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Reactions of 1,4-Dianion of Methyl 2-Thienyl Ketone *N*-Ethoxycarbonylhydrazone with Derivatives of Carboxylic Acids, and the Synthesis of Pyrazolotriazin-7-ones

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Abstract—1,3,5-trisubstituted pyrazoles were obtained by reaction of carboxylic acids derivatives with 1,4-dianion of methyl 2-thienyl ketone *N*-ethoxycarbonylhydrazone. The dianion was prepared by treating the hydrazone with butyllithium in THF at –78°C. Besides were prepared 4-methyl (or 4-phenyl)-2-(2-thienyl)-6H-pyrazolo[1,5-d][1,2,4]triazin-7-ones from the corresponding 1,3,5-trisubstituted pyrazoles synthesized respectively with the use of ethyl pyruvate and ethyl phenylglyoxylate.

Pyrazoles and pyrasolotriazines are important objects of studies in the fields of medicine, agriculture etc. [1–4]. The pyrazole derivatives are known to exhibit versatile biological activity, e.g., bactericidal, pesticidal, anticonvulsant, tuberculostatic, antiphlogistic etc. Recently several new methods of pyrazole derivatives preparation were described in the literature [5–7]. However the synthesis of 3-heteryl-substituted pyrazoles has escaped the attention of researchers. Therefore the aim of this study was a synthesis of some 5-substituted 3-(2-thienyl)pyrazoles by reaction of butyl formate, methyl benzoate, ethyl benzoylacetete, methyl 3-chlorobenzoate, ethyl hexanoate, ethyl pyruvate, ethyl phenylglyoxylate, acetyl chloride, and phenoxyacetyl chloride with 1,4-dianion of methyl 2-thienyl ketone *N*-ethoxycarbonylhydrazone. Note that 1,4-dianions of N-monosubstituted hydrazones [8] attract much attention as synthetic intermediates because of their reactivity and preparative value.

The typical reaction was carried out as follows. A freshly prepared in ethanol hydrazone from methyl 2-thienyl ketone and *N*-ethoxycarbonylhydrazine [9] was dissolved in tetrahydrofuran and treated in argon atmosphere with 2 equiv of butyllithium. To the red-brown solution of lithium salt **II** obtained was added at –78°C 1 equiv of esters or acyl chlorides with subsequent acid cyclization of the reaction products by treating with 3 N hydrochloric acid. The compounds obtained were isolated by chromatography. The optimal yields of products were obtained at the ratio hydrazone:base:ester (or acyl chloride) equal to 1:2:1 in agreement with the mechanism presumed. The succession of reactions presented on the Scheme rationalizes the results obtained. Compounds **IIIf, g** were treated with phenylhydrazine in boiling methanol. The conversion of intermediate hydrazones into the corresponding 4-methyl(or 4-phenyl)-2-(2-thienyl)-6*H*-pyrazolo[1,5-d][1,2,4]triazin-7-ones (**IVa, b**) was effected by potassium hydroxide in boiling methanol [10].

In the IR spectra of compounds obtained the characteristic absorption band of vibrations of ester C=O group linked to nitrogen is observed at 1670–1690 cm^{-1}. The signals from methyl and methylene protons of the ester ethyl group appear in the ^1H NMR spectra as a triplet at 1.44–1.49 ppm and a quartet at 4.50–4.57 ppm respectively. In the spectra of compounds **IIIf, h** the methyl signals are present as singlets at 2.25 and 2.43 ppm. Besides the methylene groups of the substituents (phenacyl and phenoxymethyl) attached to the *5* position of the pyrazole ring give singlets at 4.52 ppm (compound **IIIc**) and 5.35 ppm (compound **IIIi**). In the spectrum of compound **IIIe** the multiplet from the proton of the hexyl substituent is observed at 1.07–1.36 ppm. The spectra of compounds **IVa, b** also are consistent with the assumed structure [11]. In the ^{13}C NMR spectra of the newly obtained compounds the signals of C=O group are present at 139.53–150.00 ppm. On the other hand, the signal from C=O group of phenacyl in compound **IIIc** appeared at 201.60 ppm, that of acetyl in compound **IIIf** at 191.12 ppm, and phenacyl in compound **IIIg** at 183.49 ppm. The structure of these compounds was also confirmed by mass spectra.

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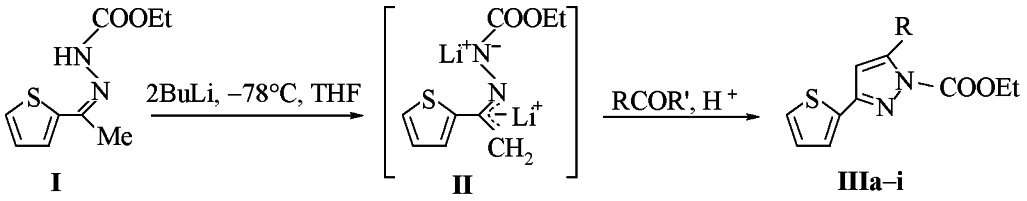
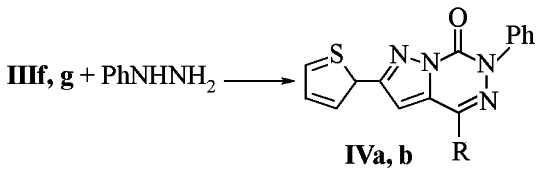
Scheme.





III$(24), R = H (**a**), Ph (**b**), $PhCOCH_2$ (**c**), 3-ClC_6H_4 (**d**), C_6H_{13} (**e**), Ac (**f**), PhCO (**g**), Me (**h**), $PhOCH_2$ (**i**); **IV**, R = Me (**a**), Ph (**b**); R' = OBu, OMe, OEt, Cl.

EXPERIMENTAL

Melting points were determined in open capillaries on melting-point apparatus Electrothermal IA 9100 and are reported without correction. IR spectra were obtained on spectrometer Philips PU 9714 from KBr pellets if not indicated otherwise. NMR spectra were registered on spectrometers Nicolet (300 MHz) (compounds **IIIa, e–h, IVa, b**) and Varian (200 MHz) in $CDCl_3$ with TMS as internal reference. Mass spectra of the newly prepared compounds were measured on Shimadzu GC/MS QP 2000A at ionizing electrons energy 70 eV. Column chromatography was performed on silica gel 60 (70–230 mesh) of E.Merk AG. Thin-layer chromatography was carried out on silica gel plates Merk 5554 and Watmann 4410222 with fluorescent indicators.

5-Substituted ethyl 3-(2-thienyl)pyrazole-1-carboxylates IIIa–i. General procedure. To a solution of 2.42 mmol of compound **I** in THF at –78°C was added 5.32 mmol of butyllithium in hexane, and the mixture was stirred under argon atmosphere. To the arising brown-red solution was added dropwise a solution of 2.18 mmol of an ester or acyl chloride in THF. On complete decoloration of the solution (compound **II**) the mixture was additionally stirred at –78°C for 2 h, then the solvent was evaporated in a vacuum. The residue was treated with concn HCl, acetic acid, water, and methanol (10 ml each). The mixture was stirred for 2 h at room temperature. On evaporating methanol the residue was extracted with ether, and the extract was subjected to column chromatography on silica gel, eluent toluene. On evaporating the solvent pure compound **III** was obtained.

Ethyl 3-(2-thienyl)pyrrole-1-carboxylate (IIIa) was obtained from butyl formate. Yield 78%. mp 129°C. IR spectrum, ν, cm^{-1}: 1670. ^1H NMR spectrum (300 MHz), δ, ppm: 1.45–1.49 t (3H, CH_3), 4.50–4.56 q (2H, OCH_2), 6.62–8.14 m (9H, H arom). ^{13}C NMR spectrum, δ, ppm: 14.88 (CH_3), 65.31 (CH_2), 149.97 (NC=O), 107.54–151.88 (C arom). Mass spectrum, *m/z*: 222.26 $[M]_0$ ($C_{10}H_{10}N_2O_2S$).

Ethyl 3-(2-thienyl)-5-phenylpyrazole-1-carboxylate (IIIb) was obtained from methyl benzoate. Yield 92%. mp 114°C. IR spectrum, ν, cm^{-1}: 1680. ^1H NMR spectrum (200 MHz), δ, ppm: 1.44–1.48 t (3H, CH_3), 4.51–4.55 q (2H, CH_2), 6.52–7.65 m (9H, H arom). ^{13}C NMR spectrum, δ, ppm: 13.90 (CH_3), 62.80 (CH_2), 141.31 (NC=O), 105.37–158.97 (C arom). Mass spectrum, *m/z*: 298.35 $[M]_0$ ($C_{16}H_{14}N_2O_2S$).

Ethyl 3-(2-thienyl)-5-phenacylpyrazole-1-carboxylate (IIIc) was obtained from ethyl 3-oxo-3-phenylpropionate. Yield 53%. mp 136°C. IR spectrum, ν, cm^{-1}: 1690, 1750. ^1H NMR spectrum (200 MHz), δ, ppm: 1.45–1.46 t (3H, CH_3), 4.52 s (2H, C^5CH_2), 4.50–4.54 q (2H, OCH_2), 7.05–7.72 m (9H, H arom). ^{13}C NMR spectrum, δ, ppm: 13.90 (CH_3), 38.41 (CH_2), 62.80 (OCH_2), 139.53 (NC=O), 18.17–155.38 (C arom), 201.60 (C=O). Mass spectrum, *m/z*: 240.39 $[M]_0$ ($C_{18}H_{16}N_2O_3S$).

Ethyl 3-(2-thienyl)-5-(3-chlorophenyl)pyrazole-1-carboxylate (IIId) was obtained from methyl

m-chlorobenzoate. Yield 58%. mp 108°C. IR spectrum, ν, cm^{-1}: 1680. ^1H NMR spectrum (200 MHz), δ, ppm: 1.46–1.48 t (3H, CH_3), 4.53–4.57 q (2H, CH_2), 6.86–7.88 m (8H, H arom). ^{13}C NMR spectrum, δ, ppm: 13.90 (CH_3), 62.81 (CH_2), 141.31 (NC=O), 105.37– 158.97 (C arom). Mass spectrum, *m/z*: 332.80 $[M]_0$ ($C_{16}H_{13}ClN_2O_2S$).

Ethyl 5-hexyl-3-(2-thienyl)pyrazole-1-carboxylate (IIIe) was obtained from ethyl heptanoate. Yield 72%. mp 138°C. IR spectrum, ν, cm^{-1}: 1670. ^1H NMR spectrum (300 MHz), δ, ppm: 1.07–1.36 m (9H, $CH_2CH_2CH_2CH_3$), 1.44– 1.48 t (3H, $OCH_2\underline{CH_3}$), 1.67–1.73 m (2H, CH_2), 2.95–2.97 t (2H, C^5CH_2), 4.51–4.57 q (2H, OCH_2), 6.38–7.72 m (4H, H arom). ^{13}C NMR spectrum, δ, ppm: 13.89 (CH_3), 14.01 (CH_3), 27.37–31.46 (CH_2), 62.80 (OCH_2), 141.51 (NC=O), 109.33–160.40 (C arom). Mass spectrum ©…"qt®, *m/z*: 306.42 $[M]_0$ ($C_{16}H_{22}N_2O_2S$).

Ethyl 5-acetyl-3-(2-thienyl)pyrazole-1-carboxylate (IIIf) was obtained from ethyl pyruvate. Yield 44%. mp 98°C. IR spectrum, ν, cm^{-1}: 1670, 1720. ^1H NMR spectrum (300 MHz), δ, ppm: 1.43–1.45 t (3H, $OCH_2\underline{CH_3}$), 2.25 s (3H, CH_3), 4.53–4.59 q (2H, OCH_2), 7.22–7.55 (4H, H arom). ^{13}C NMR spectrum, δ, ppm: 12.75 (CH_3), 63.43 (OCH_2), 143.16 (NC=O), 112.55– 156.31 (C arom), 191.12 (C=O). Mass spectrum, *m/z*: 264.30 $[M]_0$ ($C_{12}H_{12}N_2O_3S$).

Ethyl 5-benzoyl-3-(2-thienyl)pyrazole-1-carboxylate (IIIg) was obtained from ethyl 2-oxo-2-phenylacetate. Yield 56%. mp 107°C. IR spectrum, ν, cm^{-1}: 1690, 1710. ^1H NMR spectrum (300 MHz), δ, ppm: 1.42–1.48 t (3H, CH_3), 4.51–4.54 q (2H, CH_2), 7 .04–8.27 m (9H, H arom). ^{13}C NMR spectrum, δ, ppm: 13.93 (CH_3), 62.8 (CH_2), 140.71 (NC=O), 110.30–157.41 (C arom). Mass spectrum, *m/z*: 325.36 $[M]$ ($C_{17}H_{13}N_2O_3S$).

Ethyl 5-methyl-3-(2-thienyl)pyrazole-1-carboxylate (IIIh) was obtained from acetyl chloride. Yield 23%. mp 126°C. IR spectrum, ν, cm^{-1}: 1690. ^1H NMR spectrum (300 MHz), δ, ppm: 1.43–1.46 t (3H, $OCH_2\underline{CH_3}$), 2.43 s (3H, CH_3), 4.51–4.57 q (2H, CH_2), 6.49–7.72 m (4H, H arom). ^{13}C NMR spectrum, δ, ppm: 13.04 (CH_3), 13.90 (CH_3), 62.80 (CH_2), 141.67 (NC=O), 105.69–159.58 (C arom). Mass spectrum, *m/z*: 236.29 $[M]_0$ ($C_{11}H_{12}N_2O_2S$).

Ethyl 3-(2-thienyl)-5-phenoxymethylpyrazole-1-carboxylate (IIIi) was obtained from phenoxyacetyl chloride. Yield 43%. mp 139°C. IR spectrum, ν, cm^{-1}: 1685. ^1H NMR spectrum (200 MHz), δ, ppm: 1.44–1.48 t (3H, CH_3), 4.51–4.57 q (2H, $O\underline{CH_2}CH_3$), 5.35 s (2H, CH_2), 6.72–7.72 m (9H, H arom). ^{13}C NMR spectrum, δ, ppm: 14.25 (CH_3), 62.95 (CH_2), 64.80 (CH_2), 139.30 (NC= O), 104.07–160.50 (C arom). Mass spectrum, *m/z*: 328.39 $[M]_0$ ($C_{17}H_{16}N_2O_3S$).

4-Substituted 2-(2-thienyl)-6-phenylpyrazolo-[1,5-*d*]-[1,2,4]triazin-7(6H)-ones (IVa, b). General procedure. To a solution of 1 mmol of compound **IIIf** or **IIIg** in 10 ml of methanol was added at stirring a solution of 1 mmol of phenylhydrazine in 10 ml of methanol, and the mixture was stirred for 4 h at room temperature. The solvent was evaporated in a vacuum, and the residue was purified by column chromatography (eluent cyclohexane–ethyl acetate, 2 : 1).

4-Methyl-2-(2-thienyl)-6-phenylpyrazolo[1,5-*d*]-[1,2,4]triazin-7(6H)-one (IVa). mp 162°C. IR spectrum, ν, cm^{-1}: 1685. ^1H NMR spectrum (300 MHz), δ, ppm: 2.48 s (3H, CH_3), 6.36–8.92 m (9H, H arom). ^{13}C NMR spectrum, δ, ppm: 12.77 (CH_3), 105.42–158.25 (C arom). Mass spectrum, *m/z*: 308.36 $[M]_0$ ($C_{16}H_{12}N_4OS$).

2-(2-Thienyl)-4,6-diphenylpyrazolo[1,5-d][1,2,4]-triazin-7(6H)-one (IVb). mp 132°C. IR spectrum, ν, cm^{-1}: 1678. ^1H NMR spectrum (300 MHz), δ, ppm: 6.43–8.87 m (14H, H arom). ^{13}C NMR spectrum, δ, ppm: 109.42– 156.13 (C arom). Mass spectrum, *m/z*: 370.42 $[M]_0$ ($C_{21}H_{14}N_4OS$).

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