Bulgarian Chemical Communications, Volume 41, Number 3 (pp. 226–229) 2009

Base-catalyzed synthesis of 2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones and isolation of intermediates using microwave irradiation

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Received September 13, 2008, Revised October 15, 2008

A simple and fast method for the synthesis of some 3-substituted-5,6-dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones has been developed *via* base-catalyzed cyclocondensation of ethyl 2-amino-4,5-dimethyl-thiophene-3-carboxylate with isothiocyanates. The uncyclized intermediates, ethyl 4,5-dimethyl-2-[(substituted carbamothioyl)amino]thiophene-3-carboxylates, were isolated when the reactions were carried out under microwave irradiation. These intermediates subsequently underwent cyclization in t-butanol in the presence of potassium *t*-butoxide on heating under reflux to give the desired bicyclic products.

Key words: ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate, isothiocyanates, 2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones, microwave irradiation.

INTRODUCTION

Our interest in thieno[2,3-d]pyrimidine synthesis emerges from the numerous reports on their diverse biological activities [1–10]. Various methods have already been proposed for the synthesis of these compounds and the most general ones involve cyclocondensation of suitably functionalized thiophenes with different electrophiles such as chloroformamidine [11], α-substituted acetonitriles [12], formic acid [13], phosgene [14], ethyl chloroformate [14] and guanidine [15]. To the best of our knowledge, base-catalyzed cyclocondensation of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) with isothiocyanates for the synthesis of 3-substituted- 5,6-dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones (**3a**–**e**) and the utilization of microwave irradiation for isolation of the intermediates (**2a**–**e**) has not been reported in the literature.

Prompted by these findings and due to our interest in the synthesis of heterocyclic compounds [16–25] and in continuation of our previous works on the synthesis of thieno[2,3-d]pyrimidine derivatives [26–28], we report here a simple and fast method for the synthesis of 3-substituted-5,6-dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones (**3a**–**e**) through cyclocondensation of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) with isothiocyanates under basic conditions.

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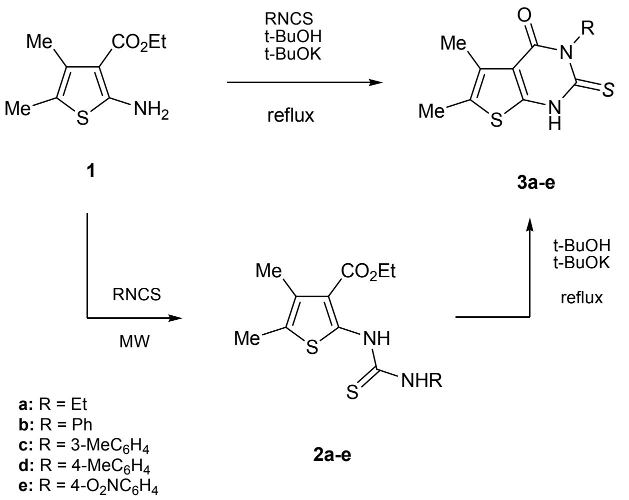
RESULTS AND DISCUSSION

The starting material (**1**) was prepared according to the literature method [29]. Cyclocondensation of this compound with isothiocyanates in the presence of potassium *t*-butoxide in *t*-butanol under reflux gave products identified as 3-substituted-5,6-dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones (**3a**–**e**). Under this conditions, attempts to isolate the reaction intermediates (**2a**–**e**) failed when we monitored the course of the reactions carefully (Scheme 1).

Due to our interest in the utilization of microwave irradiation for the synthesis of heterocyclic compounds [30–33], we tried to extend this non-conventional synthetic method for the synthesis of compounds **3a**–**e**. Therefore, ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) was allowed to interact with isothiocyanates under microwave irradiation under solvent-free conditions at 800 W. During monitoring of the reaction mixture by TLC ($CHCl_3$:MeOH = 95:5), surprisingly, we observed that unexpected products, with R_f-values different from those expected for compounds **3a**–**e**, were being formed. During work up and identification, it was established that a condensation and not a cyclocondensation reaction had occurred and the intermediates ethyl 4,5-dimethyl-2-[(substituted carbamothioyl)amino]thiophene-3-carboxylates (**2a**–**e**) were isolated. The reaction did not proceed to form cyclic products even after prolonged irradiation, but when the latter compounds were heated under reflux for 3 hours in the presence of potassium *t*-butoxide in *t*-butanol, cyclization reaction occurred and the cyclic products **3a–e** were obtained (Scheme 1).

The structure of the synthesized compounds was deduced from their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of **2a** did not show the NH_2 signal of the precursor 1 at δ 5.61 ppm, but instead of it showed two broad signals at δ 9.62 and 11.80 ppm belonging to the NH groups indicating the formation of compound **2a**. The IR spectrum showed the absorption bands at 1651, 3215 and 3299 cm^{-1} for carbonyl and two NH groups respectively. The MS of **2a** showed a molecular ion peak at m/z 286 (M^+) corresponding to the molecular formula $C_{12}H_{18}N_2O_2S_2$. This compound gave also satisfactory elemental analysis data (See Experimental).



Scheme 1.

In conclusion, we have developed a facile method for the synthesis of 3-substituted-5,6-dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones (**3a–e**) through cyclocondensation of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) with isothiocyanates in *t*-butanol containing potassium *t*-butoxide as a base catalyst. Using microwave irradiation, the uncyclized intermediates **2a–e** were isolated.

EXPERIMENTAL

Melting points were measured on a Stuart Model SMP3 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. Elemental analysis was performed on a Thermo Finnigan Flash EA micro-analyzer. Reactions were performed in a domestic microwave oven Model LG MS-543XD.

Preparation of 3-substituted-5,6-dimethyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones **(3a–e)**. *General Procedure .Method A*. To a solution of the ethyl 2-amino-4,5-dimethyl-thiophene-3-carboxylate (**1**) (5 mmol) and potas-sium *t*-butoxide (2 mmol) in *t*-butanol (20 ml), the appropriate isothiocyanate (6 mmol) was added. The reaction mixture was heated under reflux for 6 hours. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH = 93:7), the solvent was evaporated in vacuum, the residue was dissolved in water (15 ml) and subsequently neutralized by 1 N HCl. The crude product was collected and recrystallized from ethanol to give compounds **3a–e** in 75, 77, 68, 86 and 74% yields, respectively.

Method B. A mixture of ethyl 4,5-dimethyl-2-[(substituted carbamothioyl)amino]thiophene-3-carboxylates (**2a–e**) (3 mmol) and potassium *t*-butoxide (1 mmol) in *t*-butanol (15 ml) was heated under reflux for 3 hours. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH = 93:7), the solvent was evaporated in vacuum, the residue was dissolved in water (15 ml) and subsequently neutralized by 1 N HCl. The crude product was collected and recrystallized from ethanol to give compounds **3a–e** in 79, 78, 73, 91 and 75% yields, respectively.

3-Ethyl-5,6-dimethyl-2-thioxo-2,3-dihydrothieno-[2,3-d]pyrimidin-4(1H)-one (**3a**). M.p. 257–259°C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.17 (t, 3H, J = 7 Hz, CH_3), 2.24 (s, 6H, 2CH_3), 4.36 (q, 2H, J = 7 Hz, CH_2), 13.45 (br, 1H, NH); IRS (KBr disc): ν 1684 (C=O), 3137 cm^{-1} (NH); MS, m/z: 240 (M^+); Analytically calculated for $C_{10}H_{12}N_2OS_2$: C 49.97; H 5.03; N 11.66; S 26.68. Found: C 50.24; H 5.21; N 11.35; S 26.91.

5,6-Dimethyl-3-phenyl-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (**3b**). M.p. 325–327°C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.24 (s, 6H, 2CH_3), 7.0–7.6 (m, 5H, phenyl), 13.65 (s br, 1H, NH); IRS (KBr disc): ν 1703 (C=O), 3152 cm^{-1} (NH); MS, m/z: 288 (M^+); Analytically calculated for $C_{14}H_{12}N_2OS_2$: C 58.31; H 4.19; N 9.71; S 22.24. Found: C 58.67; H 3.98; N 9.50; S 22.45.

5,6-Dimethyl-3-(3-methylphenyl)-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (**3c**). M.p. 295–297°C; ^{1}H NMR (DMSO-d$_6$, δ ppm): 2.25 (s, 3H, CH_3), 2.29 (s, 6H, 2CH_3), 6.85–7.45 (m, 4H, arom-H), 13.61 (br, 1H, NH); IRS (KBr disc): ν 1709 (C=O), 3163 cm^{-1} (NH); MS, m/z: 302 (M^+); Analytically calculated for $C_{15}H_{14}N_2OS_2$: C 59.57; H 4.67; N 9.26; S 21.21. Found: C 59.28; H 4.89; N 9.51; S 20.97.

5,6-Dimethyl-3-(4-methylphenyl)-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (**3d**). M.p.

270°C (dec); ^{1}H NMR (DMSO-d$_6$, δ ppm): 2.24 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.90–7.25 (overlapped doublets, 4H, arom-H), 13.60 (br, 1H, NH); IRS (KBr disc): ν 1703 (C=O), 3155 cm^{-1} (NH); MS, m/z: 302 (M^+); Analytically calculated for $C_{15}H_{14}N_2OS_2$: C 59.57; H 4.67; N 9.26; S 21.21. Found: C 59.34; H 4.46; N 9.48; S 21.43.

5,6-Dimethyl-3-(4-nitrophenyl)-2-thioxo-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (**3e**). M.p. 340–342°C; ^{1}H NMR (DMSO-d$_6$, δ ppm): 2.25 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 7.40–8.45 (overlapped doublets, 4H, arom-H), 13.68 (s br, 1H, NH); IRS (KBr disc): ν 1707 (C=O), 3170 cm^{-1} (NH); MS, m/z: 333 (M^+); Analytically calculated for $C_{14}H_{11}N_3O_3S_2$: C 50.44; H 3.33; N 12.60; S 19.24. Found: C 50.71; H 3.62; N 12.73; S 19.01.

Preparation of ethyl 4,5-dimethyl-2-[(substituted carbamothioyl)amino]thiophene-3-carboxylates (**2a–e**). *General Procedure*. A mixture of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**1**) (3 mmol) and the appropriate isothiocyanate (4 mmol) was subjected to microwave irradiation at 800 W for 2–3 min (4–5 times). After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH = 95:5) the crude product was recrystallized from ethanol to give compounds **2a–e** in high yields.

Ethyl 2-[(ethylcarbamothioyl)amino]-4,5-dimethylthiophene-3-carboxylate (**2a**). Time 5×2 min; Yield 75%; m.p. 165–167°C; ^{1}H NMR (DMSO-d$_6$, δ ppm): 1.44 (t, 3H, J = 6.5 Hz, CH_3), 1.58 (t, 3H, J = 7 Hz, CH_3), 2.32 (s, 6H, 2CH_3), 4.41 (q, 2H, J = 6.5 Hz, CH_2), 4.52 (q, 2H, J = 7 Hz, CH_2), 9.62 (br, 1H, NH), 11.80 (br, 1H, NH); IRS (KBr disc): ν 1651 (C=O), 3215, 3299 cm^{-1} (two NH); MS, m/z: 286 (M^+); Analytically calculated for $C_{12}H_{18}N_2O_2S_2$: C 50.32; H 6.33; N 9.78; S 22.39. Found: C 50.05; H 6.11; N 10.06; S 22.21.

Ethyl 4,5-dimethyl 2-[(phenylcarbamothioyl)-amino]thiophene-3-carboxylate (**2b**). Time 4×3 min; Yield 90%; m.p. 170–172°C; ^{1}H NMR (DMSO-d$_6$, δ ppm): 1.22 (t, 3H, J = 7 Hz, CH_3), 2.17 (s, 6H, 2CH_3), 4.20 (q, 2H, J = 7 Hz, CH_2), 7.0–7.6 (m, 5H, phenyl), 10.91 (s, 1H, NH), 11.79 (s, 1H, NH); IRS (KBr disc): ν 1664 (C=O), 3175, 3282 cm^{-1} (two NH); MS, m/z: 334 (M^+); Analytically calculated for $C_{16}H_{18}N_2O_2S_2$: C 57.46; H 5.42; N 8.38; S 19.17. Found: C 57.78; H 5.19; N 8.64; S 18.98.

Ethyl 4,5-dimethyl-2-{[(3-methylphenyl)carbamothioyl]amino}thiophene-3-carboxylate (**2c**). Time 5×3 min; Yield 84%; m.p. 168–169°C; ^{1}H NMR (DMSO-d$_6$, δ ppm): 1.48 (t, 3H, J = 7.5 Hz, CH_3), 2.30 (s, 6H, 2CH_3), 2.47 (s, 3H, CH_3), 4.37 (q, 2H, J = 7.5 Hz, CH_2), 7.1–7.6 (m, 4H, arom-H), 11.12 (s, 1H, NH), 12.10 (s, 1H, NH); IRS (KBr disc): ν 1659 (C=O), 3165, 3180 cm^{-1} (two NH); MS, m/z: 348 (M^+); Analytically calculated for $C_{17}H_{20}N_2O_2S_2$: C 58.59; H 5.78; N 8.04; S 18.40. Found: C 58.94; H 6.01; N 7.81; S 18.59.

Ethyl 4,5-dimethyl 2-{[(4-methylphenyl)-carbamothioyl]amino}thiophene-3-carboxylate (**2d**). Time 4×3 min; Yield 89%; m.p. 165–167°C; ^{1}H NMR (DMSO-d$_6$, δ ppm): 1.25 (t, 3H, J = 7 Hz, CH_3), 2.18 (s, 6H, 2CH_3), 2.29 (s, 3H, CH_3), 4.11 (q, 2H, J = 7 Hz, CH_2), 7.1–7.5 (overlapped doublets, 4H, arom-H), 10.89 (s, 1H, NH), 11.78 (s, 1H, NH); IRS (KBr disc): ν 1658 (C=O), 3178, 3200 cm^{-1} (two NH); MS, m/z: 348 (M^+); Analytically calculated for $C_{17}H_{20}N_2O_2S_2$: C 58.59; H 5.78; N 8.04; S 18.40. Found: C 58.81; H 5.54; N 7.87; S 18.73.

Ethyl 4,5-dimethyl 2-{[(4-nitrophenyl)carbamothioyl]amino}thiophene-3-carboxylate (**2e**). Time 5×3 min; Yield 78%; m.p. 213–215°C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.26 (t, 3H, J = 7 Hz, CH_3), 2.22 (s, 6H, 2CH_3), 4.30 (q, 2H, J = 7 Hz, CH_2), 7.7–8.4 (overlapped doublets, 4H, arom-H), 11.61 (s, 1H, NH), 12.08 (s, 1H, NH); IRS (KBr disc): ν 1654 (C=O), 3184, 3205 cm^{-1} (two NH); MS, m/z: 379 (M^+); Analytically calculated for $C_{16}H_{17}N_3O_4S_2$: C 50.64; H 4.52; N 11.07; S 16.90. Found: C 50.35; H 4.77; N 10.79; S 16.62.

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СИНТЕЗА НА 2-ТИОКСО-2,3-ДИХИДРОТИЕНО[2,3-d]ПИРИМИДИН-4(1H)-ОНИ ЧРЕЗ БАЗИЧНА КАТАЛИЗА И ИЗОЛИРАНЕ НА МЕЖДИННИ СЪЕДИНЕНИЯ С ИЗПОЛЗВАНЕ НА МИКРОВЪЛНОВО ОБЛЪЧВАНЕ

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Постъпила на 13 септември 2008 г.; Преработена на 15 октомври 2008 г.

(Резюме)

Предложен е прост и бърз метод за синтезата на 3-заместени-5,6-диметил-2-тиоксо-2,3-дихидротиено[2,3-d]пиримидин-4(1H)-они чрез циклокондензация на 2-амино-4,5-диметилтиофен-3-карбоксиетилат с изотиоцианати чрез базична катализа. Нециклизиралите междинни продукти 4,5-диметил-2-[(заместени карбаматотиоил)амино]тиофен-3-карбоксилати са изолирани когато реакциите се провеждат при микровълново облъчване. Тези междинни продукти впоследствие циклизират в *t*-бутанол в присъствие на калиев *t*-бутоксид при нагряване с обратен хладник до получаване на желаните бициклични продукти.