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SYNTHESIS OF 5-SUBSTITUTED-3-PHENACYLOXIME-1,2,4-OXADIAZOLES FROM ACETYLATED OR BENZOYLATED BENZOYLTHIACETAMIDE WITH HYDROXYLAMINE HYDROCHLORIDE

SPECTRAL EVIDENCE FOR A TETRAHEDRAL CARBINOLAMINE INTERMEDIATE

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Abstract—Acetylated and benzoylated benzoylthiacetamide **1a, b** reacts with hydroxylamine hydrochloride in refluxing ethanol to yield 3 - acetylamino - and 3 - benzoylamino - 5 - phenyl - isoxazoles **2a, b**, while 3 - phenacyloxime - 5 - substituted - 1,2,4 - oxadiazoles **4a, b** are formed in the presence of sodium acetate or in pyridine.

When refluxed in ethanol containing small amounts of concentrated hydrochloric acid, the above 1,2,4-oxadiazoles **4a, b** rearrange to the corresponding isoxazoles **2a, b**.

The reaction in pyridine has been studied at 35° by using ^1H and ^{13}C NMR spectroscopy. It has been possible to detect an adduct between the carbinolamine intermediate, resulting from the addition of hydroxylamine to the keto carbonyl group, and the starting thiamide.

During the past few years an increasing interest in 1,2,4-oxadiazole derivatives has been developed. Some of these attained enough popularity as antitussive agents and as coronary vasodilators and local anaesthetics.[1]

Although many methods[2] are available for the synthesis of 3,5 - disubstituted - 1,2,4 - oxadiazoles, none is satisfactory for the synthesis of the 3-phenacyl derivatives.[3] We here report the synthesis of the oxime of such derivatives from acetylated or benzoylated benzoylthiacetamide **1a, b** and hydroxylamine hydrochloride in ethanol in the presence of sodium acetate or in pyridine.

We also discuss the reaction pathway and, on account of the detailed informations available by the ^1H and ^{13}C NMR spectra, we present direct evidence of a tetrahedral carbinolamine intermediate, whose existence has been elegantly proved by Cocivera and Effio for nucleophilic additions of NH_2OH to carbonyl compounds.[4]

Previous studies[5] concerning the cyclization of **1a, b** to isoxazoles are reinvestigated for examining the different reactivity of carbonyl and thiocarbonyl groups.

RESULTS AND DISCUSSION

Synthesis. According to previous results,[5] treatment of **1a, b** with hydroxylamine hydrochloride in boiling ethanol led to the formation of the isoxazoles **2a, b** (Scheme 1), whose structures were confirmed on the basis of spectral data. Particularly, the presence of the fragments at *m/e* 105 and 159 in the mass spectrum of **1a** (Table 1) and *m/e* 105 and 97 in that of **1b**, due to the cleavage of the O–N and C_4–C_5 bonds, appeared to be diagnostical for the structural assignments. Examination of the crude reaction mixture by ^1H NMR showed that **2** was the only isomer formed.

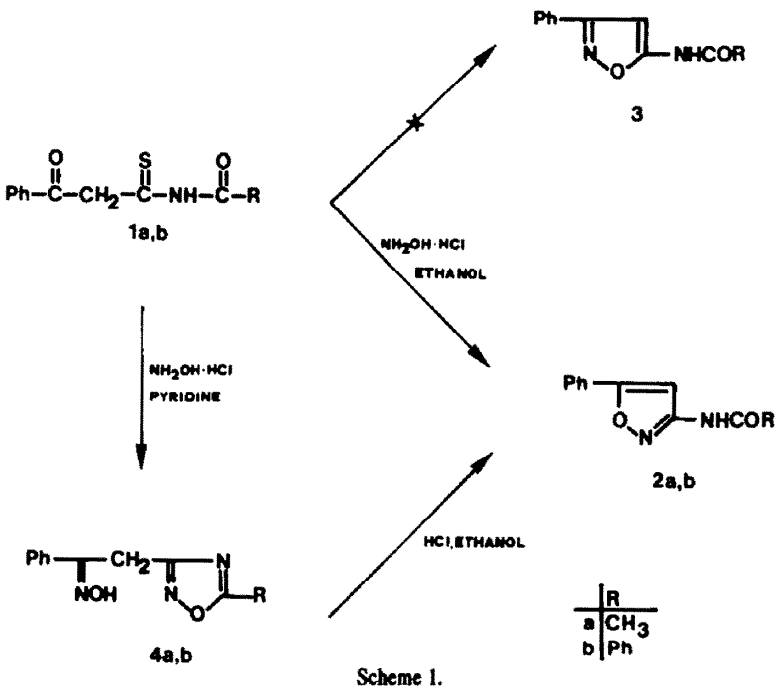
Moreover, treatment of **1a, b** with an excess of hydroxylamine hydrochloride in ethanol, in the presence of sodium acetate, or in pyridine for 2 hr at 50°, gave only **4a, b** in nearly quantitative yields (Scheme 1). The structures were established by mass spectra, which showed the characteristic fragmentation pattern of the 1,2,4-oxadiazole nucleus,[6] and by NMR spectra. Attempts to obtain phenacyl derivatives, by hydrolyzing the oxime, failed. 1,2,4-Oxadiazoles **4a, b** underwent ready rearrangement to isoxazoles **2a, b**, by refluxing in ethanol containing small amounts of concentrated hydrochloric acid.

Mechanism. To elucidate the reaction pathway, firstly, ^1H and ^{13}C NMR parameters were obtained for **1a**. In several solvents (pyridine-d_5, benzene-d_6 and dimethylsulfoxide-d_6) proton resonances for an intramolecularly H-bonded tautomer **5**, whose structure was confirmed by ^{13}C NMR data, were observed. Transformation into the keto form **1a** occurred very quickly in the presence of small amounts of bases. ^1H NMR parameters for both keto and enol forms of **1a** are given in Table 2.

The ^{13}C NMR spectrum of **1a**, in pyridine-d_5, is reported in Fig. 2(a). The ^{13}C chemical shifts are given in Table 3. Resonances were assigned on the basis of their characteristic chemical shifts[7] as well as the benzoylacetamide enol form (Table 3). As follows from the model compound chemical shifts, carbonyl chemical shift differs greatly (19.5 ppm) between keto and enol forms, as observed by Levy.[8]

Acetylated benzoylthiacetamide **1a** was then dissolved in pyridine-d_5 containing one equivalent amount of hydroxylamine hydrochloride (1:1 molar ratio) and the resulting mixture was examined by ^1H NMR spectrometry shortly after preparation.

Figure 1 illustrates the 90 MHz ^1H NMR spectra, at 35°, obtained before and after (15 min) the addition of



Scheme 1.

Table 1. Mass Spectra (70 eV) of compounds 2a and 4a

Compound	m/e(rel.intensity)
2a	266(5), 265(25), 264(100,M^+), 263(21), 249(12), 237(5), 236(22), 223(9),222(31), 221(8), 220(6), 209(5), 208(7), 207(6), 206(5), 187(5), 159(5), 118(5), 106(39), 105(51), 102(12), 77(36), 76(8), 63(5), 52(5), 51(24).
4a	218(9), 217(61,M^+), 202(11), 201(41), 187(23), 175(22), 160(16), 159(40), 146(29), 145(55), 128(21), 117(11), 105(58), 104(42), 103(100), 98(41), 77(69), 60(17), 56(22), 52(16), 51(31), 50(13), 43(64).

Table 2. ^{1}H NMR (90 MHz) chemical shifts[a] of 1a[b]

Solvent	$-CH_3$ (enol)	$-CH_3$ (keto)	-CH(enol)	$-CH_2$(keto)	-SH(enol)	-NH(enol)	-NH(keto)	ArH
C_6D_6	1.12(s)	-	8.71(s)	-	15.87(bs)	-[c]	-	7.3-8.3(m
$(CD_3)_2SO$[d]	2.20(s)	2.13(s)	8.18(s)	5.03(s)	15.73(bs)	11.55(bs)	-[c]	7.2-8.3(m
C_5D_5N	2.28(s)[e]	-	8.78(s)	-	14.33(bs)	12.27(bs)[d]	-	7.3-8.3(m

[a] Chemical shifts in parts per million (δ) from internal Me_4Si. Multiplicity:m,multiplet;s,singlet;bs,broad singlet.

[b] Concentrations of 7%w/v were used.

[c] Masked by aromatic protons.

[d] Keto/Enol ratio:1/5.

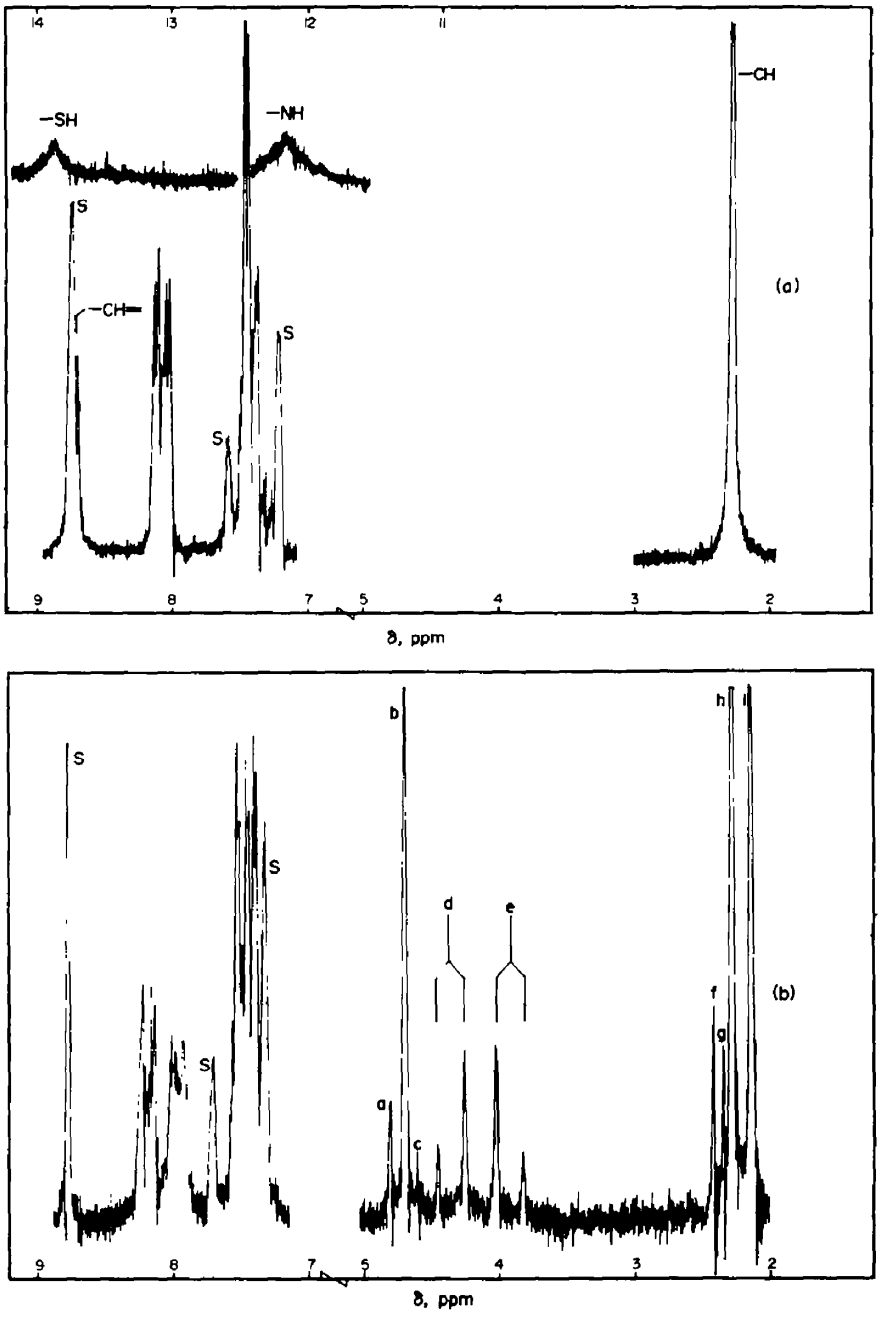


Fig. 1. 90 MHz ^1H NMR spectra, at 35°, of **1a**, in pyridine-d_5, before (a) and 15 min after the addition (b) of one equivalent of $NH_2OH \cdot HCl$. The labelled signals are due to the CH_2 and CH_3 protons of monoxime **8** (a, f), adduct **7** (b, d, e, h, i) and final product **4a** (c, g).

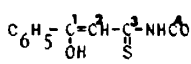
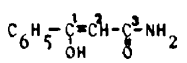
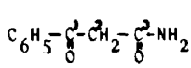
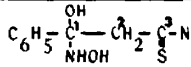
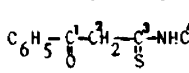
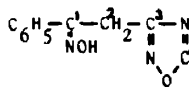
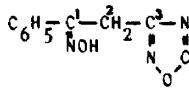
hydroxylamine hydrochloride to the solution of **1a** in pyridine-d_5.

Surprisingly, several intermediates have a mean life long enough with respect to the NMR time scale. As can be seen from Fig. 1(b), the peaks of the starting material, in the enol form, disappeared immediately and were replaced by an AB quartet (labeled d and e), centered at δ4.20 (J = 19.1 Hz), and a singlet at δ4.74 (labeled b), in the region of the methylene protons, and two Me signals at δ2.17 and δ2.33 (labeled h and i). These signals retained an integration ratio 2:2:3:3 during the whole time of the reaction. Such a spectral feature can be ascribed to an adduct between the starting compound in the keto form and the tetrahedral carbinolamine intermediate **6**, in which the methylene protons resonate as an AB-type multiplet, being diastereotopic. A tentative structure of such an adduct is represented by **7**. No relative configuration of the chiral centers has been attempted.

Little amounts of the 1,2,4-oxadiazole **4a** were also observed (singlets at δ3.72 and δ2.41, labeled c and g).

Resonances at δ4.88 and δ2.38 (signals a and f), are attributable to the monoxime **8**. In fact, after that the equilibrium was reached with only one equivalent of hydroxylamine hydrochloride at 35°, upon increasing the probe temperature from 35 to 60°, the intensity of the

Table 3. ^{13}C NMR chemical shifts in pyridine-d_5[a]

	Compound	C-1	C-2	C-3	C-4	C-5
1c		177.2	100.7	195.1	169.5	25.0
	 [d]	176.3	89.3	170.9		
		195.8	47.6	170.1		
7		[c]	42.2[b]	195.0	168.1	23.1
		192.8	49.7[b]	195.0	168.1	23.1
4a		[c]	23.4	168.0	177.3	12.0
4b		[c]	23.9	169.0	177.1	-

[a] Ppm relative to internal TMS;
[b] May be interchanged;
[c] Masked by solvent signals;
[d] Keto/enol ratio: 2/3.

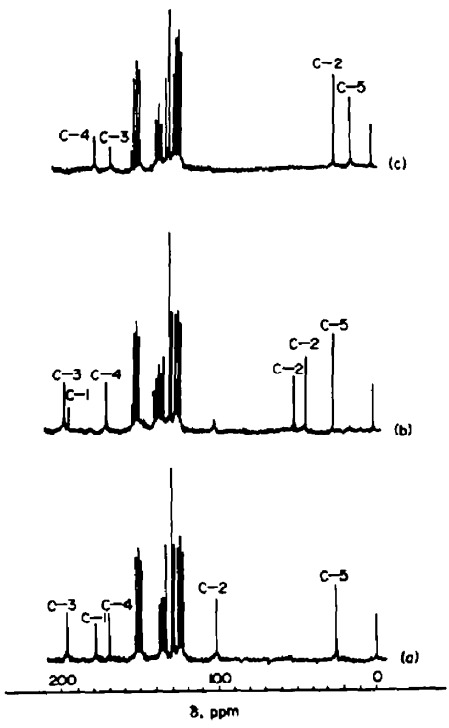


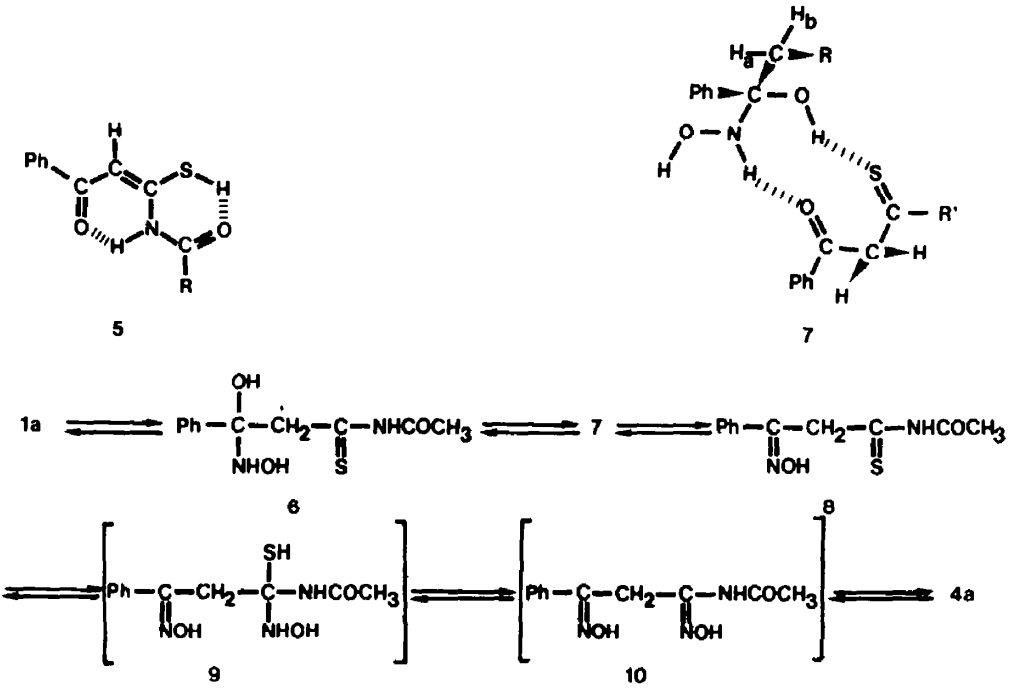
Fig. 2. ^{13}C NMR spectra (20.1 MHz), in pyridine-d_5, at 35°, of **1a** before (a) and after (b) the addition of one equivalent of $NH_2OH \cdot HCl$ and of **4c** (c). The labelling corresponds to that given in Table 3.

signals labeled a and f increases at the expense of the adduct **7**, the signals due to **4a** remaining unchanged. In the alternative assignments of a and f signals to **9** and **10** intermediates, an increase of the cyclization product signals would be expected.

In the presence of an excess of hydroxylamine hydrochloride (1:3 molar ratio), the reaction rate increased and nearly quantitative formation of **4a** was observed in 4 hr at 35°. A small amount (5%) of the *anti*-isomer also could be detected.

In order to confirm the initial addition of hydroxylamine to the C=O and the formation of the carbinolamine intermediate, ^{13}C NMR spectrum of **1a** also have been recorded, in pyridine-d_5, after the addition of one equivalent of hydroxylamine hydrochloride. The resulting spectrum is shown in Fig. 2(b). The signals at 100.7 and 177.2 ppm disappeared and were replaced by two signals at 42.2 and 49.8 ppm, which are triplets in the fully coupled spectrum, attributable to the methylene carbons of the dimeric complex between **1a** in the keto form (CO signal at 192.8 ppm) and the carbinolamine intermediate **6**. No signals of **4a** were present. All ^{13}C NMR data are summarized in Table 3. Resonances of **4a** were assigned on the basis of their characteristic chemical shifts. The signal at 177.3 ppm was assigned to C-4 on the basis of the expected oxygen deshielding, as observed in similar pentatomic heterocycles.[9]

The following conclusions can be drawn from the above results: (1) the C=O group is more reactive, in pyridine, than the C=S and the addition of hydroxylamine to C=S follows the dehydration of **6** to produce



Scheme 2.

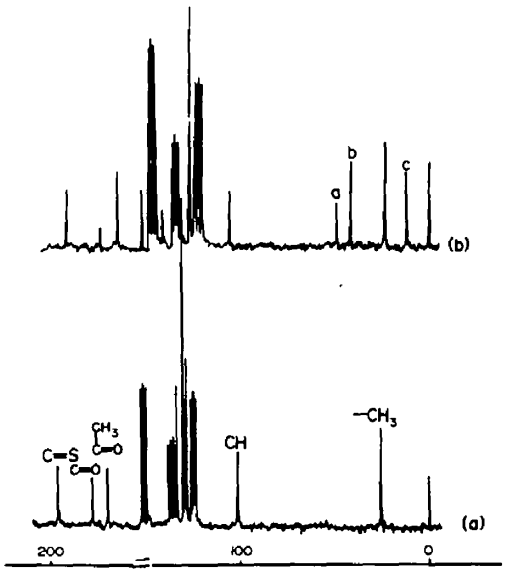


Fig. 3.

the oxime **8**, unable to cyclize to the isoxazole **3**; (ii) the starting thiamide, by forming a dimeric structure with the carbinolamine intermediate **6**, probably plays an important role in promoting hydrogen transfer from N to the O-atom in the dehydration step (several authors attribute this role to water in a number of reaction in such medium[10]); (iii) although no intermediate was observable, by NMR spectroscopy, during the reaction of **1a** with hydroxylamine hydrochloride in ethanol, we can hypothesize, on account of the sensitivity of **4a** to the acidic hydrolysis, that the formation of the isoxazole nucleus in such medium, is attributable to a higher reactivity of the thiocarbonyl group in the presence of acid.

EXPERIMENTAL

Proton NMR spectra were recorded on a Perkin–Elmer R-32 spectrometer operating at 90 MHz, with TMS as an internal standard. The CMR spectra were recorded as Poulse Fourier transformed NMR (20.1 MHz; Bruker WP-80) spectra with broad band decoupling using deuterium signal lock. Typical conditions were: 5 kHz width; 8 K data; pulse width 1 μsec (17°). Mass spectra were obtained at 70 eV by direct insertion into the ion source of a LKB 9000S instrument. Elemental analyses were checked with a C. Erba Elemental Analyzer. M.ps are uncorrected.

Preparation of the solution for NMR-measurements

150 mg (0.72 mmol) of **1a** were dissolved in 1.5 ml of pyridine-d_5, containing 1% TMS. 50 mg (0.72 mmol) of NH_2OH·HCl were then added.

Materials. Compounds **1a, b** and **2a, b** were prepared as described previously,[5] whereas benzoylacetamide was prepared by Haufer method.[11]

3-Phenacyloxime-5-substituted-1,2,4-oxadiazoles **4a, b**

(a) To a mixture of 50 mmol NH_2OH·HCl in 100 ml EtOH containing 2 g NaOAc were added 10 mmol of **1a**. The mixture was stirred for 2 hr at 50°. The resulting ppt was removed by filtration, washed with water and crystallized from EtOH, yield 85%.

(b) To a soln of 10 mmol of **1a** in 25 ml pyridine were added 50 mmol NH_2OH·HCl. The mixture was stirred for 2 hr at 50°. After pouring into water (200 ml), the resulting ppm was removed by filtration and crystallized from EtOH, yield 80%. M.p. 151–2° (Found: C, 60.68; H, 4.58; N, 19.57. Calc. for $C_{11}H_{11}N_3O_2$: C, 60.81; H, 5.10; N, 19.34%). δ(Py-d_5) 2.28 (3 H, s, CH_3), 4.58 (2 H, s, CH_2), 7.0–8.2 (5 H, m, ArH), 14.0 (1 H, broad singlet, NOH). Similar results were obtained for **4b**. M.p. 86–7°. (Found: C, 68.85; H, 4.69; N, 15.23. Calc. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05%). δ(Py-d_5) 4.76 (2 H, s, CH_2), 7.3–8.4 (10 H, m, ArH), 14.0 (1 H, broad singlet, NOH).

Hydrolysis of **4a, b** *to* **2a, b.** A soln of 10 mmol of **4a, b** in 20 ml EtOH and 1 ml conc HCl was refluxed for 1 hr. The mixture was cooled to room temp and the resulting white crystals were filtered off and crystallized from EtOH. These products were identical in all respects with **2a, b**, prepared from **1a, b** with hydroxylamine hydrochloride in EtOH.[5]

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