*Chemistry of Heterocyclic Compounds, Vol. 41, No. 7, 2005*

# SYNTHESIS OF DERIVATIVES OF PYRAZOLIN-1H-3-ONES FROM 2'-N-SUBSTITUTED MONOHYDRAZIDES OF CYCLOHEXENEDICARBOXYLIC ACIDS

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*2-(6-Aryl-4-methylcyclohex-3-enecarbonyl)-4-ethoxycarbonylpyrazolin-1H-3-ones have been synthesized from 2'-N-(2,2-diethoxycarbonylvinyl)monohydrazides of 6-aryl-4-methylcyclohex-3-ene-1,1-dicarboxylic acids by boiling in DMF, pyridine, or toluene in the presence of potassium carbonate. Under analogous conditions, but without potassium carbonate, 2'-N-substituted hydrazides of cyclohexenecarboxylic acids are obtained.*

**Keywords:** hydrazide, ethoxymethylenemalonic acid diethyl ester, pyrazoline, pyrazolin-5-one, cyclohexenecarboxylic acid.

After the Knorr synthesis of antipyrine (2,3-dimethyl-1-phenylpyrazolin-5-one) [1] work continued on the preparation of new pyrazolin-5-ones, since many of them are widely used in color photography and are applied in medicine as pharmacological preparations with analgesic and antipyretic action [2-4].

Results are given in the present paper on a study of the possibility of obtaining pyrazolin-5-ones from 2'-N-(2,2-dicarbethoxyethylenyl)monohydrazides of 6-aryl-4-methylcyclohex-3-ene-1,1-dicarboxylic acids **1a-e**, synthesized by us previously by condensing monohydrazides of 6-Ar-4-methylcyclohex-3-ene-1,1-dicarboxylic acids with diethyl ethoxymethylenemalonate [5].

One of the methods of obtaining pyrazolin-5-ones is based on the cyclization of N-substituted hydrazides obtained analogously to compound **1** [6-9]. Reaction is effected in a melt at 170-175°C [6], on boiling in water [7, 8], or ethanol [9] in the presence of potassium carbonate [8, 9], sodium carbonate [7], or sodium ethylate [9].

Attempts by us to cyclize monohydrazides **1a-e** under the conditions indicated above were unsuccessful. After boiling hydrazides **1a-e** in ethanol or acetonitrile for 3 h in the presence of potassium carbonate the starting compound **1** was isolated from the reaction medium, and an increase in the duration of the reaction to 10 h led to a mixture of substances. Chromatographically heterogeneous products were also obtained on melting hydrazides **1a-e** or boiling them in water with 1 equiv. potassium carbonate. By using a 2-10-fold excess of potassium carbonate the N-substituted hydrazides **1a-e** were hydrolyzed to the initial N-unsubstituted hydrazides (Scheme 1).

We found that the desired pyrazolin-5-ones **2** may be synthesized on carrying out the cyclization in solvents having a boiling point above 100°C. Boiling N-substituted hydrazides **1a-e** with 3 equiv. potassium carbonate in DMF, pyridine, or toluene leads to a 50-80% yield of 2-acyl-4-ethoxycarbonylpyrazolin-1H-3-ones **2a-e** and/or their tautomers 1-acyl-3-ethoxycarbonyl-2-hydroxypyrazoles **3a-e**. The formation of compounds **2** and **3** are the result of decarboxylation accompanying cyclization.

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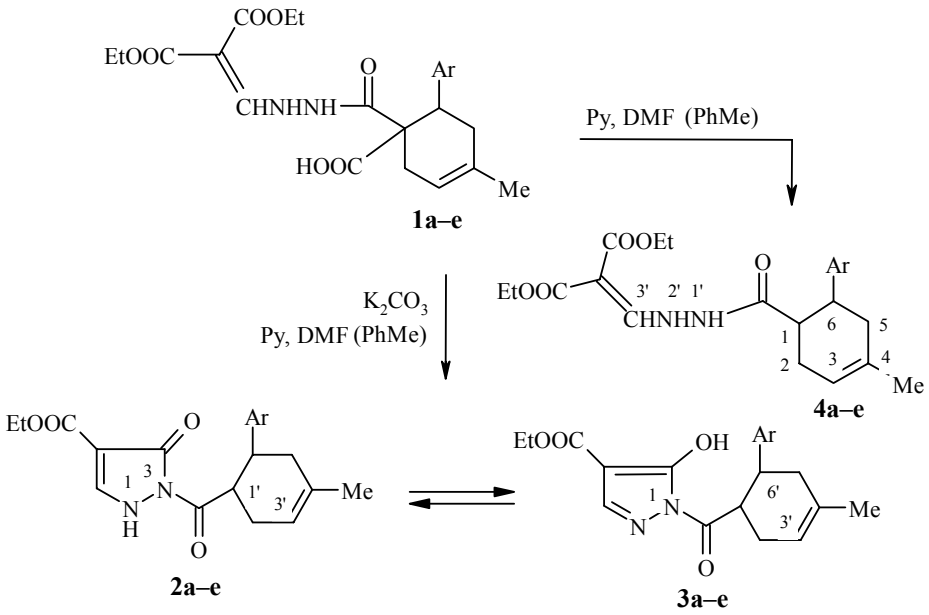
Scheme 1




**2-4** Ar = $C_6H_4X$-*p*; **a** X = H, **b** X = F, **c** X = Cl, **d** X = Br, **e** X = $NO_2$

Under the conditions described above, but without potassium carbonate, decarboxylation products were obtained from 1,1-cyclohexenedicarboxylic acid monohydrazides **1a-e**. These were cyclohexenecarboxylic acid hydrazides **4a-e**.

It is known that pyrazolinones having one unsubstituted nitrogen atom in the ring may exist in two tautomeric forms [3, 6, 9].

TABLE 1. Characteristics of the Synthesized Compounds **2**(**3**) and **4**

| Compound | Empirical formula | Found, % / Calculated, % | | | | mp, °C | Yield, % |
|---|---|---|---|---|---|---|---|
| | | C | H | N | Hal | | |
| **2(3)a** | $C_{20}H_{22}N_2O_4$ | 67.50 / 67.78 | 6.28 / 6.26 | 7.82 / 7.90 | | 213-214 | 62.7 |
| **2(3)b** | $C_{20}H_{21}FN_2O_4$ | 64.34 / 64.50 | 5.68 / 5.68 | 7.43 / 7.52 | | 202-204 | 59.2 |
| **2(3)c** | $C_{20}H_{21}ClN_2O_4$ | 61.80 / 61.78 | 5.51 / 5.44 | 7.17 / 7.20 | 9.20 / 9.12 | 209-210 | 50.1 |
| **2(3)d** | $C_{20}H_{21}BrN_2O_4$ | 55.51 / 55.43 | 4.79 / 4.88 | 6.51 / 6.46 | 18.31 / 18.44 | 210-211 | 55.3 |
| **2(3)e** | $C_{20}H_{21}N_3O_6$ | 60.05 / 60.14 | 5.28 / 5.30 | 10.43 / 10.52 | | 190-192 | 80.1 |
| **4a** | $C_{22}H_{28}N_2O_5$ | 65.88 / 65.97 | 7.13 / 7.06 | 6.81 / 6.99 | | 85-87 | 66.0 |
| **4b** | $C_{22}H_{27}FN_2O_5$ | 63.03 / 63.15 | 6.46 / 6.50 | 6.63 / 6.69 | | 128-130 | 71.2 |
| **4c** | $C_{22}H_{27}ClN_2O_5$ | 60.69 / 60.76 | 6.31 / 6.26 | 6.39 / 6.44 | 8.20 / 8.15 | 103-105 | 57.2 |
| **4d** | $C_{22}H_{27}BrN_2O_5$ | 55.21 / 55.12 | 5.74 / 5.68 | 5.80 / 5.84 | 16.99 / 16.67 | 102-104 | 48.2 |
| **4e** | $C_{22}H_{27}N_3O_7$ | 59.41 / 59.32 | 6.20 / 6.11 | 9.51 / 9.43 | | 107-109 | 66.7 |

TABLE 2. Spectral Characteristics of the Synthesized Compounds **2**(**3**) and **4**

| Compound | IR spectrum*, $cm^{-1}$ | | $^1H$ NMR($CDCl_3$), δ, ppm (SSCC, *J*, Hz) |
|---|---|---|---|
| | C=O | NH/OH | |
| **2(3)a** | 1718, 1648 | 3152 | 1.22 (3H, t, *J* = 7.2, $CH_3$); 1.61 (3H, s, 4'-$CH_3$); 2.11-2.52 (4H, m, $2CH_2$); 3.21 (1H, m, CH); 4.22 (2H, q, *J* = 7.2, $CH_2$); 4.46 (1H, m, CH); 5.42 (1H, br. s, H-3'); 7.13 (5H, m, $C_6H_5$); 7.81 (1H, s, H-5); 12.10 (1H, br. s, NH) |
| **2(3)b** | 1718, 1668 | 3152 | 1.25 (3H, t, *J* = 7.0, $CH_3$); 1.65 (3H, s, 4'-$CH_3$); 2.18-2.40 (4H, m, $2CH_2$); 3.21 (1H, m, CH); 4.22 (2H, q, *J* = 7.0, $CH_2$); 5.39 (1H, br. s, H-3'); 6.77-7.15 (4H, m, Ar); 7.68 (1H, s, H-5); 9.98 (1H, br. s, NH) |
| **2(3)c** | 1720, 1656 | 3144 | 1.31 (3H, t, *J* = 7.0, $CH_3$); 1.68 (3H, s, 4'-$CH_3$); 2.14-2.67 (4H, m, $2CH_2$); 3.27 (1H, m, CH); 4.22 (2H, q, *J* = 7.0, $CH_2$); 4.58 (1H, m, CH); 5.47 (1H, br. s, H-3'); 7.19 (5H, m, Ar); 7.92 (1H, s, H-5); 13.19 (1H, br. s, NH) |
| **2(3)d** | 1720, 1668 | 3144 | 1.23 (3H, t, *J* = 7.0, $CH_3$); 1.64 (3H, s, 4'-$CH_3$); 2.15-2.42 (4H, m, $2CH_2$); 3.21 (1H, m, CH); 4.15 (1H, m, CH); 4.21 (2H, q, *J* = 7.0, $CH_2$); 5.47 (1H, br. s, H-3'); 6.98 (2H, m, Ar); 7.37 (2H, m, Ar); 7.49 (1H, br. s, H-5); 9.89 (1H, br. s, NH) |
| **2(3)e** | 1712, 1650 | 3146 | 1.28 (3H, s, *J* = 7.0, $CH_3$); 1.78 (3H, s, 4'-$CH_3$); 2.24-2.62 (4H, m, $2CH_2$); 3.77 (1H, m, CH); 4.08 (1H, m, CH); 4.29 (2H, q, *J* = 7.0, $CH_2$); 5.57 (1H, br. s, H-3'); 7.16 (2H, m, Ar); 7.73 (1H, s, H-5); 8.04 (2H, m, Ar); 11.80 (1H, br. s, NH) |
| **4a** | 1726, 1712, 1650 | 3360, 3240 | 1.16 (6H, m, $2CH_3$); 1.67 (3H, s, 4-$CH_3$); 2.26-3.41 (6H, m, 2CH, $2CH_2$); 4.11 (4H, m, $2CH_2$); 5.37 (1H, br. s, H-3); 7.16-7.61 (7H, m, $C_6H_5$, H-3', NH); 9.56 (1H, br. s, NH) |
| **4b** | 1728, 1710, 1648 | 3355, 3230 | 1.22 (3H, t, *J* = 7.0, $CH_3$); 1.25 (3H, t, *J* = 7.0, $CH_3$); 1.71 (3H, s, 4-$CH_3$); 2.21-3.31 (4H, m, $2CH_2$); 2.71 (1H, m, CH); 3.38 (1H, m, CH); 4.11 (4H, m, $2CH_2$); 5.40 (1H, br. s, H-3); 6.91-7.22 (7H, m, Ar); 7.44 (1H, br. s, H-1'); 7.64 (1H, d , *J* = 11.0, H-3'); 9.71 (1H, d, *J* = 11.0, H-2') |
| **4c** | 1726, 1708, 1650 | 3320, 3220 | 1.23 (6H, m, $2CH_3$); 1.67 (3H, s, 4-$CH_3$); 2.09-2.51 (4H, m, $2CH_2$); 2.71 (1H, m, CH); 3.36 (1H, m, CH); 4.09 (4H, m, $2CH_2$); 5.44 (1H, br. s, H-3); 7.16 (4H, m, Ar); 7.66 (1H, br. s, NH), 7.91 (1H, br. s, H-3'); 9.71 (1H, br. s, NH) |
| **4d** | 1720, 1707, 1646 | 3353, 3225 | 1.22 (6H, m, $2CH_3$); 1.67 (3H, s, 4-$CH_3$); 2.20-2.32 (4H, m, $2CH_2$); 2.81 (1H, m, CH); 3.44 (1H, m, CH); 3.95 (4H, m, $2CH_2$); 5.44 (1H, br. s, H-3); 6.93 (2H, m, Ar); 7.27 (3H, m, Ar, H-3'); 8.31 (1H, br. s, NH); 8.69 (1H, br. s, NH) |
| **4e** | 1725, 1708, 1648 | 3350, 3230 | 1.26 (6H, m, $2CH_3$); 1.67 (3H, s, 4-$CH_3$); 2.18-2.41 (4H, m, $2CH_2$); 2.75 (1H, m, CH); 3.45 (1H, m, CH); 4.11 (4H, m, $2CH_2$); 5.44 (1H, br. s, H-3); 7.22 (3H, m, Ar, H-1'); 7.64 (1H, d, *J* = 12.0, H-3'); 8.02 (2H, m, Ar); 9.53 (1H, d, *J* = 12.0, H-2') |

* In nujol.

In the $^1H$ NMR spectra of the cyclization products taken in chloroform there were broadened signals at 9.89-13.19 ppm which may be assigned equally probably to the protons of the NH and OH groups of tautomers **2** and **3**. Determination of the tautomeric form with the aid of $^1H$ NMR is ambiguous (i.e. in $CHCl_3$ it might only be the OH tautomer).

The data of IR spectra in nujol may be more reliable. Two absorption bands were observed for the stretching vibrations of the carbonyl groups at 1712-1720 (ester) and 1648-1668 $cm^{-1}$ (amide), and also the very characteristic OH absorption of the tautomer at 3144-3152 $cm^{-1}$.

On the basis of literature information [9] on the tautomerism of 1-aryl-4-ethoxycarbonyl-3-pyrazolin-5-ones, and also on analysis of the data of IR and $^1H$ NMR spectra for the cyclization products obtained by us, it may be proposed that in chloroform they exist as substituted pyrazolinones **2a-e,** but in mineral oil and in the solid state they exist predominantly as hydroxypyrazoles **3a-e**.

## EXPERIMENTAL

The $^1$H NMR spectra spectra were obtained on a WH 90DS (90 MHz) instrument, solvent $CDCl_3$, internal standard was HMDS (δ 0.05 ppm). The IR spectra were recorded on a Specord IR 75 instrument in nujol.

The homogeneity of the synthesized compounds was checked with the aid of TLC on Silufol plates in chloroform–methanol–acetic acid, 95:5:3.

The characteristics of the synthesized compounds are given in Table 1, and the IR and $^1$H NMR data are given in Table 2.

**2-N-(6-Aryl-4-methylcyclohex-3-enecarbonyl)-4-ethoxycarbonyl-1H-pyrazolin-3-ones (2a-e) and/or 1-(6-Aryl-4-methylcyclohex-3-enecarbonyl)-4-ethoxycarbonyl-5-hydroxypyrazoles (3a-e).** A solution of hydrazide **1** (2 mmol) and potassium carbonate (6 mmol) in DMF, pyridine, or toluene (4 ml) was boiled for 2 h. The reaction mixture was cooled and poured into water (in the case of DMF into pyridine) or extracted several times with water (in the case of toluene). The aqueous solution was acidified with dilute hydrochloric acid to pH ~3. The precipitate of product **2/3** was filtered off, dried, and recrystallized from ethanol.

**2'-N-(2,2-Diethoxycarbonylvinyl)hydrazides of 6-Aryl-4-methylcyclohex-3-enecarboxylic Acids (4a-e).** A solution of hydrazide **1a** (2 mmol) in DMF, pyridine, or toluene (4 ml) was boiled for 2 h, then cooled, poured into water (in the case of DMF or pyridine), and acidified to pH ~6-7. The precipitate of solid product **4** was filtered off, dried, and recrystallized from aqueous ethanol. When using toluene, the solvent was distilled off, and the residue recrystallized from aqueous ethanol.

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