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Microwave-Assisted and Conventional Synthesis of Benzothieno [3,2-e] [1,3,4] triazolo[4,3-c]pyrimidines: A Comparative Study

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ABSTRACT. Benzothieno[2,3-*d*]pyrimidines (**2**,**3**,**4**) and benzothieno[3,2-e][1,3,4]triazolo[4,3-c] pyrimidines (**5a–c**) were synthesized from the precursor 2-amino-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile 1 by employing the conventional method as well as the microwave irradiation technique. The precursor 2-amino-3-cyanothiophene analogue 1 was synthesized by employing the well-known Gewald reaction. In the present work it has been found that the microwave supported syntheses are more efficient than the conventional classical heating methods. The structures of all the compounds were ascertained by spectral and analytical data.

Key words: Conventional method, Microwave irradiation, Thienopyrimidine, Triazolothienopyrimidine

INTRODUCTION

Heterocyclic compounds containing the thienopyrimidine nucleus have been prepared by several scientists because of their diverse biological properties.[1–5] For instance, a number of thienopyrimidines are known to possess antimalerial, antiallergic, hypocholesterolemic, analgesic, anti-inflammatory, diuretic, CNS depressant and antiviral activities.[6,7] In view of these fascinating and encouraging results and in continuation of our work on biologically active nitrogen and sulfur heterocycles,[8] we have synthesized some thienopyrimidine and triazolothienopyrimidine derivatives. Addition to the conventional method the microwave irradiation technique has also been employed for the synthesis of some thienopyrimidines (**2**,**3**,**4**) and triazolothienopyrimidines (**5a–c**) and the results have been compared. Microwave irradiation provides an alternate to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. In the past few decades, many significant advances in organic chemistry, such as the novel synthetic reagents and methods, as well as the advent of an array of analytical apparatus and techniques, have made the organic synthesis more dynamic and effective than ever before. However, the practical aspects for carrying out laboratory-scale reactions have changed little during this period. Especially when heating is necessary, oil baths and heating jackets are the main equipments used. These traditional heating techniques are slow and time-consuming, and sometimes can lead to overheating and decomposition of the substrate and product. To overcome these problems microwaves have been employed in organic chemistry to reduce the reaction times from hours to minutes, to increase yields and selectivity and to be cleaner chemistries. The well-known Gewald reaction was adopted for the synthesis of the precursor 2-amino-3-cyanothiophene **1**.

EXPERIMENTAL

Experimental Protocols

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on Shimadzu FTIR – 8400S spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR were recorded on Bruker 300 MHz FT NMR spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. Mass spectrum was recorded on Finnigan MAT (Model MAT8200) spectrometer and elemental analyses were carried out using Heraus CHN rapid analyzer.

Synthesis

2-Amino-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (1)

To a well stirred mixture of 1, 3 cyclohexanedione (9.6 g, 50 mmole) and malononitrile (4.9 g, 50 mmole) in ethanol (45 mL) was added elemental sulfur (1.68 g, 50.25 mmole). To this cooled reaction mixture was added diethylamine (5 mL) with vigorous stirring during 1 min. Reaction mixture was stirred at 40–45 °C for about 1 h. The yellow-orange solid

separated was filtered, washed with hot ethanol and recrystallised from dioxane to yield analytically pure yellow needles. Yield 70%, m.p. 215–217 °C; IR cm^{-1}: 3339, 3190, 2962, 2901, 2210, 1645, 1623; ^1H NMR (300 MHz, DMSO) δ: 2.27 (t, 2H, CH_2), 2.50 (m, 2H, CH_2), 2.72 (t, 2H, CH_2), 8.30 (s, 2H, NH_2, D_2O exchangeable). Anal. calcd. for $C_9H_8N_20S$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.31; H, 4.21; N, 14.63% [8].

6,7-Dihydro-3H, 5H-benzo[4,5]thieno[2,3-d]pyrimidin-4, 8-dione (2)

***Method A*:** A mixture of 2-amino-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile **1** (1 g) and formic acid (15 mL) was heated under microwave irradiation at 90 °C for 15 minutes. The excess of formic acid was removed under reduced pressure. The resulting residue was crystallized from ethanol to yield pale yellow granules. Yield 80%, m.p. 154–156 °C; IR cm^{-1}: 3087, 2955, 1672, 1585, 1375, 990; ^1H NMR (300MHz, $CDCl_3$) δ: 2.45 (t, 2H, CH_2), 2.72 (m, 2H, CH_2), 2.93 (t, 2H, CH_2), 7.51 (s, C_2–H, pyrimidine), 11.98 (br s, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72. Found: C, 54.41; H, 3.55; N, 12.86% [8].

***Method B*:** A mixture of **1** (1 g) and formic acid (15 mL) was heated under reflux for 5 h. The excess of formic acid was removed under reduced pressure. The resulting residue was crystallized from ethanol to yield pale yellow granules. Yield 77%.

4-Chloro-6,7-dihydro[1]benzothieno[2,3-d]pyrimidin-8-one (3)

***Method A*:** Mixture of compound **2** (0.5 g) with phosphorus oxychloride (1.75 mL) was heated under microwave irradiation at 95 °C for 10 minutes The reaction mixture was allowed to cool to room temperature and poured into ice-water (200 g), the solid that separated was filtered off and crystallized from petroleum ether. Yield 75%, m.p. 96–98 °C; IR (KBr) νcm^{-1}: 3144, 1680, 1528, 1350, 970; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.20 (t, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.80 (t, 2H, CH_2), 8.66 (s, 1H, C_2–H, pyrimidine). Anal. calcd. for $C_{10}H_7ClN_2OS$: C, 50.32; H, 2.96; N, 11.74. Found: C, 50.46; H, 3.09; N, 11.89.

***Method B*:** A solution of **2** (0.5 g) in dry dioxane (7.5 mL) was treated with phosphorus oxychloride (1.75 mL) and the mixture was stirred under reflux for 3 h. The reaction mixture was allowed to cool to room temperature and poured into ice-water (200 g), the solid that separated was filtered off and crystallized from petroleum ether. Yield 71%.

4-Hydrazino-6,7-dihydro[1]benzothieno[2,3-d]pyrimidin-8-one (4)

***Method A*:** A mixture of compound **3** (0.5 g) and hydrazine hydrate 80% (1.8 mL) in ethanol (13 mL) was heated under microwave irradiation at 50 °C for 20 minutes. The reaction mixture was allowed to cool to room temperature. The deposited so precipitate was filtered off and crystallized from dioxane. Yield 81%, m.p. 150–152 °C; IR (KBr) νcm^{-1}: 3389, 3340, 3336, 3109, 1649, 1571; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.21 (t, 2H, CH_2), 2.38 (m, 2H, CH_2), 2.75 (t, 2H, CH_2), 4.50 (br s, 2H, NH_2, D_2O exchangeable), 5.66 (br s, 1H, NH, D_2O exchangeable), 7.99 (s, C_2–H, pyrimidine). Anal. calcd. for $C_{10}H_{10}N_4OS$: C, 51.27; H, 4.30; N, 23.91. Found: C, 51.36; H, 4.45; N, 23.99%.

***Method B*:** A mixture of compound **3** (0.5 g) and hydrazine hydrate 80% (1.8 mL) in ethanol (13 mL) was heated at 50 °C for 3 h. The reaction mixture was allowed to cool to room temperature. The deposited so precipitate was filtered off and crystallized from dioxane. Yield 77%.

8,9,10,11-Tetrahydro[1]benzothieno[3,2-e][1,3,4] triazolo-[1,5-c]pyrimidin-8-one (5a)

***Method A*:** A mixture of compound **4** (0.5 g), formic acid (2 mL), and a catalytic amount of concentrated hydrochloric acid was heated under microwave irradiation at 90 °C for 30 minutes. The reaction mixture was allowed to cool to room temperature and poured into water (200 mL). The precipitate that was formed was collected by filteration, washed with ethanol (50 mL), dried and crystallized from dioxane:ethanol mixture(2:1). Yield 88%, m.p. 147–149 °C; IR (KBr) νcm^{-1}: 3042, 2941, 1666, 1615, 1522, 1485, 1432; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.31 (t, 2H, CH_2), 2.48 (m, 2H, CH_2), 2.75 (t, 2H, CH_2), 8.20 (s, C_2–H, pyrimidine), 9.10 (s, 1H, triazole). Anal. calcd. for $C_{11}H_8N_4OS$: C, 54.09; H, 3.30; N, 22.94. Found: C, 54.18; H, 3.44; N, 23.09%.

***Method B*:** A mixture of compound **4** (0.5 g), formic acid (2 mL), and a catalytic amount of concentrated hydrochloric acid was heated under reflux for 7 hours. The reaction mixture was allowed to cool to room temperature and poured into water (200 mL). The precipitate that was formed was collected by filteration, washed with ethanol (50 mL), dried and crystallized from dioxane:ethanol mixture (2:1). Yield 84%.

3-Methyl-8,9,10,11-Tetrahydro[1]benzothieno[3,2-e] [1,3,4]triazolo-[1,5-c]-pyrimidin-8-one (5b)

***Method A*:** A mixture of compound **4** (0.5 g), glacial acetic acid (6 mL) was heated under microwave irradiation at 85 °C for 25 minutes. The reaction mixture was allowed to cool to room temperature and poured into water (200 mL).

The precipitate that was formed was collected by filteration, dried and crystallized from acetic acid. Yield 65%, m.p. 170–172 °C; IR (KBr) νcm^{-1}: 3009, 2935, 1665, 1610, 1509, 1424; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.31 (t, 2H, CH_2), 3.25 (s, 3H, CH_3), 2.45 (m, 2H, CH_2), 2.80 (t, 2H, CH_2), 8.30 (s, C2-H, pyrimidine). Anal. calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.87; H, 3.98; N, 21.74%.

***Method B*:** A mixture of compound **4** (0.5 g), glacial acetic acid (6 mL) was heated under reflux for 15 hours. The reaction mixture was allowed to cool to room temperature and poured into water (200 mL). The precipitate that was formed was collected by filteration, dried and crystallized from acetic acid. Yield 58%.

3-Phenyl-8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1, 3, 4]triazolo[1,5-c]-pyrimidin-8-one (5c)

***Method A*:** A mixture of compound **4** (0.5 g), Benzoyl chloride (6 mL) was heated under microwave irradiation at 80 °C for 30 minutes. The reaction mixture was allowed to cool to room temperature and poured into water (200 mL). The precipitate that was formed was collected by filteration, washed with ethanol (50 mL), dried and crystallized from dioxane:ethanol mixture (2:1). Yield 67%, m.p. 178–180 °C; IR (KBr) νcm^{-1}: 2989, 2954, 1662, 1614, 1520, 1475, 1411; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.20 (t, 2H, CH_2), 2.45 (m, 2H, CH_2), 2.65 (t, 2H, CH_2), 7.34–7.69 (m, 5H, phenyl protons), 8.78 (s, C2–H, pyrimidine). Anal. calcd. for $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49. Found: C, 63.78; H, 3.84; N, 17.56%.

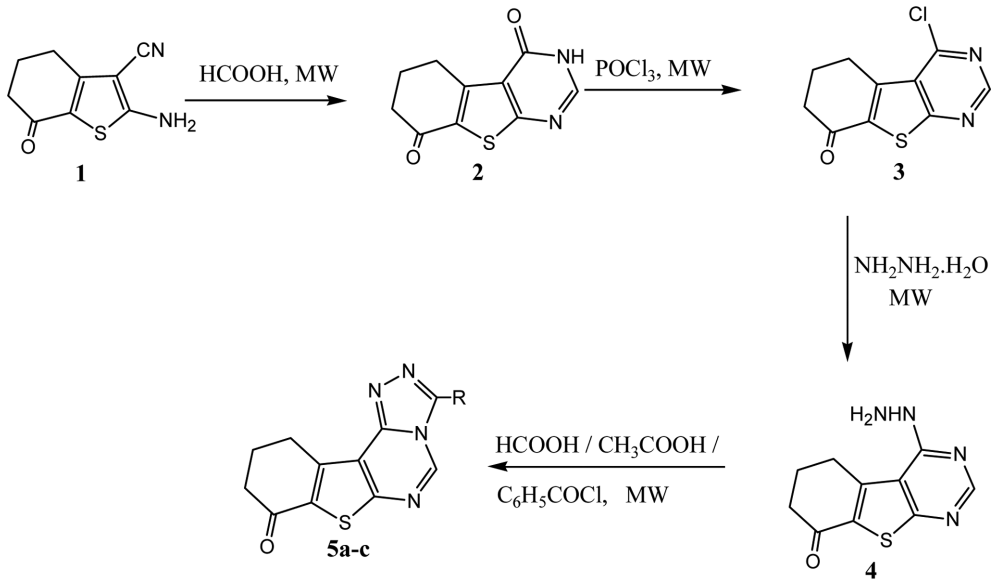
***Method B*:** A mixture of compound **4** (0.5 g), Benzoyl chloride (6 mL) was stirred under reflux for 8 hours. The reaction mixture was allowed to cool to room temperature and poured into water (200 mL). The precipitate that was formed was collected by filteration, washed with ethanol (50 mL), dried and crystallized from dioxane:ethanol mixture (2:1). Yield 64%.

RESULTS AND DISCUSSION

The reaction sequence employed for the synthesis of title compounds is shown in *Scheme* 1. The precursor 2-amino-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile **1** was prepared from 1,3-cyclohexanedione respectively under conditions reported by K. Gewald.[8–12] Formation of thiophene having a-aminonitrile was characterized by the presence of band at 2210 cm^{-1} due to cyano group and N–H stretching bands at 3339 and 3190 cm^{-1}. Further it is also supported by the presence of D_2O exchangeable broad singlet at δ 8.30 in ^{1}H NMR spectrum due to NH_2 group.

Thienopyrimidin-4-one **2** was prepared by the microwave irradiation of 2-amino-3-cyanothiophene **1** in presence of formic acid. The structure of **2** was ascertained by the absence of 2210 cm^{-1} due to cyano group and the presence of $\nu_{c=o}$ in IR and a signal at δ 7.51 due to N=CH. And also a D_2O exchangeable broad singlet at δ 11.90 for NH in the ^{1}H NMR spectrum, along with the other expected signals.

Thienopyrimidin-4-one **2** on treatment with dry dioxane



R = H, CH_3, Ph

***Scheme* 1.**

***Table* 1.** Comparative data of conventional and microwave-assisted synthesis

Compounds	Microwave-assisted (*method-A*)		Conventional (*method-B*)	
	Time (min) at 560 W	% Yield	Time (h)	% Yield
2	15	80	5	77
3	10	75	3	71
4	20	81	3	77
5a	30	88	7	84
5b	25	65	15	58
5c	30	67	8	64

and phosphorous oxychloride afforded the 4-chlorothieno pyrimidine **3**. Formation of these products was confirmed by the absence of ν_{NH} and $\nu_{C=O}$ bands in IR. Thus obtained 4-chlorothienopyrimidine **3** on treatment with hydrazine hydrate afforded the hydrazino derivative **4**. Formation of the products was confirmed by the presence of bands at 3386, 3340 and 3336 cm^{-1} in IR spectrum, due to amino functional groups. ^1H NMR spectrum shows D_2O exchangeable singlets at δ 4.50 and 5.66 due to amino groups and the C_2–H of pyrimidine resonated at δ 7.98 as a singlet along with other expected signals.

The compound **4** was further converted into triazolothienopyrimidine derivatives (**5a–c**) by treatment with aliphatic acids such as formic or acetic acid or acid chlorides such as benzoyl chloride. The formation of triazole ring involving both amino groups was evident by the absence of absorption bands due to either of these groups in the IR spectrum of **4**. Further ^1H NMR spectrum also exhibited the presence of singlet at around δ 8.56 due to pyrimidine.

Under conventional heating methods, these reactions need long reaction time, high-energy consumption and the need of large amounts of solvents for work up and purification. But, the use of microwave irradiation technique resulted in a remarkable acceleration of the reactions, with the reaction times decreasing significantly from hours to minutes and also the increase in the yield which as shown in *Table* 1.

CONCLUSION

In the present research work we have synthesized thienopyrimidines and tetracyclic triazole fused thienopyrimidines by both the conventional and the microwave irradiation methods from the precursor 2-amino-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3- carbonitrile **1**, which in turn was prepared by employing the well-known Gewald reaction. We herein report a comparative study of these syntheses under microwave irradiation and by conventional method. A fast, environment-friendly, and facile method under microwave irradiation is presented. The microwave irradiation provided a remarkable rate of accelaration for the reaction, and the reaction time decreased significantly. And, in antimicrobial screening some of the synthesized compounds have shown promising activities.

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