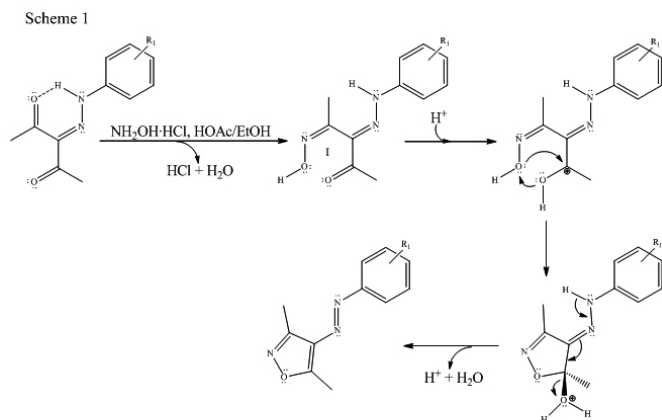


FACILE SYNTHESIS OF ISOXAZOLES AND PYRAZOLES FROM β -DIKETOHYDRAZONESCARLOS BUSTOS¹, EDUARDO SCHOTT³, MARCELA RÍOS¹, CHRISTIAN SÁNCHEZ¹ AND JUAN-GUILLERMO CÁRCAMO²¹Instituto de Química, Universidad Austral de Chile, Avda. los Robles s/n, Casilla 567, Valdivia, Chile.²Instituto de Bioquímica, Universidad Austral de Chile, Avda. los Robles s/n, Casilla 567, Valdivia, Chile.³Departamento de Ciencias Químicas, Universidad Andrés Bello, República 275, Santiago de Chile, Chile.

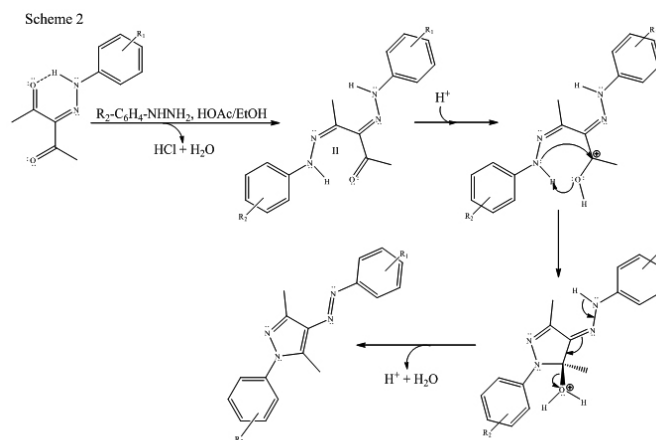
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ABSTRACT

New 3,5-dimethyl-4-[(*E*)-4-(R_1 -phenyl)diazenyl]isoxazoles and 3,5-dimethyl-1-(R_2 -phenyl)-4-[(*E*)-(R_1 -phenyl)diazenyl]-1*H*-pyrazoles may be obtained by reaction of 3-[2-(R_1 -phenyl)hydrazono]pentane-2,4-dione with $H_2NOH \cdot HCl$ and $R_2-C_6H_4-NHNH_2$, respectively. The reactions were performed in ethanol as solvent and catalyzed by glacial acetic acid.



$R_1 = 4-OH(1)$; $4-OCH_3(2)$; $4-COCH_3(3)$; $4-COOCH_2CH_3(4)$; $4-H(5)$; $4-CH_3(6)$; $4-Cl(7)$; $4-Br(8)$; $2-CO_2H(9)$; $4-CO_2H(10)$; $4-CN(11)$; $4-NO_2(12)$; $4-N(CH_3)_2(13)$



$R_1 = 4-OH$; $4-OCH_3$; $4-COCH_3$; $4-COOCH_2CH_3$; $4-H$; $4-CH_3$; $4-Cl$; $4-Br$; $2-CO_2H$; $4-CO_2H$; $4-CN$; $4-NO_2$; $4-N(CH_3)_2$; $R_2 = 4-OCH_3$; $4-CN$; $4-CO_2H$; $2,3,4,5,6-F_5$

The biological activity of substituted isoxazoles and pyrazoles has been of interest in the last years, due to the versatility of their properties. In fact, several isoxazoles¹⁻⁷ and pyrazoles⁸⁻²² have a remarkable importance in medicine and particularly pyrazole's chemistry has been extended toward the catalysis²³ and coordination chemistry²⁴⁻²⁵. On the other hand, it is well known that β -diketones as pentane-2,4-dione, $CH_2(COCH_3)_2$, in basic medium, may couple with substituted diazonium salts²⁶⁻²⁷ yielding series of compounds that belong to the β -diketohydrazone family, namely 3-[2-(R_1 -phenyl)hydrazono]pentane-2,4-dione, see Schemes. In this work, we show that these compounds may be used as precursors for obtaining easily heterocycles series, namely isoxazole and pyrazole derivatives.

Preliminary studies²⁸⁻³⁰ have shown that β -diketohydrazone, react with hydroxylamine hydrochloride (molar ratio 1:1 at reflux temperature for 18 h), using acetic acid as catalyst, in ethanol, affording in good yields (>70 %) 3,4,5-trisubstituted isoxazoles, such as 3,5-dimethyl-4-[(*E*)-4-(R_1 -phenyl)diazenyl]isoxazoles, Scheme 1. The solid compounds are often precipitated by addition of excess of water. After addition of water some of them yield insoluble oils due to the formation of an immiscible ethylacetate/water mixture. However, under vigorous stirring and cooling about 0 °C, the corresponding solids are obtained.

In accord with Scheme 1, we propose that the reaction forms an oxime intermediate whose reactivity center, Z - β -keto oxime (I), under prolonged heating in HOAc medium, suffers an addition-displacement reaction affording the corresponding products.

Likewise, under similar conditions, Scheme 2, these β -diketohydrazone also react with monosubstituted arylhydrazines, $R_2-C_6H_4-NHNH_2$ (molar ratio 1:1 under reflux temperature for 36 h), affording in good yields (>65 %) series of 1,3,4,5-tetrasubstituted pyrazoles, of the type 3,5-dimethyl-1-(R_2 -phenyl)-4-[(*E*)-(R_1 -phenyl)diazenyl]-1*H*-pyrazoles. The corresponding pyrazoles may be isolated by similar procedures to those used for isoxazoles.

In this case we believe that the reactivity center, Z - β -keto hydrazone (II), of the ketodihydrazone intermediate, Scheme 2, after protonation of the carbonyl group, also suffers an addition-displacement reaction to yield the corresponding pyrazoles.

These series of compounds have been characterized using elemental analysis, gas-chromatography/mass-spectrometry and spectroscopic methods (UV-visible, IR, ¹H NMR, ¹³C NMR). A typical two-dimensional HBMBC spectrum of one member of the isoxazoles series, is shown in Figure 1. Besides, the crystalline and molecular structures of one isoxazole²⁸ and two pyrazoles²⁹⁻³⁰ have been recently authenticated by X-Ray diffraction analysis. Some additional synthetic details may be found in these previous reports²⁸⁻³⁰.

Additional studies on this subject, involving other β -diketone precursors, *v. gr.* $CH_2(COR_1)(COR_2)$, ($R_1 = Ph$, $R_2 = Me$, Ph), $CH_2(COCH_3)(CO_2Et)$ or $CH_2(CO_2Et)_2$, are currently in progress whose results will be published at due time. Finally, the biological activity of isoxazoles will be evaluated as the following stage.

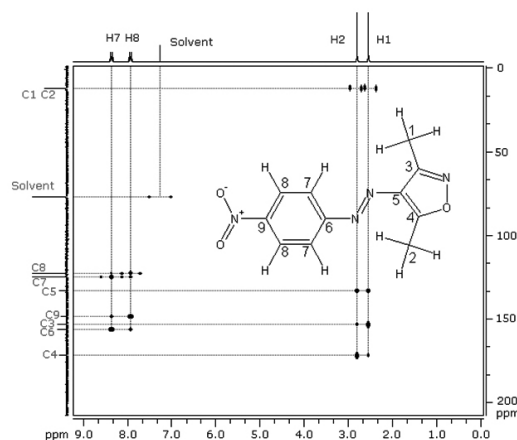


Figure 1: HBMBC spectrum obtained in $CDCl_3$ on a Bruker AC 200P Spectrometer (¹H) (¹³C at 50.3 MHz, *J* mod. sequence ¹H 200.1 MHz) using internal TMS.

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