Coumarins: Fast Synthesis by Knoevenagel Condensation under Microwave Irradiation†

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Condensation of salicyaldehyde or its derivatives with various derivatives of ethyl acetate in the presence of piperidine leads to the synthesis of coumarins by a solvent free reaction under microwave irradiation.

Coumarins are nowadays an important group of organic compounds that are used as additives to food and cosmetics,[1] optical brightening agents[2] and dispersed fluorescent and laser dyes.[3] The derivatives of coumarin usually occur as secondary metabolites present in seeds, roots and leaves of many plant species. Their function is far from clear, though suggestions include waste products, plant growth regulators, fungistats and bacteriostats.[4] It is therefore of utmost importance that the synthesis of coumarin and its derivatives should be achieved by a simple and effective method.

Coumarins can be synthesised by methods such as Claisen rearrangement, Perkin reaction and Pechmann reaction as well as Knoevenagel condensation.[5] Some of the industrially important coumarins contain a 4-methyl substituted group [*e.g.*, 7-hydroxy-4-methylcoumarin (Coumarin 47 or Coumarin 460) and 7-diethylamino-4-methylcoumarin (Umbelliferon 47)] and can be prepared by the Pechman reaction, *via* readily available 1,3-disubstituted compounds and their acetoacetic esters.[2]

It was recently shown that the Pechman reaction could be quickly achieved using microwave irradiation of the reagents in a household microwave oven.[6] Since solvent free phase-transfer catalytic reactions under microwave irradiation is the main topic in our laboratory,[7] it has prompted us to present our results of the synthesis of coumarins by Knoevenagel condensation under such conditions. Both Knoevenagel reaction[8] and synthesis of coumarin by Knoevenagel condensation[9] have been the subject of microwave induced reactions; in the case of coumarins the only example that has been given is the synthesis of 3-ethoxycarbonylcoumarin (ethyl 2-oxo-2*H*-1-benzopyran-3-carboxylate).

The aim of the present paper is to show that under microwave irradiation the Knoevenagel condensation can be successfully applied to the synthesis of a number of coumarins, and the scope of the method is very broad. We report a very simple, fast and general procedure where the condensation of salicylaldehyde or its derivatives with various derivatives of ethyl acetate (*e.g.*, R^3CH_2COEt; $R^3 = CO_2Et$, COMe, CN, *p*-$C_6H_4NO_2$) in the presence of piperidine under solvent-free conditions leads to the synthesis of coumarins (Fig. 1).

The solvent-free conditions under microwave irradiation offers several advantages:[10] solvents are often expensive, toxic, difficult to remove in the case of aprotic dipolar solvents with high boiling point, and are environmentally polluting agents. Moreover, liquid–liquid extraction is avoided in the isolation of reaction products, and the absence of solvent prevents the risk of hazardous explosions when the reaction takes place in a microwave oven. The reactions (*i.e.*, the synthesis of coumarins) were usually complete within 1–10 min and gave improved yield over conventional methods in a shorter time. Moreover, the work-up procedure is simply reduced to the recrystallization of product from an appropriate solvent. Experimental results are given in Table 1.

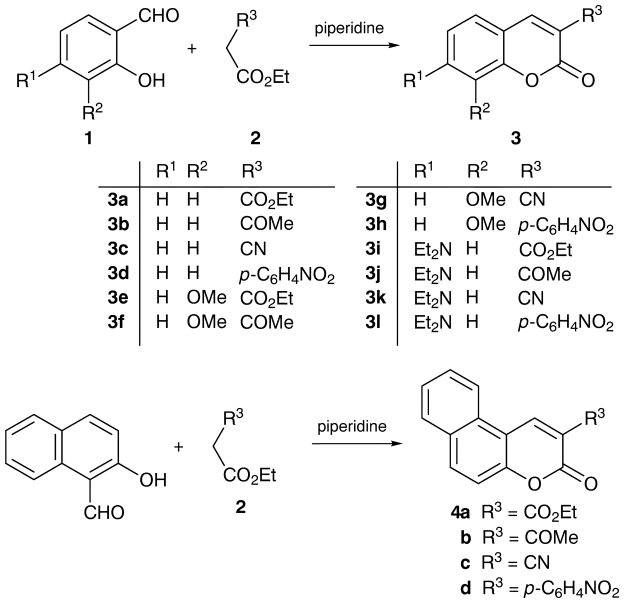
In summary, the method leads to a notable improvement in reaction conditions for coumarin synthesis by Knoevenagel condensation and takes advantage of both solvent free reaction conditions and microwave activation. As shown in Table 1, the reaction time is reduced to only a few minutes by using microwave dielectric heating. The reactions can be run safely in good yields, and the work-up procedure is reduced to the recrystallization of the desired products.

Table 1 Results of coumarin syntheses by Knoevenagel reaction under microwave irradiation

		Experimental					Literature	
Compound	Power (%)	Time/min	T^a/C	Yield (%)	Mp^b/°C	Solvent	Yield (%)	Mp/°C
3a[c]	10	10	129	89	91–92	EtOH	83	93–94[11]
3b[c]	20	1	90	94	120–122	EtOH	—	124[12]
3c[c]	20	4	201	76	182–184	EtOH	65	184–185[13]
3d[d]	40	5	220	85	274–275	$MeCO_2H$	78	268–269[14]
3e[c]	10	10	131	72	89–91	EtOH	62	88–90[15]
3f[c]	—	—	r.t.[e]	90	167–169	butan-2-one	94	173–174[15]
3g[c]	—	—	r.t.[e]	90	224–225	$MeCO_2H$	35	224–226[15]
3h[d]	10	5	90	78	294–296	$MeCO_2H$	—	300[16]
3i[c]	20	6	220	55	80–82	EtOH	40	77–78[17]
3j[c]	20	6	136	88	152–153	EtOH	74	151–153[18]
3k[c]	10	10	165	80	225–226	MeCN	77	229[18]
3l[d]	10	6	122	90	265–267	MeCN	87	263[18]
4a[c]	20	5	170	80	117–118	dioxane	70	118[19]
4b[c]	10	8	87	75	186–188	$MeCO_2H$	79	190[18]
4c[c]	10	10	100	82	296–298	$CHCl_3$	80	298–299[19]
4d[d]	20	3	170	75	297–299	DMF	76	303[18]

[a]Final temperature reached by the reaction mixture. [b]Melting points, measured on a Boetius-PHMK 05 microscope plates, are uncorrected. [c]Hydroxyaldehyde (100 mmol), carbonyl compound (**2**) (110 mmol) and piperidine (2.0 mmol). [d]Hydroxyaldehyde (50 mmol), carbonyl compound (**2**) (55 mmol) and piperidine (1.0 mmol); [e]r.t. = room temperature (in this case it is not necessary to apply microwave power).

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



	R^1	R^2	R^3
3a	H	H	CO_2Et
3b	H	H	COMe
3c	H	H	CN
3d	H	H	p-$C_6H_4NO_2$
3e	H	OMe	CO_2Et
3f	H	OMe	COMe

	R^1	R^2	R^3
3g	H	OMe	CN
3h	H	OMe	p-$C_6H_4NO_2$
3i	Et_2N	H	CO_2Et
3j	Et_2N	H	COMe
3k	Et_2N	H	CN
3l	Et_2N	H	p-$C_6H_4NO_2$

4a $R^3 = CO_2Et$
b $R^3 = COMe$
c $R^3 = CN$
d $R^3 = p$-$C_6H_4NO_2$

Fig. 1 Synthesis of coumarins by Knoevenagel condensation under microwave irradiation

Experimental

Reactions were carried out under atmospheric pressure in an open vessel adapted to a Synthwave 402 microwave monomode reactor (Prolabo). All the compounds were identified by GC-MS, IR and NMR and gave satisfactory results in comparison with authentic samples. Melting points are in good agreement with literature data (Table 1).

General Procedure.—A mixture of a hydroxyaldehyde (100 mmol), carbonyl compound (**2**) (110 mmol) and piperidine (0.20 g, 2.4 mmol) was irradiated with microwaves for the time indicated in Table 1. At the end of exposure to microwaves, the reaction mixture was cooled to room temperature, and the crude product recrystallised from an appropriate solvent (Table 1) to obtain the coumarins **3** and **4**.

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