J. Chil. Chem. Soc., 54, Nº 3 (2009)

FACILE SYNTHESIS OF ISOXAZOLES AND PYRAZOLES FROM β-DIKETOHYDRAZONES

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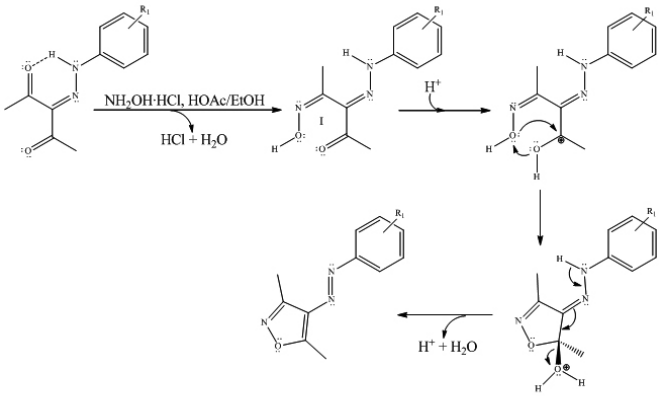
(Received: January 26, 2009 - Accepted: March 17, 2009)

ABSTRACT

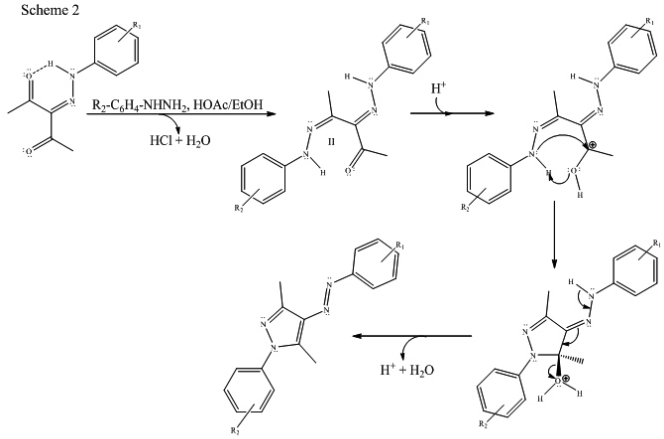
New 3,5-dimethyl-4-[(*E*)-4-(R_1-phenyl)diazenyl]isoxazoles and 3,5-dimethyl-1-(R_2-phenyl)-4-[(*E*)-(R_1-phenyl)diazenyl]-1*H*-pyrazoles may be obtained by reaction of 3-[2-(R_1-phenyl)hydrazono)]pentane-2,4-dione with $H_2NOH{\cdot}HCl$ and R_2-4-C_6H_4-$NHNH_2$, respectively. The reactions were performed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

Scheme 1



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**)

Scheme 2



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 isoxazoles[1-7] and pyrazoles[8-22] have a remarkable importance in medicine and particularly pyrazole's chemistry has been extended toward the catalysis[23] and coordination chemistry[24-25]. 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 salts[26-27] yielding series of compounds that belong to the β-diketohydrazones 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 studies[28-30] have shown that β-diketohydrazones, 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 ºC, the corresponding solids are obtained.

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

Likewise, under similar conditions, Scheme 2, these β-diketohydrazones 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-ketohydrazone (**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, ^{1}H NMR, ^{13}C NMR). A typical two-dimensional HBMC spectrum of one member of the isoxazoles series, is shown in Figure 1. Besides, the crystalline and molecular structures of one isoxazole[28] and two pyrazoles[29-30] have been recently authenticated by X-Ray diffraction analysis. Some additional synthetic details may be found in these previous reports[28-30].

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.

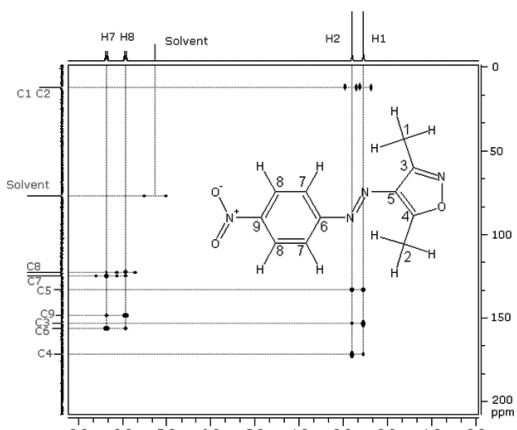


Figure 1: HBMC spectrum obtained in $CDCl_3$ on a Bruker AC 200P Spectrometer (^{1}H) (^{13}C at 50.3 MHz, *J* mod. sequence ^{1}H 200.1 MHz) using internal TMS.

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ACKNOWLEDGMENTS

The author greatly acknowledges the financial support received from FONDECYT (Grant 1080269) and DID-UACh, of the Universidad Austral de Chile (Grant S 2006-45).

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