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Synthesis of Alkyl-1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylates

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Abstract—Alkyl-1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylates were obtained by bromination of dialkyl-2-(2-methylbenzylidene)malonates with *N*-bromosuccinimide followed by the cyclization of dialkyl-2-(2-bromomethylbenzylidene)malonates.

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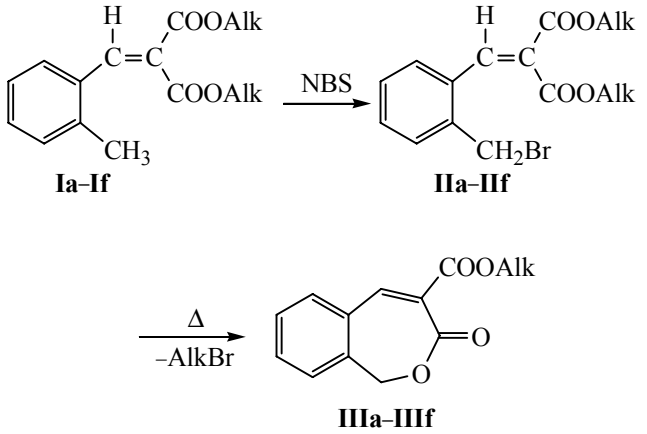
The information on the synthesis of substituted esters of oxepinecarboxylic acids is scanty. For instance, methyl esters of substituted oxepinecarboxylic acids are metabolites of the enzymatic epoxidation of substituted methyl benzoates [1–3], a substituted ethyl 2-oxo-2,5-dihydrobenzo[*b*]oxepine-3-carboxylate is obtained alongside the other products in reaction of diazoacetaldehyde dimethyl acetal with ethyl coumarin-3-carboxylate [4].

We prepared alkyl-1,3-dihydro-3-oxobenzo[*c*]-oxepine-4-carboxylates along the following procedure. The bromination of dimethyl 2-(2-methylbenzylidene)malonate (**Ia**) with *N*-bromosuccinimide (NBS) led to the formation of dimethyl 2-(2-bromomethylbenzylidene)malonate (**IIa**). At heating compound **IIa** for 1 h at 190°C bromomethane liberated, and a cyclization occurred providing methyl 1,3-dihydro-3-oxobenzo-[*c*]oxepine-4-carboxylate (**IIIa**). The other esters **IIIb–IIIf** were obtained without isolation of intermediate products **IIb–IIf** (see the scheme). The temperature of the reaction mixture and heating time were adjusted according the liberation of the corresponding alkyl bromide.

Scheme.



Ia–If **IIa–IIf** **IIIa–IIIf**

Alk = Me (**a**), Et (**b**), Pr (**c**), *i*-Pr (**d**), Bu (**e**), *i*-C_5H_{11} (**f**).

The composition and structure of compounds **IIa, IIIa–IIIf** were confirmed by elemental analyses, IR and ^{1}H NMR spectra. The IR spectra of compounds **IIIa–IIIf** contain characteristic absorption bands of carbonyl groups of ester fragments at 1705–1715 cm^{-1} and lactone fragments in the region 1730–1745 cm^{-1}, and also bands of C=C bonds in the region 1660–1680 cm^{-1}. In the ^{1}H NMR spectra characteristic singlets from vinyl protons =C=CH– and of protons of the methylene groups attached to the benzene ring appear at δ 7.96–8.11 and 4.99–5.07 ppm respectively.

EXPERIMENTAL

IR spectra of compounds **IIa, IIIa–IIIf** were recorded on a spectrophotometer Specord 75IR from mulls in mineral oil. ^{1}H NMR spectra were registered from solutions in $CDCl_3$ on spectrometers Tesla BS-576A (operating frequency 100 MHz) (compounds **IIa, IIIa, IIIb, IIId**) and Mercury Plus-300 (operating frequency 300 MHz) (compounds **IIIc, IIIe, IIIf**), internal reference HMDS (δ 0.05 ppm).

Dialkyl 2-(2-bromomethylbenzylidene)-malonates (IIa–IIf). General procedure. A solution of 0.1 mol of compound **Ia–If**, 0.1 mol of *N*-bromosuccinimide, and 0.1 g of azobisisobutyronitrile in 60 ml of anhydrous tetrachloromethane was boiled in the light till the disappearance of N-bromosuccinimide. On cooling the succinimide was filtered off, washed with CCl_4 (20 ml), the organic layer was washed with H_2O and dried with Na_2SO_4. On evaporating the solvent compound **IIa** was recryatallized from ethanol. Compounds **IIb–IIf** were used for preparation of compounds **IIIb–IIIf** without additional purification.

Dimethyl 2-(2-bromomethylbenzylidene)-malonate (IIa). Yield 26.6 g (85%), mp 80–81°C. IR spectrum, ν, cm^{-1}: 1720 (C=O), 1660 (C=C). ^1H NMR spectrum, δ, ppm: 3.65 s (3H, MeO), 3.82 s (3H, MeO), 4.44 s (2H, CH_2Br), 7.14–7.40 m ($4H_{arom}$), 8.02 s (1H, CH=). Found, %: C 48.38; H 3.94; Br 26.48. $C_{12}H_{12}BrO_4$. Calculated, %: C 48.02; H 4.03; Br 26.62.

Alkyl 1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylates IIIa–IIIf. *General procedure.* Compounds **IIa–IIf** were heated at 190–220°C with simultaneous distilling off the alkyl bromide. The reaction product was distilled in a vacuum (1 mm Hg) and recrystallized from a mixture benzene–hexane, 1 : 1. The yield was calculated with respect to the amount of compound **Ia–If** brought into the reaction.

Methyl 1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylate (IIIa) was obtained from compound **IIa** at 190°C over 1 h. Yield 16.4 g (77%), mp 81– 82°C. IR spectrum, ν, cm^{-1}: 1735, 1715 (C=O), 1680 (C=C). ^1H NMR spectrum, δ, ppm: 3.86 s (3H, MeO), 5.00 s (2H, CH_2Ar), 7.30–7.46 m ($4H_{arom}$), 8.04 s (1H, CH=). Found, %: C 65.91; H 4.73. $C_{12}H_{10}O_4$. Calculated, %: C 66.05; H 4.62.

Ethyl 1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylate (IIIb) was obtained from compound **IIb** at 200°C over 1.5 h. Yield 17.4 g (75%), mp 105– 106°C. IR spectrum, ν, cm^{-1}: 1730, 1715 (C=O), 1660 (C=C). ^1H NMR spectrum, δ, ppm: 1.36 t (3H, CH_3, *J* 7.0 Hz), 4.32 q (2H, OCH_2CH_3, *J* 7.0 Hz), 5.07 s (2H, CH_2Ar), 7.33–7.45 m ($4H_{arom}$), 8.07 s (1H, CH=). Found, %: C 67.01; H 5.34. $C_{13}H_{12}O_4$. Calculated, %: C 67.24; H 5.21.

Propyl 1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylate (IIIc) was obtained from compound **IIc** at 205°C over 2 h. Yield 17.7 g (72%), mp 101– 102°C. IR spectrum, ν, cm^{-1}: 1740, 1705 (C=O), 1665 (C=C). ^1H NMR spectrum, δ, ppm: 1.01 t (3H, CH_3, *J* 7.2 Hz), 1.78 m (2H, $OCH_2CH_2CH_3$, *J* 7.2 Hz), 4.28 t (2H, OCH_2CH_2, *J* 7.2 Hz), 5.07 s (2H, CH_2Ar), 7.44– 7.58 m ($4H_{arom}$), 8.12 s (1H, CH=). Found, %: C 68.12; H 5.56. $C_{14}H_{14}O_4$. Calculated, %: C 68.28; H 5.73.

Isopropyl 1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylate (IIId) was obtained from compound **IId** at 210°C over 2.5 h. Yield 13.3 g (54%), mp 91–92°C. IR spectrum, ν, cm^{-1}: 1745, 1705 (C=O), 1660 (C=C). ^1H NMR spectrum, δ, ppm: 1.34 d [6H, $OCH(CH_3)_2$, *J* 5.6 Hz], 4.99 s (2H, CH_2Ar), 5.09 m [1H, $OCH(CH_3)_2$], 7.33–7.46 m ($4H_{arom}$), 7.96 s (1H, CH=). Found, %: C 68.39; H 5.62. $C_{14}H_{14}O_4$. Calculated, %: C 68.28; H 5.73.

Butyl 1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylate (IIIe) was obtained from compound **IIe** at 215°C over 4 h. Yield 18.0 g (69%), mp 59– 60°C. IR spectrum, ν, cm^{-1}: 1745, 1705 (C=O), 1670 (C=C). ^1H NMR spectrum, δ, ppm: 0.96 t (3H, CH_3, *J* 7.3 Hz), 1.45 m (2H, $CH_2CH_2CH_3$), 1.73 m (2H, $OCH_2CH_2CH_2$), 4.31 t (2H, OCH_2CH_2, *J* 6.8 Hz), 5.06 s (2H, CH_2Ar), 7.44–7.57 m ($4H_{arom}$), 8.11 s (1H, CH=). Found, %: C 69.01; H 6.36. $C_{15}H_{16}O_4$. Calculated, %: C 69.22; H 6.20.

Isopentyl 1,3-dihydro-3-oxobenzo[*c*]oxepine-4-carboxylate (IIIf) was obtained from compound **IIf** at 220°C over 5 h. Yield 12.3 g (45%), mp 57–58°C. IR spectrum, ν, cm^{-1}: 1735, 1705 (C=O), 1665 (C=C). ^1H NMR spectrum, δ, ppm: 0.96 d [6H, $CH(CH_3)_2$, *J* 6.6 Hz], 1.64 q (2H, CH_2CH_2CH, *J* 6.8 Hz), 1.77 m [1H, $CH_2CH(CH_3)_2$], 4.34 t (2H, OCH_2CH_2, *J* 7.0 Hz), 5.06 s (2H, CH_2Ar), 7.44–7.60 m ($4H_{arom}$), 8.10 s (1H, CH=). Found, %: C 69.88; H 6.46. $C_{16}H_{18}O_4$. Calculated, %: C 70.06; H 6.61.

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