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SYNTHESIS OF 1-ACYL-5-AMINO-4-ETHOXYCARBONYLPYRAZOLES FROM MONOHYDRAZIDES OF CYCLOHEXENEDICARBOXYLIC ACIDS AND ETHYL ETHOXYMETHYLENECYANOACETATE

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Heating monohydrazides of cyclohexenedicarboxylic acids with ethyl ethoxymethylenecyanoacetate at reflux gives the corresponding N-substituted hydrazides. This reaction carried out in pyridine gives 1-acyl-5-amino-4-ethoxycarbonylpyrazoles.

Keywords: hydrazides, pyrazoles, cyclohexenedicarboxylic acid, ethyl ethoxymethylenecyanoacetate.

Pyrazole derivatives such as antipyrine, phenylbutazone, oxyphenbutazone, and sulfinpyrazole are used as nonsteroidal analgesics and antipyretics [1-4].

The introduction of acyl and aracyl groups into indomethacin and ketophenylbutazone significantly enhances their therapeutic activity and lipid solubility [5, 6].

These findings led us to study the synthesis of 1-acyl-5-amino-4-ethoxycarbonylpyrazoles from ethyl ethoxymethylenecyanoacetate (**1**) and monohydrazides of 2-(4-R-phenyl)-4-cyclohex-4-ene-1,1-dicarboxylic acids **2a-e** described in our previous work [7].

Similar syntheses have been described in the literature. Despite the presence of three reaction sites in ester **1**, the condensation of this compound with hydrazides occurs exclusively at the ethoxymethylene group. The prolonged heating of ethyl ester **1** with hydrazides of substituted benzoic acids in methanol at reflux in the presence of catalytic amounts of glacial acetic acid gave 5-amino-1-aroyl-4-ethoxycarbonylpyrazoles [10, 11].

Brief heating of ester **1** and 4(2)-methoxyhydrazides of benzoic acids at reflux gave the corresponding hydrazones, which, according to Bagrov [9], are incapable of further cyclization.

We have found that both linear and cyclic products may be formed in the reaction of enol ester **1** with hydrazides of cyclohexenedicarboxylic acids **2a-e**, depending on the reaction conditions. The linear intermediate can undergo cyclization. Heating enol ester **1** with hydrazides **2a-e** in ethanol at reflux for 1 h gives N-substituted hydrazides **3a-e** [12], while heating the reaction components in pyridine at reflux for 1 h leads to pyrazoles **4a-e** (Scheme 1).

The products, 1-acyl-5-amino-4-ethoxycarbonylpyrazoles **4a-e**, are stable crystalline compounds.

The reaction of pyrazoles **4a-e** with formamide under conditions for the synthesis of pyrazolopyrimidines [8] leads to amides **5a-e** [13], while the alkaline hydrolysis of these compounds according to Schmidt and Drye [8] gave previously unreported cyclohexenecarboxylic acids **6a-e** [14] instead of the expected pyrazolecarboxylic acids.

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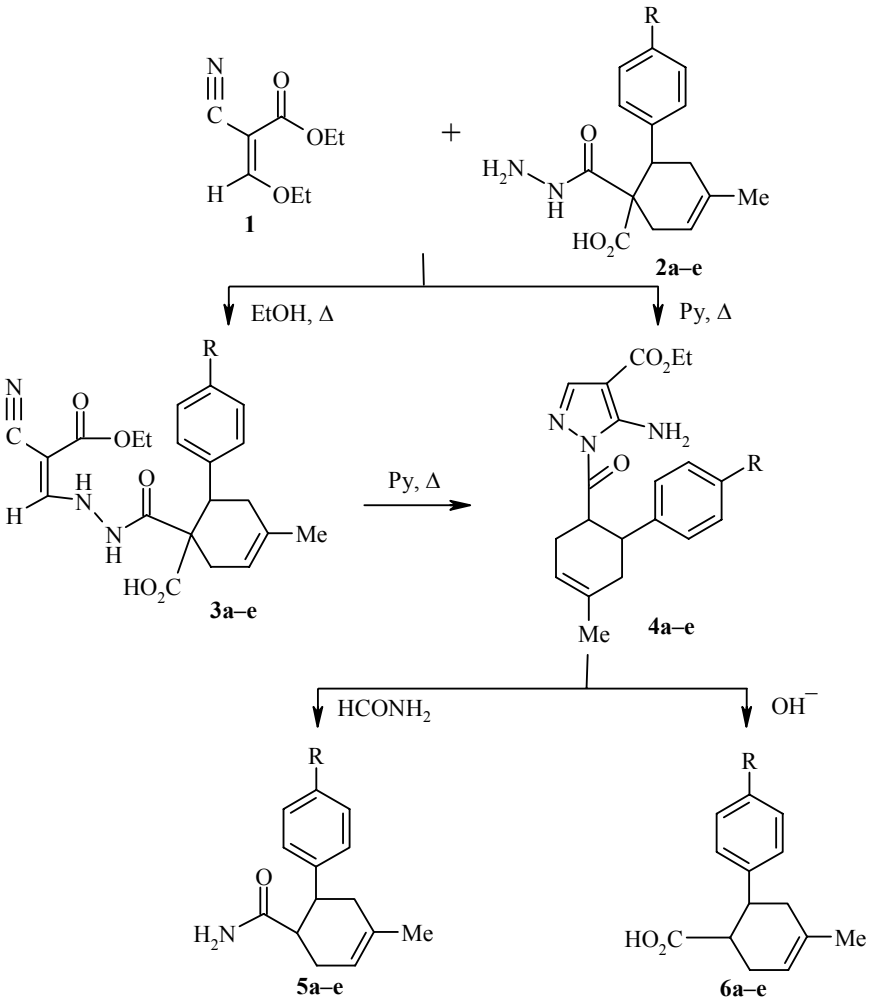
Scheme 1



a R = H; **b** R = F; **c** R = Cl; **d** R = Br; **e** R = NO_2

TABLE 1. Characteristics of 1-Acyl-5-amino-4-ethoxycarbonylpyrazoles **4a-e**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal		
4a	$C_{20}H_{23}N_3O_3$	68.02 / 67.97	6.58 / 6.56	11.72 / 11.89		95-98	49.4
4b	$C_{20}H_{22}FN_3O_3$	64.82 / 64.68	6.00 / 5.97	11.02 / 11.31		119-120	64.3
4c	$C_{20}H_{22}ClN_3O_3$	61.85 / 61.93	5.79 / 5.72	10.72 / 10.83	9.18 / 9.14	142-144	58.4
4d	$C_{20}H_{22}BrN_3O_3$	55.70 / 55.56	5.10 / 5.13	9.84 / 9.72	18.54 / 18.48	150-151	59.4
4e	$C_{20}H_{22}N_4O_5$	60.40 / 60.29	5.60 / 5.57	14.18 / 14.06		172-173	62.3

TABLE 2. ^{1}H NMR Spectra of 1-Acyl-5-amino-4-ethoxycarbonylpyrazoles **4a-e**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
4a	1.27 (3H, t, *J* = 7, CH_3); 1.69 (3H, s, CH_3); 2.09-2.51 (4H, m, $2CH_2$); 3.58 (1H, m, CH); 3.91 (1H, m, CH); 4.18 (2H, m, $2CH_2$); 5.44 (1H, m, =CH–); 6.89-7.21 (7H, m, Ar, NH_2); 7.58 (1H, s, =CH–)
4b	1.27 (3H, t, *J* = 7, CH_3); 1.71 (3H, s, CH_3); 2.11-2.71 (4H, m, $2CH_2$); 3.61 (1H, m, CH); 3.91 (1H, m, CH); 4.24 (2H, q, *J* =7, CH_2); 5.44 (1H, m, =CH–); 6.69–6.93 (6H, m, Ar, NH_2); 7.62 (1H, s, =CH–)
4c	1.28 (3H, t, *J* = 7, CH_3); 1.67 (3H, s, CH_3); 2.09–2.71 (4H, m, $2CH_2$); 3.61 (1H, m, CH); 3.89 (1H, m, CH); 4.24 (2H, q, *J* = 7, CH_2); 5.44 (1H, m, =CH–); 6.84 (2H, m, *J* = 8, Ar); 6.92 (2H, br. s, NH_2); 7.08 (2H, m, *J* = 8, Ar); 7.62 (1H, s, =CH–)
4d	1.28 (3H, t, *J* = 7, CH_3); 1.73 (3H, s, CH_3); 2.08-2.73 (4H, m, $2CH_2$); 3.67 (1H, m, CH); 3.96 (1H, m, CH); 4.18 (2H, q, *J* = 7, CH_2); 5.44 (1H, m, =CH–); 6.84 (2H, m, *J* = 7, Ar); 7.01 (2H, br. s, NH_2); 7.27 (2H, m, *J* = 7, Ar); 7.64 (1H, s, =CH–)
4e	1.28 (3H, t, *J* = 7, CH_3); 1.73 (3H, s, CH_3); 2.11-2.62 (4H, m, $2CH_2$); 3.73 (1H, m, CH); 4.04 (1H, m, CH); 4.29 (2H, q, *J* = 7, CH_2); 5.59 (1H, m, =CH–); 6.89 (2H, br. s, NH_2); 7.07 (2H, m, *J* = 8, Ar); 7.62 (1H, s, =CH–); 8.04 (2H, m, *J* = 8, Ar)

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a WH-90DS spectrometer at 90 MHz in $CDCl_3$ with HMDS (δ 0.05 ppm) as the internal standard. The purity of the products was checked by thin-layer chromatography on Silufol plates using 95:5:3 chloroform–methanol–glacial acetic acid as the eluent.

The physicochemical and spectral data of these products are given in Tables 1 and 2.

A sample of ethyl ethoxymethylenecyanoacetate (**1**) was provided by BAPEKS.

5-Amino-1-[1-carbonyl-2-(4-R-phenyl)-4-cyclohex-4-ene]-4-ethoxycarbonylpyrazoles 4a-e. A solution of hydrazides **2a-e** (2 mmol) and an equimolar amount of ethyl ester **1** in pyridine (4 ml) was heated at reflux for 1 h. Pyridine was distilled off and the residue was recrystallized from ethanol (for **4a** and **4c-e**) or 2:1 ethanol–water (for **4b**).

Pyrazoles 4a-e were synthesized analogously from linear N-substituted hydrazides **3a-e**.

Amides of 2-(4-R-Phenyl)-4-cyclohex-4-ene-1-carboxylic Acids 5a-5e. A solution of pyrazole **4a-e** (1 mmol) and formamide (0.6 ml) was heated for 8 h at 190-200°C. The mixture was cooled and 1 N aq. NaOH (~2 ml) was added. The precipitate was filtered off and recrystallized from 1:1 ethanol–water. The data for these samples of **5a-e** were identical to those of samples previously obtained [13].

2-(4-R-Phenyl)-4-cyclohex-4-ene-carboxylic Acids 6a-e. Samples of pyrazoles **4a-e** (1 mmol) were dissolved upon heating in aq. NaOH (2.5 ml). After 15 min, the mixtures were cooled and an equal volume of water was added. The mixture was acidified to pH ~5 by adding a 1:1 mixture of concentrated hydrochloric acid and water. The residue was filtered off and recrystallized from 2:1 methanol–water. The data for these samples of **6a-e** were identical to those obtained in our previous work [14].

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