J. Iran. Chem. Soc., Vol. 8, No. 1, March 2011, pp. 107-114.

JOURNAL OF THE
Iranian
Chemical Society

$Zn(OAc)_2$ Catalyzed Microwave Irradiated Synthesis of Substituted Thieno[2, 3-d]pyrimidin-4(3H)-one

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(Received 11 December 2009, Accepted 27 April 2010)

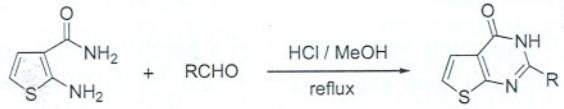
Different Lewis acids were screened to catalyze the reaction of 2-amino-thiophene-3-carboxylate, orthoformate and aryl amine to form 2-substituted thieno[2,3-d]pyrimidin-4(3H)-one. $Zn(OAc)_2$ was demonstrated to efficiently catalyze the reaction. 20 substituted thieno[2,3-d]pyrimidines were synthesized by adding 0.5% mol $Zn(OAc)_2$ as catalyst under microwave irradiation.

Keywords: Thienopyrimidine, Microwave irradiation, $Zn(OAc)_2$, Catalyze

INTRODUCTION

Thieno[2,3-d]pyrimidin-4(3H)-one analogs have been widely documented because of their effective antitumor activity [1,2,3]. In 2005, Wang [4] identified thieno[2,3-d] pyrimidin-4(3H)-one analogs as a novel class of anti-proliferative agents. Wang also reported in the same paper [4] the synthesis of the latter from 2-amino-3-carboxamido-thiophenes and various substituted benzaldehydes. By this method, however, only 2-substitued thieno[2,3-d]pyrimidin-4(3H)-one could be synthesized and the reaction needed to be catalyzed by a strong HCl acid (Scheme 1).

In 2008, Obushak [5] and Peinador [6] separately reported the synthesis of substituted thieno[2,3-d]pyrimidin-4(3H)-ones from 2-amino-thiophene-3-carboxylate in two steps. In the first step, 2-amino-thiophene-3-carboxylate was transformed into 2-(3H-tetrazol-1-yl)-thiophene-3-carboxylate or 2-(triphenyl phosphoranylideneamino)-thiophene-3-carboxylate. In the second step, the latter was transformed into substituted thieno[2,3-d]pyrimidin-4(3H)- ones (Scheme 2).



Scheme 1

Recently, Jain [7] reported the synthesis of substituted thieno[2,3-d]pyrimidin-4(3H)-ones from 2-amino-thiophene-3-carboxylate using formamide as cyclization reagent under microwave irradiation. However, by this method only 2-unsubstituted thieno[2,3-d]pyrimidin-4(3H)-ones could be synthesized and the reaction time was about 25 min. under microwave irradiation (Scheme 3).

To the best of our knowledge, the synthesis of 3-substituted thieno[2,3-d]pyrimidin-4(3H)-one from 2-amino-thiophene-3-carboxylate by one step procedure has not been reported to date. Herein, we disclose a one-step convenient synthesis of 2-substituted thieno[2,3-d]pyrimidin-4(3H)-one scaffold from 2-amino-thiophene-3-carboxylate catalyzed by $Zn(OAc)_2$ under microwave irradiation.

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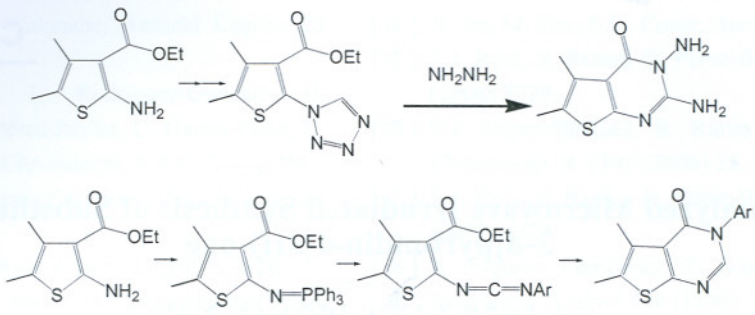


Scheme 2

Scheme 3

EXPERIMENTAL

Melting points were obtained on a hot-plate microscope apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV-600 spectrophotometer. IR spectra were obtained on a Nicolet FT-IR 740 spectrometer (KBr disc). Microwave was used on a Beijing Zhongxi Yuanda ZC24chempower microwave synthesizer.

General Procedure for Synthesis of Thieno[2,3-d]pyrimidin-4(3H)-ones 5a-5t

A mixture of ethyl 2-amino-thiophene-3-carboxylate (1 mmol), orthoformate (5 mmol), arylamine (1.1 mmol), $Zn(OAc)_2$ (0.005 mmol) and 5 ml EtOH was irradiated at 350 w for 5 min in a microwave synthesizer. The reaction mixture was allowed to cool to room temperature, and then poured onto ice water. The resulting precipitated solid was filtered, washed with chilled water and dried. The crude product on recrystallization from methanol-dimethylformamide (10:1) yielded the requisite thieno[2,3-d]pyrimidin- 4(3H)-ones.

5,6-Dimethyl-3-phenylthieno[2,3-d]pyrimidin-4(3H)-one (5a). White needle. M.p.: 162-164 °C. IR (KBr): 3427 (NH), 1690 (CO), 1596 (Ar) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.52-7.55 (t, J = 7.5 Hz, 2H), 7.47-7.50 (t, J = 7.3 Hz, 1H), 7.38-7.39 (d, J = 7.5 Hz, 2H), 2.49 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.9, 157.8, 145.1, 137.2, 131.4, 130.0, 129.5, 129.1, 127.2, 123.7, 13.1. MS (*m/z*): 257 (M^++1), 186, 154, 123, 99.

5,6-Dimethyl-3-*p*-tolylthieno[2,3-d]pyrimidin-4(3H)-one (5b). White needle. M.p.: 182-184 °C. IR (KBr): 3446 (NH), 1687 (C=O), 1565 (Ar) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.32-7.33 (d, J = 8.0 Hz, 2H), 7.25-7.26 (d, J = 8.0 Hz, 2H), 2.48 (s, 3H), 2.43 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.0, 158.0, 145.3, 139.2, 134.6, 131.2, 130.1, 130.0, 126.9, 123.7, 21.2, 13.1. MS (*m/z*): 271 (M^++1), 154, 126, 118.

3-(4-Methoxyphenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (5c). White needle. M.p.: 164-166 °C. IR (KBr): 3447 (NH), 1683 (CO), 1607 (Ar), cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.96 (s, 1H), 7.29-7.30 (d, J = 8.3 Hz, 2H), 7.02-7.03 (d, J = 8.3 Hz, 2H), 3.86 (s, 3H), 2.48 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.0, 159.9, 158.6, 158.1, 147.9, 145.4, 129.4, 128.9, 128.3, 125.9, 120.3, 115.1, 55.6, 21.3, 13.1. MS (*m/z*): 287 (M^++1), 154, 126, 99

3-(4-Chlorophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (5d). White needle. M.p.: 220-222 °C. IR (KBr): 3446 (NH), 1687 (CO), 1564 (Ar), cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.50-7.52 (d, J = 8.5 Hz, 2H), 7.33-7.35 (d, J = 8.5 Hz, 2H), 2.48 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.0, 157.6, 144.9, 144.6, 135.7, 135.2, 131.7, 130.1, 129.7, 129.4, 128.6, 123.6, 13.1, 13.0. MS (*m/z*): 291 (M^++1), 207, 154, 126, 99.

3-(3-Chlorophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (5e). Pale yellow needle. M.p.: 148-150

°C. IR (KBr): 3426 (NH), 1689 (CO), 1565 (Ar) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 7.94 (s, 1H), 7.47-7.48 (d, J = 9.0 Hz, 2H), 7.28 (s, 1H), 7.27-7.31 (m, 1H), 2.48 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.0, 157.5, 144.5, 138.2, 135.1, 131.8, 130.5, 130.1, 129.4, 127.7, 125.6, 123.6, 13.2, 13.1. MS (*m/z*): 291 (M^++1), 291, 154, 126, 99.

Methyl-4-oxo-3-phenyl-5-methyl-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate (5f). Pale yellow needle. M.p.: 158-160 °C. IR (KBr): 3431 (NH), 1709 (CO), 1686 (CO), cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.13 (s, 1H), 7.55-7.57 (t, J = 7.8 Hz, 2H), 7.50-7.53 (t, J = 7.8 Hz, 1H), 7.38-7.40 (d, J = 7.2 Hz, 2H), 3.92 (s, 3H), 2.95 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.2, 162.8, 157.9, 148.2, 144.8, 136.6, 129.7, 129.5, 127.1, 123.9, 123.8, 52.5, 15.2. MS (*m/z*): 301 (M^++1), 269, 230, 198, 140, 110.

Methyl-4-oxo-3-(*p*-tolyl)-5-methyl-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate (5g). White needle. M.p.: 216-218 °C. IR (KBr): 3438 (NH), 1731 (CO), 1694 (CO), 1567 (Ar) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.34-7.35 (d, J = 8.1 Hz, 2H), 7.25-7.26 (d, J = 8.1 Hz, 2H), 3.92 (s, 3H), 2.95 (s, 3H), 2.44(s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.2, 162.8, 158.0, 148.4, 144.9, 139.7, 134.0, 130.3, 126.8, 123.9, 123.7, 52.2, 21.2, 15.2. MS (*m/z*): 315 (M^++1), 198, 118.

Methyl-4-oxo-3-(4-methoxyphenyl)-5-methyl-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate (5h). Slightly yellow needle. M.p.: 238-240 °C. IR (KBr): 3434 (NH), 2956, 1731, 1694 (CO), 1610 (CO) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.29-7.30 (d, J = 8.3 Hz, 2H), 7.03-7.05 (d, J = 8.3 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 2.95 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.1, 162.5, 158.1, 148.3, 144.5, 139.6, 134.0, 130.2, 126.8, 124.2, 123.9, 61.4, 21.2, 15.2, 14.3. MS (*m/z*): 331 (M^++1), 230, 198, 134.

Methyl-4-oxo-3-(2-pyridyl)-5-methyl-3,4-dihydrothieno [2,3-d]pyrimidine-6-carboxylate (5i). White needle. M.p.: 236-238 °C. IR (KBr): 3421 (NH), 1720 (CO), 1687 (CO), 1563 (Ar), cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.62-8.63 (m, 1H), 8.56 (s, 1H), 7.90-7.92 (m, 1H), 7.80-7.82 (m, 1H), 7.42-7.44 (m, 1H), 3.92 (s, 3H), 2.97 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.2, 163.8, 158.5, 150.4, 150.1, 148.5, 145.9, 139.1, 125.0, 124.8, 124.6, 122.9, 53.2, 16.2. MS (*m/z*): 302 (M^++1), 230, 198, 110, 96.

Ethyl-4-oxo-3-phenyl-5-methyl-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate (5j). White needle. M.p.: 160-162 °C. IR (KBr): 3446 (NH), 1681 (CO), 1567 (CO), 1495 (Ar) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.54-7.57 (t, J = 7.8 Hz, J = 7.2 Hz, 2H), 7.50-7.53 (t, J = 7.8 Hz, 1H), 7.38-7.40 (d, J = 7.2 Hz, 2H), 4.37-4.41 (q, J = 7.1 Hz, 2H), 2.95 (s, 3H), 1.40-1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.1, 162.4, 157.9, 148.1, 144.5, 136.7, 129.7, 129.5, 127.1, 124.4, 123.9, 61.4, 15.2, 14.3. MS (*m/z*): 315 (M^++1), 287, 212, 184, 104.

Ethyl-4-oxo-3-(*p*-tolyl)-5-methyl-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate (5k). White needle. M.p.: 152-154 °C. IR (KBr): 3426 (NH), 1714 (CO), 1681 (CO) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.34-7.35 (d, J = 7.7 Hz, 2H), 7.25-7.26 (d, J = 7.7 Hz, 2H), 4.37-4.40 (q, J = 7.0 Hz, 2H), 2.95 (s, 3H), 2.44 (s, 3H), 1.40-1.42 (t, J = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.1, 162.5, 158.1, 148.3, 144.5, 139.6, 134.1, 130.2, 126.8, 124.2, 123.9, 61.4, 21.2, 15.2, 14.3. MS (*m/z*): 329 (M^++1), 301, 212, 184, 118.

Ethyl-4-oxo-3-(*p*-methoxyphenyl)-5-methyl-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate (5l). White needle. M.p.: 136-138 °C. IR (KBr): 3407 (NH), 1718 (CO), 1690 (CO), 1610 (Ar) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.29-7.30 (d, J = 8.2 Hz, 2H), 7.03-7.04 (d, J = 8.2 Hz, 2H), 4.37-4.40 (q, J = 7.0 Hz, 2H), 3.87 (s, 3H), 2.95 (s, 3H), 1.40-1.42 (t, J = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.1, 162.5, 160.2, 158.2, 148.4, 148.0, 144.5, 129.2, 128.3, 124.3, 123.9, 114.8, 108.6, 60.1, 55.6, 16.1, 15.2. MS (*m/z*): 345 (M^++1), 317, 212, 184, 134.

Ethyl-4-oxo-3-(2-pyridyl)-5-methyl-3,4-dihydrothieno [2,3-d]pyrimidine-6-carboxylate (5m). White needle. M.p.: 128-130 °C. IR (KBr): 3407 (NH), 1723 (CO), 1692 (CO) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.62-8.63 (m, 1H), 8.55 (s, 1H), 7.90-7.92 (m, 1H), 7.80-7.82 (m, 1H), 7.41-7.43 (m, 1H), 4.37-4.40 (q, J = 7.1 Hz, 2H), 2.97 (s, 3H), 1.40-1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.1, 162.4, 157.5, 149.4, 149.1, 147.4, 144.5, 138.1, 124.4, 124.0, 123.6, 121.9, 61.4, 16.1, 15.2. MS (*m/z*): 316 (M^++1), 134, 124, 92.

6-Acetyl-5-methyl-3-phenyl-thieno[2,3-d]pyrimidine-4 (3H)-one (5n). Yellow needle. M.p.: 136-138 °C. IR (KBr): 3380 (NH), 1677 (CO), 1647 (CO) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 7.55-7.58 (t, J = 7.5 Hz, J = 7.3 Hz, 2H), 7.51-7.53 (t, J = 7.5 Hz, 1H), 7.26-7.38 (d, J = 7.3 Hz, 2H), 2.96 (s, 3H), 2.62 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$)

δ: 191.7, 165.1, 158.2, 148.4, 142.7, 136.6, 134.2, 129.7, 127.1, 124.3, 30.6, 15.8. MS (*m/z*): 285 (M^++1), 228, 214, 182, 140, 112, 85.

6-Acetyl-5-methyl-3-*p*-tolyl-thieno[2,3-d]pyrimidine-4 (3H)-one (5o). Yellow needle. M.p.: 208-210 °C. IR (KBr): 3448 (NH), 1692 (CO), 1645 (CO) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.34-7.35 (d, *J* = 8.2 Hz, 2H), 7.25-7.26 (d, *J* = 8.2 Hz, 2H), 2.96 (s, 3H), 2.61 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 191.7, 165.1, 158.3, 148.6, 142.7, 139.7, 134.0, 130.3, 126.8, 124.3, 30.6, 21.2, 15.8. MS (*m/z*): 299 (M^++1), 214, 182, 118, 90.

6-Acetyl-5-methyl-3-(*p*-methoxyphenyl)-thieno[2,3-d] pyrimidine-4(3H)-one (5p). Orange needle. M.p.: 144-146 °C. IR (KBr): 3447 (NH), 1694 (CO), 1648 (CO) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.13 (s, 1H), 7.29-7.30 (d, *J* = 8.7 Hz, 2H), 7.04-7.05 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 2.96 (s, 3H), 2.62 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 191.7, 165.1, 160.2, 158.5, 148.7, 142.7, 134.0, 129.1, 128.2, 124.3, 114.9, 55.6, 30.6, 15.8. MS (*m/z*): 315 (M^++1), 214, 182, 134, 127.

6-Acetyl-5-methyl-3-(pyridin-2-yl)-thieno[2,3-d] pyrimidine-4(3H)-one (5q). Light yellow needle. M.p.: 190-192 °C. IR (KBr): 3447 (NH), 1697 (CO), 1667 (CO) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.63-8.64 (m, 1H), 8.56 (s, 1H), 7.90-7.93 (m, 1H), 7.80-7.81 (m, 1H), 7.42-7.44 (m, 1H), 2.97 (s, 3H), 2.62 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 191.7, 165.1, 157.7, 149.4, 149.0, 147.7, 142.8, 138.1, 134.0, 124.1, 121.9, 30.6, 15.8. MS (*m/z*): 286 (M^++1), 244, 182, 140, 96.

3,4,5,6,7,8-Hexahydro-4-oxo-3-phenyl-benzothieno[2,3-d]pyrimidine (5r). Yellow needle. M.p.: 170-172 °C. IR (KBr): 3447 (NH), 1678 (CO), 1560 (Ar) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.52-7.55 (t, *J* = 7.3 Hz, 2H), 7.47-7.49 (t, *J* = 7.8 Hz, *J* = 7.3 Hz, 1H), 7.38-7.39 (d, *J* = 7.8 Hz, 2H), 3.01-3.03 (t, *J* = 6.1 Hz, 2H), 2.80-2.82 (t, *J* = 6.1 Hz, 2H), 1.87-1.91 (m, 2H), 1.82-1.86 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.8, 157.5, 145.1, 137.2, 134.6, 132.1, 129.5, 129.1, 127.2, 122.9, 25.6, 25.3, 22.9, 22.2. MS (*m/z*): 283 (M^++1), 180, 152, 118.

3,4,5,6,7,8-Hexahydro-4-oxo-3-(*p*-toyly)-benzothieno[2, 3-d]pyrimidine (5s). Yellow needle. M.p.: 126-128 °C. IR (KBr): 3447 (NH), 1686 (CO), 1546 (Ar) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 7.96 (s, 1H), 7.31-7.32 (d, *J* = 7.8 Hz, 2H), 7.25-7.26 (d, *J* = 7.8 Hz, 2H), 3.01-3.02 (t, *J* = 6.0 Hz, 2H), 2.79-2.80 (t, *J* = 6.0 Hz, 2H), 2.42 (s, 3H), 1.80-1.96 (m, 2H), 1.87-1.92 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.8, 157.7, 145.3, 139.2, 134.6, 134.4, 132.0, 130.1, 126.9, 122.9, 25.6, 25.2, 22.9, 22.2, 21.2. MS (*m/z*): 297 (M^++1), 180, 164, 118.

The structure of compound **5s** was reconfirmed by x-ray (Fig. 1) [9].

3,6-Diphenyl-pyrimido[5′,6′:4,5]thieno[2,3,d] pyrimidine-4,5(3H,6H)-dione (5t). Green needle. M.p.: >300 °C. IR (KBr): 3447 (NH), 1682 (CO), 1677 (CO) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 8.17 (s, 2H), 7.51-7.53 (t, *J* = 7.3

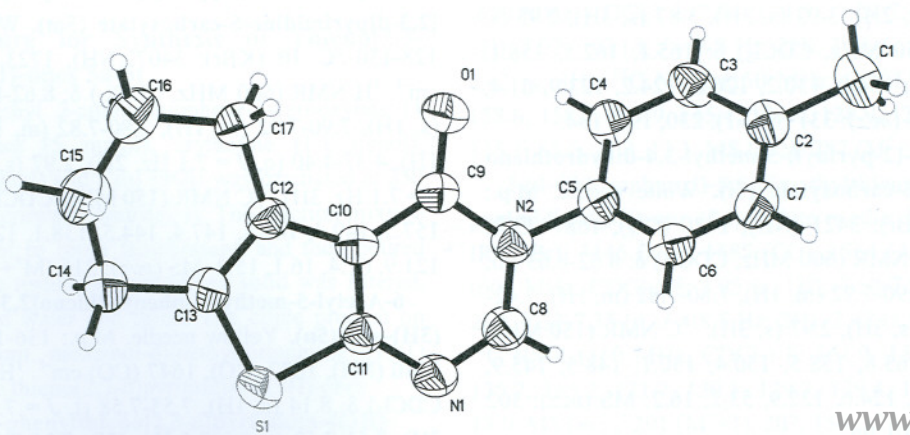
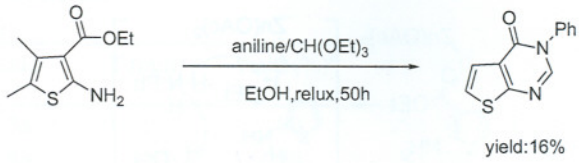


Fig. 1. The single structure of compound 5s.

Hz, J = 6.7 Hz, 4H), 7.47-7.49 (t, J = 6.7 Hz, 2H), 7.41-7.42 (t, J = 7.3 Hz, 4H). MS (m/z): 373 (M^++1), 287, 154, 134.

RESULTS AND DISCUSSION

We first intended to synthesize 3-phenyl thieno[2,3-d]pyrimidin-4(3H)-one from 2-amino-thiophene-3-carboxylate, aniline and orthoformate. But the yield was very low even after being refluxed in EtOH for 50 h (Scheme 4). We also used other polar solvents such as DMSO, THF or dioxane instead of EtOH, but we found out that the solvent did not have adequate effect to improve the yield of this reaction.



Scheme 4

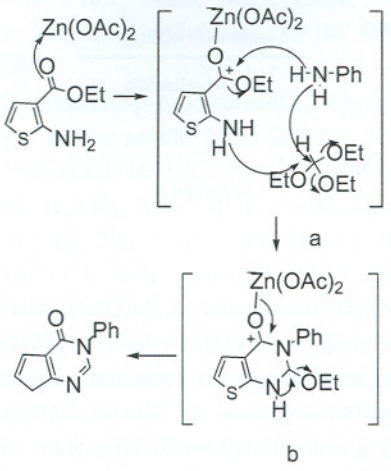
Nevertheless, when the catalytic amount of Lewis acid was added to the mixture of 2-amino-thiophene-3-carboxylate, aniline and orthoformate, after about 24h of refluxing, the yield of 3-phenyl thieno[2,3-d]pyrimidin-4(3H)-one could be improved to be moderate. Encouraged by this result, we screened all of the Lewis acids we could obtain and found out that $Zn(OAc)_2$ was the best catalyst. The results are presented in Table 2 which shows that 1% mol of $Zn(OAc)_2$ can catalyze this reaction quite adequately with a yield of 77%. If 0.5% mol of $Zn(OAc)_2$ was used in this reaction, the yield would be 72%. If, however, the amount of $Zn(OAc)_2$ was reduced to 0.1% mol, the yield would still be satisfactory (61%).

Accordingly, we propose a mechanism of the $Zn(OAc)_2$ catalyzed reaction as shown in Scheme 5. The $Zn(OAc)_2$ reacts with 2-amino-thiophene-3-carboxylate to form a carbocation which easily reacts with aniline and orthoformate to form intermediate a and b. This, in turn, gives the optimal compound, namely, 3-phenyl thieno[2,3-d]pyrimidin-4(3H)-one.

When we tried the reaction under microwave irradiation instead of normal heating using 0.5% mol $Zn(OAc)_2$ as catalyst, the yield was enhanced to 90% and the reaction time was reduced to only 5 min (Scheme 6).

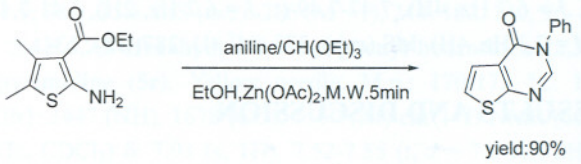
Table 2. Synthesis of 3-Phenyl thieno[2,3-d] pyrimidin-4(3H)-one in Refluxing EtOH Catalyzed by Different Lewis Acid

Lewis acid	Amount (mol%)	Refluxing time(h)	Yield (%)
$NiCl_2$	1	40	39
$Ni(OAc)_2$	1	48	63
AgCl	1	20	21
$AlCl_3$	1	24	51
$FeCl_2$	1	24	33
$FeCl_3$	1	24	48
$CuSO_4$	1	20	18
BF_3	1	24	62
$PdCl_2$	1	24	19
PdO	1	48	17
$ZnCl_2$	1	20	31
$MgSO_4$	1	24	20
$Zn(OAc)_2$	1	24	77
$Zn(OAc)_2$	0.5	24	72
$Zn(OAc)_2$	0.1	24	61



Scheme 5

Encouraged by the aforementioned results and with the suitable reaction conditions at hand, we tested the feasibility of the protocol using various arylamine and substituted thiophenes. Fortunately, this one-step procedure provided a straightforward synthetic route to the thieno[2,3-d]pyrimidin-4(3H)-one and additionally generated a set of functionalized molecules that are not readily available by other synthetic



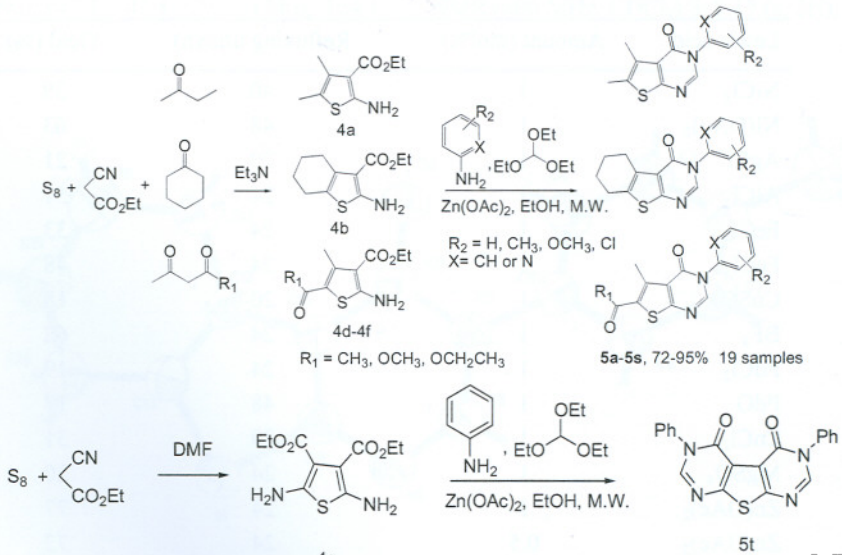
Scheme 6

methods. By this method, 2,5-diamino-thiophene-3,4-dicarboxylate can also be transformed into 5t. All the results are presented in Scheme 7 and Table 3.

In conclusion, we have established a new strategy for the synthesis of thieno[2,3-d]pyrimidin-4(3H)-one core structure catalyzed by $Zn(OAc)_2$ under microwave irradiation. The easy availability of the starting material, simple and convenient synthetic procedure for the formation of thieno[2,3-d] pyrimidin-4(3H)-one core structure render this method especially useful in synthetic and medicinal chemistry.

ACKNOWLEDGMENTS

This research was supported by the Cultivation and Construction Fund for the State Key Subject of Physical Chemistry. We thank the Testing Center of Yangzhou



Scheme 7

Table 3. Synthesis of Substituted-thieno[2,3-d]pyrimidin-4(3H)-one

Entry	R_1	R_2	X	Product	T (min)	Yield (%)[a]	m.p. (°C)[d]
1[b]		H	C	**5a**	5	90	162-164
2[b]		4-CH_3	C	**5b**	4.5	89	192-184
3[b]		4-OCH_3	C	**5c**	4	92	164-166
4[b]		4-Cl	C	**5d**	7	76	220-222
5[b]		3-Cl	C	**5e**	8	72	148-150
6	-OCH_3	H	C	**5f**	5	83	158-160
7	-OCH_3	4-CH_3	C	**5g**	4.5	87	216-218
8	-OCH_3	4-OCH_3	C	**5h**	4	95	238-240
9	-OCH_3	H	N	**5i**	6	82	236-238
10	-OCH_2CH_3	H	C	**5j**	5	84	160-162
11	-OCH_2CH_3	4-CH_3	C	**5k**	4.5	86	152-154
12	-OCH_2CH_3	4-OCH_3	C	**5l**	4	92	136-138
13	-OCH_2CH_3	H	N	**5m**	6	80	128-130
14	-CH_3	H	C	**5n**	5	87	136-138
15	-CH_3	4-CH_3	C	**5o**	4.5	88	208-210
16	-CH_3	4-OCH_3	C	**5p**	4	91	144-146
17	-CH_3	H	N	**5q**	6	81	190-192
18[c]		H	C	**5r**	5	83	170-172
19[c]		4-CH_3	C	**5s**	4.5	82	126-128
20				**5t**	5	88	>300

[a]Isolated yield. [b]Butan-2-one used as substrate. [c]Cyclohexanone used as substrate. [d]All the melting points list here are first report.

University for the characterization of our compounds. We also gratefully acknowledge the help we received from Dr. Liting Du for the crystal refinement.

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[9] CCDC 749793 contains the supplementary crystallographic data for the structures reported in this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif