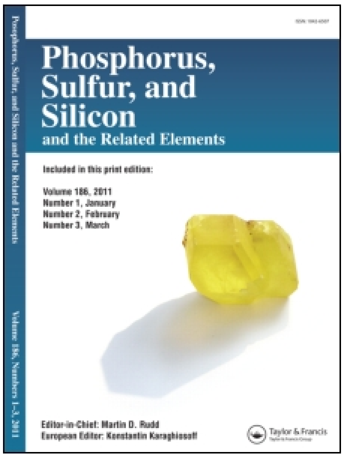

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AN EFFICIENT AND CONVENIENT SYNTHESIS OF FUROCOUMARINS VIA PECHMANN REACTION ON $ZnCl_2/Al_2O_3$ UNDER MICROWAVE IRRADIATION

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Furocoumarins were rapidly synthesized via Pechmann condensation of 6-hydroxybenzofurans with ethylacetoacetate catalyzed by $ZnCl_2/Al_2O_3$ *under solvent-free condition.*

Keywords: Al_2O_3; furocoumarins; microwave irradiation; Pechmann condensation; $ZnCl_2$

The beneficial effects of furocoumarins have been investigated over a vast number of years. The ancient Egyptians recognized the ability of furocoumarins to treat skin disorders.[1] Furocoumarins have been utilized to treat psoriasis and vitiligo as well as bacterial and viral infections.[2] Since furocoumarins have achieved medical significance, convenient synthetic routes are needed to generate the parent three-ring backbone.

Furocoumarins have been synthesized by many different routes, but the majority of these routes employ many steps and often result in very low yields.[3] Total synthesis of linear furocoumarins recently have been achieved via an intramolecular Diels-Alder reaction[4] and by benzannulation reaction of carbene complexes with acetylenes respectively.

We have shown that the Pechmann reaction could be achieved quickly using microwave irradiation of the reagents in household microwave oven.[6] In continuation of our interest in conducting of organic synthesis on inorganic supports and solventless system,[7] we devised a one-step formation of the pyrone ring of furocoumarins **2** on P_2O_5/molecular sieve 3 Å by microwave activated Pechmann reaction of

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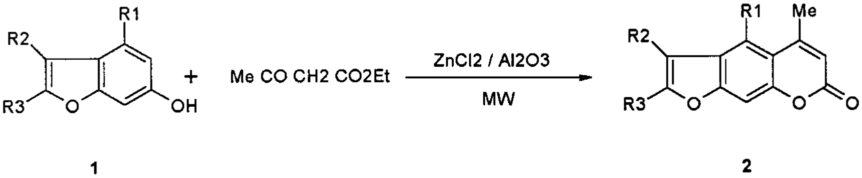
6-hydroxybenzofurans and ethylacetoacetate. Through this route furocoumarins were not synthesized in good yields and undesired products were produced. Other types of solid supports were also compared and $ZnCl_2/Al_2O_3$ was found to give the best yields.

The reaction is conducted by exposure of a mixture of 6-hydroxybenzofurans, ethylacetoacetate, $ZnCl_2$ and Al_2O_3 to microwave irradiation (Scheme 1). Most of benzofuranic compounds disappeared within a few minutes as determined by TLC.



SCHEME 1

In summary the method describes a noticeble improvement in the reaction condition for the preparation of the pyrone ring of furocoumarins by the Pechmann reaction and takes advantages of both solventless condition reaction and microwave activation.

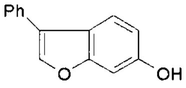
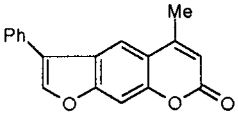
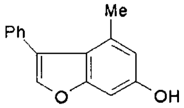
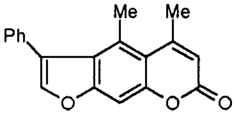
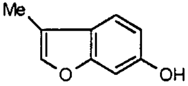
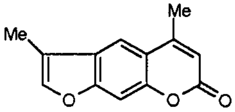
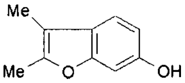
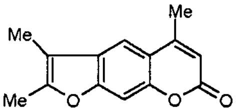
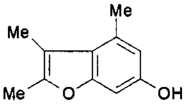
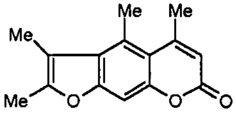
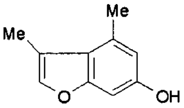
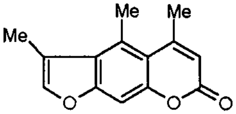
EXPERIMENTAL SECTION

Al_2O_3 powder (60 G neutral, Type E) was purchased from Merck Chemical Co. MP(s) were recorded on Electrothermal 9100 apparatus and are uncorrected. ^1H-NMR spectra were recorded on a 250 MHz Spectroscop or 60 MHz Bruker and ^{13}C-NMR spectra were recorded on a 250 MHz Spect-using TMS as an internal standard. IR spectra were measured on a Perkin-Elmer model 854.

GENERAL PROCEDURE

An appropriate hydroxy benzofuran (10 mmol), ethyl acetoacetate (10 mmol), $ZnCl_2$ (10 mmol) and Al_2O_3 (3 g) were mixed thoroughly using a spatula in a beaker. The beaker was placed in a household microwave oven. The progress of the reaction was monitored by TLC. The residue was taken up in hot chloroform and filtered. The filtrate was evaporated to dryness and the crude produce was dissolved in chloroform and was purified by dry-column flash chromatography on silica gel (Merck kieselgel 60, 0.015–0.040 mm) using n-hexane/ethyl acetate for elution, from which an analytical sample by recrystallization from suitable solvent was prepared. Melting points, yields, reaction times, and crystallizing solvents are given in Table I.

TABLE I Preparation of Furocoumarins Under Microwave Irradiation in Solvent-Free Condition

Entry	Substrate	Product	Time (min)	Yield (%)	Product m.p. (°C)	Cryst. solv.
a			3	61	182	Ethanol (96%)
b			3.5	57	230	Ethanol (96%)
c			3.2	59	227	Ethanol/Chloroform
d			2.5	63	202	Ethanol/Chloroform
e			3	62	229	Ethanol (96%)
f			3.5	58	215	Ethanol/Chloroform

Selected Spectroscopic Data for 2a

^{1}HNMR δ ($CDCl_3$, 250 MHz): 2.52 (s, 3H, 4-Me), 6.32 (s, 1H, olefinic CH), 7.43–8 (m, 8H, aromatic protons), ^{13}CNMR ($CDCl_3$, 60 MHz): 19.6, 100, 114, 116, 117, 122, 124, 127, 128, 129, 131, 143, 152, 153, 157, 161, IR, ν (KBr disc): 1695 cm^{-1}.

Selected Spectroscopic Data for 2b

^{1}HNMR δ ($CDCl_3$, 60 MHz): 2.27 (s, 3H, Me), 2.53 (s, 3H, 4-Me), 6.28 (s, 1H, olefinic CH), 7.2–7.8 (m, 7H, aromatic protons), IR, ν (KBr disc): 1710 cm^{-1}.

Selected Spectroscopic Data for 2c

^{1}HNMR δ ($CDCl_3$, 250 MHz): 2.29 (s, 3H, Me), 2.51 (s, 3H, 4-Me), 6.23 (s, 1H, olefinic CH), 7.3 (s, 1H, aromatic proton), 7.46 (s, 1H, aromatic proton), 7.58 (s, 1H, aromatic proton), ^{13}CNMR ($CDCl_3$, 60 MHz): 6.72, 18.1, 19.1, 100.8, 111.7, 113, 114.4, 115.26, 126.25, 141.3, 114.5, 152, 161, IR, ν (KBr disc): 1710 cm^{-1}.

Selected Spectroscopic Data for 2d

^{1}HNMR δ ($CDCl_3$, 250 MHz): 2.13 (s, 3H, Me), 2.39 (s, 3H, Me), 2.50 (s, 3H, 4-Me), 6.4 (s, 1H, olefinic CH), 7.28 (s, 1H, aromatic proton), 7.50 (s, 1H, aromatic proton), ^{13}CNMR ($CDCl_3$, 60 MHz): 6.7, 14.8, 19.9, 97, 100.1, 109.4, 111, 114, 114.5, 127, 151, 152, 155.3, 161.4, IR, ν (KBr disc): 1700 cm^{-1}.

Selected Spectroscopic Data for 2e

^{1}HNMR δ ($CDCl_3$, 60 MHz): 2.13 (s, 3H, Me), 2.27 (s, 3H, Me), 2.39 (s, 3H, Me), 2.51 (s, 3H, 4-Me), 6.24 (s, 1H, olefinic CH), 7.5 (s, 1H, aromatic proton), IR, ν (KBr disc): 1705cm^{-1}.

Selected Spectroscopic Data for 2f

^{1}HNMR δ ($CDCl_3$, 60 MHz): 2.15 (s, 3H, Me), 2.3 (s, 3H, Me), 2.52 (s, 3H, 4-Me), 6.31 (s, 1H, olefinic CH), 7.3 (s, 1H, aromatic proton), 7.4 (s, 1H, aromatic proton), IR, ν (KBr disc): 1695 cm^{-1}.

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