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THE FIRST AND RELIABLE SYNTHESIS OF THIENO[2,3-*e*][1,2,4]-TRIAZOLO[1,5-*c*]PYRIMIDIN-5(6*H*)-ONES *VIA* THEIR [4,3-*c*] COMPOUNDS BY DIMROTH REARRANGEMENT

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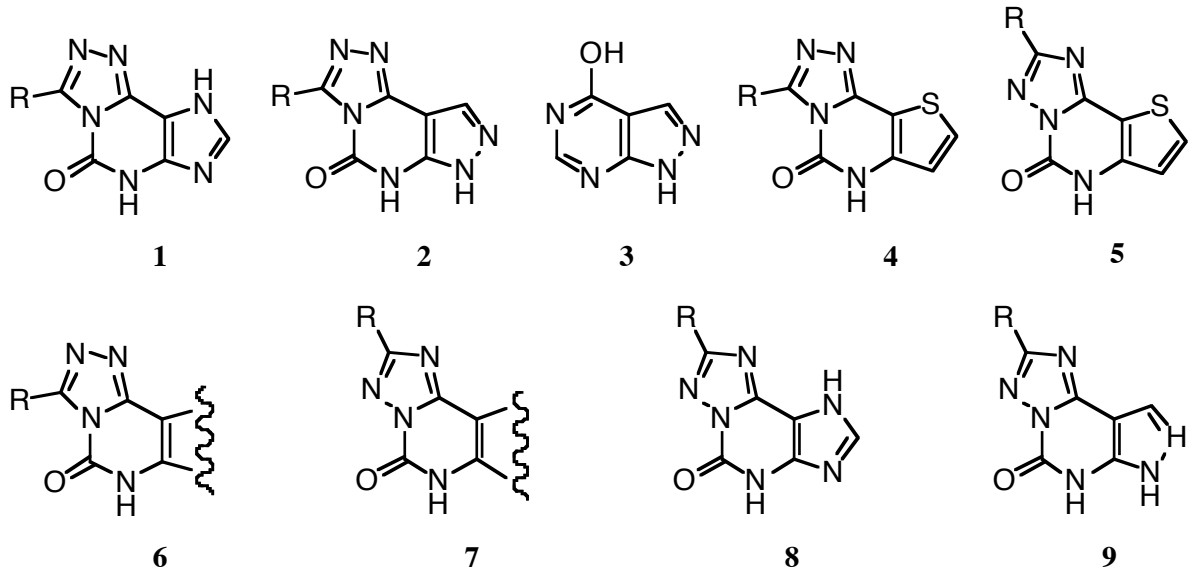
Abstract – This paper describes a reliable and general synthesis of thieno[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one (**5a**) and its 2-substituted derivatives (**5b–i**) as a novel ring system prepared by nimble isomerization of their [4,3-*c*] compounds (**4a–i**), which were produced by condensation of 4-hydrazinothieno-[3,2-*d*]pyrimidin-2(1*H*)-one (**12**) with appropriate triethyl orthoesters or by oxidative cyclization of 4-(benzylidenehydrazino)thieno[3,2-*d*]pyrimidin-2(1*H*)-ones (**13c–i**). The [1,5-*c*] isomers (**5a–c**) were further prepared by condensation of 3-amino-4-imino-2-oxo-1,2,3,4-tetrahydrothieno[3,2-*d*]pyrimidine (**16**) with appropriate triethyl orthoesters as a synthetic method for a reliable structure of the tricyclic ring systems.

INTRODUCTION

Since the discovery in our laboratory that 9*H*-[1,2,4]triazolo[3,4-*i*]purines (**1**)[1] and 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones (**2**)[2] had more potent inhibitory activities against bovine milk xanthine oxidase (XO) *in vitro* than that of allopurinol (**3**) which has been used extensively for the clinical control of uric acid production in gout and hyperuricemia,[3] such tricyclic hetero compounds have aroused considerable recent interest for us. Though allopurinol is a medicine which toxicity is comparatively rare, a life-threatening toxicity syndrome such as vasculitis, rash, eosinophilia, hepatitis, progressive renal failure has been reported after its use.[4] Allopurinol is a structural analogue of hypoxanthine and a potent inhibitor of XO, which catalyzes the conversion of hypoxanthine and xanthine to uric acid.[5] The XO inhibitory activities have been discovered in some newly synthesized compounds and previously known compounds.[6] However, the clinically effective XO inhibitors for the treatment of hyperuricemia and gout have not been developed yet since allopurinol was introduced for clinical use in

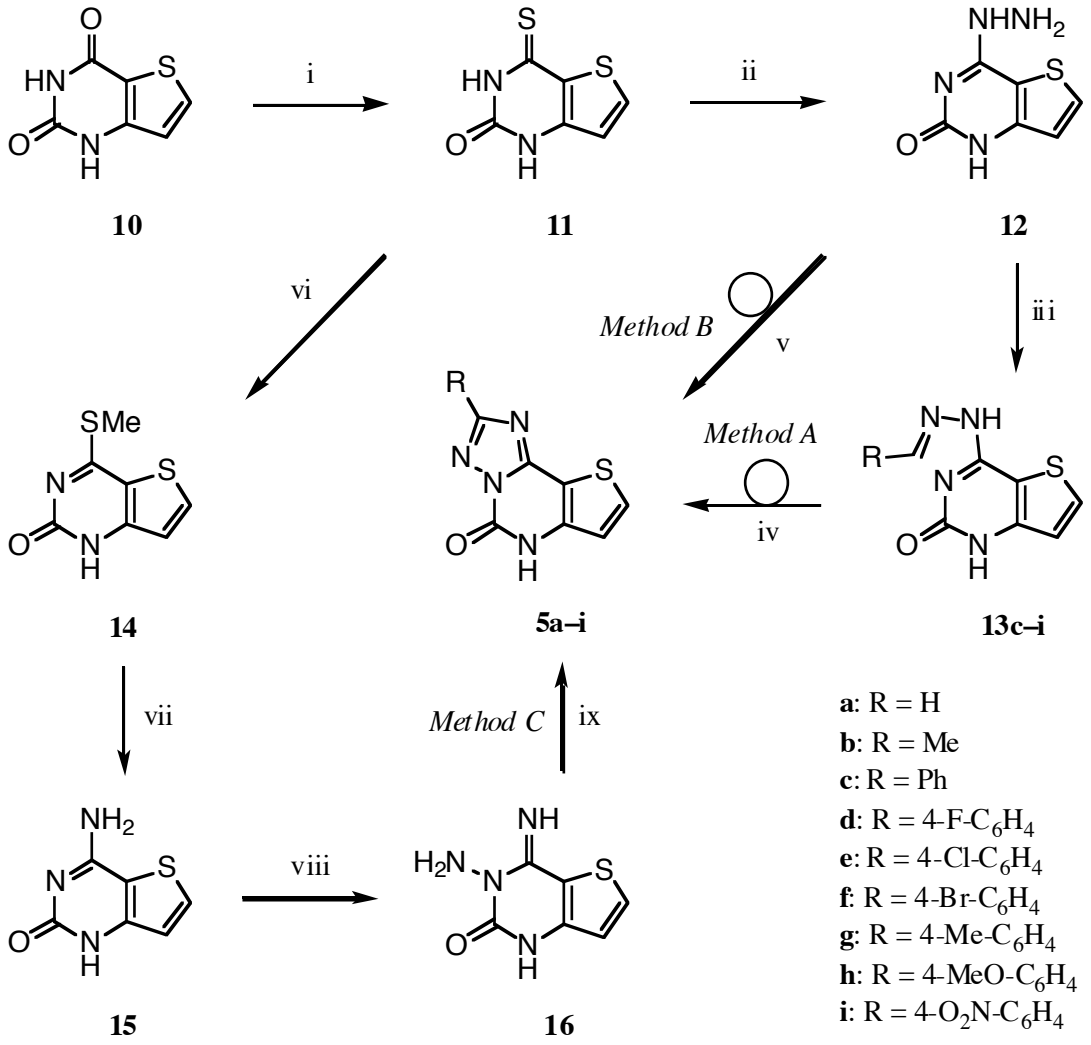
1963.[3,7] On the basis of the above observations, we have designed to prepare the new compounds such as thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones (**4**) and thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidin-5(6*H*)-ones (**5**) as new ring systems. Initially, we thought that such tricyclic hetero compounds (**1**, **2**, **4**) fused with a [1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-one ring (**6**) were quite stable. On the contrary, we have recently found the [4,3-*c*] compounds (**6**) were easily isomerized into the corresponding [1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones (**7**).[8] Since the [4,3-*c*] systems (**6**) with an oxo or thioxo group at the 5-position were rapidly rearranged into their [1,5-*c*] isomers (**7**) even in neutral solution at room temperature,[9] it was difficult to isolate such tricyclic hetero compounds (**1**, **2**, **4**) fused with [1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones (**6**) without isomerization. We have just recently found out that the structures of compounds (**1**) and (**2**) in our recent papers[1,2] had already rearranged into their isomers (**8**) and (**9**), respectively. Therefore, the proper structure reported in there must be not compounds (**1**) and (**2**) but compounds (**8**) and (**9**). Here we report a reliable and general synthesis of thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one (**5a**) and its 2-substituted derivatives (**5b–i**) as a novel ring system and new class of the XO inhibitors.



Scheme 1

RESULTS AND DISCUSSION

As the sequential synthetic pathway is shown in Scheme 2, the first key intermediate, 4-hydrazinothieno-[3,2-*d*]pyrimidin-2(1*H*)-one (**12**), was prepared starting from thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**10**) according to the procedure described by Primeau *et al.*[10] *via* 2-oxo-4-thioxo-1,2,3,4-tetrahydro-thieno[3,2-*d*]pyrimidine (**11**). That is, refluxing the thienopyrimidinedione (**10**) with Lawesson's reagent in 1,4-dioxane gave the 4-thioxo compound (**11**) in 82% yield. Then, treatment of **11** with aqueous hydrazine under reflux afforded the desired 4-hydrazino derivative (**12**) in 76% yield.



Scheme 2 *Reagent and conditions*: i, Lawesson's Reagent, 1,4-dioxane, reflux, 30 min; ii, $NH_2NH_2 \bullet H_2O$, water, reflux, 1.5 h; iii, ArCHO, EtOH, rt, 40–48 h; iv, 70% HNO_3, TFA, rt, 30 min or 70 °C, 45 min; v, $RC(OEt)_3$, AcOH, 80 °C, 10 min; vi, MeI, 2N NaOH, 5 °C, 10 min; vii, 28% aq. NH_3, sealed tube, 150 °C, 7 h; viii, $H_2NO\text{-}SO_3H$, 1N NaOH, rt, 1.5 h; ix, $RC(OEt)_3$, AcOH or TFA, 70–80 °C, 10–60 min.

Subsequent reaction of **12** with appropriate aryl aldehydes in ethanol at room temperature yielded the corresponding hydrazones (**13c–i**) in good yields as shown in Table 1. The oxidative ring closure of **13c–i** to the tricyclic compounds (**5c–i**) was successfully carried out by treatment of **13c–i** with 70% nitric acid in TFA at room temperature or 70 °C to yield the corresponding 2-arylthieno[2,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones (**5c–i**) in 50–60% yields as shown in Table 3 (*Method A*). While the unsubstituted compound, thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one (**5a**), was prepared by heating the 4-hydrazino derivative (**12**) with excess triethyl orthoformate in AcOH at 80 °C. The 2-methyl (**5b**) and 2-phenyl derivatives (**5c**) were likewise synthesized by the heating with triethyl orthoacetate and triethyl orthobenzoate, respectively (*Method B*). In order to prove to be either **4** or **5** as the structure of products which were prepared by *Methods A* and *B*, we tried another synthetic method.

Table 1 Physical and analytical data for the compounds (**13c–i**)

Compd No.	R	Yield (%)	Mp[a] (°C)	Formula (R_f)[b]	Analysis (%) Calcd (Found) C	H	N
13c	Ph	73	> 300	$C_{13}H_{10}N_4OS \cdot 1/10H_2O$ (0.56, A)	57.38 (57.10	3.78 3.85	20.59 20.62)
13d	4-F-C_6H_4	76	> 300	$C_{13}H_9FN_4OS$ (0.75, B)	54.16 (54.00	3.15 3.40	19.43 19.34)
13e	4-Cl-C_6H_4	82	> 300	$C_{13}H_9ClN_4OS \cdot 1/3H_2O$ (0.54, A)	50.24 (50.63	3.14 3.05	18.03 18.35)
13f	4-Br-C_6H_4	80	> 300	$C_{13}H_9BrN_4OS \cdot 1/3H_2O$ (0.70, B)	43.96 (44.07	2.74 2.73	15.77 15.93)
13g	4-Me-C_6H_4	85	> 300	$C_{14}H_{12}N_4OS$ (0.48, A)	59.14 (58.80	4.25 4.32	19.70 19.57)
13h	4-MeO-C_6H_4	78	> 300	$C_{14}H_{12}N_4O_2S \cdot 1/6H_2O$ (0.73, B)	55.43 (55.04	4.10 4.13	18.47) 18.60)
13i	4-O_2N-C_6H_4	76	> 300	$C_{13}H_9N_5O_3S \cdot 1/3H_2O$ (0.70, B)	48.59 (48.90	3.03 3.14	21.80 21.51)

[a]All compounds were recrystallized from DMF and were obtained as colorless powdery crystals except for **13i** (orange).
[b]Solvent system for TLC: (A) AcOEt; (B) AcOEt : EtOH (4:1 v/v).

The second key intermediate, 4-aminothieno[3,2-*d*]pyrimidin-2(1*H*)-one (**15**), was prepared by amination of the 4-methylthio derivative (**14**) which was obtained by methylation of **11** in the usual way, with 28% aqueous ammonia under heating. Then the requisite precursor, 3-amino-4-imino-2-oxo-1,2,3,4-tetrahydrothieno[3,2-*d*]pyrimidine (**16**), was synthesized by *N*-amination of **15** with excess hydroxylamine-*O*-sulfonic acid in 1N NaOH solution at room temperature. Heating **16** thus obtained with appropriate triethyl orthoesters afforded the corresponding thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one (**5a**) and its 2-substituted derivatives (**5b**,**c**), which were identical to the compounds (**5a–c**) prepared by *Methods A* and *B*, respectively (*Method C).* All new compounds (**5a–i**) and (**11–16**) exhibited satisfactory elemental combustion analyses except for **16** and IR and ^{1}H-NMR spectral data consistent with the structures as indicated in Tables 1–4.

In conclusion, we have established an efficient and reliable synthesis of thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one (**5a**) and its 2-substituted derivatives (**5b–i**) *via* rearrangement of thieno[2,3-*e*]-[1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones (**4a–i**). Thus the ring system for compounds (**4**) was very

Table 2 IR and ^{1}H-NMR spectroscopic data for the compounds (**13c–i**)

Compd No.	ν_{max} (Nujol)/cm^{-1}	δ_H [300 MHz; $(CD_3)_2SO$; Me_4Si]
13c	3140, 3060 (NH) 1660 (C=O)	6.83 (1H, d, *J* 5.4, 7-H), 7.35–7.58 (3H, m, Ph-*m*, *p*-H), 7.80–7.95 (2H, m, Ph-*o*-H), 8.00 (1H, d, *J* 5.4, 6-H), 8.38 (1H, s, N=C*H*Ph), 11.00 (2H, br s, 2 x NH)
13d	3140, 3060 (NH) 1655 (C=O)	6.83 (1H, d, *J* 5.4, 7-H), 7.32 (2H, dd, $J_{H,H}$ 8.7, $J_{H,F}$ 9.0, Ar-*m*-H), 7.92 (2H, dd, $J_{H,H}$ 8.7, $J_{H,F}$ 5.7, Ar-*o*-H), 8.00 (1H, d, *J* 5.4, 6-H), 8.38 (1H, s, N=C*H*Ar), 11.09 (2H, br s, 2 x NH)
13e	3140, 3065 (NH) 1660 (C=O)	6.83 (1H, d, *J* 5.4, 7-H), 7.54 (2H, d, *J* 8.7, Ar-*m*-H), 7.88 (2H, d, *J* 8.7, Ar-*o*-H), 8.01 (1H, d, *J* 5.4, 6-H), 8.38 (1H, s, N=C*H*Ar), 11.13 (2H, br s, 2 x NH)
13f	3140, 3065 (NH) 1655 (C=O)	6.83 (1H, d, *J* 5.4, 7-H), 7.68 (2H, d, *J* 8.7, Ar-*m*-H), 7.81 (2H, d, *J* 8.7, Ar-*o*-H), 8.00 (1H, d, *J* 5.4, 6-H), 8.36 (1H, s, N=C*H*Ar), 11.15 (2H, br s, 2 x NH)
13g	3140, 3065 (NH) 1660 (C=O)	2.36 (3H, s, Me), 6.82 (1H, d, *J* 5.4, 7-H), 7.29 (2H, d, *J* 8.1, Ar-*m*-H), 7.76 (2H, d, *J* 8.1, Ar-*o*-H), 8.00 (1H, d, *J* 5.4, 6-H), 8.34 (1H, s, N=C*H*Ar), 11.04 (2H, br s, 2 x NH)
13h	3160, 3100 (NH) 1700 (C=O)	3.82 (3H, s, OMe), 6.82 (1H, d, *J* 5.4, 7-H), 7.05 (2H, d, *J* 8.7, Ar-*m*-H), 7.82 (2H, d, *J* 8.7, Ar-*o*-H), 7.97 (1H, d, *J* 5.4, 6-H), 8.31 (1H, s, N=C*H*Ar), 10.87 and 11.04 (each 1H, each br s, 2 x NH)
13i	3120, 3070 (NH) 1670 (C=O)	6.87 (1H, d, *J* 5.1, 7-H), 8.07 (1H, d, *J* 5.1, 6-H), 8.11 (2H, d, *J* 8.1, Ar-*o*-H), 8.33 (2H, d, *J* 8.1, Ar-*m*-H), 8.51 (1H, s, N=C*H*Ar), 11.26 (2H, br s, 2 x NH)

unstable to isolate and easy to be isomerized into their isomers (**5**) even in neutral solution at room temperature. The compounds (**5a–i**) reported in this paper were examined for the XO inhibitory activities against bovine milk xanthine oxidase *in vitro* and were mostly found to be slightly less active than that of allopurinol.

EXPERIMENTAL

Mps were obtained on a Yanagimoto micro-melting point hot-stage apparatus and were uncorrected. Microanalyses were measured by a Yanako CHN Corder MT-5 apparatus. IR spectra were recorded using a JASCO FT/IR-200 spectrophotometer as Nujol mulls. ^{1}H-NMR spectra were obtained using a Varian VXR 300 MHz spectrometer with TMS as an internal standard. In all cases, chemical shifts are in ppm downfield to TMS. *J* values are given in Hz. All reagents were of commercial quality from

Table 3 Physical and analytical data for the compounds (**5a–i**)

Compd No.	R	Yield[a] (%)	Mp[b] (°C)	Formula (R_f)[c]	Analysis (%) Calcd (Found) C	H	N
5a	H	65 (*B*) 52 (*C*)	> 300	$C_7H_4N_4OS$ (0.70, B)	43.74 (43.68	2.10 2.38	29.15 28.96)
5b	Me	60 (*B*) 55 (*C*)	> 300	$C_8H_6N_4OS$ (0.41, A)	46.59 (46.24	2.93 3.22	27.17 26.96)
5c	Ph	56 (*A*) 82 (*B*) 60 (*C*)	> 300	$C_{13}H_8N_4OS \cdot 1/3H_2O$ (0.58, A)	56.92 (57.07	3.18 3.16	20.43 20.56)
5d	4-F-C_6H_4	50 (*A*)	> 300	$C_{13}H_7FN_4OS \cdot 1/10H_2O$ (0.78, B)	54.20 (54.05	2.52 2.72	19.45 19.23)
5e	4-Cl-C_6H_4	55 (*A*)	> 300	$C_{13}H_7ClN_4OS \cdot 1/10H_2O$ (0.80, B)	51.27 (51.01	2.38 2.60	18.40 18.25)
5f	4-Br-C_6H_4	53 (*A*)	> 300	$C_{13}H_7BrN_4OS \cdot 3/5H_2O$ (0.70, B)	43.61 (43.27	2.31 2.17	15.65 15.54)
5g	4-Me-C_6H_4	60 (*A*)	> 300	$C_{14}H_{10}N_4OS \cdot H_2O$ (0.48, A)	55.99 (55.60	4.03 3.70	18.65 18.46)
5h	4-MeO-C_6H_4	62 (*A*)	> 300	$C_{14}H_{10}N_4O_2S \cdot H_2O$ (0.51, A)	53.16 (53.17	3.82 3.50	17.71 17.90)
5i	4-O_2N-C_6H_4	52 (*A*)	> 300	$C_{13}H_7N_5O_3S \cdot H_2O$ (0.70, B)	47.13 (47.00	2.74 2.37	21.14 20.79)

[a]Each yield of (*A*), (*B*), and (*C*) was obtained by *Method A*, *Method B*, and *Method C*, respectively, as shown in Scheme 2.
[b]All compounds were recrystallized from EtOH or DMF and were obtained as colorless powdery crystals or needles except for **5i** (pale yellow).
[c]Solvent system for TLC: (A) AcOEt; (B) AcOEt : EtOH (4:1 v/v).

freshly opened containers and were used without further purification. Reaction progress was monitored by analytical thin layer chromatography (TLC) on pre-coated glass plates (silica gel 70 FM Plate-Wako) using the solvent systems of A [AcOEt : EtOH (4:1)] and B [AcOEt : EtOH (1:1)] unless being cited in the table and products were visualized by UV light. The reaction temperatures are indicated as the temperature of the oil bath.

2-Oxo-4-thioxo-1,2,3,4-tetrahydrothieno[3,2-*d*]pyrimidine (11)

Table 4 IR and ^{1}H-NMR spectroscopic data for the compounds (**5a–i**)

Compd No.	ν_{max} (Nujol)/cm^{-1}	δ_H [300 MHz; $(CD_3)_2SO$; Me_4Si]
5a	3105 (NH) 1750 (C=O)	7.14 (1H, d, *J* 5.4, 7-H), 8.08 (1H, d, *J* 5.4, 8-H), 8.42 (1H, s, 2-H), 12.75 (1H, br s, NH)
5b	3100 (NH) 1740 (C=O)	2.44 (3H, s, Me), 7.12 (1H, d, *J* 5.4, 7-H), 8.06 (1H, d, *J* 5.4, 8-H), 12.57 (1H, br s, NH)
5c	3105 (NH) 1720 (C=O)	7.16 (1H, d, *J* 5.4, 7-H), 7.52–7.59 (3H, m, Ph-*m*, *p*-H), 8.10 (1H, d, *J* 5.4, 8-H), 8.17–8.24 (2H, m, Ph-*o*-H), 12.80 (1H, br s, NH)
5d	3100 (NH) 1730 (C=O)	7.16 (1H, d, *J* 5.1, 7-H), 7.38 (2H, dd, $J_{H,H}$ 8.7, $J_{H,F}$ 9.0, Ar-*m*H), 8.11 (1H, d, *J* 5.1, 8-H), 8.23 (2H, dd, $J_{H,H}$ 8.7, $J_{H,F}$ 5.4, Ar-*o*H), 12.70 (1H, br s, NH)
5e	3150 (NH) 1720 (C=O)	7.15 (1H, d, *J* 5.1, 7-H), 7.61 (2H, d, *J* 8.4, Ar-*m*-H), 8.10 (1H, d, *J* 5.1, 8-H), 8.19 (2H, d, *J* 8.4, Ar-*o*-H), 12.84 (1H, br s, NH)
5f	3150 (NH) 1730 (C=O)	7.16 (1H, d, *J* 5.1, 7-H), 7.59 (2H, d, *J* 8.4, Ar-*m*-H), 8.12 (1H, d, *J* 5.1, 8-H), 8.13 (2H, d, *J* 8.4, Ar-*o*-H), 12.78 (1H, br s, NH)
5g	3160 (NH) 1725 (C=O)	2.39 (3H, s, Me), 7.15 (1H, d, *J* 5.1, 7-H), 7.36 (2H, d, *J* 8.1, Ar-*m*-H), 8.08 (2H, d, *J* 8.1, Ar-*o*-H), 8.10 (1H, d, *J* 5.1, 8-H), 12.72 (1H, br s, NH)
5h	3120 (NH) 1730 (C=O)	4.03 (3H, s, OMe), 7.15 (1H, d, *J* 5.1, 7-H), 7.55 (2H, d, *J* 9.0, Ar-*m*-H), 8.11 (1H, d, *J* 5.1, 8-H), 8.43 (2H, d, *J* 9.0, Ar-*o*-H), 12.78 (1H, br s, NH)
5i	3110 (NH) 1725 (C=O)	7.17 (1H, d, *J* 5.4, 7-H), 8.12 (1H, d, *J* 5.4, 8-H), 8.39 (2H, d, *J* 9.0, Ar-*o*-H), 8.45 (2H, d, *J* 9.0, Ar-*m*-H), 13.10 (1H, br s, NH)

A mixture of thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**10**)[10] (0.5 g, 2.97 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent, 1.2 g, 2.97 mmol) in 1,4-dioxane (10 mL) was heated under reflux for 30 min. After the reaction was complete, the solution was evaporated *in vacuo* and the residue was triturated with AcOEt to give crystals, which were collected by filtration and recrystallized from EtOH to afford the 4-thioxo derivative (**11**) (0.45 g, 82%) as pale yellow powdery crystals, mp 291–293 °C; R_f (A) 0.79; IR (Nujol) ν_{max}/cm^{-1}: 3180, 3080 (NH), 1670 (C=O); ^{1}H-NMR [$(CD_3)_2SO$] δ: 6.93 (1H, d, *J* 5.4, 7-H), 8.11 (1H, d, *J* 5.4, 6-H), 12.36 (2H, br s, 2 x NH); *Anal.* Calcd for $C_6H_4N_2OS_2$: C, 39.11; H, 2.19; N, 15.20, Found: C, 38.88; H, 2.31; N, 15.05.

4-Hydrazinothieno[3,2-*d*]pyrimidin-2(1*H*)-one (12)

A mixture of the 4-thioxo derivative (**11**) (1.0 g, 5.43 mmol) and hydrazine monohydrate (0.8 g, 16 mmol) in water (10 mL) was heated under reflux for 1.5 h. Upon cooling to rt after the reaction was complete, the resulting precipitates were collected by filtration and washed with water and EtOH to afford the hydrazino derivative (**12**) (0.75 g, 76%) as colorless powdery crystals (from 70% aqueous DMF), mp 301–303 °C; R_f (B) 0.34; IR (Nujol) ν_{max} or δ_{max}/ cm^{-1}: 3320 (ν_{as}, NH_2), 3170 (ν_s, NH_2), 3090, 3080 (ν NH), 1665 (ν, C=O), 1645 (δ, NH_2); ^{1}H-NMR [$(CD_3)_2SO$] δ: 4.87 (2H, br s, NH_2), 6.81 (1H, d, *J* 5.4, 7-H), 7.88 (1H, d, *J* 5.4, 6-H), 10.50 (2H, br s, 2 x NH); *Anal*. Calcd for $C_6H_6N_4OS$: C, 39.55; H, 3.32; N, 30.75, Found: C, 39.54; H, 3.22; N, 30.76.

General Procedure for the Preparation of 4-Benzylidenehydrazinothieno[3,2-*d*]pyrimidin-2(1*H*)-one (13c) and Its 4-(4-Substituted benzyl) derivatives (13d–i)

A mixture of the hydrazino derivative (**12**) (0.2 g, 1.1 mmol) and an appropriate aryl aldehyde (1.65 mmol) in EtOH (20 mL) was stirred at rt for 40–48 h. After the reaction was complete, the precipitated crystals were collected by filtration, washed with AcOEt, and recrystallized from DMF to afford the corresponding hydrazones (**13c–i**) as shown in Tables 1 and 2.

General Procedure for the Preparation of Thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-one (5a) and Its 2-Substituted derivatives (5b–i)

(1) *Method A*: a solution of an appropriate arylaldehyde hydrazone (**13c–i**) (1.2 mmol) with 70% nitric acid (0.16 g, 1.78 mmol) in TFA (12 mL) was stirred at rt for 30 min except for **13i**, which was heated at 70 °C for 45 min. After the reaction was complete, the solvent was evaporated in *vacuo* to afford the solid. The resulting solid was washed with 0.5% aqueous $KHCO_3$ and recrystallized from an appropriate solvent to give the corresponding thienotriazolopyrimidines (**5c–i**) as shown in Tables 3 and 4.

(2) *Method B*: a mixture of the hydrazino derivative (**12**) (0.2 g, 1.1 mmol) with an appropriate triethyl orthoester (11 mmol) in AcOH (6 mL) was heated at 80 °C for 10 min. After cooling to rt, the precipitated crystals were collected by filtration, washed with water and EtOH, and recrystallized from EtOH to afford the corresponding thienotriazolopyrimidines (**5a–c**) as shown in Tables 3 and 4.

(3) *Method C*: a mixture of 3-amino-4-imino-2-oxo-1,2,3,4-tetrahydrothieno[3,2-*d*]pyrimidine (**16**) (0.2 g, 1.1 mmol) with triethyl orthoformate (0.81 g, 5.5 mmol) in TFA (6 mL) was heated at 70 °C for 1 h. After the reaction was complete, the solvent was evaporated *in* vacuo. The resulting solid was washed with 0.5% aqueous $KHCO_3$ and recrystallized from EtOH to yield the pure product (**5a**). In a similar manner as above, heating the compound (**16**) (0.2 g, 1.1 mmol) with triethyl orthoacetate (0.89 g, 5.5 mmol) and triethyl orthobenzoate (1.23 g, 5.5 mmol) in AcOH (5 mL) at 80 °C for 10 min gave the

product (**5b**) and (**5c**), respectively, which were precipitated after the reactions were complete and were recrystallized from EtOH as shown in Table 3.

4-Methylthiothieno[3,2-*d*]pyrimidin-2(1*H*)-one (14)

To a cooling solution of the 4-thioxo derivative (**11**) (0.5 g, 2.71 mmol) in 2N NaOH solution (10 mL) at 5 °C was added MeI (1.15 g, 8.10 mmol) dropwise. The solution was vigorously shaken for 10 min to afford precipitates. The precipitates were collected by filtration, dissolved in hot water, and acidified with 10% HCl solution. The reprecipitated crystals thus obtained were collected by filtration and dried under reduced pressure to yield the 4-methylthio derivative (**14**) (0.27 g, 50%) as colorless powdery crystals (from EtOH), mp 276–278 °C; R_f (A) 0.69; IR (Nujol) ν_{max}/cm^{-1}: 3060 (NH), 1650 (C=O); ^{1}H-NMR [$(CD_3)_2SO$] δ: 2.61 (3H, s, SMe), 7.00 (1H, d, *J* 5.4, 7-H), 8.10 (1H, d, *J* 5.4, 6-H), 12.00 (1H, br s, NH); *Anal*. Calcd for $C_7H_6N_2OS_2 \bullet 1/4H_2O$: C, 41.46; H, 3.23; N, 13.82, Found: C, 41.84; H, 3.05; N, 13.87.

4-Aminothieno[3,2-*d*]pyrimidin-2(1*H*)-one (15)

A mixture of the 4-methylthio derivative (**14**) (1.0 g, 5.04 mmol) and 28% aqueous NH_3 (50 mL) was heated in a steel sealed tube at 150 °C (10 kg/cm^2) pressure for 7 h. After the reaction was complete, the precipitates were collected by filtration, washed with EtOH, and recrystallized from 70% aqueous DMF to afford 4-amino derivative (**15**) (0.58 g, 70%) as colorless powdery crystals, mp > 300 °C; R_f (A) 0.36; IR (Nujol) ν_{max} or δ_{max} cm^{-1}: 3340 (ν_{as}, NH_2), 3250 (ν_s, NH_2), 3080 (ν NH), 1665 (ν, C=O), 1630 (δ, NH_2); ^{1}H-NMR [$(CD_3)_2SO$] δ: 6.88 (1H, d, *J* 5.4, 7-H), 7.50 (2H, br s, NH_2), 7.91 (1H, d, *J* 5.4, 6-H), 11.10 (1H, br s, NH); *Anal*. Calcd for $C_6H_5N_3OS \bullet 9/10H_2O$: C, 39.29; H, 3.74; N, 22.91, Found: C, 39.54; H, 3.71; N, 22.75.

3-Amino-4-imino-2-oxo-1,2,3,4-tetrahydrothieno[3,2-*d*]pyrimidine (16)

To a solution of 4-amino derivative (**15**) (0.3 g, 1.79 mmol) in 1N NaOH solution (9 mL) at rt was added a solution of hydroxylamine-*O*-sulfonic acid (0.6 g, 5.31 mmol) in water (6 mL) dropwise. Then, the solution was stirred at rt for 1.5 h to give the precipitates, which were collected by filtration and washed with water to afford the 3-amino derivative (**16**) (0.1 g, 30%) as colorless powdery crystals, mp 280–281 °C; R_f (A) 0.32; IR (Nujol) ν_{max} or δ_{max} cm^{-1}: 3330 (ν_{as}, NH_2), 3260 (ν_s, NH_2), 3190, 3040 (ν NH), 1670 (ν, C=O), 1640 (δ, NH_2); ^{1}H-NMR [$(CD_3)_2SO$] δ: 5.44 (2H, s, NH_2), 7.15 (1H, d, *J* 5.4, 7-H), 7.41 (1H, s, NH), 7.95 (1H, d, *J* 5.4, 6-H), 11.10 (1H, br s, NH). The product (**16**) was obtained as a single compound and was used for the following reactions without further purification because it was difficult to purify since it was insoluble in usual solvents.

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