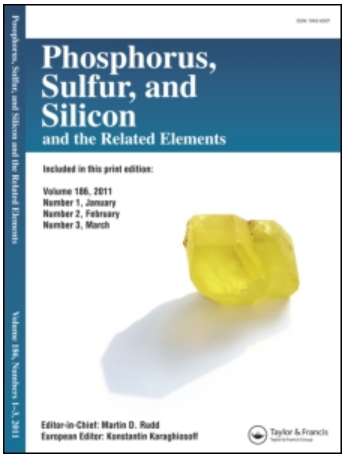

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Efficient Synthesis and Fungicidal Activities of 3,5,6,8-Tetrahydro-4*H*-thiopyrano[4',3' :4,5]thieno[2,3-d]pyrimidin-4-ones

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Efficient Synthesis and Fungicidal Activities of 3,5,6,8-Tetrahydro-4*H*-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones

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*The carbodiimides **4**, obtained from reactions of iminophosphorane **3** with aromatic isocyanates, reacted with amines, phenols, or ROH to give 2-substituted 3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno [2,3-d]pyrimidin-4-ones **6** in the presence of a catalytic amount of sodium alkoxide or solid potassium carbonate in satisfactory yields. Compounds **6** exhibited fungicidal activity. For example, compounds **6e**, **6m,** and **6s** showed 70% inhibition activities against Dothiorella gregaria in 100 mg/L.*

Keywords Aza-Wittig reaction; carbodiimide; fungicidal activity; iminophosphorane; thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-one

INTRODUCTION

The derivatives of heterocycles containing the thienopyrimidinones possess a broad spectrum of biological activities. They proved to show significant antifungal, antibacterial, antimicrobial, anticonvulsant, and angiotensin antagonistic activities.[1–7] Some of these compounds also show good antimalarial[8] or potent multitargeted receptor tyrosine kinase inhibitive activities.[9] However, there are few reports about the related thiopyranothienopyrimidinone systems,[10–12] which are of considerable interest as potential biological active heterocycles or pharmaceuticals. Recently we have become interested in the preparation

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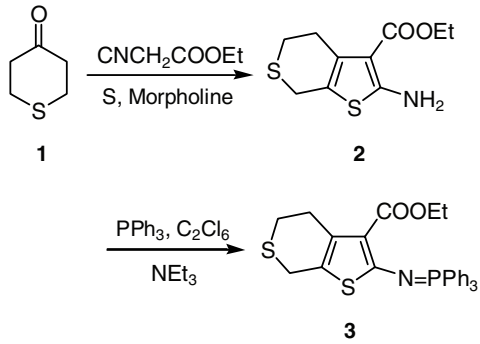
of N-heteroaryliminophosphoranes because these species are promising building blocks for the synthesis of nitrogen heterocycles.[13–16] Herein we wish to report an efficient synthesis and fungicidal activity of various 2-substituted 3,5,6,8-tetrahydro-4*H*-thiopyrano[4′,3′:4,5] thieno[2,3-d]pyrimidin-4-ones via iminophosphorane **3**.

RESULTS AND DISCUSSION

The ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-c]thiopyran-3-carboxylate **2**, easily obtained by Gewald method from tetrahydrothiopyran-4-one **1**, ethyl cyanoacetate, and sulfur in the presence of morpholine,[11] was converted to iminophosphorane **3** by treatment with triphenylphosphine, hexachloroethane, and triethylamine in dry acetonitrile (Scheme 1).



SCHEME 1

Iminophosphorane **3** reacted with an equimolar quantity of the aromatic isocyanates to give the carbodiimides **4**, which were allowed to react with aliphatic amines to provide guanidine intermediates **5** (Y = NR^1R^2). By treatment with sodium ethoxide in ethanol at room temperature, the intermediates **5** underwent intramolecular heterocyclization to give the expected 2-amino 3,5,6,8-tetrahydro-4*H*-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones **6a–6i** in satisfactory yields. The results are listed in Table I. The reaction of carbodiimide **4** with phenols produced 2-aryloxy-3,5,6,8-tetrahydro-4*H*-thiopyrano[4′,3′:4,5]thieno[2,3-d] pyrimidin-4-ones **6j–6o** (Y = OAr) in the presence of catalytic amount of potassium carbonate in good yields (Table I). When carried out in the presence of catalytic amount of RO^-Na^+, the reaction of carbodiimide **4** with ROH took place smoothly and 2-alkoxy-3,5,6,8-tetrahydro-4*H*-

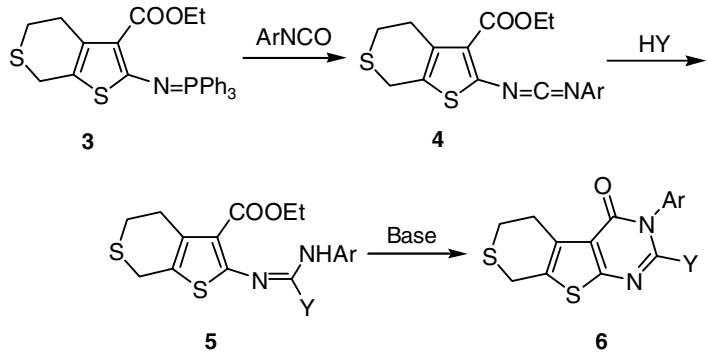
TABLE I Preparation of Compounds 6

No.	Ar	Y	Conditions	Yield (%)[a]
6a	Ph	1-piperidinyl	r.t./4 h	77
6b	Ph	1-pyrrolidinyl	r.t./4 h	88
6c	4-ClC_6H_4	4-morpholinyl	r.t./4 h	80
6d	4-ClC_6H_4	1-piperidinyl	r.t./6 h	83
6e	4-ClC_6H_4	1-pyrrolidinyl	r.t./6 h	82
6f	4-ClC_6H_4	NEt_2	r.t./6 h	85
6g	4-FC_6H_4	4-morpholinyl	r.t./6 h	92
6h	4-FC_6H_4	1-piperidinyl	r.t./5 h	88
6i	4-FC_6H_4	1-pyrrolidinyl	r.t./5 h	90
6j	Ph	PhO	r.t./5 h	84
6k	Ph	4-ClC_6H_4O	r.t./6 h	82
6l	Ph	4-MeC_6H_4O	r.t./4 h	89
6m	4-ClC_6H_4	PhO	r.t./5 h	82
6n	4-ClC_6H_4	4-ClC_6H_4O	r.t./6 h	80
6o	4-ClC_6H_4	4-MeC_6H_4O	r.t./5 h	81
6p	Ph	MeO	r.t./4 h	70
6q	Ph	EtO	r.t./6 h	75
6r	4-ClC_6H_4	MeO	r.t./5 h	71
6s	4-FC_6H_4	EtO	r.t./6 h	77

[a] Isolated yields based on iminophosphorane**3**.

thiopyrano[4′,3′:4,5]thieno[2,3-d] pyrimidin-4-ones **6p**–**6s** (Y = OR) were obtained in satisfactory yields (Table I, Scheme 2).

The structure of the synthesized compound **6** was confirmed by its spectral data and elemental analyses. For example, the IR spectra of **6a** revealed a C=O absorption band at 1678 cm^{-1}. The ^1H NMR spectral data of **6a** show the signals of $–NCH_2$ at 3.07 ppm as triplets,



SCHEME 2

TABLE II The Fungicidal Activities of Compounds 6

Compound	Inhibition rate (%, 100 mg/L)			
	Botrytis cinereaper	*Gibberella zeae*	*Dothiorella gregaria*	*Colletotrichum gossypii*
6a	13	17	60	9
6b	26	22	60	18
6c	39	35	60	18
6d	26	22	40	23
6e	48	26	70	18
6f	35	13	30	9
6g	35	22	30	18
6h	22	22	50	18
6i	30	30	60	23
6j	39	22	50	18
6k	26	22	0	13
6l	57	35	50	22
6m	22	27	70	14
6n	30	48	50	32
6o	22	30	50	23
6p	22	22	40	22
6q	35	22	50	13
6r	43	30	50	23
6s	30	35	70	27

and signals of piperidinyl ring's $CH_2CH_2CH_2$ at 1.22–1.41 ppm as multiplets. The thiopyran ring's signals appeared at 3.78 ppm (8-CH) as singlet and 2.91, 3.25 ppm (5,6-CH) as triplets. The phenyl signals appeared at 7.31–7.49 ppm. The MS spectrum of **6a** shows molecule ion peak (M^+) at m/z 383 with 100% abundance.

The biological activities of **6** were investigated, and the results showed that they exhibited moderate to low fungicidal activities. As indicated in Table II, most of the compounds showed moderate fungicidal activity against *Dothiorella gregaria* at a dosage of 100 mg/L, whereas all of them exhibited low fungicidal activities against *Botrytis cinereaper*, *Gibberella zeae*, and *Colletotrichum gossypii*. Compounds **6e**,**6m,** and**6s** showed the best inhibition activities (70%) against *Dothiorella gregaria* in 100 mg/L. (See Table II)

EXPERIMENTAL

Melting points were determined using a X-4 model apparatus and were uncorrected. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. MS were measured on a

Finnigan Trace MS spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus 600 (600 Hz) spectrometer and chemical shifts (δ) were given in ppm using $(CH_3)_4Si$ as an internal reference ($\delta = 0$). Elementary analyses were taken on a Vario EL III elementary analysis instrument.

Preparation of Ethyl 2-Amino-4,7-dihydro-5H-thieno[2,3-c] thiopyran-3-carboxylate (2)

To a stirred mixture of tetrahydrothiopyran-4-one (**1**; 5.8 g, 0.05 mol), sulfur (1.6 g, 0.05 mole), and ethyl cyanoacetate (5.7 g, 0.05 mol) in ethanol (20 mL), morpholine (6 mL) was added. The mixture was stirred at 45°C for 1 h. The product was crystallized after cooling. The formed yellow solid was separated and recrystallized from methanol to give **2** as light yellow crystals, 10.1 g (83%), m.p. 86–88°C, Lit.[11] m.p. 87–89°C.

Preparation of Ethyl 2-[(Triphenylphosphanylidene)amino]-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-carboxylate (3)

To a mixture of ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-c]thiopyran-3-carboxylate (**2**; 1.94 g, 8 mmol), triphenylphosphine (3.14 g, 12 mmol), and hexachloroethane (2.84 g, 12 mmol) in dry CH_3CN (30 mL), triethylamine (2.42 g, 24 mmol) at room temperature was added dropwise. The mixture was stirred for 2 h at room temperature. After the reaction mixture was poured into cold water (100 mL), the precipitate obtained was recrystallized from ethanol to give the desired iminophosphorane **3** in 89% yield with m.p. 200–202°C. ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, $J = 6.6$ Hz, CH_3), 2.82 (t, 2H, $J = 6.0$ Hz, CH_2), 3.03 (t, 2H, $J = 6.0$ Hz, CH_2), 3.44 (s, 2H, CH_2), 4.29 (q, 2H, $J = 6.6$ Hz, OCH_2), 7.47–7.81 (m, 15H, Ar-H). MS: m/z (%) 503 (M^+, 100%), 430 (59), 262 (88), 183 (67), 108 (50). Elemental Anal. Calcd. for $C_{28}H_{26}NO_2PS_2$: C, 66.88; H, 5.20; N, 2.78. Found: C, 66.62; H, 5.12; N, 2.97.

Preparation of 2-Dialkylamino-3,5,6,8-tetrahydro-4*H*-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones 6a–6i

To a solution of iminophosphorane **3** (1.01 g, 2 mmol) in anhydrous CH_2Cl_2 (10 mL), aromatic isocyanate (2 mmol) was added under nitrogen atmosphere at room temperature. After the reaction mixture was left unstirred for 6–12 h at 0–5°C, the iminophosphorane **3** had disappeared (TLC monitored). The solvent was removed under reduced

pressure and Et_2O/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimides **4**, which were used directly without further purification. To the solution of **4** in dichloromethane (10 mL) was added dialkylamine (2 mmol). After the reaction mixture was left unstirred for 4–6 h, the solvent was removed and anhydrous EtOH (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 6–12 h at room temperature. The solution was condensed, and the residue was recrystallized from EtOH to give the expected cyclic compounds **6a–6i** in good yields.

3-Phenyl-2-(1-piperidinyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6a)

Colorless crystals, m.p. 200–202°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.22–1.41 (m, 6H, $CH_2CH_2CH_2$), 2.91 (t, 2H, $J = 6.0$ Hz, CH_2), 3.07 (t, 4H, $J = 4.8$ Hz, $2NCH_2$), 3.25 (t, 2H, $J = 6.0$ Hz, CH_2), 3.78 (s, 2H, CH_2), 7.31–7.49 (m, 5H, Ar-H); IR (cm^{-1}), 1678, 1529, 1366, 1247; MS m/z (%), 383 (100, M^+), 368 (17), 350 (30), 77 (14). Elemental Anal. Calcd. for $C_{20}H_{21}N_3OS_2$: C, 62.63; H, 5.52; N, 10.96. Found: C, 62.87; H, 5.37; N, 10.88.

3-Phenyl-2-(1-pyrrolidinyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6b)

Colorless crystals, m.p. 226–228°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.68–1.74 (m, 4H, CH_2CH_2), 2.91 (t, 2H, $J = 6.0$ Hz, CH_2), 3.03 (t, 4H, $J = 5.4$ Hz, $2NCH_2$), 3.23 (t, 2H, $J = 6.0$ Hz, CH_2), 3.76 (s, 2H, CH_2), 7.30–7.48 (m, 5H, Ar-H); IR (cm^{-1}), 1689, 1528, 1343, 1296; MS m/z (%), 369 (100, M^+), 336 (42), 131 (15), 77 (21). Elemental Anal. Calcd. for $C_{19}H_{19}N_3OS_2$: C, 61.76; H, 5.18; N, 11.37. Found: C, 61.71; H, 5.02; N, 11.53.

3-(4-Chlorophenyl)-2-(4-morpholinyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6c)

Colorless crystals, m.p. 235–236°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.92 (t, 2H, $J = 5.4$ Hz, CH_2), 3.10 (t, 4H, $J = 4.2$ Hz, $2NCH_2$), 3.24 (t, 2H, $J = 5.4$ Hz, CH_2), 3.46 (t, 4H, $J = 4.2$ Hz, $2OCH_2$), 3.79 (s, 2H, CH_2), 7.29–7.49 (m, 4H, Ar-H); IR (cm^{-1}), 1684, 1535, 1362, 1246; MS m/z (%), 419 (100, M^+), 386 (26), 197 (16), 111 (19). Elemental Anal. Calcd. for $C_{19}H_{18}ClN_3O_2S_2$: C, 54.34; H, 4.32; N, 10.01. Found: C, 54.13; H, 4.38; N, 10.19.

3-(4-Chlorophenyl)-2-(1-piperidinyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6d)

Colorless crystals, m.p. 218–220°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.27–1.44 (m, 6H, $CH_2CH_2CH_2$), 2.91 (t, 2H, $J = 6.0$ Hz, CH_2), 3.06 (t, 4H, $J = 4.8$ Hz, $2NCH_2$), 3.23 (t, 2H, $J = 6.0$ Hz, CH_2), 3.78 (s, 2H, CH_2), 7.27–7.46 (m, 4H, Ar-H); IR (cm^{-1}), 1689, 1528, 1368, 1247; MS m/z (%), 417 (100, M^+), 384 (31), 194 (18), 84 (16). Elemental Anal. Calcd. for $C_{20}H_{20}ClN_3OS_2$: C, 57.47; H, 4.82; N, 10.05. Found: C, 57.42; H, 4.64; N, 10.21.

3-(4-Chlorophenyl)-2-(1-pyrrolidinyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6e)

Colorless crystals, m.p. 231–232°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.70–1.78 (m, 4H, CH_2CH_2), 2.91 (t, 2H, $J = 6.0$ Hz, CH_2), 3.05 (t, 4H, $J = 6.0$ Hz, $2NCH_2$), 3.21 (t, 2H, $J = 6.0$ Hz, CH_2), 3.75 (s, 2H, CH_2), 7.25–7.45 (m, 4H, Ar-H); IR (cm^{-1}), 1686, 1552, 1325, 1225; MS m/z (%),403 (100, M^+), 388 (17), 370 (37), 165 (12). Elemental Anal. Calcd. for $C_{19}H_{18}ClN_3OS_2$: C, 56.49; H, 4.49; N, 10.40. Found: C, 56.58; H, 4.55; N, 10.49.

3-(4-Chlorophenyl)-2-diethylamino-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6f)

Colorless crystals, m.p. 248–250°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.86 (t, 6H, $J = 7.2$ Hz, $2CH_3$), 2.92 (t, 2H, $J = 6.0$ Hz, CH_2), 3.06 (t, 4H, $J = 7.8$ Hz, $2NCH_2$), 3.23 (t, 2H, $J = 6.0$ Hz, CH_2), 3.78 (s, 2H, CH_2), 7.22–7.46 (m, 4H, Ar-H); IR (cm^{-1}), 1682, 1529, 1379, 1249; MS m/z (%), 405 (100, M^+), 376 (21), 266 (24), 197 (27). Elemental Anal. Calcd. for $C_{19}H_{20}ClN_3OS_2$: C, 56.21; H, 4.97; N, 10.35. Found: C, 56.48; H, 4.75; N, 10.22.

3-(4-Fluorophenyl)-2-(4-morpholinyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6g)

Colorless crystals, m.p. 282–283°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.92 (t, 2H, $J = 6.0$ Hz, CH_2), 3.09 (t, 4H, $J = 4.2$ Hz, $2NCH_2$), 3.24 (t, 2H, $J = 5.4$ Hz, CH_2), 3.45 (t, 4H, $J = 4.2$ Hz, $2OCH_2$), 3.79 (s, 2H, CH_2), 7.18–7.34 (m, 4H, Ar-H); IR (cm^{-1}), 1693, 1536, 1365, 1243; MS m/z (%), 403 (100, M^+), 370 (22), 197 (8), 95 (18). Elemental Anal. Calcd. for $C_{19}H_{18}FN_3O_2S_2$: C, 56.56; H, 4.50; N, 10.41. Found: C, 56.41; H, 4.36; N, 10.47.

3-(4-Fluorophenyl)-2-(1-piperidinyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6h)

Colorless crystals, m.p. 263–265°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.27–1.44 (m, 6H, $CH_2CH_2CH_2$), 2.92 (t, 2H, $J = 6.0$ Hz, CH_2), 3.07 (t, 4H, $J = 4.2$ Hz, $2NCH_2$), 3.24 (t, 2H, $J = 6.0$ Hz, CH_2), 3.79 (s, 2H, CH_2), 7.18–7.31 (m, 4H, Ar-H); IR (cm^{-1}), 1685, 1528, 1370, 1247; MS m/z (%), 401 (100, M^+), 368 (36), 178 (15), 84 (19). Elemental Anal. Calcd. for $C_{20}H_{20}FN_3OS_2$: C, 59.83; H, 5.02; N, 10.47. Found: C, 59.87; H, 4.88; N, 10.71.

3-(4-Fluorophenyl)-2-(1-pyrrolidinyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6i)

Colorless crystals, m.p. 220–222°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.72–1.78 (m, 4H, CH_2CH_2), 2.91 (t, 2H, $J = 6.0$ Hz, CH_2), 3.05 (t, 4H, $J = 6.0$ Hz, $2NCH_2$), 3.21 (t, 2H, $J = 6.0$ Hz, CH_2), 3.76 (s, 2H, CH_2), 7.15–7.30 (m, 4H, Ar-H); IR (cm^{-1}), 1685, 1529, 1344, 1217; MS m/z (%), 387 (100, M^+), 354 (39), 149 (24), 95 (24). Elemental Anal. Calcd. for $C_{19}H_{18}FN_3OS_2$: C, 58.89; H, 4.68; N, 10.84. Found: C, 58.72; H, 4.41; N, 10.91.

Preparation of 2-Aryloxy-3,5,6,8-tetrahydro-4*H*-thiopyrano[4′,3′:4,5]thieno[2,3-d] pyrimidin-4-ones 6j–6o

To the solution of **4** prepared above in dry acetonitrile (10 mL) was added substituted phenol (2 mmol) and cat. solid K_2CO_3 (0.03 g, 0.2 mmol). The mixture was stirred for 4–6 h at room temperature and filtered. The filtrate was condensed, and the residue was recrystallized from dichloromethane-petroleum ether to give 2-arlyoxy-3,5,6,8-tetrahydro-4*H*-thiopyrano[4′,3′:4,5] thieno[2,3-d]pyrimidin-4-ones **6j–6o**.

2-Phenoxy-3-phenyl-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6j)

Colorless crystals, m.p. 268–269°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.95 (t, 2H, $J = 6.0$ Hz, CH_2), 3.31 (t, 2H, $J = 5.4$ Hz, CH_2), 3.79 (s, 2H, CH_2), 7.12–7.56 (m, 10H, Ar-H); IR (cm^{-1}), 1696, 1550, 1358, 1208; MS m/z (%), 392 (100, M^+), 359 (74), 253 (24), 77 (32). Elemental Anal. Calcd. for $C_{21}H_{16}N_2O_2S_2$: C, 64.26; H, 4.11; N, 7.14. Found: C, 64.13; H, 4.35; N, 7.20.

2-(4-Chlorophenoxy)-3-phenyl-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6k)

Colorless crystals, m.p. 237–239°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.93 (t, 2H, $J = 6.0$ Hz, CH_2), 3.28 (t, 2H, $J = 5.4$ Hz, CH_2), 3.78 (s,

2H, CH_2), 7.05–7.56 (m, 9H, Ar-H); IR (cm^{-1}), 1691, 1551, 1354, 1209; MS m/z (%), 426 (100, M^+), 393 (79), 253 (40), 77 (31). Elemental Anal. Calcd. for $C_{21}H_{15}ClN_2O_2S_2$: C, 59.08; H, 3.54; N, 6.56. Found: C, 59.31; H, 3.51; N, 6.39.

2-(4-Methylphenoxy)-3-phenyl-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6l)

Colorless crystals, m.p. 254–255°C, ^1H NMR ($CDCl_3$, 600 MHz) δ 2.35 (s, 3H, CH_3), 2.93 (t, 2H, $J = 6.0$ Hz, CH_2), 3.29 (t, 2H, $J = 5.4$ Hz, CH_2), 3.77 (s, 2H, CH_2), 6.98–7.54 (m, 9H, Ar-H); IR (cm^{-1}), 1689, 1552, 1354, 1200; MS m/z (%), 406 (100, M^+), 373 (68), 253 (36), 77 (28). Elemental Anal. Calcd. for $C_{22}H_{18}N_2O_2S_2$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.93; H, 4.23; N, 6.95.

3-(4-Chlorophenyl)-2-phenoxy-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6m)

Colorless crystals, m.p. 279–281°C, ^1H NMR ($CDCl_3$, 600 MHz) δ 2.93 (t, 2H, $J = 6.0$ Hz, CH_2), 3.28 (t, 2H, $J = 5.4$ Hz, CH_2), 3.77 (s, 2H, CH_2), 7.10–7.52 (m, 9H, Ar-H); IR (cm^{-1}), 1702, 1549, 1355, 1206; MS m/z (%), 426 (100, M^+), 393 (61), 287 (23), 77 (26). Elemental Anal. Calcd. for $C_{21}H_{15}ClN_2O_2S_2$: C, 59.08; H, 3.54; N, 6.56. Found: C, 59.18; H, 3.31; N, 6.74.

2-(4-Chlorophenoxy)-3-(4-chlorophenyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6n)

Colorless crystals, m.p. 210–211°C, ^1H NMR ($CDCl_3$, 600 MHz) δ 2.92 (t, 2H, $J = 6.0$ Hz, CH_2), 3.26 (t, 2H, $J = 6.0$ Hz, CH_2), 3.77 (s, 2H, CH_2), 7.05–7.51 (m, 8H, Ar-H); IR (cm^{-1}), 1697, 1550, 1356, 1212; MS m/z (%), 460 (100, M^+), 427 (60), 287 (29), 111 (21). Elemental Anal. Calcd. for $C_{21}H_{14}Cl_2N_2O_2S_2$: C, 54.67; H, 3.06; N, 6.07. Found: C, 54.51; H, 3.13; N, 5.91.

3-(4-Chlorophenyl)-2-(4-methylphenoxy)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6o)

Colorless crystals, m.p. 253–255°C, ^1H NMR ($CDCl_3$, 600 MHz) δ 2.36 (s, 3H, CH_3), 2.93 (t, 2H, $J = 6.0$ Hz, CH_2), 3.27 (t, 2H, $J = 5.4$ Hz, CH_2), 3.77 (s, 2H, CH_2), 6.97–7.51 (m, 8H, Ar-H); IR (cm^{-1}), 1689, 1550, 1356, 1203; MS m/z (%), 440 (100, M^+), 407 (61), 287 (34), 91 (25). Elemental Anal. Calcd. for $C_{22}H_{17}ClN_2O_2S_2$: C, 59.92; H, 3.89; N, 6.35. Found: C, 59.74; H, 3.73; N, 6.39.

Preparation of 2-Alkoxy-3,5,6,8-tetrahydro-4H-thiopyrano [4′,3′:4,5] thieno[2,3-d] pyrimidin-4-ones 6p–6s

To the solution of **4** prepared above in ROH (10 mL) was added several drops of RONa in ROH. The mixture was stirred for 4–6 h at room temperature. The solution was condensed, and the residue was recrystallized from dichloromethane-petroleum ether to give 2-alkoxy-3,5,6,8-tetrahydro-4*H*-thiopyrano[4′,3′:4,5]thieno[2,3-d] pyrimidin-4-ones **6p–6s**.

2-Methoxy-3-phenyl-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6p)

Colorless crystals, m.p. 147–149°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.93 (t, 2H, $J = 6.0$ Hz, CH_2), 3.26 (t, 2H, $J = 5.4$ Hz, CH_2), 3.80 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3), 7.14–7.48 (m, 5H, Ar-H); IR (cm^{-1}), 1652, 1542, 1384, 1237; MS m/z (%), 330 (41, M^+), 297 (37), 283 (100), 77 (52). Elemental Anal. Calcd. for $C_{16}H_{14}N_2O_2S_2$: C, 58.16; H, 4.27; N, 8.48. Found: C, 58.37; H, 4.44; N, 8.41.

2-Ethoxy-3-phenyl-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6q)

Colorless crystals, m.p. 203–204°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.23 (t, 3H, $J = 7.2$ Hz, CH_3), 2.93 (t, 2H, $J = 6.0$ Hz, CH_2), 3.27 (t, 2H, $J = 5.4$ Hz, CH_2), 3.80 (s, 2H, CH_2), 4.40 (q, 2H, $J = 7.2$ Hz, OCH_2), 7.19–7.51 (m, 5H, Ar-H); IR (cm^{-1}), 1689, 1549, 1355, 1206; MS m/z (%), 344 (100, M^+), 311 (50), 283 (39), 164 (29). Elemental Anal. Calcd. for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.24; H, 4.85; N, 8.21.

3-(4-Chlorophenyl)-2-methoxy-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6r)

Colorless crystals, m.p. 197–199°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.93 (t, 2H, $J = 6.0$ Hz, CH_2), 3.24 (t, 2H, $J = 5.4$ Hz, CH_2), 3.79 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3), 7.15–7.46 (m, 4H, Ar-H); IR (cm^{-1}), 1700, 1555, 1350, 1092; MS m/z (%), 364 (100, M^+), 349 (37), 331 (70), 153 (30). Elemental Anal. Calcd. for $C_{16}H_{13}ClN_2O_2S_2$: C, 52.67; H, 3.59; N, 7.68. Found: C, 52.53; H, 3.78; N, 7.41.

2-Ethoxy-3-(4-fluorophenyl)-3,5,6,8-tetrahydro-4H-thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-4-ones (6s)

Colorless crystals, m.p. 128–130°C, ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.24 (t, 3H, $J = 7.2$ Hz, CH_3), 2.93 (t, 2H, $J = 6.0$ Hz, CH_2), 3.26 (t, 2H, $J = 5.4$ Hz, CH_2), 3.79 (s, 2H, CH_2), 4.40 (q, 2H, $J = 7.2$ Hz, OCH_2),

7.15–7.20 (m, 4H, Ar-H); IR (cm^{-1}), 1676, 1518, 1344, 1090; MS m/z (%), 362 (100, M^+), 329 (35), 301 (34), 151 (23). Elemental Anal. Calcd. for $C_{17}H_{15}FN_2O_2S_2$: C, 56.34; H, 4.17; N, 7.73. Found: C, 56.48; H, 4.10; N, 7.81.

Bioassays of Fungicidal Activities

The tested samples were dissolved in 10 mL of DMF at a concentration of 500 mg/L. The solutions (2 mL) were mixed rapidly with thawed potato glucose agar culture medium (8 mL) under 50°C. The mixture was poured into Petri dishes. After the dishes were cooled, the solidified plates were incubated with 4 mm mycelium disk, inverted, and incubated at 28°C for 48 h. The mixed medium without sample was used as the blank control. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I is the growth inhibition rate (%), C is the control settlement radius (mm), and T is the treatment group fungi settlement radius (mm).

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