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POLYFUNCTIONAL PYRAZOLES. 7*. ETHYL 1-ARYL-4-FORMYLPYRAZOLE-3-CARBOXYLATES IN THE SYNTHESIS OF 2-ARYL-2,4-DIHYDRO-6*H*-THIENO-[3,4-*c*]PYRAZOL-6-ONES

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A convenient method has been developed for the synthesis of 2,4-dihydro-6H-thieno[3,4-c]pyrazol-6-ones by means of an intramolecular cyclization of 4-sulfanylmethylpyrazole-3-carboxylic acids. The latter were prepared from ethyl 4-formylpyrazole-3-carboxylates via the intermediate 4-hydroxymethyl-, 4-chloromethyl-, and 4-thioureidomethyl derivatives.

Keywords: 2,4-dihydro-6*H*-thieno[3,4-*c*]pyrazol-6-ones, ethyl 4-formylpyrazole-3-carboxylates, 4-sulfanylmethylpyrazole-3-carboxylic acids, cyclization.

Derivatives of the thieno[3,4-*c*]pyrazole heterocyclic system find use in medicinal chemistry, thanks to their marked anti-inflammatory, analgesic, and antithrombotic activity [2]. These substances are also promising for treatment of cardiovascular and hypoglycaemic conditions [3]. In addition, several members of this series have recently been proposed as novel types of biosynthesis inhibitors for gram-positive bacteria [4].

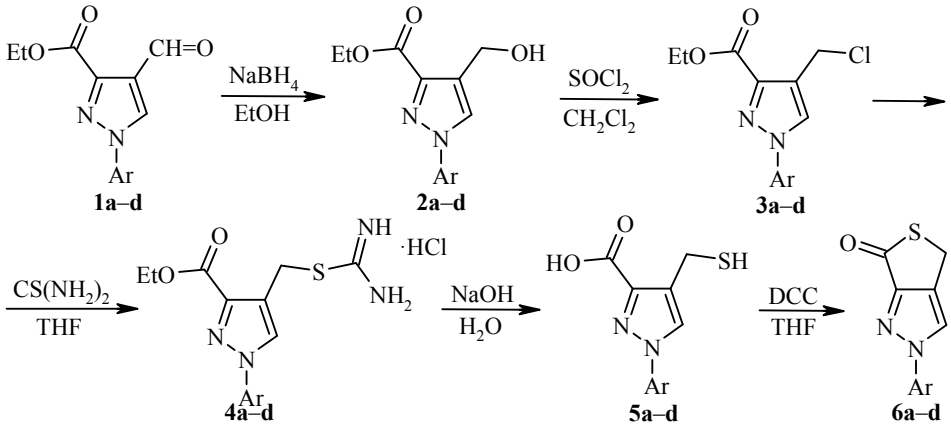

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TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **2-6 a-d**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
2a	$C_{13}H_{14}N_2O_3$	63.08 / 63.40	5.89 / 5.73	11.49 / 11.38	134-135	75
2b	$C_{13}H_{13}ClN_2O_3$	55.78 / 55.62	4.58 / 4.67	10.09 / 9.98	147–148	77
2c	$C_{14}H_{16}N_2O_3$	64.31 / 64.60	6.04 / 6.20	11.03 / 10.76	139–140	71
2d	$C_{13}H_{12}Cl_2N_2O_3$	49.65 / 49.54	3.71 / 3.84	9.06 / 8.89	151-152	68
3a	$C_{13}H_{13}ClN_2O_2$	58.74 / 58.99	5.11 / 4.95	10.65 / 10.58	84-85	87
3b	$C_{13}H_{12}Cl_2N_2O_2$	52.47 / 52.19	4.18 / 4.04	9.21 / 9.36	113-114	84
3c	$C_{14}H_{15}ClN_2O_2$	60.60 / 60.33	5.50 / 5.42	10.27 / 10.05	96-97	88
3d	$C_{13}H_{11}Cl_3N_2O_2$	46.55 / 46.81	3.10 / 3.32	8.27 / 8.40	150-151	80
4a	$C_{14}H_{17}ClN_4O_2S$	49.11 / 49.34	5.08 / 5.03	16.31 / 16.44	225-227	94
4b	$C_{14}H_{16}Cl_2N_4O_2S$	45.07 / 44.81	4.35 / 4.30	15.12 / 14.93	220-222	95
4c	$C_{15}H_{19}ClN_4O_2S$	50.92 / 50.77	5.21 / 5.40	15.86 / 15.79	210-211	92
4d	$C_{14}H_{15}Cl_3N_4O_2S$	40.77 / 41.04	3.60 / 3.69	13.51 / 13.67	229-231	96
5a	$C_{11}H_{10}N_2O_2S$	56.45 / 56.40	4.12 / 4.30	11.72 / 11.96	146-147	69
5b	$C_{11}H_9ClN_2O_2S$	49.33 / 49.17	3.45 / 3.38	10.51 / 10.42	138-140	65
5c	$C_{12}H_{12}N_2O_2S$	58.34 / 58.05	4.60 / 4.87	11.03 / 11.28	187-188	72
5d	$C_{11}H_8Cl_2N_2O_2S$	43.81 / 43.58	2.63 / 2.66	9.05 / 9.24	206-208	74
6a	$C_{11}H_8N_2OS$	60.83 / 61.09	3.85 / 3.73	12.71 / 12.95	168-169	67
6b	$C_{11}H_7ClN_2OS$	52.96 / 52.70	2.87 / 2.81	11.33 / 11.17	191-193	74
6c	$C_{12}H_{10}N_2OS$	62.71 / 62.59	4.30 / 4.38	12.39 / 12.16	173-175	77
6d	$C_{11}H_6Cl_2N_2OS$	46.46 / 46.33	2.41 / 2.12	10.04 / 9.82	201-203	63

The majority of published methods for thieno[3,4-*c*]pyrazole synthesis are based on pyrazolo-annelation reactions of hydrogenated thiophene ring, which often occur nonselectively [5-8]. An alternative method for annelation of a thiophene ring to a pyrazole ring was developed by the authors of [9] for the condensation of 3,4-dibenzoylpyrazoles with P_4S_{10}, to give novel 10-π-electron thieno[3,4-*c*]pyrazoles with a "tetravalent" sulfur. However, this variant of forming the indicated bicyclic system has subsequently been seldom used.

We propose a novel variant of such an annelation based on the known [10] transformation of ethyl-4-chlorobut-2-ene structural fragments to thiolactones. In the present work, we demonstrate the ready construction of such a fragment based on our recently developed preparative synthesis of 4-formylpyrazole-3-carboxylic acids [11].

The indicated esters **1a-d** were used as the starting material in a chain of subsequent reactions, which led to a novel 2,4-dihydro-6*H*-thieno[3,4-*c*]pyrazole derivatives. Our proposed scheme includes a selective reduction of the aldehyde group in compounds **1a-d** by sodium borohydride, to form the 4-hydroxymethyl derivatives **2a-d**. The latter were treated with thionyl chloride and readily formed the 4-chloromethyl derivatives **3a-d**. Their reaction with thiourea gave a virtually quantitative yield of the thiouronium salts **4a-d**, which underwent

TABLE 2. Spectroscopic Characteristics of Compounds **2-6 a-d**

Compound	IR spectrum, ν, cm^{-1}*		^1H NMR spectrum, δ, ppm (*J*, Hz)
	C=O	OH (NH)*[2]	
1	2	3	4
2a	1720	3470	1.34 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.30 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.67 (2H, d, *J* = 4.6, $C\underline{H}_2OH$); 5.18 (1H, t, *J* = 4.6, OH); 7.40 (1H, t, *J* = 7.4, H Ph); 7.58 (2H, t, *J* = 7.6, H Ph); 7.85 (2H, d, *J* = 8.2, H Ph); 8.44 (1H, s, H-5)
2b	1720	3475	1.33 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.32 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.68 (2H, d, *J* = 5.0, $C\underline{H}_2OH$); 5.20 (1H, t, *J* = 5.0, OH); 7.58 (2H, d, *J* = 8.0, H Ar); 7.94 (2H, d, *J* = 8.0, H Ar); 8.51 (1H, s, H-5)
2c	1725	3480	1.34 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.26 (3H, s, CH_3); 4.30 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.68 (2H, d, *J* = 4.0, $C\underline{H}_2OH$); 5.14 (1H, t, *J* = 4.0, OH); 7.32 (2H, d, *J* = 7.8, H Ar); 7.76 (2H, d, *J* = 7.8, H Ar); 8.41 (1H, s, H-5)
2d	1715	3460	1.33 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 4.30 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 4.66 (2H, d, *J* = 4.8, $C\underline{H}_2OH$); 5.11 (1H, t, *J* = 4.8, OH); 7.76-7.83 (2H, m, H Ar); 8.21 (1H, d, *J* = 2.4, H Ar); 8.59 (1H, s, H-5)
3a	1725	—	1.35 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 4.36 (2H, q, *J* = 6.8, $C\underline{H}_2CH_3$); 4.92 (2H, s, CH_2Cl); 7.42 (1H, t, *J* = 7.2, H Ph); 7.56 (2H, t, *J* = 7.6, H Ph); 7.87 (2H, d, *J* = 8.4, H Ph); 8.78 (1H, s, H-5)
3b	1725	—	1.35 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.36 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.91 (2H, s, CH_2Cl); 7.61 (2H, d, *J* = 8.5, H Ar); 7.91 (2H, d, *J* = 8.5, H Ar); 8.81 (1H, s, H-5)
3c	1720	—	1.36 (3H, t, *J* = 6.0, $CH_2C\underline{H}_3$); 2.36 (3H, s, CH_3); 4.36 (2H, q, *J* = 6.0, $C\underline{H}_2CH_3$); 4.91 (2H, s, CH_2Cl); 7.35 (2H, d, *J* = 8.1, H Ar); 7.75 (2H, d, *J* = 8.1, H Ar); 8.73 (1H, s, H-5)
3d	1725	—	1.35 (3H, t, *J* = 6.5, $CH_2C\underline{H}_3$); 4.36 (2H, q, *J* = 6.5, $C\underline{H}_2CH_3$); 4.90 (2H, s, CH_2Cl); 7.81-7.94 (2H, m, H Ar); 8.24 (1H, d, *J* = 1.5, H Ar); 8.88 (1H, s, H-5)
4a	1730	3340-3385	1.35 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.36 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.64 (2H, s, CH_2S); 7.44 (1H, t, *J* = 7.0, H Ph); 7.57 (2H, t, *J* = 7.4, H Ph); 7.91 (2H, d, *J* = 7.8, H Ph); 8.78 (1H, s, H-5); 9.22-9.26 (4H, m, N^+H_2)
4b	1715	3320-3365	1.35 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.36 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.64 (2H, s, CH_2S); 7.63 (2H, d, *J* = 8.8, H Ar); 7.89 (2H, d, *J* = 8.8, H Ar); 8.80 (1H, s, H-5); 9.36 (4H, br. s, N^+H_2)
4c	1720	3310-3350	1.34 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$); 2.36 (3H, s, CH_3); 4.30 (2H, q, *J* = 6.9, $C\underline{H}_2CH_3$); 4.60 (2H, s, CH_2S); 7.36 (2H, d, *J* = 8.4, H Ar); 7.72 (2H, d, *J* = 8.4, H Ar); 8.70 (1H, s, H-5); 9.31 (4H, br. s, N^+H_2)
4d	1725	3330-3380	1.36 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$); 4.35 (2H, q, *J* = 6.9, $C\underline{H}_2CH_3$); 4.61 (2H, s, CH_2S); 7.84-7.91 (2H, m, H Ar); 8.17 (1H, d, *J* = 1.6, H Ar); 8.86 (1H, s, H-5); 9.36 (4H, br. s, N^+H_2)
5a	1705	2430-2850	2.86 (1H, t, *J* = 6.0, SH); 3.87 (2H, d, *J* = 6.0, $C\underline{H}_2SH$); 7.38 (1H, t, *J* = 7.2, H Ph); 7.57 (2H, t, *J* = 7.8, H Ph); 7.92 (2H, d, *J* = 7.8, H Ph); 8.62 (1H, s, H-5); 13.08 (1H, br. s, COOH)
5b	1700	2460-2890	2.87 (1H, t, *J* = 4.2, SH); 3.85 (2H, d, *J* = 4.2, $C\underline{H}_2SH$); 7.61 (2H, d, *J* = 8.6, H Ar); 7.90 (2H, d, *J* = 8.6, H Ar); 8.58 (1H, s, H-5); 13.12 (1H, br. s, COOH)
5c	1700	2450-2840	2.36 (3H, s, CH_3); 2.85 (1H, t, *J* = 5.0, SH); 3.86 (2H, d, *J* = 5.0, $C\underline{H}_2SH$); 7.34 (2H, d, *J* = 8.0, H Ar); 7.73 (2H, d, *J* = 8.0, H Ar); 8.60 (1H, s, H-5); 13.06 (1H, br. s, COOH)
5d	1705	2440-2830	2.87 (1H, t, *J* = 4.8, SH); 3.85 (2H, d, *J* = 4.8, $C\underline{H}_2SH$); 7.78-7.90 (2H, m, H Ar); 8.17 (1H, d, *J* = 2.1, H Ar); 8.66 (1H, s, H-5); 13.06 (1H, br. s, COOH)

TABLE 2 (continued)

1	2	3	4
5d	1705	2440-2830	2.87 (1H, t, *J* = 4.8, SH); 3.85 (2H, d, *J* = 4.8, $C\underline{H_2}SH$); 7.78-7.90 (2H, m, H Ar); 8.17 (1H, d, *J* = 2.1, H Ar); 8.66 (1H, s, H-5); 13.06 (1H, br. s, COOH)
6a*[3]	1700	—	4.52 (2H, s, CH_2S); 7.34 (1H, t, *J* = 7.2, H Ph); 7.57 (2H, t, *J* = 7.2, H Ph); 7.90 (2H, d, *J* = 7.8, H Ph); 8.68 (1H, s, H-3)
6b	1705	—	4.51 (2H, s, CH_2S); 7.63 (2H, d, *J* = 8.4, H Ar); 7.91 (2H, d, *J* = 8.4, H Ar); 8.70 (1H, s, H-3)
6c	1700	—	2.36 (3H, s, CH_3); 4.50 (2H, s, CH_2S); 7.35 (2H, d, *J* = 8.0, H Ar); 7.77 (2H, d, *J* = 8.0, H Ar); 8.66 (1H, s, H-3)
6d*[4]	1700	—	4.54 (2H, s, CH_2S); 7.85-7.96 (2H, m, H Ar); 8.24 (1H, d, *J* = 2.4, H Ar); 8.78 (1H, s, H-3)

*Absorption bands for the SH groups of compound **5a-d** overlapped with those for the OH groups.

*[2] For compounds **4a-d**.

*[3] ^{13}C NMR spectrum, δ, ppm: 27.2 (C-4); 119.7 (C-2',6'); 125.4 (C-3a); 128.1 (C-4'); 129.7 (C-3',5'); 132.2 (C-3); 139.5 (C-1'); 152.9 (C-6a); 188.6 (C-6).

*[4] ^{13}C NMR spectrum, δ, ppm: 27.4 (C-4); 121.1 (C-6'); 122.1 (C-2'); 125.8 (C-3a); 132.5 (C-3); 133.8 (C-4'); 134.0 (C-3'); 134.1 (C-5'); 138.9 (C-1'); 153.1 (C-6a); 188.3 (C-6).

alkaline hydrolysis to give the 4-sulfanylmethylpyrazole-3-carboxylic acids **5a-d**. The latter represent a model of bifunctional, electrophile-nucleophile type system and react with the condensing reagent dicyclohexylcarbodiimide (DCC) in THF *via* an intramolecular cyclization, to give the 2,4-dihydrothieno[3,4-c]pyrazol-6-ones **6a-d** in 63-77% yields (Table 1).

The composition of the synthesized intermediate compounds **2-5 a-d** and the target compounds **6a-d** was confirmed from the results of elemental analysis (Table 1), and their structures are in agreement with IR, ^{1}H NMR and ^{13}C NMR spectra (Table 2).

Hence the developed method is characterized by the use of readily available reagents and high yields in all of the synthetic steps, and can be recommended as an efficient method for the preparation of novel 2,4-dihydro-6*H*-thieno[3,4-*c*]pyrazol-6-ones.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 and 125 MHz, respectively) using DMSO-d_6 with TMS as internal standard. Elemental analysis was carried out on a Perkin Elmer CHN analyzer. Melting points for the compounds prepared were determined on a Koffler hot stage apparatus, and are not corrected. Compounds **1a-d** were prepared as reported in [11].

Ethyl 1-Aryl-4-hydroxymethyl-1*H*-pyrazole-3-carboxylates 2a-d (General Method). $NaBH_4$ (5 g) was added with stirring to a suspension of the ester **1a-d** (0.1 mol) in EtOH (50 ml) and stirred for 2 h at room temperature. The reaction mixture was poured into ice water (300 ml) and left for 10 h at 0-5ºC. The precipitate formed was filtered off, washed with water (2×50 ml), dried, and crystallized from EtOH.

Ethyl 1-Aryl-4-chloromethyl-1*H*-pyrazole-3-carboxylates 3a-d (General Method). $SOCl_2$ (3.6 g, 0.03 mol) was added with stirring to a solution of ester **2a-d** (0.02 mol) in CH_2Cl_2 (40 ml), stirred at room

temperature for 2 h, and then for 1 h at 40ºC. The mixture was cooled, solvent and excess $SOCl_2$ were distilled off, and the residue was washed with hexane (2×30 ml) and crystallized from EtOH.

Ethyl 1-Aryl-4-[(carbamidoylsulfanyl)methyl]-1*H*-pyrazole-3-carboxylate Hydrochlorides 4a-d (General Method). A mixture of ester **3a-d** (0.015 mol) and thiourea (1.2 g, 0.016 mol) in THF (30 ml) was refluxed for 1 h, cooled, and the solid product was filtered off, washed with Et_2O (2×20 ml), dried, and crystallized from EtOH.

Ethyl 1-Aryl-4-sulfanylmethyl-1*H*-pyrazole-3-carboxylates 5a-d (General Method). The thiouronium salt **4a-d** (0.01 mol) was added to 20% NaOH solution (20 ml) and heated for 2-3 h to full dissolution. The solution was cooled, poured into water (100 ml) and filtered. The filtrate was acidified with 20% HCl solution (40 ml), cooled to 10ºC, and the precipitate formed was filtered off, washed with water (2×30 ml), dried, and crystallized from 60% aqueous AcOH.

2-Aryl-2,4-dihydro-6*H*-thieno[3,4-*c*]pyrazol-6-ones 6a-d (General Method). A solution of DCC (1.05 g, 5 mmol) in THF (5 ml) was added with stirring to a solution of the thiol **5a-d** (5 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 10 h, and the precipitated dicyclohexylurea was filtered off and washed with cold THF (3 ml). The filtrate was evaporated and the residue was crystallized from a mixture of EtOAc and hexane (2:1).

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