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An Easy Route to Synthesize 1,5-Arylodiazepin-2-ones

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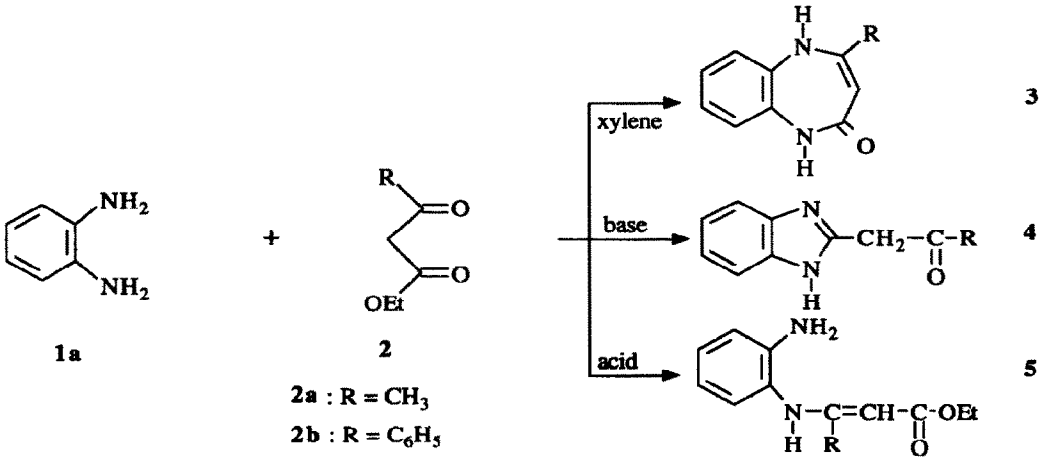
Abstract: *A series of 1,5-arylodiazepin-2-ones is prepared by the condensation of the appropriate o-β-arylenediamines with β-ketoesters in xylene under microwave irradiation. The reaction time is shortened to 10 mn. and the products are obtained in high yields. No by products are observed. Specific effects of microwaves are evidenced as no reaction occurs by classical heating in the same conditions.*

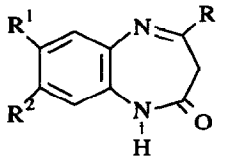
In 1986 Gedye[1,2] and Giguere[3] showed that some organic synthesis could be carried out in domestic microwave ovens[4], by operating in closed and transparent Teflon vessels. Since then, several investigations have been reported on this subject[5-15]. Therefore, any condensation reactions where water and/or alcohol are eliminated constitute good condidates for microwave.

The condensation of ethyl acetoacetate or ethyl benzoylacetate with orthophenylenediamine has attracted much interest in view of its final products. It has been shown that this reaction depends in great part on the experimental conditions [16-18,20] (scheme 1).



Scheme 1

Davoll[17], on reinvestigating this reaction in xylene showed that compound **4** reported by Sexton[16] as a benzimidazole derivative is rather the benzodiazepinone **6** accompanied by compound **8**. He also established thas ethyl-β-o-aminoanilinocrotonate **5** obtained in acidic medium is not an intermediate in the formation of compounds **6** and **8**. The cyclisation of **5** by a thermal heating in the same medium leads to benzimidazolic derivative **9**.



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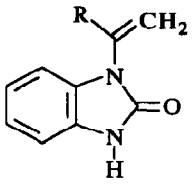

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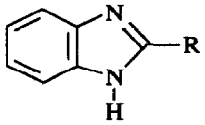
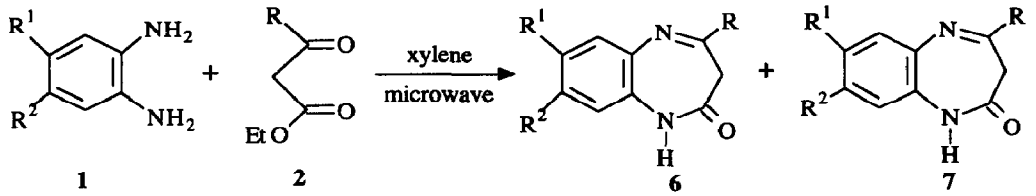


9

In 1960 Rossi et al[18] confirmed these results by a reaction involving **1a** and **2** in refluxing xylene during 90 mn. They obtained compounds **6** (35%), **8** (26%) and **5** (12%) R=CH_3, R^1=R^2=H). However, if the reaction is left longer, the mixture of **6+8+9** or only **8+9** could be obtained after 6 hours refluxing in xylene. Taking into account all these divergent results reported in the literature about the reactivity of **1a** with **2**, and with the purpose of synthesize only arylodiazepinonic derivatives, we examined this condensation in xylene under microwave irradiation (scheme 2).



1 **2** **6** **7**

1a: R^1=R^2=H
1b: R^1=R^2=Me
1c: R^1=H; R^2=Me
1d: R^1=H; R^2=CO_2Et
1e: R^1=H; R^2=NO_2
1f: R^1=H; R^2=Cl

2a: R=CH_3
2b: R=C_6H_5

6a: R=Me; R^1=R^2=H
6b: R=Me; R^1=R^2=Me
6c+7c: R=Me; R^1=H; R^2=Me
6d+7d: R=Me; R^1=H; R^2=CO_2Et
6e+7e: R=Me; R^1=H; R^2=NO_2
6f: R=Ph; R^1=R^2=H
6g: R=Ph; R^1=R^2=Me
6h+7h: R=Ph; R^1=H; R^2=Me
6i+7i: R=Ph; R^1=H; R^2=Cl
6j+7j: R=Ph; R^1=H; R^2=CO_2Et
6k+7k: R=Ph; R^1=H; R^2=NO_2

Scheme 2

The experimental procedure is very easy and consists on using a 100 ml erlenmeyer containing 20 ml of xylene, 15 mmoles of β-ketoester and 10 mmoles of orthophenylenediamine or its derivatives, the mixture is then activated by an exposition to microwave irradiation (700 W, multimode reactor) during 10 mn. Whatever the nature of the substituent on the o-phenylenediamine, the 1,5-arylodiazepin-2-ones crystallise by cooling in xylene. The crystalls are then filtered and washed with 2x5 ml diethylether. The next table indicates the time, the final temperature (T_{mw}) and the yield of each reaction under microwave (mw) or by classical heating (Δ) in the same conditions.

Products	a Final temperature T_{mw} [°C]	b % Yield mw	c % Yield Δ $t_{\Delta} = t_{mw}$
6a	136	83	0
6b	136	86	0
6c+7c	139	82	0
6d+7d	136	88	0
6e+7e	136	90	0
6f	139	88	0
6g	136	92	0
6h+7h	136	84	0
6i+7i	138	97	0
6j+7j	136	80	0
6k+7k	139	98	0

[a] temperature (T_{mw}) measured at the end of the reaction, [b] yield of isolated products obtained under microwave activation, [c] yield of products by classical thermal heating at the same temperature, and during the same time.

It results from these observations that :

* The yields of compounds **6** (or **6+7**) are nearly quantitative.
* The reactions are carried out at atmospheric pressure where as those worked out in solution by Gedye and Giguere are often followed by explosions due to the high pressures and the use of polar solvents.
* Whatever the nature of the aromatic reagent, the reaction time does not exceed 10 mn.
* The mixture of the two arylodiazepinones obtained with dissymetrical arylenediamine is revealed by TLC, where two slightly superposed spots are observed when one spot is observed if symetrical arylenediamine is used.
* The microwaves act by specific effects (which are not necessarily thermal) on the reactivity of **1+2**. The same reagents, when treated in the classical way under the same conditions of time (10 mn) and temperature (T_{mw}) do not react.
* The intrinsic effects on the selectivity are fairly important in view of the specificity of the reaction: only compounds **6**[19] (or **6+7**) are obtained, they do not undergo any [1,3] sigmatropic rearrangement into 1-(α-

methylvinyl)-2-benzimidazolinones[20].

This one way synthesis of arylodiazepinones seems to be very easy, efficient and represents an interesting alternative to all methods reported in the litterature. We are now extending this kind of synthesis on neutral, acidic and alkaline mineral supports.

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