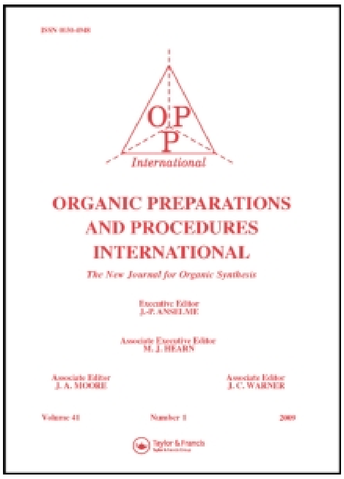

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A RAPID METHOD FOR THE CYCLIZATION OF 2'-HYDROXYCHALCONES INTO FLAVONES

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A RAPID METHOD FOR THE CYCLIZATION OF 2'-HYDROXYCHALCONES INTO FLAVONES

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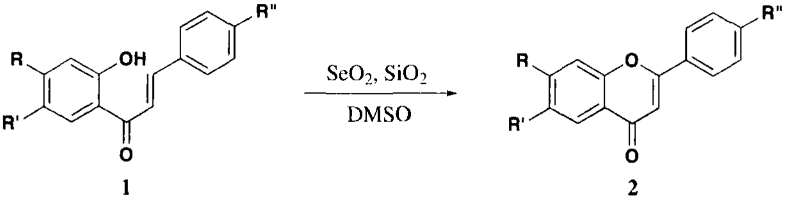
Among flavonoids, flavones are the most widely distributed in plants. They display a wide variety of biological activities[1] and have proven to be useful for the treatment of various diseases.[2] A number of methods are known for the preparation of flavones from 2'-hydroxychalcones.[3-5] The most commonly used route is the oxidative cyclization of 2'-hydroxychalcones using SeO_2 in isoamyl alcohol which requires prolonged heating (16-72 hrs) leading to the formation of number of side-products and lower yield. A new reagent[6] SeO_2-DMSO which requires the shortest time period (1-2 hrs), involves dimethyl sulfoxide which is a highly toxic solvent.

The use of surface active catalysts and inorganic reagents together with an efficient coupling with microwave activation has received much attention in recent years[7,8] because of their enhanced selectivity, milder conditions and lower cost than those associated with conventional homogeneous reaction procedures. As part of our program to develop environmentally benign synthetic procedures[9] using microwave irradiation, we now report a simple procedure for the cyclization of 2'-hydroxychalcones (**1**) using selenium dioxide and traces of dimethyl sulfoxide over silica gel. In the literature, SeO_2-^tBuOOH on silica gel has been described as an efficient oxidant of allylic methyl groups under microwave irradiation.[10]



a) R = H, R' = H, R'' = H
b) R = H, R' = H, R'' = OMe
c) R = H, R' = H, R'' = Me
d) R = H, R' = H, R'' = NO_2
e) R = OH, R' = H, R'' = OMe
f) R = H, R' = OMe, R'' = H
g) R = H, R' = Me, R'' = H
h) R = H, R' = Me, R'' = OMe

Different reaction conditions were tested for the cyclization of 2'-hydroxychalcones to flavones, the most acceptable being the use of SeO_2 over silica containing traces of DMSO. The effect of DMSO, well known as an oxidative agent and energy transfer medium, was studied. When the reaction was carried out using SeO_2 over silica under microwave irradiation, only traces of flavones were formed (5-10% as detected on tlc) even after 20 minutes of irradiation. Furthermore, when the reaction (in the case of **2a**) was carried out using SeO_2/o-dichlorobenzene/SiO_2 under the same conditions of temperature and time (Table 1), it has been found that no reaction has taken place. However, if 6 mmol of DMSO for 5 mmol of chalcone were added to the reaction mixture, a quantitative conversion of 2'-hydroxychalcones into flavones took place in only 5-7 minutes, demonstrating the role of DMSO as an oxidative agent as well as energy transfer medium. Thus, SeO_2-DMSO over silica is an efficient reagent for the oxidative cyclization of 2'-hydroxychalcones to flavones.

TABLE 1. Comparative Results between DMSO and *o*-Dichlorobenzene as Energy Transfer Medium-Oxidative Agent

Compound	Energy transfer medium/ Oxidative agent	Final[a] Temp. (°C)	Reaction Time (min)	Yield (%)
2a	DMSO	107-109	5	80
2a	*o*-Dichlorobenzene	107-109	5	0

a) Final temperature was measured by immersion of a glass thermometer at the end of exposure to microwave irradiation (approximate temperature range)

Finally, the synthesis of **2a** was attempted by change of the activation method using a thermo-regulated oil-bath under the same reaction time and temperature as for the microwave assisted method. It has been found that lower yields were obtained using an oil-bath even after extensive reaction time (Table 2). Experiments performed at higher power or longer time duration did not provide any additional advantage, rather decomposition took place.

Comparative studies under thermal and microwave irradiation conditions using DMSO/SiO_2 under similar set of conditions as well as using DMSO/SiO_2 and o-dichlorobenzene/SiO_2 have led to the conclusion that the oxidative cyclization is best achieved under the experimental conditions reported herein *i.e.* SeO_2/DMSO/SiO_2.

TABLE 2. Comparative Results using Conventional Heating (Δ) and Microwave Activation (MW) (power 400 W) for Dry Media Synthesis onto SeO_2/DMSO/SiO_2

Compound	Method	Reaction Time (min)	Final[a] Temp.(°C)	Yield (%)
2a	Δ	5	107-109	<10
2a	Δ	60	107-109	46
2a	MW	5	107-109	80

a) Final temperature was measured by immersion of a glass thermometer at the end of exposure to microwave irradiation (approximate temperature range)

The compounds synthesized were characterized by elemental analysis, spectral data (IR, ^{1}H NMR, mass spectra) and comparison with authentic samples prepared following known methods.

TABLE 3. Microwave-induced Synthesis of Flavones

Compound	Yield (%)	Time (min)	mp (^{0}C)	*lit.* mp (^{0}C)
2a	80	5	95-97	96[11]
2b	79	6	153-155	155-157[11]
2c	77	7	107-109	108-109[11]
2d	82	6	244-246	244-245[11]
2e	77	6	260-262	263-264[12]
2f	86	5	159-161	161[11]
2g	78	7	118-120	120-121[6]
2h	88	7	170-172	169-170[6]

In conclusion, we have developed a simple and mild method for the cyclization of 2'-hydroxychalcones to flavones using SeO_2/DMSO/SiO_2 under microwave irradiation. An important specific (non-thermal) microwave effect is evidenced here by comparison with classical heating under the same conditions (5 min MW: 80%, Δ <5%).

EXPERIMENTAL SECTION

Melting points were recorded on Buchi melting point apparatus using open capillaries and are uncorrected. Reactions were carried out in a domestic microwave oven manufactured by BPL Sanyo Utilities equipped with turntable plate, which allows the selection of output power up to 650 Watts. IR spectra were recorded on Shimadzu 435 spectrophotometer using KBr disc (in cm^{-1}). ^{1}H NMR spectra were recorded on Varian EM-390 (90 MHz) or Bruker AM-250 (250 MHz) using TMS as an internal standard. The mass spectra were performed on Delsi/NERMAG spectral 30 spectrometer. All compounds gave elemental analysis and spectral data in agreement with the proposed structure.

Procedure for the Cyclization of 2'-hydroxychalcones to Flavones (2a-h).- To a mixture of 2'-hydroxychalcone (5 mmol), selenium dioxide (6 mmol) in an open vessel and dichloromethane (5 mL) was added silica gel (1-2 g) and the mixture was swirled for 1 min. The solvent was removed under gentle vacuum and to the solid matrix, dimethyl sulfoxide (6 mmol) was added and thoroughly mixed with the help of a glass rod. The reaction mixture was irradiated in a microwave oven for the appropriate time (Table 1) at 400 Watts (monitored by tlc). After irradiation, the product was extracted with dichloromethane (3 x 10 mL) followed by filtration. After removal of the solvent under vacuum, the product was obtained by crystallization from the appropriate solvents such as benzene: pet. ether, ethanol or aqueous ethanol.

In an alternate procedure for preparing the solid matrix without use of a solvent, it was calculated that for 2 mmol of 2'-hydroxychalcone, 5 mmol of DMSO was required. The reaction temperature and yield remain unchanged, but there was decrease of reaction time. In a typical case, *e.g.* for **2a**, the reaction time decreased from 5 to 3 minutes.

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