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MICROWAVE-ASSISTED CYCLOCONDENSATION UNDER SOLVENT-FREE CONDITIONS: QUINOXALINE-2,3-DIONE

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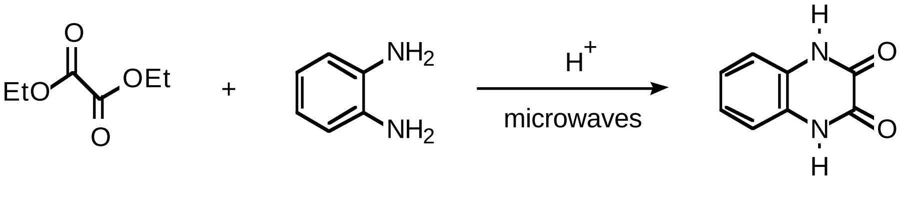
Abstract - Use of monomodal microwave techniques together with solvent-free conditions in the condensation of 1,2-phenylenediamine with diethyl oxalate gives the quinoxaline-2,3-dione in good to high yields after 2-3 min. The method is simple, rapid and avoids prolonged heating with corrosive mineral acids.

Heterocycles are predominant structures in the lead compounds of many drug families. Robust, flexible methods for synthesizing rings can be advantageous for drug discovery programs, since small substituent changes can potentially have beneficial effects on a drug's properties. Many cyclizations, however, require high temperatures and long reaction times - conditions that are not compatible with sensitive materials. Microwave dielectric heating has been increasingly used to speed up difficult reactions involving polar substrates.[1] We have previously attempted to use monomodal microwave heating[2] to accelerate the cyclocondensation of diethyloxalate **(1)** with 1,2-phenylenediamine **(2)** and analogs[3,4] to generate quinoxaline-2,3-diones **(3)**, which are structural units in many antagonists[5] for the excitatory amino acid system**.** Typically the cyclization proceeds slowly in refluxing solvents and/or mineral acids.[6] Acidic media couple avidly with oscillating microwave fields, which allows for very rapid heating of such samples. However, when the high microwave input powers required for this cyclization were used, the closed vessels exploded and only very low yields could be obtained. Here we wish to describe the successful use of solid supports[7] and/or solvent-free media with focused microwave fields to achieve the heterocyclization.



1 **2** **3**

RESULTS AND DISCUSSION

The influences of the solid support and/or acidic media, temperature and time of treatment were screened in a large number of experiments. When the reactions were attempted using the supports together with solvents that couple well with microwaves (H_2O, CH_3CN, DMSO and propylene carbonate), only trace amounts of **3** were obtained (<2%, data not shown). The trends observed for solvent-free conditions are demonstrated by the results given in Table 1. The individual experiments chosen here were those in which highest yields were obtained at the mildest conditions (i.e. lowest temperatures and shortest reaction times) for each support or reagent tested.

Table 1: Microwave-assisted cyclization using equimolar amounts of **1** and **2**

Entry	Solid Support	Acidic Reagents	T_{med} (°C)	Time (min)	Yield %
1.1	SiO_2	-	160	3	21
1.2	KH_2PO_4	-	160	3	31
1.3	KH_2PO_4	-	150	6	46
1.4	Dowex 50x8	-	150	3	33[a]
1.5	KSF	-	130	2	29[a]
1.6	-	9N H_2SO_4 [c]	150	4	19[b]
1.7	-	2M HCl [c]	85	3.5	15[b]
1.8	-	*p*-TsOH [d]	130	3	54

[a] Complex product mixture [b] Extensive hydrolysis of **1** to oxalic acid [c] 0.3 mL [d] 5.3 mg

In the absence of solvents, comparable yields were obtained using Dowex 50x8 and KSF (*ca.* 30%, little improvement with t >3 min). However, other unidentified products were obtained and the Dowex resin began to degrade at T_{med} > 100 °C. Cleaner mixtures, but lower yields were obtained with silica. Of the supports tested, highest yields were obtained at t = 6 min with the anhydrous KH_2PO_4, which may catalyze the reaction and can subsequently be dissolved to aid recovery of the products (Entry 1.3). The input power required to heat the supports to the desired temperature increased as the extent to which they couple with the electromagnetic field (Dowex>KSF>SiO_2>>KH_2PO_4) decreased. By comparison, in both H_2SO_4 and HCl decomposition of the ethyl oxalate to the less reactive oxalic acid predominated, even though some product could be obtained when the vessels were not closed and the temperature was carefully monitored. Additions of small amounts of HCl or H_2SO_4 to the solid supports did not improve the yields obtained (data not shown).

Condensations may be driven by evaporation of volatile products released during the reaction. It has been previously reported[8] that, in esterifications performed on acidic solid supports (KSF, K10 and zeolites), complete displacement of the equilibrium was not achieved since chemisorption and competing hydrolysis occurred before the water evaporated. Trace amounts of *p*-toluenesulfonic acid (*p*-TsOH) greatly improved the esterification yields. Here, the use of *p*-TsOH nearly doubled the yields (Entry 1.8) over those obtained with the solid supports. Results were comparable to those obtained using KH_2PO_4, but were achieved with lower input powers and at shorter times.

In many types of chemical processing, one or more of the starting materials may be particularly precious. Their conversions are often maximized by manipulating the molar ratios of the substrates. In this cyclocondensation, using a 10-fold excess of **2** gave better conversions of **1** with SiO_2 and KSF supports, but not with KH_2PO_4 or Dowex (examples of the trends found are given in Table 2). Of the solid supports tested, SiO_2 gave the best yields and cleanest mixtures. When the limiting reagent was instead **2** (e.g. entry 2.3), the conversions were slightly lower, but still better than in the equimolar experiments. Nearly complete conversions were obtained with *p*-TsOH (Entry 2.9).

Table 2: Effect of changing molar ratios on the microwave-assisted reaction of **1** and **2**

Entry	Solid Support	Acidic Reagents	Ratio[a] **1** : **2**	T_{med} (°C)	Time (min)	Yield[b] %
2.1	SiO_2	-	0.1 : 1	140	1	56
2.2	SiO_2		0.1 : 1	140	3	89
2.3	SiO_2		10 : 1	155	3	66
2.4	KH_2PO_4	-	0.1 : 1	140	3	31
2.5	Dowex 50x8	-	0.1 : 1	150	3	34
2.6	KSF	-	0.1 : 1	170	3	63[c]
2.7	KSF	-	0.5 : 1	170	3	36[c]
2.8	-	9N H_2SO_4[e]	0.1 : 1	150	3	8[d]
2.9	-	*p*-TsOH[f]	0.1 : 1	140	2.5	94

[a] The amount of **2** was constant and **1** was varied [b] Based on the limiting reagent [c] Complex product mixture; [d] Extensive hydrolysis of **1** to oxalic acid; [e] 0.3 mL; [f] 5.3 mg

The condensations of 1,2-phenylenediamines with β-keto esters in xylene and in polar aprotic solvents to yield 1,5-benzodiazepin-2-ones[9] and benzimidazolin-2-ones,[10] respectively, have been previously facilitated by microwave treatment. To our knowledge, this study is the first report of the successful microwave-assisted 1,2-phenylenediamine cyclization with a 1,2-diester. The use of solid supports or solvent-free conditions was critical for obtaining good yields for the acid-catalyzed diamidation after such short reaction times. In a recent report,[11] microwave-assisted monoamidations with aromatic, but not aliphatic, esters were also accomplished using a basic solid support, potassium *tert*-butoxide. Both of these solvent-free methods avoid the conventional approaches in which substrates are heated with corrosive mineral acids for prolonged periods. The yields of and the times required for the heterocyclization are competitive with those reported for the more difficult of the monoamidations, although comparison of the reaction conditions is not possible since the sample temperatures were not monitored in the previous study.[11] However, the amidation reported here was successful for the aliphatic ester and base-sensitive functional groups in other potential amines would probably be tolerated.

In summary, a diamidation with concurrent heterocyclization giving the quinoxaline-2,3-dione ring system has been rapidly achieved using microwave dielectric heating. The comparison of a number of supports and solvent-free conditions indicated that yields were highest using *p*-toluenesulphonic acid. Conversions of 55%, 66% and 89-94% were obtained in $\leq$ 3 min for molar ratios of **1** to **2** = 1:1, 10:1 and 1:10, respectively.

EXPERIMENTAL PROCEDURE

Solid supports: A solution of **2** (30 mg, 0.28 mmol) in CH_3CN (1 mL) was mixed with the solid support (Dowex 50x8 100-200, KSF, SiO_2, KH_2PO_4) (28 mg) in a 10 mL flask. The solvent was removed by evaporation at reduced pressure. The mixture was transferred to the microwave reaction vessel and a solution of **1** (0.014- 2.8 mmol) in CH_2Cl_2 (0.5 mL) was added. After stirring for a few seconds, the CH_2Cl_2 was removed by evaporation. Reactions were performed in an open reaction vessel[2] which could be reproducibly positioned in the single-mode microwave device (Microwell 10, Personal Chemistry AB, Uppsala, Sweden). The sample temperature was continually measured by an optical fiber thermometer - Nortech Fibronic- inserted into the mixture during the microwave treatment. After an initial pulse (15-30 sec) to rapidly raise the temperature, the input power was varied manually to achieve the desired T_{med}.

At the end of the microwave treatment, the vessel was cooled and the substrates and products were subsequently dissolved or extracted from the solid support using DMSO (5 mL). Aliquots were analyzed using liquid chromatography. The following experimental set-up was used: μ-Bondapak C18 column (7.8 x 300 mm, 10 μm, Waters); mobile phase CH_3CN: H_3PO_4 (0.01M) 20:80; flow 2.5 mL/min giving retention times of 4.6, 6.6 and 17.9 min for **2**, **3** and **1**, respectively. Eluents were monitored by UV-detection and conversions were calculated by comparison of the area of the product peak with that of reference quinoxaline-2,3-dione (Aldrich) in standard solutions.

Acidic reagents, solvent-free conditions: A mixture of **1** (0.028-0.28 mmol), **2** (0.28 mmol), together with HCL (2M, 0.3 mL), H_2SO_4 (9N, 0.3 mL) or *p*-TsOH (0.028 mmol) was placed in the reaction vessel previously described.[2] The microwave irradiation, isolation and analysis were performed as above.

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