

Metal Complexes of 6-Acetyl-4-aryl-2-ethoxycarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine Oximes

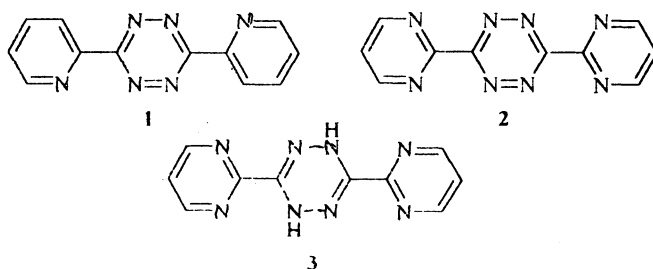
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Nitrilimines (**5a–c**) react with 1-ethoxycarbonyl-1-methylhydrazine (**6**) to give the corresponding 3-acetyl-1,2,4,5-tetrazines (**8a–c**). Oximes of these tetrazines (**9a–c**) and their Pd(II) (**10a**) and Ni(II) (**11b**) complexes were prepared and characterized using IR, MS, NMR and electronic spectra.

Key Words: Metal Complexes, Nitrilimines, Tetrazines, Oximes.

INTRODUCTION

1,2,4,5-Tetrazines represent an important class of heterocyclic compounds that have many practical and synthetic applications¹. In the past twenty years, 1,2,4,5-tetrazine and its derivatives have gained great attention as ligands to transition metals. Different 3,6-disubstituted 1,2,4,5-tetrazine have been studied for their complexing behaviour. The most widely studied ligands are 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**1**)², 3,6-bis(2'-pyrimidyl)-1,2,4,5-tetrazine (**2**)³ and 1,4-dihydro-3,6-bis(2'-pyrimidyl)-1,2,4,5-tetrazine (**3**)³.



We have reported recently that the reaction of nitrilimines (**5a–c**) generated *in situ* from the respective hydrazonoyl halides (**4a–c**) with 1-alkoxycarbonyl-1-methylhydrazine (**6**) yielded the acyclic adducts (**7a–c**) which upon thermal oxidative cyclization produced the unexpected tetrahydro-1,2,4,5-tetrazines (**8a–c**) (Scheme 1). Some of these tetrazines (**8c**) are now under investigation for their effectiveness against cancer by the National Cancer Institute (USA)⁵. Such

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interesting results have encouraged us to prepare oximes of the compounds (9a-c) and examine their coordination attitude with nickel(II) and palladium(II) ions.

EXPERIMENTAL

Melting points were determined on Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer (KBr discs). ^1H - and ^{13}C -NMR spectra were recorded on a Bruker 300 MHz instrument for solutions in CDCl_3 at 21°C . Electron impact mass spectra were run on Finnigan Mat 8200 and 8400 spectrometers at 70 eV. Hydrazonoyl halides (4a-c)⁶, 1-ethoxycarbonyl-1-methylhydrazine (6)⁷ and the tetrazines (8a-c)⁴ were prepared according to known literature procedures.

Synthesis of 6-acetyl-4-aryl-2-ethoxycarbonyl-1,2,3,4-tetrahydro-s-tetrazine oximes (9a-c)

To a solution of the respective tetrazine (8a-c) (3 mmol) in methanol (70 mL) was added hydroxylamine hydrochloride (15 mmol) and sodium acetate (15 mmol). The resulting mixture was stirred overnight at room temperature. The solvent was then evaporated in a dish at room temperature and the residue was washed with water (100 mL). The insoluble product was isolated and recrystallized from diethyl ether or chloroform/petroleum ether (40 – 60°C).

The following compounds were synthesized using this method:

6-Acetyl-2-ethoxycarbonyl-4-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine oxime (9a)

From 0.83 g (3 mmol) of (8a): yield 0.78 g (90%); m.p. 155 – 156°C ; ^1H NMR (CDCl_3): 7.3–6.9 (m, 5H, aromatic protons), 11.66/11.48 (bs, 1H, OH), 8.82/8.39 (s, 1H, NH), 2.01/1.95 (s, 3H, $\text{CH}_3\text{C}=\text{N}$), 5.06/4.85 (s, 2H, CH_2 —ring); 4.10 (q, 2H, OCH_2), 1.2 (t, 3H, $-\text{CH}_2\text{CH}_3$), ^{13}C NMR (CDCl_3): 149.5/148.7 (C=NOH), 145.8/139.5 (C=N), 148.3/143.1, 129.0, 122.1/120, 117.2/114.1 (aromatic carbons), 60.04 (CH_2 —ring), 62.3, 61.2 (OCH_2), 14.4 ($-\text{CH}_2\text{CH}_3$), 9.4/9.0 ($\text{CH}_3\text{C}=\text{N}$), 156.5 (O—C=O); MS: m/z 291 (M^+), 274 ($\text{M}^+ - \text{OH}$), 105 ($\text{C}_6\text{H}_5\text{NCH}_2^+$), 77 (C_6H_5^+);

High resolution mass spectrum (M^+): Found: 291.133237; Calcd.: 291.133139; mass difference for $\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_3 = -0.34$; IR (cm^{-1}): 3335 $\nu(\text{O}-\text{H})$, 3290 $\nu(\text{N}-\text{H})$, 1681 $\nu(\text{C}=\text{O})$, 1591 $\nu(\text{C}=\text{N})$.

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_3$: C = 53.60; H = 5.88; N = 24.04; Found: C = 53.34; H = 5.61; N = 24.36.

6-Acetyl-4-(4-fluorophenyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine oxime (9b)

From 0.44 g (1.5 mmol) of (8b): yield 0.38 g (83%); m.p. 140 – 141°C ; MS: m/z 309 (M^+ , $\text{C}_{13}\text{H}_{16}\text{FN}_5\text{O}_3$), 292 ($\text{M}^+ - \text{H}$), 123 ($\text{FC}_6\text{H}_4\text{NCH}_2^+$), 95 ($\text{C}_6\text{H}_4\text{F}^+$); IR (cm^{-1}): 3363 $\nu(\text{O}-\text{H})$, 3287 $\nu(\text{N}-\text{H})$, 1689 $\nu(\text{C}=\text{O})$, 1596 $\nu(\text{C}=\text{N})$. Complicated NMR spectrum was obtained due to tautomerism and coupling with the fluorine atom; however, the main NMR signals can be observed.

6-Acetyl-2-ethoxycarbonyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine oxime (9c)

From 0.93 g (3 mmol) of (8c): yield 0.53 g (54%), m.p. 127 – 129°C ; ^1H NMR (CDCl_3): 7.2–7.0 (m, 4H, aromatic protons), 11.6 (bs, 1H, OH), 8.6 (bs, 1H, NH),

2.1 (s, 3H, CH₃C=N), 5.0/4.9 (s, 2H, CH₂-ring); 4.2/4.1 (m, 2H, OCH₂), 1.2 (m, 3H, —CH₂CH₃); ¹³C NMR (CDCl₃): 151.0/150.6 (C=NOH), 142.4/138.4 (C=N), 147.5/144.4, 129.3/129.1, 129.0/126.5, 119.8/116.1 (aromatic carbons), 61.3/58.1 (CH₂-ring), 63.6; 62.7 (OCH₂), 14.4 (—CH₂CH₃), 8.9 (CH₃C=N, 156.9/153.0 (O—C=O); MS: m/z 325 (M⁺), 308 (M⁺—OH), 139 (ClC₆H₄NCH₂⁺), 111 (C₆H₄Cl⁺); high resolution mass spectrum (M⁺) Found: 325.094055; Calcd.: 325.094167; mass difference for C₁₃H₁₆N₅O₃Cl = -0.35; IR (cm⁻¹): 3347 ν(O—H), 3294 ν(N—H), 1693 ν(C=O), 1601 ν(C=N).

Anal. Calcd. for C₁₃H₁₇N₅ClO₃: C = 47.93; H = 4.95; N = 21.50. Found: C = 47.58; H = 4.72; N = 21.72.

Synthesis of 6-acetyl-4-phenyl-2-ethoxycarbonyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine oximes metal(II) complexes (10a, 11b)

To a solution of the tetrazine oxime (**9a**, **b**) (2 mmol) in absolute ethanol (25 mL) was added a solution of metal acetate (1 mmol) in absolute ethanol (25 mL). The resulting reaction mixture was stirred at room temperature for 30 min with palladium(II) acetate and overnight with nickel(II) acetate and refrigerated for 2 h. The solid product was collected by suction filtration, washed with cold ethanol (5 mL) and dried *in vacuo*.

The following complexes were prepared as follows:

Bis(6-acetyl-2-ethoxycarbonyl-4-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine oxime) palladium(II) (10a)

From 0.29 g (1 mmol) of (**9a**): yield 0.25 g (72 %); m.p. 229–230°C; MS: m/z 686 (M⁺); ¹H NMR (DMSO-d₆): 17.1, 11.0 (bs, 2H, 2OH), 7.2 (m, 10H, aromatic protons), 5.7 (bs, 4H, 2CH₂-ring), 3.9 (q, 4H, 2OCH₂), 2.0 (s, 6H, 2CH₃C=N), 1.5 (t, 6H, —2CH₂CH₃), ¹³C NMR (DMSO-d₆): 154.5 (O—C=O), 153.4 (C=NOH), 151.4 (C=N), 62.1 (OCH₂), 61.7 (CH₂-ring), 14.8 (—CH₂CH₃), 11.0 (CH₃C=N); IR (cm⁻¹): 3233 ν(O—H), 1688 ν(C=O), 1597ν (C=N).

Anal. Calcd. for C₂₆H₃₂N₁₀O₆Pd: C = 45.48; H = 4.66; N = 20.41. Found: C = 44.97; H = 4.84; N = 20.16.

Bis(6-acetyl-2-ethoxycarbonyl-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-1,2,4,5-tetrazine oxime) nickel(II) (11b)

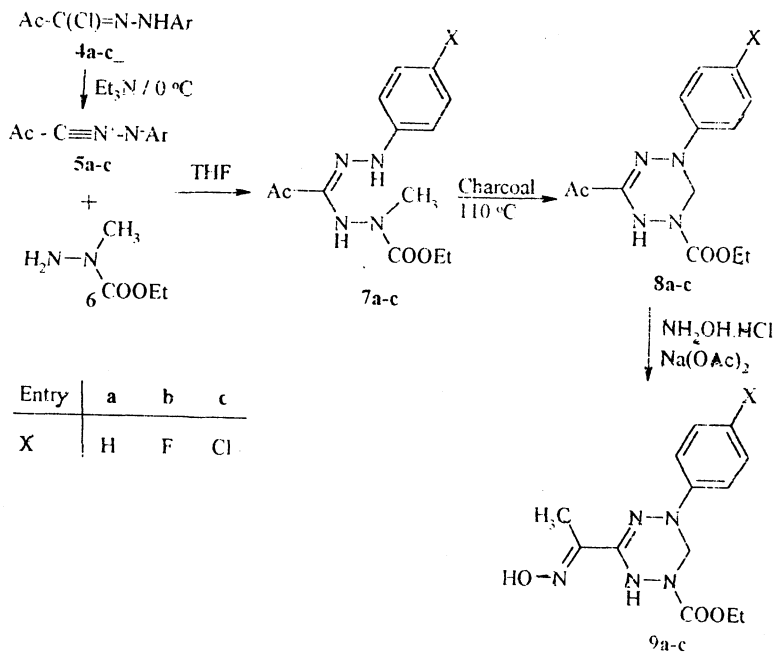
From 0.19 g (0.6 mmol) of (**9b**): yield 0.05 g (25%) m.p. 230–231°C; MS: m/z 674 (M⁺); IR (cm⁻¹): 3448 ν(O—H), 1686 ν(C=O), 1595 ν(C=N).

RESULTS AND DISCUSSION

The oximes (**9a–c**) are readily accessible *via* oximation of the acetyl group at C₆ of the tetrazines (**8a–c**) using five-fold excess of hydroxylamine hydrochloride in presence of sodium acetate at room temperature (**Scheme 1**).

The assignment of structures (**9a–c**) is based on analytical and spectral data.

The IR spectra of these compounds in KBr revealed the presence of one NH absorption band at about 3294 cm⁻¹. The bands of OH groups appear at about 3347 cm⁻¹ and C=N stretching band appears in the region 1601–1591 cm⁻¹. The electron impact (EI) mass spectra of (**9a–c**) display the correct molecular ions in accordance with the suggested structures. High Resolution Mass Spectra were done for the compounds (**9a**, **c**).



Scheme 1. Synthesis of 1,2,4,5-tetrazine oximes (9a-c)

^1H NMR shows a signal at about 8.6 ppm for one N—H group in compounds (9a, c). The signal of the OH appears at about 11.5 ppm. Signal doubling is observed in both ^1H - and ^{13}C -NMR spectra of the oximes (9a, c), apparently due to the presence of these compounds in two tautomeric structures.

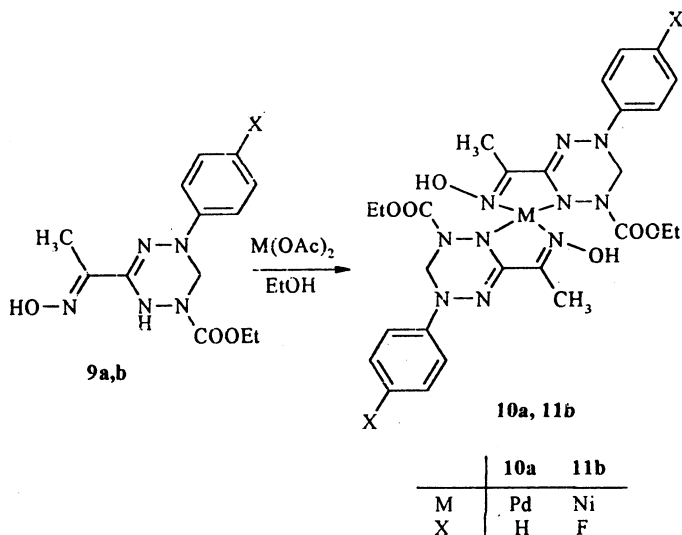
^{13}C NMR spectra display the characteristic signals of the suggested structures. The signals of N—CH₂—N appear at about 60 ppm. The signals of the C=NOH appear at about 151 ppm and the signals of C=N appear at about 140 ppm. In addition, the signals of the methyl groups of CH₃—C=N and CH₃—CH₂— appear at about 8 ppm and 14 ppm, respectively. DEPT 135° and DEPT 90° experiments were done to distinguish between the different kinds of carbons (quaternary, CH, CH₂ and CH₃).

6-Acetyl-1,2,4,5-tetrazine oxime (9a) reacted with palladium(II) acetate, in two to one mole ratio in ethanol at room temperature for 30 min, to give a good yield of a red brown complex (10a) (Scheme 2).

On the other hand, the reaction of 6-acetyl-1,2,4,5-tetrazine oxime (9b) with nickel(II) acetate tetrahydrate, in two to one mole ratio in ethanol at room temperature over night, gave a very poor yield of a green complex (11b).

The IR spectra of solid complexes (10a, b) in KBr show OH band at about 3233 cm⁻¹ for palladium(II) complex (10a) and 3448 cm⁻¹ for nickel(II) complex (11b). The electron impact (EI) mass spectra of (10a, 11b) display the correct molecular ions in accordance with the suggested structures.

IR and mass spectra indicated that the complexes are neutral ML₂ complexes (Scheme 2). ^1H and ^{13}C NMR spectra of the complex (10a) are in accordance



Scheme 2. Complexes of 1,2,4,5-tetrazine oximes

with the suggested structure. Two signals (17.1 ppm and 11.0 ppm) appear for the OH group, apparently due to hydrogen bonding. The electronic spectra of the Pd(II) complex (**10a**) display two absorption bands around 22830 cm^{-1} and 17540 cm^{-1} which are consistent with square-planar Pd(II) complexes⁸.

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