Pergamon

Tetrahedron Vol. 51, No. 41, pp. 11251-11256, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00672-9

5-Hydroxy-4,5-Dihydropyrazoles

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Abstract: The use of β-diketones with strong electron-withdrawing substituents in reaction with hydrazine and its monosubstituted derivatives leads to the stable intermediates of pyrazole synthesis - 5-hydroxy-4,5-dihydropyrazoles or their open chain isomers.

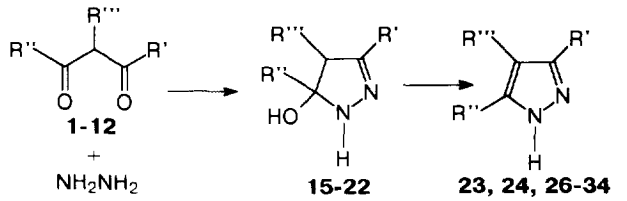
The interaction of hydrazines with β-dicarbonyl compounds is known to be a method of synthesis of pyrazoles.[1] All possible intermediates resulting from interactions of 1,3-dicarbonyl compounds with hydrazine and its alkyl- and aryl derivatives were detected by special NMR techniques.[2-5] In despite of this fact only in a few cases stable 5-hydroxy-4,5-dihydropyrazoles, the key intermediates of pyrazole synthesis, can be isolated.[6-8] Meanwhile 5-hydroxy-4,5-dihydropyrazoles are of interest as polydentate ligands.[9-10] Some of their nickel and copper chelates display antimicrobial activity.[11] 5-Hydroxy-4,5-dihydropyrazoles react with hydrazines to form 5-hydrazino-4,5-dihydropyrazoles [12-13] and with hydroxylamine to give 5-hydrazino-4,5-dihydroisoxazoles.[14]

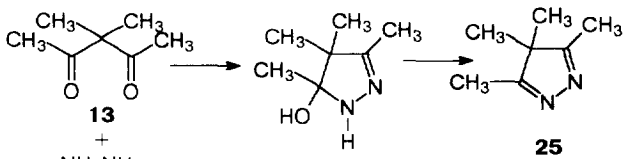
In the present work we followed up the unfluence of structure factors on the possibility of formation of these compounds. In accordance with this problem we widely varied the electronic and steric substituent effects of β-dicarbonyl and hydrazine components.

According to the ^{1}H NMR spectra at room temperature the reaction mixtures of hydrazine with acetylacetone (**1**) and with α-methylacetylacetone (**2**) consist only of starting materials and final pyrazoles. Obviously, nucleophilic attack of hydrazine on the carbonyl group of diketone is rate-determining. The next transformations happen quickly.

Formation of 5-hydroxy-4,5-dihydropyrazoles (**14-16**) was detected in the reaction mixtures of hydrazine with α,α-dimethylacetylacetone (**13**), with acetylpynacoline (**3**) and with dipyvaloylmethane (**4**). In the ^{1}H NMR spectra of these products (Table 1) there are signals of non-equivalent substituents in 4-position of the ring. The difference of diketones (**1-2**) from diketones (**3-5**) can be explained in the following manner. Obviously, the water elimination for 5-hydroxy-4,5-dihydropyrazoles occurs as E2 type. The bulky tret.-butyl group in 5-position of derivatives (**15-16**) prevents formation of the bond between the proton in 4-position and the external base (hydrazine) and solvation of the eliminated hydroxyl group. The slow elimination of water for 5-hydroxy--4,5-dihydropyrazoles (**14**) is caused by the absence of aromatisity in the transition state because of the structure

factors.Our attempts to stop the reaction on the stage of 5-hydroxy-4,5-dihydropyrazoles formation were unsuccessfull. Only the corresponding pyrazoles (**25-27**) were isolated.





1, 23	R' = R'' = CH_3, R''' = H;	**2, 24**	R' = R'' = R''' = CH_3;
3, 15, 26	R' = CH_3, R'' = t-C_4H_9, R''' = H;	**4, 16, 27**	R' = R'' = t-C_4H_9, R''' = H;
5, 17, 28	R' = CH_3, R'' = CF_3, R''' = H;	**6, 18**	R' = CH_3, R'' = C_3F_7, R''' = H;
7, 19, 29	R' = t-C_4H_9, R'' = CF_3, R''' = H;	**8, 20, 30**	R' = C_6H_5, R'' = CF_3, R''' = H;
9, 31	R' = CH_3, R'' = $C_6H_4OCH_3$-4, R''' = H;	**10, 32**	R' = CH_3, R'' = C_6H_5, R''' = H;
11, 21, 33	R' = CH_3, R'' = C_6H_4Cl-4, R''' = H;	**12, 22, 34**	R' = CH_3, R'' = $C_6H_4NO_2$-4, R''' = H

Table 1. The ^{1}H NMR data of 5-hydroxy-4,5-dihydropyrazoles **14-16**, **21**, **42**, **43** and monohydrazones **37-40**

Compound	δ, ppm [a]			
	R'	R''	CH_2	OH(NH), s
14	1.80 s	1.46 s	0.88 (CH_3), 1.01 (CH_3)	[b]
15	1.91 s	1.02 s	2.40, 2.83 (J_{AB} 18.0)	[b]
16	1.14 s	0.99 s	2.47, 2.83 (J_{AB} 18.0)	[b]
21	1.95 s	7.3-7.9 m	2.80 br. s	[b]
37	1.96 s	2.05 s	3.42 br. s	9.50
38	6.7-8.2 m	2.11 s	3.78 br. s	9.35
39	6.7-8.0 m	2.06 s	4.02 br. s	9.30
40	2.06 s	2.20 s	3.60 br. s	[b]
42	1.93 s	1.69 s	2.92, 3.06 (J_{AB} 18.0)	[b]
43	2.06 s	6.7-8.2 m	3.12, 3.28 (J_{AB} 18.0)	[b]

[a] **14-16**, **21** - in $CDCl_3$, **37-40**, **42**, **43** - in mixture $CDCl_3$ - DMSO-d_6 (1:1). [b] The signal was not detected.

The situation definitely changes in the case of diketones (**5-8**) possessing one terminal perfluoralkyl substituent. Their interaction with hydrazine leads to the corresponding 5-hydroxy-4,4-dihydopyrazoles pyrazolines (**17-20**, Table 2). In the ^{1}H NMR spectra of these compounds there are signals of non-equivalent

protons at the 4-position of the ring. The quadruplet signals of C-5 atom in ^{13}C NMR spectra of compounds **19**, **20** (J=30.0 and 31.9 Hz correspondingly, see Experimental) unambiguously proved the geminal arrangement of the perfluoroalkyl and hydroxyl groups.

Further we used aroylacetones (**9-12**). Here the primary attack takes place at the acetyl group.[5] So we have the possibility to follow up the influence of the substituent in the aromatic ring on the stability of the 5-hydroxy- 4,5dihydropyrazole structure.

The reaction with aroylacetones (**9-11**) resulted in pyrazoles (**31-33**) but in the case of diketone (**11**) the intermediate 5-hydroxy-4,5-dihydropyrazole (**21**, Table 1) possessing the weak electron-withdrawing substituent was detected by ^1H NMR.

Table 2. 5-Hydroxy-4,5-dihydropyrazoles **17-20, 22, 44, 45** and monohydrazone **41**

Compound		δ, ppm[a]			
(Yield, %)	Mp °C	R'	R''	CH_2	OH (NH), s
17 (87)	85-86	1.99 s	-	2.75, 3.07 (J_{AB} 18.0)	5.85
18 (77)	98-99	1.90 s	-	2.69, 2.97 (J_{AB} 18.0)	6.10
19 (52)	135-136	1.15 s	-	2.82, 2.97 (J_{AB} 18.0)	5.95
20 (45)	159-160	7.4-8.1 m	-	2.82, 2.97 (J_{AB} 18.0)	5.95
22 (52)	200-203	1.95 s	7.8-8.1 m	2.78 br. s	6.26
41 (40)[c]	154-155	2.13 s	7.4-8.4 m	4.18 s	[b]
		2.16 s	7.4-8.4 m	4.30 s	[b]
44 (55)	124-125	2.09 s	7.0-8.0 m	2.82, 2.97 (J_{AB} 18.0)	[b]
45 (36)	97- 99	2.16 s	6.7-8.2 m	3.13, 3.38 (J_{AB} 18.0)	[b]

[a] **17-19** - in $CDCl_3$, **20**, **22** - in DMSO-d_6, **41**, **44**, **45** - in mixture $CDCl_3$ - DMSO-d_6 (1:1). [b] The signal was not detected. [c] The mixture of stereoisomers.

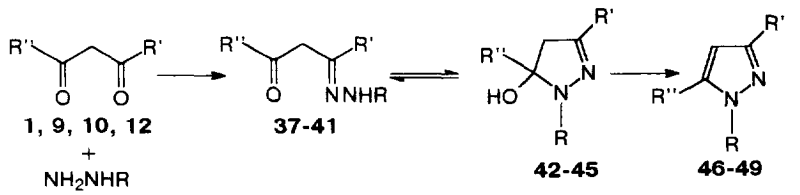
If the strong electron-withdrawing substituent is used [diketone (**12**)], then interaction leads to the desired 5-hydroxy-4,5-dihydropyrazole (**22**, Table 2). In all the discussed cases their structure was proved by the presence in ^1H NMR spectra of AB-system of diastereotopic protons in 4-position of the ring.

The inclusion of the strong electron-withdrawing substituent into the hydrazine component, acyl group for example, is known to stabilize the 5-hydroxy-4,5-dihydropyrazole structure or its linear tautomers.[15-17] Here we used 4-nitro- and 2,4-dinitrophenylhydrazines (**35-36**) with a weaker acceptor group. Their reaction, of the latter especially, with diketones slowly occurs.

The 5-hydroxy-4,5-dihydropyrazole signals (**42-44**, Table 2) are observed in ^1H NMR spectra of the reaction mixtures of acetylacetone (**1**), 4-methoxybenzoylacetone (**9**) and benzoylacetone (**10**) with 4-nitropenylhydrazine (**35**). In the case of diketones (**9-10**) in ^1H NMR spectra there are the singlets of CH_2-group of the linear forms, obviously hydrazones (**38-39**, Table 1). These reactions concluded with the pyrazole (**46-48**) formation. It is impossible to interrupt the process at the first step.

The interaction of 4-nitrobenzoylacetone (**12**) with 4-nitropenylhydrazine (**35**) leads to stable 5-hydroxy-4,5-dihydropyrazole (**45**). The hydrazone (**40**, Table 1) is observed in the case of the reaction of

acetylacetone (**1**) with 2,4-dinitrophenylhydrazine (**36**). The pyrazole (**49**) was the end product of this condensation.



35 R = $C_6H_4NO_2$-4,
38, 43, 47 R = $C_6H_4NO_2$-4, R' = CH_3, R'' = $C_6H_4OCH_3$-4;
39, 44, 48 R = $C_6H_4NO_2$-4, R' = CH_3, R'' = C_6H_5;
41 R = $C_6H_3(NO_2)_2$-2,4, R' = CH_3, R'' = C_6H_5;
45 R = $C_6H_4NO_2$-4, R' = CH_3, R'' = $C_6H_4NO_2$-4;
36 R = $C_6H_3(NO_2)_2$-2,4,
40, 49 R = $C_6H_3(NO_2)_2$-2,4, R' = R'' = CH_3;
37, 42 R = $C_6H_4NO_2$-4, R' = R'' = CH_3;
46 R = $C_6H_4NO_2$-4, R' = R'' = CH_3

The reaction of benzoylacetone (**10**) with 2,4-dinitrophenylhydrazine (**36**) stops on the hydrazone formation stage [(**41**), the mixture of syn-, anti-isomers, Table 2]. Its cyclization does not occurs for several months. It is determined by the common effect of suppression both of the nucleophilic and electrophilic reaction centres.

Thus, the reaction of hydrazine and its monosubstituted derivatives β-diketones possessing strong electron-withdrawing substituents leads to stable intermediates, viz., 5-hydroxy-4,5-dihydropyrazoles or their linear isomers. On the whole the presence of a strong electron-withdrawing substituent at 1- or 5-position of the 5-hydroxy-4,5-dihydropyrazole ring is a necessary condition of their stability that determines the preparative opportunities of the synthesis of these substances. 5-Hydroxy-4,5-dihydropyrazoles, as we believe, are promising reagents for the further chemical transformations.

Experimental

The ^1H NMR (100 MHz) and ^{13}C NMR (20.41 Mhz) spectra were recorded with a Tesla-BS-497 spectrometer using HMDS as an internal standard (unless otherwise stated). The purity of the compounds was checked by TLC using Silufol-UV-254 plates. The elemental analysis data (C, H, N) of the new compounds agreed with calculated values to within 0.2%. Solvents were dried by standard methods.

Interaction of β-dicarbonyl compounds with hydrazines.

Method A. Equimolar mixture (50 mmol) of hydrazinehydrate (3.3 ml of 80% solution) and of the corresponding ketone was stirred in 20 ml of $CHCl_3$ for 1 h, dried over $CaCl_2$ and was evaporated under reduced pressure. The residue was washed with 50 ml hexane and dried on air. By this way 5-hydroxy-4,5-dihydrxypyrazolines **17** and **22** were obtained. In case of reaction with diketones **6-8** the products **18-20** immediately separated by filtration, washed with $CHCl_3$, hexane and dried in air. The end products of of interaction of 1,3-diketones **1-4**, **9-11**, **13** were pyrazoles **23-27**, **31-34**.

Method B. Benzoylacetone **10** (1.65 g, 10 mmol) was added to 4-nitrophenylhydrazine **35** (1.53 g, 10 mmol) in $CHCl_3$-DMSO (3:1, 20 ml) solution. After stirring for 24 h reaction mixture was diluted with 20 ml of water, organic layer was separated, washed with water, evaporated under reduced pressure and the residue was washed with 50 ml hexane and dried on air Derivatives **41** and **45** were synthesized analogously from diketones

10 and **12** and from hydrazines **35-36**. The corresponding hydrazones **37**, **38**, **40** and 5-hydroxy-4,5-dixydropyrazoline **42** and **43** were not isolated in pure state in case of reaction of compounds **1** and **9** with hydrazine **35** and of diketone **1** with hydrazine **36**. They immediately transformed into corresponding pyrazoles **46**, **47**, **49** or were synthesized with significant admixtures of the latter.

3-t-Butyl-5-trifluoromethyl-5-hydroxy-4,5-dihydropyrazole 19. ^{13}C NMR (DMSO-d_6) δ ppm 28.1 (CH_3), 33.3 [$\underline{C}(CH_3)_3$], 40.7 (CH_2), 91.1 (C_5, q J_{CCF} 30.0), 124.6 (CF_3, q), 158.5 (C=N).

3-Phenyl-5-trifluoromethyl-5-hydroxy-4,5-dihydropyrazole 23. was synthesized by interaction of hydrazinehydrate (50 mmol) with acetylacetone (50 mmol) in solution of $CHCl_3$. Pyrazoles **24-27, 31-34** were similarly synthesized by reaction of hydrazinehydrate with the compounds **2-4**, **9-13**.

23 - 109 °C [18a], **24** - 135-136 °C [18b], **25** - 50-55 °C [18b], **26** - 145-146 °C [18c], **32** - 128-129 °C [18d], **34** - 198-199 °C [18e].

3,5-di-t-Butylpyrazole 27. Yield: 76%. Mp 190-191 °C. ^1H NMR ($CDCl_3$) δ ppm 1.40 (s, 18 H), 5.80 (s, 1 H).

3-Methyl-5-(4-methoxyphenyl)pyrazole 31. Yield: 61%. Mp 234-236 °C. ^1H NMR ($CDCl_3$) δ ppm 2.23 (s, 3 H), 3.80 (s, 3 H), 6.27 (s, 1 H), 6.95-7.35 (m, 4 H).

3-Methyl-5-(4-chlorohenyl)pyrazole 33. Yield: 45%. Mp 144-45 °C. ^1H NMR ($CDCl_3$) δ ppm 2.15 (s, 3 H), 6.25 (s, 1 H), 7.30-7.70 (m, 4 H).

Method B. Reaction mixtures of hydrazinehydrate (10 mmol) and of diketones **5**, **7**, **8** (10 mmol) were allowed to stand for 2 months in $CHCl_3$-DMSO (1:1) solution. The mixture was diluted with 20 ml of water, the organic layer was separated, washed with water, dried with $CaCl_2$ and the solvent was evaporated under reduced pressure. The residue was washed with 50 ml hexane and dried in air. Under these conditions 5-hydroxypyrazoline **18** does not aromatize. Pyrazoles **46-49** were synthesized analogously over 3-7 days from 1,3-diketones **1**, **9**, **10** and hydrazines **35**, **36**.

28 - 89-90 °C [18f], **30** - 121-123 °C [18g], **46** - 154-156 °C [18h], **48** - 102-103 °C [18i], **49** - 148-150 °C [18j].

3-t-Butyl-5-trifluoromethylpyrazole 29. Yield: 57%. Mp 182-183 °C. ^1H NMR ($CDCl_3$) δ ppm 1.68 (s, 9 H), 6.62 (s, 1 H).

3-t-Butyl-5-trifluoromethylpyrazole 30. ^{13}C NMR (DMSO-d_6) δ ppm 101.4 (CH, d J 72.6), 144.5 (s, C=N).

3-Methyl-5-(4-methoxyphenyl)-1-(2,4-dinitrophenyl)pyrazole 47. Yield: 62%. Mp 147-149 °C. ^1H NMR ($CDCl_3$) δ ppm 2.30 (s, 3 H), 3.72 (s, 3 H), 6.25 (s, 1 H), 7.30-8.15 (m, 7 H).

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(*Received in UK* 4 *July* 1995; *revised* 11 *August* 1995; *accepted* 18 *August* 1995)