Microwave Assisted Synthesis of Thiazolo[3,2-*b*][1,2,4]-triazoles Containing 1,8-Naphthyridine Moiety

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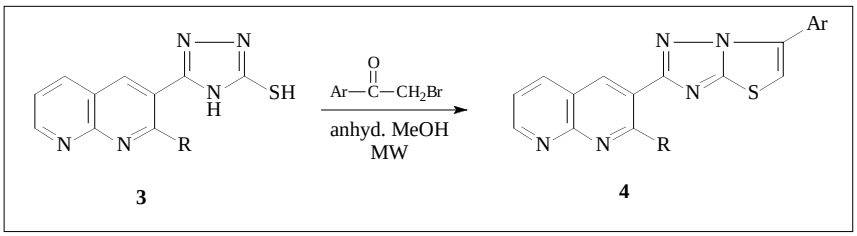

A simple and efficient protocol for the synthesis of 5-aryl-2-(2-substituted-1,8-naphthyridin-3-yl)-thiazolo[3,2-*b*][1,2,4]triazoles (**4**) is achieved by cyclocondensation of 3-(2-substituted-1,8-naphthyridin-3-yl)-1,2,4-triazoles (**3**) with α-halogenoketones in anhyd. methanol under microwave irradiation. The products are obtained in good yields and in a state of high purity.

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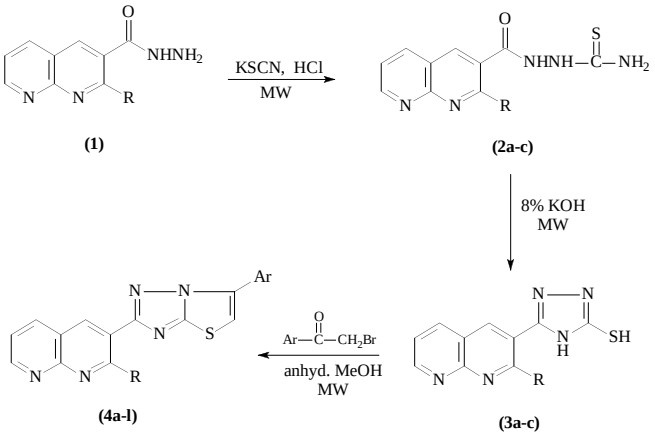
INTRODUCTION

1,8-Naphthyridine derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activity [1-4]. Various 1,2,4-triazoles [5-7] and thiazole derivatives [8,9] occupy an important place in medicinal chemistry as they show a variety of pharmacological and microbiological activities. Microwave (MW) activation as a non-conventional energy source has become a very popular and useful technology in organic chemistry [10-12]. Many reactions proceeded must faster under microwave irradiation and with higher yields compared to conventional heating. Microwave irradiation has also been applied to organic synthesis in open vessels using organic solvents such as methanol, ethanol, *N,N*-dimethylformamide (DMF), 1,2-dichloroethane (DCE), *o*-dichlorobenzene, *etc*. as energy transfer media which absorb microwave energy efficiently through dipole rotation. In view of this and in continuation of our interest in microwave-assisted organic transformations on 1,8-naphthyridine derivatives [13-17], we report herein, a convenient, practical and efficient method for the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles containing 1,8-naphthyridine moiety under microwave irradiation.

RESULTS AND DISCUSSION

The reaction of 2-substituted-1,8-naphthyridine-3-carboxylic acid hydrazides (**1**) with potassium thiocyanate in conc. HCl under microwave irradiation resulted in the formation of 1-(2-substituted-1,8-naphthyridine-3-carbonyl)-3-thiosemicarbazides (**2**), which on base catalyzed cyclization under microwave irradiation yielded the corresponding 3-(2-substituted-1,8-naphthyridin-3-yl)-5-mercapto-1,2,4-triazoles (**3**).

Scheme 1



Cyclocondensation of **3** with α-halogenoketones in anhyd. methanol under microwave irradiation furnished the respective 5-aryl-2-(2-substituted-1,8-naphthyridin-3-yl)thiazolo[3,2-*b*][1,2,4]triazoles (**4**). The reaction proceeds efficiently in good yields at ambient pressure within a few minutes. The transformation is facile, clean and efficient and is devoid of any by-products. The experimental procedure is very simple. Furthermore, it is to be noted that highly pure products were obtained using this simple procedure and in most cases no further purification was needed. Interestingly, this reaction proceeds only to a minor extent (5-8% in 2.5 – 5.0 min) when conducted under conventional conditions in an oil-bath preheated to 110°C (temperature measured at the end

Table 1

Physical and analytical data of 1-(2-substituted-1,8-naphthyridine-3-carbonyl)-3-thiosemicarbazides (**2**) and 3-(2-substituted-1,8-naphthyridin-3-yl)-5-mercapto-1,2,4-triazoles (**3**).

Compd	R	Reaction time (min)	M.P. (°C)	Yield (%)	Mol. formula	Elemental analysis Found / (Calcd)		
						C	H	N
2a	CH_3	3.0	252-254	92	$C_{11}H_{11}N_5OS$	50.74 (50.57)	4.25 (4.21)	26.89 (26.82)
2b	CF_3	3.5	240-242	90	$C_{11}H_8F_3N_5OS$	41.78 (41.90	2.59 (2.54)	22.30 (22.22)
2c	C_6H_5	4.5	230-231	88	$C_{16}H_{13}N_5OS$	59.62 (59.44)	4.07 (4.02)	21.60 (21.67)
3a	CH_3	3.0	>320	90	$C_{11}H_9N_5S$	54.50 (54.32)	3.74 (3.70)	28.89 (28.81)
3b	CF_3	4.0	300-302	89	$C_{11}H_6F_3N_5S$	44.59 (44.44)	2.08 (2.02)	23.57 (23.66)
3c	C_6H_5	5.0	306-308	92	$C_{16}H_{11}N_5S$	62.78 (62.95)	3.56 (3.61)	22.95 (22.87)

Table 2

Physical and analytical data of 5-aryl-2-(2-substituted-1,8-naphthyridin-3-yl)thiazolo[3,2-*b*][1,2,4]triazoles **4**.

Compd	R	Ar	Reaction time (min)	M.P. (°C)	Yield (%)	Mol. Formula	Microanalysis calculated [Found] %		
							C	H	N
4a	CH_3	C_6H_5	2.5	230-232	86	$C_{19}H_{13}N_5S$	66.62 (66.47)	3.83 (3.79)	20.47 (20.41)
4b	CH_3	*p*-ClC_6H_4	3.0	240-241	90	$C_{19}H_{12}ClN_5S$	60.58 (60.40	3.23 (3.18)	18.60 (18.54)
4c	CH_3	*p*-BrC_6H_4	3.5	250-252	88	$C_{19}H_{12}BrN_5S$	54.19 (54.03)	2.89 (2.84)	16.65 (16.58)
4d	CH_3	*p*-$C_6H_5C_6H_4$	4.5	140-143	89	$C_{25}H_{17}N_5S$	71.74 (71.60)	3.42 (3.47)	16.79 (16.71)
4e	CF_3	C_6H_5	3.0	160-162	85	$C_{19}H_{10}F_3N_5S$	57.59 (57.43)	2.56 (2.52)	17.68 (17.63)
4f	CF_3	*p*-ClC_6H_4	4.0	150-151	88	$C_{19}H_9ClF_3N_5S$	52.98 (52.84)	2.04 (2.09)	16.16 (16.22)
4g	CF_3	*p*-BrC_6H_4	3.5	180-182	85	$C_{19}H_9BrF_3N_5S$	47.75 (47.90)	1.85 (1.89)	14.79 (14.71)
4h	CF_3	*p*-$C_6H_5C_6H_4$	4.5	192-194	86	$C_{25}H_{14}F_3N_5S$	64.60 (64.42)	2.92 (2.96)	14.88 (14.80)
4i	C_6H_5	C_6H_5	3.5	140-141	84	$C_{24}H_{15}N_5S$	71.30 (71.11)	3.75 (3.70)	17.35 (17.28)
4j	C_6H_5	*p*-ClC_6H_4	4.0	180-183	87	$C_{24}H_{14}ClN_5S$	65.69 (65.53)	3.14 (3.19)	15.85 (15.93)
4k	C_6H_5	*p*-BrC_6H_4	4.5	200-202	86	$C_{24}H_{14}BrN_5S$	59.68 (59.50)	2.85 (2.89)	14.41 (14.46)
4l	C_6H_5	*p*-$C_6H_5C_6H_4$	5.0	124-125	88	$C_{30}H_{19}N_5S$	74.68 (74.84)	3.91 (3.95)	14.63 (14.55)

of exposure during microwave experiment) which confirms the rate increase during microwave heating.

The structural assignments of compounds **2-4** were based on their elemental analyses and spectral (IR and ^{1}H NMR) data. To the best of our knowledge this is the first report on rapid synthesis of thiazolo[3,2-*b*][1,2,4]triazoles under microwave irradiation.

In conclusion, we have demonstrated a convenient and highly efficient protocol for the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles under microwave irradiation. High yield, short reaction time, simple operation and pure products are advantages of this procedure.

EXPERIMENTAL

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr) (ν_{max}: cm^{-1}) were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ,

ppm) using TMS as internal standard. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyser. Irradiation was carried out in a domestic microwave oven (LG MG 556 P, 2450 MHz). The starting compounds **1** were prepared according to the reported procedures [18-21].

General procedure for the synthesis of 1-(2-substituted-1,8-naphthyridine-3-carbonyl)-3-thiosemicarbazides (2). A mixture of **1** (20.0 mmol), potassium thiocyanate (20.0 mmol), conc. HCl (10 ml) and water (30 ml) was subjected to microwave irradiation at 400 watts intermittently at 30 sec intervals for the specified time (Table 1). On completion of the reaction, as monitored by TLC, the reaction mixture was cooled, the solid thus obtained was filtered and washed with water and recrystallized from methanol to give **2**.

2a: IR: 3320, 3287, 3110 ($NHNHCSNH_2$), 1686 (CONH), 1601 (C=N), 1136 cm^{-1} (C=S).

2b: IR: 3509, 3274, 3160 ($NHNHCSNH_2$), 1712 (CONH), 1626 (C=N), 1130 cm^{-1} (C=S).

2c: IR: 3474, 3296, 3088 ($NHNHCSNH_2$), 1680 (CONH), 1600 (C=N), 1138 cm^{-1} (C=S).

General procedure for the synthesis of 3-(2-substituted-1,8-naphthyridin-3-yl)-5-mercapto-1,2,4-traizoles (3). Compound **2** (20.0 mmol) in 8% KOH (50 ml) was exposed to microwaves at 400 watts intermittently at 30 sec intervals for the specified time (Table 1). On completion of reaction, as monitored by TLC, the reaction mixture was cooled to room temperature, diluted with cold water and neutralized with dilute acetic acid. The solid thus obtained was collected by filtration, washed with water and recrystallized from methanol to give **3**.

3a: IR: 3385 (NH), 2574 (SH), 1618 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.03 (s, 3H, CH_3), 8.62 (s, 1H, C_4'-H), 8.25 (m, 1H, C_5'-H), 7.54 (m, C_6'-H), 9.14 (m, 1H, C_7'-H), 13.40 (brs, 1H, SH), 13.72 (brs, 1H, NH).

3b: IR: 3347 (NH), 2553 (SH), 1615 cm^{-1} (C=N)

3c: IR: 3325 (NH), 2565 (SH), 1610 cm^{-1} (C=N)

General procedure for the synthesis of 5-aryl-2-(2-substituted-1,8-naphthyridin-3-yl)-thiazolo[3,2-*b*][1,2,4]triazoles (4). A mixture of **3** (20.0 mmol), α-halogenoketone (20.0 mmol) and anhyd. methanol (40 ml) was subjected to microwave irradiation at 200 watts intermittently at 30 sec intervals for specified time (Table 2). On completion of reaction, as monitored by TLC, the reaction mixture was cooled and treated with chilled water. The precipitate thus obtained was collected by filtration, washed with water and recrystallized from ethanol to afford **4**.

4a: IR: 1608 (C=C), 1595 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.04 (s, 3H, CH_3), 8.20 (m, 1H, C_5'-H), 8.09 (m, 2H, C_4'-H, C_6'-H), 9.18 (m, 1H, C_7'-H), 7.40 – 7.62 (m, 6H, C_6-H, 5Ar-H).

4b: IR: 1605 (C=N), 1591 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.01 (s, 3H, CH_3), 8.26 (m, 1H, C_5'-H), 8.00 (m, 2H, C_4'-H, C_6'-H), 9.08 (m, 1H, C_7'-H), 7.42 – 7.63 (m, 5H, C_6-H, 4Ar-H).

4c: IR: 1610 (C=C), 1586 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.04 (s, 3H, CH_3), 8.26 (m, 1H, C_5'-H), 7.99 (m, 2H, C_4'-H, C_6'-H), 9.09 (m, C_7'-H), 7.55 – 7.70 (m, 5H, C_6-H, 4Ar-H).

4d: IR; 1602 (C=C), 1592 cm^{-1} (C=N), ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.02 (s, 3H, CH_3), 8.12 (m, 1H, C_5'-H), 7.71 (m, 2H, C_4'-H, C_6'-H), 9.09 (m, 1H, C_7'-H), 7.45 – 7.67 (m, 10H, C_6-H, 9Ar-H).

4e: IR: 1609 (C=C), 1598 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.74 (m, 1H, C_5'-H), 8.06 (m, 2H, C_4'-H, C_6'-H), 9.28 (m, 1H, C_7'-H), 7.36–7.68 (m, 6H, C_6-H, 5Ar-H).

4f: IR: 1603 (C=C), 1589 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.45 (m, 1H, C_5'-H), 8.04 (m, 2H, C_4'-H, C_6'-H), 9.28 (m, 1H, C_7'-H), 7.48 – 7.76 (m, 5H, C_6-H, 4Ar-H).

4g: IR: 1605 (C=C), 1591 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.42 (m, 1H, C_5'-H), 7.95 (m, 2H, C_4'-H, C_6'-H), 9.28 (m, 1H, C_7'-H), 7.44–7.74 (m, 5H, C_6-H, 4Ar-H).

4h: IR; 1608 (C=C), 1595 cm^{-1} (C=N); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.44 (m, 1H, C_5'-H), 8.02 (m, 2H, C_4'-H, C_6'-H), 9.15 (m, 1H, C_7'-H), 7.46–7.83 (m, 10H, C_6-H, 9Ar-H).

4i: IR: 1605 (C=C), 1592 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.24 (m, 1H, C_5'-H), 8.00 (m, 2H, C_4'-H, C_6'-H), 9.05 (m, 1H, C_7'-H), 7.38 – 7.61 (m, 6H, C_6-H, 5Ar-H).

4j: IR: 1610 (C=C), 1589 cm^{-1} (C=N): ^1H NMR ($CDCl_3$): δ 8.25 (m, 1H, C_5'-H), 7.95 (m, 2H, C_4'-H, C_6'-H), 9.06 (m, 1H, C_7'-H), 7.38 – 7.55 (m, 5H, C_6-H, 4Ar-H).

4k: IR: 1610 (C=C), 1585 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.27 (m, C_5'-H), 7.89 (m, 2H, C_4'-H, C_6'-H), 9.12 (m, 1H, C_7'-H), 7.42 – 7.65 (m, 5H, C_6-H, 4Ar-H).

4l: IR: 1605 (C=C), 1590 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 8.32 (m, 1H, C_5'-H), 8.08 (m, 2H, C_4'-H, C_6'-H), 9.10 (m, 1H, C_7'-H), 7.44 – 7.84 (m, 10H, C_6-H, 9Ar-H).

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