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A new method for the synthesis of Quinoxaline derivatives

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Introduction

In recent years there has been a boom in the so-called solvent-free "green or clean chemistry". An example of this can be found in those processes that involve direct reagent exposure to microwave radiation with the aim of obtaining pure products in high yields, eliminating the use of solvents, catalysts, solid supports, and so on.

Microwave radiation because of its high penetration depth leads to a rapid and uniform heating so that the synthesis processes can be carried out in significantly lower times than when using other energy sources. Therefore, this is a quick, low-cost and easy handling approach (Loupy *et al.*, 1998).

Other advantage of using microwave radiation is that in some cases there is either a less proportion or absence of secondary products (cleaner reactions), and easy product isolation and purification, thus higher yield of reaction.

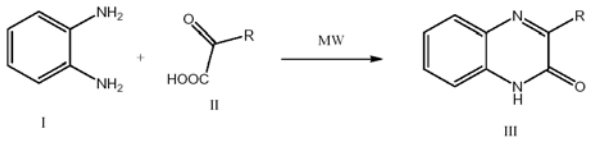
In continuation of previous works on synthesis of quinoxalinones with potential pharmacological activity (Abasolo *et al.*, 1987), and due to the need for a better method of synthesis of these compounds we have studied the condensation of *o*-phenylenediamine, **I**, with various α-ketoacids, **II**, using microwave radiation, thus obtaining the quinoxaline skeleton for the synthesis of non-nucleosidic inhibitors of the reverse transcriptase (Bal *et al.*, 2005).

Methodology

Starting compounds were: *o*-phenylenediamine and several α-ketoacids: piruvic, 2-ketobutyric, phenylpiruvic, oxalic, oxalacetic and α-ketoglutaric acids. Reactions are carried out without solvents. In each case equimolar quantities of both reagents were used. These reagents were placed in an Erlenmeyer flask, mixed closely together, and further irradiated using a home-made ´Itedo' trademark microwave. Reaction times varied between 5 and 13 minutes as maximum; testing an initial 600 watts potency, and increasing it to 750 watts in the case of not observing any results.

The reaction was monitored by TLC at intervals of 30 seconds, thus observing either the disappearance of reagents or the appearance of products.

Reaction scheme



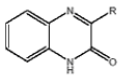
I II III

R= -CH$_3$ -C$_2$H$_5$ -CH$_2$C$_6$H$_5$ -OH -CH$_2$COOH -(CH$_2$)$_2$COOH

Results

In the condensation reactions of *o*-phenylenediamine with α-ketoacids leading to **III**, the following parameters were used giving rise to the results shown in Table 1.

Table 1. Positive result (+) indicates that the corresponding quinoxalinone was obtained. Products' structures were confirmed by physical and spectroscopic properties.



III

Condensation with this ketoacid	Potency (Watts)	Time (min)	Result	Yield %	III R
Piruvic	750	8.5	+	88	-CH$_3$
2-Ketobutyric	650	3.5	+	95	-C$_2$H$_5$
Phenylpiruvic	750	13	mixture	-	-CH$_2$-C$_6$H$_5$
Oxalic	750	6	+	90	-OH
Oxalacetic	750	11	+	90	-CH$_2$-COOH
α-Ketoglutaric	650	5	+	97	-(CH$_2$)$_2$-COOH

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Conclusions

According to results we can confirm that using microwave radiation working times diminish considerably in comparison with other possible routes of synthesis of quinoxalines, for example, the biocatalytic route using yeasts (Baez *et al.*, 2003).

Moreover, important yields were obtained, thus being overcome one of the limitations of conventional and complex Hinsberg reaction (1987).

Then, the advantages of this approach with respect to the other two are: a- Quickness and simplicity b- Economy c- Easy product isolation d- Lack of sideproducts reaction e- Work effectiveness at larger scales.

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

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