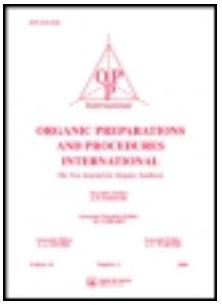

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A NOVEL ROUTE TO 4-ARYLIDENE-2-PHENYL-5(4H)-OXAZOLONES

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A NOVEL ROUTE TO 4-ARYLIDENE-2-PHENYL-5(4H)-OXAZOLONES

Submitted by (09/09/97)

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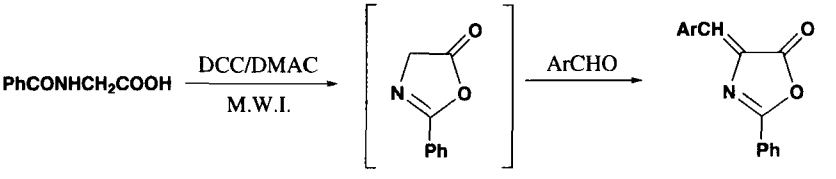
Current interest in our laboratory[1] in the use of microwave[2] energy led us to investigate it use for the synthesis of azlactones which are important synthons for biologically active molecules.[3,4] A literature survey showed that arylidene oxazolones have been prepared by the condensation of hippuric acid with aromatic aldehydes in the presence of catalyst such as acetic anhydride and sodium acetate,[5] potassium carbonate,[6] zinc chloride[7] and N-chloroacetyl-benzamide-sodium acetate.[8] The reactions involve cyclodehydration of hippuric acid to its azlactone followed by condensation of methylene group of the azlactone with the aromatic aldehyde.[7] We now report a new convenient method for the synthesis of azlactones.

Arylaldehydes along with hippuric acid when subjected to microwave irradiation (MWI) at 2450 MHz for 1.5-2.0 min using N,N-dimethylacetamide (DMAC) as a suitable energy transfer solvent and N,N-dicyclohexylcarbodiimide (DCC) as a condensing agent.

A shortcoming of classical preparation of aromatic azlactones from phenolic aldehydes with acetic anhydride and sodium acetate[5] is that the hydroxy group are always acetylated and also 1-1.5 h heating is required.[7] In comparison, the reaction using microwave energy is completed in just 1.5-2.0



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min without affecting the phenolic hydroxyl groups and provide good to excellent yields of products compared to 48-60% yields using conventional heating. The analytical and spectral data of products (**1a-j**) are in agreement with those reported in literature.[7,9,10] Thus the present method is superior to

other methods in terms of high yields and reduced reaction times. The azlactones prepared are shown in the Table 1.

Table 1. Yields and mps of Arylidene Oxazolones **1a-j**

Product	Ar	Time (min.)[a]	Yield (%)	mp.	lit. mp.
1a	C_6H_5	1.5	75	170-171	170[7]
1b	4-ClC_6H_4	1.5	80	204-206	205[7]
1c	4-$MeOC_6H_4$	1.5	72	165-166	165[7]
1d	4-MeC_6H_4	1.5	76	143-144	145[7]
1e	4-$O_2NC_6H_4$	1.5	73	177-178	177[9]
1f	2-HOC_6H_4	2.0	60	168-170	169[9]
1g	4-$Me_2NC_6H_4$	2.0	64	209-210	210-211[10]
1h	3,4(OCH_2O)C_6H_3	2.0	69	198-199	197[6]
1i	3-MeO-4-HOC_6H_3	2.0	62	157-158	158[9]
1j	3,4(MeO)$_2C_6H_3$	2.0	69	151-152	150[10]

a) Total time of irradiation at 700 watts.

EXPERIMENTAL SECTION

Mps were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a recorded on a Perkin-Elmer R-32 instrument using TMS as internal reference. Microwave irradiations were carried out in Padmini Essentia oven, Model Brownie at 2450 MHz. For safety reasons, all the experiments with microwave ovens should be performed in an efficient hood in order to avoid contact with vapors.

General Procedure for the Preparation of 4-Arylidene-2-phenyl-5(4H)-oxazolones (1a-j).- A mixture of hippuric acid (0.895 g, 5 mmol), DCC (1.238 g, 6 mmol) and DMAC (5 mL) contained in an Erlenmeyer flask (100 mL) was placed in the microwave oven and irradiated for 35 seconds. Then the aldehyde (5 mmol) was added and the mixture was irradiated further for 55 seconds (**1a-e**)/85 seconds (**1f-j**) (see Table 1). The reaction mixture was cooled and 50 mL of H_2O was added. The aqueous layer was decanted. The gummy residue was treated with 15% aq. acetic acid (100 mL), stirred for 30 min. and extracted with diethyl ether (2x50 mL). Dicyclohexylurea which separated at the interface of two layers, was removed by gravity filtration. The organic layer was washed with 5% $NaHCO_3$ (50 mL) and sodium metabisulfite (50 mL) solution. Finally, ethereal layer was washed with water, dried over Na_2SO_4 (anhyd.) and evaporated to afford the product which was recrystallized from benzene (Table 1).

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IMPROVED PREPARATION OF FLURBIPROFEN†

Submitted by (10/30/97) M. N. Deshmukh* and V. Lakshminarayana

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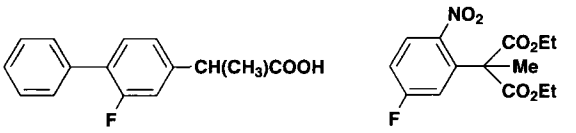
Diethyl 2-methyl-2-(3-fluoro-4-nitrophenyl)malonate (**4**) is an important intermediate for the manufacture of the non-steroidal anti-inflammatory drug, flurbiprofen (**1**). The reported methods for its synthesis involve arylation of diethyl methylmalonate (**2**) with 2,4-difluoronitrobenzene (**3**) using a strong base such as sodium hydride in DMSO (57%),[1] sodium hydroxide or K_2CO_3 in DMF at



1 **5**

30-160° (51-80%).[2] The arylation was also carried out in DMF using K_2CO_3 and traces of 18-crown-6,[2c] albeit leading to a mixture of *ortho* (**5**) and *para* (**4**) products. Further the reaction times are longer