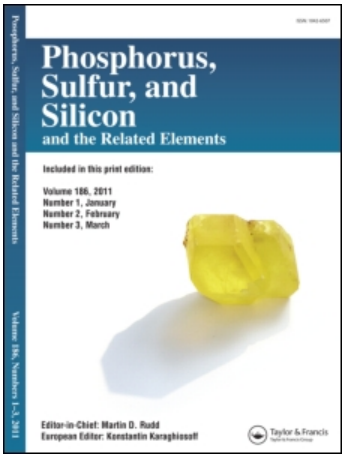

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Rostamizadeh, Shahnaz , Mollahoseini, Kambiz and Moghadasi, Samar(2006) 'A One-Pot Synthesis of 4,5-Disubstituted-1,2,4-triazole-3-thiones on Solid Support under Microwave Irradiation', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 8, 1839 — 1845
To link to this Article: DOI: 10.1080/10426500500542992
URL: http://dx.doi.org/10.1080/10426500500542992

Phosphorus, Sulfur, and Silicon, 181:1839–1845, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500542992

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A One-Pot Synthesis of 4,5-Disubstituted-1,2,4-triazole-3-thiones on Solid Support under Microwave Irradiation

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*4,5-Di-substituted-1,2,4-triazole-3-thiones (**4a–f**) have been prepared in one stage from the reaction of acid hydrazide **1** with alkyl or aryl isothiocyanate **2** in the presence of a KOH (10%) solution on the surface of silica gel as well as on the surface of montmorillonite K10 under microwave irradiation. These triazoles have also been prepared from the reaction of 4-substituted-1-aroyl thiosemicarbazides **3a–e**, with a KOH (10%) solution on the surface of silica gel under microwave irradiation.*

Keywords Acid hydrazide; isothiocyanate; microwave irradiation; solid support

INTRODUCTION

In recent years, there has been much attention in the use of surfaces of inorganic oxides, such as silica, alumina, etc., as a nonconventional reaction medium for the preparation of organic compounds.[1,2] Moreover, advantages of using microwave energy for conducting synthetic transformations, at highly accelerated rates, has become popular among organic chemists.[3,4] A combination of microwave heating together with using solid supports is now a very useful technique for conducting organic reactions.

Many compounds bearing five-membered heterocyclic rings in their structure have an extensive spectrum of pharmacological activities. Among them,1,2,4-triazole derivatives have attracted considerable interest and can be used as antifungal,[5,6] antibacterial,[7,18]

Received January 4, 2005; accepted November 1, 2005.
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TABLE I The Condesation of Acid Hydrazides 1 and Corresponding Aryl or Alkyl Isothiocyanates 2

Product	R_1	R_2
a	C_6H_5	C_6H_5
b	4-Cl-C_6H_4	C_6H_5
c	C_6H_5	CH_3
d	4-Cl-C_6H_4	CH_3
e	4-NO_2-C_6H_4	C_6H_5
f	CH_3	C_6H_5

antiinflammatory,[8] antiasthmatic,[9] antidepressant,[10] tuberculotherapeutic,[11] hypoglycemic,[12] and diuretic[13] activities.

RESULTS AND DISCUSSION

In the twenty-first century, for which time is an important aspect to all of us, finding methods that make longer reactions easy is very important. In this research, we take advantage of microwave heating together with using mineral solid supports, such as silica gel, alumina, etc., to prevent the formation of byproducts, bring about a simple work-up, and therefore shorten the reaction time.

1,2,4-Triazole-3-thiones have been prepared from the reaction of thiosemicarbazide with acyl halides and a subsequent cyclization of the intermediate acylthiosemicarbazides in basic media.[14–17,10] They also have been prepared from the reaction of acid hydrazides and isothiocyanates.[5,18–22] A formation of these compounds from the reaction of acid hydrazides with carbon disulfide and hydrazine hydrate was also reported in the literature.[8c] The reaction of aroyl isothiocyanates with hydrazine derivatives has also led to the formation of these types of compounds.[23,24,10] A thionation of 1,2,4-triazole-3-ones is another synthetic route to these compounds.[25]

A continuation of our work on the synthesis of 1,2,4-triazoles,[26] and also the considerable biological activities of these useful triazoles, prompted us to synthesize them via a very simple method.

In the present work, 3H-1,2,4-triazole-3-thiones-2,4-dihydro-4-phenyl(methyl)-5-(4-substituted phenyl or methyl) have been prepared by two methods (Scheme 1, Table 1). In the first one (Method A), we first prepared 4-substituted-1-aroyl thiosemicarbazides **3a–f** from the reaction of acidhydrazides **1** and phenyl isothiocyanates **2** on the surface of silica gel under microwave irradiation (Table II). A subsequent

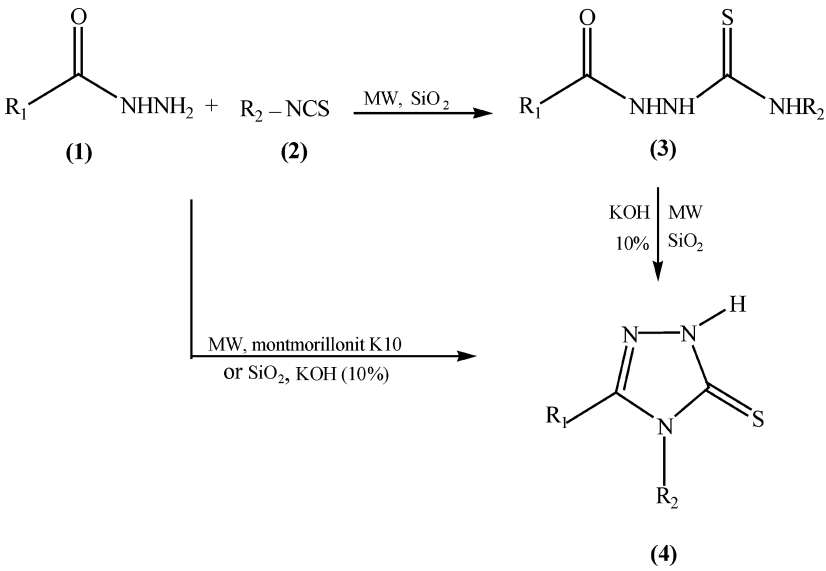
TABLE II The Preparation of Intermediates 3a–f

Product	Time (min)	Power (W)	Yield (%)
3a	10	750	60
3b	8	750	66
3c	8	750	70
3d	8	750	70
3e	8	750	67
3f	8	750	68

cyclization of these intermediates with a 10% KOH solution on the surface of silica gel under microwave irradiation resulted in the formation of the triazoles **4a–f** (Table III). In this method, only the intermediate 1-benzoyl-4-phenyl-thiosemicarbazide **3a** was identified, and for the rest, **3b–f**, only the final products 1,2,4-triazole-3-thiones **4a–f** were characterized by a comparison of their spectral and physical data with those of known samples. In Method B, it was then decided to repeat the reaction by mixing all the starting materials in one stage as a one-pot procedure. In this method for the preparation of 1,2,4-triazole-3-thiones **4a–f**, an optimization of the reaction conditions was carried out for the preparation of compound **4a**. (a) The mixture of benzhydrazide **1a**, phenylisothiocyanate **2a**, and KOH 10% was first heated at 130°C under reflux condition. After refluxing the mixture for 9 h, the product **4a** obtained in a low yield. (b) The same reaction was also carried out in the presence of silica gel. In this case, the reaction had gone to completion after 3 h without any significant change in the yield of product **4a**. (c) It was then decided to do the same experiment on the surface of silica gel under microwave irradiation. In this experiment, the product **4a** obtained in an 82% yield after 8 min. (d) When we used montmorillonit K10 instead of silica gel, the same product was obtained in an 86% yield after 6 min without

TABLE III The Yield and Physical Characteristics of 4,5-Substituted-1,2,4-triazole-3-thiones on the Surface of Silica Gel (Method A)

Product	Time (min)	Power (W)	Yield (%)	M.P. (°C)	Lit. M.P. (°C)	Ref.
4a	8	750	82	280–282	277–278	13
4b	6	750	80	271–272	272–273	27
4c	6	750	70	166	164–166	10
4d	6	750	75	209–210	210–212	10
4e	6	750	85	268–269	270–271	17
4f	8	750	70	214–215	215	28



SCHEME 1

any significant change in the chemical yield. Repetition of this experiment on the surface of clayfen, neutral, and basic alumina, resulted in the formation of more than one product. It should be noted that different irradiation power was also studied in which 750 W was the best condition.

Therefore, the triazoles-3-thiones **4a–f** were prepared from the reaction of acidhydrazide **1**, phenyl isothiocyanates **2**, and 10% KOH solution, on the surface of silica gel as well as on the surface of montmorillonit K10, under microwave irradiation (Scheme 1, Table IV).

TABLE IV The Yield and Physical Characteristics of 4,5-Substituted-1,2,4-triazole-3-thiones on the Surface of Silica Gel and Montmorillonite at 750 W (Method B)

	Time (min)		Yield (%)				
Product	SiO_2	K10	SiO_2	K10	M.P. (°C)	Lit. M.P. (°C)	Ref.
4a	8	6	85	86	280–282	277–278	13
4b	8	4	88	87	271–272	272–273	27
4c	10	6	78	81	166	164–166	10
4d	10	6	75	78	209–210	210–212	10
4e	6	4	90	88	268–269	270–271	17
4f	8	8	77	72	214–215	215	28

Thus, it seems that Method B, the one-pot procedure, provided an easy route to these types of triazoles without isolating the intermediates **3a**–**f**, in comparison to Method A. Also, by performing the reaction on the surface of montmorillonit K10, the reaction time was shortened without any significant change in chemical yields. A moderate yield, short reaction time, and easy work-up are advantages of this method in comparison to the procedures in the literature.

EXPERIMENTAL

All products are known compounds and were identified by comparison of their spectral and physical data with those of known samples. Melting points were taken on an Electrothermal 9100 aparatus. IR spectra were recorded with Shimadzu IR-480 spectrometer (KBr). The 1H NMR spectra were determined in $CDCl_3$ on a Bruker DRX-500 Avance (500 MHz). Microwave irradiation was carried out using a domestic microwave oven (Moulinex 2735A). Acid hydrazides were obtained according to the literature[29] by treating the corresponding esters with hydrazine in ethanol under microwave irradiation.

The General Procedure for the Synthesis of 1-Aroyl-4-substituted Thiosemicarbazide (3a–e)

A mixture of methyl or phenyl isothiocyanates (1.5 mmol), acid hydrazides (1 mmol), and SiO_2 (2 g) was well ground in a mortar and then subjected to microwave irradiation in an open Pyrex beaker at an appropriate power and time (Table II). The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was extracted with ethyl acetate (250 mL). The extracts were then combined, washed with water, and dried over $MgSO_4$. An evaporation of the solvent under vacuo gave the corresponding 1-aroyl-4-substituted thiosemicarbazides.

The General Procedure for the Synthesis of 3H-1,2,4-Triazole-3-thiones-2,4-dihydro-4-phenyl(methyl)-5-(4-substituted Phenyl or Methyl) (Method A)

A mixture of 1-aroyl-4-substituted thiosemicarbazides (2 mmol), KOH (10%) (2–3 mL), and SiO_2 (2 gr), was well ground in a mortar and then subjected to microwave irradiation in an open Pyrex beaker at an appropriate power and time (Table III). The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was extracted with ethyl acetate (250 mL); the extracts were then

combined, washed with water, and dried over $MgSO_4$. An evaporation of the solvent under vacuo gave the corresponding 4,5-di-substituted-1,2,4-triazole-3-thiones. The products were further purified by recrystallization from ethaol.

The General Procedure for the Synthesis of 3H-1,2,4-Triazole-3-thiones-2,4-dihydro-4-phenyl(methyl)-5-(4-substituted Phenyl or Methyl (Method B)

A mixture of methyl or phenyl isothiocyanates (1.5 mmol), acid hydrazides (1 mmol), KOH (10%) (2–3 mL), montmorillonit K10, or silica gel (2 g) was well ground in a mortar and then subjected to microwave irradiation in an open Pyrex beaker at an appropriate power and time (Table IV). The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was extracted with ethyl acetate (250 mL); the extracts were then combined, washed with water, and dried over $MgSO_4$. An evaporation of the solvent under vacuo gave the corresponding 4,5-di-substituted-1,2,4-triazole-3-thiones. The products were further purified by recrystallization from ethanol.

In conclusion, we have developed the one-pot synthesis of 4,5-di-substituted-1,2,4-triazole-3-thiones to demonstrate once more that a great simplification can be achieved by carrying out organic reactions both on solid support and by exposing them to microwave irradiations.

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