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POLYFUNCTIONAL PYRAZOLES. 10*. SYNTHESIS OF 5-OXO-4,5,7,9-TETRAHYDROPYRAZOLO[3,4-*e*][1,2,3]-TRIAZOLO[1,5-*a*][1,3]DIAZEPINE-3-CARBOXAMIDES IN A TANDEM REACTION OF ETHYL 4-(AZIDO-METHYL)PYRAZOLE-3-CARBOXYLATES WITH CYANOACETAMIDES

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4-(Azidomethyl)pyrazole-3-carboxylic acid ethyl esters react with cyanoacetamides in THF solution in the presence of t-BuOK resulting in the formation of 5-oxo-4,5,7,9-tetrahydropyrazolo[3,4-e][1,2,3]-triazolo[1,5-a][1,3]diazepine-3-carboxamides.

Keywords: 4-(azidomethyl)pyrazole-3-carboxylic acid ethyl esters, cyanoacetamides, pyrazolo[3,4-*e*]-[1,2,3]triazolo[1,5-*a*][1,3]diazepines, tandem reactions.

Tandem reactions are an effective tool in modern organic synthesis that has been successfully used to construct a variety of acyclic, carbo- and heterocyclic systems [2-6]. In the field of heterocyclic compound chemistry, for instance, tandem condensation of alkyl 2-azidobenzoates with activated acetonitriles is a basis for efficient synthesis of [1,2,3]triazolo[1,5-*a*]quinazoline derivatives [7-9], such as the known selective serotonin 5-HT_6 receptor antagonists [7] and inhibitors of the biosynthesis of teichoic acid, a component of the cell wall of many gram-positive bacteria [9]. Among the azidobenzoate pyrazole analogs such transformations are described only for ethyl 5-azido-1-methyl-4-pyrazolecarboxylate, reaction of which with activated nitriles gave 3-substituted pyrazolo[4,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines [10]. To us it seemed worthwhile to exploit the synthetic potential of tandem reactions of other pyrazole functional derivatives with cyanoacetic acid amides to obtain new condensed heterocyclic compounds.

In this work, 4-(azidomethyl)pyrazole-3-carboxylic acid esters **2a-c**, formed in essentially quantitative yields by reacting 4-chloromethylpyrazole-3-carboxylic acid ethyl ester **1a-c** [11] with sodium azide in DMF solution at 50°C, were studied as potential substrates for tandem condensation reactions. A characteristic of

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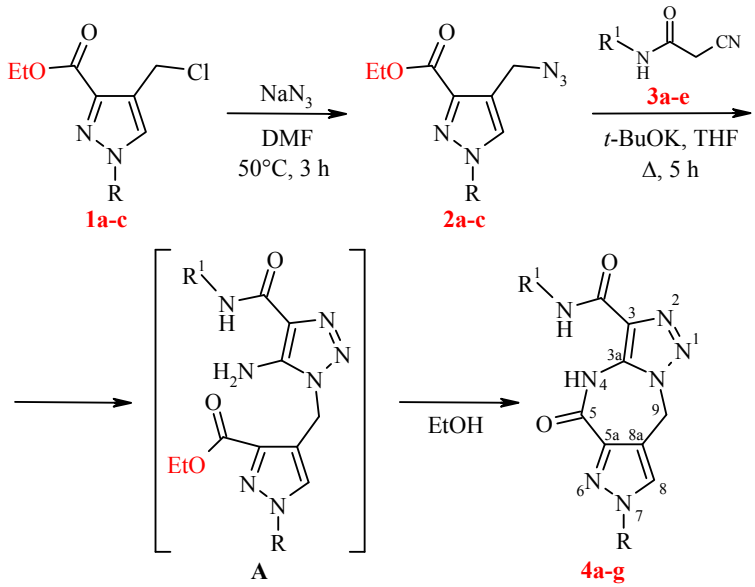
compounds **2a-c** is the location of the azide group in the γ-position relative to the ester group, which is an important prerequisite for the formation of a seven-membered heterocyclic system. Of the compounds with this placement of substituents, only 2-azidobenzylacetate have been previously used in cyclocondensation with cyanoacetamide [12].

We have found that 4-(azidomethyl)pyrazole-3-carboxylic acid esters **2a-c** react with cyanoacetamides **3a-e** in refluxing THF in the presence of *t*-BuOK, forming pyrazolo[3,4-*e*][1,2,3]triazolo[1,5-*a*]diazepine-3-carboxamides **4a-g** in 53-67% yields. This transformation is presumably an example of a tandem reaction that begins with the cycloaddition to the azido group of a carbanion, generated from cyanoacetamide, and the formation of an intermediate polyfunctional triazole **A**, susceptible to the formation of the diazepine cycle due to the intramolecular attack of the triazole amino group on the ethoxycarbonyl group of the pyrazole ring.



1a, **2a**, **4a**,**b** R = Me; **1b**, **2b**, **4c-e** R = Ph; **1c**, **2c**, **4f**,**g** R = 4-BrC_6H_4; **3a**, **4c** R^1 = H; **3b**, **4d** R^1 = Ph; **3c**, **4a** R^1 = 4-ClC_6H_4; **3d**, **4b**,**e**,**f** R^1 = 4-MeC_6H_4; **3e**, **4g** R^1 = 4-$MeOC_6H_4$

Compounds **4a-g** are the first representatives of a previously unknown heterocyclic system, which holds promise as a scaffold for the design of bioactive substances owing to the presence of endo- and exocyclic amide fragments in its structure. The structure of target compounds was confirmed by various analytical methods (Tables 1-4). It should be noted that the absence of signals in the downfield region (160-190 ppm) of the ^{13}C NMR spectra excludes the possibility for the formation of the alternative Claisen condensation/cycloaddition tandem reaction products, 9-oxo-5,7,9,10-tetrahydropyrazolo[3,4-*e*]tetrazolo[1,5-*a*]azepine-10-carboxamides. Employing the APT method for the analysis of ^{13}C NMR spectra and comparison with published data [8, 13] allowed for a comparatively accurate assignment of signals to the corresponding carbon atoms in the triazolodiazepine cycle: C-3 (127-128 ppm), C-3a (137-139), C-5 (157-159), C-5a (141-143), C-8a (116-118), C-9 (42-43 ppm).

Thus, in this study the efficiency of using the condensation of 4-(azidomethyl)pyrazole-3-carboxylic acid ethyl ester with cyanoacetamides for one-pot synthesis of derivatives of a previously unknown pyrazolo[3,4-*e*][1,2,3]triazolo[1,5-*a*][1,3]diazepine heterocyclic system was demonstrated.

EXPERIMENTAL

IR spectra were acquired on a UR-20 spectrophotometer in KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 and 125 MHz, respectively) in DMSO-d_6 with TMS as internal standard. Mass spectra were acquired on an Agilent LC/MSD SL mass spectrometer; Zorbax SB-C18

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **2a-c**, **4a-g**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
2a*	$C_8H_{11}N_5O_2$	46.21 / 45.93	5.51 / 5.30	33.69 / 33.48	—	82
2b	$C_{13}H_{13}N_5O_2$	57.83 / 57.56	5.04 / 4.83	25.65 / 25.82	42-45	89
2c	$C_{13}H_{12}BrN_5O_2$	44.48 / 44.59	3.31 / 3.45	20.21 / 20.00	73-75	76
4a	$C_{15}H_{12}ClN_7O_2$	50.61 / 50.36	3.41 / 3.38	27.53 / 27.41	235-237	53
4b	$C_{16}H_{15}N_7O_2$	57.06 / 56.97	4.59 / 4.48	29.17 / 29.06	229-231	59
4c	$C_{14}H_{11}N_7O_2$	54.50 / 54.37	3.51 / 3.58	31.92 / 31.70	255-257	58
4d	$C_{20}H_{15}N_7O_2$	62.59 / 62.33	4.11 / 3.92	25.37 / 25.44	258-260	66
4e	$C_{21}H_{17}N_7O_2$	63.39 / 63.15	4.46 / 4.29	24.30 / 24.55	>300	63
4f	$C_{21}H_{16}BrN_7O_2$	52.96 / 52.73	3.55 / 3.37	20.68 / 20.50	273-275	67
4g	$C_{21}H_{16}BrN_7O_3$	50.80 / 51.03	3.13 / 3.26	20.05 / 19.84	268-270	61

*An oily viscous substance.

TABLE 2. IR and Mass Spectra of Compounds **2a-c**, **4a-g**

Compound	IR spectrum, ν, cm^{-1}			Mass spectrum, *m/z* $[M+H]^+$	Compound	IR spectrum, ν, cm^{-1}		Mass spectrum, *m/z* $[M+H]^+$
	C=O	N–H	N_3			C=O	N–H	
2a	1725	—	2140	210	**4c**	1660, 1695	3300, 3390	310
2b	1730	—	2145	272	**4d**	1665, 1700	3290, 3400	386
2c	1730	—	2145	351	**4e**	1665, 1700	3295, 3400	400
4a	1660, 1700	3290, 3385	—	358	**4f**	1660, 1700	3285, 3405	479
4b	1665, 1700	3295, 3395	—	338	**4g**	1660, 1695	3290, 3400	495

column 4.6×15 mm, 1.8 μm (PN 82(c)75-932); mobile phase A: MeCN–H_2O, 95:5, 0.1% trifluoroacetic acid, mobile phase B: 0.1% aqueous trifluoroacetic acid; flow: 3 ml/min; injection volume: 1 μl; UV detection: 215, 254, 285 nm; atmospheric-pressure CI, scan range *m/z* 80-1000. Elemental analysis was performed on a Perkin Elmer CHN Analyzer at the analytical laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Melting points were determined on a Kofler hot bench and are uncorrected.

Compounds **1a-c** were prepared according to the published method [11].

4-Chloromethyl-1-methyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (1a). Yield 75%. Colorless crystalline substance. Mp 64-66°C (EtOH). IR spectrum, ν, cm^{-1}: 1725 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (3H, t, *J* = 7.2, CH_3); 3.89 (3H, s, NCH_3); 4.27 (2H, q, *J* = 7.2, CH_2); 4.81 (2H, s, CH_2); 7.96 (1H, s, H-5). Found, %: C 47.61; H 5.50; N 13.64. $C_8H_{11}ClN_2O_2$. Calculated, %: C 47.42; H 5.47; N 13.82.

TABLE 3. ^{1}H NMR Spectra of Compounds **2a-c**, **4a-g**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
2a	1.29 (3H, t, *J* = 7.4, CH_3); 3.91 (3H, s, CH_3); 4.27 (2H, q, *J* = 7.4, CH_2); 4.49 (2H, s, CH_2); 7.93 (1H, s, H-5)
2b	1.33 (3H, t, *J* = 7.2, CH_3); 4.33 (2H, q, *J* = 7.2, CH_2); 4.60 (2H, s, CH_2); 7.41 (1H, t, *J* = 7.8, H Ph); 7.55 (2H, t, *J* = 8.0, H Ph); 7.87 (2H, d, *J* = 8.0, H Ph); 8.74 (1H, s, H-5)
2c	1.33 (3H, t, *J* = 6.8, CH_3); 4.34 (2H, q, *J* = 6.8, CH_2); 4.59 (2H, s, CH_2); 7.73 (2H, d, *J* = 8.4, H Ar); 7.85 (2H, d, *J* = 8.4, H Ar); 8.76 (1H, s, H-5)
4a	3.94 (3H, s, CH_3); 5.73 (2H, s, 9-CH_2); 7.39 (2H, d, *J* = 7.6, H Ar); 7.86 (2H, d, *J* = 7.6, H Ar); 7.96 (1H, s, H-8); 9.95 (1H, s, NH); 10.72 (1H, s, NH)
4b	2.26 (3H, s, CH_3); 3.94 (3H, s, CH_3); 5.72 (2H, s, 9-CH_2); 7.13 (2H, d, *J* = 7.8, H Ar); 7.68 (2H, d, *J* = 7.8, H Ar); 7.96 (1H, s, H-8); 9.96 (1H, s, NH); 10.47 (1H, s, NH)
4c	5.77 (2H, s, 9-CH_2); 7.42-8.08 (7H, m, H Ph, NH_2); 8.72 (1H, s, H-8); 10.08 (1H, s, NH)
4d	5.82 (2H, s, 9-CH_2); 7.10-8.04 (10H, m, H Ph); 8.74 (1H, s, H-8); 10.24 (1H, s, NH); 10.57 (1H, s, NH)
4e	2.27 (3H, s, CH_3); 5.81 (2H, s, 9-CH_2); 7.13 (2H, d, *J* = 7.2, H Ar); 7.43-7.58 (3H, m, H Ar); 7.70 (2H, d, *J* = 8.0, H Ar); 7.85 (2H, d, *J* = 8.0, H Ar); 8.83 (1H, s, H-8); 10.23 (1H, s, NH); 10.51 (1H, s, NH)
4f	2.27 (3H, s, CH_3); 5.82 (2H, s, 9-CH_2); 7.14 (2H, d, *J* = 8.0, H Ar); 7.70 (2H, d, *J* = 8.0, H Ar); 7.76 (2H, d, *J* = 8.5, H Ar); 7.83 (2H, d, *J* = 8.5, H Ar); 8.78 (1H, s, H-8); 10.26 (1H, s, NH); 10.49 (1H, s, NH)
4g	3.73 (3H, s, CH_3); 5.81 (2H, s, 9-CH_2); 6.93 (2H, d, *J* = 7.8, H Ar); 7.72-8.03 (6H, m, H Ar); 8.76 (1H, s, H-8); 10.24 (1H, s, NH); 10.48 (1H, s, NH)

TABLE 4. ^{13}C NMR Spectra of Compounds **4a-g**

Compound	Chemical shifts, δ, ppm								
	C-3	C-3a	C-5	C-5a	C-8	C-8a	C-9	C(O)NH	R, R^1
4a	127.4	137.4	159.0	141.2	129.9	116.3	42.8	159.2	39.5; 121.8; 127.5; 128.3; 136.7
4b	127.7	137.7	158.8	141.7	129.2	116.5	42.4	159.2	21.7; 39.4; 120.9; 126.3; 129.7; 136.2
4c	127.1	137.1	158.6	143.1	127.9	117.7	42.8	162.9	119.4; 127.4; 129.7; 136.2
4d	127.3	138.8	158.9	143.3	127.9	118.0	42.8	159.2	119.4; 120.5; 126.9; 127.4; 128.6; 129.8; 136.4; 138.3
4e	127.9	138.8	158.9	143.4	128.0	118.0	42.8	159.1	20.3; 119.3; 120.5; 127.4; 128.9; 129.7; 132.9; 135.7; 136.3
4f	128.0	138.0	158.7	143.6	127.4	118.2	42.8	159.0	20.4; 120.3; 120.5; 121.2; 128.8; 132.5; 132.9; 135.7; 136.2
4g	127.9	137.9	157.9	143.6	127.5	118.3	42.8	158.7	55.1; 113.7; 120.4; 121.3; 122.0; 127.5; 131.2; 132.6; 155.5

1-(4-Bromophenyl)-4-chloromethyl-1*H*-pyrazole-3-carboxylic Acid Ethyl Ester (1c). Yield 86%. Mp 96-98°C (EtOH). IR spectrum, ν, cm^{-1}: 1730 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.2, CH_3); 4.36 (2H, d, *J* = 7.2, CH_2); 4.90 (2H, s, CH_2); 7.73-7.96 (4H, m, H Ar); 8.81 (1H, s, H-5). Found, %: C 45.72; H 3.68; N 8.34. $C_{13}H_{12}BrClN_2O_2$. Calculated, %: C 45.44; H 3.52; N 8.15.

4-Azidomethyl-1-methyl(aryl)-1*H*-pyrazole-3-carboxylic Acid Ethyl Esters 2a-c (General Method). NaN_3 (1.62 g 0.025 mol) was added to a solution of 4-chloromethylpyrazole **1a-c** (0.01 mol) in DMF (20 ml). The mixture was stirred at 50°C for 3 h. The reaction mixture was cooled and poured into ice water (100 ml). The formed precipitate (compounds **2b**,**c**) was filtered off, washed with ice water (2×20 ml), dried in air, and recrystallized from ethanol. Alternatively, the oily layer (compound **2a**) was extracted with CH_2Cl_2 (2×30 ml), dried over anhydrous Na_2SO_4, and the solvent was removed. An analytically pure oily substance was obtained.

1-Methyl(aryl)-5-oxo-4,5,7,9-tetrahydropyrazolo[3,4-*e*][1,2,3]triazolo[1,5-*a*][1,3]diazepine-3-carboxamides 4a-g (General Method). Cyanoacetamide **3a-e** [14, 15] (0.002 mol) and *t*-BuOK (0.25 g, 0.0022 mol) were successively added to a solution of azidomethylcarboxylate **2a-c** (0.002 mol) in THF (15 ml). The mixture was heated under reflux for 5 h. The solvent was removed by distillation. The residue was dissolved in water (30 ml) and acidified with 10% HCl to pH 3. The formed precipitate was filtered off, washed with water (2×10 ml), dried, and recrystallized from PhMe.

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