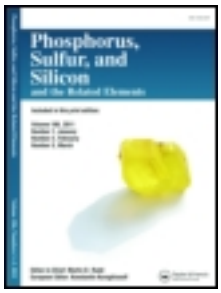

Phosphorus, Sulfur, and Silicon and the Related Elements

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Microwave Assisted Synthesis of 6-Aryl-3-substituted-5H-[1,2,4]-triazolo[4,3-b][1,2,4]triazoles: A Case for a Comparative Study

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MICROWAVE ASSISTED SYNTHESIS OF 6-ARYL-3-SUBSTITUTED-5H-[1,2,4]-TRIAZOLO[4,3-b][1,2,4]TRIAZOLES: A CASE FOR A COMPARATIVE STUDY

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A simple and fast synthesis of 6-aryl-3-substituted-5H-[1,2,4]-triazolo[4,3-b][1,2,4]triazoles ***4*** *in high yields has been developed by microwave assisted heterocyclization of N-(3-methylthio-5-substituted-4H-1,2,4-triazol-4-yl)benzenecarboximidamides* ***3****. The effectiveness of the microwave irradiation and conventional heating for the formation of compounds* ***4*** *has been investigated.*

Keywords: 1,2,4-Triazolo[4,3-b][1,2,4]triazoles; conventional heating; heterocyclization; methyl iodide; microwave irradiation; photographic coupler

1,2,4-Triazolo[4,3-b][1,2,4]triazoles are very interesting compounds with diverse properties. These compounds have been considered as antifungal[1] and photographic couplers.[2–4] The routes to 1,2,4-triazolo-[4,3-b][1,2,4]triazoles mainly involve heterocyclization of suitably substituted-1,2,4-triazoles with appropriate reagents such as acid chlorides, hydroximoyl chloride, halonitriles, isocyanates, carbon disulfide, and diarylcarbodiimides in suitable solvents (see for example references[5–10]). A literature survey disclosed that aryl nitriles have been relatively little explored for the synthesis of 1,2,4-triazolo[4,3-b][1,2,4]triazoles and there are only two references cited in the literature dealing with this matter.[11,12] Thus, it seemed of interest to examine the reaction of aryl nitriles with substituted 1,2,4-triazoles as a

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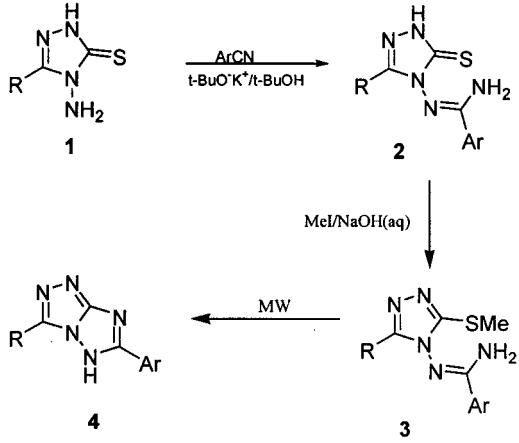
convenient procedure for the synthesis of some 1,2,4-triazolo[4,3-b][1,2,4]triazoles **4**. In the present work we have investigated the reaction of aryl halides with N-(3-methylthio-5-substituted-4H-1,2,4-triazol-4-yl)benzenecarboximidamides **3** for the synthesis of some 6-aryl-3-substituted-5H-1,2,4-triazolo[4,3-b][1,2,4]triazoles **4** using microwave irradiation.

Microwave irradiation is a nonconventional energy source whose popularity and synthetic utility in organic chemistry has increased considerably in recent years.[13–16] The rapid heating induced by such radiation avoids harsh classical conditions and the decomposition of the reagents, leading to the formation of products under mild reaction conditions, thus increasing the yield.

RESULTS AND DISCUSSIONS

Treatment of 4-amino-5-substituted-4H-[1,2,4]triazole-3-thiones **1** with aromatic nitriles in the presence of potassium t-butoxide in t-butanol under reflux gave products identified as N-(3-substituted-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4yl)benzenecarboximidamide **2** (Scheme 1 and Table I). Furthermore, methylation of compounds **2** with methyl iodide in the presence of sodium hydroxide at room temperature



a:R=Me, Ar=C_6H_5
b:R=Me, Ar=4-Cl-C_6H_4
c:R=Me, Ar=4-Br-C_6H_4
d:R=Me, Ar=4-Me-C_6H_4
e:R=H, Ar=C_6H_5

SCHEME 1

TABLE I N-(3-Substituted-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)benzenecarboximidamide (**2a–e**) and N-(3-methylthio-5-substituted-4H-[1,2,4]triazol-4-yl)benzenecarboximidamide (**3a–e**)

Entry	Reaction time (hours)	Yield (%)	m.p. (0°C)	C calcd. (found)	H calcd. (found)	N calcd. (found)	Spectral data
2a	6	88	284–286	51.48 (51.37)	4.75 (4.66)	30.02 (30.15)	^{1}H NMR: δ (d_6-DMSO), 2.13 (s, 3H, Me), 7.2 (s, 2H, NH_2), 7.3–8.1 (m, 5H, Ph), 13.14 (s, 1H, NH); IR (KBr disc), ν, NH_2, 3300–3400 cm^{-1}; C=N, 1645 cm^{-1}; MS m/z, M^+ 233
2b	4	82	298–300	44.86 (44.99)	3.76 (3.62)	26.16 (26.04)	^{1}H NMR: δ (d_6-DMSO), 2.10 (s, 3H, Me), 7.41 (s, 2H, NH_2), 7.5–8.1 (m, 4H, *P*-Cl-C_6H_4), 13.25 (broad, 1H, NH); IR (KBr disc), ν, NH_2, 3300–3400 cm^{-1}; C=N, 1643 cm^{-1}; MS m/z, M^+ 267.5
2c	6	75	286–288	38.47 (38.31)	3.22 (3.14)	22.43 (22.54)	^{1}H NMR: δ (d_6-DMSO), 2.09 (s, 3H, Me), 7.39 (s, 2H, NH_2), 7.5–8.0 (m, 4H, *P*-Br-C_6H_4), 13.25 (broad, 1H, NH); IR (KBr disc), ν, NH_2, 3300–3460 cm^{-1}; C=N, 1643 cm^{-1}; MS m/z, M^+ 312
2d	3	86	308–310	53.42 (53.29)	5.30 (5.43)	28.32 (28.21)	^{1}H NMR: δ (d_6-DMSO), 2.10 (s, 3H, Me), 2.37 (s, 3H, Me), 7.1–8.0 (m, 6H, NH_2 and aromatic ring), 13.20 (s, 1H, NH); IR (KBr disc), ν, NH_2, 3300–3450 cm^{-1}; C=N, 1644 cm^{-1}; MS m/z, M^+ 247
2e	6	78	230–232	49.30 (49.43)	4.14 (4.06)	31.94 (31.82)	^{1}H NMR: δ (d_6-DMSO), 7.1–8.0 (m, 7H, NH_2 and Ph), 8.30 (s, 1H, N=CH), 13.48 (broad, 1H, NH); IR (KBr disc), ν, NH_2, 3300–3400 cm^{-1}; C=N, 1641 cm^{-1}; MS m/z, M^+ 219
3a	0.5	81	255–257	53.42 (53.31)	5.30 (5.23)	28.32 (28.43)	^{1}H NMR: δ (d_6-DMSO), 2.17 (s, 3H, Me), 2.52 (s, 3H, S–Me), 7.30–8.0 (m, 7H, Ph and NH_2); IR (KBr disc), ν, NH_2, 3200–3350 cm^{-1}; C=N, 1665 cm^{-1}; MS m/z, M^+ 247

(Continued on next page)

TABLE I N-(3-Substituted-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)benzenecarboximidamide (**2a–e**) and N-(3-methylthio-5-substituted-4H-[1,2,4]triazol-4-yl)benzenecarboximidamide (**3a–e**) *(Continued)*

Entry	Reaction time (hours)	Yield (%)	m.p. (0°C)	C calcd. (found)	H calcd. (found)	N calcd. (found)	Spectral data
3b	0.5	85	237–239	46.89 (46.75)	4.29 (4.38)	24.85 (24.96)	^{1}H NMR: δ (d_6-DMSO), 2.16 (s, 3H, Me), 2.52 (s, 3H, S—Me), 7.3–8.1 (m, 6H, NH_2 and *P*-Cl-C_6H_4); IR (KBr disc), ν, NH_2, 3300–3400 cm^{-1}; C=N, 1656 cm^{-1}; MS m/z, M^+ 281.5
3c	0.5	71	232–234	40.50 (40.63)	3.71 (3.59)	21.47 (21.39)	^{1}H NMR: δ (d_6-DMSO), 2.16 (s, 3H, Me), 2.52 (s, 3H, S—Me), 7.3–8.0 (m, 6H, NH_2 and *P*-Br-C_6H_4); IR (KBr disc), ν, NH_2, 3300–3400 cm^{-1}; C=N, 1654 cm^{-1}; MS m/z, M^+ 326
3d	0.5	78	251–253	55.15 (55.22)	5.78 (5.84)	26.80 (26.69)	^{1}H NMR: δ (d_6-DMSO), 2.16 (s, 3H, Me), 2.37 (s, 3H, Me), 2.52 (s, 3H, S—Me), 7.15–7.95 (m, 6H, NH_2 and aromatic ring); IR (KBr disc), ν, NH_2, 3300–3400 cm^{-1}; C=N, 1656 cm^{-1}; MS m/z, M^+ 261
3e	0.5	74	228–230	51.48 (51.36)	4.75 (4.91)	30.02 (30.11)	^{1}H NMR: δ (d_6-DMSO), 2.57 (s, 3H, S—Me), 7.25–8.05 (m, 7H, Ph and NH_2), 8.47 (s, 1H, N=CH); IR (KBr disc), ν, NH_2, 3300–3400 cm^{-1}; C=N, 1654 cm^{-1}; MS m/z, M^+ 233

TABLE II Fast Heterocyclisation Reaction of N-(3-methylthio-5-substituted-4H-[1,2,4]triazol-4-yl)benzenecarboximidamides (**3a–e**) under Microwave Irradiation

Products	R	Ar	Yield (%)	m.p. °C	Lit[17]
4a	CH_3	C_6H_5	72	227–229	226–228
4b	CH_3	4-Cl-C_6H_4	77	260–262	263–264
4c	CH_3	4-Br-C_6H_4	58	276–278	—
4d	CH_3	4-Me-C_6H_4	68	237–239	238–240
4e	H	C_6H_5	56	215–216	216–218

afforded the corresponding N-(3-methylthio-5-substituted-4H-1,2,4-triazol-4-yl)benzenecarboximidamide **3**. The structures of the products were deduced from their spectra and elemental analysis (Table I). For example, the ^{1}H NMR spectrum of **3a** in d_6-DMSO shows two singlets at δ 2.17 ppm (3H, Me) and 2.52 ppm (3H, —SMe) and a multiplet at δ 7.30–8.0 ppm (7H, Ph, and NH_2). The IR spectrum of this compound shows two bands in the region 3350–3200 cm^{-1} due to the NH_2 group. The spectral data for compounds **3** are given in Table I.

When compounds **3** in a little amount of N,N-dimethylacetamide were subjected to microwave irradiation for the indicated time (Table III), the cyclic products **4** were obtained (Table II). The structure of the new product **4c** was established from its analytical and spectral data and for known compounds **4a**, **b**, **d**, and **e** by comparison with authentic samples.

It is noteworthy that reaction times required are longer in the absence of microwave irradiation. We investigated the effectiveness of the microwave irradiation and conventional heating for the formation of compounds **4a–e**. The results are summarized in Table III. It can be concluded that the synthesis of compounds **4a–e** under microwave irradiation were 36–72 times faster and the yields are higher than conventional heating methods. This ratio between the reaction time using

TABLE III Comparison of Time and Yields on the Formation of Compounds **4a–e** Using Microwave and Conventional Heating

	Conventional heating		Microwave heating			
Product	t/min (°C)	Yield (%)	Power/W	t/min	Yield (%)	t_c/t_{mw}
4a	360(120)	21	700	7	72	51
4b	360(110)	25	700	5	77	72
4c	360(130)	19	1000	10	58	36
4d	360(120)	23	700	10	68	36
4e	360(130)	14	1000	10	56	36

conventional heating and microwave irradiation (t_c/t_{mw}) shows the microwave heating effect.

In conclusion, we have developed a simple, efficient and fast practical method for one-pot conversion of N-(3-methylthio-5-substituted-4H-1,2,4-triazol-4-yl)benzencarboximidamides into 6-aryl-3-substituted-5H-1,2,4-triazolo[4,3-b][1,2,4]triazoles by applying microwave irradiation in solvent free conditions.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 Spectrometer. Mass spectra were obtained from Varian CH-7 instrument at 70 eV. Elemental analyses were performed by Tarbiat Modarres University, Tehran, Iran.

Compounds **4a**, **b**, **d**, **e** were known compounds and their physical data, IR, and NMR spectra were essentially identical with those of authentic samples.

N-(3-Substituted-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)benzenecarboximidamide 2a–e

Typical Procedure

A mixture of 4-amino-3-methyl-4H-[1,2,4]triazole-5-thione **1** (1.30 g, 0.01 mol), benzonitrile (1.23 g, 0.012 mol) and Potassium t-butoxide (2.24 g, 0.02 mol) in t-butanol (60 ml) was heated under reflux for 6 h. After the completion of the reaction, the precipitate was filtered off dissolved in water, and subsequently neutralized by 1N HCl. The crude product was collected and recrystallized from ethanol to give compounds **2a** in high yield (see Table I).

N-(3-Methylthio-5-substituted-4H-[1,2,4]triazol-4-yl)-benzenecarboximidamides 3a–e

Typical Procedure

To a stirred solution of the foregoing compound **2a** (1.17 g, 0.005 mol) in sodium hydroxide (0.28 g, 0.007 mol) and water (30 ml), methyl iodide (0.71 g, 0.005 mol) was gradually added. The stirring was continued for 0.5 h at room temperature. The crude product was filtered and recrystallized from acetonitrile to give compound **3a** in good yield (see Table I).

6-Aryl-3-substituted-5H-1,2,4-triazolo[4,3-b][1,2,4]-triazoles 4a–e

Typical Procedure

The foregoing compound **3a** (0.49 g, 0.002 mol) in a little amount of N,N-dimethylacetamide were subjected to microwave irradiation for 7 min. The crude product was recrystallized from benzene-ethanol to give compound **4a** in good yield (see Table III).

4c,6-(4-bromo-phenyl)-3-methyl-5H-[1,2,4]triazolo[4,3-b][1,2,4]triazole, Anal. Calcd for $C_{10}H_8BrN_5$:C, 43.19; H, 2.90; N, 25.18, Found: C, 43.08; H, 2.98; N, 25.09. ^{1}H NMR: δ (d_6-DMSO), 2.56 (s, 3H, Me), 7.6–8.2 (m, 4H, *p*-Br-C_6H_4), 13.4 (broad, 1H, NH); IR (KBr disc): ν, 3060, 2920, 1630 cm^{-1}; MS: m/z, M^+ 278.

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