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SHORT COMMUNICATIONS

Synthesis of New Pyrazole and Triazole Derivatives Containing a Saturated γ-Lactone Ring

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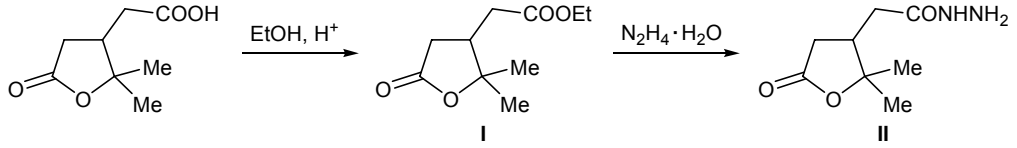
Pyrazole ring is a structural fragment of molecules of many medicines, including such common drugs as phenazone and aminophenazone [1]. Some pyrazoles, e.g., tartrazine (yellow dye), are also used in food industry [2]. Triazole derivatives also exhibit a broad spectrum of biological activity [3]. Therefore, synthesis of compounds whose molecules contain both γ-lactone and pyrazole or triazole rings attracts some interest, for such compounds are expected to possess important properties.

5,5-Dimethyl-2-oxotetrahydrofuran-4-ylacetohydrazide (**II**) was selected as starting compound; it was synthesized from the corresponding acid [4] through ester **I** according to Scheme 1. Pyrazole derivatives were prepared using acetylacetone and ethyl acetoacetate as 1,3-dicarbonyl compounds. Presumably, the reaction of hydrazide **II** with acetylacetone involved intermediate formation of the corresponding hydrazone which underwent intramolecular cyclization to substituted pyrazole **III** (Scheme 2). Pyrazolone **IV** was synthesized by reaction of hydrazide **II** with ethyl acetoacetate (Scheme 3).

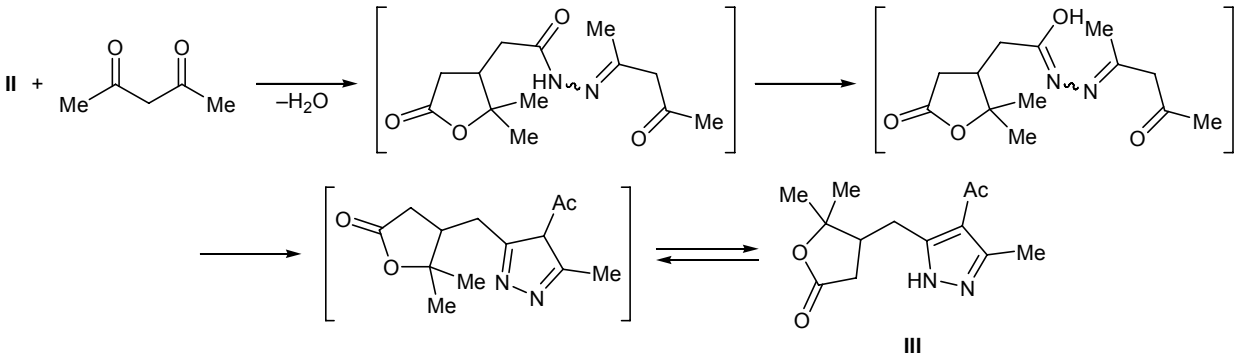
It is known that intermediate products formed by cyanoacetylation of hydrazines with ethyl cyanoacetate and its α-alkyl and α,α-dialkyl derivatives undergo isomerization into aminopyrazolones on heating or in the presence of base catalyst [5]. The product isolated in the reaction of hydrazide **II** with ethyl cyanoacetate was identified as aminopyrazolone **V** (Scheme 4) on the basis of the IR and ^{1}H NMR data.

Taking into account published data on reactions of carboxylic acid hydrazides with triethyl orthoformate [6], an attempt was made to perform an analogous reaction with hydrazide **II**. The reaction smoothly af-

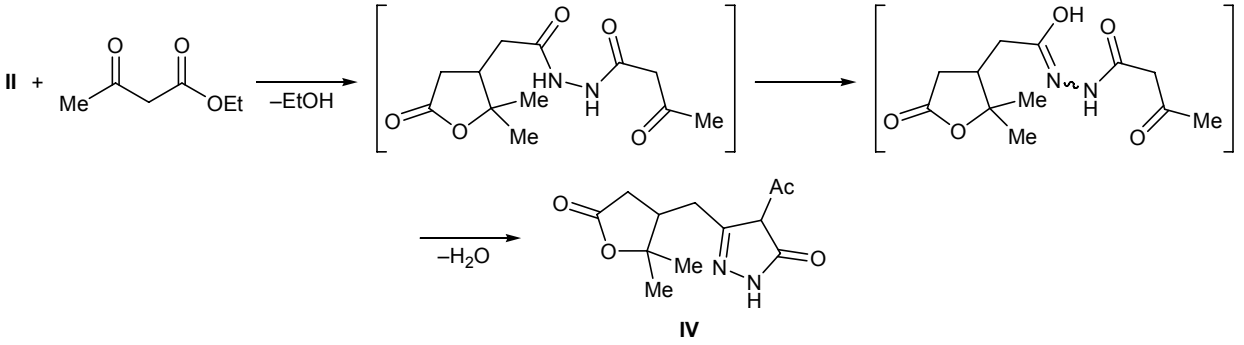
Scheme 1.



Scheme 2.

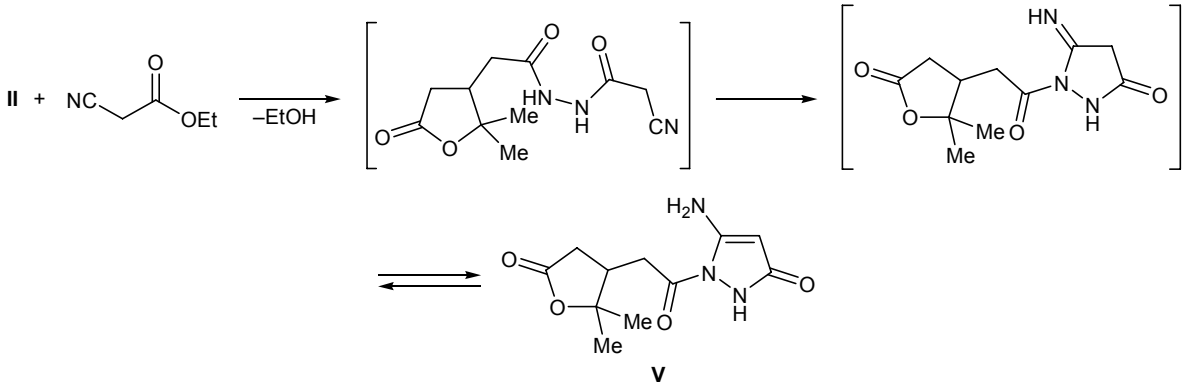


Scheme 3.



IV

Scheme 4.

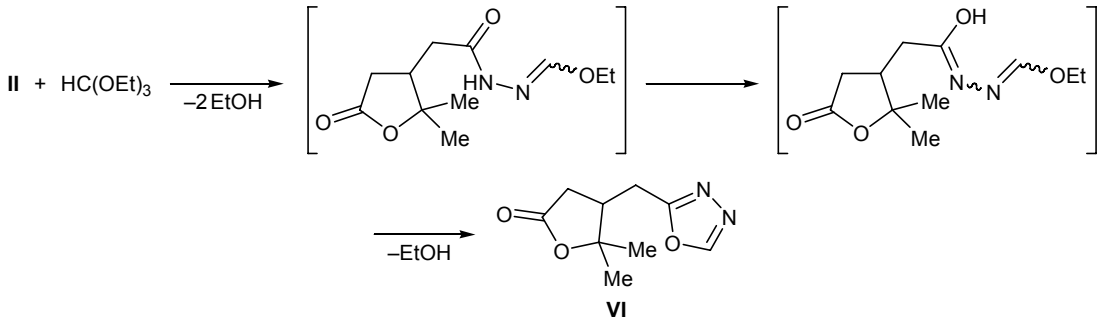


V

forded oxadiazole **VI** in a high yield (92%; Scheme 5). With a view to synthesize triazole derivatives containing a γ-lactone ring, hydrazide **II** was brought into reaction with carboxylic acid amides at 180–200°C under solvent-free conditions according to the procedure described in [7, 8]. 1,2,4-Triazoles **VIIa**–**VIIc** were thus obtained (Scheme 6).

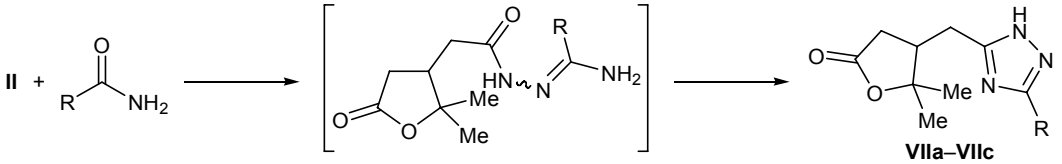
Ethyl 2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)acetate (I). A mixture of 40 g (0.22 mol) of 5,5-dimethyltetrahydro-2-oxofuran-4-ylacetic acid,

Scheme 5.



VI

Scheme 6.



VIIa–VIIc

R = H (**a**), Me (**b**), Ph (**c**).

80 ml of ethanol, and 2.6 ml of concentrated sulfuric acid was heated for 6 h under reflux (on a water bath). Ethanol was distilled off, 50 ml of water was added to the residue, and the mixture was extracted with diethyl ether. The extract was dried over magnesium sulfate and evaporated, and the residue was distilled under reduced pressure. Yield 33 g (75%), bp 145°C (3 mm), mp 39–40°C, R_f 0.90 (acetone–hexane, 5:1). IR spectrum: ν 1770 cm^{-1} (C=O, ester). ^{1}H NMR spectrum, δ, ppm: 1.00–1.40 m (9H, CH_3, $CH_2C\mathbf{H}_3$), 2.00–2.80 m (5H), 4.10 q (2H, OCH_2). Found, %: C 60.25; H 7.80. $C_{10}H_{15}O_4$. Calculated, %: C 60.30; H 7.54.

2-(2,2-Dimethyl-5-oxotetrahydrofuran-3-yl)-acetohydrazide (II). A solution of 10 g (0.05 mol) of ester **I** in 15 ml of ethanol was heated to the boiling point, 2.95 g (0.05 mol) of 85% hydrazine hydrate in 5 ml of ethanol was slowly added dropwise, and the mixture was heated for 2 h more under reflux. After cooling, the precipitate was filtered off and recrystallized. Yield 9 g (96%), mp 130–131°C (from ethanol), R_f 0.85 (acetone–hexane, 5:1). IR spectrum, ν, cm^{-1}: 3360, 3220 (NH); 1770 (C=O, lactone); 1680 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.27 s and 1.42 s (3H each, CH_3), 1.90 d (2H, CH_2, J = 4.5 Hz), 1.95 d (2H, CH_2, J = 4.5 Hz), 2.50 m (1H), 2.65 br.s (3H). Found, %: C 51.50; H 7.40; N 14.78. $C_8H_{13}N_3O_3$. Calculated, %: C 51.90; H 7.03; N 15.14.

4-(4-Acetyl-3-methyl-1*H*-pyrazol-5-ylmethyl)-5,5-dimethyltetrahydrofuran-2-one (III). A mixture of 0.93 g (5 mmol) of hydrazide **II** and 1.5 g (15 mmol) of acetylacetone was heated for 10 h at 100°C. After cooling, the precipitate was filtered off and recrystallized. Yield 0.9 g (75%), mp 108°C (from ethanol), R_f 0.76 (acetone–benzene, 3:1). IR spectrum, ν, cm^{-1}: 3200 (NH), 1775 (C=O, lactone), 1730 (C=O, ketone), 1600 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.60 s and 1.70 s (3H each, 5-CH_3), 2.50 s (3H, NCH_3), 2.90 s (3H, Ac), 3.00–3.60 m (5H, 3-H, 4-H, 4-CH_2), 6.20 s (1H, NH). Found, %: C 62.67; H 7.43; N 11.70. $C_{13}H_{18}N_2O_3$. Calculated, %: C 62.40; H 7.20; N 11.20.

4-Acetyl-3-(2,2-dimethyl-5-oxotetrahydrofuran-3-ylmethyl)-4,5-dihydro-1*H*-pyrazol-5-one (IV). A mixture of 0.5 g (2.6 mmol) of hydrazide **II** and 0.4 g (3 mmol) of ethyl acetoacetate was heated for 6 h at 120–130°C. After cooling, the precipitate was filtered off and recrystallized. Yield 0.45 g (75%), mp 110°C (from ethanol), R_f 0.63 (acetone–benzene, 3:1). IR spectrum, ν, cm^{-1}: 3240 (NH), 1770 (C=O, lactone), 1710 (C=O, ketone), 1620 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.30 s and 1.50 s (3H each, 2′-CH_3), 2.10 s (1H, 4-H), 2.40 s (3H, Ac), 2.45–2.80 m (5H, 3′-H, 4′-H, 3′-CH_2), 5.80–5.95 br.s (1H, NH). Found, %: C 57.15; H 6.95; N 11.35. $C_{12}H_{17}N_2O_4$. Calculated, %: C 56.92; H 6.72; N 11.11.

5-Amino-1-[2-(2,2-dimethyl-5-oxotetrahydrofuran-3-yl)-2-oxoethyl]-2,5-dihydro-1*H*-pyrazol-3-one (V). A mixture of 1 g (5.3 mmol) of hydrazide **II** and 0.6 g (5.3 mmol) of ethyl cyanoacetate was heated for 10 h at 120–130°C. After cooling, the precipitate was filtered off and recrystallized. Yield 0.47 g (35%), mp 154°C (from ethanol), R_f 0.46 (acetone–benzene, 3:1). IR spectrum, ν, cm^{-1}: 3340, 3280 (NH, NH_2); 1775 (C=O, lactone); 1660 (C=O, amide); 1640 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.25 s and 1.40 s (3H each, 2′-CH_3), 2.10–2.65 m (5H, 3′-H, 4′-H, 3′-CH_2), 4.10–4.50 br.s (1H, 4-H). Found, %: C 52.36; H 6.00; N 17.03. $C_{11}H_{15}N_3O_4$. Calculated, %: C 52.17; H 5.93; N 16.60.

5,5-Dimethyl-4-(1,3,4-oxadiazol-2-ylmethyl)-tetrahydrofuran-2-one (VI). A mixture of 0.93 g (5 mmol) of hydrazide **II** and 2.25 g (0.02 mol) of triethyl orthoformate was heated for 6 h on a boiling water bath. After cooling, the precipitate was filtered off and recrystallized. Yield 0.9 g (92%), mp 128°C (from ethanol), R_f 0.60 (acetone–benzene, 3:1). IR spectrum, ν, cm^{-1}: 1770 (C=O, lactone); 1650, 1630 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.30 s and 1.50 s (3H each, 5-CH_3), 2.50–2.75 m (5H, 3-H, 4-H, 4-CH_2), 4.10 br.s (1H, 5′-H). Found, %: C 55,29; H 6,37; N 14.70. $C_9H_{12}N_2O_3$. Calculated, %: C 55.10; H 6.12; N 14.28.

Substituted 1,2,4-triazoles VIIa–VIIc (*general procedure*). A mixture of 1 g (5.3 mmol) of hydrazide **II** and 5.3 mmol of formamide, acetamide, or benzamide was heated for 4–5 h at 180–200°C. The crystalline material was purified by recrystallization.

5,5-Dimethyl-4-(1*H*-1,2,4-triazol-5-ylmethyl)-tetrahydrofuran-2-one (VIIa). Yield 0.6 g (63%), mp 130°C (from ethanol), R_f 0.50 (acetone–benzene, 3:1). IR spectrum, ν, cm^{-1}: 3240 (NH), 1775 (C=O, lactone), 1615 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.15 s and 1.25 s (3H each, 5-CH_3), 2.10–2.60 m (5H, 3-H, 4-H, 4-CH_2), 3.60 s (1H, 3′-H). Found, %: C 55.58; H 6.60; N 21.30. $C_9H_{13}N_3O_2$. Calculated, %: C 55.38; H 6.67; N 21.54.

5,5-Dimethyl-4-(3-methyl-1*H*-1,2,4-triazol-5-ylmethyl)tetrahydrofuran-2-one (VIIb). Yield 0.8 g

(72%), mp 160°C (from ethanol), R_f 0.25 (acetone–benzene, 3:1). IR spectrum, ν, cm^{-1}: 3230 (NH), 1770 (C=O, lactone), 1610 (C=N). ^1H NMR spectrum, δ, ppm: 1.30 s and 1.50 s (3H each, 5-CH_3), 2.00 s (3H, 3′-CH_3), 2.30–2.75 m (5H, 3-H, 4-H, 4-CH_2). Found, %: C 58.00; H 7.35; N 21.00. $C_{10}H_{15}N_3O_2$. Calculated, %: C 57.42; H 7.18; N 20.09.

5,5-Dimethyl-4-(3-phenyl-1*H*-1,2,4-triazol-5-ylmethyl)tetrahydrofuran-2-one (VIIc). Yield 0.9 g (65%), mp 204°C (from ethanol), R_f 0.66 (acetone–benzene, 3:1). IR spectrum, ν, cm^{-1}: 3200, 3070 (C–H_{arom}); 1770 (C=O, lactone); 1615 (C=N); 1590 (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 1.20 s and 1.25 s (3H each, 5-CH_3), 2.25–2.60 m (5H, 3-H, 4-H, 4-CH_2), 7.55 m (C_6H_5). Found, %: C 66.15; H 6.08; N 15.76. $C_{15}H_{17}N_3O_2$. Calculated, %: C 66.42; H 6.27; N 15.50.

The IR spectra were measured on a Specord 75IR spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were recorded on a Varian Mercury 300 spectrometer (300 MHz) using tetramethylsilane as internal reference. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor and by UV irradiation.

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