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Microwave-assisted synthesis of 3-arylcoumarins

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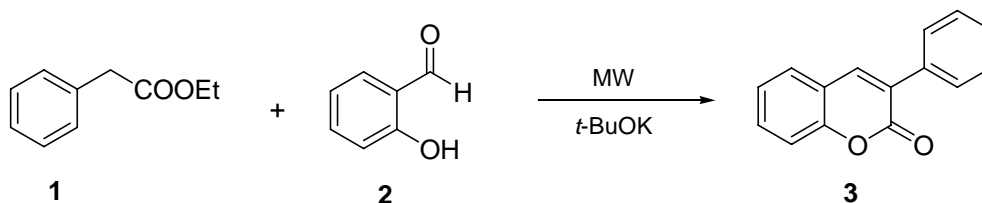
*Abstract: 3-arylcoumarins are prepared in good yields by microwave assisted solvent-free condensation of phenylacetic acids and phenylacetic esters, using potassium *tert*-butoxide as base.*

The 3-arylcoumarins are closely related to the flavonoids. The most studied 3-phenylcoumarin is coumestrol, in fact, it gives name to a whole family of compounds (coumestanes) with important biological properties. Coumestrol is considered one of the most important phytoestrogens, along with isoflavones and lignans. Phytoestrogens have attracted much attention in recent years as they have beneficial properties in diseases of great impact on our day, such as cancer, heart disease, osteoporosis and menopausal symptoms. Natural or synthetic 3-arylcoumarins have significant biological properties, such as inhibitors of various types of peroxidase,¹ enzymes in the glycolytic path of *Trypanosoma cruzi*² being potential anti-protozoos³ and moderate antifungic activity.⁴ There are also 3-arylcoumarins that inhibit the oxidative metabolism of neutrophils stimulated by immune response.⁵

Continuing with our studies on microwave assisted organic synthesis,⁶⁻¹⁶ we draw our attention to this kind of compounds since there are only two previous reports on the use of microwaves to prepare 3-arylcoumarins. Wei et al.¹⁷ condensate phenylacetic acids and salicylaldehyde derivatives in the presence of Et₃N and Ac₂O. Bogdal¹⁸ prepared a 3-arylcoumarin by Knoevenagel condensation using piperidine as base.

Due to our own experience in Knoevenagel condensations assisted with microwaves using potassium *tert*-butoxide, we investigated the application of these conditions to the synthesis of 3-arylcoumarins. As a model, the synthesis of 3-phenylcoumarin from ethyl phenylacetate and salicylaldehyde was chosen (scheme 1).¹⁹ Different sets of conditions (reaction times, temperatures and reagent molar ratio of ethyl phenylacetate, salicylaldehyde and potassium *tert*-butoxide) were tried (table 1), finding the best yield (91%) for a molar ratio PhCH₂CO₂Et: salicylaldehyde: *t*-BuOK 1:2:0.5, irradiating with 300W power at 100°C and

simultaneous cooling (table 1, entry 9). Longer irradiation times rendered lower yield of 3-arylchromen-2-one (85%, table 1, entry 7).



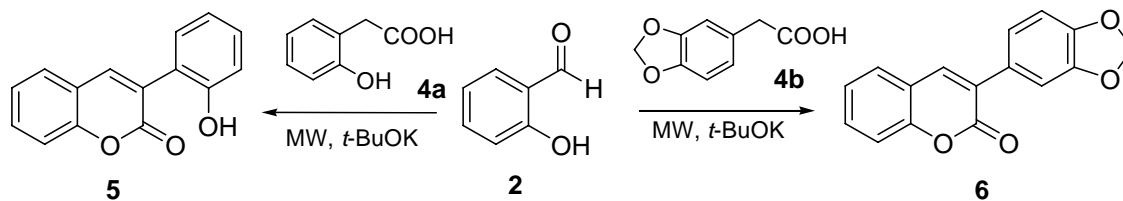
Scheme 1

Table 1

Entry	Molar ratio 1 : 2 : <i>t</i> -BuOK	Irradiation time (min)	T (°C)	Yield of 3 (%)
1	1:1:0.1	10	180	24
2	1:1:0.1	3	100	18
3	1:1:0.1	20	100	50
4	1:1:0.4	30	100	50
5	1.5:1:0.4	30	100	79
6	1.5:1:1	30	100	60
7	2:1:0.5	45	100 ($P_{\text{max}}^{\text{a}}$)	85
8	2:1:0.5	20	80 ($P_{\text{max}}^{\text{a}}$)	10
9	2:1:0.5	15	100 ($P_{\text{max}}^{\text{a}}$)	91

^a P_{max} = Power maximum (irradiation with simultaneous cooling with pressured air at room temperature of the irradiation chamber in order to maximize the absorption of microwaves).

Phenylacetic acids instead of their esters were tried (scheme 2). So, 3-(2-hydroxyphenyl)-2H-chromen-2-one (**5**) and 3-(benzo[d][1,3]dioxol-5-yl)-2H-chromen-2-one (**6**) were prepared, in very good yields, from 2-(2-hydroxyphenyl)acetic acid (**4a**) and 3,4-(methylenedioxy)phenylacetic acid (**4b**), respectively, using the same conditions described above (table 2, entries 2 and 4).



Scheme 2

Table 2

Entry	Molar ratio 4 : 2 : <i>t</i> -BuOK	Irr. time (min)	T (°C)	Compound (yield, %)
1	1.5:1:0.5	15	100 ($P_{\text{max}}^{\text{a}}$)	5 (77)
2	2:1:0.5	15	100 ($P_{\text{max}}^{\text{a}}$)	5 (88)
3	1.5:1:0.5	15	100 ($P_{\text{max}}^{\text{a}}$)	6 (63)
4	2:1:0.5	15	100 ($P_{\text{max}}^{\text{a}}$)	6 (87)

^a P_{max} = Power maximum

In summary, a microwave-assisted direct synthesis for 3-arylcoumarins under solventless conditions, catalyzed with potassium *tert*-butoxide is reported. The examples studied promise a wide field of application, which is still under study.

General procedure:

In a special glass tube for microwave oven (CEM, Discover) were mixed thoroughly phenylacetic acid or its ethyl ester (2 mmol), salicylaldehyde (1 mmol) and *t*-BuOK (0.5 mmol). The mixture was irradiated using a power of 300W, for 15 minutes at 100°C, with continuous sample cooling by means of pressured air at room temperature. The reaction was suspended in dichloromethane and the resulting solid filtered off. The organic solution was evaporated and the residue additionally purified by chromatography.

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References and notes

1. Kabeya, L. M.; De Marchi, A. A.; Kanashiro, A.; Lopes, N. P.; Da Silva, C. H. T. P.; Pupo, M. T.; Lucisano-Valim, Y. M. *Bioorg. Med. Chem.* **2007**, *15*, 1516-1524.
2. De Marchi, A. A.; Castilho, M. S.; Nascimento, P. G. B.; Archanjo, F. C.; Del Ponte, G.; Oliva, G.; Pupo, M. T. *Bioorg. Med. Chem.* **2004**, *12*, 4823-4833.
3. Singh, S.; Kishen-Malik, B.; Kumar-Sharma, D. *Chem. Biol. Drug Des.* **2008**, *71*, 554-562.
4. Arnoldi, A.; Farina, G.; Galli, R.; Merlini, L.; Grazia-Parrino, M. *J. Agric. Food Chem.* **1986**, *34*, 185-188.
5. Kabeya, L. M.; Da Silva, C. H. T. P.; Kanashiro, A.; Campos, J. M.; Azzolini, A. E. C. S.; Polizello, A. C. M.; Pupo, M. T.; Lucisano-Valim, Y. M. *Eur. J. Med. Chem.* **2008**, *3*, 996-1007.
6. Vázquez-Tato, M. P. *Synlett* **1993**, 506.
7. Oliveira-Campos, A. M. F.; Sivasubramanian, A.; Rodrigues, L. M.; Seijas, J. A.; Vázquez-Tato, M. P.; Peixoto, F.; Abreu, C. G.; Cidade, H.; Oliveira, A. E.; Pinto, M. *Helvetica Chimica Acta* **2008**, *91*, 1336-1345.
8. Seijas, J. A.; Vázquez-Tato, M. P.; Crecente-Campo, J. *Tetrahedron* **2008**, *64*, 9280-9285.
9. Seijas, J. A.; Vázquez-Tato, M. P.; Carballido-Reboredo, M. R. *J. Org. Chem.* **2005**, *70*, 2855-2858.

10. Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M.; Rodríguez-Parga, J. *Green Chem.* **2002**, 390-391.
11. Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M. *Synlett* **2001**, 875-877.
12. Seijas, J. A.; Vázquez-Tato, M. P.; González-Bande, C.; Martínez, M. M.; López-Pacios, B. *Synthesis* **2001**, 999-1000.
13. Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M. *Tetrahedron Lett.* **2000**, 41, 2215-2217.
14. Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M.; Núñez-Corredoira, G. *J. Chem. Res. (S)* **1999**, 420-421.
15. Seijas, J. A.; Vázquez-Tato, M. P.; Carballido-Reboredo, M. R.; Crecente-Campo, J.; Romar-López, L. *Synlett* **2007**, 313-317.
16. Seijas, J. A.; Vázquez-Tato, M. P.; Crecente-Campo, J. *Synlett* **2007**, 2420-2424.
17. Wei, J.; Ma, W.-H.; Xu, Q. *Jingxi Yu Zhuanyong Huaxuepin* **2006**, 14, 8-12. Chemical Abstracts CAN 148:285003.
18. Bogdal D. *J. Chem. Research (S)* **1998**, 468-469.
19. To our knowledge no previous synthesis for 3-phenylcoumarin has been previously described using these two starting materials.