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Synthesis of 4-Hydroxy-4,5-dihydro-1,2,4-triazol-5-ones

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Summary. A series of hydroxamic acid ethoxycarbonylhydrazides was obtained by reactions of ester ethoxycarbonylhydrazones with hydroxylamine. The corresponding 3-substituted 4-hydroxy-4,5-dihydro-1,2,4-triazol-5-ones were synthesized by cyclization of these hydroxamic acid derivatives in basic medium.

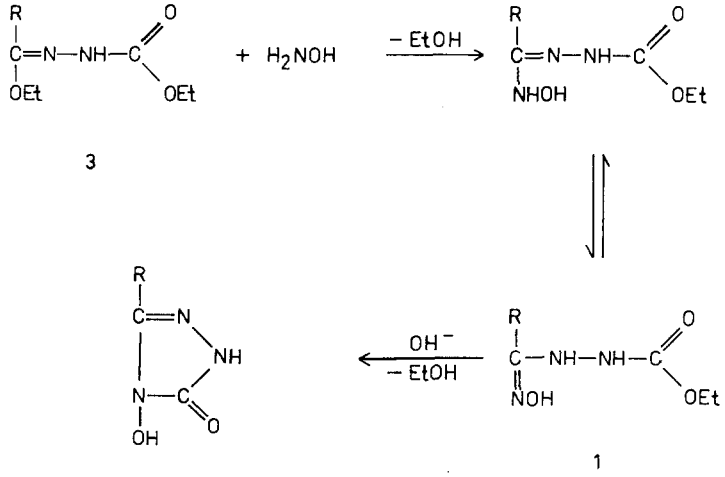
Keywords. Ester ethoxycarbonylhydrazones; Hydroxamic acid ethoxycarbonylhydrazides; 4-Hydroxy-4,5-dihydro-1,2,4-triazol-5-ones.

Synthesen von 4-Hydroxy-4,5-dihydro-1,2,4-triazol-5-onen

Zusammenfassung. Durch Reaktion von Esterethoxycarbonylhydrazonen und Hydroxylamin wurde eine Reihe von Hydroxamsäureethoxycarbonylhydraziden gewonnen; Cyclisierung dieser Verbindungen durch Base gab die entsprechenden 3-substituierten 4-Hydroxy-4,5-dihydro-1,2,4-triazol-5-one.

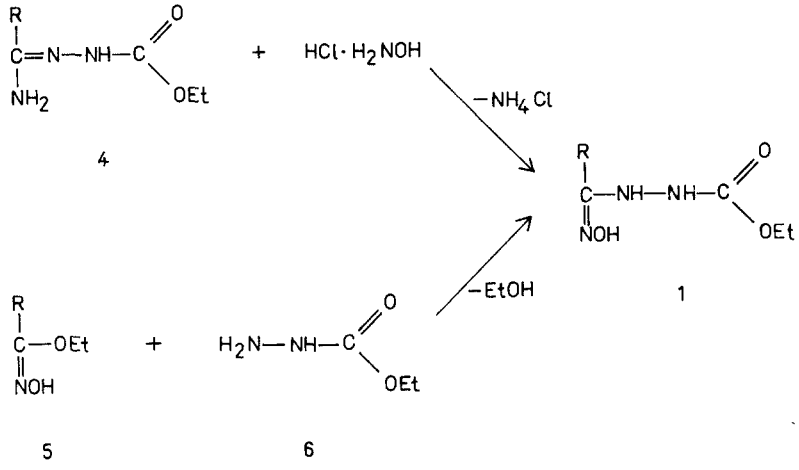
Introduction

A study involving a synthetic route for the preparation of some 4-hydroxy-4,5-dihydro-1,2,4-triazol-5-ones has recently been reported [1]. Other studies reporting several 4-hydroxy-4,5-dihydro-1,2,4-triazol-5-one derivatives [2] and a series of 4-



Scheme 1

hydroxy-4*H*-1,2,4-triazoles [3–5] have also been made. In the present study, a new method for the synthesis of 3-alkyl(aryl)-4-hydroxy-4,5-dihydro-1,2,4-triazol-5-ones (**2**) was developed. Thus, hydroxamic acid ethoxycarbonylhydrazides (N-hydroxamide ethoxycarbonylhydrazones) (**1**) were obtained by the reactions of ester ethoxycarbonylhydrazones (**3**) with hydroxylamine and cyclized to the corresponding compounds **2** by the action of hydroxide ions (Scheme 1). Moreover, some of compounds **1** were also synthesized by different routes starting from amide ethoxycarbonylhydrazones (**4**) or hydroxamic acide esters (**5**) (Scheme 2).



Scheme 2

Experimental Part

Melting points were determined with a Büchi oil heated melting point apparatus and are uncorrected. The infrared spectra were run as potassium bromide pellets using a Perkin-Elmer 377 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 60 A spectrometer or a Bruker AC-200 FT instrument. The ultraviolet absorption spectra were measured between 210 and 350 nm with a Varian spectrophotometer, using 10 mm quartz cells. Combustion analyses were performed on a Carlo Erba 1106 elemental analyzer. Potentiometric titrations were carried out using an Orion Model 601A digital *pH* meter equipped with an Ingold *pH* electrode.

The starting compounds **3** and **4** were synthesized by methods previously reported [6–8]. Ethyl acetohydroxamate (which is an important compound of type **5**) was obtained from Fluka.

Synthesis of Hydroxamic Acid Ethoxycarbonylhydrazides (**1**)

Method A: Hydroxylamine hydrochloride (0.01 mol) was dissolved in 40 ml of absolute ethanol and treated with an ethanolic sodium ethoxide solution prepared by dissolving sodium (0.01 mol) in 15 ml of absolute ethanol. After stirring 15 min at room temperature, a solution of type **3** ester ethoxycarbonylhydrazone (0.01 mol) in 50 ml of absolute ethanol was added into the mixture. After the addition, the mixture was refluxed for 4 h and cooled. The precipitate was filtered and the filtrate was evaporated at 30–35° under reduced pressure. Recrystallization of the crude product from an appropriate solvent gave pure compound **1**.

Method B: A solution of hydroxylamine hydrochloride (0.01 mol) in 40 ml of absolute ethanol was added to the solution of type **4** amide ethoxycarbonylhydrazone (0.01 mol) in 100 ml of absolute ethanol. The mixture was refluxed for 5 h and then filtered. Evaporation of the filtrate at 30–35° under reduced pressure and several recrystallizations of the residue from an appropriate solvent afforded pure compound **1**.

Method C: A mixture of ethyl acetohydroxamate (**5**) (0.01 mol) and ethyl carbazate (**6**) (0.01 mol) in 30 ml of absolute ethanol was refluxed for 4 h and cooled. After the evaporation of the mixture at 30–35° under reduced pressure, the crude product was recrystallized from *Et*O*Ac*-Benzene (1 : 1) and identified as compound **1 a**.

Table 1. Experimental data for compounds **1** and **2**

Compd.	*R*	Yield[a] (%)	M.p. (°C) (crystallized from)	Molecular[b] formula (*M*)
1 a	*Me*	65[c]	132 (*Ac*O*Et*-Benzene) (1 : 1)	$C_5H_{11}N_3O_3$ (161.16)
1 b	*Et*	67[d]	92 ($CHCl_3$)	$C_6H_{13}N_3O_3$ (175.19)
1 c	*Pr*	68	87 (Et_2O)	$C_7H_{15}N_3O_3$ (189.21)
1 d	CH_2Ph	70	100 (Et_2O)	$C_{11}H_{15}N_3O_3$ (237.25)
1 e	$CH_2C_6H_4 \cdot Cl(-p)$	56	142 (*Ac*O*Et*-Benzene) (1 : 2)	$C_{11}H_{14}ClN_3O_3$ (271.70)
1 f	*Ph*	54[e]	128 (Benzene)	$C_{10}H_{13}N_3O_3$ (223.23)
1 g	$C_6H_4 \cdot Cl(-p)$	61	105 (Petroleum ether) (40–60°)	$C_{10}H_{12}ClN_3O_3$ (257.68)
2 a	*Me*	79	223[f] (Acetone)	$C_3H_5N_3O_2$ (115.09)
2 b	*Et*	68	187 (Abs. *Et*OH-Benzene) (1 : 3)	$C_4H_7N_3O_2$ (129.12)
2 c	*Pr*	71	133[g] (Acetone)	$C_5H_9N_3O_2$ (143.15)
2 d	CH_2Ph	60	182[h] (Acetone)	$C_9H_9N_3O_2$ (191.19)
2 e	$CH_2C_6H_4 \cdot Cl(-p)$	57	220 (*Et*OH – H_2O) (1 : 3)	$C_9H_8ClN_3O_2$ (225.64)
2 f	*Ph*	73	233[i] (*Et*OH – H_2O) (1 : 3)	$C_8H_7N_3O_2$ (177.16)

[a] According to method A for compounds **1**
[b] All elemental analyses (C, H, N) are in accordance with calculated values
[c] 42% and 63% for method B and method C, respectively
[d] 30% for method B
[e] 34% for method B
[f] Ref. [1]: 222°
[g] Ref. [1]: 133-134°
[h] Ref. [1]: 182-183°
[i] Ref. [1]: 232-234°

Synthesis of 3-Alkyl(aryl)-4-hydroxy-4,5-dihydro-1,2,4-triazol-5-ones (**2**) (General Method)

Hydroxamic acid ethoxycarbonylhydrazides (**1**) (0.01 mol) was dissolved in 20 ml of methanol and treated with 50 ml of 2 *N*-NaOH (or 50 ml of 5% Na_2CO_3 solution) with constant shaking. The mixture was heated at 50–55° for 2 h and cooled. After acidification with conc. HCl, the mixture was evaporated on a water-bath and the residue was dried. The solid residue was extracted with warm absolute ethanol, acetone and ethyl acetate. The extracts were collected and evaporated at 30–35° under reduced pressure. Recrystallization of the crude product from an appropriate solvent gave pure compound **2**.

Results

Data about the reactions and compounds synthesized are compiled in Table 1.

IR, ^{1}H-NMR, ^{13}C-NMR, and UV spectral data of the compounds are presented in Tables 2–5. pK_a values of compounds **2** are given in Table 6.

Discussion

In this study, three different methods were developed for the preparation of hydroxamic acid ethoxycarbonylhydrazides (**1**) and a new method was found to be useful for the synthesis of 3-alkyl(aryl)-4-hydroxy-4,5-dihydro-1,2,4-triazol-5-ones (**2**). Compounds **2** could not be obtained by thermal cyclization of compounds **1**. However, compounds **1** were cyclized to the corresponding compounds of type **2** under the action of NaOH or Na_2CO_3 solution. It seems likely that the role of hydroxide ions in this cyclization is catalytic, as reported for the cyclization of amide ethoxycarbonylhydrazones [9]. Due to the acidic character of compounds **2** it is necessary to acidify the alkaline solution after cyclization (see Exp.).

It has been reported that N-oxide forms were assigned to some 4-hydroxy-4H-1,2,4-triazole derivatives [5]. Similarly, the existence of N-oxide forms of compounds **2** might be thought as shown in structures **2** and **2A**. However, the lack of a strong band between 1 200–1 300 cm^{-1} in the IR spectra [10, 11, 5] and the

Table 2. IR data for compounds **1** and **2** (KBr, cm^{-1})

Compd.	NH and OH	C = O	C = N	Substituted benzenoid ring
1a	3350, 3230, 2980	1720	1650	–
1b	3300, 3220, 2985	1725	1645	–
1c	3310, 3200, 2980	1710	1653	–
1d	3350, 3270, 3010	1710	1638	765, 715
1e	3310, 3185, 2985	1700	1652	840
1f	3280, 3150, 2990	1710	1635	780, 710
1g	3250, 3130, 2980	1690	1630	840
2a	3310, 3143	1712	1650	–
2b	3310, 3147	1715	1650	–
2c	3310, 3150	1735	1652	–
2d	3310, 3158	1706	1665	746, 706
2e	3324, 3165	1695	1654	827
2f	3310, 3178	1700	1654	767, 692

Table 3. ^{1}H-NMR data for compounds **1** and **2** (δ/ppm in *DMSO-d_6*)

Compd.	CH_3	CH_2	NH	OH	Aromatic H
1a	1.25 (t) 1.75 (s)	4.20 (q)	7.70 (s) 9.00 (s)	9.33 (s)	–
1b	0.97 (t) 1.69 (t)	1.99 (q) 4.05 (q)	7.36 (s) 8.87 (s)	9.20 (s)	–
1c	0.90 (t) 1.25 (t)	1.53 (sext) 2.14 (t) 4.14 (q)	7.30 (s) 8.80 (s)	9.10 (s)	–
1d	1.03 (t)	3.60 (s) 4.07 (q)	7.50 (s) 8.75 (s)	9.30 (s)	7.20 (m, 5H)
1e	1.05 (t)	3.60 (s) 4.10 (q)	7.55 (s) 8.75 (s)	9.35 (s)	7.20 (m, 4H)
1f	1.15 (t)	4.07 (q)	7.90 (s) 9.05 (s)	10.20 (s)	7.60 (m, 5H)
1g	1.20 (t)	4.00 (q)	7.92 (s) 9.00 (s)	10.20 (s)	7.50 (m, 4H)
2a	2.10 (s)	–	11.34 (s)	10.95 (s)	–
2b	1.15 (t)	2.30 (q)	11.35 (s)	10.95 (s)	–
2c	0.85 (t)	1.56 (sext) 2.42 (t)	11.35 (s)	10.90 (s)	–
2d	–	3.85 (s)	11.48 (s)	11.03 (s)	7.20 (m, 5H)
2e	–	4.05 (s)	12.05 (s)	11.10 (s)	7.70 (m, 4H)
2f	–	–	11.95 (s)	11.07 (s)	7.35 (m, 5H)

Table 4. ^{13}C-NMR data for compounds **2** (δ/ppm in *DMSO-d_6*)

Compd.	Triazole C_3	Triazole C_5	Aliphatic C	Aromatic C
2a	143.05	151.05	10.21	–
2b	147.00	151.83	17.84, 9.96	–
2c	145.65	151.61	25.98, 18.71, 13.35	–
2d	144.99	151.63	30.31	135.41, 128.67 (2C) 128.47 (2C), 126.76
2e	144.56	151.47	29.55	134.32, 131.42 130.55 (2C), 128.35 (2C)
2f	143.16	151.96	–	130.13, 128.72 (2C) 126.47 (2C), 126.05

Table 5. UV data for compounds **1** and **2**[a]

Compd.	λ_{max} (nm)	$\varepsilon \cdot 10^{-3}$	Compd.	λ_{max} (nm)	$\varepsilon \cdot 10^{-3}$
1a	225	0.7	2a[b]	224	0.5
1b	226	0.6	2b	224	0.6
1c	227	0.7	2c	224	0.8
1d	223	4.1	2d	222	2.2
	257	0.5		257	0.5
1e	225	6.9	2e	224	6.1
	258	0.6		258	0.3
1f	222	4.7	2f[c]	225	4.1
	247	4.8		257	6.1
	276	1.5		274	4.7
1g	225	7.7			
	267	11.6			
	277	12.6			

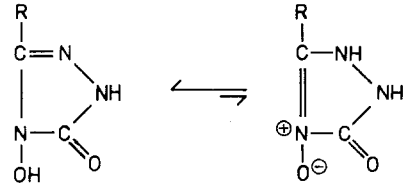
[a] All measurements were carried out for 10^{-4}–10^{-3} *M* solutions in ethanol (95%)
[b] In dioxane λ_{max} ($\varepsilon_{max} \cdot 10^{-3}$): 252 (1.2)
[c] In dioxane λ_{max} ($\varepsilon_{max} \cdot 10^{-3}$): 272 (5.4), 274 (5.5), 277 (5.7)

Table 6. pK_a values of compounds **2**[a]

Compd.	pK_a (at 25 °C)
2a	6.17
2b	6.29
2c	6.34
2d	6.52
2f	6.11

[a] All potentiometric titrations were performed in aqueous medium by using 0.1 *N* NaOH as titrant

lack of an absorption maximum between 315–350 nm in the UV spectra (in dioxane) [11–13, 5] revealed that compounds **2** could not exist in their N-oxide forms **2A**. Furthermore, the N-hydroxy forms of compounds **2** were also consistent with the NMR spectra [7, 9].



2 2A

The pK_a values of 3-alkyl-4,5-dihydro-1,2,4-triazol-5-ones have been determined in aqueous solution as 9.60–9.91 [14]. In the present study, the pK_a values of compounds **2** (see Table 6) reveal that the acidities of 3-alkyl(aryl)-4-hydroxy-4,5-dihydro-1,2,4-triazol-5-ones (**2**) are stronger than those of 3-alkyl-4,5-dihydro-1,2,4-triazol-5-ones. It is likely that the stronger acidity of a type **2** compound originates from the hydroxyl group attached to the N-4 position.

In the ^{13}C-NMR spectra of compounds **2** the aryl ring carbon atoms were assigned by comparison of the observed chemical shifts to those calculated by means of substituent parameters [15].

The chemical shift values of the NH protons in the ^{1}H-NMR spectra of **2** were in agreement with the reported values for 4,5-dihydro-1,2,4-triazol-5-one derivatives [7, 9, 16].

On the other hand, the λ_{max} values for **2** were in conformity with the reported values for 3-substituted- and 3,4-disubstituted-4,5-dihydro-1,2,4-triazol-5-ones [8, 17–19]. As expected, the introduction of an aryl group into the structures of compounds **1** and **2** led to hyperchromic shifts in the UV absorption spectra.

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