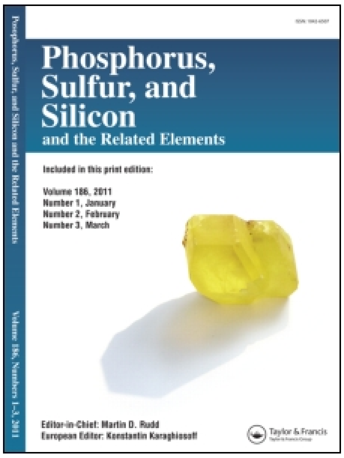

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INVESTIGATION OF THE EFFECTS OF SOME HEAT SINKS IN MICROWAVE-ASSISTED SYNTHESIS OF SOME BIGINELLI COMPOUNDS

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Pyrimidine derivatives ***4a–e*** *were synthesized by Biginelli reaction under microwave irradiation. The effectiveness of different baths or containers including ceramic, silica gel, potsherd, alumina, and molecular sieve as heat sinks in mediating the microwave irradiation for the formation of* ***4a–e*** *has been investigated. All one-pot condensations of β-Ketoester* ***1****, aryl aldehyde* ***2****, and (thio)urea* ***3*** *in heat sinks provide high yields of the desired compounds, particularly when reactions are run at low temperature. In addition, we found that potsherd and ceramic are suitable heat sinks for preparation of these cyclocondensation products under microwave irradiation.*

Keywords: Biginelli reaction; heat sink; irradiation; microwave; potsherd; pyrimidine

INTRODUCTION

Microwave irradiation is a nonconventional energy source that has been of special interest in organic chemistry in recent years.[1–9] During the past decade a number of publications and reviews advocated the advantage and usage of microwave irradiation in the synthesis of organic compounds. This novel method is therefore seen as a clean process that could revolutionize the world of organic chemistry. Some of the interesting features of this method are the rapid reaction rates, simplicity, and cleaner reaction conditions.[4–8] Microwave irradiation generates rapid intense heating of polar substance, which results in reduction of reaction time compared to conventional heating. In fact, some reactions that do not occur or that occur in very low yield under classical conditions can occur under microwave irradiation in high yield. The main reasons for

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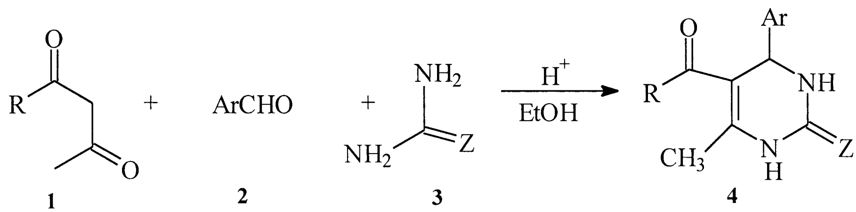
the observed rate enhancement in microwave-assisted transformation in comparison to conventional heating are not fully understood.

The significant applications of microwave in organic synthesis as an essential instrument prompted us to reinvestigate the effects of some heat sinks in microwave-assisted synthesis of some Biginelli compounds.

RESULTS AND DISCUSSION

β-Ketoester **1**, aryl aldehyde **2**, and (thio)urea **3** were reacted under microwave irradiation to give pyrimidine derivatives **4** as shown in Scheme 1.



4a) R = Me, Ar = Ph, Z = S

4b) R = EtO, Ar =2,5-dimethoxyphenyl, Z = O

4c) R = EtO, Ar = Ph, Z = O

4d) R = EtO, Ar = Ph, Z = S

4e) R = t-BuO, Ar = 4-Chlorophenyl, Z = O

SCHEME 1

In order to carry out Biginelli condensation reactions a 1.1:1.1:1.5 molar ratio of three compounds **1**, **2**, and **3** as reactants were subjected to microwave irradiation in the presence of a solid substance capable of acting as a heat sink (Alumina, potsherd, silica gel, ceramic, and molecular sieve). When reactants are subjected to microwave irradiation at constant times, the temperature and yield of each reaction are dependent on the type of the heat sink used. When the potsherd is used as a heat sink, the reaction runs at the lowest temperature and produces the product at the highest yield. Moreover, when reactions are run in the presence of the same heat sinks, yields go down as time and temperature go up (Table I). At high temperature (90–150°C) the decomposition of the reagents is a fast process, which in turn leads to lower

TABLE I Preparation of **4a** under Microwave Condition and with Different Heat Sinks

	t = 30 s		t = 50 s		t = 100 s	
Heat sink	T (°C)	Yield (%)	T (°C)	Yield (%)	T (°C)	Yield (%)
Alumina	55	95	68	87	95–100	68
Potsherd	40	97	63	90	90	81
Silica gel	60	71	75	65	>100	50
Ceramic	45	93	72	85	>100	78
Molecular sieve	65	75	88	63	>100	48

yields. However, rapid heating induced by microwave irradiation avoids the forcing classical conditions and the decomposition of materials. This leads to the formation of products under mild conditions, with consequent significant increases in yield. Among the five heat sinks used in this study, the potsherd was found to be the best one for the synthesis of the Biginelli compounds because it gave higher yields of products. It allows the rapid synthesis of these compounds without using polyphosphate ester as a reaction mediator, which has been suggested by Varma and coworkers.[10]

The method is very easy and it can be utilized for different aldehydes **2** and (thio)ureas **3** depending on X and Z groups to prepare entries **4b–e** (Table II).

In order to investigate the effect of different heat sinks, we used water as a standard material for these experiments. Similar to experimental method, a 25 ml beaker containing 10 ml of distilled water was placed inside a larger container filled with appropriate heat sink and then inserted into the microwave oven. The beaker was then subjected to microwave irradiation at 50% power level for different times. The results of these experiments are shown in Table III.

TABLE II Preparation of Pyrimidine Derivatives **4b–e** under Microwave Irradiation with Different Heat Sinks and Different Irradiation Times

	Alumina t = 30 s		Potsherd t = 50 s		Ceramic t = 100 s	
Entry	T (°C)	Yield (%)	T (°C)	Yield (%)	T (°C)	Yield (%)
4b	44	95	66	91	67	92
4c	50	93	71	96	83	93
4d	40	95	74	89	85	92
4e	44	90	59	87	66	93

TABLE III Temperature of 10 ml Water after Microwave Irradiation Using Different Heat Sinks for Different Times

	T (°C)		
Heat sink	t = 30 s	t = 50 s	t = 100 s
Alumina	57	66	72
Potsherd	59	60	62
Silica gel	61	74	78
Ceramic	64	65	65
Molecular sieve	60	80	80

Using different heat sinks in all experiments, especially using potsherd, it appears that the water temperature is not proportionally increased as the irradiation time increased. The temperature does not reach the boiling point of water (100°C) even at 100 s irradiation time (Table III). This effect can moderate the reaction conditions of Biginelli condensation without decompositions of starting materials. The observations show that among these heat sinks the potsherd and ceramic are more suitable mediators for Biginelli condensation reactions under microwave irradiation.

EXPERIMENTAL

All chemicals were of reagent-grade quality and used without further purification. Melting points were measured on an electrothermal digital melting point apparatus. ^{1}H NMR spectra were recorded on a Brucker 500 MHz spectrometer. Chemical shifts are reported in ppm relative to TMS (tetramethylsilane) as an internal standard. Spectra acquired in deuterated dimethylsulfoxide (DMSO). IR spectra were performed on a Galaxy FTIR 500 spectrophotometer. The reaction was routinely monitored by thin layer chromatography (TLC) on silica gel plates. Reactions were performed in a Samsung microwave oven with a 230 V-50 Hz power source, 900 W output, and 2450 MHz operating frequency. The final temperature of reaction mixture was measured on a thermocouple.

General Procedure

β-Ketoester (2.2 mmol), aryl aldehyde (3.0 mmol), and (thio)urea (3.0 mmol), along with few drops of ethanol (or solvent free), were placed in a 25 ml glass beaker and stirred at room temperature for 3 min with a magnetic stirrer. The beaker was placed inside a larger container filled with appropriate heat sink and was then inserted into the microwave oven. The mixture was then subjected to microwave irradiation at 50% power level for desired time. After cooling the reaction mixture, water (5 ml) was added and stirred at room temperature for 2 h. The crude products were filtered and recrystallized from ethanol to give the pure products. The characterization data of the compounds **4(b–e)** are given in our earlier reports.[11–13]

5-Acetyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydopyrimidine (4a)

m.p. 208–209°C. IR (KBr): υ = 3300, 3200, 3120, 2995, 1625 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ(ppm) = 2.05 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 5.31 (s, 1H, H-4), 7.23 (s, 5H, H_{arom}), 9.50 (brs, 1H, NH), 10.02 (brs, 1H, NH). MS: (m/z %) = 246 (M^+, 75%), 203 (20%), 169 (43%), 44 (72%), 42 (100%), 39 (37%).

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