Synthesis of 5-Aryl-3-(4-pyridyl)-1,2,4-oxadiazoles

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The title oxadiazoles were formed in the reaction of *N*-(4-pyridylmethyl)arylamides with nitrosyl chloride in low yields.

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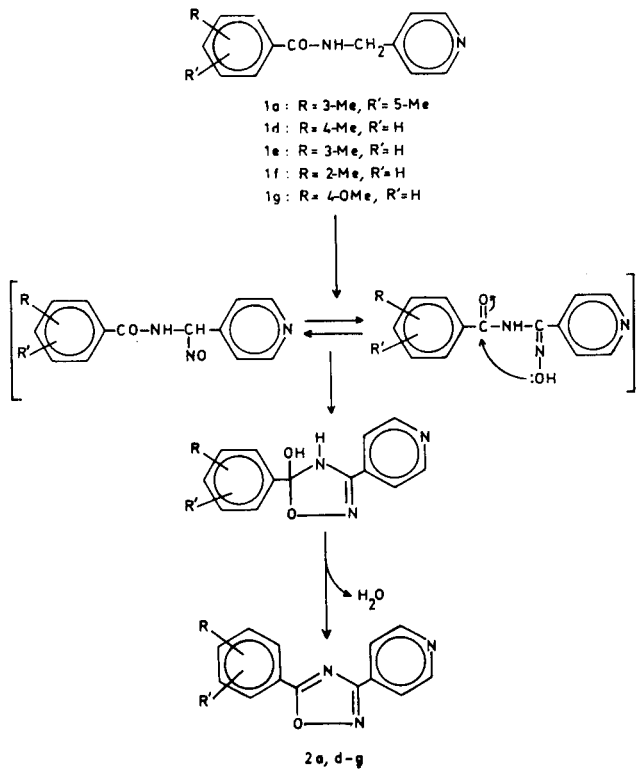
In 1970 Braña *et al.* [1] synthesized *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide (Picobenzide, **1a**), a partial analogue of neuroleptics. Its pharmacological properties together with its active pharmacokinetics [2] and low antidopaminergic activity provided the reason for its selection for neuroleptoanalgesia.

The pharmacological screening of Picobenzide exhibits, among others, the following secondary effects: antispasmodic towards histamine, acetylcholine and barium chloride, weak anticonvulsant towards electroshock and slightly less anti-inflammatory than dexametasone [3-6].

As part of a research program currently under way in our laboratories to develop new derivatives of Picobenzide and looking for a greater increase and a greater selectivity of its collateral effects of therapeutic interest, we were interested in functionalizing the amide nitrogen of Picobenzide with an amino group in order to introduce, starting from it, other functionalities such as derivatives of aldehydes, ketones, *etc.*

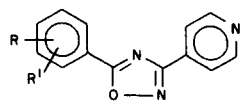
The chosen synthetic route was the nitrosation of the amide nitrogen of Picobenzide followed by reduction of the NO group to the NH_2, as it was described by Achiwa *et al.* [7] for the synthesis of α-hydrazinoacids.

In several attempts, using sodium nitrite and hydrochloric acid in various concentrations, temperatures and reaction times, we have always recovered the *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide unchanged, when reaction was held in aqueous media as well as in organic solvents.



Considering the above results, we looked for a more powerful nitrosating agent, selecting nitrosyl chloride, as France *et al.* [8] claimed this reagent to be a good nitros-

Table I



Compound	Formula	R	R'	Yield, % [a]	Mp, °C	Crystallization Solvent
2a	$C_{15}H_{13}N_3O$	3-Me	5-Me	49	127-128	acetonitrile
2d	$C_{14}H_{11}N_3O$	4-Me	H	17	136-137	acetone-water
2e	$C_{14}H_{11}N_3O$	3-Me	H	16	114-115	acetone-water
2f	$C_{14}H_{11}N_3O$	2-Me	H	12	126-127	acetone-water
2g	$C_{14}H_{11}N_3O_2$	4-OMe	H	17	174-175	cyclohexane

[a] Analytically pure product.

ating agent for amides that had hitherto resisted nitrosation by other reagents.

Generating this reagent *in situ* by reaction of isoamyl nitrite with dry gaseous hydrogen chloride and using absolute ethanol as the solvent, modification of the starting material was again not observed. However, when nitrosyl chloride, obtained by the Morton and Wilcox procedure [9], is bubbled through a solution of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide in dry chloroform, a white crystalline product (mp 127-128° from acetonitrile) was obtained.

The ir spectrum of this compound does not show any band in the 3500-3100 cm^{-1} region nor in the 1700-1620 cm^{-1} but two C=N stretching bands at 1610 and 1580 cm^{-1} were observed. Also, it shows three stretching and deformation N-O bands at 1310, 760 and 700 cm^{-1} respectively.

The 60 MHz pmr spectrum only shows the following signals: at δ ppm 2.4 the singlet corresponding to the 6H or two methyl groups attached to a phenyl ring, at 7.0 and 7.6 the phenyl H_4 and phenyl H_2 and H_6 signals as two singlets, and at 7.8 and 8.6 two doublets corresponding to the AA'BB' system of 4-substituted pyridine.

The base peak of mass spectrum is the M^+, 251. The second peak in importance is the m/e 131 (70), corresponding to an empirical formula of C_9H_9N, as assignable to the Me_2-C_6H_3-$CN^{\cdot+}$ structure. Likewise, there is a peak at m/e 121 (15) due to the 131 loss, and aromatic peaks at m/e 105 (7) and 77 (10).

On the basis of these spectral data together with quantitative elementary analysis, molecular formula $C_{15}H_{13}N_3O$, corresponding to 5-(3,5-dimethylphenyl)-3-(4-pyridyl)-1,2,4-oxadiazol structure was proposed for this compound.

The mechanism for oxadiazole formation is the initial nitrosation of the active methylene group of *N*-(4-pyridylmethyl)-3,5-dimethylbenzamide as there are numerous data in the literature concerning nitrosation of methylene groups attached to electron-withdrawing groups [10], which generally tautomerize to the oxime. After having been transformed into the hydroxyimine derivative, the compound formed is cyclized into the 1,2,4-oxadiazole by nucleophilic attack of the oxime OH to the carbonyl group, as shown in Scheme 1.

In order to confirm that nitrosyl chloride attack occurs at the Picobenzide methylene group owing to its high reactivity, reaction of *N*-(3-pyridylmethyl)-3,5-dimethylbenzamide (**1b**) and *N*-(2-pyridylmethyl)-3,5-dimethylbenzamide (**1c**) with nitrosyl chloride was carried out under the same conditions as above. No reaction was observed in either case.

Upon treating *N*-[(α-acetoxy)-4-pyridylmethyl]-3,5-dimethylbenzamide with nitrosyl chloride, 3,5-dimethylbenzamide, its hydrolysis product, was obtained [11]. This result indicates that oxadiazole is not formed in this case, as it is stable in aqueous medium, and supports the proposed mechanism.

The oxadiazoles in Table I have been obtained in order to establish the generality of this reaction for 4-pyridylmethylbenzamides.

EXPERIMENTAL

The melting points were obtained on a Büchi apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer model 257 spectrophotometer. The pmr spectra were determined with a Varian T-60 A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian model MAT 711 spectrometer. The elemental analysis were performed by Centro Nacional de Quimica Orgánica, Madrid.

General Procedure.

Nitrosyl chloride gas [9] was bubbled for two hours, at the rate of 2-3 bubbles/minute, through a solution containing 0.01 mole of *N*-pyridylmethylbenzamide in 50 ml of dry chloroform. The mixture was kept overnight at room temperature and then poured into 50 ml of water, making it basic with diluted potassium carbonate solution. The organic layer was then separated and the aqueous layer extracted three times with 25 ml portion of chloroform. The organic extracts were combined and dried over magnesium sulfate followed by evaporation of the solvent. The residual oily product was treated with ethyl acetate and the unchanged starting material largely crystallized. The solvent was evaporated *in vacuo* to give a reddish oily product which was treated with acetone-water (70:30) in the refrigerator to give the 5-aryl-3-(4-pyridyl)-1,2,4-oxadiazole.

5-(3,5-Dimethylphenyl)-3-(4-pyridyl)-1,2,4-oxadiazole (**2a**).

This compound had mp 127-128° (acetonitrile); ir (potassium bromide): ν 1610, 1580 (C=N), 760, 700 (N-O), cm^{-1}; pmr (deuteriochloroform): δ 2.4 (s, 6H, $2CH_3$), 7.0 (s, 1H, H_4-Ph), 7.6 (s, 2H, H_2 and H_6-Ph), 7.8 (d, 2H, H_3 and H_5-Py), 8.6 (d, 2H, H_2 and H_6-Py) ppm; ms: m/e 251 (M^+, 100), 165 (10), 131 (70), 121 (15), 116 (20), 105 (7), 77 (10).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.87; H, 5.28; N, 16.72.

5-(4-Methylphenyl)-3-(4-pyridyl)-1,2,4-oxadiazole (**2d**).

This compound had mp 136-137° (acetone-water); ir (potassium bromide): ν 1605, 1580 (C=N), 750, 695 (N-O) cm^{-1}; pmr (deuteriochloroform): δ 2.4 (s, 3H, CH_3), 7.2 (m, 2H, H_3 and H_5-Ph), 7.8 (m, 2H, H_2 and H_6-Ph), 7.9 (d, 2H, H_3 and H_5-Py), 8.5 (d, 2H, H_2 and H_6-Py) ppm; ms: m/e 237 (M^+, 90), 121 (30), 116 (100), 91 (25), 77 (15).

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.62; H, 4.79; N, 17.44.

5-(3-Methylphenyl)-3-(4-pyridyl)-1,2,4-oxadiazole (**2e**).

This compound had mp 114-115° (acetone-water); ir (potassium bromide): ν 1610, 1575 (C=N), 750, 695 (N-O) cm^{-1}; pmr (deuteriochloroform): δ 2.4 (s, 3H, CH_3), 7.2 (m, 2H, H_4 and H_5-Ph), 7.8 (broad s, 4H, H_2 and H_6-Ph, H_3 and H_5-Py), 8.6 (broad s, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found; C, 70.71; H, 4.77; N, 17.50.

5-(2-Methylphenyl)-3-(4-pyridyl)-1,2,4-oxadiazole (**2f**).

This compound had mp 126-127° (acetone-water); ir (potassium bromide): ν 1610, 1570 (C=N), 750, 700 (N-O) cm^{-1}; pmr (deuteriochloroform): δ 2.7 (s, 3H, CH_3), 7.2 (s, 3H, H_4, H_5 and H_6-Ph), 7.8 (m, 3H, H_3-Ph, H_3 and H_5-Py), 8.6 (d, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.67; H, 4.72; N, 17.63.

5-(4-Methoxyphenyl)-3-(4-pyridyl)-1,2,4-oxadiazole (**2g**).

This compound had mp 174-175° (cyclohexane); ir (potassium bromide): ν 1615, 1570 (C=N), 760, 700 (N-O), cm^{-1}; pmr (deuteriochloroform):

δ 3.7 (s, 3H, OCH_3), 6.8 (m, 2H, H_3 and H_5-Ph), 7.8 (m, 4H, H_2 and H_6-Ph, H_3 and H_5-Py), 8.5 (d, 2H, H_2 and H_6-Py) ppm.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.37; N, 16.59. Found: C, 66.06; H, 4.20; N, 16.81.

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