 1.



I, R^1 = $PhCH_2$ (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**); **II**, **III**, R^1 = $PhCH_2$, R^2 = H, R^3 = Me, R^4 = Et (**a**); R^1 = $PhCH_2$, R^2 = R^3 = R^4 = Me (**b**); **IV**, **V**, R^1 = 4-MeC_6H_4, R^2 = H, R^3 = Me, R^4 = Et (**a**); R^1 = 4-MeC_6H_4, R^2 = H, R^3 = Et, R^4 = Me (**b**); R^1 = 4-MeC_6H_4, R^2 = R^3 = R^4 = Me (**c**); R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = R^4 = Me (**d**); R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = Et, R^4 = Me (**e**).

mp 161–162°C. IR spectrum, ν, cm^{-1}: 1670, 1730, 1790 (C=O); 3360 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.08 s (6H, CH_3), 3.50 s (3H, OCH_3), 3.57 s and 3.90 s (2H, 3-H, 4-H), 4.07 d (2H, C**H**$_2$Ph), 6.90–7.50 m (8H, Ph, C_6H_3Br), 8.80 t (1H, NH). Found, %: C 57.23; H 4.71; N 2.96. $C_{22}H_{22}BrNO_5$. Calculated, %: C 57.40; H 4.82; N 3.04.

3-R^1-1-R^2-1-R^3-9-Bromo-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones Va–Ve were synthesized in a similar way using 4.67 g (0.028 mol) of ethyl α-bromopropionate, 5.06 g (0.028 mol) of methyl α-bromobutyrate, or 5.06 g (0.028 mol) of methyl α-bromoisobutyrate. When the reaction mixture no longer boiled spontaneously, it was heated for 30 min, 8 ml of THF was added, and the mixture was heated for an additional 30 min.

9-Bromo-1-methyl-3-(4-methylphenyl)-2,3,4,-4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (Va). Yield 60%, mp 251–254°C. ^{1}H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 1.27 d (3H, C**H**$_3$CH), 2.30 s (3H, C**H**$_3$C$_6$H$_4$), 2.60–3.00 m (1H, CH_3C**H**), 3.40–4.00 m (1H, C**H**CHCH$_3$), 4.33 d (1H, CHCO), 6.80–7.70 m (7H, C_6H_3, 4-CH_3C_6**H**$_4$). Found, %: C 57.80; H 3.78; N 3.49. $C_{20}H_{16}BrNO_4$. Calculated, %: C 57.99; H 3.89; N 3.38.

9-Bromo-1-ethyl-3-(4-methylphenyl)-2,3,4,-4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (Vb). Yield 62%, mp 282–283°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 t (3H, C**H**$_3$CH$_2$), 1.50–2.10 m (2H, CH$_3$C**H**$_2$), 2.30 s (3H, C**H**$_3$C$_6$H$_4$), 2.70–3.20 m (1H, CH$_3$CH$_2$C**H**), 3.70–4.20 m (1H, C**H**CHCH$_2$CH$_3$), 4.53 d (1H, CHCO), 6.70–7.70 m (7H, C_6H_3, 4-CH_3C_6**H**$_4$). Found, %: C 58.72; H 4.12; N 3.15. $C_{21}H_{18}BrNO_4$. Calculated, %: C 58.89; H 4.24; N 3.27.

9-Bromo-1,1-dimethyl-3-(4-methylphenyl)-2,3,4,-4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (Vc). Yield 82%, mp 250–252°C. ^{1}H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 1.03 s and 1.30 s [6H, $(CH_3)_2$C], 2.33 s (3H, C**H**$_3$C$_6$H$_4$), 3.80 d and 4.30 d (2H, CHCH), 6.80–7.70 m (7H, C_6H_3, 4-CH_3C_6**H**$_4$). Found, %: C 58.79; H 4.17; N 3.41. $C_{21}H_{18}BrNO_4$. Calculated, %: C 58.89; H 4.24; N 3.27.

9-Bromo-3-(4-methoxyphenyl)-1-methyl-2,3,4,-4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (Vd). Yield 77%, mp 240–243°C. ^{1}H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 1.26 d (3H, C**H**$_3$CH); 2.60–3.00 m (1H, CH_3C**H**); 3.30–3.90 m (1H, C**H**$CHCH_3$); 3.76 s (3H, CH_3O); 4.32 d (1H, CHCO); 6.97 s (4H, C_6H_4); 7.06 d, 7.47 s, 7.54 d (3H, C_6H_3). Found, %: C 55.70; H 3.64; N 3.43. $C_{20}H_{16}BrNO_5$. Calculated, %: C 55.83; H 3.75; N 3.26.

9-Bromo-1-ethyl-3-(4-methoxyphenyl)-2,3,4,4a,-5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (Ve). Yield 83%, mp 223–227°C. ^{1}H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 0.97 t (3H, C**H**$_3$CH$_2$); 1.50–2.10 m (2H, CH_3C**H**$_2$); 2.60–3.10 m (1H, CH_3CH_2C**H**); 3.70–4.10 m (1H, C**H**$CHCH_2CH_3$); 4.37 d (1H, CHCO); 6.87 s (4H, C_6H_4); 7.04 d, 7.46 s, 7.53 d (3H, C_6H_3). Found, %: C 56.80; H 4.15; N 3.01. $C_{21}H_{18}BrNO_5$. Calculated, %: C 56.77; H 4.08; N 3.15.

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