HETEROCYCLES, Vol. 92, No. 5, 2016, pp. 866 - 885. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 29th January, 2016, Accepted, 22nd March, 2016, Published online, 30th March, 2016
DOI: 10.3987/COM-16-13427

EFFICIENT CONSTRUCTIONS OF THE FOUR DIFFERENT THIENOPYRIMIDINONE SKELETONS VIA VARIOUS CYCLOCONDENSATION OF *o*-AMINOTHIENONITRILE WITH CARBONYL COMPOUNDS

Junjuan Yang, Daxin Shi, Kai Zhang, Zhangtao Zhao, Fadong Qiu, Yujiao Bi, Qi Zhang, and Jiarong Li*

School of Chemical Engineering and Environment, Beijing Institute of Technology, 100081 Beijing, China; E-mail: jrli@bit.edu.cn

Abstract – A series of new thienopyrimidinone derivatives were synthesized *via* a novel, straightforward and efficient tandem cyclocondensation of *o*-aminothienonitrile **1** and carbonyl compounds **2** in different conditions. The synthesized four thienopyrimidinone skeletons were thieno[2,3-*d*]pyrimidinone **3**, *tert*-hydroxythieno[2,3-*d*]pyrimidinone **4**, symmetrical tetracycle thienothiophene-pyrimidone **5** and thienopyrimidine **6** respectively. Their plausible mechanisms were proposed. The properties of compound **5** were investigated.

INTRODUCTION

Thienopyrimidinone derivatives are a highly significant class of nitrogen and sulfur heterocycles and have received a great interest for pharmaceutical applications and their wide biological activities such as anticancer, antimalarial, antiinflammatory, antiplasmodial, anticonvulsant and sensitizer (Figure 1).[1] Therefore, much attentions have been devoted to the synthesis of thienopyrimidinones. The classical synthetic approach toward thienopyrimidinone employed the condensation of cyclic ketones and *o*-aminothiophene dicarboxamide, which are usually obtained from the hydrolysis of the corresponding *o*-aminonitriles.[2] And there is still a clear need for versatile methods under environmentally benign conditions and available starting. The seeking of an efficient synthesis of the thienopyrimidinone is one of the challenges in modern synthetic community and *o*-aminothienonitrile **1** seemed to be the precursor of choice to meet this objective.[3] Recently, tandem or domino reaction and multicomponent one-pot processes are the most common approaches to meet the demand of sustainability and green chemistry.[4] Based on the above considerations and following on our previous investigations on green synthetic protocol of heterocyclic compounds,[5,6] we wish to report the green method for synthesis the new thienopyrimidinone derivatives (Figure 2, compounds **3**, **4**, **5**, **6**) with different skeletons through controlled cyclization pathways of *o*-aminothienonitrile and carbonyl compounds in tandem one-pot reaction which have not been reported.

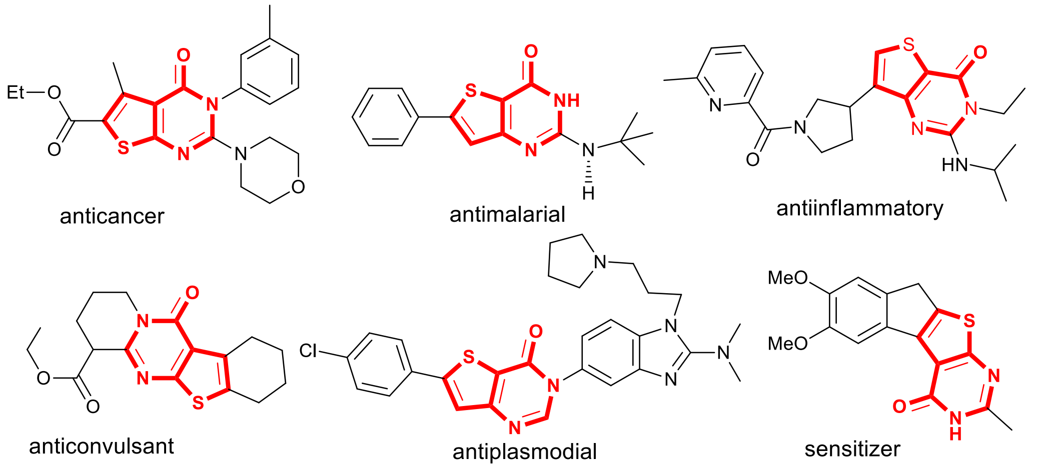


Figure 1. Selected example of biologically active thienopyrimidinone

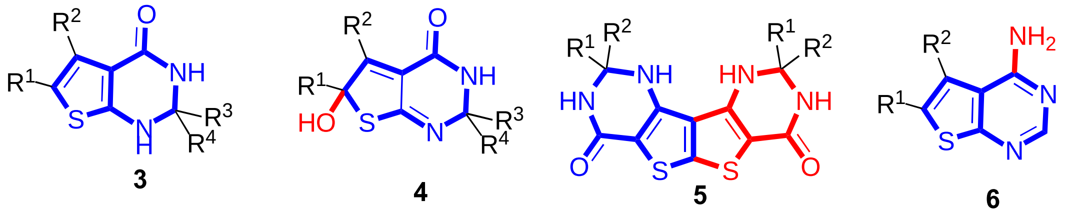


Figure 2. The synthesized thienopyrimidinone skeletons in our research

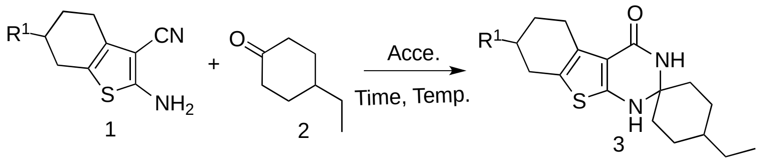
RESULTS AND DISCUSSION

As an eco- and atom-economy, efficient synthetic method of fused heterocycle, cyclocondensations of aromatic *o*-aminonitriles and carbonyl compounds *via* PDF reaction (the Pinner to Dimroth rearrangement in the Friedlander conversion)[7] led to a lot of different nitrogen-containing heterocyclic compounds such as dihydroquinazoline,[8] benzo[*f*]pyrimidinone,[7] pyrazolopyrimidinone,[9] pyrido[2,3-*d*]pyrimidinone[10] and pyrimido[4,5-*d*]pyrimidinone.[6] Intrigued by the important bioactivity of thieno[2,3-*d*]pyrimidinone and the extension of PDF reaction, we focused our attentions on the convenient synthesis of sulfur-containing heterocyclic compounds, and the four different thienopyrimidinone skeleton derivatives were synthesized from the tandem one-pot condensation of *o*-aminothienonitrile and carbonyl compounds in the presence of base or Lewis acid.

THIENO[2,3-*d*]PYRIMIDINONE DERIVATIVES (3)

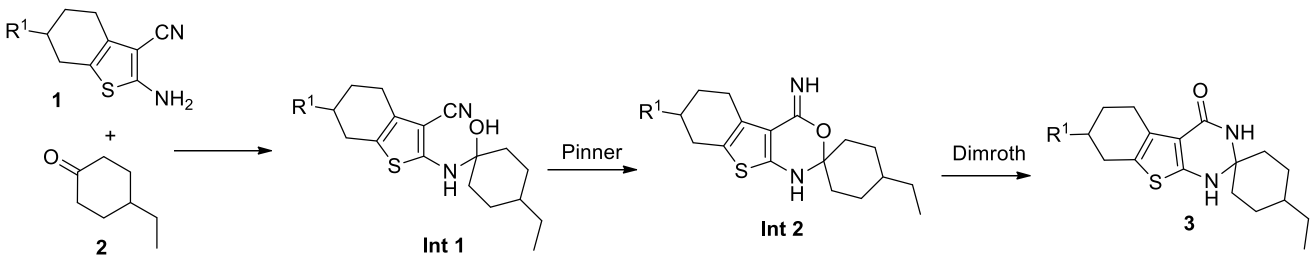
The key raw substrate *o*-aminothienonitrile **1** used in our study was prepared from the Gewald reaction

Table 1. Optimized conditions for the synthesis of thieno[2,3-*d*]pyrimidinone **3**[a]



Entry	Accelerant (1 equiv)	Solvents	Temp. (°C)	Time (h)	R^1	Product	Yield[b]
1	$ZnCl_2$	**2**	120	3	H	**3a**	trace
2	NaOH	**2**	120	3	H	**3a**	75.3
3	MeONa	**2**	120	3	H	**3a**	80.8
4	EtONa	**2**	120	3	H	**3a**	85.5
5	EtONa	EtOH	reflux	3	H	**3a**	69.5
6	EtONa	MeCN	reflux	3	H	**3a**	50.5
7	EtONa	DMF	120	3	H	**3a**	32.5
8	EtONa	**2**	80	3	H	**3a**	65.6
9	EtONa	**2**	100	3	H	**3a**	80.6
10	EtONa	**2**	140	3	H	**3a**	83.2
11	EtONa	**2**	120	1	H	**3a**	54.7
12	EtONa	**2**	120	2	H	**3a**	76.3
12	EtONa	**2**	120	4	H	**3a**	86.9
14	EtONa	**2**	120	5	H	**3a**	88.2
15	EtONa	**2**	120	3	Me	**3b**	86.1
16	EtONa	**2**	120	3	Et	**3c**	87.2

[a] Reactions conditions: **1** (1 mmol), **2** (1.5 mmol), Acce. (1 equiv) in solvent (3.0 mL). [b] Isolated yields.



Scheme 1. The synthesis of thieno[2,3-*d*]pyrimidinone **3**

according to the literature procedure.[11] The reactivity of the *o*-aminothienonitriles **1a** toward active ketones **2a** as model substrates was investigated to optimize the conditions from the various accelerant ($ZnCl_2$, pyridine, NaOH, KOH, MeONa, EtONa), temperature, time and solvents, and the appreciated results were presented in Table 1. Additionally, 120 °C was a better reaction temperature compared to the others (entries 8-10). On the other hand, the yield of compound **3** was increased with the rasing of time, but 3.0 h was the better selection (entries 11-14). Furthermore, treatment of compound **1** with cyclohexanone **2** in presence of accelerant of EtONa under the optimum conditions gave the thieno[2,3-*d*]pyrimidinone **3a**, **3b** and **3c** in good yield of 85.5%, 86.1% and 87.2% respectively (entries 4, 15 and 16). The structures of **3** were established based on the spectral data.[12] For example, the IR spectrum of compound **3b** showed absorb bands at 3247, 3208 (NH) and 1618 cm^{-1} (C=O). Its ^1H NMR (400 Hz, DMSO-d_6) revealed singlet at 7.28 and 7.11 ppm assigned for two NH and its HRMS spectrum showed the ESI peak at 319.1843. Based on the data and our previous results, the possible mechanism can be explained as follows: Firstly, intermediate **Int 1** was produced by the addition of the amino group of **1** onto the carbonyl of cyclohexanone **2** and creation of a N-C bond; Then the OH group of **Int 1** attacked the nitrile group of the *o*-aminothienonitriles **1** to afford oxazine **Int 2** *via* intramolecular Pinner reaction. Thereafter, **Int 2** rearranged to the final product **3** (Dimroth rearrangement). And we named it as PDF conversion (Scheme 1).[7]

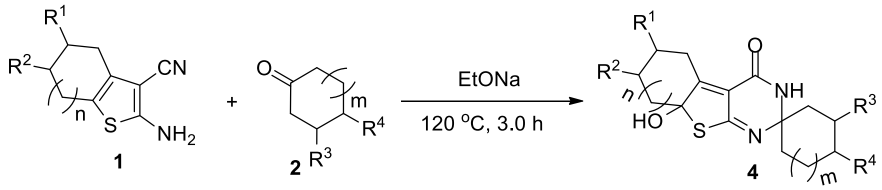
TERTIARY HYDROXYL THIENO[2,3-*d*]PYRIMIDINONE DERIVATIVES (4)

For reducing the toxicity and increasing the biological activity, modified functional group on drug skeleton was a conventional process and introducing a hydroxyl group has been considered as a facile strategy in the pharmaceutical research. It was worthy to synthesize the *tert*-hydroxythieno[2,3-*d*]pyrimidinone **4** which both the tertiary hydroxyl group and thieno[2,3-*d*]pyrimidinone framework are combined into such a molecule. Normally, the traditional synthesis of a *tert*-hydroxyl heterocyclic derivatives includes a two step process: the organic heterocyclic skeleton was firstly constructed; and then the tertiary hydroxyl group was introduced by microbial epoxidation,[13] vivo oxidation of secondary hydroxyl series,[14] alkylation of carbonyl compound,[15] hydroxylation of *α*-furyllithium,[16] asymmetric Michael addition[17] and photocatalytic oxygention.[18] Notably, photocatalytic reactions played important roles in both natural and artificial systems. Inspired by the interesting works of photo-assisted synthesis and the previous results, we sought to develop a method for the preparation of the *tert*-hydroxythieno[2,3-*d*]pyrimidinone **4** *via* a green one-step tandem process of *o*-aminothienonitrile and carbonyl compounds.

Initially, the reaction of the *o*-aminothienonitrile **1a** and ketone **2a** afforded the fused heterocyclic derivatives **4a** containing a *tert*-hydroxyl substituted thieno[2,3-*d*]pyrimidinone in the presence of EtONa at 120 °C with the 380 nm UV lamp irradiation (Table 2, entry 1). And a series of *o*-aminothienonitriles **1** and ketones **2** were employed to apply this reaction to give more corresponding *tert*-hydroxythieno[2,3-*d*]pyrimidinones **4** (Table 2). Interestingly, only the reaction of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile **1a** and cyclohexanone **2a** ($m = n = 1$) provided the aimed product **4**, and other designed product ($m \neq 1$ or $n \neq 1$) was not obtained according to our experiment results (entries 1-9). Evidently, the substituted group on **1** and **2** significantly impacted the preparation of **4** and only the six-membered naphthenic hydrocarbon substituted **1** and **2** ($m = n = 1$)

could receive the corresponding derivatives **4** with good yields perhaps for the steric hindrance and ring tension. A series of six-membered naphthenic hydrocarbon substituted substrates **1** and **2** (m = n = 1) could be used for the synthesis of the *tert*-hydroxylated fused thiophene derivatives **4** (entries 10-21). The results showed that the reactions were tolerated and afforded derivatives **4b**-**4m** respectively when **1** and **2** bear an electron-donating group (R^2 = *m*-, *p*-, Me, Et). The hydroxylated fused thiophene derivatives **4** were formed in one-pot of the different six-membered naphthenic hydrocarbon substituted on compounds **1** and **2** perhaps for the thermodynamic stability of six-membered ring and low strain of cyclohexane collective effect.[19]

Table 2. The synthesis of *tert*-hydroxythieno[2,3-*d*]pyrimidinone **4**[a]



Entry	n	m	R^1	R^2	R^3	R^4	Product	Yield[b]
1	1	1	H	H	H	H	**4a**	65.7
2	0	0	H	H	H	H	--[c]	trace
3	0	1	H	H	H	H	--	trace
4	0	2	H	H	H	H	--	trace
5	1	0	H	H	H	H	--	trace
6	1	2	H	H	H	H	--	trace
7	2	0	H	H	H	H	--	trace
8	2	1	H	H	H	H	--	trace
9	2	2	H	H	H	H	--	trace
10	1	1	H	H	H	Me	**4b**	73.5
11	1	1	H	H	H	Et	**4c**	60.2
12	1	1	H	H	Me	H	**4d**	80.1
13	1	1	Me	H	H	H	**4e**	57.8
14	1	1	Me	H	Me	H	**4f**	66.3
15	1	1	Me	H	H	Me	**4g**	57.6
16	1	1	Me	H	H	Et	**4h**	75.2
17	1	1	H	Me	H	H	**4i**	71.5
18	1	1	H	Me	Me	H	**4j**	78.3
19	1	1	H	Me	H	Me	**4k**	72.1
20	1	1	H	Et	Me	H	**4l**	70.8
21	1	1	H	Et	H	Me	**4m**	59.6

[a] Reactions conditions: **1a** (1 mmol), EtONa (1 equiv) in corresponding ketones **2** (3.0 mL) at 120 °C for 3.0 h under irradiation with 380 nm UV lamp. [b] Isolated yields. [c] The products **4** were not found by TLC or MS.

The chemical structures of target compounds **4** were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS, while product **4a** was unequivocally confirmed by X-ray diffraction analysis (Figure 3).

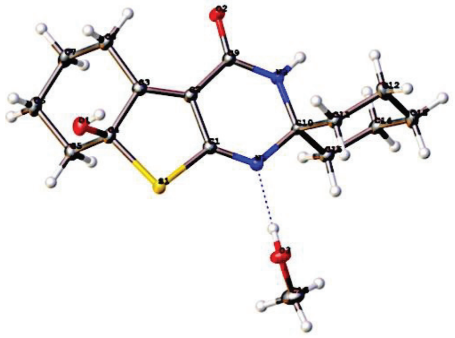
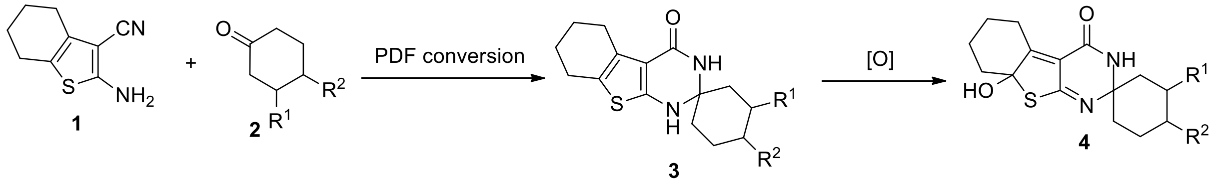


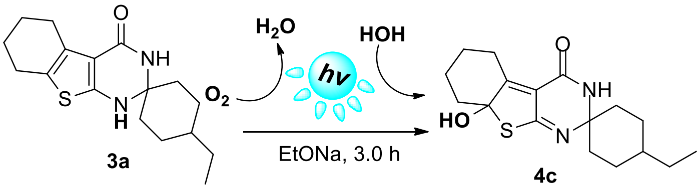
Figure 3. Molecular structure of compound **4a**

Based on the synthesis of heterocyclic compounds **3**, the mechanism can be explained as follows: Intermediate **3** was produced by the PDF reaction, and then **3** slowly translate to the hydroxylated target materials **4** *via* a tandem reaction of photo-oxygenation (Scheme 2).[20]



Scheme 2. The synthesis of *tert*-hydroxythieno[2,3-*d*]pyrimidinone derivatives **4**

In order to prove the proposed mechanism, the intermediate **3** was tried to be separated, and fortunately, **3a** was detected by TLC and isolated by thin-layer chromatography in the reaction of **1** with carbonyl compound **2** with the 380 nm UV lamp irradiation after 1.0 h. Then **3a** was induce-oxygenated in ketones solvent in the presence of EtONa with the 380 nm UV lamp irradiation and gave the targeted product **4c** in 60.2% yield (Scheme 3).



Scheme 3. The synthesis of **4c** by the oxidation of **3a** under the UV lamp irradiation

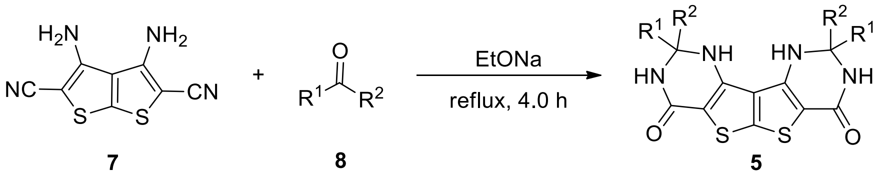
SYMMETRICAL TETRACYCLE THIENOTHIOPHENEPYRIMIDONE DERIVATIVES (5)

As well documented in the literature, organic compound of the 10*π* rich thieno[2,3-*d*]thiophene, a bifused skeleton, have attracted considerable attention in the development of axially chiral systems and nonlinear optics materials.[21] In the last decades, thieno[2,3-*d*]thiophene derivatives have found applications as pesticides, ligand of transition metal and clathrate crystals, dyes, etc.[22] Taking into account the importance of symmetrical thieno[2,3-*d*]thiophene and thienopyrimidinone cores in both biological and chemical fields, the direct approaches to the preparation of symmetrical tetracycle thienothiophene-pyrimidone derivatives (**5**) *via* an efficient tandem procedure was remain highly valuable additions.

SYNTHESES

3,4-Diaminothieno[2,3-*d*]thiophene-2,5-dicarbonitrile **7** was prepared according to the literature methods.[23] Initial attempts were made by heating a mixture of equal molar amounts of **7** and cyclic ketones **8** under refluxing in the presence of EtONa for 4.0 h and the corresponding tetrahydrothienothiophenepyrimidone compounds **5h** was obtained in a moderate yields through PDF conversion. The reactions with a series of ketones including aliphatic ketones and aromatic ketones or aldehyde were all investigated and the results were summarized in Table 3.

Table 3. The synthesis of symmetric fused thienopyrimidinone derivatives **5**[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	Me	Me	**5a**	74
2	Me	Et	**5b**	61
3	Me	*n*Pr	**5c**	62
4	Et	Et	**5d**	60
5	Me	*i*Pr	**5e**	56
6	Me	*i*Bu	**5f**	66
7	R^1+R^2=$(CH_2)_4$		**5g**	62
8	R^1+R^2=$(CH_2)_5$		**5h**	68
9	R^1+R^2=$(CH_2)_6$		**5i**	64
10	R^1+R^2=$(CH_2)_5Me$		**5j**	50
11	Me	Ph	**5k**	76
12	Et	Ph	**5l**	71
13	H	*n*Pr	**5m**	69

[a] Reactions conditions: **7** (1 mmol), EtONa (2 equiv) in corresponding ketones **8** or ethanol (3.0 mL) refulx for 4.0 h. [b] Combined yield of isolated crude products.

While the cyclic ketones such as cyclopentanone, cyclohexanone, cycloheptanone and methylcyclohexanone were used, the reaction in ethanol had the moderate yield (Table 3, entries 1-4) perhaps for the ring tension of cyclic ketones. Theoretically, the steric hindrance and ring tension may effect on the reaction. As expected, the larger steric hindrance of ketones afforded the lower yields (Table 3, entries 4-13).

STRUCTURE ANALYSIS

Figure 4. Molecular structure of compound of **5a** (left) and **5h** (right)

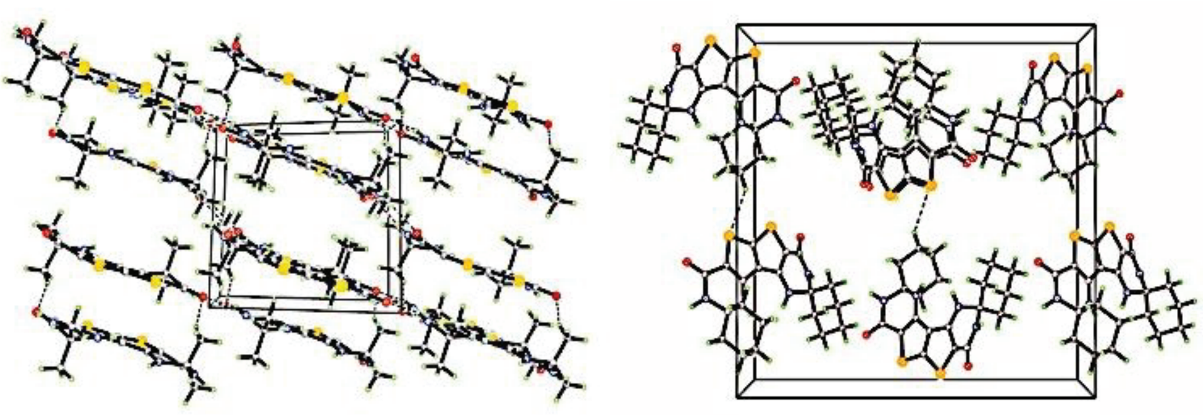


Figure 5. Packing diagram of compound **5a** (left) and **5h** (right)

The target compounds **5** were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS, while product **5a** and **5h** were confirmed by X-ray diffraction analysis (Figure 4). Compounds **5** were symmetrical and showed the similar structure containing a tetracyclic thienothiophenepyrimidone fused system. In these tetracyclic fused ring system, the tetrahydrothienothiophenepyrimidone center afford the π-conjugated interaction rigid planar structure which could lead to the large ultraviolet absorption and photoluminescence.[24] Furthermore, novel intermolecular interactions were noticed. As shown in Figure 5, in the packing crystal of compound **5a** and **5h**, there were numbers of molecular pairs and they packed in a parallel and face to face style. Each molecular pair were joined by hydrogen bonds, π-conjugation and formed a dimer.[25] Based on the special structure of hydrogen bond and π-conjugated interaction, we can conjecture that compound **5** will show better thermal stable and good optical properties.

THERMAL STABLE PROPERTIES

The thermal properties of selected **5a** and **5h** were gauged by thermogravimetric analysis (TGA). Both of them exhibited high thermal stability as demonstrated by its TGA (Figure 6), with its rapid weight loss temperature being up to 330.0 and 335.0 ºC. Notable, the weight loss temperature at 150 ºC attributed to the loss of DMF crystallization. Additionally, **5h** showed a higher melting temperature with a higher molecular weight.

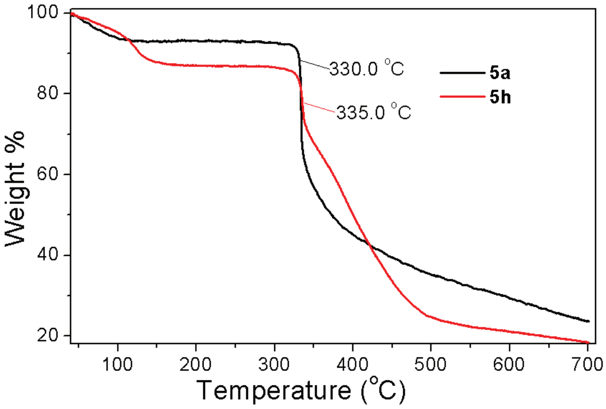


Figure 6. TG plots of **5a** and **5h** under N_2 atmosphere

OPTICAL PROPERTIES

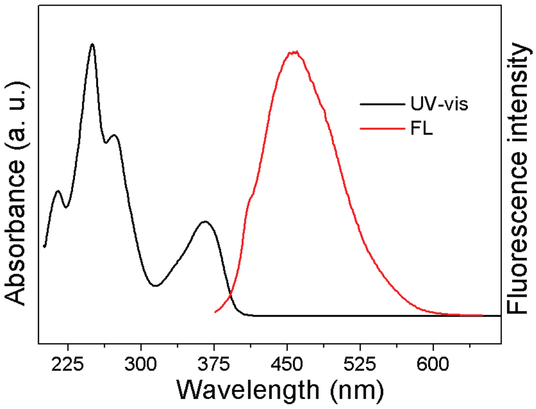


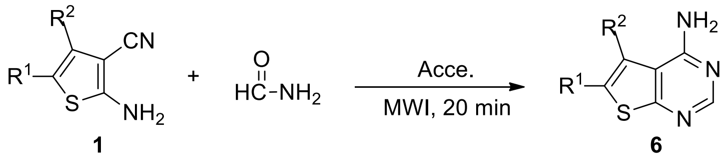
Figure 7. UV-vis absorption spectra (UV-vis) and fluorescence emission (FL) excited at 365 nm (right) of compound **5h** in ethanol solution at room temperature with the same concentration of 10 µM

The optical properties of compound **5h** was examined by UV-vis and photoluminescence (PL) techniques in ethanol solvent (Figure 7). As shown in Figure 7, compound **5h** exhibited characteristic absorptions in EtOH with a sharp absorption band centered at 238 nm and a broad one centered at 365 nm assigned to a planar aromatic tetracyclic thienothiophenepyrimidone skeletons center π-conjugated interactions. Additionally, compound **5h** gave a good fluorescent emission ($\Phi = 0.18$) at 478 nm in MeCN and a better fluorescent emission ($\Phi = 0.21$) at 475 nm in EtOH. These results revealed that compound **5** have excellent thermally stable properties and good optical properties with the more potential applications in organic semiconductor.[24]

THIENOPYRIMIDINES DERIVATIVES (6)

In view of the potential use of thienopyrimidines **6** as biological agents and drugs,[25] in a follow up of this investigation,[26] we turned our attention on the possibility for the synthesis of heterocyclic thienopyrimidines center *via* green process. The traditional synthetic approach towards thienopyrimidines suffered from the tedious synthetic routes and time-consuming experimental procedures. Classically, microwave irradiation has taken an important role in chemical laboratory practice for clean, fast and convenient energy source. With respect to the valuable thienopyrimidines and in continuation of our efforts on the green reaction of *o*-aminothienonitrile,[9,27] an immediate, simple and straightforward protocol for the synthesis of thienopyrimidines **6** was studied through the condensation of *o*-aminothienonitrile and formamide catalyzed by $ZnCl_2$ in DMF under microwave irradiation, and some results were presented here (Table 4).

Table 4. The synthesis of thienopyrimidines derivatives **6**[a]



Entry	Accelerant (1 equiv)	Solvents	R^1+R^2	Product	Yield[b]
1	EtONa	DMF	$R^1+R^2 = (CH_2)_3$	**6a**	56.9
2	EtONa	DMF	$R^1+R^2 = (CH_2)_4$	**6b**	61.2
3	EtONa	DMF	$R^1+R^2 = (CH_2)_5$	**6c**	63.1

[a] All reactions were carried out at variable power in a Biotage microwave reactor for 20 min using **1** (1 mmol), formamide (0.5 mL) and $ZnCl_2$ (1.2 equiv) in DMF (1.5 mL) at reflux for 4.0 h. [b] Isolated yields.

CONCLUSION

In conclusion, the four new thienopyrimidinone skeletons were synthesized *via* a tandem one-pot cyclocondensation reaction of *o*-aminothienonitrile and carbonyl compounds in different conditions. The mild conditions, simple execution and good yields of products, made it an efficient and promising synthetic strategy to build thienopyrimidinone skeletons with the potential applications in drugs or semiconductor. The synthetic derivatives showed good thermal stable and optical properties.

EXPERIMENTAL

General Methods: The starting materials **1** and **7** were prepared according to the literature methods.[11,23] The solvents and other reagents were purchased from commercial sources and used without further purification. Melting points were determined using XT4 microscope melting point apparatus (uncorrected). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer with KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at a Bruker 400 or 500 MHz spectrometer with TMS as the internal standard. Mass spectra were obtained with ESI ionization using a Bruker APEX IV and ZAB-HS mass spectrometer. Ultravioletevisible (UV-vis) absorption were measured on a Hitachi U-3900H spectropho-tometer using quartz cells of 1.0 cm path length (190-1100 nm scan range). Fluorescence spectra measurements were performed on a Hitachi F-7000 spectrofluorimeter with quartz cuvettes of 1.0 cm path length with a xenon lamp as the excitation source. Luminescence quantum yields were measured using a solution of quinine sulfate in sulfuric acid (0.5M) as a standard (Φ = 0.54)[28] and were corrected for the different refraction indexes of the solvents. TGA was recorded on TGDTA 6200 LAB SYS.

General Procedure for the Synthesis of 3: To a mixture of compound **1** (1 mmol) and corresponding ketones **2** (3 mL), 1 equiv of sodium ethoxide was added dropwise under stirring, and then the reaction mixture was heated at 120 °C for 3.0 h. The reaction mixture was cooled to room temperature after the reaction finished with TLC monitoring. The resulting precipitate was collected by filtration. The crude products were recrystallized from 95% EtOH to afford pure compounds **3**.

4'-Ethyl-5,6,7,8-tetrahydro-1*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(3*H*)-one (3a): White solid; mp 278-279 °C; IR (KBr, υ, cm^{-1}) 3247, 3207, 3026, 2928, 2851, 1618, 1573, 1536, 1597, 1438; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 7.29 (s, 1H), 7.11 (s, 1H), 2.65 (q, *J* = 8.0 Hz, 2H), 2.45 (t, *J* = 8.0 Hz, 2H), 2.00 (t, *J* = 8.0 Hz, 2H), 1.71-1.13 (m, 13H), 0.85 (t, *J* = 12.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 162.1, 156.4, 132.2, 118.2, 108.8, 92.8, 77.4, 70.9, 37.8, 35.8, 28.2, 26.9, 25.9, 24.3, 23.5, 22.5, 12.1; HRMS (ESI): calcd For $C_{17}H_{24}N_2OS$ [M+H]$^+$ 305.16821; found 305.16848.

4'-Ethyl-7-methyl-5,6,7,8-tetrahydro-1*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(3*H*)-one (3b): White solid; mp 259-260 °C; IR (KBr, υ, cm^{-1}) 3387, 3248, 3208, 3029, 2950, 2918, 2846, 2832, 1619, 1574, 1536, 1496, 1439; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 7.28 (s, 1H), 7.11 (s, 1H), 2.88-2.84 (m, 1H), 2.56-2.47 (m, 1H), 2.12-1.14 (m, 16H), 1.00 (d, *J* = 8.0 Hz, 3H), 0.87 (t, *J* = 16.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 162.2, 156.5, 131.9, 117.8, 108.7, 93.0, 77.5, 37.8, 35.8, 32.5, 30.9, 29.7, 28.4, 28.2, 26.9, 25.6, 21.9, 12.1; HRMS (ESI): calcd For $C_{18}H_{26}N_2OS$ [M+H]$^+$ 319.1839; found 319.1843.

4',7-Diethyl-5,6,7,8-tetrahydro-1*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(3*H*)-one (3c): White solid; mp 250-252 °C; IR (KBr, υ, cm^{-1}) 3246, 3208, 3025, 2955, 2919, 2872, 2850, 1618, 1575, 1537, 1497, 1437; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.29 (s, 1H), 7.15 (s, 1H), 2.89-2.85 (m, 1H), 2.56-2.47 (m, 1H), 2.09-2.00 (m, 3H), 1.78-1.13 (m, 16H), 0.85-0.81 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.2, 156.5, 132.1, 117.9, 108.7, 70.9, 70.3, 37.8, 36.5, 35.8, 30.3, 28.9, 28.7, 28.2, 27.1, 26.9, 25.7, 12.1, 11.8; HRMS (ESI): calcd For $C_{19}H_{28}N_2OS$ $[M+H]^+$ 333.19951; found 333.19909.

General Procedure for the Synthesis of 4: To a mixture of compound **1** (1 mmol) and corresponding ketones **2** (3 mL), 1 equiv of sodium ethoxide was added dropwise under stirring with 380 nm UV lamb irradiation, and then the reaction mixture was heated at 120 °C for 3.0 h. The reaction mixture was cooled to room temperature after the reaction finished with TLC monitoring. The compounds **4** were obtained by column chromatography on silica gel (200-300 mesh silica gels) with EtOAc–petroleum ether (1:3, v: v) as eluent or by filtration.

8a-Hydroxy-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4-(5*H*)-one (4a): White solid; mp 209-211 °C; IR (KBr, *υ*, cm^{-1}) 3402, 3184, 3054, 2962, 2921, 2834, 1676, 1653, 1629, 1455, 1427, 1410; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.56 (s, 1H), 6.96 (s, 1H), 3.89 (d, *J* = 12Hz, 1H), 2.52 (t, *J* = 12.0 Hz, 1H), 2.35 (q, *J* = 15.0 Hz, 1H), 1.89-1.21 (m, 15 H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 166.3, 165.6, 158.6, 115.5, 92.2, 76.8, 40.4, 40.1, 39.9 26.7, 25.6, 24.8, 21.9, 21.8, 21.7; HRMS (ESI): calcd For $C_{15}H_{20}N_2O_2S$ $[M+H]^+$ 293.13183; found 293.13143.

8a-Hydroxy-3'-methyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4b): White solid; mp 223-224 °C; IR (KBr, *υ*, cm^{-1}) 3398, 3182, 3058, 2942, 2933, 2867, 2839, 1677, 1653, 1630, 1455, 1409; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.51 (s, 1H), 6.94 (s, 1H), 3.98 (d, *J* = 15 Hz, 1H), 2.52 (t, *J* = 4.0 Hz, 1H), 2.33 (q, *J* = 12 Hz, 1H), 1.78-1.25 (m, 14H), 0.85 (q, *J* = 20 Hz,3 H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 166.9, 166.5, 159.4, 115.9, 92.9, 77.8, 49.3, 48.7, 33.7, 27.1, 27.0, 26.7, 26.0, 22.6, 22.2, 20.7; HRMS (ESI): calcd For $C_{16}H_{22}N_2O_2S$ $[M+H]^+$ 307.14748; found 307.14738.

8a-Hydroxy-4'-methyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4c): White solid; mp 212-213 °C; IR (KBr, *υ*, cm^{-1}) 3408, 3204, 3068, 2951, 2931, 2863, 2842, 1674, 1650, 1637, 1441, 1396; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.54 (s, 1H), 6.95 (s, 1H), 3.89 (d, *J* = 12Hz, 1H), 2.52 (t, *J* = 4.0 Hz, 1H), 1.89-1.29 (m, 15H), 0.931 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 166.9, 166.5, 159.2, 115.9, 92.8, 77.2, 77.1, 40.4, 40.2, 31.9, 31.1, 29.9, 28.8, 28.7, 27.1, 26.0, 22.5, 22.2, 20.8; HRMS (ESI): calcd For $C_{16}H_{22}N_2O_2S$ $[M+H]^+$ 307.14748; found 307.14743.

4'-Ethyl-8a-hydroxy-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4d): White solid; mp 227-229 °C; IR (KBr, *υ*, cm^{-1}) 3225, 2929, 2852, 1665, 1619, 1536, 1497, 1440; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.51 (s, 1H), 6.93 (s, 1H), 3.88 (d, *J* = 12.0 Hz, 1H), 2.63-1.13 (m, 16H), 0.85-0.84 (m, 5H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 161.6, 161.2, 155.9, 117.7, 92.2, 76.9, 70.4, 43.2, 41.2, 38.1, 35.3 28.9, 26.6, 25.5, 23.8, 22.1, 12.0; HRMS (ESI): calcd For $C_{17}H_{24}N_2O_2S$ [M+H]$^+$ 321.16313; found 321.16352.

8a-Hydroxy-6-methyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4e): White solid; mp 214-215 °C; IR (KBr, *υ*, cm^{-1}) 3400, 3187, 3058, 2954, 2927, 2871, 1677, 1654, 1631, 1455, 1428, 1407; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.53 (s, 1H), 6.91 (s, 1H), 3.87 (q, *J* = 12 Hz, 1H), 2.51 (t, *J* = 4.0 Hz, 1H), 2.26-1.21 (m, 14H), 1.00-0.98 (m, 3H), 0.84-0.82 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 166.5, 166.2, 158.8, 115.5, 92.5, 76.7, 43.4, 38.3, 31.5, 29.5, 28.5, 26.8, 25.7, 22.2, 21.8, 20.5; HRMS (ESI): calcd For $C_{16}H_{22}N_2O_2S$ [M+H]$^+$ 307.14748; found 307.14752.

8a-Hydroxy-3',6-dimethyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4f): White solid; mp 241-242 °C; IR (KBr, *υ*, cm^{-1}) 3401, 3185, 3060, 2953, 2922, 2869, 1677, 1652, 1630, 1454, 1429, 1408; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.51 (s, 1H), 6.93 (s, 1H), 3.86 (q, *J* = 12 Hz, 1H), 2.50 (t, *J* = 8.0 Hz, 1H), 2.02-1.36 (m, 14H), 0.87-0.85 (m, 3H), 0.84-0.83 (m, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 166.8, 166.4, 159.3, 115.8, 92.4, 77.8, 49.2, 48.7, 42.8, 34.4, 34.0, 33.7, 30.6, 26.9, 26.7, 22.6, 20.5; HRMS (ESI): calcd For $C_{17}H_{24}N_2O_2S$ [M+H]$^+$ 321.16313; found 321.16289.

8a-Hydroxy-4',6-dimethyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4g): White solid; mp 212-213 °C; IR (KBr, *υ*, cm^{-1}) 3399, 3192, 3065, 2951, 2926, 2870, 2846, 1675, 1650, 1629, 1450, 1397; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.54 (s, 1H), 6.91 (s, 1H), 3.87 (q, *J* = 12 Hz, 1H), 2.49 (t, *J* = 4.0 Hz, 1H), 2.08-1.40 (m, 14H), 1.00-0.98 (m, 3H), 0.94-0.91 (m, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 166.3, 166.2, 159.2, 116.0, 92.3, 77.2, 42.8, 41.6, 34.4, 34.0, 31.9, 31.1, 29.8, 28.8, 28.6, 22.6, 20.7; HRMS (ESI): calcd For $C_{17}H_{24}N_2O_2S$ [M+H]$^+$ 321.16313; found 321.16355.

4'-Ethyl-8a-hydroxy-6-methyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4h): White solid; mp 232-234 °C; IR (KBr, *υ*, cm^{-1}) 3389, 3250, 3087, 2931, 2855, 2843, 1671, 1649, 1627, 1449, 1429; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.53 (s, 1H), 6.92 (s, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.31 (d, *J* = 12.0 Hz, 1H), 2.50-0.97 (m, 16H), 0.86-0.83 (m, 6H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 165.7, 165.4, 158.6, 115.5, 91.7, 76.9, 69.2, 42.3, 41.2, 38.2, 35.4, 33.5, 30.6, 30.2, 29.0, 28.3, 22.1, 11.6; HRMS (ESI): calcd For $C_{18}H_{26}N_2O_2S$ [M+H]$^+$ 335.17878; found 335.17880.

8a-Hydroxy-7-methyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4i): White solid; mp 220-221 °C; IR (KBr, *υ*, cm^{-1}) 3401, 3184, 3058, 2948, 2916, 2868, 2862, 1678, 1655, 1629, 1456, 1411; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.52 (s, 1H), 6.91 (s, 1H), 3.87 (q, *J* = 20 Hz, 1H), 2.49 (t, *J* = 20.0 Hz, 1H), 2.36 (q, *J* = 15 Hz, 1H), 1.86-1.04 (m, 14H), 0.98-0.85 (m, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 166.4, 166.1, 159.0, 116.1, 92.9, 77.3, 51.5, 40.6, 35.2, 28.4, 25.4, 25.3, 22.3, 22.2, 22.1, 21.3; HRMS (ESI): calcd For $C_{16}H_{22}N_2O_2S$ [M+H]$^+$ 307.14748; found 307.14730.

8a-Hydroxy-3',7-dimethyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4j): White solid; mp 246-248 °C; IR (KBr, υ, cm^{-1}) 3402, 3185, 3060, 2948, 2926, 2867, 2838, 1678, 1655, 1627, 1456, 1411; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.51 (s, 1H), 6.95 (s, 1H), 3.87 (q, *J* = 12 Hz, 1H), 2.50 (t, *J* = 8.0 Hz, 1H), 2.37 (q, *J* = 8 Hz, 1H), 1.79-1.33 (m, 12H), 1.06-1.01 (m, 1H), 0.86-0.82 (m, 6H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 166.6, 166.5, 159.3, 116.0, 93.0, 77.9, 51.5, 49.3, 49.2, 33.7, 28.4, 27.0, 25.4, 22.6, 21.3, 20.5, 20.2; HRMS (ESI): calcd For $C_{17}H_{24}N_2O_2S$ [M+H]$^+$ 321.16313; found 321.16273.

8a-Hydroxy-4',7-dimethyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4k): White solid; mp 214-215 °C; IR (KBr, υ, cm^{-1}) 3410, 3194, 3064, 2950, 2927, 2869, 1675, 1652, 1626, 1451, 1399; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.54 (s, 1H), 6.94 (s, 1H), 3.87 (q, *J* = 16 Hz, 1H), 2.50 (t, *J* = 12.0 Hz, 1H), 2.40 (q, *J* = 12 Hz, 1H), 1.86-1.06 (m, 13H), 0.94-0.91 (m, 3H), 0.86-0.82 (m, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 166.5, 166.4, 159.2, 116.1, 93.0, 77.2, 51.5, 40.4, 38.6, 35.2, 31.9, 29.9, 28.8, 28.4, 25.4, 21.3. 20.1; HRMS (ESI): calcd For $C_{17}H_{24}N_2O_2S$ [M+H]$^+$ 321.16313; found 321.16291.

8a-Hydroxy-4',7-dimethyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4l): White solid; mp 230-232 °C; IR (KBr, υ, cm^{-1}) 3407, 3182, 3059, 2948, 2922, 2850, 1677, 1655, 1629, 1456, 1411; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.53 (s, 1H), 6.97 (s, 1H), 3.88 (q, *J* = 12 Hz, 1H), 2.50-2.37 (m, 1H), 1.92-0.86 (m, 21H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 166.8, 159.3, 115.9, 93.1, 77.9, 49.4, 49.2, 32.9, 28.4, 25.4, 22.6, 20.5, 11.9; HRMS (ESI): calcd For $C_{18}H_{26}N_2O_2S$ [M+H]$^+$ 335.17878; found 335.17828.

8a-Hydroxy-4',7-dimethyl-6,7,8,8a-tetrahydro-3*H*-spiro[benzo[4,5]thieno[2,3-*d*]pyrimidine-2,1'-cyclohexan]-4(5*H*)-one (4m): White solid; mp 235-237 °C; IR (KBr, υ, cm^{-1}) 3400, 3194, 3064, 2949, 2924, 2868, 1676, 1651, 1637, 1450, 1399; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) (δ, ppm): 8.56 (s, 1H), 6.96 (s, 1H), 3.88 (q, *J* = 8 Hz, 1H), 2.51-0.86 (m, 23H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) (δ, ppm): 166.8, 159.2, 116.2, 93.1, 77.2, 49.4, 34.8, 32.9, 28.8, 28.6, 28.4, 25.4, 11.9; HRMS (ESI): calcd For $C_{18}H_{26}N_2O_2S$ [M+H]$^+$ 335.17878; found 335.17834.

General Procedure for the Synthesis of 5: To a mixture of compound **7** (1 mmol) and corresponding ketones **8** (3 mL), 2 equiv of sodium ethoxide was added dropwise under stirring, and then the reaction mixture was heated under reflux for 4.0 h. The reaction mixture was cooled to room temperature after the reaction finished with TLC monitoring. The resulting precipitate was collected by filtration. The target product compounds **5** were obtained through washing alternately with water and EtOH for several times and then dried.

2,2,9,9-Tetramethyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-4,7(1*H*,8*H*)-dione (5a): yellow solid; mp > 300 ºC; IR (KBr, υ, cm^{-1}) 3264, 2977, 1638, 1592, 1545, 1399, 1181, 1116, 766, 602, 509; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.61 (s, 2H, NH), 7.22 (s, 2H, NH), 1.50 (s, 12H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.0, 147.6, 143.1, 126.2, 106.0, 69.0, 28.0; HRMS (ESI): calcd For $C_{14}H_{16}N_4O_2S_2$ $[M+H]^+$ 337.07874; found 337.07849.

2,9-Dimethyl-2,9-diethyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-4,7(1*H*,8*H*)-dione (5b): Yellow solid; mp > 300 ºC; IR (KBr, υ, cm^{-1}) 3263, 2969, 2929, 1631, 1607, 1554, 1403, 1117, 764, 601; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.61 (s, 2H, NH), 7.16 (d, *J* = 7.41 Hz, 2H, NH), 1.79 (dd, *J* = 7.78, 16.07 Hz, 4H, CH_2), 1.47 (t, *J* = 13.77 Hz, 6H, CH_3), 0.90 (dd, *J* = 7.14, 16.51 Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 160.9, 147.4, 143.0, 142.9, 126.2, 105.5, 105.4, 71.7, 71.6, 32.2, 26.4, 26.0, 8.4, 8.3; HRMS (ESI): calcd For $C_{16}H_{20}N_4O_2S_2$ $[M+H]^+$ 365.11004; found 365.10963.

2,9-Dimethyl-2,9-dipropyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-4,7(1*H*,8*H*)-dione (5c): Yellow solid; mp > 300 ºC; IR (KBr, υ, cm^{-1}) 3262, 2959, 2932, 2871, 1639, 1602, 1557, 1453, 1402, 1158, 1117, 766, 601, 513; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.62 (s, 2H, NH), 7.11 (d, *J* = 12.72 Hz, 2H, NH), 1.70 (d, *J* = 38.01 Hz, 4H, CH_2), 1.47 (d, *J* = 4.05 Hz, 6H, CH_3), 1.40 (s, 4H, CH_2), 0.87 (d, *J* = 6.14 Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 160.9, 147.4, 143.0, 142.9, 126.1, 105.6, 71.4, 71.3, 42.1, 26.8, 26.5, 16.8, 14.0; HRMS (ESI): calcd For $C_{18}H_{24}N_4O_2S_2$ $[M+H]^+$ 393.14134; found 393.14025.

2,2,9,9-Tetraethyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-4,7(1*H*,8*H*)-dione (5d): Yellow solid; mp > 300 ºC; IR (KBr, υ, cm^{-1}) 3357, 3269, 3059, 2970, 2934, 1643, 1601, 1551, 1405, 1376, 1119, 767, 614; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.51 (s, 2H, NH), 6.97 (s, 2H, NH), 1.78 (dd, *J* = 13.63, 7.01 Hz, 4H, CH_2), 1.68 (dd, *J* = 13.21, 6.86 Hz, 4H, CH_2), 0.91 (d, 12H, *J* = 6.34 Hz, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.1, 147.2, 143.1, 126.1, 104.7, 74.5, 30.8, 8.2; HRMS (ESI): calcd For $C_{18}H_{24}N_4O_2S_2$ $[M+H]^+$ 393.14134; found 393.14033.

2,9-Dimethyl-2,9-diisopropyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-4,7(1*H*,8*H*)-dione (5e): Yellow solid; mp > 300 ºC; IR (KBr, υ, cm^{-1}) 3360, 3273, 3090, 2965, 2876, 1642, 1602, 1563, 1466, 1399, 1363, 1329, 1172, 1135, 765, 722, 616, 479; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.76 (s, 2H, NH), 7.24 (s, 2H, NH), 2.31-2.22 (m, 2H, CH), 1.39 (s, 6H, CH_3), 0.95-0.85 (m, 12H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 160.3, 147.2, 142.2, 126.1, 105.9, 73.5, 34.2, 21.0, 17.0, 16.3; HRMS (ESI): calcd For $C_{18}H_{24}N_4O_2S_2$ $[M+H]^+$ 393.14134; found 393.14084.

2,9-Dimethyl-2,9-diisobutyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]-pyrimidine-4,7(1*H*,8*H*)-dione (5f): Yellow solid; mp > 300 °C; IR (KBr, υ, cm^{-1}) 3259, 2955, 2869, 1639, 1604, 1558, 1466, 1401, 1160, 1121, 765, 614, 508; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ: 7.55 (s, 2H, NH), 7.13 (s, 2H, NH) 1.83-1.71 (m, 4H, CH_2), 1.50 (s, 6H, CH_3), 0.91-0.84 (m, 14H, $CH(CH_3)_2$); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ: 160.8, 147.3, 142.8, 126.1, 105.3, 71.5, 47.7, 27.0, 24.2, 23.5; HRMS (ESI): calcd For $C_{20}H_{28}N_4O_2S_2$ [M+H]$^+$ 421.17264; found 421.17296.

1'*H*,8'*H*-dispiro[cyclopentane-1,2'-pyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-9',1''-cyclopentane]-4',7'(3'*H*,10'*H*)-dione (5g):[2c] Yellow solid; mp 276-278 °C; IR (KBr, υ, cm^{-1}) 3252, 3072, 2951, 2873, 1712, 1607, 1550, 1402, 1325, 1190, 1124, 1030, 950, 767, 655, 623, 512; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ: 7.84 (s, 2H, NH), 7.27 (s, 2H, NH), 1.93-1.68 (m, 16H, CH_2); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ: 161.4, 147.7, 143.7, 126.3, 107.3, 78.7, 38.3, 22.0; MS (ESI): *m/z* = 411.1 [M+Na]$^+$.

1'*H*,8'*H*-dispiro[cyclohexane-1,2'-pyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-9',1''-cyclohexane]-4',7'(3'*H*,10'*H*)-dione (5h): Yellow solid; mp > 300 °C; IR (KBr, υ, cm^{-1}) 3251, 3058, 2931, 2855, 1722, 1613, 1552, 1407, 1341, 1275, 1121, 1074, 765, 585, 558; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ: 7.66 (s, 2H, NH), 6.90 (s, 2H, NH), 1.95-1.26 (m, 20H, CH_2); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ: 161.0, 147.4, 142.5, 127.7, 108.3, 69.3, 35.7, 24.8, 21.5; HRMS (ESI): calcd For $C_{20}H_{24}N_4O_2S_2$ [M+H]$^+$ 417.14134; found 417.13992.

1'*H*,8'*H*-dispiro[cycloheptane-1,2'-pyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyramidine-9',1''-cycloheptane]-4',7'(3'*H*,10'*H*)-dione (5i): Yellow solid, mp > 300 °C; IR (KBr, υ, cm^{-1}) 3250, 2923, 2851, 1611, 1553, 1410, 1125, 843, 763, 616; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ: 7.75 (s, 2H, NH), 7.12 (s, 2H, NH), 2.03-1.91 (m, 8H, CH_2), 1.53 (s, 16H, CH_2); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ: 160.7, 147.3, 142.4, 126.9, 107.2, 73.8, 39.1, 28.7, 21.1; HRMS (ESI): calcd For $C_{22}H_{28}N_4O_2S_2$ [M+H]$^+$ 445.17264; found 445.17216.

2,2''-Dimethyl-1'*H*,8'*H*-dispiro[cyclohexane-1,2'-pyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]-pyrimidine-9',1''-cyclohexane]-4',7'(3'*H*,10'*H*)-dione (5j): Yellow solid; mp > 300 °C; IR (KBr, υ, cm^{-1}) 3262, 2926, 2866, 1610,1555, 1408, 1342, 1255, 1123, 765, 572; ^{1}H NMR (DMSO-*d6*, 400 MHz) δ: 7.64 (s, 2H, NH), 7.03 (d, *J* = 9.18 Hz, 2H, NH), 2.23-1.42 (m, 18H, CH_2), 0.91-0.86 (m, 6H, CH_3); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ: 160.8, 147.8, 143.0, 126.1, 106.4, 70.7, 70.0, 44.6, 35.7, 33.7, 31.2, 28.9, 26.7, 22.1, 21.5, 20.3; HRMS (ESI): calcd For $C_{22}H_{28}N_4O_2S_2$ [M+H]$^+$ 445.17264; found 445.17125.

2,9-Dimethyl-2,9-diphenyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-4,7(1*H*,8*H*)-dione (5k): Yellow solid; mp > 300 °C; IR (KBr, υ, cm^{-1}) 3373, 3249, 3078, 2990, 2936, 1641, 1606, 1547, 1444, 1392, 1218, 1152, 1083, 759, 696, 647; ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ: 8.63 (s, 2H, NH), 8.31 (s, 2H, NH), 7.58-7.27 (m, 10H, ArH), 1.81(s, 6H, CH_3); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ: 161.4, 147.5, 147.2, 142.8, 128.0, 127.5, 126.0, 124.8, 108.6, 71.9, 30.1; HRMS (ESI): calcd For $C_{24}H_{20}N_4O_2S_2$ $[M+H]^+$ 461.11004; found 461.10905.

2,9-Diethyl-2,9-diphenyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-4,7(1*H*,8*H*)-dione (5l): Yellow solid; mp > 300 °C; IR (KBr, υ, cm^{-1}) 3377, 3258, 3060, 2971, 2935, 2878, 1638, 1601, 1552, 1446, 1399, 1288, 1197, 1147, 841, 757, 697, 605; ^1H NMR (DMSO-d_6, 400 MHz) δ: 8.50 (s, 2H, NH), 8.07 (s, 2H, NH), 7.57-7.28 (m, 10H, ArH) 2.01-1.93 (m, 4H, CH_2), 1.12 (s, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.7, 150.4, 147.3, 143.1, 128.0, 127.5, 126.4, 125.0, 108.0, 75.3, 34.5, 9.4; HRMS (ESI): calcd For $C_{26}H_{24}N_4O_2S_2$ $[M+H]^+$ 489.14134; found 489.14065.

2,9-Dipropyl-2,3,9,10-tetrahydropyrimido[4'',5'':4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine-4,7-(1*H*,8*H*)-dione (5m): Yellow solid; mp > 300 °C; IR (KBr, υ, cm^{-1}) 3264, 3055, 2956, 2932, 2871, 1624, 1600, 1559, 1454, 1418, 1382, 1256, 1117, 891, 767, 605; ^1H NMR (DMSO-d_6, 400 MHz) δ: 7.64 (s, 2H, NH), 7.17 (s, 2H, NH), 4.79 (s, 2H, CH), 1.74 (s, 4H, CH_2), 1.47 (s, 4H, CH_2), 0.93 (d, J = 6.96 Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.1, 148.1, 144.8, 126.1, 108.3, 65.7, 35.4, 17.1, 13.8; HRMS (ESI): calcd For $C_{16}H_{20}N_4O_2S_2$ $[M+H]^+$ 365.11004; found 365.10969.

General Procedure for the Synthesis of 6: The microwave reactor "Initiator" (manufactured by Biotage, formerly Personal Chemistry) was used in all reactions: A solution of corresponding **1** (1 mmol), 0.5 mL methanamide, $ZnCl_2$ (1.2 mmol) and 1.5 mL DMF were added in a 5 mL tube, sealed and heated to 160 °C for 20 min. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and the precipitate was isolated by filtration and then purified by crystallization from 95% EtOH to provide the pure compounds **6**.

6,7-Dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-amine (6a):[26d] White solid; mp 265-267 °C; IR (KBr, υ, cm^{-1}) 3416, 3304, 2949, 2898, 1687, 1645, 1500, 1472; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.36 (s, 1H), 5.40 (s, 2H, NH_2), 3.07-3.00 (m, 4H), 2.59-2.54 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 169.5, 156.3, 151.5, 134.8, 134.6, 110.7, 27.7, 27.3, 25.9; MS (ESI): m/z = 192.1 $[M+H]^+$.

5,6,7,8-Tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-amine (6b):[26d] White solid; mp 277-278 °C; IR (KBr, υ, cm^{-1}) 3362, 3318, 2927, 2899, 1649, 1570, 1505, 1439; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.35 (s, 1H), 5.37 (s, 2H, NH_2), 2.93 (t, J = 8.0 Hz, 2H), 2.82 (t, J = 8.0 Hz, 2H), 1.93-1.90 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 165.9, 158.6, 153.4, 131.4, 127.4, 115.5, 25.9, 25.3, 22.7, 22.4; MS (ESI): m/z = 206.1 $[M+H]^+$.

6,7,8,9-Tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-amine (6c):[26e] White solid; mp 274-285 °C; IR (KBr, υ, cm^{-1}) 3323, 3139, 2925, 2840, 1650, 1557, 1499, 1436; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.34 (s, 1H), 5.39 (s, 2H, NH_2), 3.02 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 1.92 (quint, J = 12.0 Hz, 2H), 1.86-1.80 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 164.7, 158.6, 152.9, 135.5, 132.6, 116.6, 31.2, 29.0, 27.3, 26.9; MS (ESI): m/z = 220.2 $[M+H]^+$.

ACKNOWLEDGEMENTS

This work was supported by the grant of Beijing Institute of Technology. We are grateful for analytical help of Chinese Academy of Agricultural Sciences, sciences institute of chemistry, Chinese Academy of Sciences, Beijing University of Chemical Technology and Peking University.

REFERENCES

1. (a) F. J. Gamo, L. M. Sanz, J. Vidal, C. De Cozar, E. Alvarez, J. L. Lavandera, D. E. Vanderwall, D. V. S. Green, V. Kumar, S. Hasan, J. R. Brown, C. E. Peishoff, L. R. Cardon, and J. F. Garcia-Bustos, *Nature*, 2010, **465**, 305; (b) D. González Cabrera, C. Le Manach, F. Douelle, Y. Younis, T.-S. Feng, T. Paquet, A. T. Nchinda, L. J. Street, D. Taylor, C. de Kock, L. Wiesner, S. Duffy, K. L. White, K. M. Zabiulla, Y. Sambandan, S. Bashyam, D. Waterson, M. J. Witty, S. A. Charman, V. M. Avery, S. Wittlin, and K. Chibale, *J. Med. Chem.*, 2014, **57**, 1014; (c) Y. Endo, K. Kawai, T. Asano, S. Amano, Y. Asanuma, K. Sawada, Y. Onodera, N. Ueo, N. Takahashi, Y. Sonoda, N. Kamei, and T. Irie, *Bioorg. Med. Chem.*, 2015, **25**, 1910; (d) H. B. Borate, R. A. Annadate, S. S. Vagh, M. M. Pisal, S. B. Deokate, M. A. Arkile, N. J. Jadhav, L. U. Nawale, and D. Sarkar, *MedChemComm.*, 2015, **6**, 2209; (e) M. Modica, M. Santagati, F. Russo, L. Parotti, L. De Gioia, C. Selvaggini, M. Salmona, and T. Mennini, *J. Med. Chem.*, 1997, **40**, 574; (e) J. H. Park, S. Y. Hong, J. Kim, H. J. Lee, H. H. Lee, K. Y. Kim, S. W. Lee, H.-M. Oh, M.-C. Rho, B.-G. Lee, and Y.-H. Song, *Heterocycles*, 2015, **91**, 835; (f) A. J. Peat, P. L. Feldman, D. Garrido, Y. C. Guo, and D. L. Hertzog, *Heterocycles*, 2006, **70**, 587.
2. (a) S. B. Kanawade, S. P. Patil, P. S. Nikam, S. A. Gangurde, M. N. Jachak, and R. B. Toche, *J. Heterocycl. Chem.*, 2012, **49**, 363; (b) S. Bondock, A. E.-G. Tarhoni, and A. A. Fadda, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2007, **182**, 1915; (c) H. Moustafa, A. Khodairy, and A. El-Saghier, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 1211.
3. (a) C. Martins, M. C. Carreiras, R. León, C. de los Ríos, M. Bartolini, V. Andrisano, I. Iriepa, I. Moraleda, E. Gálvez, M. García, J. Egea, A. Samadi, M. Chioua, and J. Marco-Contelles, *Eur. J. Med. Chem.*, 2011, **46**, 6119; (b) J. B. Campbell and J. W. Firor, *J. Org. Chem.*, 1995, **60**, 5243.
4. (a) J. H. Kim, Y. O. Ko, J. Bouffard, and S. G. Lee, *Chem. Soc. Rev.*, 2015, **44**, 2489; (b) D. Hack, M. Blumel, P. Chauhan, A. R. Philipps, and D. Enders, *Chem. Soc. Rev.*, 2015, **44**, 6059.
5. (a) L. Yang, D. Shi, S. Chen, H. Chai, D. Huang, Q. Zhang, and J. Li, *Green Chem.*, 2012, **14**, 945; (b) J. Tang, J. Li, L. Zhang, S. Ma, D. Shi, Q. Zhang, L. Yang, X. Wang, X. Liu, and C. Liu, *J. Heterocycl. Chem.*, 2012, **49**, 533; (c) L. J. Zhang, J. L. Yu, W. L. Wang, H. Li, D. D. Xu, Y. D. Bi, and F. De Liu, *Tetrahedron Lett.*, 2014, **55**, 710.
6. M. Liu, J. Li, S. Chen, D. Huang, H. Chai, Q. Zhang, and D. Shi, *RSC Adv.*, 2014, **4**, 35629.

7. J. Li, L. Zhang, D. Shi, Q. Li, D. Wang, C. Wang, Q. Zhang, L. Zhang, and Y. Fan, *Synlett*, 2008, 233.
8. (a) J. Li, X. Chen, D. Shi, S. Ma, Q. Li, Q. Zhang, and J. Tang, *Org. Lett.*, 2009, **11**, 1193; (b) F. Tamaddon and F. Pouramini, *Synlett*, 2014, **25**, 1127; (c) S. Schramm, E. Schmitz, and E. Gründemann, *J. Prakt. Chem.*, 1984, **326**, 279.
9. L. J. Zhang, D. X. Shi, and J. R. Li, *Synth. Commun.*, 2009, **39**, 4010.
10. L. Yang, J. Li, H. Chai, H. Lu, Q. Zhang, and D. Shi, *Chinese J. Chem.*, 2013, **31**, 443.
11. (a) K. Gewald, E. Schinke, and H. Böttcher, *Chem. Ber.*, 1966, **99**, 94; (b) R. Bai, P. Liu, J. Yang, C. Liu, and Y. Gu, *ACS Sustain. Chem. Eng.*, 2015, **3**, 1292.
12. Y. G. Hu, A. H. Zheng, X. Z. Ruan, and M. W. Ding, *Beilstein J. Org. Chem.*, 2008, **4**, 49.
13. O. Takahashi, J. Umezawa, K. Furuhashi, and M. Takagi, *Tetrahedron Lett.*, 1989, **30**, 1583.
14. (a) H. Y. Zhu, J. Desai, A. B. Cooper, J. Wang, D. F. Rane, P. Kirschmeier, C. Strickland, M. Liu, A. A. Nomeir, and V. M. Girijavallabhan, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1228; (b) M. Kobayashi, *Tetrahedron*, 2000, **56**, 1661.
15. (a) F. Wångsell, F. Russo, J. Sävmarker, Å. Rosenquist, B. Samuelsson, and M. Larhed, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4711; (b) P. Smirnov, E. Katan, J. Mathew, A. Kostenko, M. Karni, A. Nijs, C. Bolm, Y. Apeloig, and I. Marek, *J. Org. Chem.*, 2014, **79**, 12122.
16. Y. Chujo, M. Morimoto, and I. Tomita, *Polym. Bull.*, 1992, **29**, 617.
17. T.-S. Zhu, S.-S. Jin, and M.-H. Xu, *Angew. Chem. Int. Ed.*, 2012, **51**, 780.
18. (a) I. Kikaš, O. Horváth, and I. Škorić, *Tetrahedron Lett.*, 2011, **52**, 6255; (b) D. Vuk, I. Kikaš, K. Molčanov, O. Horváth, and I. Škorić, *J. Mol. Struct.*, 2014, **1063**, 83.
19. (a) R. D. Bach and O. Dmitrenko, *J. Am. Chem. Soc.*, 2006, **128**, 4598; (b) N. V. Timosheva, A. Chandrasekaran, R. O. Day, and R. R. Holmes, *Organometallics*, 2001, **20**, 233; (c) E. Sanna, C. López, P. Ballester, C. Rotger, and A. Costa, *Eur. J. Org. Chem.*, 2015, 7656.
20. (a) G. Guillena, D. J. Ramón, and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (b) W.-Y. Gao, K. Leng, L. Cash, M. Chrzanowski, C. A. Stackhouse, Y. Sun, and S. Ma, *Chem. Commun.*, 2015, **51**, 4827.
21. S. H. Mashraqui, Y. S. Sangvikar, S. G. Ghadigaonkar, M. Ashraf, and M. Meetsma, *Tetrahedron*, 2008, **64**, 8837.
22. (a) S. H. Mashraqui, M. Ashraf, H. Hariharasubrahmanian, R. M. Kellogg, and A. Meetsma, *J. Mol. Struct.*, 2004, **689**, 107; (b) V. P. Litvinov, in *Advances in Heterocyclic Chemistry*, ed. by A. R. Katritzky, Academic Press, 2006, Vol. 90, pp. 125-203.
23. A. A. Zubarev, N. A. Larionova, L. A. Rodinovskaya, V. Y. Mortikov, and A. M. Shestopalov, *ACS Comb. Sci.*, 2013, **15**, 546.
24. L. Zang, Y. Che, and J. S. Moore, *Acc. Chem. Res.*, 2008, **41**, 1596.

25. J. Yang, J. Li, P. Hao, F. Qiu, M. Liu, Q. Zhang, and D. Shi, *Dyes Pigm.*, 2015, **116**, 97.
26. (a) N. Shetty, R. Lamani, and I. Khazi, *J. Chem. Sci.*, 2009, **121**, 301; (b) J. Mulla, M. Khazi, S. Panchamukhi, Y.-D. Gong, and I. Khazi, *Med. Chem. Res.*, 2014, **23**, 3235; (c) M. E. Azab, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2008, **183**, 1766; (d) B. E. Sleebs, G. Nikolakopoulos, I. P. Street, H. Falk, and J. B. Baell, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5992; (e) A. El-Gazzar, M. Hegab, S. Swelam, and A. Aly, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 123.
27. J. R. Li, S. L. Ma, Y. J. Sun, J. M. Zhao, and Z. M. Zhou, *Synth. Commun.*, 2006, **36**, 1537.
28. (a) I. B. Berlman, in *Handbook of Fluorescence Spectra of Aromatic Molecules*, 2nd ed., Academic Press, New York, 1971; (b) M. Montalti, A. Credi, L. Prodi, and M. T. Gandolfi, in *Handbook of Photochemistry*, 3rd ed., Taylor & Francis, Boca Raton, FL, 2006.