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Reaction of Methyl 1-Bromocyclopentane- and -cyclohexanecarboxylates with Zinc and 2-Arylmethylideneindan-1,3-diones

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Abstract—Methyl 1-bromocyclopentanecarboxylate and methyl 1-bromocyclohexanecarboxylate reacted with zinc and 2-arylmethylideneindan-1,3-diones to give methyl-1-[(aryl)(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)-methyl]cyclopentane(or cyclohexane)carboxylates and 4′-aryl-2′*H*-spiro[cyclopentane(or cyclohexane)-1,3′-indeno[1,2-*b*]pyran]-2′,5′(4′*H*)-diones.

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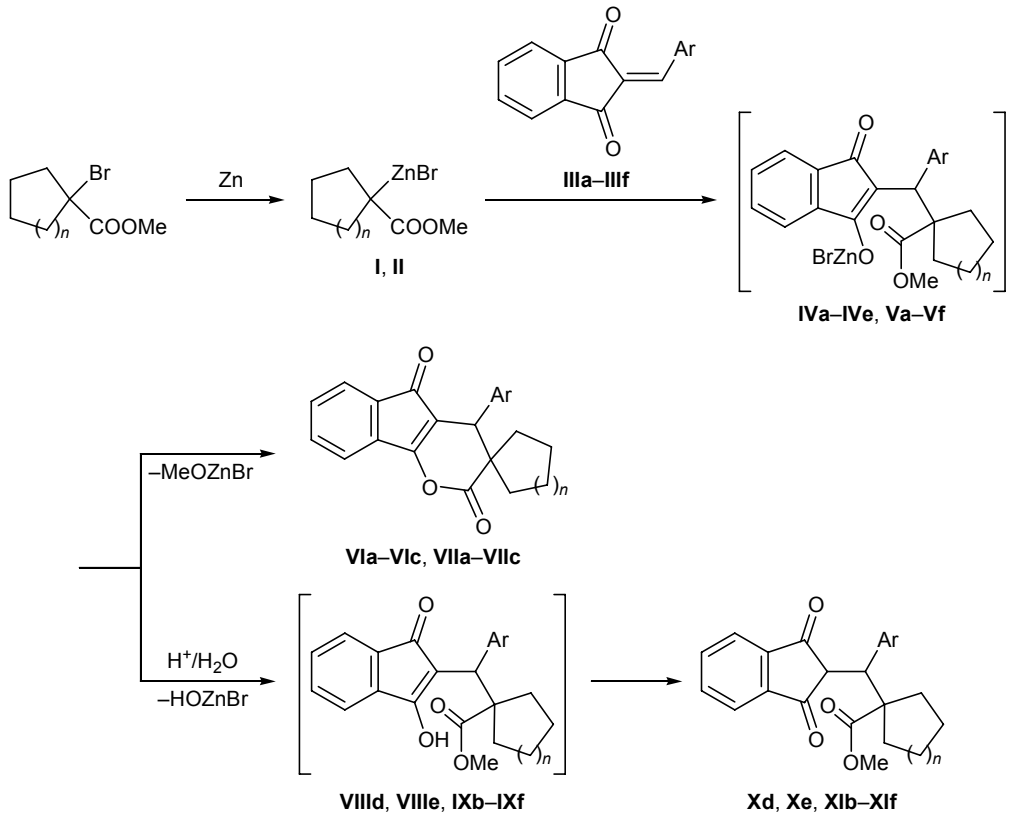
Reformatsky reagents react with α,β-unsaturated ketones following both 1,2- and 1,4-addition patterns, and the 1,4-addition products are capable of undergoing cyclization to give unsaturated lactones, derivatives of dihydropyran-2-one [1]. Substituted spirodihydropyran-2-ones were isolated in reactions of alicyclic Reformatsky reagents with unsaturated ketones [2–8]. In continuation of these studies we examined reactions of 2-arylmethylideneindan-1,3-diones **IIIa**–**IIIf** with bromozinc derivatives **I** and **II** obtained from methyl 1-bromocyclopentane- and -cyclohexanecarboxylates. We found that Reformatsky reagents **I** and **II** add to unsaturated cyclic diketones **IIIa**–**IIIf** at the 1,4-positions with formation of intermediates **IVa**–**IVe** and **Va**–**Vf**. The final products were either 4′-aryl-2′*H*-spiro[cyclopentane-1,3′-indeno[1,2-*b*]pyran]-2′,5′(4′*H*)-diones **VIa**–**VIc** and 4′-aryl-2′*H*-spiro[cyclohexane-1,3′-indeno[1,2-*b*]pyran]-2′,5′(4′*H*)-diones **VIIa**–**VIIc** resulting from cyclization of intermediates **IV** and **V** or methyl 1-[(aryl)(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)methyl]cyclopentanecarboxylates **Xd** and **Xe** and methyl 1-[(aryl)(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)methyl]cyclohexanecarboxylates **XIb**–**XIf** formed by hydrolysis of **IV** and **V** (Scheme 1).

It was also found that 2-arylmethylideneindan-1,3-diones **III** are considerably less reactive than 2-arylmethylidene-1,3-diphenylpropane-1,3-diones [5] toward Reformatsky reagents. When the reactions of **III** with bromozinc derivatives **I** and **II** were carried out under the conditions reported previously (heating for 4 h in a boiling mixture of benzene, ethyl acetate, and HMPA at a ratio of 20:5:1), appreciable amounts (up to 40–50%) of unreacted compounds **III** were isolated. To increase the conversion, the reaction time was prolonged to 8 h; however, in most cases, the reaction mixtures contained small amounts of the initial diketones. Further increase of the reaction time, as well as replacement of benzene by toluene to raise the reaction temperature, resulted in considerable tarring.

It was found previously that reactions of alicyclic Reformatsky reagents with 2-arylmethylidene-2,3-dihydro-1*H*-inden-1-ones [7] give only the corresponding lactonization products. The lower yield of the heterocyclic products in the reactions of 2-arylmethylideneindan-1,3-diones with alicyclic Reformatsky reagents as compared to analogous reactions of 2-arylmethylidene-2,3-dihydro-1*H*-inden-1-ones may be related to reduced nucleophilicity of the enolate oxygen atom due to conjugation with the carbonyl group in intermediates **IV** and **V**.

The IR spectra of 4′-aryl-2′*H*-spiro[cycloalkane-1,3′-indeno[1,2-*b*]pyran]-2′,5′(4′*H*)-diones **VI** and **VII** contained absorption bands belonging to stretching vibrations of the ketone and lactone carbonyl groups in the regions 1715–1724 and 1775–1789 cm^{-1}, respectively. In the ^1H NMR spectra of these compounds, the most characteristic were singlets from the 4′-H protons at δ 3.65–3.88 ppm. Methyl 1-[(aryl)(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)methyl]cycloalkanecarboxylates **X** and **XI** displayed in the IR spectra absorption bands due to the ketone and ester carbonyl groups at 1705–1717 and 1737–1742 cm^{-1}, respectively. The methoxy protons resonated in the ^1H NMR spectra of **X** and **XI** at δ 3.61–3.79 ppm, and the CH signals were observed

Scheme 1.



I, **IV**, **VI**, **VIII**, **X**, n = 1; **II**, **V**, **VII**, **IX**, **XI**, n = 2; Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 3,4-$(MeO)_2C_6H_3$ (**c**), 3-BrC_6H_4 (**d**), 4-$MeOC_6H_4$ (**e**), 4-MeC_6H_4 (**f**).

at δ 3.55–3.66 and 3.63–4.18 ppm. The latter signals were mostly doublets with a coupling constant of lower than 2.4 Hz. However, because of accidental coincidence of chemical shifts, the CH signals in the spectra of **XIb** and **XIc** appear as two-proton singlets.

Compounds **VIc**, **XId**, and **XIf** were tested for analgesic activity, and the activity of compounds **VIc** and **XId** was found to be comparable with that of Metamizole while compound **XIf** turned out to be even superior to Metamizole.

EXPERIMENTAL

The IR spectra of compounds **VIa**–**VIc**, **VIIa**–**VIIc**, **Xd**, **Xe**, and **XIb**–**XIf** were recorded on a Perkin Elmer Spectrum Two spectrometer with Fourier transform from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury Plus-300 spectrometer (300 MHz) using $CDCl_3$ as solvent and tetramethylsilane as internal reference.

General procedure for the reaction of methyl 1-bromocycloalkanecarboxylates with 2-arylmethylideneindan-1,3-dione. A mixture of 1.5 g of zinc prepared as fine turnings, a catalytic amount of mercury(II) chloride, 5 mmol of 2-arylmethylideneindan-1,3-dione, 5.3 mmol of methyl 1-bromocycloalkanecarboxylate, 20 mL of benzene, 5 mL of ethyl acetate, and 1 mL of HMPA was heated for 8 h under reflux. The mixture was cooled, the liquid phase was separated from excess zinc by decanting and treated with 5% acetic acid, the organic layer was separated, and the aqueous layer was extracted with two portions of ethyl acetate. The extracts were combined with the organic phase and dried over anhydrous sodium sulfate, the solvent was distilled off, and ethyl acetate was added to the residue to isolate compound **VIa**–**VIc** or **VIIa**–**VIIc** which was then recrystallized from ethyl acetate. Ethanol was added to the mother liquor, and compound **Xd**, **Xe**, or **XIb**–**XIf** was filtered off and recrystallized from ethanol.

4′-Phenyl-2′*H*-spiro[cyclopentane-1,3′-indeno-[1,2-*b*]pyran]-2′,5′(4′*H*)-dione (VIa). Yield 0.69 g (42%), mp 186–187°C. IR spectrum, ν, cm^{-1}: 1779, 1715. ^{1}H NMR spectrum, δ, ppm: 1.23–2.39 m (8H, CH_2), 3.88 s (1H, CH), 7.06–7.93 m (9H, H_{arom}).

Found, %: C 79.67; H 5.35. $C_{22}H_{18}O_3$. Calculated, %: C 79.98; H 5.49.

4′-(4-Bromophenyl)-2′*H*-spiro[cyclopentane-1,3′-indeno[1,2-*b*]pyran]-2′,5′(4′*H*)-dione (VIb). Yield 0.88 g (34%), mp 138–139°C. IR spectrum, ν, cm^{-1}: 1789, 1724. ^1H NMR spectrum, δ, ppm: 1.21–2.39 m (8H, CH_2), 3.85 s (1H, CH), 6.97 d and 7.29 d (4H, C_6H_4, J = 8.7 Hz), 7.81–7.95 m (4H, H_{arom}). Found, %: C 64.76; H 4.31; Br 19.72. $C_{22}H_{17}BrO_3$. Calculated, %: C 64.56; H 4.19; Br 19.52.

4′-(3,4-Dimethoxyphenyl)-2′*H*-spiro[cyclopentane-1,3′-indeno[1,2-*b*]pyran]-2′,5′(4′*H*)-dione (VIc). Yield 0.92 g (47%), mp 156–158°C. IR spectrum, ν, cm^{-1}: 1783, 1720. ^1H NMR spectrum, δ, ppm: 1.22–2.36 m (8H, CH_2), 3.75 s (3H, MeO), 3.77 s (3H, MeO), 3.84 s (1H, CH), 6.61 s (3H, C_6H_3), 7.78–7.93 m (4H, H_{arom}). Found, %: C 73.62; H 5.81. $C_{24}H_{22}O_5$. Calculated, %: C 73.83; H 5.68.

4′-Phenyl-2′*H*-spiro[cyclohexane-1,3′-indeno-[1,2-*b*]pyran]-2′,5′(4′*H*)-dione (VIIa). Yield 0.79 g (46%), mp 223–224°C. IR spectrum, ν, cm^{-1}: 1775, 1720. ^1H NMR spectrum, δ, ppm: 0.96–2.62 m (10H, CH_2), 3.71 s (1H, CH), 7.04–8.00 m (9H, H_{arom}). Found, %: C 79.97; H 5.73. $C_{23}H_{20}O_3$. Calculated, %: C 80.21; H 5.85.

4′-(4-Bromophenyl)-2′*H*-spiro-[cyclohexane-1,3′-indeno[1,2-*b*]pyran]-2′,5′(4′*H*)-dione (VIIb). Yield 0.59 g (28%), mp 205–206°C. IR spectrum, ν, cm^{-1}: 1780, 1715. ^1H NMR spectrum, δ, ppm: 0.92–2.59 m (10H, CH_2), 3.68 s (1H, CH), 6.96 d and 7.28 d (4H, C_6H_4, J = 8.7 Hz), 7.79–7.94 m (4H, H_{arom}). Found, %: C 65.12; H 4.68, Br 18.62. $C_{23}H_{19}BrO_3$. Calculated, %: C 65.26; H 4.52; Br 18.88.

4′-(3,4-Dimethoxyphenyl)-2′*H*-spiro[cyclohexane-1,3′-indeno[1,2-*b*]pyran]-2′,5′(4′*H*)-dione (VIIc). Yield 0.49 g (24%), mp 168–170°C. IR spectrum, ν, cm^{-1}: 1782, 1721. ^1H NMR spectrum, δ, ppm: 0.95–2.59 m (10H, CH_2), 3.65 s (1H, CH), 3.75 s (3H, MeO), 3.77 s (3H, MeO), 6.60 s (3H, C_6H_3), 7.76–7.91 m (4H, H_{arom}). Found, %: C 74.41; H 6.03. $C_{25}H_{24}O_5$. Calculated, %: C 74.24; H 5.98.

Methyl 1-[(3-bromophenyl)(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)methyl]cyclopentanecarboxylate (Xd). Yield 0.95 g (43%), mp 134–135°C. IR spectrum, ν, cm^{-1}: 1742, 1707. ^1H NMR spectrum, δ, ppm: 1.22–2.37 m (8H, CH_2), 3.58 d (1H, C**H**Ar, J = 2.1 Hz), 3.61 s (3H, MeO), 3.96 d (1H, 2-H, J = 2.1 Hz); 7.02 t (1H, J = 8.7 Hz), 7.23 d (1H, J = 8.7 Hz), 7.26 d (1H, J = 8.7 Hz), 7.42 s (1H) (3-BrC_6H_4); 7.72–7.94 m (4H, H_{arom}). Found, %: C 62.81; H 4.67; Br 18.25. $C_{23}H_{21}BrO_4$. Calculated, %: C 62.60; H 4.80; Br 18.11.

Methyl 1-[(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)(4-methoxyphenyl)methyl]cyclopentanecarboxylate (Xe). Yield 1.16 g (59%), mp 114–115°C. IR spectrum, ν, cm^{-1}: 1737, 1705. ^1H NMR spectrum, δ, ppm: 1.22–2.38 m (8H, CH_2), 3.55 d (1H, C**H**Ar, J = 2.4 Hz), 3.61 s (3H, MeO), 3.67 s (3H, MeO), 3.95 d (1H, 2-H, J = 2.4 Hz), 6.63 d and 7.15 d (4H, C_6H_4, J = 8.7 Hz), 7.70–7.89 m (4H, H_{arom}). Found, %: C 73.63; H 6.07. $C_{24}H_{24}O_5$. Calculated, %: C 73.45; H 6.16.

Methyl 1-[(4-bromophenyl)(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)methyl]cyclohexanecarboxylate (XIb). Yield 0.75 g (33%), mp 153–155°C. IR spectrum, ν, cm^{-1}: 1741, 1717. ^1H NMR spectrum, δ, ppm: 1.08–2.37 m (10H, CH_2), 3.66 s (2H, C**H**Ar, 2-H), 3.75 s (3H, MeO), 7.14 d and 7.23 d (4H, C_6H_4, J = 8.7 Hz), 7.72–7.87 m (4H, H_{arom}). Found, %: C 63.56; H 5.13; Br 17.32. $C_{24}H_{23}BrO_4$. Calculated, %: C 63.31; H 5.09; Br 17.55.

Methyl 1-[(3,4-dimethoxyphenyl)(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)methyl]cyclohexanecarboxylate (XIc). Yield 0.68 g (31%), mp 108–109°C. IR spectrum, ν, cm^{-1}: 1740, 1707. ^1H NMR spectrum, δ, ppm: 1.09–2.39 m (10H, CH_2), 3.63 s (2H, C**H**Ar, 2-H), 3.73 s (3H, MeO), 3.76 s (3H, MeO), 3.79 s (3H, MeO); 6.56 d (1H, J = 8.1 Hz), 6.69 d (1H, J = 8.1 Hz), 6.91 s (1H) (C_6H_3); 7.68–7.86 m (4H, H_{arom}). Found, %: C 71.29; H 6.31. $C_{26}H_{28}O_6$. Calculated, %: C 71.54; H 6.47.

Methyl 1-[(3-bromophenyl)(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)methyl]cyclohexanecarboxylate (XId). Yield 1.39 g (61%), mp 166–168°C. IR spectrum, ν, cm^{-1}: 1741, 1710. ^1H NMR spectrum, δ, ppm: 1.07–2.33 m (10H, CH_2), 3.65 d (1H, C**H**Ar, J = 1.8 Hz), 3.66 d (1H, 2-H, J = 1.8 Hz), 3.73 s (3H, MeO); 7.00 t (1H, J = 8.7 Hz), 7.22 d (1H, J = 8.7 Hz), 7.27 d (1H, J = 8.7 Hz), 7.42 s (1H) (C_6H_4); 7.71–7.89 m (4H, H_{arom}). Found, %: C 63.61; H 5.04; Br 17.71. $C_{24}H_{23}BrO_4$. Calculated, %: C 63.31; H 5.09; Br 17.55.

Methyl 1-[(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)(4-methoxyphenyl)methyl]cyclohexanecarboxylate (XIe). Yield 1.32 g (65%), mp 117–118°C. IR spectrum, ν, cm^{-1}: 1739, 1705. ^1H NMR spectrum, δ, ppm: 1.08–2.36 m (10H, CH_2), 3.62 d (1H, C**H**Ar, J = 1.8 Hz), 3.65 d (1H, 2-H, J = 1.8 Hz), 3.66 s (3H, MeO), 3.74 s (3H, MeO), 6.62 d and 7.14 d (2H each, C_6H_4, J = 9.3 Hz), 7.68–7.85 m (4H, H_{arom}). Found, %: C 73.52; H 6.58. $C_{25}H_{26}O_5$. Calculated, %: C 73.87; H 6.45.

Methyl 1-[(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)(4-methylphenyl)methyl]cyclohexanecarboxylate (XIf). Yield 1.31 g (67%), mp 136–137°C. IR spectrum, ν, cm^{-1}: 1740, 1709. ^1H NMR spectrum, δ, ppm: 1.07–2.40 m (10H, CH_2), 2.33 s (3H, Me), 3.57 d (1H, C**H**Ar, J = 2.1 Hz), 3.69 s (3H, MeO), 4.18 d (1H, 2-H, J = 2.1 Hz), 6.91–7.87 m (8H, H_{arom}). Found, %: C 76.71; H 6.84. $C_{25}H_{26}O_4$. Calculated, %: C 76.90; H 6.71.

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REFERENCES

1. Vul'fson, N.S. and Vinograd, L.Kh., *Reaktsii i metody issledovaniya organicheskikh soedinenii. Reaktsiya Reformatskogo* (Reactions and Methods of Investigation of Organic Reactions. Reformatsky Reaction), Moscow: Khimiya, 1967, vol. 17.
2. Kirillov, N.F. and Gavrilov, A.G., *Russ. J. Gen. Chem*., 2008, vol. 78, p. 1422.
3. Kirillov, N.F. and Gavrilov, A.G., *Russ. J. Org. Chem*., 2008, vol. 44, p. 963.
4. Kirillov, N.F., Gavrilov, A.G., Vakhrin, M.I., and Feshin, V.P., *Russ. J. Gen. Chem*., 2011, vol. 81, p. 1195.
5. Kirillov, N.F., Nikiforova, E.A., and Vakhrin, M.I., *Russ. J. Gen. Chem*., 2011, vol. 81, p. 1243.
6. Kirillov, N.F., Gavrilov, A.G., Vasyanin, A.N., Shurov, S.N., Vakhrin, M.I., and Slepukhin, P.A., *Russ. J. Gen. Chem*., 2012, vol. 82, p. 289.
7. Kirillov, N.F., Gavrilov, A.G., and Vakhrin, M.I., *Russ. J. Org. Chem*., 2012, vol. 48, p. 368.
8. Kirillov, N.F., Gavrilov, A.G., Slepukhin, P.A., Vakhrin, M.I., Vasyanin, A.N., and Shurov, S.N., *Russ. J. Org. Chem*., 2012, vol. 48, p. 767.