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Calcium acetate catalyzed synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones under solvent-free conditions

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Abstract—Eight 4-arylidene-2-phenyl-5(4*H*)-oxazolones (azlactones) have been prepared via Erlenmeyer synthesis from aromatic aldehydes and hippuric acid using calcium acetate under solvent-free conditions with microwave irradiation.

4-Arylidene-2-phenyl-5(4*H*)-oxazolones are important synthons for the synthesis of several biologically active molecules.[1] They are also precursors of amino acids containing an aromatic side chain and can be converted to the latter by treatment with red phosphorus and hydrogen iodide. A number of methods are available for the synthesis of azlactones[2–8] including the recent use of anhydrous zinc chloride[9] or bismuth(III) acetate as catalysts.[10]

The replacement of toxic organic solvents is one of the most important goals in *Green Chemistry*, which inevitably lead to solvent emission and/or waste. The use of reagents supported on solid inorganic supports is also an area currently under active investigation. These not only avoid the use of solvents for carrying out reactions but also induce significant simplifications to the reaction procedures.

The use of microwave irradiation for carrying out organic reactions is a well-established procedure since reactions are clean, fast and economical. Coupling of the two techniques, that is, organic reactions using supported reagents with microwave irradiation has been a field, which has shown excellent results leading to the development of many reaction procedures, which are environmental friendly falling in the domain of *Green Chemistry*. Work in this direction has recently been reviewed.[11]

The synthesis of azlactones under MW irradiation has been reported in open vessels using acetic anhydride, which acts both as reagent and as the organic phase.[12a,e] Acetic anhydride is a well-known toxic reagent and its use for carrying out reactions under microwave irradiation in open vessels would spoil the cavity of the oven and also lead to the emission of toxic vapours into the environment. Thus, the use of acetic anhydride as a supported reagent was explored in continuation of our ongoing work on the use of supported reagents with microwave irradiation.[13]

We selected calcium acetate as the support/catalyst, which, besides being inexpensive and nontoxic, has not been reported to have been used for this synthesis. In view of the importance of azlactones as synthons for biologically important compounds and the advantages offered by coupling microwave activation with dry media reactions, we report here a solvent-free procedure for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones **3a**–**h** (Table 1) from arylaldehydes **1** and hippuric acid **2** using calcium acetate under microwave irradiation[14] (Scheme 1).

The activity of calcium acetate for the synthesis of azlactone **3a** was first checked by mixing it with different supports such as neutral and basic alumina, K_2CO_3, $KF–Al_2O_3$ (Table 2). The best results were obtained when calcium acetate was used alone as the support. The amount of calcium acetate was found to be crucial for

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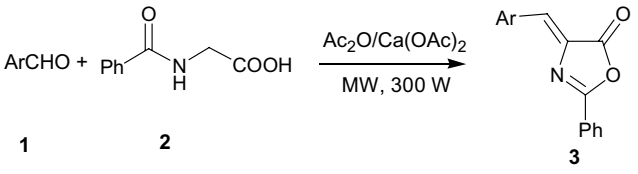
Table 1. Microwave-induced synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones **3a**–**h** using $Ca(OAc)_2$ (power = 300 W)

Product	Time (min)	Reaction temperature[a] (°C)	Yield[b] (%)	Mp (°C) found/reported
3a	5	48–50	97	169–170/170[9]
3b	3	74–76	99	164–165/165[9]
3c	3	57–60	80	143–144/145–146[17]
3d	6	57–59	70	203–204/197[12e]
3e	3	48–50	72	164–165/166[18]
3f	5	45–47	99	194–195/195–196[19]
3g	3	70–72	94	150–152/151–152[9]
3h	3	55–58	91	130–131/130[9]

[a] The final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during the microwave experiment and was an approximate temperature range.
[b] Yield of isolated products.



3a Ar = C_6H_5 **3b** Ar = 4-$MeOC_6H_4$
3c Ar = 4-MeC_6H_4 **3d** Ar = 4-ClC_6H_4
3e Ar = 2-$NO_2C_6H_4$ **3f** Ar = 3-$NO_2C_6H_4$
3g Ar = 3,4-$(OMe)_2C_6H_3$ **3h** Ar = -CH=CHC_6H_4

Scheme 1.

Table 2. Effect of solid support in dry media for the synthesis of **3a** under microwave irradiation (power = 300 W)

Support	Time[a] (min)	Reaction temperature[b] (°C)	Yield[c] (%)
$Ca(OAc)_2$/B Al_2O_3	4	100–105	42
$Ca(OAc)_2$/N Al_2O_3	5	55–57	0
$Ca(OAc)_2/K_2CO_3$	5	45–47	53
$Ca(OAc)_2$/KF–Al_2O_3	5	98–100	28
$Ca(OAc)_2$/B Al_2O_3/ K_2CO_3	5	40–42	0
$CaCO_3$	5	60–62	70
$Ca(OAc)_2$	**5**	**48–50**	**97**
NH_4OAc	5	80–91	10
NaOAc	5	70–72	10

B Al_2O_3: basic alumina; N Al_2O_3: neutral alumina.
[a] Time at which maximum yield was obtained.
[b] The final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of the exposure during the microwave experiment and was an approximate temperature range.
[c] Yield of isolated products.

obtaining optimum results. It has been found that for 1 mmol of aldehyde, 1 mmol of hippuric acid and 3 mmol of acetic anhydride, 0.5 g of calcium acetate was required. A power setting of 300 W appeared to be the best compromise between efficiency and safety.[15]

Calcium acetate appeared to be an efficient catalyst. Blank experiments have shown the fundamental role of calcium cations, whereas $Ca(OAc)_2$ led to a quasi-quantitative yield (97%), NaOAc and NH_4OAc gave only 10% yields. On the other hand, acetate anions seem to be less influential as $CaCO_3$ led to a more satisfactory yield of 70%. This effect can be attributed to the carbonyl complexation by calcium cations leading to electrophilic assistance during nucleophilic attack on this group. When the reaction was carried out by irradiating hippuric acid **2** alone, oxazolone **4** was formed in 10 min and could be isolated in 70% yield ($Ca(OAc)_2$ and Ac_2O were both required for the cyclization to azlactones **3**).

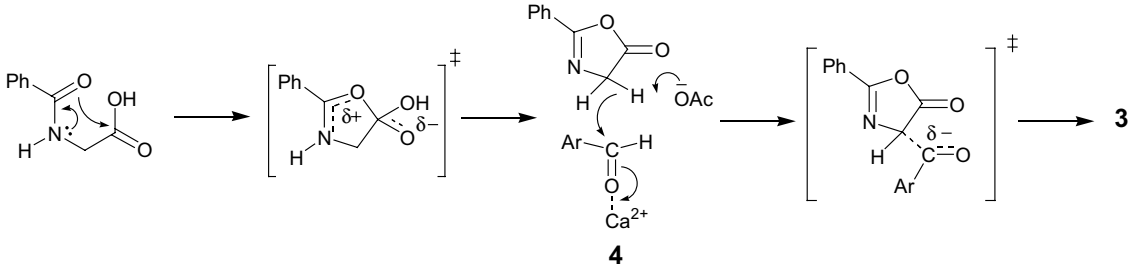
In order to check the possibility of the existence of a specific (nonpurely thermal) microwave effect accelerating the reaction with respect to conventional heating, a pre-heated oil bath was used as a source of heat in comparative experiments (Table 3). Lower yields were obtained with conventional heating under the same conditions of time and temperature. This observation is consistent with the reaction mechanism of the reaction as depicted in Scheme 2, which involves a polar transition state starting from a neutral ground state. This enhancement in polarity during the reaction progress can thus induce an improved stabilization of the transition state by microwaves (dipole–dipole interaction), leading to a lowering in the activation energy.[16]

General procedure for the synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones **3a**–**h**. The appropriate aromatic aldehyde **1** (1 mmol), hippuric acid **2** (1 mmol) and acetic anhydride (3 mmol) were introduced into a beaker (50 mL). Calcium acetate (0.5 g) was added and the contents mixed thoroughly with a glass rod. The paste so obtained was irradiated in a microwave oven at a power output of 300 W for the appropriate time (Table 1). After irradiation, cold methanol (20 mL) was added for extraction. The solid obtained after solvent evaporation was washed with hot water (3 × 20 mL), dried and

Table 3. Comparison of microwave activation (MW) and thermal heating (Δ) in the case of **3a** under microwave irradiation (power = 300 W)

Product	Method	Reaction temperature[a] (°C)	Time (min)	Yield (%)
3a	**MW**	**48–50**	**5**	**97**
	Δ	48–50	5	50
	Δ	48–50	35[b]	81

[a] The final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during the microwave experiment and was an approximate temperature range.
[b] Time at which maximum yield was obtained.



Scheme 2.

crystallized from ethyl acetate: pet. ether as yellow coloured crystals in 70–99% yields.

The structures of the products were confirmed by IR, ^{1}H NMR, mass spectroscopy and by comparison with authentic samples prepared according to literature methods.

In conclusion, a reliable, rapid and environmentally benign method for synthesizing 4-arylidene-2-phenyl-5(4*H*)-oxazolones has been developed, which involves the use of inexpensive and relatively nontoxic reagents and calcium acetate under microwave irradiation. In addition, high yields of the products, short reaction times, ease of work-up and low cost make the above method advantageous in comparison to other existing methods.

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