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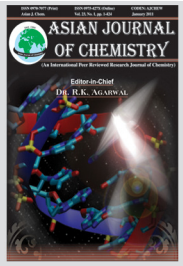

# Synthesis of Some Thieno[2,3-d]pyrimidin-4(3*H*)-ones Using Microwave Irradiation Under Solvent-Free Conditions

A. DAVOODNIA*, M. KOSARI and N. TAVAKOLI-HOSEINI

Department of Chemistry, Islamic Azad University, Mashhad Branch, Mashhad, Iran

*Corresponding author: Fax: +98 511 8424020; Tel: +98 511 8435000; E-mail: adavoodnia@mshdiau.ac.ir

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Some new derivatives of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones have been prepared *via* condensation reaction of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate with triethylorthoacetate followed by cyclocondensation with amines or hydrazines using microwave irradiation in solvent-free condition.

**Key Words: Thieno[2,3-d]pyrimidin-4(3*H*)-ones, Microwave irradiation, Solvent-free condition.**

## INTRODUCTION

Thieno[2,3-*d*]pyrimidines are a class of fused heterocycles. Some of which have interesting biological activities. These compounds are reported to possess significant analgesic[1,2], antiviral[3], fungicidal[4] and antiinflammatory[5-7] activities. Furthermore, a number of these compounds showed CNS depressing[8] and DHFR inhibitory activities[9] and are useful as muscle relaxants[7], sedatives[7], diuretics[10], pesticides and herbicides[11].

Various methods have already been proposed for the synthesis of these compounds and the most general ones involves cyclocondensation of suitably functionalized thiophenes with different electrophiles such as chloroformamidine[9], α-substituted acetonitriles[12], formic acid[13], phosgen[14], ethyl chloroformate[14] and guanidine[15]. To the best of our knowledge, microwave assisted synthesis of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**4a-e**) through condensation reaction of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) with triethylorthoacetate followed by cyclocondensation with amines or hydrazines has not been reported in the literature.

The application of microwave irradiation to organic synthesis for conducting reactions at accelerated rates is an emerging technique. In fact, in recent years, the use of microwaves has become popular among chemists both as a means to improve classical organic reactions and promote new reactions[16-20].

In light of these findings and due to our interest in the synthesis of new heterocyclic compounds[21-31] and in continuation of our previous works using microwave irradiation in organic reactions[32-36] in this paper we wish to report the synthesis of some thieno[2,3-d]pyrimidin-4(3*H*)-ones (**4a-e**) through condensation reaction of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) with triethylorthoacetate followed by cyclocondensation with amines or hydrazines under conventional heating and microwave irradiation in solvent-free conditions (**Scheme-I**).

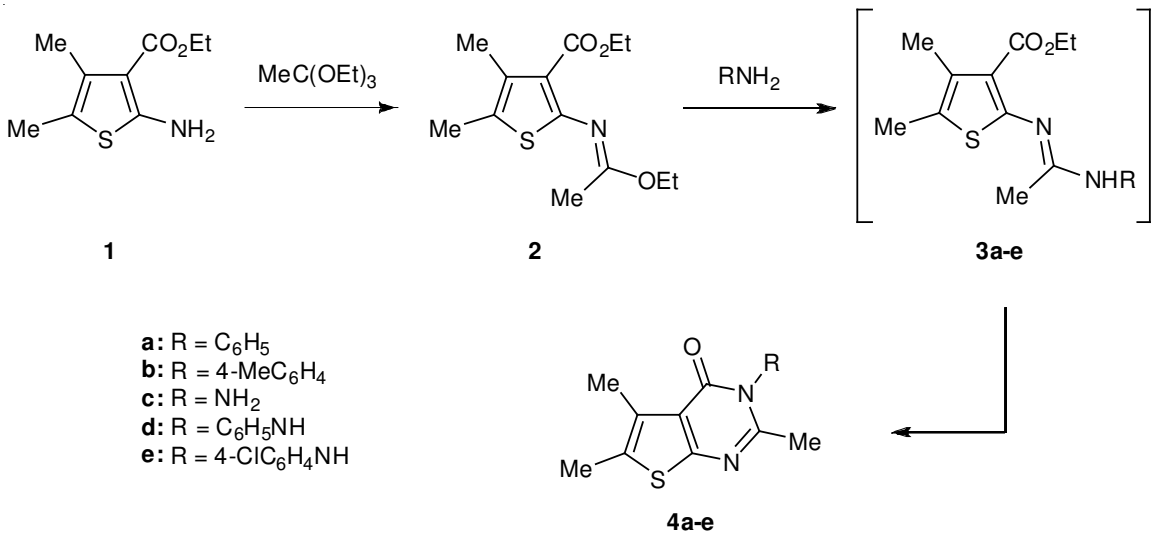
## EXPERIMENTAL

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The $^1$H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were determined on a Shimadzu GCMS 17A instrument.

### Synthesis of ethyl 2-(1-ethoxyethylideneamino]-4,5-dimethylthiophene-3-carboxylate (2):

**Method A:** A mixture of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) (2 mmol) and triethylorthoacetate (3 mmol) was subjected to microwave irradiation at 900 W for the indicated time. After the completion of the reaction (monitored by TLC, *n*-hexane:ethylacetate, 75:25), the crude product was recrystallized from ethanol to give compound **2** in 89 % yield (Table-1).

**Method B:** A mixture of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) (2 mmol) and triethylorthoacetate (2.3 mmol) in ethanol (10 mL) was heated under reflux for 1 h. After the completion of the reaction (monitored by TLC, *n*-hexane:ethyl acetate, 75:25), the solvent was evaporated *in vacuo*. The crude product was collected and recrystallized from ethanol to give compound **2** in 70 % yield (Table-1).




**Scheme-I:** Synthesis of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones

TABLE-1
COMPARISON OF TIME AND YIELDS ON THE FORMATION OF COMPOUNDS **2** AND **4a-e** USING MICROWAVE IRRADIATION AND CONVENTIONAL HEATING

| Entry | R | Products | Conventional heating | | Microwave irradiation | | m.p. (ºC) | $t_c/t_{mw}$ |
|---|---|---|---|---|---|---|---|---|
| | | | Time (min) $t_c$ | Yield (%)[a] | Time (min) $t_{mw}$ | Yield (%)[a] | | |
| 1 | – | **2** | 60 | 70 | 10 | 89 | 112-114 | 6.0 |
| 2 | $C_6H_5$- | **4a** | 300 | 76 | 9 | 90 | 172-174 | 33.3 |
| 3 | 4-$MeC_6H_4$- | **4b** | 240 | 74 | 6 | 89 | 177-180 | 40.0 |
| 4 | $NH_2$- | **4c** | 60 | 90 | 4 | 96 | 208-210 | 15.0 |
| 5 | $C_6H_5NH$- | **4d** | 300 | 87 | 9 | 90 | 90-93 | 33.3 |
| 6 | 4-$ClC_6H_4NH$- | **4e** | 300 | 71 | 9 | 88 | 265-268 | 33.3 |

[a]Isolated yields

**General procedure for the synthesis of thieno[2,3-d]pyrimidin-4(3*H*)-ones (4a-e)**

**Method A:** A mixture of ethyl 2-(1-ethoxyethylidene-amino]-4,5-dimethylthiophene-3- carboxylate (**2**) (2 mmol) and the respective amines or hydrazines (2.3 mmol) was subjected to microwave irradiation at 900 W for the indicated time. After the completion of the reaction (monitored by TLC, *n*-hexane:ethyl acetate, 75:25), the crude product was recrystallized from ethanol to give compounds **4a-e** in 88-96 % yields (Table-1).

**Method B:** A mixture of ethyl 2-(1-ethoxyethylidene-amino]-4,5-dimethylthiophene-3- carboxylate (**2**) (2 mmol) and the respective amines or hydrazines (2.2 mmol) in ethanol (10 mL) was heated under reflux for 1-5 h. After the completion of the reaction (monitored by TLC, *n*-hexane:ethyl acetate, 75:25), the solvent was evaporated *in vacuo*. The crude product was collected and recrystallized from ethanol to give compounds **4a-e** in 71-90 % yields (Table-1).

**Spectral data of compounds 2 and 4a-e**

**Ethyl 2-[(ethoxyethylidene)amino]-4,5-dimethylthiophene-3-carboxylate (2):** FTIR (KBr, $\nu_{max}$, $cm^{-1}$):1665 (C=O). $^1H$ NMR ($CDCl_3$) δ: 1.20-1.45 (two overlaped triplet, 6H, $2CH_3$), 1.92 (s, 3H, $CH_3$), 2.24 (s, 6H, $2CH_3$), 4.10-4.40 (two overlaped quartet, 4H, $2CH_2$). MS: m/z 269 ($M^+$).

**2,5,6-Trimethyl-3-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (4a):** FTIR (KBr, $\nu_{max}$, $cm^{-1}$): 1669 (C=O). $^1H$ NMR ($CDCl_3$) δ: 2.04 (s, 6H, $2CH_3$), 2.84 (s, 3H, $CH_3$), 7.20-7.90 (m, 5H, arom-H). MS: m/z 270 ($M^+$).

**2,5,6-Trimethyl-3-(4-methylphenyl)thieno[2,3-*d*]-pyrimidin-4(3*H*)-one (4b):** FTIR (KBr, $\nu_{max}$, $cm^{-1}$): 1668 (C=O). $^1H$ NMR ($CDCl_3$) δ: 2.23 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$), 2.46 (s, 6H, $2CH_3$), 7.00-7.40 (dd, 4H, aromatic). MS: m/z 284 ($M^+$).

**3-Amino-2,5,6-trimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (4c):** FTIR (KBr, $\nu_{max}$, $cm^{-1}$): 3340, 3314 ($NH_2$), 1674 (C=O). $^1H$ NMR ($CDCl_3$) δ: 2.34 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$), 2.62 (s, 3H, $CH_3$), 4.87 (s, 2H, $NH_2$). MS: m/z 209 ($M^+$).

**2,5,6-Trimethyl-3-(phenylamino)thieno[2,3-*d*]-pyrimidin-4(3*H*)-one (4d):** FTIR (KBr, $\nu_{max}$, $cm^{-1}$): 3218 (NH), 1673 (C=O). $^1H$ NMR ($CDCl_3$) δ: 2.42 (s, 3H, $CH_3$), 2.44 (s, 3H, $CH_3$), 2.63 (s, 3H, $CH_3$), 3.12 (br, 1H, NH), 6.60-7.60 (m, 5H, aromatic). MS: m/z 285 ($M^+$).

**3-(4-Chlorophenylamino)-2,5,6-trimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (4e):** FT IR (KBr, $\nu_{max}$, $cm^{-1}$): 3264 (NH), 1650 (C=O). $^1H$ NMR ($CDCl_3$) δ: 2.18 (s, 3H, $CH_3$), 2.27 (s, 6H, $2CH_3$), 4.40 (br, 1H, NH), 7.10-7.80 (m, 5H, aromatic). MS: m/z 319 ($M^+$), 321 ($M^+ + 2$).

## RESULTS AND DISCUSSION

The starting material ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) was prepared according to the literature method[37]. First, it was treated with triethylorthoacetate

under microwave irradiation in solvent-free condition at 900W for the indicated time, using a domestic microwave oven Model LG MS-543XD, to afford the ethyl 2-(1-ethoxyethylidene-amino]-4,5-dimethylthiophene-3-carboxylate (**2**) (data in Table-1 and experimental section). Next, treatment of this compound with amines or hydrazines using microwave irradiation in solvent-free conditions were explored. Thus, the reactants were mixed together and then irradiated at 900W for the indicated time to give thieno[2,3-d]pyrimidin-4(3*H*)-ones (**4a-e**) in high yields. However, under these conditions, attempts to isolate the intermediates **3a-e** failed when we carefully monitored the reactions. The structural assignment of compounds **2** and **4a-e** was based upon spectral data.

In order to draw a comparison between microwave irradiation and conventional heating for preparation of the compounds **2** and **4a-e**, the same reaction mixtures were heated under reflux in ethanol for the indicated time (Table-1). By comparing the data in Table-1, it is obvious that the microwave irradiation approach for the synthesis of compounds **2** and **4a-e** is faster and the yields are higher than conventional heating method.

## Conclusion

We have developed a facile and efficient approach for the synthesis of thieno[2,3-d]pyrimidin-4(3*H*)-ones under microwave irradiation in solvent-free condition and also by thermal heating. In comparison, the reactions carried out with the assistance of microwave technique are faster and the yields are higher than conventional method.

## ACKNOWLEDGEMENTS

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