13rd International Electronic Conference on Synthetic Organic Chemistry (ECSOC-13), 1-30 Novermber 2009
http://www.mdpi.org/ecsoc-13 & http://www.usc.es/congresos/ecsoc/13/

[E013]

Synthesis of 4-phenylcoumarin from 2-hydroxybenzophenone imine and diethyl malonate by microwave assisted Knoevenagel condensation

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Abstract: Three steps synthesis of neoflavonoid skeleton (4-phenylcoumarin) from 2-hydroxybenzophenone imine was carried out in good yield. The key step is a microwave assisted solventless Knoevenagel condensation, and a microwave assisted solventless decarboxylation is involved.

Coumarin nucleus is widely distributed in natural products, such as neoflavonoids (4-arylcoumarins) and 3-arylcoumarins, among others.
The use of microwave irradiation in the synthesis of coumarins has been extensively studied,[i] mostly achieved by Knoevenagel condensation of salicyl aldehydes and active methylene compounds. Besides the use of aldehydes,[ii] there are some reports on the use of 2-hydroxyacetophenones,[iii] but none on the use of 2-hydroxybenzophenones for the synthesis of 4-arylcoumarins. There are also some papers on Knoevenagel condensation of benzophenones with different activated methylene compounds in moderated yields.[iv] These precedents joined to early works by Charles[v] on the reactivity of benzophenones towards active methylene, led us to use the imine of 2-hydroxybenzophenone **1** instead of the ketone. The active methylene compound chosen was diethyl malonate, due to its symmetry that would not bring any E/Z isomerism in the condensation product (Figure 1).

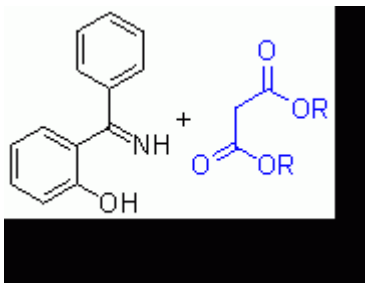
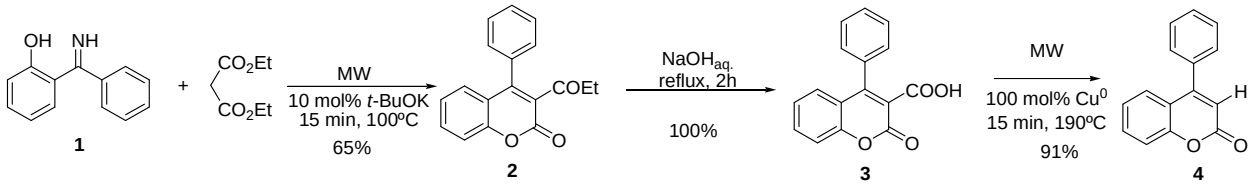


Figure 1

Thus, Knoevenagel condensation was performed under microwave irradiation in solventless conditions, in the presence of *t*-BuOK. This base was chosen due to its success in our previous synthesis of 3-arylcoumarines.[vi] After several experiments, it was found that the optimal temperature was 100ºC, higher temperatures led to partial carbonization of the reaction mixture. So, the desired product ethyl 2-oxo-4-phenyl-2H-chromene-3-carboxylate

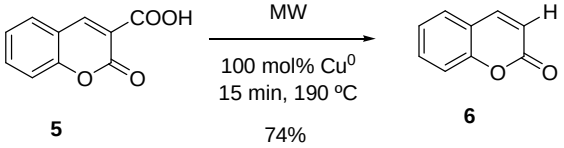
(**2**) was obtained in a 65% yield. This was hydrolyzed in basic medium to acid **3**, quantitatively (Scheme 1).



Scheme 1

The next step required the decarboxylation of 2-oxo-4-phenyl-2H-chromene-3-carboxylic acid (**3**). Decarboxylation of 3-carboxycumarins has been described in moderate yield using sodium hydroxide at 160ºC,[vii] or using copper metal at high temperatures (300ºC) under nitrogen atmosphere with yields near 80%.[viii] Copper salts method is compatible with microwave irradiation, as demonstrated by Frederiksen[ix] and Jones,[x] seeming to be the best option. For the optimization of reaction conditions commercial 2-oxo-2H-chromene-3-carboxylic acid (**5**) was used as a model.

Thus, acid **5** was treated with copper metal, and other copper(II) salts (carbonate and chloride) in the absence of solvent or ionic liquids (1-butyl-3-methyl imidazolium chloride). In all cases decarboxylation was observed, but the best yields of coumarin (**6**) were obtained with copper metal (74%). The optimized conditions were 15 minutes at 190 º C with an irradiation power of 300W in a monomode microwave oven (Scheme 2).



Scheme 2

These conditions were applied to the decarboxylation of coumarin **3** rendering 4-phenylcoumarin (**4**) in very good yield (91%, Scheme 2).

In summary, it has been successfully synthesized the skeleton present in neoflavonoids from easily and economically accessible starting materials. The route consists of 3 stages with an overall yield of 59%. This communication is the first report on microwave assisted Knoevenagel synthesis of 4-arylcoumarins.

Acknowledgements

XUNTA DE GALICIA for financial support: PGIDIT05PXIB26201PR and USC for a predoctoral fellowship to JCC.

Experimental procedure

Ethyl 2-oxo-4-phenyl-2H-chromene-3-carboxylate **(2)**. 2-(Imino(phenyl)methyl)phenol (**1**) (197 mg, 1 mmol), diethyl malonate (320 mg, 2 mmol) and *t*-BuOK (22 mg, 0.2 mmol) was irradiated in a monomode microwave oven (CEM Discover, open vessel, 300W at 100ºC measured with an IR sensor) for 15 min. The crude was dissolved in dichloromethane (30 mL) and purified by column chromatography on silica gel (AcOEt/hexane, 3:7) giving **2** (125 mg, 65%) as a solid. M.p. 117.4-118.9 ºC (hexane). IR (*Golden-Gate*): 1733 (C=O), 1706 (C=O), 1606, 1449, 1369, 1266, 1246, 1043, 1027, 756, 702, 603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.1 Hz, $OCH_2C\underline{H}_3$), 4.07 (q, 2H, J=7.1 Hz, $OC\underline{H}_2CH_3$), 7.18-7.26 (m, 2H, ArH), 7.34-7.40 (m, 3H, ArH), 7.48-7.50 (m, 3H, ArH), 7.57 (ddd, 1H, J=8.6, J=6.7 y J=2.2 Hz, ArH).

2-Oxo-2H-chromene-3-carboxylic acid (3). A suspension of **2** (590 mg, 2 mmol) in 20% aq. NaOH (20 mL) was refluxed for 2h. Subsequently it was acidified with HCl conc. and extracted with CH_2Cl_2 (3x20 mL). The organic phase was dried over Na_2SO_4 and evaporated, to give **3** (533 mg, 100%) as a white solid. M.p.171.8-173.4 ºC (hexane-CH_2Cl_2). IR (*Golden-Gate*): 3063 (OH), 1747 (C=O), 1669 (C=O), 1600, 1561, 1451, 1372, 1216, 1054, 764, 702, 672, 601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, 1H, J=8.1 y 1.6 Hz, ArH), 7.23-7.32 (m, 3H, ArH), 7.48 (dd, 1H, J=8.4 y 0.8 Hz, ArH), 7.49-7.56 (m, 3H, ArH), 7.69 (ddd, 1H, J=8.6, J=7.1 y J=1.7 Hz, ArH), 9.11 (br s, 1H, OH).

4-phenyl-2H-chromen-2-one (4). A mixture of **3** (266 mg, 1 mmol) and copper powder (63 mg, 1 mmol) was irradiated in a monomode microwave oven (CEM Discover, open vessel 300W and 190ºC measured at an IR sensor) for 15 min. The crude reaction mixture was dissolved in dichloromethane (30 mL) and washed with 10% aq. NaOH (3x15 mL). The organic phase was dried over Na_2SO_4 and evaporated to give 4-phenylcoumarin **4** (200 mg, 91%) as a white solid. M.p. 104.2-105.6 ºC (hexane). UV λ_{max} (MeOH): 203, 280, 321 nm. IR (*Golden-Gate*): 1713 (C=O), 1600, 1561, 1446, 1368, 865, 771, 745, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.37 (s, 1H, COCH), 7.19-7.25 (m, 1H, ArH), 7.40 (dd, 1H, J=8.2 y 0.7 Hz, ArH), 7.43-7.47 (m, 2H, ArH), 7.49-7.60 (m, 5H, ArH).

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