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SHORT COMMUNICATIONS

Synthesis of Thieno[2,3-*e*][1,4]diazepine Derivatives

N. T. Pokhodylo, O. Ya. Shiika, and M. D. Obushak

Ivan Franko Lviv National University, ul. Kirilla i Mefodiya 6, Lviv, 79005 Ukraine
e-mail: obushak@in.lviv.ua

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Strong interest of researchers in 1,4-diazepine derivatives is determined by broad spectrum of their biological activity [1–3]. 1,4-Benzodiazepine fragment is classed with preferred (privileged) structures [4–6]; it is present in more than 40 medicinal agents with different therapeutic effects [7–9]. Therefore, development of methods for the synthesis of new fused heterocyclic systems on the basis of 1,4-diazepines is encouraged. For example, bioisosterism of thiophene and benzene rings [10] was successfully employed in the synthesis of new 1,4-thieno[1,4]diazepine-containing drugs, such as Olanzapine, Clotiazepam, and Brotizolam [2, 11]. Taking into account the above stated, new synthetic approaches to thieno[1,4]diazepines may be quite promising.

In recent time thieno[2,3-*e*][1,4]diazepines were successfully synthesized via the Ugi reaction [2, 3]. In addition, syntheses of these compounds from proline derivatives and 2-aminobenzenethiols or dithianediol were reported [12–14].

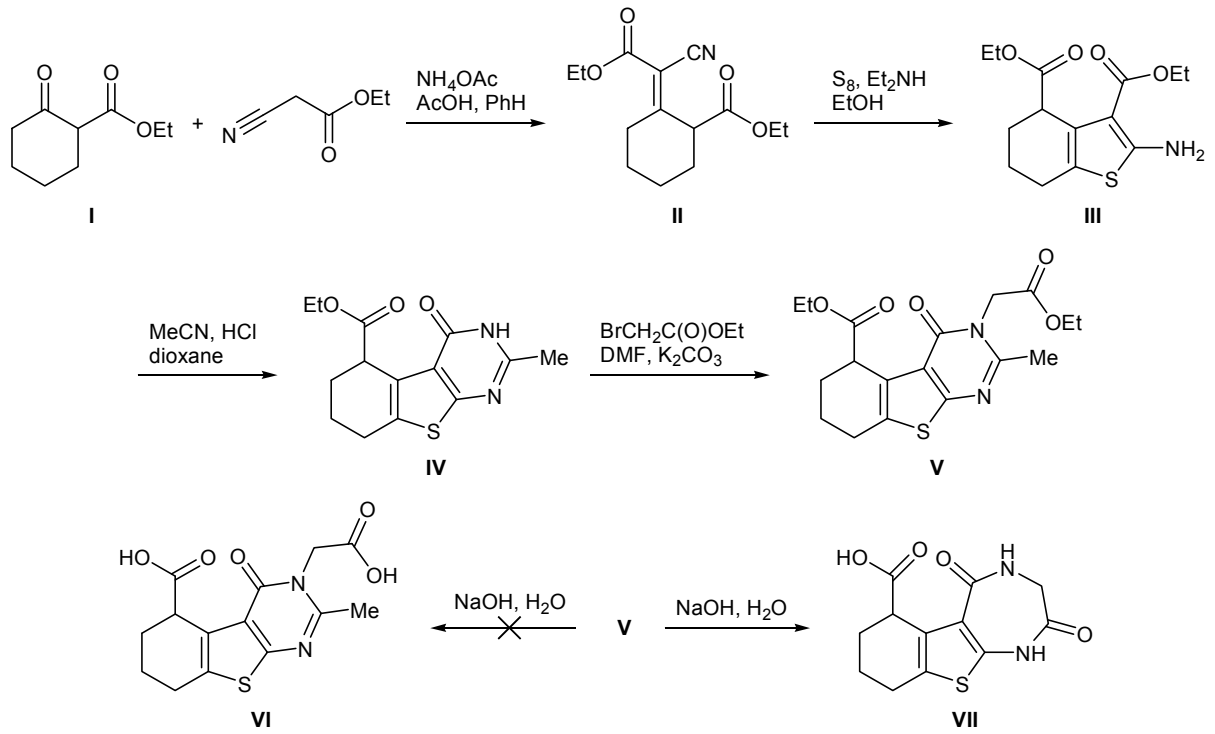
We have developed a procedure for the preparation of thieno[2,3-*e*][1,4]diazepines starting from thieno-[2,3-*d*]pyrimidine derivatives. This procedure is expected to extend the range of practically important 1,4-diazepines. As starting compounds we used 2-aminothiophenes prepared via the two-step Gewald reaction. Knoevenagel condensation of ethyl 2-oxocyclohexane-1-carboxylate (**I**) with ethyl cyanoacetate gave nitrile **II** which reacted with molecule sulfur to produce 2-aminothiophene **III**. The latter was brought into reaction with acetonitrile in acid medium, and thienopyrimidinone **IV** thus obtained was alkylated with ethyl bromoacetate. Alkaline hydrolysis of ester **V** might be expected to afford carboxylic acid **VI** which, however, was not formed under these conditions. Instead, recyclization of **V** led to the formation of thieno[2,3-*e*][1,4]diazepine system **VII**.

Thus, we have demonstrated the possibility for convenient transformation of thieno[2,3-*d*]pyrimidines into thieno[2,3-*e*][1,4]diazepines. This novel recyclization is promising from the viewpoint of synthesis of biologically active compounds.

Ethyl 2-(2-oxo-1-cyano-2-ethoxyethylidene)-cyclohexanecarboxylate (II). A mixture of 8 mL (0.05 mol) of ester **I**, 6 mL (0.05 mol) of ethyl cyanoacetate, 0.4 g (0.005 mol) of ammonium acetate, and 0.6 mL (0.01 mol) of acetic acid in 30 mL of benzene was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated. The mixture was cooled to room temperature and washed with a small amount of water, and the organic layer was separated and evaporated. Yield 11 g (83%). The properties of the product were consistent with published data [15, 16].

Diethyl 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3,4-dicarboxylate (III). Compound **II**, 13.25 g (0.05 mol), was dissolved in 25 mL of ethanol, 1.6 g (0.05 mol) of sulfur and 5 mL (0.05 mol) of diethylamine were added, and the mixture was heated for 2–3 h under reflux with stirring. The mixture was cooled to room temperature, water was added until crystallization started, and the precipitate was filtered off, washed with ethanol, and dried in air. Yield 11 g (74%), mp 100–101°C; published data [15]: mp 100.5–101.5°C. ^{1}H NMR spectrum, δ, ppm: 1.21 t (3H, CH_3, J = 7.1 Hz), 1.23 t (3H, CH_3, J = 7.1 Hz), 1.62–1.76 m (2H, CH_2), 1.84–1.91 m (2H, CH_2), 2.47 m (2H, CH_2), 3.80 br.s (1H, CH), 3.93–4.21 m (4H, OCH_2), 7.14 s (2H, NH_2). Mass spectrum: m/z 298 $[M + H]^+$. Found, %: C 56.62; H 6.51; N 4.85. $C_{14}H_{19}NO_4S$. Calculated, %: C 56.55; H 6.44; N 4.71. M 297.37.

Ethyl 2-methyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine-5-carboxylate (IV). Compound **III**, 1.5 g (5 mmol), was dissolved in



25 mL of dioxane saturated with hydrogen chloride, 0.5 mL (10 mmol) of acetonitrile was added, and the mixture was stirred for 24 h at 40°C. The mixture was then evaporated under reduced pressure, the residue was treated with 10 mL of water, and 20% aqueous sodium hydroxide was added dropwise until pH 7. The precipitate was filtered off, washed with ethanol, and dried in air. Yield 1.1 g (75%), mp >250°C. ^{1}H NMR spectrum, δ, ppm: 1.21 t (3H, CH_3, J = 7.1 Hz), 1.75–1.94 m (2H, CH_2), 2.03 d (2H, CH_2, J = 5.2 Hz), 2.33 s (3H, 2-CH_3), 2.67–2.82 m (2H, CH_2), 3.98 t (1H, CH, J = 5.1 Hz), 4.06 q (2H, OCH_2, J = 7.1 Hz), 12.15 s (1H, NH). Mass spectrum: m/z 293 $[M + H]^+$. Found, %: C 57.60; H 5.69; N 9.70. $C_{14}H_{16}N_2O_3S$. Calculated, %: C 57.52; H 5.52; N 9.58. M 292.36.

Ethyl 3-(2-ethoxy-2-oxoethyl)-2-methyl-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine-5-carboxylate (V). Thienopyrimidine **IV**, 1.46 g (5 mmol), was dissolved in 5 mL of DMF, 2.1 g (15 mmol) of potassium carbonate and 0.7 mL (6 mmol) of ethyl bromoacetate were added under stirring, and the mixture was stirred for 24 h at room temperature. The mixture was treated with 10 mL of water, and the organic layer was separated, dried over Na_2SO_4, and evaporated. Yield 1.76 g (93%), oily substance. ^{1}H NMR spectrum, δ, ppm: 1.19 t (3H, CH_3, J = 7.1 Hz), 1.29 t (3H, CH_3, J = 7.1 Hz), 1.81–1.88 m (2H, CH_2), 2.03 d (2H, CH_2, J = 4.9 Hz), 2.67–2.85 m (2H, CH_2), 3.05 s (3H, 2-CH_3), 3.99 m (1H, CH), 4.02–4.09 m (2H, OCH_2), 4.20 q (2H, OCH_2, J = 7.1 Hz), 4.77 d and 4.87 d (1H each, NCH_2, J = 17.7 Hz). Mass spectrum: m/z 379 $[M + H]^+$. Found, %: C 57.21; H 5.94; N 7.51. $C_{18}H_{22}N_2O_5S$. Calculated, %: C 57.13; H 5.86; N 7.40. M 378.44.

2,5-Dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-benzo-[4,5]thieno[2,3-*e*][1,4]diazepine-6-carboxylate (VII). A solution of 1.89 g (5 mmol) of thienopyrimidine **V** in 5 mL of ethanol was added to a 20% aqueous solution of sodium hydroxide (0.4 g, 0.01 mol), and the mixture was heated to 70°C under stirring and kept for 1 h at room temperature. The mixture was evaporated and acidified with aqueous HCl, and the precipitate was filtered off, washed with water, and dried in air. Yield 0.57 g (41%), mp 182–184°C (from EtOH–H_2O). ^{1}H NMR spectrum, δ, ppm: 1.63–1.68 m (1H, CH_2), 1.75–1.90 m (1H, CH_2), 2.13–2.45 m (4H, CH_2), 4.41 s (2H, CH_2, diazepine), 4.67 m (1H, CH), 8.71 s (1H, NH), 9.41 s (1H, NH). Mass spectrum: m/z 281 $[M + H]^+$. Found, %: C 51.50; H 4.39; N 10.08. $C_{12}H_{12}N_2O_4S$. Calculated, %: C 51.42; H 4.32; N 9.99. M 280.30.

The ^{1}H NMR spectra were recorded on a Varian Mercury spectrometer at 400 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The mass spectra (atmospheric pressure chemical ionization) were obtained on an Agilent 1100 LC/MSD instrument.

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