Chemistry of Heterocyclic Compounds, Vol.35, No. 1, 1999

RECYCLIZATION OF 1-ACYL(THIOACYL)-5-HYDROXY-2-PYRAZOLINES TO 1,3,4-OXA(THIA)DIAZOL-2-INE DERIVATIVES ON ACETYLATION

K. N. Zelenin, V. V. Alekseev, A. K. Zelenin, and Yu. S. Sushkova

The acetylation of 1-acyl(thioacyl)-5-hydroxy-2-pyrazoline produces recyclization to the corresponding 4-acyl-5-(2-oxoalkyl)-1,3,4-oxa(thia)diazol-2-ine.

The acylhydrazones of β-dicarbonyl compounds are multitautomeric systems, which in solution are represented by equilibrium mixtures of two linear forms (hydrazone A and enhydrazine B) and a cyclic form (5-hydroxy-2-pyrazoline C), of which the last usually predominates or is unique [1]. In the case of thioacylhydrazones of β-dicarbonyl compounds, the situation is more complicated by the equilibrium involving a further cyclic form: 1,3,4-thiadiazoline (D) [2]. An aspect of any multitautomeric system is that in principle it is capable of ambidentate reaction, which can lead to a series of nontrivial products and requires special research. As a model, we took the acetylation by acetic anhydride, on the basis that the acetylation of nitrogen derivatives of 1,3-dicarbonyl compounds has been researched and discussed in detail [3].

The benzoylhydrazone of benzoylacetaldehyde I has the enhydrazine tautomeric form B predominant in solution, and it resembles the enamine forms of the imines of 1,3-dicarbonyl compounds [3] in undergoing acetylation on the nitrogen atom $N_{(2)}$ of the tautomeric pentad with the formation of compound IX (scheme, Table 1). This compound exists as the trans isomer (SSCC for the olefin protons 13.2 Hz, Table 2), and its spectral parameters (Tables 2 and 3) agree with the data for a sample prepared by acetylating the sodium salt of benzoyl acetaldehyde benzoylhydrazone by the use of acetyl chloride [4].

It is not difficult to interpret the acetylation data for the thiobenzoylhydrazone of acetylacetone VII, which in solution is a tautomeric mixture of the corresponding 5-hydroxy-2-pyrazoline form (C) and the 1,3,4-thiadiazoline (D) one [2]. Here, as expected, the attack by acetic anhydride is primarily at the 4-NH group of the 1,3,4-thiadiazoline form D, which is more nucleophilic than the hydroxyl group in the pyrazoline tautomer C. This leads to the formation of the corresponding 4-acyl-5-(2-oxoalkyl)-1,3,4-thiadiazol-2-ine (XV) (Tables 1-3).

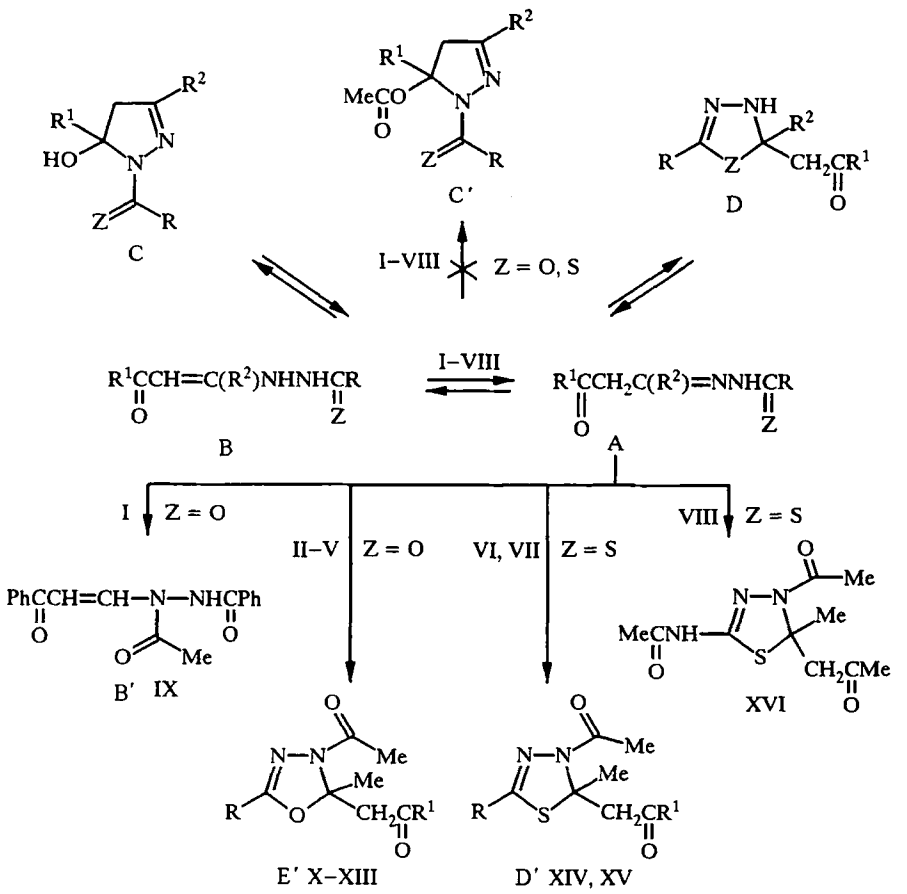
The structure is implied primarily by the ^{13}C NMR spectrum, in which the resonance signal from the sp^3-hybrid carbon atom $C_{(5)}$ (78.3 ppm) is in the range characteristic of 5-(2-oxoalkyl)-1,3,4-thiadiazol-2-ines (75-85 ppm), not that of the 1-thioacyl-5-hydroxy-2-pyrazolines (95-105 ppm) [2]. The carbon spectrum also has signals from the C=O bond carbon atoms of the ketone and amide groups at 205.0 and 171.0 ppm respectively. Other details of the ^1H and ^{13}C NMR spectra agree with the proposed structure.

The further acetylacetone thioacylhydrazone VI exists entirely in the 5-hydroxy-2-pyrazoline form C [2], and it is acetylated by acetic anhydride in the same way, namely via the 1,3,4-thiadiazol-2-ine form (D). This gives rise to the 4-acetyl-2-benzyl-5-methyl-5-(2-oxopropyl)-1,3,4-thiadiazol-2-ine (XIV). As in the case of compound

---

Military Medical Academy, St. Petersburg 194175, Russia; e-mail: zelenin@infopro.spb.su. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 90-96, January, 1999. Original article submitted February 14, 1998.

0009-3122/99/3501-0087$22.00©1999 KluwerAcademic/Plenum



I – V Z = O; VI – VIII Z = S; I R^2 = H, II – VIII R^2 = Me; I, IV, IX, XII R = R^1 = Ph;
II, X R = Me, R^1 = Ph; III, VII, XI, XV R = Ph, R^1 = Me; V, VIII R = Ph, R^1 = 4-$MeOC_6H_4$;
VI, XIV R = $PhCH_2$, R^1 = Me; VIII R = NH_2, R^1 = Me

IX, the NMR data agree completely with the data for the product from acetylation of the sodium salt of the corresponding acetylacetone thioacylhydrazone described previously [5].

Therefore the acetylation causes recyclization of the 5-hydroxy-1-thioacyl-2-pyrazoline to the 5-(2-oxoalkyl)-1,3,4-thiadiazol-2-ine.

A similar reaction occurs in the case of the acetylacetone thiosemicarbazone, which has the structure of the corresponding 5-hydroxy-1-thiocarbamoyl-2-pyrazoline VIII [6]. This substance on acetylation also recyclizes to a derivative having the 1,3,4-thiadiazoline ring, but with the difference that the bisacylated derivative XVI was obtained. The formation of such bisacylated derivatives is characteristic also for thiosemicarbazones of monocarbonyl compounds [7].

Structures difficult to interpret occur in the acetylation products of the acylhydrazones of 1,3-dicarbonyl compounds II-V, which exist in solution mainly in the form of the 5-hydroxypyrazol-2-ines (C) [1]. The tautomeric 1,3,4-oxadiazoline form (E) for these derivatives is not known, and so it is most likely to expect the acylation products derived from the reaction with the hydroxyl group in position 5, which is the unique nucleophilic center of a unique stable form (C). We have drawn that conclusion previously when discussing the structures of acetylation products from the sodium salts of acylhydrazones of 1,3-dioxo compounds, which have linear structures [4, 8].

However, we have the above evidence from the acetylation of thioacylhydrazones on the one hand and from the acylation of hydrazones of monocarbonyl compounds on the other, where the corresponding 4-acyl-1,3,4-oxadiazolines are formed [9], so this should be considered a possibility in the present case. It is impossible to make an unambiguous choice between the alternatives 5-acetoxy-2-pyrazoline (C′) and 4-acetyl-1,3,4-oxadiazoline (E′) isomers simply on the basis of the chemical shift for the sp^3-hybrid $C_{(5)}$ carbon atom, although this is possible for

TABLE 1. Characteristics of Compounds IX-XVI

Compound	Empirical formula	Found, % / Calculated, %			mp,°C	Yield, %
		C	H	N		
IX	$C_{18}H_{16}N_2O_3$	70,25 / 70,12	5,15 / 5,23	9,20 / 9,08	153...155	54
X	$C_{14}H_{16}N_2O_3$	64,63 / 64,59	5,97 / 6,20	10,80 / 10,76	Oil*	42
XI	$C_{14}H_{16}N_2O_3$	64,77 / 64,59	6,07 / 6,20	10,59 / 10,76	Oil*	37
XII	$C_{19}H_{18}N_2O_3$	70,95 / 70,79	5,52 / 5,63	8,58 / 8,69	105...106*	51
XIII	$C_{20}H_{20}N_2O_4$	68,17 / 68,15	5,74 / 5,72	7,99 / 7,95	79...80*	47
XIV	$C_{15}H_{18}N_2O_2S$	62,14 / 62,04	6,18 / 6,25	9,77 / 9,65	38...40*[2]	45
XV	$C_{14}H_{16}N_2O_2S$	60,73 / 60,84	5,76 / 5,84	10,04 / 10,14	84...86*[2]	53
XVI	$C_{10}H_{15}N_3O_3S$	46,55 / 46,68	5,97 / 5,88	16,20 / 16,33	156...158	28

* Eluent acetone-benzene-CCl_4, 1:1:2.

*[2] Recrystallization solvent petroleum ether.

the thio derivatives. On account of the identical O,N environments, the resonance signals in both cases should be in the region of 95-105 ppm.

To provide a reliable structure analysis, we recorded the ^{13}C NMR spectrum for the product of acetylation for benzoylacetone benzoylhydrazone IV (compound XII, Table 3) under conditions of double resonance.

Suppression of the signal from the *ortho* protons in the aromatic rings converted the signal at 154.4 ppm into a singlet (presence of the C_6H_5—C=N group), while the signal at 195.7 ppm became a triplet (characteristic region for carbon atoms in aromatic ketones, presence of C_6H_5—C(O)—CH_2 group). In the case of the possible formation of the acetylation product via the hydroxyl group in 5-hydroxy-2-pyrazoline (C), the latter signal should be represented by a triplet from the C_6H_5—$C_{(5)}$—CH_2 group and lie at a much stronger field at 95-105 ppm.

TABLE 2. PMR Data on Compounds IX-XVI, δ, ppm (SSCC, Hz)

Compound	Solvent	R	R^1	R^2, s	CH_3CON, s	CH_2, AB-system
IX	DMF-d_7	7,30...7,60; 7,80...8,08, m	7,30...7,60; 7,80...8,08, m	8,50	2,24	6,60 d (13,2, CH)
X	DMF-d_7	1,76, s	7,39...7,58; 7,85...7,94, m	1,74	1,94	3,70; 4,00
XI	$CDCl_3$	7,20...7,45; 7,70...7,80, m	2,04, s	1,74	2,22	3,18; 3,56
XII	$CDCl_3$	7,20...7,56; 7,66...7,94, m	7,20...7,56; 7,66...7,94, m	1,91	2,20	3,69; 4,12
XIII	$CDCl_3$	6,73...6,82; 7,61...7,70, m	3,55, s 7,30...7,45, 7,75...7,94, m	1,91	2,21	3,64; 4,05
XIV	$CDCl_3$	3,65, s; 7,23, w. s	1,99, s	1,77	2,23	3,63; 4,51
XV	$CDCl_3$	7,25...7,35; 7,53...7,52, m	2,06, s	1,90	2,30	3,30; 4,26
XVI	DMSO-d_6	2,08, s	1,98, s	1,77	2,08	3,17; 3,83

* J_{AB} 17,0...18,0 Hz

TABLE 3. ^{13}C NMR Data on Compounds IX-XVI, δ, ppm

Compound	Tautomeric composition of initial ylidene derivative (solvent)	Form of acylated derivative	Solvent	C(5)	N—C=O	R^1—C=O	C=N	R^1	R^2	CH_3CON	CH_2
IX	I, A, 10%, B, 90% ($DMSO-d_6$)	B'	$DMF-d_7$	141,4 (CH)	166,7, 172,8	189,6	—	*	—	21,4	104,5 (CH)
X*[2]	II, C, 100% ($CDCl_3$)	E'	$CDCl_3$	98,4	171,2	195,5	154,6	*	24,6	21,9	43,5
XI	III, C, 100% ($CDCl_3$)	E'	$CDCl_3$	97,9	166,1	202,2	152,9	31,0	24,1	22,0	47,3
XII	IV, C, 100% ($CDCl_3$)	E'	$CDCl_3$	99,4	167,6	195,7	154,4	*	25,1	22,3	44,4
XIII	V, C, 100% ($CDCl_3$)	E'	$CDCl_3$	99,2	167,3	193,6	154,0	55,3*	24,6	22,0	43,2
XIV	VI, C, 100% ($CDCl_3$)	D'	$CDCl_3$	78,6	170,7	204,6	148,5	30,0	27,4	24,1	36,9 53,3
XV	VII, C, 50%, D, 50% ($CDCl_3$)	D'	$CDCl_3$	78,3	171,0	205,0	149,8	30,2	27,5	24,5	53,8
XVI	VIII, C, 100% ($CDCl_3$)	D'	$CDCl_3$	74,9	168,3, 168,9	205,3	144,6	30,0	27,1	22,3 23,6	52,3

* Region for aromatic carbon atoms 126-136 ppm.
*[2] Signal of R^1 carbon atoms 11.2 ppm.

Suppression of the methyl group signals converts the resonance signal from the carbon atom in the amide carbonyl group at 167.6 ppm into a singlet (CH_3—C(O)—N group) and that for the sp^3 hybrid carbon atom (99.4 ppm) into a triplet (CH_3—C—CH_2 group). The methyl group on $C_{(5)}$ is further evidence for that compound existing as the isomer E′, since acetylation of tautomer C in this position, as mentioned above, one should find a phenyl radical. Therefore, the compound previously given the structure of the corresponding 5-acetoxy-2-pyrazoline [4, 8] in fact is 4-acetyl-5-methyl-5-(2-oxopropyl)-2-phenyl-1,3,4-oxadiazoline-2.

The same structure occurs in other acylation products from the 5-hydroxy-2-pyrazolines II, III, and V (compounds X, XI, and XIII in Tables 1-3). The spectra of those compounds also have characteristic resonance signals from the sp^3-hybrid carbon atoms (98-99 ppm) and ketone carbon atoms (193-203 ppm) in the 1,3,4-oxadiazoline form E′ (Table 3).

The recyclization on acetylization of 1-acyl(thioacyl)-5-hydroxy-2-pyrazolines is a general feature, no matter what the nature of the heteroatom of the substituent in position 1. One considers that this property should be extended to the related derivatives of 1,3-dicarbonyl compounds, including semicarbazones, guanylhydrazones, and so on.

These results may be considered as an application of the view on ring-ring tautomeric systems [10] for the directional synthesis of 4-acyl-1,3,4-oxa(thia)diazol-2-ines that contain a carbonyl group in position 5 as additional substituent, which can be subject to further modification.

EXPERIMENTAL

The PMR spectra were recorded with a Tesla BS 497 (100 MHz), while the ^{13}C NMR spectra were recorded with a Bruker AC-200 (50.32 MHz). The initial derivatives of the 1,3-dicarbonyl compounds I-VII have been described previously and were made by standard methods involving the reaction of the corresponding carbonyl compounds with hydrazides. Compound I – mp 141 – 142°C (142°C [11]); II - 113 – 114°C (114 – 116°C [12]); III - 79 – 80°C (79°C [13]); IV - 133 – 134°C (134 – 135°C [14]); V - 159 – 160°C (158 – 159°C [14]); VI - 55°C (55°C [2]); VII - 62°C (62°C [2]).

5-hydroxy-3,5-dimethyl-1-thiocarbamoyl-2-pyrazoline (VIII). A solution of 2.7 g (30 mmole) of thiosemicarbazide in 10 ml of dimethylsulfoxide was added to a solution of 3.2 ml (31 mmole) of acetylacetone in 3 ml of DMSO at 5°C. The mixture was kept for 2.5 h and then treated with 30 ml of water containing ice. After 15 min, a precipitate began to form. The mixture was left to stand for an hour, the precipitate was filtered off and dried in a vacuum desiccator. Yield 3.65 g (71%), mp 73 – 74°C (91 – 92 [6]). PMR spectrum (DMSO-d_6): 1.99 (3H, s, CH_3); 2.22 ((3H, s, CH_3); 3.15 (2H, w. s, CH_2); 6.85 (1H, s, OH); 8.07 ppm (2H, s, NH_2). Found, %: C 45.99; H 7.20. $C_6H_{11}N_3O_2$. Calculated, %: C 45.85; H 7.05.

4-acetyl-5-methyl-5-(2-oxo-2-phenylethyl)-2-phenyl-1,3,4-oxadiazol-2-ine (XII). To a solution of 3.0 g (15 mmole) of 1-benzoyl-2-pyrazoline IV in 30 ml of methylene chloride 3 ml (37.5 mmole) of pyridine and 9 ml (95 mmole) of acetic anhydride were added. After 5 h, the volatile products were evaporated under vacuum. The residue was purified on a silica gel, and eluted with an acetone–benzene–CCl_4 1:1:2 mixture. Yield 2.46 g (51%), mp 105 – 106°C. Tables 1-3 give the elemental analysis and the spectral characteristics. Compound XII is analogous in physicochemical characteristics to the compound made by acetyl chloride acetylation of the sodium salt of benzoylacetone benzoylhydrazone [4].

2-(1-acetyl-2-benzoylhydrazino)vinylphenylketone (IX), 4-acetyl-2,5-dimethyl-5-(2-oxo-2-phenylethyl)-1,3,4-oxadiazol-2-ine (X), 4-acetyl-5-methyl-5-(2-oxopropyl)-2-phenyl-1,3,4-oxadiazol-2-ine (XI), 4-acetyl-5-methyl-5-[2-oxo-2-(4′-methoxyphenyl)ethyl]-2-phenyl-1,3,4-oxadiazol-2-ine (XIII), 4-acetyl-2-benzyl-5-methyl-5-(2-oxopropyl)-1,3,4-thiadiazol-2-ine (XIV), 4-acetyl-5-methyl-5-(2-oxopropyl)-2-phenyl-1,3,4-thiadiazol-2-ine (XV) were prepared in the same way as compound XII by acetic anhydride acetylation of compounds I-III and V-VII correspondingly. In the case of compound I, the residue after removing the volatile reaction products was kept in a refrigerator for 3 days. The precipitated crystals were filtered off, washed with hexane, and dried in a vacuum desiccator. In the production of compounds XIV and XV, the residue after removal of the volatile products from the reaction mixture was recrystallized from petroleum ether. The characteristics

and spectral data for compounds IX-XI and XIII-XV (Tables 1-3) were virtually the same as those of these compounds made by acetyl chloride acetylation of the corresponding sodium salts of acetyl acetone and benzoyl acetone acetyl hydrazones and benzoyl hydrazones [4, 8], and the same applies to acetyl acetone phenothioacetyl hydrazones and thiobenzoyl hydrazones [5].

4-acetyl-2-acetylamino-5-methyl-5-(2-oxopropyl)-1,3,4-thiadiazol-2-ine (XVI) was made in the same way as for compound XIII from 2.4 g (15 mmole) of 5-hydroxy-2-pyrazoline VIII by storing the reaction mixture for a month. After a month, the volatile products were evaporated off under vacuum and the residue was kept in a refrigerator for 2 days. The deposited crystals were filtered off, washed with hexane, and dried under vacuum. Yield 1.08 g (28%), mp 156 – 158°C. Tables 1 – 3 give the characteristics and spectral data on compound XVI.

REFERENCES

1. S. I. Yakimovich and K. N. Zelenin, Zh. Obshch. Khim., **65**, 705 (1995).
2. K. N. Zelenin, V. V. Alekseev, V. A. Khrustalev, S. I. Yakimovich, V. N. Nikolaev, and N. V. Koshmina, Zh. Org. Kh., **290**, 180 (1984).
3. S. I. Yakimovich, L. A. Kayukova, and K. B. Erzhanov, Acylating Nitrogen Derivatives of Carbonyl Compounds [in Russian], Nauka, Alma-Ata (1985).
4. K. N. Zelenin, I. P. Bezhan, B. A. Ershov, and A. K. Zelenin, Tetrahedron, **50**, 11447 (1994).
5. K. N. Zelenin, B. A. Ershov, A. K. Zelenin, Yu. S. Sushkova, and V. V. Alekseev, Zh. Obshch. Khim., **66**, 347 (1996).
6. K. N. Zelenin, O. V. Solod, and A. B. Tomchin, Zh. Obshch. Khim., **57**, 584 (1987).
7. S. Andreae and E. Schmitz, Z. Chem., **23**, 450 (1983).
8. A. K. Zelenin, B. A. Ershov, I. P. Bezhan, and K. N. Zelenin, Khim. Geterotsikl. Soedin., No. 4, 564 (1993).
9. V. N. Yandovskii, Zh. Org. Kh., **12**, 1093 (1976).
10. K. N. Zelenin and V. V. Alekseyev, Topics in Heterocyclic Systems - Synthesis, Reactions and Properties, O. A. Attanasi and D. Spinelli, (editors), Research Signpost, Trivandrum (1996), p. 141.
11. S. I. Yakimovich and V. N. Nikolaev, Zh. Org. Kh., **19**, 880 (1983).
12. S. I. Yakimovich, V. N. Nikolaev, and E. Yu. Kutsenko, Zh. Org. Kh., **19**, 2333 (1983).
13. V. G. Yusupov, S. I. Yakimovich, S. D. Nasiridinov, and N. A. Parpiev, Zh. Org. Kh., **16**, 415 (1980).
14. S. I. Yakimovich, V. N. Nikolaev, and E. Yu. Kutsenko, Zh. Org. Kh., **18**, 762 (1982).