

HETEROCYCLES, Vol. 92, No. 12, 2016, pp. 2244 - 2251. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 8th September, 2016, Accepted, 21st October, 2016, Published online, 10th November, 2016
DOI: 10.3987/COM-16-13573

METHODOLOGY TO ACCESS THIAZO[3',2':2,3]PYRIDO[4,5-*d*]- THIAZOLO[3,2-*a*]PYRIMIDINONES

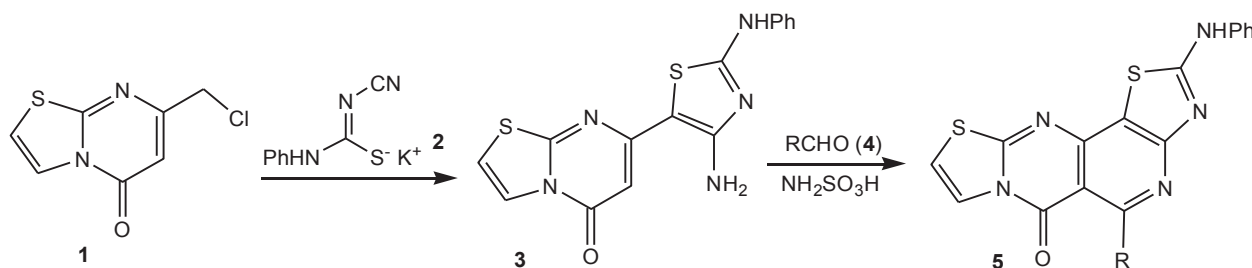
Dao-Lin Wang,^{*a} Dong Wang,^a Qiao-Min Li,^b and Jian-Hua Qian^a

^aLiaoning Key Laboratory of Synthesis & Application of Functional Compound,
College of Chemistry & Chemical Engineering, Bohai University, Jinzhou
121001, P. R. China; wangdaolin@sina.com

^b Liaoning Huaxing Mechanical & Electrical Engineering Co., Ltd, Jinzhou
121000, P. R. China

Abstract — A synthesis of model thiazolo[3',2':2,3]pyrido[4,5-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones (**5**), based on the classical Pictet-Spengler method, is described. The key intermediate, 7-(3-amino-5-phenylaminothiazol-2-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**3**), was synthesized from 7-chloromethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**1**) with potassium *N*-phenyl-*N'*-cyanoimidothiocarbonate (**2**) by Thorpe-Ziegler isomerization. Cyclocondensation of the intermediate amine with aromatic aldehydes, using sulfamic acid under Pictet-Spengler reaction conditions, delivered the target compounds **5a-m**.

Pyrimidines represent a class of heterocyclic compounds of great importance in biological chemistry. Moreover, fused pyrimidines have drawn the attention of medicinal chemists as chemotherapeutic agents, where several members of this class have earned valued places in chemotherapy as effective agents.¹ Besides, some derivatives of thiazolo[3,2-*a*]pyrimidines are known to exhibit versatile biological activity such as anticancer,² antitumor,³ antiinflammatory,⁴ antinociceptive,⁵ antiviral,⁶ and antibiofilm properties,⁷ while the thiazolopyrimidine skeleton is present in drugs proposed as immunomodulators (TEI 3096).⁸ Owing to these remarkably broad pharmacological properties, a variety of synthetic methods have been reported for the preparation of thiazolo[3,2-*a*]pyrimidinone derivatives.⁹⁻¹¹ Recently, we reported the synthesis of novel fused benzofuro- and pyridothieno-fused thiazolo[3,2-*a*]pyrimidinones¹² via the Pictet-Spengler reaction.¹³ In continuation of our interest on the construction of complex thiazolo[3,2-*a*]pyrimidine skeletons, herein we report the synthesis of some new fused heterocyclic systems: thiazolo[3',2':2,3]pyrido[4,5-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones by the application of Pictet-Spengler reaction (Scheme 1).



Scheme 1. Syntheses of thiazolopyrido-fused thiazolopyrimidines

To access the target thiazolo[3',2':2,3]pyrido[4,5-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones, we envisioned a strategy by which the Pictet-Spengler cyclization key reaction step consists of a condensation reaction of amine **3** with various aromatic aldehydes.

The key intermediate amine, 7-(3-amino-5-phenylaminothiazol-2-yl)-5H-thiazolo[3,2-*a*]pyrimidin-5-one (**3**) was obtained by the condensation of 7-chloromethyl-5H-thiazolo[3,2-*a*]pyrimidin-5-one (**1**) with potassium *N*-phenyl-*N'*-cyanoimidothiocarbonate (**2**) *via* Thorpe-Ziegler isomerization,¹⁴ in 85% yield. Elemental analysis ($\text{C}_{15}\text{H}_{11}\text{N}_5\text{OS}_2$) and spectral data supported its structure. Its IR spectrum contains absorption peaks at 3426, 3356 and 1682 cm^{-1} , demonstrating the presence of NH and C=O functions, respectively. Its ^1H NMR spectrum (DMSO-*d*₆) shows the presence of a D₂O exchangeable broad singlet at δ 7.67 (2H) and 10.62 ppm (1H) which can be attributed to the NH₂ and NH protons, respectively. The singlet peak at δ 5.45 corresponding to C₆-H of thiazolo[3,2-*a*]pyrimidine nucleus. The multiplet between 7.02-7.89 ppm (7H) corresponding to the aromatic protons of benzene and thiazole nucleus.

In an initial endeavor, we selected benzaldehyde **4a** as model aromatic aldehyde to react with equimolar amounts of intermediate amine **3a** for the preparation of 6-phenyl-9-phenylamino-5H-thiazolo[3',2':2,3]-pyrido[4,5-*d*]thiazolo[3,2-*a*]pyrimidin-5-one **5a** and investigated the optimal reaction conditions. The reaction was carried out under neat conditions at 120 °C without and with different acid catalysts such as *p*-toluenesulfonic acid (*p*-TsOH), trifluoroacetic acid (TFA), and sulfamic acid (SA) each 10 mol% in HOAc. The maximum yield was obtained using SA. It can be seen that the reaction did not proceed even after 24 h in the absence of this catalyst (Table 1, entry 1). Although a lower catalyst loading of 5 mol% accomplished this condensation, 10 mol% of SA was optimal in terms of reaction time and isolated yield (Table 1, entry 4). Increasing the amount from 10 to 15 mol% has no effect on the product yield and reaction time (Table 1, entry 6).

In addition, various solvents such as DMF, DMSO, toluene, and MeCN were screened for the optimal reaction conditions. The best catalytic activity was observed in HOAc compared to other organic solvents (Table 1, entries 7-10).

Table 1. Optimization of reaction conditions on the synthesis of **5a**^a

Entry	Catalyst / (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	none	HOAc	120	24	Trace
2	<i>p</i> -TsOH (10)	HOAc	120	10	63
3	TFA (10)	HOAc	120	9	72
4	SA (10)	HOAc	120	8	81
5	SA (5)	HOAc	120	10	74
6	SA (15)	HOAc	120	8	78
7	SA (10)	DMF	120	12	76
8	SA (10)	DMSO	120	10	68
9	SA (10)	toluene	110	24	48
10	SA (10)	MeCN	80	20	65

* Reaction conditions: **3** (1.0 mmol), benzaldehyde (**4a**, 1.0 mmol), solvent (20 mL).

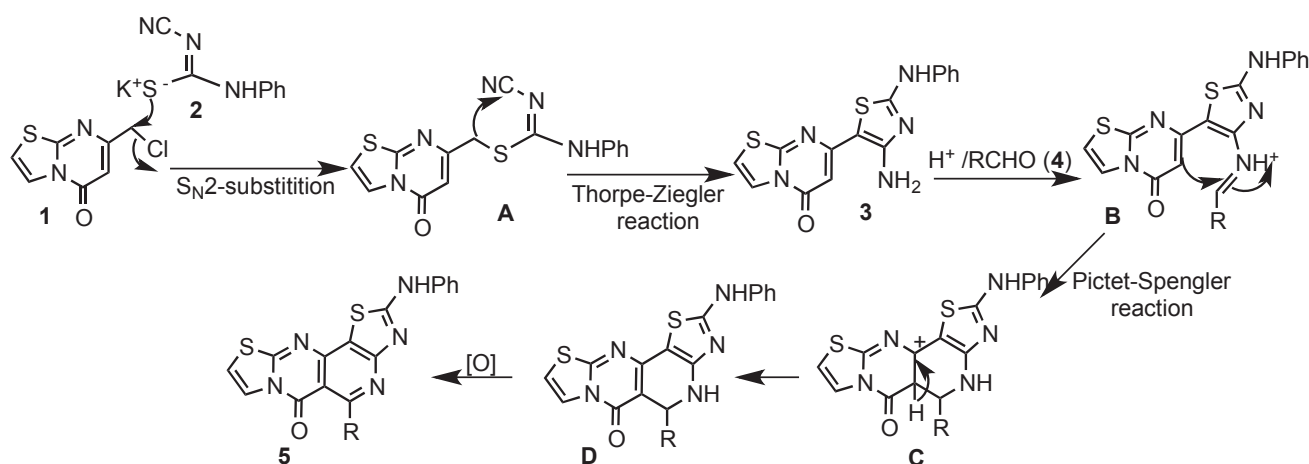
With these optimized reaction conditions in hand, we then planned to examine the versatility of the methodology for the preparation of thiazolopyridine fused thiazolo[3,2-*a*]pyrimidines. The substrate scope of the SA catalyzed coupling of **1** with aromatic aldehydes **4** is shown in Table 2 and it was found that this protocol could be applied not only to the aromatic aldehydes with either electron-donating groups (e.g., methyl, methoxy, hydroxy) or electron-withdrawing groups (e.g., fluoro, chloro, and nitro groups), but also to heterocyclic aldehydes. Therefore, we concluded that the electronic nature of the substituents of aldehydes has no significant effect on this reaction.

Table 2. Synthesis of thiazolo[3',2':2,3]pyrido[4,5-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones **5**

Entry	4 / R	Time / h	Product	Yield / %
1	4a C ₆ H ₅	6	5a	81
2	4b 4-MeC ₆ H ₄	5	5b	82
3	4c 2-MeOC ₆ H ₄	6	5c	78
4	4d 3-MeOC ₆ H ₄	5	5d	82
5	4e 4-MeOC ₆ H ₄	6	5e	85
6	4f 3,4-(MeO) ₂ C ₆ H ₃	4	5f	86
7	4g 4-HOC ₆ H ₄	7	5g	84
8	4h 2-FC ₆ H ₄	7	5h	80
9	4i 4-FC ₆ H ₄	6	5i	85

10	4j	4-ClC ₆ H ₄	7	5j	80
11	4k	4-NO ₂ C ₆ H ₄	8	5k	76
12	4l	2-furyl	10	5l	78
13	4m	2-thienyl	11	5m	82

On the basis of these results, a plausible mechanism for the construction of fused thiazolo[3,2-*a*]-pyrimidinones is proposed (Scheme 2). The formation of ether **A** occurs through *S*-alkylation of 7-chloromethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **1** and potassium *N*-phenyl-*N'*-cyanoimidothiocarbonate (**2**). Then, the ether **A** occurred *via* Thorpe-Ziegler isomerization reaction to generate 7-(3-amino-5-phenylaminothiazol-2-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**3**). Next, the intermediate amine **3** underwent a cationic π -cyclization with aldehyde (**4**) under Pictet-Spengler cyclization to form **D**, which effects aromatisation to give tetracyclic product **5**.



Scheme 2. Proposed reaction mechanism for the formation of compound **5**

In summary, we have developed an efficient and versatile method for the preparation of thiazolopyrido-fused thiazolo[3,2-*a*]pyrimidine derivatives based on 5,6,6,5-tetracyclic systems using the modified Pictet-Spengler reaction with good yields. This method has the advantages of readily available starting materials, mild reaction conditions, and operational simplicity. Further study is underway to the scope of this methodology for some new fused heterocyclic systems.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for ¹H and 100 MHz for ¹³C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H and N analyses

were performed by a HP-MOD 1106 microanalyzer. The preparation of 7-chloromethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**1**)¹⁵ and potassium *N*-phenyl-*N'*-cyanoimidothiocarbonate (**2**)¹⁶ were according to the literature procedure. All other chemicals used in this study were commercially available.

Preparation of 7-(3-Amino-5-phenylaminothiazol-2-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (3**):** To a solution of 7-chloromethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **1** (2.01 g, 10.0 mmol) in DMF (25 mL) was added potassium *N*-phenyl-*N'*-cyanoimidothiocarbonate **2** (2.15 g, 10.0 mmol) and anhydrous potassium carbonate (2.76 g, 20.0 mmol). The mixture was heated at 100 °C for 6 h (monitored by TLC). After cooling to rt, then water (50 mL) was added and stirred for 20 min. The solid was filtered and recrystallized from HOAc to give **3** (2.90 g, 85%). Yellow crystals. mp > 300 °C; IR (KBr): ν 3426, 3356 (NH), 1680 cm⁻¹ (C=O). ¹H NMR (400 MHz, DMSO-*d*₆): δ 5.45 (s, 1H), 7.02 (d, *J* = 4.8 Hz, 1H), 7.01-7.06 (m, 5H), 7.67 (s, 2H), 7.89 (d, *J* = 4.8 Hz, 1H), 10.62 (s, 1H). *Anal.* Calcd for C₁₅H₁₁N₅OS₂: C 52.77, H 3.25, N 20.51. Found: C 52.84, H 3.32, N 20.58

Typical Procedure for the Preparation of 6-Aryl-9-phenylamino-5*H*-thiazolo[3',2':2,3]pyrido[4,5-*d*]-thiazolo[3,2-*a*]pyrimidin-5-ones. To a stirred solution of 7-(3-amino-5-phenylaminothiazol-2-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**3**) (283 mg, 1.0 mmol), aromatic aldehyde (1.0 mmol), and NH₂SO₃H (10 mg, 0.1 mmol) in DMF (20 mL) was heated at 120 °C (monitored by TLC). At the end of the reaction, the reaction mixture was cooled to rt, and then water (20 mL) was added to the mixture. The solid was filtered and recrystallized from DMF to afford the corresponding products **5a-m**.

6-Phenyl-9-phenylamino-5*H*-thiazolo[3',2':2,3]pyrido[4,5-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5a**):** Yellow crystals. mp > 300 °C; IR (KBr): ν 3347, 1682 cm⁻¹ (C=O); ¹H NMR (400 MHz, CF₃CO₂D): δ 7.16 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 4.8 Hz, 1H), 7.45-7.51 (m, 4H), 7.54-7.58 (m, 5H), 8.08 (d, *J* = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 175.5, 168.6, 158.1, 158.0, 155.8, 150.4, 135.6, 130.9, 130.4, 130.3, 129.4, 123.2, 123.0, 122.9, 122.5, 115.9, 113.4, 104.8. *Anal.* Calcd for C₂₂H₁₃N₅OS₂: C 61.81, H 3.07, N 16.38. Found: C 61.89, H 3.13, N 16.44.

6-(4-Methylphenyl)-9-phenylamino-5*H*-thiazolo[3',2':2,3]pyrido[4,5-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5b**):** Yellow crystals. mp > 300 °C; IR (KBr): ν 3351 (NH), 1685 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 2.47 (s, 3H), 7.18-7.20 (m, 1H), 7.30 (d, *J* = 4.8 Hz, 1H), 7.41-7.55 (m, 8H), 7.63-7.64 (m, 1H), 8.09 (d, *J* = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 175.1, 168.3, 159.0, 155.4, 144.7, 144.0, 136.5, 135.5, 130.3, 129.6, 129.1, 128.2, 126.8, 125.4, 122.8, 122.7, 113.6, 104.9, 19.6. *Anal.* Calcd for C₂₃H₁₅N₅OS₂: C 62.57, H 3.42, N 15.86. Found: C 62.65, H 3.49, N 15.95.

6-(2-Methoxyphenyl)-9-phenylamino-5*H*-thiazolo[3',2':2,3]pyrido[4,5-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (5c**):** Yellow crystals. mp > 300 °C; IR (KBr): ν 3343 (NH), 1681 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 3.78 (s, 3H), 7.14-7.18 (m, 2H), 7.29 (d, *J* = 4.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.47-7.57 (m, 6H), 7.63-7.67 (m, 1H), 8.06 (d, *J* = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 177.6,

168.5, 156.6, 156.2, 155.8, 155.3, 149.9, 135.6, 134.3, 130.3, 129.4, 129.1, 122.9, 122.4, 121.2, 118.9, 115.2, 113.4, 111.4, 106.2, 54.7. *Anal.* Calcd for C₂₃H₁₅N₅O₂S₂: C 60.38, H 3.30, N 15.31. Found: C 60.44, H 3.39, N 15.37.

6-(3-Methoxyphenyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5d): Yellow crystals. mp > 300 °C; IR (KBr): ν 3346 (NH), 1678 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 3.90 (s, 3H), 7.21 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.43-7.58 (m, 7H), 8.04 (d, J = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 175.7, 168.7, 158.6, 157.4, 155.6, 152.3, 150.3, 135.6, 131.6, 130.6, 130.3, 129.4, 123.0, 122.4, 121.6, 117.3, 115.0, 113.3, 112.5, 105.1, 55.2. *Anal.* Calcd for C₂₃H₁₅N₅O₂S₂: C 60.38, H 3.30, N 15.31. Found: C 60.46, H 3.37, N 15.36.

6-(4-Methoxyphenyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5e): Yellow crystals. mp > 300 °C; IR (KBr): ν 3340 (NH), 1675 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 4.00 (s, 3H), 7.19 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 4.8 Hz, 1H), 7.44-7.62 (m, 8H), 8.07 (d, J = 4.8 Hz, 1H); ¹³C NMR (100 MHz, CF₃CO₂D): δ 175.3, 168.5, 156.1, 155.8, 150.4, 150.3, 135.6, 130.7, 130.3, 129.9, 129.4, 123.0, 122.8, 122.5, 122.1, 114.6, 113.4, 104.7, 54.8. *Anal.* Calcd for C₂₃H₁₅N₅O₂S₂: C 60.38, H 3.30, N 15.31. Found: C 60.46, H 3.37, N 15.39.

6-(3,4-Dimethoxyphenyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5f): Yellow crystals. mp > 300 °C; IR (KBr): ν 3343 (NH), 1683 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 3.96 (s, 3H), 4.03 (s, 3H), 7.14-7.22 (m, 2H), 7.30 (d, J = 4.8 Hz, 1H), 7.37-7.38 (m, 2H), 7.64-7.66 (m, 1H), 8.13 (d, J = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 175.1, 167.9, 157.8, 154.9, 152.4, 148.4, 144.1, 136.6, 135.5, 130.4, 129.2, 125.5, 123.9, 123.1, 122.9, 122.6, 113.9, 112.2, 113.4, 104.8, 55.4, 55.0. *Anal.* Calcd for C₂₄H₁₅N₅O₃S₂: C 59.12, H 3.51, N 14.36. Found: C 59.19, H 3.60, N 14.46.

6-(4-Hydroxyphenyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5g): Yellow crystals. mp > 300 °C; IR (KBr): ν 3348 (NH), 3336 (OH), 1682 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 7.22 (d, J = 4.8 Hz, 1H), 7.43-7.44 (m, 4H), 7.49-7.55 (m, 6H), 8.01 (d, J = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 175.6, 168.7, 158.5, 155.6, 152.3, 150.3, 135.6, 132.3, 130.2, 130.0, 129.4, 128.8, 128.0, 122.9, 122.4, 113.3, 110.0, 104.9. *Anal.* Calcd for C₂₂H₁₃N₅O₂S₂: C 59.58, H 2.95, N 15.79. Found: C 59.65, H 3.04, N 15.86.

6-(2-Fluorophenyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5h): Yellow crystals. mp > 300 °C; IR (KBr): ν 3342 (NH), 1685 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 7.24-7.28 (m, 2H), 7.37-7.41 (m, 2H), 7.44-7.55 (m, 6H), 7.68-7.70 (m, 1H), 8.07 (d, J = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 168.7, 158.2, 155.2, 152.2, 149.9, 135.6, 134.7, 134.6, 130.3, 129.4, 129.0, 124.8, 124.7, 122.4, 118.7, 118.5, 116.0, 115.8, 113.3, 106.3. *Anal.* Calcd for

C₂₂H₁₂FN₅OS₂: C 59.31, H 2.72, N 15.72. Found: C 59.38, H 2.77, N 15.79.

6-(4-Fluorophenyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5i): Yellow crystals. mp > 300 °C; IR (KBr): ν 3346 (NH), 1681 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 7.25-7.28 (m, 3H), 7.44-7.48 (m, 3H), 7.53-7.59 (m, 5H), 8.05 (d, J = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 168.8, 166.8, 164.2, 157.3, 155.6, 150.3, 135.6, 130.8, 130.7, 129.4, 126.0, 125.9, 122.9, 122.5, 116.3, 116.0, 113.3, 105.0. *Anal.* Calcd for C₂₂H₁₂FN₅OS₂: C 59.31, H 2.72, N 15.72. Found: C 59.40, H 2.76, N 15.76.

6-(4-Chlorophenyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5j): Yellow crystals. mp > 300 °C; IR (KBr): ν 3349 (NH), 1684 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 7.28 (d, J = 4.8 Hz, 1H), 7.46-7.48 (m, 3H), 7.51-7.58 (m, 7H), 8.05 (d, J = 4.8 Hz, 1H); ¹³C NMR (100 MHz, CF₃CO₂D): δ 175.6, 168.7, 157.1, 155.5, 152.5, 150.2, 139.7, 135.5, 130.2, 129.4, 129.2, 128.3, 122.9, 122.4, 113.3, 113.2, 112.2, 105.0. *Anal.* Calcd for C₂₂H₁₂ClN₅OS₂: C 57.20, H 2.62, N 15.16. Found: C 57.27, H 2.68, N 15.23.

6-(4-Nitrophenyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5k): Yellow crystals. mp > 300 °C; IR (KBr): ν 3353 (NH), 1686 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 7.27 (d, J = 4.8 Hz, 1H), 7.48-7.52 (m, 4H), 7.55-7.57 (m, 2H), 7.80 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 4.8 Hz, 1H), 8.46 (d, J = 8.8 Hz, 2H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 168.7, 155.9, 155.3, 152.6, 150.0, 149.7, 149.1, 138.0, 135.4, 130.3, 129.7, 129.6, 123.8, 123.0, 122.3, 113.3, 110.0, 106.7. *Anal.* Calcd for C₂₂H₁₂N₆O₃S₂: C 55.92, H 2.56, N 17.79. Found: C 55.98, H 2.63, N 17.86.

6-(2-Furyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5l): Yellow crystals. mp > 300 °C; IR (KBr): ν 3341 (NH), 1678 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 6.80-6.81 (m, 1H), 7.26 (d, J = 4.8 Hz, 1H), 7.39-7.43 (m, 4H), 7.45-7.50 (m, 2H), 7.84-7.85 (m, 1H), 8.14 (d, J = 4.8 Hz, 1H), 8.46 (d, J = 4.2 Hz, 2H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 180.9, 175.2, 168.0, 154.5, 151.3, 150.7, 149.5, 143.9, 142.3, 135.5, 130.2, 129.5, 127.5, 123.1, 122.8, 114.5, 113.2, 102.5. *Anal.* Calcd for C₂₀H₁₁N₅O₂S₂: C 57.54, H 2.66, N 16.78. Found: C 57.63, H 2.74, N 16.85.

6-(2-Thienyl)-9-phenylamino-5H-thiazolo[3',2':2,3]pyrido[4,5-d]thiazolo[3,2-a]pyrimidin-5-one (5m): Yellow crystals. mp > 300 °C; IR (KBr): ν 3343 (NH), 1681 cm⁻¹ (C=O). ¹H NMR (400 MHz, CF₃CO₂D): δ 7.24-7.28 (m, 2H), 7.41-7.43 (m, 4H), 7.47-7.52 (m, 2H), 7.64-7.65 (m, 1H), 7.81-7.82 (m, 1H), 8.08 (d, J = 4.8 Hz, 1H). ¹³C NMR (100 MHz, CF₃CO₂D): δ 175.4, 168.5, 164.5, 155.5, 152.3, 151.6, 150.3, 135.6, 133.6, 133.3, 130.3, 129.5, 129.2, 127.9, 123.0, 122.6, 113.4, 105.3. *Anal.* Calcd for C₂₀H₁₁N₅OS₃: C 55.41, H 2.56, N 16.15. Found: C 55.49, H 2.64, N 16.24.

ACKNOWLEDGEMENTS

This work was partially supported by innovation team project of Liaoning Province Education Department (Grant No. 2015001).

REFERENCES

1. V. S. Dinakaran, B. Bomma, and K. K. Srinivasan, *Der Pharma Chemica*, 2012, **4**, 255.
2. E. E. Flefel, M. A. Salama, and M. El-Shahat, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2007, **182**, 1739.
3. A. A. Abu-Hashem, M. M. Youssef, and H. A. R. Hussein, *J. Chin. Chem. Soc.*, 2011, **58**, 41.
4. B. Tozkoparan, M. Ertan, P. Kelicen, and R. Demirdamar, *Il Farmaco*, 1999, **54**, 588.
5. O. Alam, S. A. Khan, N. Siddiqui, and W. Ahsan, *Med. Chem. Res.*, 2010, **19**, 1245.
6. S. F. Mohamed, E. M. Flefel, A. E.-G. E. Amr, and D. N. Abd El-Shafy, *Eur. J. Med. Chem.*, 2010, **45**, 1494.
7. K. Komoriya, M. Tsuchimoto, T. Naruchi, T. Okimura, and I. Yamamoto, *J. Immunopharmacol.*, 2008, **4**, 285.
8. B. Pan, R. Huang, L. Zheng, C. Chen, S. Han, D. Qu, M. Zhu, and P. Wei, *Eur. J. Med. Chem.*, 2011, **46**, 819.
9. I. V. Kulakov, *Chem. Heterocycl. Compd.*, 2009, **45**, 1019.
10. A. E. Abbas, Z. Mahdieh, R. F. Ali, and H. Azizollah, *Tetrahedron Lett.*, 2012, **53**, 1351.
11. E. A. Abd El-Galil, S. S. Maigali, and M. M. Abdulla, *Monatsh. Chem.*, 2008, **139**, 1409.
12. (a) D.-L. Wang, D. Wang, L. Yan, G.-Y. Pan, and J.-N. Yang, *Heterocycles*, 2016, **92**, 552; (b) D.-L. Wang, D. Wang, L. Yan, G.-Y. Pan, and J.-N. Yang, *Chin. Chem. Lett.*, 2016, **27**, 953.
13. (a) A. Pictet and T. T. Spengler, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 2030; (b) B. Kundu, P. K. Agarwal, S. K. Sharma, D. Sawant, A. K. Mandadapu, M. Saifuddin, and S. Gupta, *Curr. Org. Synth.*, 2012, **9**, 357.
14. (a) A. M. Shestopalov, A. E. Fedorov, and P. A. Belyakov, *Chem. Heterocycl. Compd.*, 2000, **36**, 609; (b) V. Gefenas, Ž. Stankevičiūtė, and A. Malinauskas, *Chem. Heterocycl. Compd.*, 2010, **46**, 372.
15. S. Djekou, A. Gellisa, P. Vanelle, and H. El-Kashef, *J. Heterocycl. Chem.*, 2006, **43**, 1225.
16. E. Fromm and H. Wenzel, *Ber. Dtsch. Chem. Ges.*, 1922, **55**, 804.