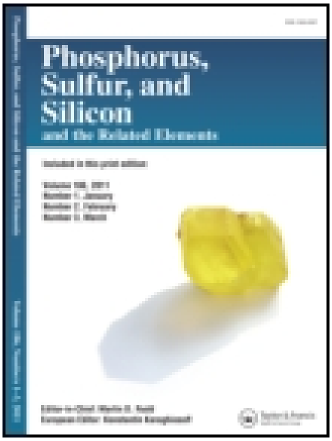

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The Microwave-Assisted Dehydrative Cyclization of Thiosemicarbazides Forming Substituted 1,2,4-Triazoles

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The Microwave-Assisted Dehydrative Cyclization of Thiosemicarbazides Forming Substituted 1,2,4-Triazoles

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Different types of 4,5-disubstituted 1,2,4-triazole-3-thiones were prepared by microwave irradiation as well as by a classical method. The beneficial effect of microwave irradiation on the dehydrative cyclization of thiosemicarbazides in different reaction media is described. Our results show that the effect of microwave irradiation on the reaction studied was the shortening of reaction times (from 2–9 h to 2–4 min) and a minor decrease (1–4%) in yields. The structure of the new compounds was established by FTIR, MS, and ^1H NMR spectral data.

Keywords Cyclization; microwave; thiosemicarbazides

INTRODUCTION

Substituted 1,2,4-triazoles are of interest because of their industry application[1] and biological activity, such as bactericidal,[2] and antiinflammatory,[3] and antiviruse activity.[4] The 1,2,4-triazole ring is obtained either by the synthesis from acyclic compounds or by the transformation of other cyclic systems. A number of methods for the synthesis of substituted 1,2,4-triazole are present in the literature.[5,6] The formation of this heterocycle can be the main reaction with semicarbazides or thiosemicarbazides, which are used extensively in the preparation of the triazolinones and triazolinethiones in an alkaline medium. However, the majority of these methods requires a long time for a completion of the reaction. The development of simple and efficient methods of synthesis of new analogues of 1,2,4-triazole compounds from readily synthesized starting material has become an important problem in our laboratory in these years. Recently, we have described the preparation of some new substituted 1,2,4-triazoles in good to moderate yields by

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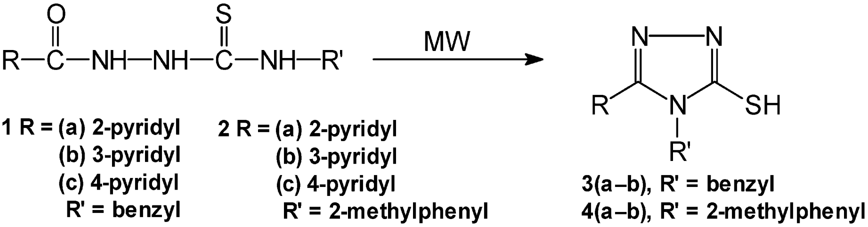
a classical method of dehydrative cyclization of the thiosemicarbazides in an alkaline madium.[7]

In the last few years, there has been an interest in the use of microwave heating in organic synthesis.[8–10] The use of such unconventional reaction conditions reveals several features, like a short reaction time compared to conventional heating, an ease of work-up after the reaction, a reduction in the usual thermal degradation, and better selectivity.[11] A reaction under "dry conditions" (i.e., the absence of a solvent, on a solid support with or without catalyst) was originally developed in the late 1980s.[12] Synthesis without solvents under microwave irradiation offers several advantages[13] because solvent are often expensive, toxic, difficult to remove, and are environmental polluting agents. The absence of a solvent reduces the risk of explosions when the reaction takes place in a closed vessel in an oven.

Now we describe here the synthesis of some 4,5-disubstituted 1,2,4-triazoles by the reaction of thiosemicarbazide in a few drops of ethanol in the presence of sodium hydroxide using microwave irradiation. For comparison of the reaction rate and the yield of the reaction, these reactions were carried out with alumina or silica gel instead of sodium hydroxide as base (Scheme 1).



SCHEME 1

RESULTS AND DISCUSSION

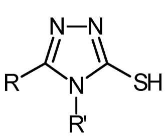
The aim of this article is to show that under microwave irradiation the intramolecular dehydrative cyclization of substituted thiosemicarbazides can be successfully applied to the synthesis of a number of substituted 1,2,4-triazoles. It is reported as a very simple, rapid, and general procedure in the presence of a base under solvent-free conditions. The time required favorably is less than those for traditional heating. The reaction is usually completed within 2–4 min and gives good to moderate yields. No product was obtained when we did not use any basic support. In the absence of ethanol, the yield of the reaction was low (Table I). The microwave-assisted synthesis of 4,5-disubstituted

TABLE I Physical Data for Compounds 4,5(a–c) Prepared by a Microwave Irradiation in a Different Base

Compounds	Base	Temp.	Time (min)	Power (W)	M.P. (°C)	Yield %
3a	Silica gel	250	5	900	182–184	32
3b	Silica gel	250	5	450	173–175	23
3c	Silica gel	250	5	900	209	25
4a	Silica gel	250	5	150	219	25
4b	Silica gel	250	5	900	234–236	25
4c	Silica gel	180	5	900	279	29
3a	Alumina	250	5	900	185	32.5
3b	Alumina	250	5	450	172–174	26
3c	Alumina	250	5	900	209–211	31
4a	Alumina	250	5	450	218–220	32
4b	Alumina	250	5	900	235	31
4c	Alumina	180	5	900	270.5	25
3a	NaOH	250	2	450	182–184	85
3b	NaOH	250	3	450	176	75
3c	NaOH	250	3	450	210	75
4a	NaOH	250	3	300	219–220	72
4b	NaOH	250	4	300	231	95
4c	NaOH	180	4	300	273	86

1,2,4-triazoles in the presence of sodium hydroxide instead of silica gel or alumina and a few drops of ethanol (10 drops) improved the yields of the products 2–3 times. Moreover, the work-up procedure was simply reduced to the acidification of the product in an appropriate solvent and filtration. The results from the experiments are shown in Tables I and II. In Table III, yields of the cyclization under different conditions

TABLE II Physical Data of Compounds 3,4(a–c) Preparation by a Classical Condition



			Reflux (h)		Reported	
Compounds	R	R′	Time	M.P. (°C)	M.P. (°C)	Yield, %
3a	2-Pyridyl	Benzyl	2	187–188	184.5[14]	84
3b	3-Pyridyl	Benzyl	9	175	175.5[14]	76
3c	4-Pyridyl	Benzyl	8	212	212.5[14]	98
4a	2-Pyridyl	2-Methylphenyl	4	219	—	83
4b	3-Pyridyl	2-Methylphenyl	9	231.5	—	76.4
4c	4-Pyridyl	2-Methylphenyl	7	273–274	—	89

TABLE III The Yields of 4,5-Disubstituted 1,2,4-Triazoles 3–4(a–c)

Compounds Reaction Condition	**3a**	**4a**	**3b**	**4b**	**3c**	**4c**
Traditional method	84	81	76	76	98	89
Microwave/NaOH	85	77	75	72	95	86
Microwave/Silica gel	32	25	23	25	25	29
Microwave/Alumina	33	32	26	31	81	25
Microwave/Silica gel/2–5 drops of ethanol	32	25	23	25	25	29
Microwave/Alumina/2–5 drops of ethanol	33	32	26	31	81	25

are compared. It is revealed from the table that the best conditions for cyclization under microwave irradiation were obtained when sodium hydroxide was used as a base and the reaction was carried out in presence of ethanol. All of the synthesized compounds were characterized by their melting points and FTIR, ^{1}H NMR, and mass spectroscopy.

EXPERIMENTAL

Melting points were determined using an electerothermal melting point apparatus. Fourier transformer infrared spectra were recorded on a Galaxy series FTIR 5000 spectrophotometer (KBr). ^{1}H NMR spectra were recorded on a Bruker 500 MHz instrument. The EIMS was recorded on a MAT-112-s-machine.

General Procedure

Method 1. Thiosemicarbazides **1–2(a–c)** (0.01 mol) were added to 80–180 mL of 4 N sodium hydroxide solution. The reaction mixture was refluxed and was allowed to cool to r.t. It was filtered, and the filtrate was acidified with 4 N hydrochloric acid. The solid was removed by filtration, washed with water, and recrystallized (ethanol/water 70:30).

Method 2. Thiosemicarbazides **1–2a–c** (1.6×10^{-4} mol) was mixed with an inorganic solid support (sodium hydroxide, silica gel, or alumina) (0.1 g). The mixture was homogenized and then was placed into a quartz tube and irradiated in a microwave oven (Samsung microwave oven CE 375 BF) for the time mentioned in Table I. After the mixture was cooled to r.t. water was added, and the mixture was filtered. The filtrate was acidified with 2 N hydrochloric acid. The precipitate was removed by filtration, washed with cool water, dried, and recrystallaized (ethanol:water 70:30). The physical data and yields of the products are tabulated in Table I.

Method 3. Thiosemicarbazides **1–2a–c** (1.6×10^{-4} mol) was mixed with inorganic solid support (sodium hydroxide, silica gel, or alumina) (0.1 g). Ethanol (2–5 drops) was added, and the mixture was homogenized and placed into a quartz tube. The previously discussed procedures were then followed.

3a: IR (KBr): $\upsilon_{\max}$ 3078–3028 (Ar-H), 2927 (C—H), 2768 (N—CH), 2588 (SH), 1585, 1276 (C=C, C=N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) 4.71 (s, 2H, CH$_2$), 4.72 (s, 0.6H, SH), 7.21 (s, 1H, Ar-H), 7.28–7.31 (d, 3H, Ar-H), 7.62–7.65 (t, 1H, Ar-H), 8.00–8.03 (t, 1H, Ar-H), 8.05–8.07 (d, 1H, Ar-H), 8.59 (s, 1H, Ar-H), 8.69 (s, 1H, Ar-H), 10.6 (s, 0.4H, NH).

3b: IR(KBr): $\upsilon_{\max}$ 3125–3016 (Ar-H), 2885 (C—H), 2727 (N—CH), 2584 (SH), 1609, 1276 (C=C, C=N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) 4.2–4.3 (d, 2H, CH$_2$), 5.1 (s, 0.6H, SH), 7.10–7.11 (d, 2H, Ar-H), 7.12–7.16 (d, 1H, Ar-H), 7.18–7.20 (d, 1H, Ar-H), 7.21(s, 1H, Ar-H), 7.24–7.25 (d, 1H, Ar-H), 7.27–7.29 (d, 1H, Ar-H), 7.30–7.33 (d, 1H, Ar-H), 7.34–7.36 (d, 1H, Ar-H), 12.8 (s, 0.4H, NH).

3c: IR(KBr): $\upsilon_{\max}$ 3254–3011 (Ar-H), 2866 (N—CH), 2651 (SH), 1651, 1388 (C=C, C=N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$), 5.4 (s, 2H, CH$_2$), 7.03–7.05 (d, 2H, Ar-H), 7.24–7.27 (t, 3H, Ar-H), 7.55–7.56 (d, 2H, Ar-H), 8.6–8.67 (d, 2H, Ar-H), 14.39 (s, 1H, NH); mass spectrum (70 ev): m/z (%) 268 (100), 267 (50), 235 (60), 169 (2), 149 (20), 131 (4), 105 (20), 91 (28), 78 (22).

4a: IR(KBr): $\upsilon_{\max}$ 3051–3028 (Ar-H), 2964 (C—H), 2859 (N—CH), 2565 (SH), 1604–1396 (C=C, C=N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) 1.9–2.2 (t, 3H, CH$_3$), 5.4 (s, 0.7 H, SH), 7.03–7.04 (d, 2H, Ar-H), 7.22–7.24 (d, 2H, Ar-H), 7.23–7.26 (d, 1H, Ar-H), 7.55–7.56 (d, 2H, Ar-H), 8.66–8.67 (d, 1H, Ar-H), 14.39 (s, 1H, NH).

4b: IR(KBr): $\upsilon_{\max}$ 3274–3058 (Ar-H), 2920 (C—H), 2859 (N—CH), 2499 (SH), 1654, 1354 (C=C, C=N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) 2.5 (s, 3H, CH$_3$), 5.8 (s, 0.65H, SH), 7.13–7.18 (q, 2H, Ar-H), 7.2–7.23 (t, 2H, Ar-H), 7.4–7.52 (q, 1H, Ar-H), 7.93–7.94 (d, 2H, Ar-H), 8.65–8.66 (d, 1H, Ar-H), 14.2 (s, 0.35H, NH). ^{13}C NMR (500 MHz, DMSO-d$_6$) 150, 149, 148, 143, 141, 139, 138, 132, 131, 128, 126, 123, 121, 16.

4c: IR(KBr): $\upsilon_{\max}$ 3174–3120 (Ar-H), 2920 (C—H), 2788 (N—CH), 2482 (SH), 1585, 1242 (C=C, C=N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) 2.3 (s, 3H, CH$_3$), 5.7 (s, 0.8H, SH), 6.55 (s, 2H, Ar-H), 7.14–7.15 (d, 2H, Ar-H), 7.41 (s, 2H, Ar-H), 8.46–8.48 (d, 2H, Ar-H), 9.45 (s, 0.2H, NH); mass spectrum (70 ev): m/z (%) 268 (100), 267 (90), 235 (100), 209 (10), 169 (40), 149 (10), 131 (65), 105 (10), 109 (40), 91 (22), 77 (22).

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