A New Synthetic Approach to Pyrazolo[3,4-*c*]-1,2,5-oxadiazoles

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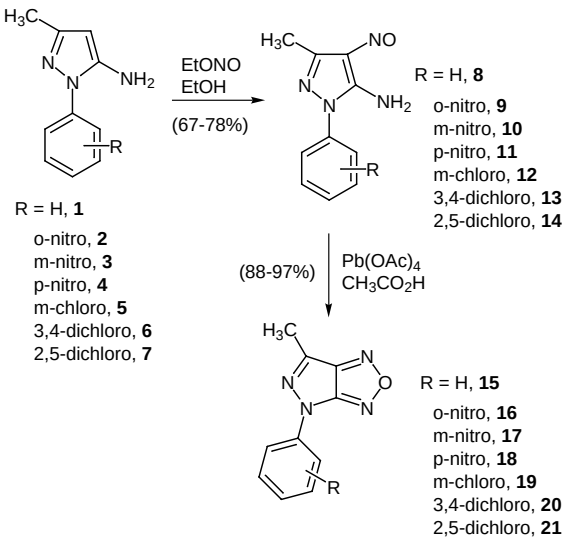
Abstract: 4-aryl-substituted-6-methyl-4*H*-pyrazolo[3,4-*c*]-1,2,5-oxadiazoles **15-21** were easily obtained through the oxidation reaction mediated by lead(IV) acetate of 5-methyl-4-nitroso-2-phenyl-2*H*-pyrazol-3-ylamines **8-14** in 88-97% yields.

Key words: lead(IV) acetate, 4-nitroso-5-aminopyrazoles, intramolecular cyclization, fluorescent dyes, purine receptor antagonists

1,2,5-Oxadiazoles (furazanes) and their derivatives are a class of interesting heterocycles, which have been the subject of intensive investigations since their discovery in the late nineteenth century.[2] The main reasons for these studies reside in the interest for their particular structure and reactivity.[3] More recently, their particular susceptibility to give rise to fluorescent compounds has gained further interest in view of their applications as reagents for biological assays, and fluorescent probes in studies of ligand-receptor interactions by fluorescence microscopy.[4]

Our continuous interest in the reactivity of substituted pyrazole derivatives and the above illustrated importance of 1,2,5-oxadiazoles, prompted us to develop a simple and efficient entry to pyrazolo[3,4-*c*]-1,2,5-oxadiazoles. For the synthesis of this latter class of compounds, we considered taking advantage of the use of lead(IV) acetate (LTA), which is a versatile and efficient oxidizing agent that has been widely used in organic synthesis, and its use has been published in several interesting reviews.[5] The oxidation of aromatic nitroso amines with LTA has been described in the literature,[6] but in most cases relatively poor yields of the corresponding 1,2,5-oxadiazoles were obtained. As an example, the treatment of 6-amino-1,3-dimethyl-5-nitrosouracil with LTA is reported to give only low yields of the corresponding furazan.[7]

In this paper, we wish to report a general, one pot-synthesis of a novel series of 4-aryl-substituted-6-methylpyrazolo[3,4-*c*]-1,2,5-oxadiazoles using this commercially available reagent. It must be outlined that, to the best of our knowledge, only two syntheses of pyrazolo[3,4-*c*]-1,2,5-oxadiazoles, starting with the pyrazoline ring and with varying degrees of success and convenience, have been reported. Namely, the Mohr's methodology[8] which involves the preparation of 6-methyl-4-phenyl-4*H*-pyrazolo[3,4-*c*]-1,2,5-oxadiazole by oxidation of 5-methyl-4-nitroso-2-phenyl-2*H*-pyrazol-3-ylamine with an alkaline aqueous solution of potassium hypochlorite. Whereas, Bertelson[9] et al. reported the synthesis of 4,6-diphenyl-4*H*-pyrazolo [3,4-*c*]-1,2,5-oxadiazole from 1,3-diphenyl-4,5-dioximino-2-pyrazoline by heating in acetic anhydride. We envisaged that the pyrazolo[3,4-*c*]-1,2,5 oxadiazole nucleus could be generated through a single step and with a minimal work-up by oxidation, mediated by lead(IV) acetate, of 5-methyl-4-nitroso-2-phenyl-substituted-2*H*-pyrazol-3-ylamine, **8-14**. The latter compounds are obtainable in large quantities by published procedures,[10] through nitrosation with ethyl nitrite of the corresponding 5-methyl-2-phenyl-substituted-2*H*-pyrazol-3-ylamine **1-7**. Moreover, compounds **8-14** are easily accessible and versatile synthetic precursors which have proven useful in the preparation of 1-phenyl-substituted-3-methyl-1*H*-pyrazolo[3,4-*b*]pyrazine-5,6-dicarboxylic acid diethyl esters.[11]



Scheme 1

As one may expect, the lead(IV) acetate mediated oxidation, was not inhibited by the presence of an electron-withdrawing group (e.g. nitro or halogens) at position-1 on the aryl group of the pyrazole moiety. As a general procedure, the nitroso amines **8-14** were dissolved in glacial acetic acid and to the resulting red solution an equimolar quantity of lead(IV) acetate trihydrate was added. The mixture became intensely green colored and after two hours at room temperature was diluted with water to precipitate the reaction products **15-21**, which were collected by filtration and crystallized from ethanol. Our results on the series of nitroso-amino pyrazoles **8-14** are shown in the Table, the yields refer to purified products **15-21**. The

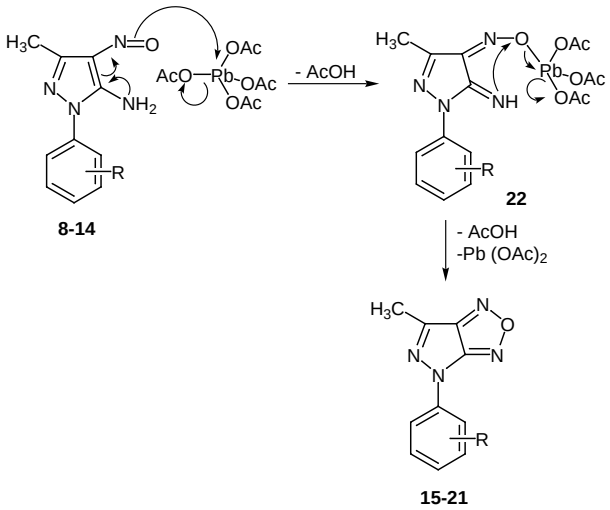
Table 4-Aryl-substituted-6-methyl-4*H*-pyrazolo[3,4-*c*]-1,2,5-oxadiazoles **15-21 P**repared

Compound	R	Yield[a] (%)	Mp (°C)	^{1}H NMR ($CDCl_3$) δ	IR (KBr) cm^{-1}
15[8]	H	78	92-95	2.66 (s, 3H), 7.23 (d, 1H, *J* = 7.80 Hz), 7.48 (t, 2H, *J* = 8.60 Hz), 7.77 (d, 2H, *J* = 8.22 Hz).	1606, 1529, 1383, 1350, 1288, 1020, 777, 745.
16	*o*-nitro	83	65-70	2.64 (s, 3H), 7.52 (t, 1H, *J* = 7.68 Hz), 7.76 (dd, 1H, *J* = 7.80, 1.22 Hz), 7.83 (t, 1H, *J* = 8.02 Hz), 7.93 (dd, 1H, *J* = 8.20, 1.22 Hz).	1598, 1548, 1507, 1457, 1281, 1123, 843, 751.
17	*m*-nitro	80	190-194	2.71 (s, 3H), 7.78 (t, 1H, *J* = 8.02 Hz), 7.96 (d, 1H, *J* = 7.88 Hz), 8.23 (d, 1H, *J* = 7.86 Hz), 8.31 (s, 1H).	1645, 1531, 1474, 1353, 1289, 1082, 986, 717, 679.
18	*p*-nitro	85	120-125	2.68 (s, 3H), 7.85 (d, 2H, *J* = 8.04 Hz), 8.33 (d, 2H, *J* = 7.28 Hz).	1647, 1594, 1519, 1470, 1343, 1259, 1093, 849, 780, 687.
19	*m*-chloro	75	100-103	2.67 (s, 3H), 7.21 (dd, 1H, *J* = 8.22, 2.02 Hz), 7.41 (t, 1H, *J* = 8.20 Hz), 7.65 (dd, 1H, *J* = 8.04, 2.02 Hz), 7.81 (d, 1H, *J* = 2.20 Hz).	1616, 1599, 1497, 1385, 1055, 777, 740.
20	3,4-dichloro	90	160-165	2.68 (s, 3H), 7.32 (dd, 1H, *J* = 8.82, 2.20 Hz), 7.48 (d, 1H, *J* = 8.62 Hz), 7.58 (d, 1H, *J* = 2.42 Hz).	1616, 1599, 1546, 1493, 1405, 1294, 1120, 818, 787.
21	2,5-dichloro	82	160-162	2.67 (s, 3H), 7.34 (d, 1H, *J* = 7.82 Hz), 7.46 (d, 1H, *J* = 7.80 H), 7.56 (s, 1H).	1611, 1544, 1478, 1386, 1071, 865, 811, 635.

[a] Yield of isolated products after crystallization.

structures of compounds **15-21** were attributed on the basis of their spectroscopic data.

As a possible mechanism for the conversion of **8-14** to **15-21**, we may advance the hypothesis that LTA reacts with the oxygen of the nitroso group at position-4 of the pyrazole ring to yield the general adduct **22.** This in turn undergoes intramolecular cyclisation with a concomitant release of lead(II) acetate and formation of the expected products **15-21**.



Scheme 2

In conclusion, we have developed an efficient and versatile method for the preparation of a new series of pyrazolo[3,4-*c*]-1,2,5-oxadiazoles which takes advantage of easily accessible precursors and commercial reagents. The extension of this procedure to heterocyclic ring systems other than pyrazoles, is currently being evaluated and, moreover, compounds **15-21** are currently being investigated in our laboratories, as potential fluorescent dyes and antagonists of the purine P2Z receptor.[12]

Reaction courses and product mixtures were routinely monitored by TLC on silica gel (pre-coated F_{254} Merck plates) and visualized with aq $KMnO_4$. ^{1}H NMR spectra were obtained in $CDCl_3$ solutions with a Bruker AC 200 spectrometer. Chemical shifts (δ) are given in ppm downfield from TMS. All products reported showed ^{1}H NMR spectra in agreement with the assigned structures. Mps were determined on a Buchi-Tottoli apparatus and are uncorrected. Elemental analyses were effected at the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara. Lead tetraacetate trihydrate (A.C.S. reagent) was purchased from Aldrich.

5-Methyl-2-phenyl-substituted-4-nitroso-2*H*-pyrazol-3-ylamines (8-14); General Procedure

A stream of ethyl nitrite was bubbled through a solution of **1-7** (5 mmol) dissolved in EtOH (20 mL) for 10 min. After this time, the solution was cooled and 10% HCl (0.5 mL) was added and the bubbling of ethyl nitrite was continued (15 min.). The red crystals were collected and recrystallized from dioxane (15 mL), to give **8-14** as pure products.

5-Methyl-2-(2-nitro-phenyl)-4-nitroso-2*H*-pyrazol-3-ylamine (9)

5-Methyl-2-(2-nitro-phenyl)-2*H*-pyrazol-3-ylamine **2**[13] (2.18 g., 10 mmol) dissolved in EtOH (20 mL) was used. After the workup,

compound **9** was obtained as a red solid. Yield: 1.8 g (73%); mp: 102 °C.

IR (KBr): ν = 3360, 1647, 1531, 1474, 1352, 1290, 1080, 718 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.78 (s, 3H), 7.68 (t, 1H, *J* = 7.8 Hz), 7.76 (t, 1H, *J* = 8 Hz), 7.92 (d, 1H, *J* = 8.2 Hz), 8.37 (d, 1H, *J* = 8.2 Hz), 8.50 (br s, 2H).

5-Methyl-2-(3-nitro-phenyl)-4-nitroso-2*H*-pyrazol-3-ylamine (10)

5-Methyl-2-(3-nitro-phenyl)-2*H*-pyrazol-3-ylamine **3**[13] (2.18 g., 10 mmol) dissolved in EtOH (20 mL) was used. After the workup, compound **10** was obtained as a red solid. Yield: 1.7 g (69%), mp: 135 °C.

IR (KBr): ν = 3358, 1642, 1531, 1476, 1350, 1238, 1070, 988, 739 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.77 (s, 3H), 7.72 (t, 1H, *J* = 8 Hz), 7.92 (d, 1H, *J* = 8 Hz), 8.22 (d, 1H, *J* = 8.4 Hz), 8.38 (s, 1H), 8.50 (br s, 2H).

Pyrazolo[3,4-*c*]-1,2,5-oxadiazoles (15-21); General Procedure

The appropriate nitroso-amine pyrazole **8-14** (10 mmol) was dissolved in glacial HOAc (10 mL) at r.t.. Then, an equimolar amount of $Pb(OAc)_4 \bullet 3H_2O$ (3.89 g., 10 mmol) was added in small portions over 10 min and the disappearance of the starting material was observed by TLC over 2 h. The solution was slowly diluted with H_2O (5 mL) and the resulting mixture, containing a yellow solid, was cooled on ice-bath and the solid filtered off. The solid, washed with H_2O (20 mL), vacuum dried, and recrystallized from EtOH (15 mL), furnished **15-21** with excellent yields (88-97%).

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