Synthesis and *S*-Methylation of 2-Thioxopyrido[3',2':4,5]thieno[3,2-*d*]-pyrimidin-4(3*H*)-ones With and Without a Phase Transfer Catalyst

Chaitanya G. Dave,* A. B. Shah and H. C. Shah

Chemical Sciences Laboratory, Loyola Centre for Research and Development
St. Xavier's College, Navarangpura, Ahmedabad 380 009, India

Received July 26, 1996

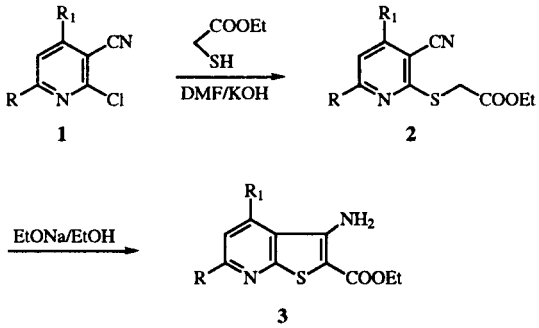
A number of 2-thioxopyrido[3',2':4,5]thieno[3,2-*d*]pyrimdin-4(3*H*)-ones (**5**) have been synthesized by cyclocondensation of 2-carbethoxy-3-amino-4-phenyl-6-substituted-thieno[2,3-*b*]pyridines (**3**) with various isothiocyanates. Compounds **5** were *S*-methylated routinely and the reactions compared under solid-liquid phase transfer conditions to obtain 2-methylthiopyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones (**6**). The new triheterocyclic pyridothienopyrimidines were prepared with the objective to study their pharmacological properties.

J. Heterocyclic Chem., **34**, 937 (1997).

Pyridothienopyimidines, an example of a triheterocylclic system, have attracted much attention due to their interesting biological activities [1-5]. Even though very little attention has been given to this type of ring system. It has also been found that the methylation of compounds **5** at position-2 enhanced analgesic and antiinflammatory activities [5]. The alkylation of ambident *S,N*-nucleophilic heterocycles under phase transfer conditions is known to give predominantly if not exclusively the *S*-alkylated products [6,7]. Therefore in this article, some new 2-thioxopyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones have been reported and their *S*-methylations have been performed in a conventional manner and under phase transfer conditions. In triheterocyclic pyridothienopyrimidines, phase transfer catalyst mediated *S*-alkylation has been studied for the first time.

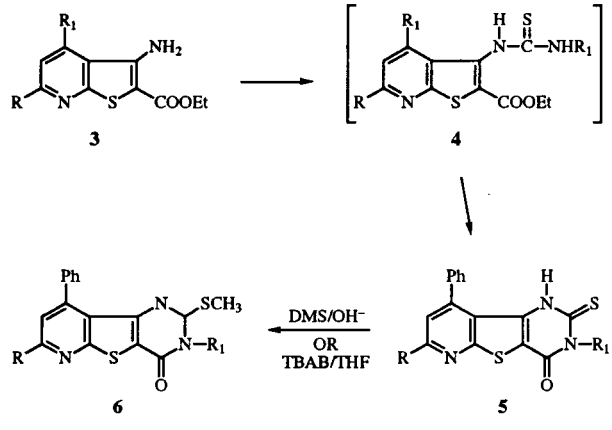
The starting 2-carbethoxy-3-aminothieno[2,3-*b*]pyridines **3** required for the synthesis of 2-thioxopyridothienopyrimidines **5** are important synthons for the annellation of a pyrimidine ring onto the thienopyridine ring system. Such compounds **3** have previously been reported by us [8] *via* an intramolecular Thorpe-Ziegler type of cyclization of intermediate 2-carbethoxymethylmercapto-3-cyanopyridines **2** which were prepared from 2-chloro-3-cyanopyridines **1** and ethyl thioglycolate as shown in Scheme **1**.

Scheme 1



2-Carbethoxy-3-amino-4-phenyl-6-substituted-thieno-[2,3-*b*]pyridines **3** on cyclocondensation with various isothiocyanates in boiling pyridine gave 2-thioxo-9-phenyl-3,7-disubstituted-1,2,3,4-tetrahydropyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **5** which were *S*-methylated using dimethyl sulphate in alkaline medium to afford 2-methylthio-9-phenyl-3,7-disubstituted pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6**. The same compounds **6** were prepared under solid-liquid phase transfer conditions in which tetra-*n*-butyl ammonium bromide was used as a phase transfer catalyst in tetrahydrofuran as solvent (Scheme 2).

Scheme 2



5,6	R	R_1
a	4-$CH_3C_6H_4$	n-C_4H_9
b	4-$CH_3C_6H_4$	C_6H_5
c	4-$CH_3C_6H_4$	2-$CH_3C_6H_4$
d	4-$CH_3C_6H_4$	3-$CH_3C_6H_4$
e	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$
g	4-$CH_3C_6H_4$	4-$OCH_3C_6H_4$
h	4-$OCH_3C_6H_4$	n-C_4H_9
i	4-$OCH_3C_6H_4$	C_6H_5
j	4-$OCH_3C_6H_4$	2-$CH_3C_6H_4$
k	4-$OCH_3C_6H_4$	3-$CH_3C_6H_4$
l	4-$OCH_3C_6H_4$	4-$CH_3C_6H_4$
m	4-$OCH_3C_6H_4$	2-$OCH_3C_6H_4$
n	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$

During the synthesis of **5**, attempts to isolate intermediate thiourea derivatives **4** under various reaction conditions like refluxing in ethanol, benzene, toluene, xylene, dioxane, *N,N*-dimethylformamide, sodium ethoxide in ethanol, and ethanol saturated with dry hydrogen chloride gas were unsuccessful while direct cyclization was achieved in boiling pyridine. However, the fusion of compounds **3** and isothiocyanates at about 225-230° provided cyclic pyridothienopyrimidines **5** in poor yields. Physical constants and ^{1}H-nmr data for **5** are recorded in Table 1. The ir spectra for compounds **5** showed absorptions in the region 3380-3340 cm^{-1} (NH), 1700-1680 cm^{-1} (C=O), around 1550 and 1365 cm^{-1} (NH-C=S) and 1205-1190 cm^{-1} (C=S).

S-Methylation of 2-thioxopyridothienopyridines **5** with dimethyl sulphate in sodium hydroxide or sodium ethoxide was unexpectedly a medium to low yield reaction (Method A), perhaps due to the poor solubility of **5** in almost all the solvents. Hence, the methylation reactions were exploited under solid-liquid phase transfer conditions. Methylation of ambident [N-C-S]$^-$ in the 2-thioxopyridothienopyrimidine system has not been reported thus far. The reactions provided selectively *S*-methylated products **6** with excellent yields (Method B). Physical constants and ^{1}H-nmr data are given in Table 2. The ir spectra of **6** exhibited absorption in the region 1680-1665 cm^{-1} (C=O) the absence of bands in the region 3380-3340 cm^{-1} (NH), 1200-1190 cm^{-1} (C=S)

Scheme 3

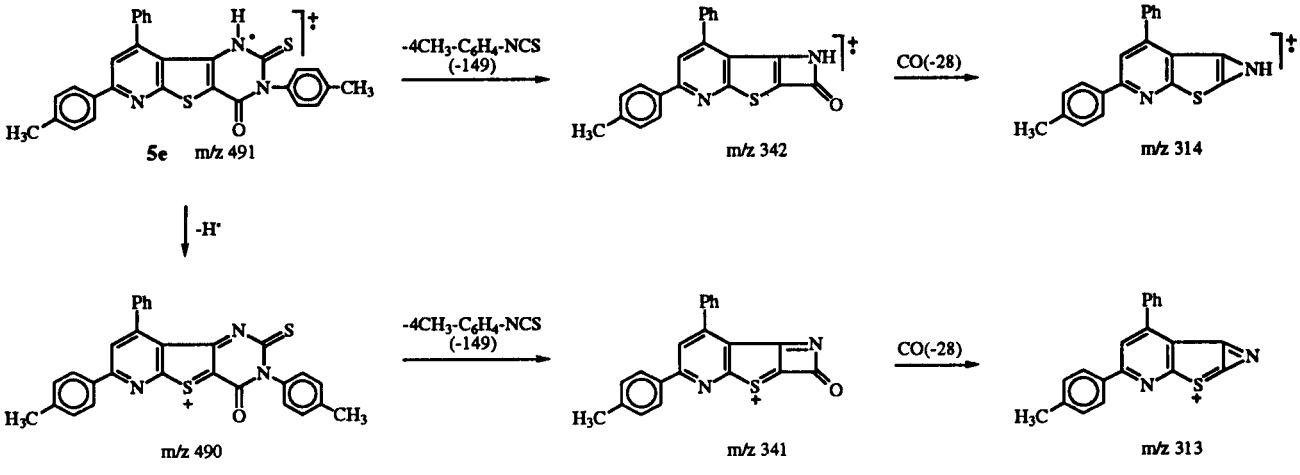


Table 1

2-Thioxopyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)ones **5a-n**

Compound No.	Yield %	Mp °C	^{1}H-NMR (δ, ppm) [a]	Molecular Formula (Molecular Weight) [b]	Analysis % Calcd./Found C	H	N
5a	55	229-230	0.8-1.11 (m, 3H, -C*H*$_3$(CH$_2$)$_3$-), 1.44-1.85 (m, 4H, -CH$_3$(CH$_2$)$_2$-CH$_2$-), 2.35 (s, 3H, CH$_3$), 4.1 (t, 2H, CH$_3$(CH$_2$)$_2$-CH$_2$-), 7.51-8.12 (m, 10H, Ar-H), 8.21 (s, 1H, NH)	$C_{26}H_{23}N_3OS_2$ (457)	68.27 68.43	5.03 5.31	9.19 9.09
5b	51	315-317	2.38 (s, 3H, CH$_3$), 7-8.21 (m, 15H, Ar-H) 8.31 (s, 1H, NH)	$C_{28}H_{19}N_3OS_2$ (477)	70.44 70.69	3.98 4.16	8.80 8.68
5c	60	323-325	2.13 (s, 3H, CH$_3$), 2.38 (s, 3H, CH$_3$), 7.12-8.21 (m, 14H, Ar-H), 8.35 (s, 1H, NH)	$C_{29}H_{21}N_3OS_2$ (491)	70.85 70.69	4.31 4.47	8.55 8.28
5d	63	305-307	2.11 (s, 3H, CH$_3$), 2.29 (s, 3H, CH$_3$), 7.12-8.21 (m, 14H, Ar-H), 8.33 (s, 1H, NH)	$C_{29}H_{21}N_3OS_2$ (491)	70.85 70.99	4.31 4.52	8.55 8.98
5e	59	309-312	2.10 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 7.10-8.30 (m, 14H, Ar-H), 8.33 (s, 1H, NH)	$C_{29}H_{21}N_3OS_2$ (491)	70.85 70.71	4.31 4.08	8.55 8.22
5f	42	289-291	2.24 (s, 3H, CH$_3$), 3.92 (s, 3H, OCH$_3$), 7.01-8.20 (m, 14H, Ar-H), 8.36 (s, 1H, NH)	$C_{29}H_{21}N_3O_2S_2$ (507)	68.64 68.49	4.14 4.01	8.28 8.53
5g	52	298-299	2.40 (s, 3H, CH$_3$), 3.86 (s, 3H, OCH$_3$), 7.12-8.22 (m, 14H, Ar-H), 8.36 (s, 1H, NH)	$C_{29}H_{21}N_3O_2S_2$ (507)	68.64 68.38	4.14 4.39	8.28 8.41

Table 1 (continued)

Compound No.	Yield %	Mp °C	^{1}H-NMR (δ, ppm) [a]	Molecular Formula (Molecular Weight) [b]	Analysis % Calcd./Found C	H	N
5h	50	219-220	--	$C_{26}H_{23}N_3O_2S_2$ (473)	65.96 65.80	4.86 4.37	8.88 9.03
5i	49	276-278	3.89 (s, 3H, CH_3), 7.2-8.20 (m, 15H, Ar-H), 8.38 (s, 1H, NH)	$C_{28}H_{19}N_3O_2S_2$ (493)	68.15 68.43	3.85 3.99	8.52 8.78
5j	53	310-311	2.30 (s, 3H, CH_3), 4.10 (s, 3H, OCH_3), 7.12-8.20 (m, 14H, Ar-H), 8.38 (s, 1H, NH)	$C_{29}H_{21}N_3O_2S_2$ (507)	68.64 68.80	4.14 3.97	8.28 8.07
5k	55	307-309	2.34 (s, 3H, CH_3), 4.14 (s, 3H, OCH_3), 7.12-8.23 (m, 14H, Ar-H), 8.34 (s, 1H, NH)	$C_{29}H_{21}N_3O_2S_2$ (507)	68.64 68.42	4.14 4.30	8.28 8.50
5l	60	272-273	2.38 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.11- 8.22 (m, 14H, Ar-H), 8.31 (s, 1H, NH)	$C_{29}H_{21}N_3O_2S_2$ (507)	68.64 68.91	4.14 4.28	8.28 8.42
5m	47	293-295	3 62 (s, 3H, OCH_3), 3 78 (s, 3H, OCH_3), 7.10- 8.19 (m, 14H, Ar-H), 8.33 (s, 1H, NH)	$C_{29}H_{21}N_3O_3S_2$ (523)	66.54 66.39	4.01 4.27	8.03 8.31
5n	49	287-289	3.68 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 7.08- 8.21 (m, 14H, Ar-H), 8.35 (s, 1H, NH)	$C_{29}H_{21}N_3O_3S_2$ (523)	66.54 66.66	4.01 3.87	8.03 7.92

[a] Compounds **5a-f** in DMSO-d_6 and compounds **5g-n** in trifluoroacetic acid. [b] The molecular weight of **5d** was determined by mass spectroscopy.

Table 2

2-Methylthiopyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-4(3*H*)-ones **6a-n**

Compound No.	Yield % Without Phase transfer (Method A)	Yield % With catalyst (Method B)	Mp °C	^{1}H-NMR (δ, ppm) [a]	Molecular Formula (Molecular Weight) [b]	Analysis % Calcd./Found C	H	N
6a	58	92	210-211	0.82-1.12 (m, 3H, -C*H*$_3$ $(CH_2)_3$-), 1.12-1.84 (m, 4H, CH_3-$(CH_2)_2CH_2$-), 1.89 (s, 3H, SCH_3), 2.40 (s, 3H, CH_3), 4.01 (t, 2H, CH3 $(CH_2)_2CH_2$-), 721-8 22 (m, 10H, Ar-H)	$C_{27}H_{25}N_3OS_2$ (471)	68.78 68.49	5.31 5.38	8.92 8.64
6b	56	90	320-322	1.79 (s, 3H, SCH_3), 2.44 (s, 3H, CH_3), 7.28-8.22 (m, 15H, Ar-H)	$C_{29}H_{21}N_3OS_2$ (491)	70.87 70.92	4.27 4.47	8.55 8.26
6c	48	88	241-243	1.81 (s, 3H, SCH_3), 2.15 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 7.14-8.23 (m, 14H, Ar-H)	$C_{30}H_{23}N_3OS_2$ (505)	71.26 70.92	4.59 4.71	8.31 8.08
6d	51	90	323-325	1.80 (s, 3H, SCH_3), 2.45 (s, 6H, CH_3), 7.66-8.20 (m, 14H, Ar-H)	$C_{30}H_{23}N_3OS_2$ (505)	71.26 70.95	4.59 4.38	8.31 8.60
6e	55	94	266-267	1.79 (s, 3H, SCH_3), 2.43 (s, 6H, CH_3), 7.09-8.26 (m, 14H, Ar-H)	$C_{30}H_{23}N_3OS_2$ (505)	71.26 71.39	4.59 4.69	8.31 8.50
6f	49	95	228-230	1.78 (s, 3H, SCH_3), 2.41 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 7.18-8.29 (m, 14H, Ar-H)	$C_{30}H_{23}N_3O_2S_2$ (521)	69.07 70.22	4.44 4.86	8.06 8.20
6g	58	89	329-331	1.76 (s, 3H, SCH_3), 2.41 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.03-8.19 (m, 14H, Ar-H)	$C_{30}H_{23}N_3O_2S_2$ (521)	69.07 68.87	4.44 4.21	8.06 7.92
6h	60	96	201-203	0.79-1.12 (m, 3H, -C*H*$_3$ $(CH_2)_3$-), 1.17-2.01 (m, 4H, CH_3-$(CH_2)_2CH_2$-), 1.85 (s, 3H, SCH_3), 3.77 (s, 3H, CH_3), 4.01 (t, 2H, CH_3 $(CH_2)_2CH_2$-), 6 76-8.13 (m, 10H, Ar-H)	$C_{27}H_{25}N_3O_2S_2$ (487)	66.52 66.21	5.13 5.00	8.62 8.47
6i	52	90	300-302	1 77 (s, 3H, SCH_3), 3.89 (s, 3H, OCH_3), 6.95-8.29 (m, 14H, Ar-H)	$C_{29}H_{21}N_3O_2S_2$ (507)	68.62 68.65	4.17 4.34	8.28 8.51
6j	56	92	292-294	1.77 (s, 3H, SCH_3), 2.12 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.91-8.28 (m, 14H, Ar-H)	$C_{30}H_{23}N_3O_2S_2$ (521)	69.09 69.37	4.41 4.69	8.06 7.97
6k	58	95	295-296	1.78 (s, 3H, SCH_3), 2.4 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.93-8.30 (m, 14H, Ar-H)	$C_{30}H_{23}N_3O_2S_2$ (521)	69.09 68.68	4.41 4.05	8.06 8.33
6l	55	94	303-305	1.74 (s, 3H, SCH_3), 2.38 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.85-8.23 (m, 14H, Ar-H)	$C_{30}H_{23}N_3O_2S_2$ (521)	69.09 69.23	4.41 4.17	8.06 8.22
6m	55	90	274-276	1 77 (s,3H, SCH_3), 3 75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.95-8.22 (m, 14H, Ar-H)	$C_{30}H_{23}N_3O_3S_2$ (537)	67.03 67.33	4.28 4.51	7.82 7.72
6n	58	88	309-311	1.76 (s,3H, SCH_3), 3-78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.92-8.20 (m, 14H, Ar-H)	$C_{30}H_{23}N_3O_3S_2$ (537)	67.03 66.84	4.28 4.00	7.82 7.60

[a] DMSO-d_6 was used as the solvent. [b] Molecular weights of **6f** and **6n** were determined by mass spectroscopy.

and 1550 and 1365 cm^{-1} (NH-C=S) were indicative of *S*-methylation of **5** at position-2.

The mass spectrum of representative **5e** exhibited a characteristic strong molecular ion peak which represented the base peak. The loss of 4-methylphenyl isothiocyanate moiety giving the fragment of type [M-R-NCS]$^+$ has been found to be typical in such classes of the compounds [9,10]. The detail fragmentation pattern of **5e** is given in Scheme 3.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The ir spectra were recorded on Buck Scientific Model M-500 IR spectrophotometer as potassium bromide pellets and frequencies are reported in cm^{-1}. The ^1H nmr spectra were observed on Varian EM-360L (60 MHz) spectrometer using TMS as the internal standard. The mass spectra were obtained on Jeol D-300 mass spectrometer at 70 ev ionizing beam.

General Procedure for the Preparation of 2-Thioxo-9-phenyl-3,7-disubstituted-1,2,3,4-tetrahydropyrido[3'2':4,5]thieno-[3,2-*d*]pyrimidin-4(3*H*)-ones **5a-n**.

To the solution of 2-carbethexy-3-amino-4-phenyl-6-substituted-thieno[2,3-*b*]pyridine (**3**, 0.01 mole) in pyridine (25 ml) was added the isothiocyanates (0.012 mole) and the reaction mixture was refluxed in an oil bath for 35-50 hours. The course of reaction was monitored by micro tlc using benzene-ethanol (8:2) as the solvent system. After completion of the reaction, it was cooled to room temperature and poured into aqueous methanol (70% v/v). The solid separated and was filtered, washed with cold aqueous methanol, dried and crystallized from ethanol and *N,N*-dimethylformamide (2:8) mixture (Table 1).

General Procedure for the Preparation of 2-Methylthio-9-phenyl-3,7-disubstituted-1,2,3,4-tetrahydropyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6a-n**.

Method A.

A mixture of **5** (0.002 mole), aqueous sodium hydroxide (1*M*, 10 ml) and ethanol (30 ml) was refluxed for 20 minutes to get clear solution. To this, dimethyl sulphate (0.0025 mole) was added with constant stirring. After the addition was completed, the reaction mixture was further stirred at room temperature for 0.5 to 1.0 hour (tlc). The solid separated was filtered, washed with water and crystallized from *N,N*-dimethylformamide (Table 2).

Method B.

To the stirred mixture of **5** (0.002 mole), powdered sodium hydroxide (0.004 mole) and tetra-*n*-butylammonium bromide (0.0001 mole) in tetrahydrofuran (35 ml) was added dimethyl sulphate (0.0025 mole) in tetrahydrofuran (10 ml) dropwise with constant stirring at room temperature. After the addition was completed, the reaction mixture was further stirred for 2 to 2.5 hours (tlc), filtered and the solvent was removed *in vacuo*. To this, aqueous methanol (80% v/v) was added and stirred for 10 minutes at rt. The solid was filtered, washed with aqueous methanol, dried and crystallized from *N,N*-dimethylformamide (Table 2).

Acknowledgements.

We wish to thank RSIC, CDRI, Lucknow for mass spectra, the Xavier Research Foundation for the financial support and Dishman Pharmaceuticals and Chemicals for the gift of Phase Transfer Catalysts.

REFERENCES AND NOTES

[1] E. E. Elslager, P. W. Jacob and M. Leslic, *J. Heterocyclic Chem.*, **9**, 775 (1972).

[2] M. Chaykovsky, M. Lin, A. Rosowsky and E. J. Modest, *J. Med. Chem.*, **10**, 118 (1973).

[3] E. Bosquet, G. Romeo, F. Guerrera, A. Caruso and M. A. Roxas, *Farmaco Ed. Sci.*, **40**, 869 (1985).

[4] A. Caruso and M. Amico-Roxas, *Farmaco Ed. Sci.*, **39**, 110 (1984).

[5] C. G. Dave, P. R. Shah, A. B. Shah, K. C. Dave and V. J. Patel, *J. Indian Chem. Soc.*, **66**, 48 (1989).

[6] R. J. Gallo, M. Makosza, H. Dou and P. Hassanaly, *Adv. Heterocyclic Chem.*, **36**, 175 (1984) and references cited therein.

[7] P. Hassanaly, H. Dou, J. Metzger, G. Assef and J. Kister, *Synthesis*, 253 (1977)

[8] C. G. Dave, P. R. Shah and A. B. Shah, *Indian J. Chem.*, **31B**, 492 (1992).

[9] E. Stark and E. Breitmaier, *Tetrahedron*, **29**, 2209 (1973).

[10] D. Koscik, P. Kristain, J. Gonda and E. Dandarova, *Collect. Czech. Chem. Commun.*, **48**, 3315 (1983).