HALOGENATED ISONIAZID DERIVATIVES. PART 2. UNUSUAL SYNTHESIS OF Δ^2-1,3,4-OXADIAZOLINE DERIVATIVES FROM ISONICOTINOYLHYDRAZONES AND DIAZOMETHANE

Rosaria Ottanà,[a] Enrico Rotondo,[b] M.Gabriella Vigorita,[a*] Carmela Zappalà,[a] and Giuseppe Giordano[b]

[a]Dipartimento Farmaco-Chimico, Università di Messina, Viale Annunziata, 98168 *Messina, Italy*

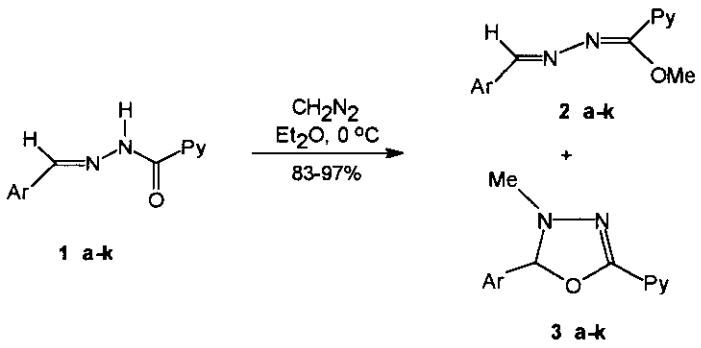
[b]Dipartimento Chimica Inorganica, Analitica e Struttura Molecolare, Università di Messina, Salita Sperone, 98100 Messina, Italy

Abstract - The synthesis of a representative group of isoniazid derivatives, namely 5-aryl-4-methyl-2-pyridyl-Δ^2-1,3,4-oxadiazolines **(3)** and 4-aryl-1-methoxy-1-pyridyl-2,3-diazabutandienes **(2)** by reaction of isonicotinoylhydrazones **(1)** with diazomethane is described A mechanism for the unexpected formation of **3** is suggested

In connection with the emergency of the acquired immunodeficiency syndrome (AIDS), which is often associated with tubercular infections, the need for new antitubercular agents becomes urgent.[1] Since isoniazid (INH) is still considered a primary drug for the chemoprophylaxis and chemotherapy of all types of tuberculosis,[2] we decided to continue the search for new INH derivatives as antitubercular drugs and possibly as anti-HIV agents

In previous papers we showed that isonicotinoylhydrazones **(1)** behave as dipolarophiles towards mercaptocarboxylic acids leading to sulphur containing heterocyclic compounds with moderate activity towards several bacterial strains.[3-5] In this paper we describe the reaction of **1** with diazomethane The

isonicotinoylhydrazones **(1a-k)** have been prepared according to known procedure [5] They have been reacted with a freshly prepared ethereal solution of diazomethane at 0°C The reaction is complete in 30-40 hours as indicated by tlc analyses. The solvent is evaporated and the crude mixture chromatographed on a silica gel column. In all cases the azine derivatives **(2)** and the oxadiazolines **(3)** have been isolated (Scheme 1) Yields and ratio of the products obtained are reported in Table 1. The structures of **2** and **3** have been assigned on the basis of analytical and spectroscopic data.



Ar		Ar		Ar	
a	Ph	**e**	4-FC_6H_4	**i**	3-F,4-$MeOC_6H_3$
b	3-ClC_6H_4	**f**	3-$CF_3C_6H_4$	**j**	2,4-$(MeO)_2C_6H_3$
c	4-ClC_6H_4	**g**	4-$CF_3C_6H_4$	**k**	2,5-$(MeO)_2C_6H_3$
d	3-FC_6H_4	**h**	2,4-$Cl_2C_6H_3$		

Py = 4-pyridyl

Scheme 1

The structure of **2** was assigned on the basis of ^1H and ^{13}C nmr spectra the carbonyl and N-H resonances are absent, and the deshielded methyl group resonances are observed at about δ 4 in the ^1H nmr and at about δ 60 in the ^{13}C nmr spectra. Similarly the Δ^2-1,3,4-oxadiazoline structure of **3** can be deduced from ^1H and ^{13}C nmr data and in some cases is supported by NOE difference experiments In the ^1H nmr spectra the N-H proton is always absent and the methine proton is observed at about δ 7 70-8 10 This value is much lower than that observed for the corresponding proton in the hydrazones **(1)** (δ 8 25-8.81) Moreover an upfield shift of about 20 ppm is observed in the ^{13}C nmr spectra for the iminic carbon of **1** when transformed into the C-5 of

Table 1. Reaction Conditions and Ratio of Compounds **(2)** and **(3)**

Entry	Compounds	Reaction Time (h)	Yields (%)	Ratio (**2**/**3**)
1	**2a**, **3a**	40	69, 20	3 45
2	**2b**, **3b**	35	59, 35	1 69
3	**2c**, **3c**	35	55, 28	1 96
4	**2d**, **3d**	35	62, 30	2 06
5	**2e**, **3e**	35	65, 32	2 04
6	**2f**, **3f**	38	58, 30	1 90
7	**2g**, **3g**	35	62, 32	1 93
8	**2h**, **3h**	30	64, 35	1 83
9	**2i**, **3i**	35	61, 35	1 74
10	**2j**, **3j**	40	79, 5	15 80
11	**2k**, **3k**	40	83, 5	16 60

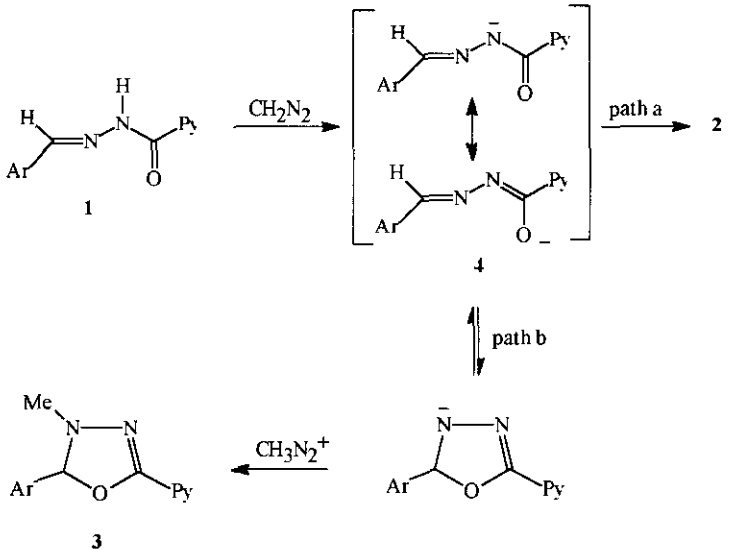
3 thus indicating a change of hybridisation The assignements of these resonances were unambigously established by a combination of 2D homo- and hetero-correlated experiments NOE difference experiments performed on **3h-k** showed about a 15% increase of the intensity of the N-methyl signal when the hydrogen at C-5 was irradiated This result strongly supports a structure that maintains the methyl and the hydrogen atom in close proximity. Moreover the comparison of the NOE results obtained with the 2,5-dimethoxy derivatives **(2k)** and **(3k)** showed that the irradiation of the 5-OCH_3 substituent on the phenyl ring of **2k** does not cause any increase of the intensity of the signal of the protons at 2-position of the pyridine ring while a small but significant positive NOE (1%) was observed in a similar experiment performed on **3k** The presence of a stereogenic center in **3k** has been demonstrated by the addition of a lanthanide chiral reagent which caused enantiomeric resolution of the proton spectrum

The formation of **2** in the reaction of **1** with diazomethane is expected because of the structural similarity of **1** with amides In fact it is well known that amides can be methylated by diazomethane at the oxygen atom [6]

Albeit both nitrogen and oxygen of amides can be methylated,[6] in our system the selective reaction at oxygen might be due to the formation of a more stable conjugated system

On the contrary the formation of **3** it is not easy to rationalise In fact the reaction of diazomethane with hydrazones of different structure usually gives Δ^2-1,2,3-triazoline derivatives.[7-11]

Several mechanisms can be envisaged for the formation of **3**, however it seems reasonable to assume that diazomethane acts as base[6] leading to the formation of the anion **(4)** (Scheme 2).



Scheme 2

Methylation of **4** at oxygen leads to the formation of **2** (path a) while nucleophilic attack of oxygen at the iminic carbon and subsequent methylation at nitrogen gives the oxadiazoline **(3)** (path b)

The proposed mechanism is also in agreement with the reduced yields of **3** when electron-donating groups in the phenyl ring are present (see Table 1, Entries 10 and 11)

In conclusion we have shown that the reaction of isonicotinoylhydrazones with diazomethane represents an easy access to the synthesis of the Δ^2-1,3,4-oxadiazoline ring system albeit in moderate yields

EXPERIMENTAL

Mps were taken on a Kofler hot-stage apparatus and are uncorrected Microanalyses were obtained using a C Erba mod 1106 elemental analyser Mass spectra were obtained on a Hewlett Packard Model 5995 GC/MS. ^{1}H and ^{13}C nmr spectra were recorded on a Bruker ARX-300 MHz spectrometer, chemical shifts are in ppm from internal Me_4Si and refer to $CDCl_3$ or DMSO-d_6 solutions, tris(3-trifluoromethylhydroxymethylene)-d-canforate [Eu(TFC)$_3$] was used as lanthanide chiral shift reagent NOE measurements were performed under nitrogen by FT difference method after a preliminar rough evaluation of the longitudinal relaxation time of the protons ^{1}H resonances assignements are supported by autocorrelated homonuclear proton two-dimensional nmr esperiments (phase sensitive 2D COSY) ^{13}C resonances were always attributed by proton-carbon heteronuclear chemical shift correlation. Carbon multiplicities were determined by DEPT and J-modulated spin-echo experiments Tlc controls were carried out on precoated silica gel plates GF 254 (Merck) Flash-chromatography was carried out with Kiselgel H (Merck)

Reaction of arylisonicotinoylhydrazones (1a-k) with diazomethane. - *General procedure* The arylisonicotinoylhydrazones **(1a-k)** (15 mmol) were suspended in a freshly prepared solution of diazomethane in ether (100 ml) and the reaction mixture was allowed to stand at 0° C until tlc analysis showed disappearance of **1** (see Table 1) The ethereal solution was evaporated and the crude mixture was chromatographed on silica gel column with ether-hexane 9 1 as eluant First fractions after in vacuo concentration gave compounds (**2**) and further ones compounds(**3**). The crude products were then crystallized from ether.

1-Methoxy-4-phenyl-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2a) Yellow oil Ms m/z 239 (M^+, 87 %) ^{1}H Nmr ($CDCl_3$) δ 4 03 (s, 3H, CH_3), 7 38-7 43 (m, 3H, ArH), 7 64 (m, 2H, Py), 7 65-7 70 (m, 2H, ArH), 8 45 (s, 1H, CH=N), 8 72 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 55 5 (q), 124 7 (d), 128 7 (d), 129 3 (d), 131 3 (d), 135 1 (s), 138 7 (s),150 2 (d), 159 5 (d, C-4), 163 6 (s) Anal Calcd for $C_{14}H_{13}N_3O$ C, 70 27, H, 5 47, N, 17 57 Found C, 70 15, H, 5 51, N, 17 33

4-Methyl-5-phenyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3a) Yellow oil Ms m/z 239 (M^+, 21%) ^{1}H Nmr ($CDCl_3$) δ 4 03 (s, 3H, CH_3), 7 49-7 90 (m, 5H, ArH), 7 64 (m, 2H, Py), 8 49 (s, 1H, CH), 8 72 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$). δ 29 1 (q), 127 8 (d), 129 4 (d), 129 5 (d), 130.7 (d), 131 5 (d), 134 7 (s), 141 0 (d, C-5),

143 0 (s), 149 9 (d), 163.6 (s) Anal. Calcd for $C_{14}H_{13}N_3O$ C, 70.27; H, 5 47, N, 17.57 Found C, 70 12, H, 5 61, N, 17 35

4-(3-Chlorophenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2b). White solid, mp 85-88 °C (from ether) Ms m/z 273 (M^+, 15%) ^{1}H Nmr ($CDCl_3$) δ 4.01 (s, 3H, CH_3), 7.28-7 55 (m, 3H, ArH), 7 63 (d, J=6.0 Hz, 2H, Py), 7 65 (s, 1H, ArH), 8 39 (s, 1H, CH=N), 8 72 (d, J=6.0 Hz, 2H, Py) ^{13}C Nmr ($CDCl_3$): δ 55 6 (q), 124 6 (d), 126.7 (d), 128 3 (d), 130.5 (d), 131 0 (d), 135 3 (s), 136 8 (s), 138.5 (s), 150 1 (d), 158.1 (d, C-4), 164 2 (s) Anal Calcd for $C_{14}H_{12}N_3OCl$ C, 61 43, H, 4 42; N, 15 35 Found: C, 61 35; H, 4 32, N, 15 21

5-(3-Chlorophenyl)-4-methyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3b) Yellow solid, mp 155-158 °C (from ether) Ms m/z 273 (M^+, 100 %). ^{1}H Nmr ($CDCl_3$) δ 3 58 (s, 3H, CH_3), 7 30-7.32 (m, 3H, ArH), 7 43 (s, 1H, ArH), 7 53 (d, J=6 1 Hz, 2H, Py), 7 72 (s, 1H, CH), 8 75 (d, J=6 1 Hz, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 29 1 (q), 122 8 (d), 125 6 (d), 127 7 (d), 130 5 (d), 130 6 (d), 135 4 (s), 136 4 (s), 139 3 (d, C-5), 143 5 (s), 149 9 (d), 169 7 (s) Anal Calcd for $C_{14}H_{12}N_3OCl$ C, 61 43, H, 4 42, N, 15 35 Found C, 61 37, H, 4.33, N, 15.27

4-(4-Chlorophenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2c) White solid, mp 70-73 °C (from ether) Ms m/z 273 (M^+, 100 %) ^{1}H Nmr ($CDCl_3$) δ 4 01 (s, 3H, CH_3), 7 34 (m, 2H, ArH), 7 60 (m, 2H, ArH), 7 64 (d, J=6 1 Hz, 2H, Py), 8 41 (s, 1H, CH=N), 8 71 (d, J=6 1 Hz, 2H, Py) ^{13}C Nmr ($CDCl_3$)· δ 55 6 (q), 124 6 (d), 129 5 (d), 129 7 (d), 133 5 (s), 137 0 (s), 138 6 (s), 150 1 (d), 158 2 (d, C-4), 163 9 (s) Anal Calcd for $C_{14}H_{12}N_3OCl$ C, 61 43, H, 4 42, N, 15.35 Found C, 61 35, H, 4 28, N, 15 22

5-(4-Chlorophenyl)-4-methyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3c) Yellow solid, mp 230-234 °C (from ether) Ms m/z 273 (M^+, 40 %) ^{1}H Nmr ($CDCl_3$) δ 3 56 (s, 3H, CH_3), 7 30-7.36 (m, 4H, ArH), 7 51 (d, J=5.7 Hz, 2H, Py), 7 74 (s, 1H, CH), 8 73 (d, J=5 7 Hz, 2H, Py) ^{13}C Nmr ($CDCl_3$)· δ 29 1 (q), 123 7 (d), 128 8 (d), 129 6 (d), 133 2 (s), 136 5 (s), 139 6 (d, C-5), 143 7 (s), 149 9 (d), 169 7 (s) Anal Calcd for $C_{14}H_{12}N_3OCl$ C, 61 43, H, 4 42, N, 15 35 Found C, 61 39; H, 4 22, N, 15 21

4-(3-Fluorophenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2d) White solid, mp 54-57°C (from ether) Ms m/z 257 (M^+, 100 %). ^{1}H Nmr ($CDCl_3$) δ 3 91 (s, 3H, CH_3), 6 94-7 30 (m, 4H, ArH), 7.54 (m,

2H, Py), 8 31 (s, 1H, CH=N), 8.62 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 55 6 (q), 114 6 (d), 118 0 (d), 124 6 (d), 124 7 (d), 130 8 (d), 137 0 (s), 138.5 (s), 150 1 (d), 158 3 (d, C-4), 163 0 (d, J=249 Hz), 165 1 (s) Anal Calcd for $C_{14}H_{12}N_3OF$ C, 65 36, H, 4.70, N, 16 34 Found C, 65 12, H, 4 55, N, 16 12

5-(3-Fluorophenyl)-4-methyl-2-(4-pyridyl)- Δ^2-1,3,4-oxadiazoline (3d). Yellow solid, mp 147-149 °C (from ether) Ms m/z 257 (M^+, 26 %). ^{1}H Nmr ($CDCl_3$) δ 3 57 (s, 3H, CH_3), 7 02-7 32 (m, 4H, ArH), 7 52 (m, 2H, Py), 7 74 (s, 1H, CH), 8 74 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 29 1 (q), 114 8 (d), 117 4 (d), 123.6 (d), 123 7 (d), 130 8 (d), 136 9 (s), 139 6 (d, C-5), 143 5 (s), 149 9 (d), 163 5 (d, J=247 Hz), 169 7 (s) Anal Calcd for $C_{14}H_{12}N_3OF$ C, 65.36; H, 4 70, N, 16 34. Found C, 65 17, H, 4 53; N, 16 24

4-(4-Fluorophenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2e). White solid, mp 110-113 °C (from ether) Ms m/z 257 (M^+, 100 %). ^{1}H Nmr ($CDCl_3$) δ 4 01 (s, 3H, CH_3), 7.08 (dd, 2H, $^3J_{HF} = {}^3J_{HH} = 8$ 2 Hz, ArH), 7 64- 7 69 (m, 4H, Py and ArH), 8.42 (s, 1H, CH=N), 8 72 (m, 2H, Py). ^{13}C Nmr ($CDCl_3$) δ 55 5 (q), 116 5 (d), 124 6 (d), 130 5 (d), 131 4 (s), 138 7 (s), 150 2 (d), 158.2 (d, C-4), 164 7 (d, J=257 Hz), 166 5 (s) Anal Calcd for $C_{14}H_{12}N_3OF$ C, 65 36; H, 4 70, N, 16 34 Found C 65 42, H, 4 49, N, 16 42

5-(4-Fluorophenyl)-4-methyl-2-(4-pyridyl)- Δ^2-1,3,4-oxadiazoline (3e). Yellow solid, mp 204-207 °C (from ether) Ms m/z 257 (M^+, 40 %) ^{1}H Nmr ($CDCl_3$) δ 3 56 (s, 3H, CH_3), 7 08 (dd, 2H, $^3J_{HF} = {}^3J_{HH} = 8$ 2 Hz, ArH), 7 43 (dd, 2H, $^3J_{HH} = 8.2$ and $^4J_{HF} = 5.5$ Hz, ArH), 7 52 (m, 2H, Py), 7 74 (s, 1H, CH), 8.72 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 29 1 (q), 116 5 (d), 123 8 (d), 129 6 (d), 130 9 (s), 139 7 (d, C-5), 143 9 (s), 149 9 (d), 164 3 (d, J=234 Hz), 169 7 (s) Anal Calcd for $C_{14}H_{12}N_3OF$ C, 65 36, H, 4 70, N, 16 34 Found C, 65 45, H, 4 56, N, 16 45

4-(3-Trifluoromethylphenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2f) Yellow solid, mp 83-87°C (from ether). Ms m/z 307 (M^+, 63 %) ^{1}H Nmr ($CDCl_3$) δ 4 03 (s, 3H, CH_3), 7 49-7 90 (m, 6H, ArH and Py), 8.72 (s, 1H, CH=N), 8 73 (d, J=6 1 Hz, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 55.7 (q), 124 4 (q, J=272 Hz), 124 6 (d), 125 4 (d), 127 6 (d), 129 8 (d), 131 4 (d), 132 0 (s), 135 9 (s), 138 6 (s), 150 2 (d), 157 9 (d, C-4), 164 5 (s) Anal Calcd for $C_{15}H_{12}N_3OF_3$ C, 58.63, H, 3 94, N, 13 68. Found C, 58 41, H, 3 72, N, 13 43

5-(3-Trifluoromethylphenyl)-4-methyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3f). Yellow solid, mp 194-196 °C (from ether). Ms m/z. 307 (M^+, 27 %) ^{1}H Nmr (DMSO-d_6) δ 3 57 (s, 3H, CH_3), 7 02-7 32 (m, 4H, ArH), 7 52 (d, J=5 9 Hz, 2H, Py), 7 74 (s, 1H, CH), 8 74 (d, J=5 9 Hz, 2H, Py). ^{13}C Nmr (DMSO-d_6) δ 29 1 (q), 123 9 (d), 124 0 (d), 126.5 (d), 129 9 (s), 124 6 (q, J=272.4 Hz), 130 1 (s), 130 6 (d), 131 0 (d), 136 2 (s), 140 6 (d, C-5), 143 9 (s), 149 8 (d), 169 1 (s) Anal. Calcd for $C_{15}H_{12}N_3OF_3$ C, 58 63, H, 3 94, N, 13.68 Found C, 58.45, H, 3 76; N, 13 48

4-(4-Trifluoromethylphenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2g) White solid, mp 70-73°C (from ether) Ms m/z: 307 (M^+, 69 %) ^{1}H Nmr ($CDCl_3$) δ 4 03 (s, 3H, CH_3), 7.63-7 79 (m, 6H, ArH and Py), 8 49 (s, 1H, CH=N), 8 73 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 55.7 (q), 124 5 (q, J=272 Hz), 124 7 (d), 126.2 (d), 128 7 (d), 132 5 (s), 137 0 (s), 138 6 (s), 150 1 (d), 157.9 (d, C-4), 164.6 (s) Anal Calcd for $C_{15}H_{12}N_3OF_3$ C, 58 63, H, 3.94, N, 13 68 Found C, 58 75, H, 4 01, N, 13 72

5-(4-Trifluoromethylphenyl)-4-methyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3g) Yellow solid, mp 190-193 °C (from ether) Ms m/z 307 (M^+, 18 %) ^{1}H Nmr ($CDCl_3$) δ 3 60 (s, 3H, CH_3), 7 51-7 63 (m, 6H, ArH and Py), 7 80 (s, 1H, CH), 8 75 (d, J=6 0 Hz, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 29.2 (q), 123 7 (d), 124 5 (q, J=272 Hz), 126 4 (d), 127 8 (d), 132.5 (s), 137 0 (s), 138 6 (s), 139 0 (d, C-5), 149 9 (d), 164 6 (s) Anal Calcd for $C_{15}H_{12}N_3OF_3$ C, 58 63, H, 3.94, N, 13 68 Found C, 58.77, H, 3 98; N, 13 75

4-(2,4-Dichlorophenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2h). White solid, mp 128-131°C (from ether). Ms m/z 307 (M^+, 100 %) ^{1}H Nmr ($CDCl_3$). δ 4 02 (s, 3H, CH_3), 7 23-7.86 (m, 5H, ArH and Py), 8.71 (s, 1H, CH=N), 8 79 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 55 7 (q), 124 5 (d), 128.1 (d), 130 2 (d), 131.1 (s), 136 1 (s), 137 1 (s), 137 3 (d), 138 6 (s), 150.2 (d), 155 2 (d, C-4), 164.6 (s) Anal Calcd for $C_{14}H_{11}N_3OCl_2$ C, 54.56; H, 3.59, N, 13 63 Found C, 54 78, H, 3 50, N, 13 72.

5-(2,4-Dichlorophenyl)-4-methyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3h) Yellow solid, mp 185-189 °C (from ether) Ms m/z 307 (M^+, 20 %) ^{1}H Nmr ($CDCl_3$) δ 3 60 (s, 3H, CH_3), 7 14-7 52 (m, 5H, ArH and Py), 8.10 (s, 1H, CH=N), 8 76 (d, J=5 2 Hz, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 29 3 (q), 123.6 (d), 128.1 (d), 128.2 (d), 129.2 (s), 130 1 (d), 131 3 (s), 136.4 (d, C-5), 143 5 (s), 149 8 (d), 169 8 (s) Anal Calcd for $C_{14}H_{11}N_3OCl_2$

C, 54 56, H, 3.59, N, 13 63. Found C, 54.79, H, 3 49, N, 13.71

4-(3-Fluoro-4-methoxyphenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2i). White solid, mp 75-78 °C (from ether) Ms m/z 287 (M^+, 100 %) ^{1}H Nmr ($CDCl_3$) δ 3 92 (s, 3H, $ArOCH_3$), 4.01 (s, 3H, CH_3), 6 94-7 49 (m, 3H, ArH), 7 66 (m, 2H, Py), 8.36 (s, 1H, CH=N), 8 73 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 55 5 (q), 56 8 (q), 113 5 (d), 115 1 (d), 128.5 (s), 138 7 (s), 150 2 (d), 153 4 (d, J=247 6 Hz), 154 6 (s), 158 1 (d, C-4), 163 6 (s) Anal Calcd for $C_{15}H_{14}N_3O_2F$ C, 62 71, H, 4 91, N, 14 63 Found C, 62 50, H, 4 71, N, 14.75

5-(3-Fluoro-4-methoxyphenyl)-4-methyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3i) Yellow solid, mp 165-168 °C (from ether) Ms m/z 287 (M^+, 51 %) ^{1}H Nmr ($CDCl_3$) δ 3 91 (s, 3H, $ArOCH_3$), 3 55 (s, 3H, CH_3), 6 88-7 17 (m, 3H, ArH), 7 50 (m, 2H, Py), 7 69 (s, 1H, CH=N), 8.72 (m, 2H, Py). ^{13}C Nmr ($CDCl_3$) δ 29 1 (q), 56 8 (q), 113 7 (d), 114 6 (d), 123 8 (d), 124 7 (d), 128 4 (s), 139 7 (d, C-5), 143 8 (s), 149 4 (d), 152 3 (d, J=244 Hz), 154 6 (s) Anal Calcd for $C_{15}H_{14}N_3O_2F$ C, 62 71, H, 4 91, N, 14 63 Found C, 62 57, H, 4 76, N, 14 79

4-(2,4-Dimethoxyphenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2j). White solid, mp 93-97 °C (from ether) Ms m/z 299 (M^+, 65 %) ^{1}H Nmr ($CDCl_3$) δ 3 78 and 3.80 (2s, 6H, $ArOCH_3$), 3 96 (s, 3H, CH_3), 6 40 (d, 1H, J=2 6 Hz, ArH), 6 50 (dd, 1H, J=2 6 and J=8 6 Hz, ArH), 7 72 (m, 2H, Py), 7 80 (d, 1H, J=8 6 Hz, ArH), 8 70 (m, 2H, Py), 8 80 (s, 1H, CH=N) ^{13}C Nmr ($CDCl_3$) δ 54 2 (q), 54 8 (q), 55 3 (q), 98 0 (d), 105 5 (d), 116 1 (s), 124.1 (d), 128 3 (d), 138 1 (s), 149 4 (d), 154 2 (s), 154.6 (d, C-4), 160 0 (s), 161 6 (s) Anal Calcd for $C_{16}H_{17}N_3O_3$ C, 64 20, H, 5 73, N, 14 04 Found C, 64 35, H, 5 66; N, 14.14

5-(2,4-Dimethoxyphenyl)-4-methyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3j) Yellow solid, mp 132-137 °C (from ether) Ms m/z 299 (M^+, 32 %) ^{1}H Nmr ($CDCl_3$) δ 3 56 (s, 3H, CH_3), 3.81 and 3 85 (2s, 6H, $ArOCH_3$), 6 43 (m, 2H, ArH), 7.38 (s, 1H, ArH), 7 52 (m, 2H, Py), 8 12 (s, 1H, CH), 8 71 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 28 5 (q), 53 4 (q), 55 4 (q), 98 0 (d), 105 6 (d), 115 6 (s), 123 1 (d), 127 1 (d), 136 4 (d, C-5), 143 7 (s), 149 2 (d), 159 3 (s), 162.5 (s), 162.7 (s) Anal Calcd for $C_{16}H_{17}N_3O_3$ C, 64 20, H, 5.73; N, 14 04 Found C, 64 33, H, 5 69, N, 14 16.

4-(2,5-Dimethoxyphenyl)-1-methoxy-1-(4-pyridyl)-2,3-diaza-1,3-butadiene (2k) White solid, mp 115-

118 °C (from ether). Ms m/z: 299 (M^+, 65 %). ^{1}H Nmr ($CDCl_3$) δ 3 75 and 3 85 (2s, 6H, $ArOCH_3$), 4.02 (s, 3H, CH_3), 6.88 (d, 1H, J=9 0 Hz, ArH), 6 95 (dd, 1H, J=3 1 and J=9.0 Hz, ArH), 7 40 (d, 1H, J=3.1 Hz, ArH), 7.68 (m, 2H, Py), 8.71 (m, 2H, Py), 8 83 (s, 1H, CH=N) ^{13}C Nmr ($CDCl_3$) δ 55 5 (q), 57 4 (q), 57.7 (q), 110.5 (s), 113 7 (d), 118 3 (d), 123 5 (s), 124 1 (d), 138.1 (s), 149 4 (d), 153.5 (d), 154.5 (d, C-4), 162.4 (s). Anal. Calcd for $C_{16}H_{17}N_3O_3$ C, 64 20; H, 5 73; N, 14 04. Found C, 64 42; H, 5.95; N, 13 89

5-(2,5-Dimethoxyphenyl)-4-methyl-2-(4-pyridyl)-Δ^2-1,3,4-oxadiazoline (3k) Yellow solid, mp 188-192 °C (from ether) Ms m/z 299 (M^+, 32 %) ^{1}H Nmr ($CDCl_3$) δ 3 53 (s, 3H, CH_3), 3 60 and 3.83 (2s, 6H, $ArOCH_3$), 6 80-6 96 (m, 3H, ArH), 7.53 (m, 2H, Py), 8 13 (s, 1H, CH), 8.70 (m, 2H, Py) ^{13}C Nmr ($CDCl_3$) δ 28 5 (q), 56 0 (q), 55.3 (q), 109 0 (d), 112 6 (d), 118 1 (d), 122 9 (s), 123.3 (d), 136 1 (d, C-5), 143 5 (s), 149 1 (d), 152.5 (s), 153 3 (s), 169 1 (s) Anal Calcd for $C_{16}H_{17}N_3O_3$ C, 64.20, H, 5.73, N, 14.04 Found C, 64 34; H, 5 92, N, 13 91

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