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1-(1-CARBOXY-2-R-4-METHYLCYCLOHEX-4-ENYL)CARBONYL- AND 1-(2-R-4-METHYL-CYCLOHEX-4-ENYL)CARBONYL-3,5-DIMETHYL(DIPHENYL)PYRAZOLES

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1-(1-Carboxy-2-R-4-methylcyclohex-4-enyl)carbonyl- and 1-(2-R-4-methylcyclohex-4-enyl)carbonyl-3,5-dimethyl(diphenyl)pyrazoles have been obtained from the reaction of monohydrazides of 2-R-methyl-4-cyclohexen-1,1-dicarboxylic acids and hydrazides of 2-R-4-methyl-4-cyclohexen-1-monocarboxylic acids with acetylacetone and dibenzoylmethane. The conditions for the formation of the pyrazoles depend on the nature of the substituents in the hydrazide starting materials and the structure of the 1,3-diketone used.

Keywords: acetylacetone, hydrazides, dibenzoylmethane, 1,3-diketones, pyrazoles.

We have studied the reactions of hydrazides of 2-R-4-methyl-4-cyclohexen-1,1-dicarboxylic acids (**1a-f**) [1] and 2-R-methyl-4-cyclohexen-1-monocarboxylic acids (**2a-e**) [2] (which we had prepared previously) with acetylacetone **3** and dibenzoylmethane **4** with the objective of preparing potentially biologically active compounds.

The reaction of monosubstituted hydrazines and hydrazides with 1,3-dicarbonyl compounds is widely used for the synthesis of pyrazoles. The process occurs *via* the formation of the corresponding hydrazones of the dicarbonyl compounds, the ease of cyclization of which depends on the structure of the starting materials [3].

Like other hydrazides, compounds **1a-f** and **2a-e** gave the corresponding pyrazoles on reactions with 1,3-diketones. We succeeded in obtaining the previously unknown 1-(1-carboxy-2-R-4-methylcyclohex-4-enyl)carbonyl-3,5-dimethyl(diphenyl)pyrazoles **5a-f**, **6a-f**, and **7a-e** by the reactions of the hydrazides **1a-f** and **2a-e** with acetylacetone **3** and dibenzoylmethane **4** (Scheme 1).

The reaction of hydrazides **1a-e** with acetylacetone **3** proceeded slowly at room temperature. Refluxing compounds **1a-e** with either acetylacetone **3** or dibenzoylmethane **4** gave a mixture of products from which it was difficult to separate pyrazole derivatives. A method of cyclization of various acylhydrazones with benzoylacetone in the presence of phosphorus oxychloride at 0°C has been described in the literature [4, 5]. Use of this catalyst was very suitable for our objectives. A catalytic amount of phosphorus oxychloride permitted formation of pyrazoles **5a-e** at room temperature in 1-6 h. The formation of pyrazoles **6a-e** from **1a-e** and dibenzoylmethane **4** occurred on refluxing the components for 1-4 h.

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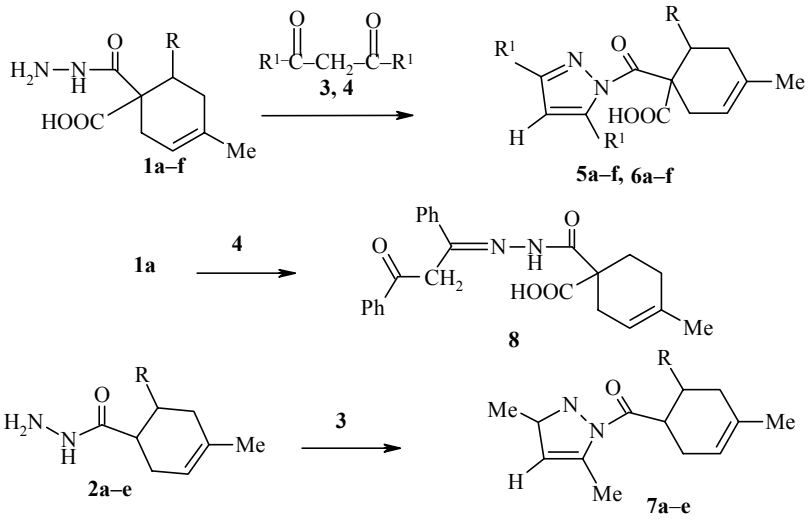
Scheme 1



1, 2, 5–7 a R = Ph**; b** R = *p*-C_6H_4–F; **c** R = *p*-C_6H_4–Cl;
d R = *p*-C_6H_4–Br; **e** R = *p*-C_6H_4–NO_2; **5**, **6 f** R = H; **3**, **5** R^1 = Me; **4**, **6** R^1 = Ph

TABLE 1. Characteristics of the Compounds Synthesized **5a-f**, **6a-f**, and **7a-e**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal		
5a	$C_{20}H_{22}N_2O_3$	71.03 / 70.99	6.72 / 6.55	8.45 / 8.28		137-139	80
5b	$C_{20}H_{21}FN_2O_3$	67.61 / 67.40	5.90 / 5.94	7.81 / 7.86	5.18 / 5.33	150-152	60
5c	$C_{20}H_{21}ClN_2O_3$	66.61 / 64.43	5.73 / 5.68	7.72 / 7.51	9.63 / 9.51	149-150	83
5d	$C_{20}H_{21}BrN_2O_3$	57.71 / 57.56	5.13 / 5.07	6.83 / 6.71	19.28 / 19.15	143-144	84.7
5e	$C_{20}H_{21}N_3O_5$	62.78 / 62.65	5.81 / 5.52	10.82 / 10.96		120-122	87
5f	$C_{14}H_{18}N_2O_3$	64.13 / 64.11	6.70 / 6.92	10.73 / 10.68		141-142	70
6a	$C_{30}H_{26}N_2O_3$	77.94 / 77.90	5.81 / 5.67	6.16 / 6.06		194-195	86
6b	$C_{30}H_{25}FN_2O_3$	75.03 / 74.98	5.41 / 5.24	5.92 / 5.83	3.92 / 3.95	163-165	79
6c	$C_{30}H_{25}ClN_2O_3$	72.44 / 72.50	5.02 / 5.07	5.60 / 5.64	7.08 / 7.13	199-200	83
6d	$C_{30}H_{25}BrN_2O_3$	66.58 / 66.55	4.72 / 4.65	5.23 / 5.17	14.82 / 14.76	196-197	84
6e	$C_{30}H_{25}N_3O_5$	70.78 / 70.99	5.03 / 4.96	8.41 / 8.28		182-183	57
6f	$C_{24}H_{22}N_2O_3$	74.71 / 74.59	5.82 / 5.74	7.38 / 7.25		183-185	83
7a	$C_{19}H_{22}N_2O$	77.62 / 77.52	7.61 / 7.53	9.68 / 9.52		91-92	51
7b	$C_{19}H_{21}FN_2O$	73.15 / 73.05	6.82 / 6.76	9.03 / 8.97	6.12 / 6.08	96-97	56
7c	$C_{19}H_{21}ClN_2O$	69.48 / 69.40	6.61 / 6.44	8.71 / 8.52	10.83 / 10.78	82-83	83
7d	$C_{19}H_{21}BrN_2O$	61.40 / 61.13	5.72 / 5.67	7.80 / 7.50	21.46 / 21.41	110-111	61
7e	$C_{19}H_{21}N_3O_3$	67.03 / 67.24	6.14 / 6.24	12.27 / 12.38		146-147	75

Compound **1f** reacted with acetylacetone **3** even at room temperature in the absence of catalyst to give pyrazole **5f**. However, compound **1f** with dibenzoylmethane **4** gave only the monohydrazone **8**, which we isolated and characterized. To obtain the diphenylpyrazole **6f** it was necessary to reflux the components in ethanol for 3 h.

The preparative method for synthesis of pyrazoles **7a-e** from the hydrazides **2a-e** and 1,3-diketones worked well when hydrazides **2a-e** and acetylacetone **3** were used. The pyrazoles **7a-e** were obtained in good yield (51-83%) by refluxing the components in ethanol without a catalyst.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds **5-7**

Com-pound	^{1}H NMR spectra, δ, ppm
5a	1.75 (3H, s, CH_3); 2.06 (3H, s, CH_3); 2.48 (3H, s, CH_3); 2.17-3.17 (4H, m, $3CH_2$); 3.73 (1H, m, CH); 5.42 (1H, m, =CH–); 5.86 (1H, s, =CH–); 7.22 (5H, centre m, C_6H_5); 10.40 (1H, br. s, COOH)
5b	1.66 (3H, s, CH_3); 2.02 (3H, s, CH_3); 2.42 (3H, s, CH_3); 2.10-3.21 (4H, m, $2CH_2$); 3.68 (1H, m, CH); 5.40 (1H, m, =CH–); 5.84 (1H, s, =CH–); 6.80-7.17 (4H, m, C_6H_4); 10.30 (1H, br. s, COOH)
5c	1.67 (3H, s, CH_3); 1.98 (3H, s, CH_3); 2.44 (3H, s, CH_3); 2.16-3.26 (4H, m, $2CH_2$); 3.67 (1H, m, CH); 5.32 (1H, m, =CH–); 5.83 (1H, s, =CH–); 6.95 (4H, m, C_6H_4); 10.03 (1H, br. s, COOH)
5d	1.69 (3H, s, CH_3); 1.96 (3H, s, CH_3); 2.44 (3H, s, CH_3); 2.18-3.40 (4H, m, $2CH_2$); 3.65 (1H, m, CH); 5.32 (1H, m, =CH–); 5.81 (1H, s, =CH–); 6.86-7.15 (4H, m, C_6H_4); 9.81 (1H, br. s, COOH)
5e	1.72 (3H, s, CH_3); 2.02 (3H, s, CH_3); 2.46 (3H, s, CH_3); 2.21-3.28 (4H, m, $2CH_2$); 3.74 (1H, m, CH); 5.37 (1H, m, =CH–); 5.87 (1H, s, =CH–); 7.22 (2H, m, C_6H_4); 7.94 (2H, m, C_6H_4); 10.10 (1H, br. s, COOH)
5f	1.64 (3H, s, CH_3); 2.08 (3H, s, CH_3); 2.44 (3H, s, CH_3); 1.77-2.62 (6H, m, $3CH_2$); 5.40 (1H, m, =CH–); 5.86 (1H, s, =CH–); 10.66 (1H, br. s, COOH)
6a	1.61 (3H, s, CH_3); 1.94-2.98 (4H, m, $2CH_2$); 3.86-4.00 (1H, m, CH); 5.47 (1H, m, =CH–); 6.86 (1H, s, =CH–); 7.33-7.77 (15H, m, $3C_6H_5$); 12.90 (1H, br. s, COOH)
6b	1.65 (3H, s, CH_3); 1.96-2.74 (4H, m, $2CH_2$); 3.42 (1H, m, CH); 5.52 (1H, m, =CH–); 7.02-8.37 (15H, m, $2C_6H_5$, C_6H_4, =CH–); 12.68 (1H, br. s, COOH)
6c	1.66 (3H, s, CH_3); 2.01-2.78 (4H, m, $2CH_2$); 3.66 (1H, m, CH); 5.58 (1H, m, =CH–); 7.08-8.05 (15H, m, $2C_6H_5$, C_6H_4, =CH–); 13.19 (1H, br. s, COOH)
6d	1.68 (3H, s, CH_3); 2.18-3.28 (4H, m, $2CH_2$); 3.70 (1H, m, CH); 5.54 (1H, m, =CH–); 6.02-8.23 (15H, m, $2C_6H_5$, C_6H_4, =CH–); 12.97 (1H, br. s, COOH)
6e	1.74 (3H, s, CH_3); 2.00-3.14 (4H, m, $2CH_2$); 3.92 (1H, m, CH); 5.66 (1H, m, =CH–); 7.22-8.29 (15H, m, $2C_6H_5$, C_6H_4, =CH–); 13.33 (1H, br. s, COOH)
6f	1.62 (3H, s, CH_3); 1.95-2.62 (6H, m, $3CH_2$); 5.33 (1H, m, =CH–); 6.48 (1H, s, =CH–); 7.26-7.71 (10H, m, $2C_6H_5$); 10.70 (1H, br. s, COOH)
7a	1.73 (3H, s, CH_3); 2.15 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.14-3.04 (4H, m, $2CH_2$); 3.57 (1H, m, CH); 4.13 (1H, m, CH); 5.51 (1H, m, =CH–); 5.91 (1H, s, =CH–); 6.88-7.17 (5H, m, C_6H_5)
7b	1.75 (3H, s, CH_3); 2.13 (3H, s, CH_3); 2.37 (3H, s, CH_3); 2.13-2.91 (4H, m, $2CH_2$); 3.62 (1H, m, CH); 4.16 (1H, m, CH); 5.53 (1H, m, =CH–); 5.95 (1H, s, =CH–); 6.84-7.29 (4H, m, C_6H_4)
7c	1.73 (3H, s, CH_3); 2.11 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.11-2.84 (4H, m, $2CH_2$); 3.64 (1H, m, CH); 4.15 (1H, m, CH); 5.51 (1H, m, =CH–); 5.96 (1H, s, =CH–); 6.82 (2H, m, C_6H_4); 7.17 (2H, m, C_6H_4)
7d	1.69 (3H, s, CH_3); 2.15 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.07-2.84 (4H, m, $2CH_2$); 3.61 (1H, m, CH); 4.10 (1H, m, CH); 5.50 (1H, m, =CH–); 5.90 (1H, s, =CH–); 6.80 (2H, m, C_6H_4); 7.38 (2H, m, C_6H_4)
7e	1.73 (3H, s, CH_3); 2.15 (3H, s, CH_3); 2.33 (3H, s, CH_3); 2.20-2.88 (4H, m, $2CH_2$); 3.73 (1H, m, CH); 4.22 (1H, m, CH); 5.53 (1H, m, =CH–); 5.93 (1H, s, =CH–); 7.15 (2H, m, C_6H_4); 8.04 (2H, m, C_6H_4)

The hydrazides **2a-e** did not react with dibenzoylmethane **4** at room temperature, but on refluxing in ethanol with or without a catalyst other products were formed along with the pyrazoles.

It follows from the above that, as expected, acetylacetone is more reactive than dibenzoylmethane in reactions with hydrazides **1** and **2**. It follows from the experimental results that the hydrazides may be placed in the following order of their tendencies to react with 1,3-diketones to form the pyrazole ring: **1f** > **1b-d** > **1a** > **1e**.

The pyrazoles **5a-f** and **6a-f** are stable at high temperatures. This was confirmed by an attempt to convert them into the corresponding decarboxylated pyrazoles, using compound **5d** as an example. Even after 3 h at its melting point, **5d** was only partially decarboxylated (monitored by chromatography with solvent system A).

The composition of the synthesized compounds was confirmed by elemental analysis, and their structure was confirmed by their ^{1}H NMR spectra in which the resonance signals for the protons of all the structural units of the molecules were observed in their characteristic ranges.

EXPERIMENTAL

The ^{1}H NMR spectra of $CDCl_3$ and DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker WH-90/DS (90 MHz) spectrometer. Purity of the compounds obtained was monitored by TLC on Silufol strips with 90:1:1 chloroform–methanol–glacial acetic acid solvent (A).

Characteristics and ^{1}H NMR spectra of the compounds synthesized are cited in Tables 1 and 2

1-(1-Carboxy-2-R-4-methylcyclohex-4-enyl)carbonyl-3,5-dimethylpyrazoles (5a-f). Acetylacetone **3** (0.0025 mol) and phosphorus oxychloride (3 drops) were added to a solution of hydrazides **1a-f** (0.002 mol) in ethanol (10 ml). (The reaction with **1f** occurred without catalyst). The mixtures were stirred at room temperature: **1a** – 2.5 h, **1b** – 1 h, **1c,d** – 2 h, **1e** – 6 h, **1f** – 0.6 h. The solution was evaporated to half its volume and an equal volume of water was added. The precipitate was filtered off. Compound **5f** was chromatographically pure. Compounds **5a-c** and **5e** were recrystallized from 1:1 ethanol–water, while compound **5d** was recrystallized from 1:1 ethyl acetate–hexane.

1-(1-Carboxy-2-R-4-methylcyclohex-4-enyl)carbonyl-3,5-diphenylpyrazoles (6a-f). Dibenzoylmethane **4** (0.0025 mol) and phosphorus oxychloride (5 drops) were added to a solution of hydrazides **1a-f** (0.002 mol) in ethanol (10 ml) (the reaction with **1f** occurred without a catalyst) and the mixtures were refluxed for : **6a** – 1.5 h, **6b-d** – 1 h, **6e** – 4h, **6f** – 3f. The solutions were filtered and the residues were washed on the filter with ethanol. Compounds **6a-f** were chromatographically pure without recrystallization.

Dibenzoylmethane 1-Carboxy-4-methyl-4-cyclohexen-1-carbohydrazone (8). A solution of hydrazide **1f** (0.002 mol) and an equimolar amount of dibenzoylmethane **4** in ethanol (10 ml) was stirred for 2 h at room temperature. The ethanol was evaporated, water (12 ml) was added, the mixture was kept for 3 h and then filtered. Yield 0.31 g (53%); mp 195-196°C (1:1 ethanol–water). ^{1}H NMR spectrum, δ, ppm: 1.56 (3H, s, CH_3); 1.83-2.46 (6H, m, 3 CH_2); 2.95-3.52 (2H, m, CH_2); 5.15 (1H, br. s, NH); 5.24 (1H, br. s, =CH); 6.70-7.52 (10H, m, 2 C_6H_5); 10.10 (1H, br. s, COOH).

1-(2-R-4-Methylcyclohex-4-enyl)carbonyl-3,5-dimethylpyrazoles (7a-e). Acetylacetone **3** (0.0025 mol) was added to a solution of hydrazides **2a-e** (0.002 mol) in ethanol (7 ml) and the mixture was refluxed for 2 h (**2e** – 3 h). The solution was evaporated to half volume, an equal volume of water was added, and the mixture was filtered. The products were recrystallized from methanol (**7e** from a 2:1 methanol–water mixture).

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