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REGIOSPECIFIC SYNTHESES OF Δ^4-1,2,4-OXADIAZOLIN-3-CARBOXYLIC ACIDS

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Abstract: Δ^4-1,2,4-Oxadiazolin-3-carboxylic acids, **3a-3i**, were obtained by 1,3-dipolar cycloaddition between Δ^2-oxazolin-5-ones, **1**, and nitrosobenzene, **2**. The reaction occurs regiospecifically at room temperature, the mesoionic form of **1** acting as the 1,3-dipole and the N=O group of **2** acting as the dipolarophile. Xylene or DMF are used as solvents. The thermally unstable aminoacids were converted into their methyl esters, **4a-4i**, by treatment with diazomethane. The esters were characterized by their physical properties.

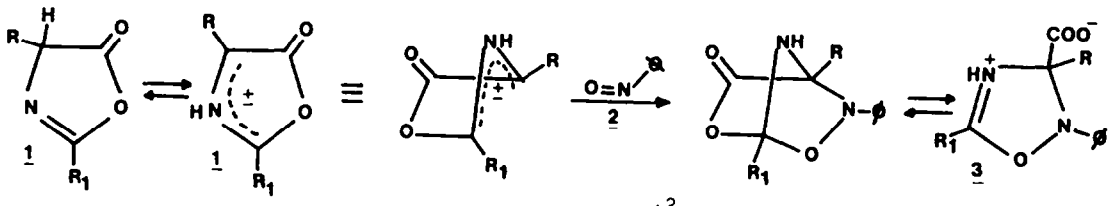
When searching for newer compounds with possible pharmacological action, those having in their structure the 1,2,4-oxadiazolinic ring are particularly interesting. This ring has been obtained first by benzamidoxime reaction on aldehydes, a reaction leading to Δ^2-oxadiazolines[1,2]; second, by addition of n-butyllithium to the azomethinic bond of 3-methyl-5-phenyl-1,2,4-oxadiazole yielding 3-methyl-5-phenyl-5-n-butyl-1,2,4-dihydrooxadiazole (which is also a Δ^2-1,2,4-oxadiazoline). However, butyllithium causes lateral lithiation of the 3-phenyl-5-methyl -1,2,4-oxadiazole, thus making the method specific and of little practical use[3]. Third, by 1,3-dipolar cycloaddition of 2,4-diphenyl- and 2-p-methylphenyl-4-phenyl-2-oxazolin-5-ones with nitrosobenzene forming regiospecifically 2,3,5-triphenyl- and 2,3-diphenyl-5-p-methylphenyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acids respectively[4]. Since this third method is apparently easy to perform, and provides only one regioisomer as a product in good yield, it seemed promising for the synthesis of the 1,2,4-oxadiazoline ring. This reaction can be regarded as a 1,3-dipolar cycloaddition between the mesoionic oxazolone structure acting as a 1,3-dipole and the N=O unsaturated group of the nitrosobenzene acting as a dipolarophile.

Oxazolone, as a 1,3-dipole, is an azomethin-ylide with two carbons as terminal atoms of the dipole and one nitrogen atom as a central element. The dipole is asymmetric and the substituent variations at the terminal atoms could modify the charge density at these ends, and so it may be possible to find a molecular inversion and a complete or partial loss of regiospecifity during cycloaddition.

The scope of this cycloaddition reaction is explored by treating nitrosobenzene with 2-aryl-4-phenyl-, 2-aryl-4-methyl- and 2-methyl-4-phenyloxazolones, which are structural oxazolone variations that could change the nature of dipole.

RESULTS AND DISCUSSION

Oxazolones **1a** to **1h** (Table 1) were isolated, purified and allowed to react with nitrosobenzene at room temperature. Aminoacids **3a** to **3h** in their zwitterionic form (Table 2) were obtained in good yields (59-88%). The oxazolone **1i** was not isolated; it was prepared in situ and allowed to react with nitrosobenzene; the corresponding aminoacid was treated with diazomethane and the methyl ester of the acid **3i** was isolated.



Scheme 1 : Ketonic **1** and mesoionic **1'** forms of Δ^2-oxazolin-5-ones and their adducts **3** with nitrosobenzene.

TABLE 1 Δ^2-Oxazolin-5-ones that were allowed to react with nitrosobenzene.

Nº	1a	1b	1c	1d	1e	1f	1g	1h	1i
R	Ph	Ph	Ph	Ph	Ph	Me	Me	Me	Ph
R_1	Ph	p-Me-Ph	p-MeO-Ph	p-Cl-Ph	p-NO_2-Ph	Ph	p-MeO-Ph	p-Cl-Ph	Me

Oxazolones **1a**, **1b** and **1f** are very soluble in xylene and react readily with nitrosobenzene. In less than 30 minutes the solution decolorizes, yielding the corresponding acids **3a**, **3b** and **3f** which start crystallizing as the reaction proceeds.

The reactions with oxazolones **1d** and **1e** do not take place in xylene at room temperature since they are insoluble. Killé and Fleury[5] described **1e** as having the mesoionic structure **1'e** (Scheme 1); this proposal was confirmed by photoelectron spectroscopy[6] and by syntheses of mesoionic oxazolones[7]. On the other hand, Petersen[8] described **1d** in the solid state as having mesoionic form **1'd**, a result confirmed by Steglich[9]. These mesoions are insoluble in xylene. When N,N-dimethylformamide was used as a solvent reaction with **2** ocurred instantaneously; both the green color of the nitrosobenzene and the dark blue color of the oxazolone solution disappeared. The latter coloration has been attributed both to the oxazolone anion formed in a reaction with basic solvents such as DMF, and to the oxazolonio-5-olate, **1'**, a tautomeric structure in equilibrium with **1**[10].

Oxazolone **1c** was allowed to react in xylene as well as in DMF; the same product was obtained in both cases, but the reaction proceeded faster in DMF.

Even though oxazolones **1g** and **1h** are soluble in xylene, they react very slowly with nitrosobenzene. This sluggishness may be explained if we consider that 1,3-dipole formation practically does not occur in this solvent. If DMF is added to the xylene solution, the reaction proceeds faster, though not so fast as 4-phenyloxazolones. DMSO and DMF are solvents that promote the formation of the oxazolone mesoionic structure[10].

In all cases under study, only one acid was obtained; this was confirmed by ^{1}H NMR spectra (Table 3) and by thin layer chromatography. These result indicate that the reaction is regiospecific.

The presence of an acid functional group can be inferred from its solubility in a basic medium, from its reaction with diazomethane yielding a mono methyl ester, and from characteristic acid bands in the IR spectra: a wide band due to an associated OH group and a carbonyl band (Table 2). The ^{1}H NMR spectra (Table 3) support the proposed structures.

The zwitterionic nature of acids **3a - 3h** can be seen clearly in the ^{1}H NMR spectra. Thus, compound **3b** in hexadeuterioacetone shows a wide singlet centered at 3.37 ppm that integrates for one proton. The signal disappears when treated with deuterium oxide. The same happens with compound **3d**; it shows a similar absorption at 9.1 ppm that disappears rapidly with deuterium oxide. For all the other acids, the acid proton signal intermingles with the aromatic proton signals (Table 3)

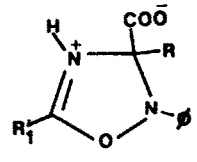
The IR spectra of the compounds **3a** and **3h** also confirm their zwitterionic structure since they show a wide band in the zones between 2646-2222 cm^{-1} and 2041-1852 cm^{-1}. These are the typical absorption zones of the NH group in ammonium type compounds[11].

TABLE 2 Δ^4-1,2,4-Oxadiazolin-3-carboxylic acids, **3**, and physical properties.

Nº	R	R_1	Prep. meth.	Yield %	m.p.ºC	IR (KBr, cm^{-1}) OH	C=O	C=N	out-of plane bend			lit.
3a	Ph	Ph	A	59.5	101-2	3100-2200	1740	1613	710	695	690	4
3b	Ph	p-Me-Ph	A	86.7	123-4	3500-2200	1744	1610	781	735	696	4
3c	Ph	p-MeO-Ph	A,B	70.6	130	3333-2500	1754	1613	840	741	699	
3d	Ph	p-Cl-Ph	C	81.6	122	3322-2203	1745	1615	842	758	695	
3e	Ph	p-NO_2-Ph	B	74.2	80-2	3175-2222	1724	1626	850	756	694	
3f	Me	Ph	A	59.3	70-1	3704-2717	1712	1618	758	701	696	
3g*	Me	p-MeO-Ph	B	69.9	126	3125-2703	1733	1613	835	758	693	
3h	Me	p-Cl-Ph	B	81.2	95	3333-2703	1724	1626	837	758	694	

* Anal. Calc. for $C_{17}H_{16}N_2O_4$: C, 65.57; H, 5.16; N, 8.97 Found: C, 65.47; H, 5.29; N, 9.02

TABLE 3 Δ^4-1,2,4-Oxadiazolin-3-carboxylic acids, **3**. ^1H NMR Spectral data.



3

Nº	Solv.	Chemical Shifts in ppm (multiplicity, integration).
3a	i	7.9-7.3 (m).
3b	i	8.1-7.1 (m, 14H); 3.77* (s broad, 1H); 2.37 (s, 3H).
3c	i	7.9-6.7 (m, 15H); 3.8 (s, 3H).
3d	j	8.3 (d, 2H, J_d = 8 Hz); 8.0-6.9 (m, 13H).
3e	i	9.72-8.42 (m, 5H); 7.88-7.32 (m, 10H).
3f	i	9.1* (s broad, 1H); 7.8-7.56 (m, 2H); 7.47-7.13 (m, 8H); 1.73 (s, 3H).
3g	i	7.36 (s, 5H); 6.9 (d, 2H, J_d = 8 Hz); 6.70 (d, 2H, J_d = 8 Hz); 3.8 (s, 3H); 1.93 (s, 3H).
3h	j	7.6 (d, 2H, J_d = 8.5 Hz); 7.47-7.10 (m, 8H); 1.8 (s, 3H).

Solv. : i = acetone-d_6; j = $CDCl_3$

* : The signal disappears on treatment with deuterium oxide.

The $\Delta^4$1,2,4-oxadiazolin-3-carboxylic acids are thermally unstable and difficult to solubilize, and so they were transformed into their methyl esters by treatment with diazomethane. The esters are stable, crystalline and moderately soluble in ordinary organic solvents.

Structure of the methyl esters of Δ^4-1,2,4-oxadiazolin-3-carboxylic acids, **4**. The esters show in their IR spectra (see Experimental) a strong stretching C=O band between 1739 and 1754 cm^{-1} and the characteristic C=N band between 1626 and 1645 cm^{-1}.

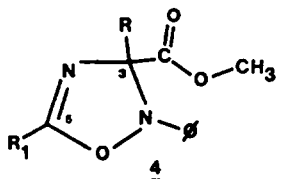
Their ^1H NMR spectra show the absorption typical of a methyl ester between 3.7 and 3.79 ppm and their ^{13}C NMR exhibit an absorption between 169.81 and 171.66 ppm (C=O) and another between 53.02 and 53.28 ppm with respect to TMS (O-CH_3) (Table 4).

Evidence of formation of the 1,2,4-oxadiazoline ring. In the IR spectra, the esters exhibit a sharp absorption between 1625 and 1645 cm^{-1} characteristic of the C=N group. This is similar to the C=N group of the lactone ring of the oxazolone.

The ^{13}C NMR spectra of **4a**, **4b**, **4g** and **4i** were determined under total proton decoupling and off-resonance proton decoupling. The most significant assignments were performed from the multiplicity obtained by off resonance proton decoupling, by the lower signal intensity of carbon having relatively long spin-lattice relaxation times, and by using known models[12] (Table 4).

The existence of a quaternary carbon at position 3 in the oxadiazoline ring and of the oxazolone type carbon supports the formation of the 5-membered ring.

TABLE 4 ^{13}C NMR Chemical Shifts of methyl Δ^4-1,2,4-Oxadiazolin-3-carboxylates, **4**



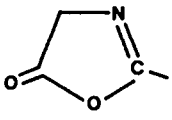
4

Nº	C-3	C-5	C=O(ester)	OCH_3(ester)
4a	106.67	162.38	169.81	53.11
4b	106.67	162.32	169.83	53.02
4g	105.65	164.12	171.66	53.28
4i	105.60	161.46	170.18	53.12

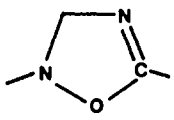
Even though there exist appreciable structural differences among the 1,3-dipoles that give rise to the esters under study, the results seem to indicate that the same kind of compound is always formed, meaning that regiospecificity does not change.

In a previous paper, we had established by the use of shift reagents that the reaction was Z-regiospecific; the same conclusion was reached by decarboxylation of the aminoacid **3b** and simultaneous ring opening of the oxadiazoline to give N-p-methylbenzoyl-N'-phenylbenzamidine. The acylamidine structure was confirmed by an alternative synthesis[4].

If cycloaddition were Z-regiospecific[13], the Δ^4-1,2,4-oxadiazolin-3-carboxylic acid obtained should have a C-5 environment similar to that of C-2 of a 2-oxazolin-5-one.



Oxazolone



1,2,4-Oxadiazoline

Thus, the chemical shifts of C-2 of the oxazolone should be similar to that of C-5 in the 1,2,4-oxadiazoline ring. Prokof'ev et al.[14] have reported for C-2 of substituted 2-methyl-4-arylidenoxazolones shifts of 159.8-166.3 ppm relative to TMS. Maquestiau et al.[15] reported a chemical shift of 161.0 ppm for C-2 of 2-p-chlorophenyl-4-phenyl-2-oxazolin-5-one, and Márquez et al.[16] have described a chemical shift of 163.44 ppm for C-2 of oxazolone **1c**. These results are in accord with our values, (Table 4).

We have concluded that, several types of 4H-oxazolones react with nitrosobenzene to give regiospecifically Δ^4-1,2,4-oxadiazolin-3-carboxylic acids. The reaction is highly affected by solvent effects and it becomes easy in solvents that promote oxazolone mesoionic structure formation such as DMF or DMSO.

EXPERIMENTAL SECTION

Infrared spectra were run as KBr microtablets in a Leitz III G spectrometer, and only the strong absorptions are reported, (cm^{-1}). The ^1H NMR spectra were determined in a Varian EM-360 spectrometer and the chemical shifts are expressed in ppm with respect to TMS. Abbreviations used: m (multiplet), d (doublet), q (quartet), s (singlet).

^{13}C NMR spectra of compounds **4a** and **4b** were obtained in a Varian CFT-20 (20 MHz) spectrometer in the Universidad de Concepción, Chile, and the spectra of the compounds **4g** and **4i** were obtained in a Jeol FX-60 (15 MHz) in the Chemistry Department of the City University, Northampton Square, London.

Elemental analyses of the compounds **4g** and **4i** were performed in the Chemistry Department of the City University, London; and the analyses of the compounds **4c-4f** and **4h** were carried out in the Pontificia Universidad Católica de Chile.

Chromatographies were carried out on Kieselgel 60F-254 silicic acid plates using di-n-butyl ether as a solvent, unless otherwise stated. Melting points are uncorrected.

SYNTHESIS: The following Δ^2-oxazolin-5-ones (yield %) were made by the literature methods cited: **1a**[4,10](87.5); **1b**[4](69.4); **1c**[16,17](93); **1d**[18](76.8); **1e**[10](72.8); **1f**[16]; **1g**[16] and **1h**[16].

Reaction of Δ^2-oxazolin-5-ones with nitrosobenzene. Formation of Δ^4-oxadiazolin-3-carboxylic acids. Three general methods were used: Method A: To one equivalent of oxazolone in xylene, a solution of 1.1 equivalents of nitrosobenzene was added with stirring in the same solvent at room temperature. The corresponding aminoacids started to separate from the solution. The mixture was stirred for 30 minutes. The crystals were filtered, washed with petroleum ether and dried[4]. Method B: a yellow suspension of 2 mM of the oxazolone in 2 ml of DMF was added to 2.1 mM of nitrosobenzene in 2 ml of DMF at room temperature. It was stirred for 5 minutes and then 30 ml of an aqueous solution of NaOH 0.25 N was added. The resulting solution was washed twice with 10 portions of ethyl ether. The aqueous solution was cooled in ice and 1:1 HCl was added up to pH 2. The precipitate thus obtained was filtered, redissolved in NaOH solution and reprecipitated with HCl. The white solid was chromatographied on silica gel and three fractions eluted with ethyl acetate. The acid was obtained from the central fraction and recrystallized from ethanol-water. Method C: The reactions were performed in ethyl ether using the same procedure as in B.

Methyl esters of Δ^4-1,2,4-oxadiazolin-3-carboxylic acids, **4**. The esters were obtained by dissolving or by suspending the crude acid in ethyl ether and adding to this solution a slight excess of diazomethane[18] in ether. The ethyl ether was evaporated and the residue recrystallized from petroleum ether (100-140º) or from methanol-water.

2,3,5-Triphenyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4a**. It was obtained as previously described[4]; m.p. 106-7. ^{13}C NMR ($CDCl_3$) ppm: 53.11; 106.67; 126.06; 127.14; 127.73; 131.71; 139.14; 143.05; 162.38; 169.81.

2,3-Diphenyl-5-p-methylphenyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4b**. It was prepared according to description[4]; m.p. 100º; Rf 0.39. ^{13}C NMR ($CDCl_3$) ppm: 21.42; 53.02; 106.67; 124.04; 125.99; 127.14; 139.18; 142.11; 143.28; 162.32; 169.83.

2,3-Diphenyl-5-p-methoxyphenyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4c**. Yield: 78.1%. White crystals from methanol-water; m.p. 138º; Rf 0.86 (1:1 methanol-di-n-butylether). Found: C, 71.04; H, 5.03; N, 7.11. Calc. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.20. IR: 1754 (C=O); 1634 (C=N); 1266; 1093; 854; 746; 694. ^1H NMR (CCl_4) ppm: 7.66 (d, 2H, J_d = 9 Hz); 7.55-7.17 (m, 10H); 6.7 (d, 2H, J_d = 9 Hz); 3.73 (s, 3H); 3.66 (s, 3H).

2,3-Diphenyl-5-p-chlorophenyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4d**. It was prepared in 41.5% yield. White crystals from methanol-water; m.p. 111-112º; Rf 0.49. Found: C, 67.18; H, 4.58. Calc. for $C_{22}H_{17}N_2O_3Cl$: C, 67.26; H, 4.36. IR: 1748 (C=O); 1634 (C=N); 1236; 1014; 831; 747; 699. ^1H NMR (CCl_4) ppm: 7.9-7.13 (m, 14H); 3.72 (s, 3H).

2,3-Diphenyl-5-p-nitrophenyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4e**. Yield: 82%. White crystals from petroleum ether (100-140º); m.p. 135-6º; Rf 0.41. Found: C, 65.49; H, 4.45; N, 10.64. Calc. for $C_{22}H_{17}N_3O_5$: C, 65.45; H, 4.25; N, 10.42. IR: 1742 (C=O); 1634 (C=N); 1515 and 1351 (NO_2); 1264; 1120; 758; 735; 695. ^1H NMR (acetone-d_6) ppm: 8.29 (d, 2H, J_d = 9 Hz); 8.1 (d, 2H, J_d = 9 Hz); 7.87-7.30 (m, 10H); 3.77 (s, 3H).

2,5-Diphenyl-3-methyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4f**. Yield: 62.5%. White crystals from petroleum ether (40-60º); m.p. 62º; Rf 0.26. Found: C, 68.69; H, 5.50. Calc. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44. IR: 1739 (C=O); 1631 (C=N); 1383; 1258; 1111; 773; 704; 694. ^1H NMR (CCl_4): ppm: 7.90-7.20 (m, 10H); 3.7 (s, 3H, CH_3-O); 1.75 (s, 3H, CH_3).

2-Phenyl-3-methyl-5-p-methoxyphenyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4g**. Yield: 95.4%. White crystals from methanol-water; m.p. 107º; Rf 0.17. Found: C, 66.06; H, 5.52; N, 8.57. Calc. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.55; N, 8.58. IR: 1751 (C=O); 1626 (C=N); 1264; 1026; 1118; 840; 755; 693. ^1H NMR (acetone-d_6) ppm: 7.66 (d, 2H, J_d = 9 Hz); 7.35 (s, 5H); 6.88 (d, 2H, J_d = 9 Hz); 3.80 (s, 3H, CH_3-O-CO); 3.73 (s, 3H, CH_3-O); 1.75 (s, 3H, CH_3-Ar). ^{13}C NMR (methanol-d_4) ppm: 24.69; 53.28; 56.01; 105.65; 115.13; 120.20; 128.26; 129.95; 130.47; 131.90; 145.02; 164.12; 171.66.

2-Phenyl-3-methyl-5-p-chlorophenyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4h**. Yield: 55%. White crystals from methanol-water; m.p. 105º; Rf 0.36. Found: C, 61.75; H, 4.61. Calc.

for $C_{17}H_{15}N_2O_3Cl$: C, 61.73; H, 4.57. IR: 1754 (C=O); 1626 (C=N); 1282; 1219; 847; 833; 757; 694. ^1H NMR ($CDCl_3$) ppm: 7.63 (d, 2H, J_d = 8 Hz); 7.40-7.13 (m, 7H); 3.79 (s, 3H, CH_3-O); 1.86 (s, 3H, CH_3).

2,3-Diphenyl-5-methyl-Δ^4-1,2,4-oxadiazolin-3-carboxylic acid methyl ester, **4**. A solution (7 ml) of N-acetyl-α-phenylglycine 2.57 g (133 mM) in Ac_2O was warmed under nitrogen to 70-80º for 20 minutes. To 1 ml of this solution, 0.203 g (1.9 mM) of **2** dissolved in 2 ml of Ac_2O and 5 ml of benzene were added. The mixture was stirred at room temperature and a solution of diazomethane in ether was added to the residue. The methyl ester was crystallized in petroleum ether (100-140º) yielding 0.125 g (22.2%) of white crystals; m.p. 85-6º; Rf 0.10. Found: C, 68.69; H, 5.48; N, 9.41. Calc. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. IR: 1739 (C=O); 1645 (C=N); 1383 (CH_3); 1258 (C-O); 1111 (O-R); 756; 702. ^1H NMR ($CDCl_3$) ppm: 7.8-7.3 (m, 10H); 3.8 (s, 3H, CH_3-O); 2.0 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) ppm: 13.41; 53.12; 105.60; 124.35; 126.04; 128.39; 128.65; 129.17; 129.56; 138.93; 141.67; 161.46; 170.18.

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