Synthesis and Spectral Properties of 4-(*ortho*-*R*-Benzylideneamine)-5-[2-(2-pyridyl)ethenyl]-3-methylisoxazole

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The preparation of several 5,4-disubstituted 3-methylisoxazoles is described. The structure of all products was corroborated by ir, ^{1}H-nmr and mass spectrometry.

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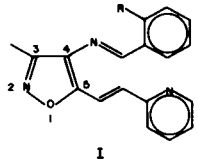
There have been several reports concerning biological interest for isoxazole and its derivative. Some of these compounds are known to have activities such as anticonvulsant [3], antibacterial [4], antiasthmatic [5] and other pharmacological properties [6,7].

Likewise, 4-nitro-5-styryl-3-methylisoxazole derivatives are useful synthetic intermediates for the construction of different ring systems such as imidazoles [8], pyridines [9], thiazolidin-4-ones [10], *etc.* With this information, it was deemed of interest to synthesize molecules possessing the isoxazole and pyridine ring.

In this report, we describe the synthesis of compound of general formula **I** (Scheme 1) following the three steps indicated in Scheme 2. The reaction of 2-pyridinecarboxaldehyde with **II** in ethanol and piperidine as the base, gave the *trans*-3-methyl-5-[2-(2-pyridyl)ethenyl]-4-nitroisoxazole **III**. Spectroscopic evidence was consistent with the structure of **III**; in the infrared spectra the appearance of absorption bands at 1630, 990 and 780 cm^{-1} indicated that the ethenyl moiety was in the *trans* configuration. The mass spectra showed the expected molecular ion and also characteristic fragmentation patterns [11], as observed for analogous 5-styryl-4-nitroisoxazoles. In the ^{1}H-nmr spectrum of **III** the peak arising from the 3-methyl protons appeared as a singlet at δ 2.58; two doublets at δ 8.62 (J = 16 Hz) and δ 7.70 (J = 16 Hz), respectively, were assigned to the methine protons joined to the ethenyl moiety. These coupling patterns were only consistent with a *trans*-configuration of the ethenyl moiety [12] and were thus in agreement with infrared evidence. The peaks due to the pyridine ring had the expected chemical shifts and multiplicities.

Scheme 1

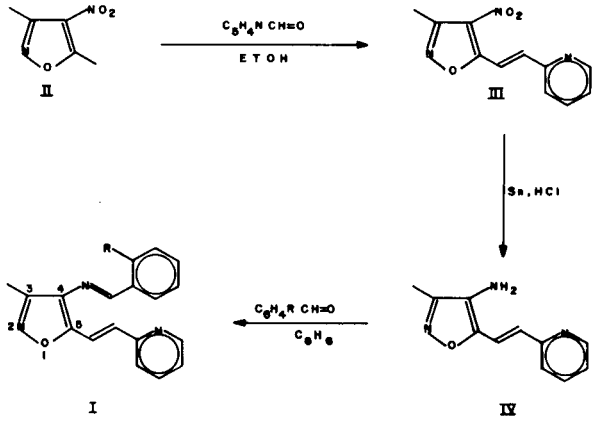


I

R

Ia = Me
Ib = OMe
Ic = OH
Id = Cl
Ie = NO_2

Scheme 2



Treatment of 4-nitroisoxazole **III** with stannous chloride-hydrochloric acid [13] in refluxing ethanol afforded **IV** (Scheme 2). In the infrared spectra of **IV** the appearance of two sharp bands at 3300 and 3400 cm^{-1} was consistent with the presence of an amine group. The primary mass spectral fragmentation of **IV** showed the molecular ion and major peaks at m/z ratios of 173 [M$^+$ -28], 172 [M$^+$ -29], 142 [M$^+$ -59], 133 [M$^+$ -68] and 105 [(M$^+$ -96), 100%]. This supported the structure of **IV** because similar behaviour was observed by us in 4-amino-5-styrylisoxazoles [14].

Condensation of **IV** with *ortho*-substituted benzaldehydes in hot ethanol led to the Schiff bases, 4-(*o*-*R*-benzylideneamine)-5-[2-(2-pyridyl)ethenyl]-3-methylisoxazoles **I** in moderate yields. The infrared spectrum of compounds **I** displayed absorption at 1630 and 1600 cm^{-1} which were assigned to -C=C- and -C=N- stretches, respectively. In the ^{1}H-nmr spectra of **I** derivatives the presence of a downfield one-portion singlet at δ 9.0 was consistent with the presence of an imine group [15]; other downfield one-proton signal as a broad doublet at δ 8.65 was assigned to

the methine proton joined to C_6 of the pyridyl moiety. Two doublets at δ 7.8-7.4 (J = 16 Hz) and δ 7.41-7.0 (J = 16 Hz), respectively, were assigned to the ethylenic protons of the pyridylethenyl moiety whereas a three-proton singlet at δ 2.45-2.3 was assigned to the 3-methyl group of the isoxazole moiety. The remaining aromatic protons in compounds **I** appeared as unresolved multiplet at δ 6.75-8.0.

On the other hand we found that the mass spectra of these compounds are very characteristic and similar to other benzylideamine-5-styrylisoxazoles [16]. The molecular ions are detectable but exhibited a low intensity (3 to 10%); the peak at m/z 132 was, as a rule, the dominant peak (100%) for all the compounds **I**. This ion then loses carbon monoxide resulting in m/z 104.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer model 337 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian FT-80 spectrometer operating at 80 MHz, in deuteriochloroform solution containing tetramethylsilane as internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Hewlett-Packard 59854-A quadropole mass spectrometer. All compounds were synthesized following reported procedures [10,13,14]. Analytical and spectral data on the new compounds are given below.

5-[2-(2-Pyridyl)ethenyl]-3-methyl-4-nitroisoxazole **III**.

This compound has mp 143-144° (ethanol); ir (potassium bromide): 1630, 1585, 1500, 1375, 1360, 990, 780, cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.58 (s, 3H), 7.70 (d, J = 16 Hz, 1H), 8.15 (d, J = 16 Hz, 1H), 8.62 (bd, J = 5 Hz, 1H).

Anal. Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92. Found: C, 57.0; H, 3.90.

4-Amino-5-[2-(2-pyridyl)ethenyl]-3-methylisoxazole **IV**.

This compound has mp 135-137° (ethanol); ir (nujol): 3400, 3300, 1625, 1600, 950, 760 cm^{-1}; ms: M$^+$ at m/z 201, m/z 132 (100%), m/z 105 (53%).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.65; H, 5.51. Found: C, 65.59; H, 5.50.

4-(*o*-Methylbenzylideneamine)-5-[2-(2-pyridyl)ethenyl]-3-methylisoxazole **Ia**.

This compound has mp 100-102° (ethanol); ir (nujol): 1630, 1600, 1590, 960, 750 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 3H), 2.56 (s, 3H), 7.0 (d, J = 16 Hz, 1H), 7.5 (d, J = 16 Hz, 1H), 8.5 (s, 1H), 8.4 (bd, J = 5 Hz, 1H).

Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.22; H, 5.65. Found: C, 75.18; H, 5.61.

4-(*o*-Methoxybenzylideneamine)-5-[2-(2-pyridyl)ethenyl-3-methylisoxazole **Ib**.

This compound has mp 123-125° (ethanol); ir (nujol): 1630, 1600, 1590, 1240, 960, 750 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.3 (s, 3H), 3.8 (s, 3H), 7.05 (d, J = 16 Hz, 1H), 7.55 (d, J = 16 Hz, 1H), 8.45 (bd, J = 5 Hz, 1H), 8.88 (s, 1H).

Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.45; H, 5.38. Found: C, 71.40; H, 5.32.

4-(*o*-Hydroxybenzylideneamine)-5-[2-(2-pyridyl)ethenyl]-3-methylisoxazole **Ic**.

This compound has mp 102-104° (ethanol); ir (nujol): 3400, 1620, 1600, 1580, 960, 750 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.4 (s, 3H), 7.1 (d, J = 16 Hz, 1H), 7.44 (d, J = 16 Hz, 1H), 8.55 (bd, 1H), 8.6 (s, 1H), 10.55 (bs, 1H).

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95. Found: C, 70.74; H, 4.90.

4-(*o*-Chlorobenzylideneamine)-5-[2-(pyridyl)ethenyl]-3-methylisoxazole **Id**.

This compound has mp 135-137° (ethanol); ir (nujol): 1630, 1600, 1590, 970, 750 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 3H), 7.41 (d, J = 16 Hz, 1H), 7.78 (d, J = 16 Hz, 1H), 8.65 (bd, J = 5 Hz, 1H), 9.0 (s, 1H).

Anal. Calcd. for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.36. Found: C, 66.72; H, 4.34.

4-(*o*-Nitrobenzylideneamine)-5-[2-(2-pyridyl)ethenyl-3-methylisoxazole **Ie**.

This compound has mp 155-157° (ethanol); ir (nujol): 1630, 1580, 1510, 1350, 960, 740 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 3H), 7.4 (d, J = 16 Hz, 1H), 7.75 (d, J = 16 Hz, 1H), 8.68 (bd, J = 5 Hz, 1H), 9.10 (s, 1H).

Anal. Calcd. for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22. Found: C, 64.62; H, 4.22.

REFERENCES AND NOTES

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[3] T. Tatee, K. Narita, S. Kurashige, S. Ito, H. Miyazaki, H. Yamanaka, M. Mizugaki, T. Sakamoto and H. Fukuda, *Chem. Pharm. Bull.*, **34**, 1643 (1986).

[4] Y. Makisumi, A. Murabayashi, K. Tawara, Y. Watanabe, T. Takahashi and T. Konishi; European Patent Appl. EP 105,548 (Cl C 07 D261/14), 18 Apr. 1984; *Chem. Abstr.*, **101**, 171234h (1984).

[5] W. J. Ross, R. G. Harrison, M. J. R. Jolley, M. C. Neville, A. Todd, J. P. Berge, W. Dawson and M. J. F. Sweatman, *J. Med. Chem.*, **22**, 412 (1979).

[6] S. Numura, K. Ishida, and Nügata Daigaku, *Nogakubu Kenbyu Hokoku*, 71 (1982).

[7] G. D. Diana and P. M. Carabateas, European Patent Appl. EP 207,454 (Cl C 07 D413/12), 07 Jan. 1987; *Chem Abstr.*, **106**., 138429k (1987).

[8] L. A. Reiter, *J. Org. Chem.*, **52**, 2714 (1987).

[9] S. Sailaja, E. Rajanarendar, J. C. Rao and A. K. Murthy, *J. Indian Chem. Soc.*, **62**, 135 (1985).

[10] E. Rajanarender, J. C. Rao and A. K. Murthy, *Indian J. Chem.,Sect. B.*, **21B**, 878 (1982).

[11] R. Martínez and E. Cortés, *J. Heterocyclic Chem.*, **17**, 585 (1980).

[12] K. Yamamoto, S. Yamazaki and I. Murata, *J. Org. Chem.*, **52**, 5439 (1987).

[13] A. Quilico and C. Musante, *Gazz. Chim. Ital.*, **72**, 399 (1942).

[14] R. Martínez and E. Cortés, *J. Heterocyclic Chem.*, **18**, 185 (1981).

[15] E. Rajanarender, C. J. Rao and A. K. Murthy, *Indian J. Chem., Sect. B*, **20B**, 839 (1981).

[16] R. Martínez and E. Cortés, *J. Heterocyclic Chem.*, **17**, 805 (1980).