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Synthesis of 6-Hetaryl-5,5-dialkyl-3,3-dimethyltetrahydropyran-2,4-diones by Reformatsky Reaction

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Abstract—Zinc enolates derived from ethyl 4-bromo-2,2,4-trimethyl-3-oxopentanoate and 4-bromo-4-ethyl-2,2-dimethyl-3-oxohexanoate react with 2-furan-, 2-thiophene-, 1-(3-nitrophenyl)-2-pyrrole-, 1-acyl-3-indole-, and 2-pyridinecarbaldehydes to give the corresponding 6-hetaryl-5,5-dialkyl-3,3-dimethyltetrahydropyran-2,4-diones.

Compounds possessing a 2,4-dioxotetrahydropyran fragment are components of various natural products, and they exhibit versatile biological activity [1–3]. We previously developed a new approach to the synthesis of 6-alkyl-, 6-alkenyl-, and 6-aryl-substituted tetrahydropyran-2,4-diones via Reformatsky reaction [4]. The goal of the present work was to elucidate the possibility for synthesizing analogous compounds having hetaryl groups in position *6* of the pyran ring. For this purpose, ethyl 4-bromo-2,2,4-trimethyl-3-oxopentanoate (**Ia**) and ethyl 4-bromo-4-ethyl-2,2-dimethyl-3-oxohexanoate (**Ib**) were converted by treatment with metallic zinc into the corresponding zinc enolates **IIa** and **IIb** which were brought into reaction with 2-furan-, 2-thiophene-, 1-(3-nitrophenyl)-2-pyrrole-, 1-acyl-3-indole-, and 2-pyridinecarbaldehydes. Primary intermediate adducts **IIIa**–**IIIi** underwent spontaneous intramolecular cyclization to afford 6-hetaryl-5,5-dialkyl-3,3-dimethyl-2,3,5,6-tetrahydropyran-2,4-diones **IVa**–**IVi** as final products (Scheme 1).

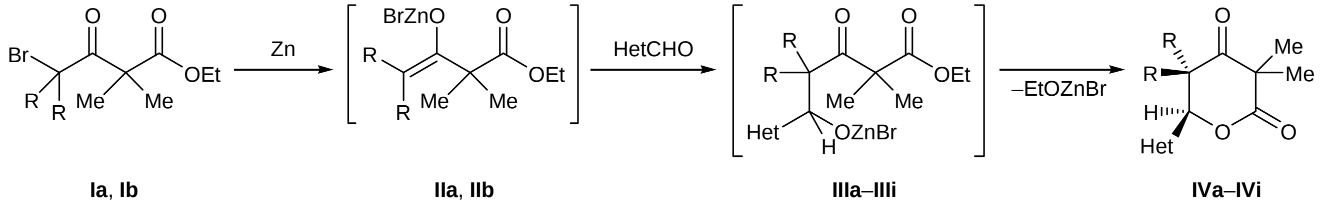
However, in the reaction of zinc enolate **IIa** with 2-pyridinecarbaldehyde, instead of the expected 5,5-diethyl-3,3-dimethyl-6-(2-pyridyl)tetrahydropyran-2,4-dione, we isolated acyclic product, ethyl 5-hydroxy-3-oxo-5-(2-pyridyl)-2,2,4,4-tetramethylpentanoate (**VI**) (Scheme 2). Presumably, cyclization of intermediate **V** is hampered owing to formation of a dative bond between the zinc atom and nitrogen atom in the pyridine ring. The probability for formation of an analogous bond in intermediate **IIIi** having two ethyl groups at C^4 is reduced for steric reasons; as a result, the corresponding tetrahydropyran-2,4-dione **IVi** is obtained.

The structure and purity of the products were confirmed by the data of elemental analysis and IR and ^1H NMR spectroscopy. The IR spectra of **IVa**–**IVi** contain absorption bands in the regions 1710–1720 and 1750–1760 cm^{-1}, which are typical of the ketone and lactone carbonyl groups in pyran-2,4-diones. In the ^1H NMR spectra of these compounds, a signal from the 6-H proton characteristically appeared at δ 5.30–6.06 ppm.

EXPERIMENTAL

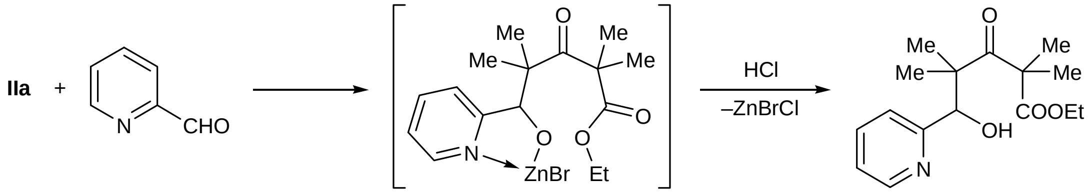
The IR spectra were recorded on a UR-20 spectrophotometer from samples dispersed in mineral oil. The ^1H NMR spectra were obtained from solutions in

Scheme 1.



I, **II**, R = Me (**a**), Et (**b**); **III**, **IV**, R = Me, Het = 2-furyl (**a**), 2-thienyl (**b**), 1-(3-nitrophenyl)-2-pyrrolyl (**d**), 1-acetyl-3-indolyl (**e**), 1-propionyl-3-indolyl (**g**), 1-butyryl-3-indolyl (**h**); R = Et, Het = 2-thienyl (**c**), 1-acetyl-3-indolyl (**f**), 2-pyridyl (**i**).

Scheme 2.



V VI

$CDCl_3$ using an RYa-2310 instrument (60 MHz); the chemical shifts were measured relative to HMDS as internal reference.

6-Hetaryl-5,5-dialkyl-3,3-dimethyltetrahydropyran-2,4-diones IVa–IVi. Ester **Ia** or **Ib**, 0.028 mol, was added dropwise to a suspension of 0.03 mol of zinc (prepared as fine turnings) in a mixture of 5 ml of diethyl ether and 5 ml of ethyl acetate. The mixture was heated to initiate the reaction and (after the entire amount of the bromo derivative was added) was heated for 0.5 h at the boiling point. Appropriate heterocyclic aldehyde, 0.018 mol, was then added, and the mixture was heated for 0.5 h at the boiling point, 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.

6-(2-Furyl)-3,3,5,5-tetramethyltetrahydropyran-2,4-dione (IVa). Yield 67%, mp 74–76°C. ^1H NMR spectrum, δ, ppm: 1.06 s and 1.13 s (3H each, 5-Me), 1.43 s (6H, 3-Me), 5.30 s (1H, 6-H), 6.40 m and 7.30 d (3H, 2-furyl). Found, %: C 65.90; H 6.75. $C_{13}H_{16}O_4$. Calculated, %: C 66.09; H 6.83.

3,3,5,5-Tetramethyl-6-(2-thienyl)tetrahydropyran-2,4-dione (IVb). Yield 72%, mp 127–129°C. ^1H NMR spectrum, δ, ppm: 1.03 s and 1.06 s (3H each, 5-Me), 1.40 s (6H, 3-Me), 5.63 s (1H, 6-H), 6.90–7.35 m (3H, 2-thienyl). Found, %: C 61.76; H 6.30; S 12.53. $C_{13}H_{16}O_3S$. Calculated, %: C 61.88; H 6.39; S 12.71.

5,5-Diethyl-3,3-dimethyl-6-(2-thienyl)tetrahydropyran-2,4-dione (IVc). Yield 86%, mp 64–66°C. ^1H NMR spectrum, δ, ppm: 0.70 t and 0.80 t (3H each, CH_2**Me**), 1.20–2.00 m (4H, C**H**$_2$Me), 1.43 s (6H, 3-Me), 6.06 s (1H, 6-H), 6.85–7.40 m (3H, 2-thienyl). Found, %: C 64.17; H 7.06; S 11.20. $C_{15}H_{20}O_3S$. Calculated, %: C 64.26; H 7.19; S 11.44.

3,3,5,5-Tetramethyl-6-[1-(3-nitrophenyl)-2-pyrrolyl]tetrahydropyran-2,4-dione (IVd). Yield 51%, mp 142–144°C. ^1H NMR spectrum, δ, ppm: 1.02 s and 1.14 s (3H each, 5-Me), 1.30 s and 1.33 s (3H each, 3-Me), 5.17 s (1H, 6-H), 6.38 m and 6.90 m (3H, 2-pyrrolyl), 7.80 m and 8.23 m (4H, C_6H_4). Found, %: C 64.15; H 5.60; N 7.99. $C_{19}H_{20}N_2O_5$. Calculated, %: C 64.04; H 5.66; N 7.86.

6-(1-Acetyl-3-indolyl)-3,3,5,5-tetramethyltetrahydropyran-2,4-dione (IVe). Yield 70%, mp 156–158°C. ^1H NMR spectrum, δ, ppm: 1.05 s (6H, 5-Me), 1.40 s and 1.46 s (3H each, 3-Me), 2.58 s (3H, COMe), 5.70 s (1H, 6-H), 7.10–7.50 m and 8.43 d (5H, 3-indolyl). Found, %: C 69.60; H 6.35; N 4.14. $C_{19}H_{21}NO_4$. Calculated, %: C 69.71; H 6.47; N 4.28.

6-(1-Acetyl-3-indolyl)-5,5-diethyl-3,3-dimethyltetrahydropyran-2,4-dione (IVf). Yield 76%, mp 130–132°C. ^1H NMR spectrum, δ, ppm: 0.70 t and 0.80 t (3H each, CH_2**Me**), 1.20–2.00 m (4H, C**H**$_2$Me), 1.40 s and 1.50 s (3H each, 3-Me), 6.00 s (1H, 6-H), 7.10–7.60 m and 8.40 d (5H, 3-indolyl). Found, %: C 70.88; H 7.01; N 4.06. $C_{21}H_{25}NO_4$. Calculated, %: C 70.97; H 7.09; N 3.94.

3,3,5,5-Tetramethyl-6-(1-propionyl-3-indolyl)tetrahydropyran-2,4-dione (IVg). Yield 60%, mp 162–163°C. ^1H NMR spectrum, δ, ppm: 1.03 s (6H, 5-Me), 1.28 t (3H, **Me**CH_2CO), 1.40 s and 1.46 s (3H each, 3-Me), 2.97 q (2H, MeC**H**$_2$CO), 5.71 s (1H, 6-H), 7.10–7.52 m and 8.40 d (5H, 3-indolyl). Found, %: C 70.22; H 6.72; N 4.17. $C_{20}H_{23}NO_4$. Calculated, %: C 70.36; H 6.79; N 4.10.

6-(1-Butyryl-3-indolyl)-3,3,5,5-tetramethyltetrahydropyran-2,4-dione (IVh). Yield 65%, mp 164–166°C. ^1H NMR spectrum, δ, ppm: 1.01 t (3H, **Me**CH_2CH_2CO), 1.04 s (6H, 5-Me), 1.39 s and 1.45 s (3H each, 3-Me), 1.73 m (2H, MeC**H**$_2CH_2CO$), 2.86 t (2H, $MeCH_2C$**H**$_2$CO), 5.73 s (1H, 6-H), 7.10–7.51 m and 8.42 d (5H, 3-indolyl). Found, %: C 70.85; H 7.00; N 4.09. $C_{21}H_{25}NO_4$. Calculated, %: C 70.97; H 7.09; N 3.94.

5,5-Diethyl-3,3-dimethyl-6-(2-pyridyl)tetrahydropyran-2,4-dione (IVi). Yield 60%, mp 58–59°C. ^1H NMR spectrum, δ, ppm: 0.70 t and 0.83 t (3H each, **Me**CH_2), 1.30–2.00 m (4H, C**H**$_2$Me), 1.43 s and

1.60 s (3H each, 3-Me), 5.50 s (1H, 6-H), 7.10–7.90 m and 8.53 d (4H, 2-pyridyl). Found, %: C 69.65; H 7.64; N 5.26. $C_{16}H_{21}NO_3$. Calculated, %: C 69.78; H 7.69; N 5.09.

Ethyl 5-hydroxy-2,2,4,4-tetramethyl-3-oxo-5-(2-pyridyl)pentanoate (VI) was synthesized as described above for compounds **IVa**–**IVi**. Yield 49%, mp 74–76°C. IR spectrum, ν, cm^{-1}: 1690, 1740 (C=O); 3400 (OH). ^1H NMR spectrum, δ, ppm: 1.03 s, ~1.12 s, 1.15 s, and 1.30 s (3H each, 2-Me, 4-Me), 1.10 t (3H, **Me**CH_2O), 4.02 q (2H, OCH_2), 4.40 br.s (1H, OH), 5.02 s (1H, 5-H), 7.00–7.80 m and 8.40 d (4H, 2-pyridyl). Found, %: C 65.40; H 7.81; N 4.68. $C_{16}H_{23}NO_4$. Calculated, %: C 65.51; H 7.90; N 4.77.

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