Pyridopyrimidines. X. Synthesis of 3-Substituted 2-Thioxo-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones and their *S*-Alkylation Under Phase Transfer Conditions

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Received July 31, 2000

2-Thioxo-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **3** were synthesized by the cyclocondensation of 2-amino-3-carbethoxy-4,6-dimethylpyridine **1** with methyl-*N*-aryldithiocarbamates **2** and compared with the condensation between **1** and aryl isothiocyanates **4**. When a comparative study of *N vs S* alkylation of ambident 2-thioxo-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **3** was carried out under liquid-liquid and solid-liquid phase transfer conditions using various alkylating agents **5**, the *S*-alkylated products **6** were obtained exclusively and selectively.

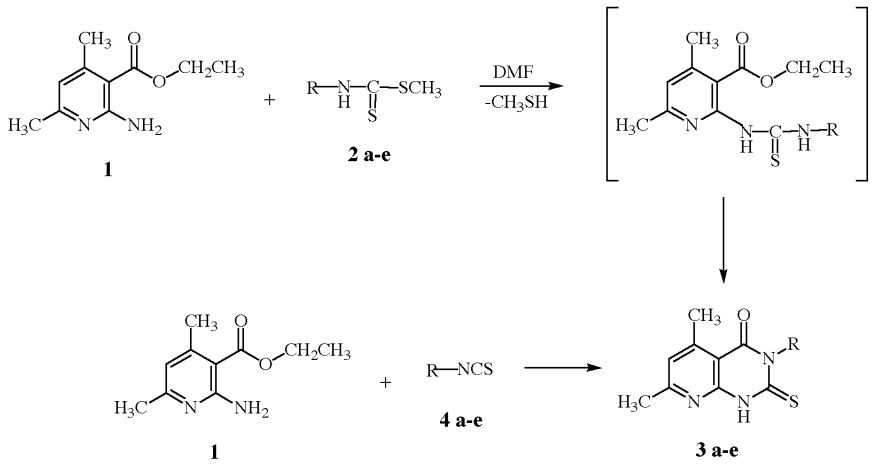
J. Heterocyclic Chem., **38**, 457 (2001).

Pyrido[2,3-*d*]pyrimidines, the 5-deaza analogues of pteridines are known to possess a variety of biological properties [1-8]. Recently, these compounds have been reported as dihydrofolate reductase inhibitors and anti-tumor agents [9,10]. Dave *et al.* [11-14] have synthesized a number of 2-thioxopyrido[2,3-*d*]pyrimidin-4(3*H*)-ones and had them screened for antibacterial activity. Further, the phase transfer catalyzed alkylation of ambident *N vs. S* system in various heterocyclic systems such as pyridin-2(1*H*)-thiones [15], 2-thioxobenzoxazole [16], thiazolidinethiones [17], 2-thioxoimidazole [18], 2-thioxopyrimidines [19], 9-thioacridones [20-21] have been found in the literature. However, there has been no report on the study of *N vs. S* alkylation in 2-thioxopyrido-[2,3-*d*]pyrimidin-4(3*H*)-one system in order to prepare biologically important fused pyrimidines.

Therefore, in continuation of our interest in fused pyrimidines and phase transfer catalysed alkylation of ambident heterocyclic system [22], it was of interest to synthesize 2-thioxo-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones, which is an ambident system, for the comparative study of *N vs. S* alkylation under liquid-liquid (L-L) and solid-liquid (S-L) phase transfer conditions. Further, the required 2-thioxo-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones as were synthesized for the first time using methyl-*N*-aryldithiocarbamates and compared with the previously reported method using aryl isothiocyanates.

When 2-amino-3-carbethoxy-4,6-dimethylpyridine (**1**) was cyclocondensed with methyl-*N*-aryldithiocarbamates (**2**), 3-substituted 2-thioxo-5,7-dimethylpyrido[2,3-*d*]-pyrimidin-4(3*H*)-ones **3** were obtained in 55-69% yields. The reaction is supposed to proceed *via in situ* cyclization of the intermediate N^1-substituted-N^2-[2-(3-carbethoxy-5,6-dimethylpyridyl)]thioureas (Method A). The same compounds **3** were prepared by the cyclocondensation reaction of **1** and aryl isothiocyanates **4** (Method B) according to the method reported by Dave *et al.* [13,14] and the result was found to be identical (Scheme 1). During the comparison, it was revealed that the yields of

Scheme 1



a: R = C_6H_5; **b**: R = 4-$CH_3C_6H_4$; **c**: R = 4-FC_6H_4; **d**: R = 4-ClC_6H_4; **e**: R = 3-Cl-4-F-C_6H_3

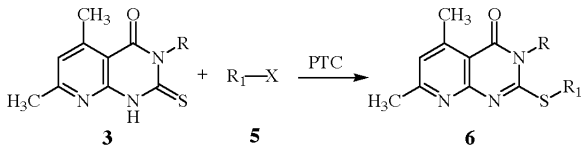
2-thioxopyrido[2,3-*d*]pyrimidines **3** were little higher when methyl-*N*-aryldithiocarbamates **2** were used as synthons. The physical data of compounds **3** are depicted in Table 1.

Table 1
Physical Data of Compound **3a-e**

Compound No.	mp °C	Yield % Method A	Yield % Method B	Molecular formula	Analysis % Calcd/Found C	H	N
3a	265-66	58	50	$C_{15}H_{13}N_3OS$	63.58	4.62	14.83
					63.89	4.38	14.95
3b	163-64	55	42	$C_{16}H_{15}N_3OS$	64.62	5.08	14.13
					64.79	5.37	14.00
3c	302-03	69	44	$C_{15}H_{12}FN_3OS$	59.78	4.01	13.94
					59.95	4.27	13.61
3d	323-25	62	35	$C_{15}H_{12}ClN_3OS$	56.68	3.80	13.22
					56.45	3.71	13.50
3e	308-10	68	43	$C_{15}H_{11}ClFN_3OS$	53.65	3.30	12.51
					53.29	3.44	12.89

When 3-substituted 2-thioxo-5,7-dimethylpyrido-[2,3-*d*]pyrimidin-4(3*H*)-ones **3** were alkylated using different alkyl halides **5**, 2-alkylthio-5,7-dimethylpyrido-[2,3-*d*]pyrimidin-4(3*H*)-ones **6** were obtained (Scheme 2). The alkylation reactions were compared using liquid-liquid (L-L) and solid-liquid (S-L) phase transfer conditions, and we were able to conclude that L-L phase transfer condition was more suitable for such type of reactions in which exclusively and selectively *S*-alkylations took place (Table 3).

Scheme 2



6	R	R_1	**6**	R	R_1
a	C_6H_5	CH_3	**k**	4-ClC_6H_4	CH_3
b	C_6H_5	C_2H_5	**l**	4-ClC_6H_4	C_2H_5
c	C_6H_5	*n*-C_3H_7	**m**	4-ClC_6H_4	*n*-C_3H_7
d	C_6H_5	*n*-C_4H_9	**n**	4-ClC_6H_4	*n*-C_4H_9
e	C_6H_5	$C_6H_5CH_2$	**o**	4-ClC_6H_4	$C_6H_5CH_2$
f	4-FC_6H_4	CH_3	**p**	3-Cl-4-FC_6H_3	CH_3
g	4-FC_6H_4	C_2H_5	**q**	3-Cl-4-FC_6H_3	C_2H_5
h	4-FC_6H_4	*n*-C_3H_7	**r**	3-Cl-4-FC_6H_3	*n*-C_3H_7
i	4-FC_6H_4	*n*-C_4H_9	**s**	3-Cl-4-FC_6H_3	*n*-C_4H_9
j	4-FC_6H_4	$C_6H_5CH_2$	**t**	3-Cl-4-FC_6H_3	$C_6H_5CH_2$

Ethylation of 2-thioxo-3-phenyl-5,7-dimethyl-pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **3a** with ethyl bromide for the formation of 2-ethylthio-3-phenyl-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **6a** was selected as a case study for the comparison and selection of phase transfer agent. Tetra-*n*-butylammonium bromide (TBAB), triethyl benzylammonium chloride (TEBA), tetraoctylammonium bromide (TOAB) and cetyl trimethylammonium bromide (CTMAB) were tested under Liquid-Liquid phase transfer conditions at room temperature (Table 2). It was observed that 10 mole % tetra-*n*-butylammonium bromide (TBAB) was the best choice out of the phase transfer catalysts studied for the ethylation of **3a**. Therefore, all the alkylations of compounds **3** were carried out in the presence of 10 mole % tetra-*n*-butylammonium bromide (TBAB). The reactions were performed using toluene as the organic phase and sodium hydroxide (50 %) as the aqueous phase. In the absence of phase transfer catalyst the reaction was found to proceed slowly; after several hours the majority of the starting compound **3a** remained in the reaction mixture (tlc).

Table 2
Comparison of Various Phase Transfer Catalysts for Ethylation of Compound **3a**

Phase Transfer Catalyst	Mole % of catalyst	Yield (%)	Time (minutes)
TBAB	5	85	60
TBAB	7.5	85	45
TBAB	10	85	30
TBAB(ultra sound)	10	85	75
TOAB	5	80	60
TOAB	10	82	45
CTMAB	5	60	180
CTMAB	10	64	90
TEBA	10	76	90

The ir (potassium bromide) spectra of 3-substituted 2-thioxo-5,7-dimethylpyrido[2,3-*d*] pyrimidin-4(3*H*)-ones **3** exhibited an NH stretching vibration in the region 3250-3120 cm^{-1}. A strong absorption band for the cyclic ketone (C=0) was observed between 1700-1680 cm^{-1}. No band was observed in the region 2600-2550 cm^{-1} corresponding to thiol (SH) functionality in any of the spectra and the presence of stretching vibration observed in the region 1225-1200 cm^{-1} confirmed the thione (C=S) structure in compounds **3**. The bands in the region 1550-1540 cm^{-1} and 1412-1390 cm^{-1} were assigned to an NH-C=S type of structure. The ir spectra of 3-substituted 2-alkylthio-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **6** (Table 4) showed a strong absorption band in the region 1700-1670 cm^{-1}, confirming the presence of a cyclic ketone structure. The absence of characteristic bands for NH and C=S around 3250-3120 cm^{-1} and 1225-1200 cm^{-1} respectively indicated the complete *S*-alkylation of compounds **3**.

^{1}H nmr (deuteriochloroform) spectral data of 3-substituted 2-alkylthio-5,7-dimethyl pyrido[2,3-*d*]-pyrimidin-4(3*H*)-ones **6** are also mentioned in Table 4. The methyl groups at position 5 and 7 were observed as resonances in the region δ 2.64-2.67 and δ 2.73-2.76 respectively. A singlet at δ 6.92-7.03 was found due to the presence of the aromatic proton at position 6. The resonances due to other aromatic protons were found in the region δ 7.10-7.70 as a multiplet.

Table 3
Physical and Analytical Data for Compounds **6a-t**

Compound No.	Time (hours)	Temperature °C	Yield %	Mp °C	Molecular formula	Analysis % Calcd./Found C	H	N
6a	0.5	35	98	195-96	$C_{16}H_{15}N_3OS$	64.62	5.08	14.13
						64.32	5.18	14.23
6b	0.5	35	85	159-60	$C_{17}H_{17}N_3OS$	65.56	5.50	13.49
						65.36	5.41	13.55
6c	1.0	50	87	97-98	$C_{18}H_{19}N_3OS$	66.43	5.88	12.91
						66.77	5.67	12.73
6d	1.5	55	88	109-10	$C_{19}H_{21}N_3OS$	67.22	6.23	12.37
						67.51	6.47	12.15
6e	0.65	35	82	125-26	$C_{22}H_{19}N_3OS$	70.75	5.13	11.25
						70.36	5.29	11.02
6f	1.0	35	85	223-24	$C_{16}H_{14}FN_3OS$	60.93	4.47	13.32
						60.68	4.63	13.70
6g	1.5	35	95	169-70	$C_{17}H_{16}FN_3OS$	61.98	4.89	12.75
						61.71	4.50	12.87
6h	3.0	50	87	145-46	$C_{18}H_{18}FN_3OS$	62.95	5.28	12.23
						63.10	5.47	12.55
6i	4.0	55	89	116-17	$C_{19}H_{20}FN_3OS$	63.84	5.64	11.75
						63.98	5.41	11.47
6j	1.0	35	94	77-78	$C_{22}H_{18}FN_3OS$	67.49	4.63	10.73
						67.68	4.28	10.95
6k	0.75	35	78	214-15	$C_{16}H_{14}ClN_3OS$	57.91	4.25	12.66
						57.70	4.41	12.47
6l	1.0	35	85	179-80	$C_{17}H_{16}ClN_3OS$	59.03	4.66	12.15
						59.40	4.31	12.36
6m	1.5	50	82	162-63	$C_{18}H_{18}ClN_3OS$	60.07	5.04	11.67
						60.23	5.19	11.43
6n	2.0	55	75	155-56	$C_{19}H_{20}ClN_3OS$	61.03	5.39	11.23
						61.40	5.65	11.12
6o	0.85	35	81	193-94	$C_{22}H_{18}ClN_3OS$	64.77	4.44	10.30
						64.56	4.13	10.64
6p	0.75	35	89	248-50	$C_{16}H_{13}ClFN_3OS$	54.93	3.74	12.01
						54.69	3.97	12.32
6q	1.5	35	90	176-77	$C_{17}H_{15}ClFN_3OS$	56.11	4.15	11.54
						56.46	4.03	11.78
6r	3.0	55	93	153-54	$C_{18}H_{17}ClFN_3OS$	57.21	4.53	11.12
						57.46	4.27	11.36
6s	3.5	55	92	128-29	$C_{19}H_{19}ClFN_3OS$	58.23	4.88	10.72
						58.05	4.57	10.34
6t	4.0	35	97	185-86	$C_{22}H_{17}ClFN_3OS$	62.03	4.02	9.86
						61.95	4.33	9.51

^{13}C nmr spectral data of 2-ethylthio-3-(4-chlorophenyl)-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one **6l** and 2-*n*-propylthio-3-(4-fluorophenyl)-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one **6h** are recorded in table 5.

EXPERIMENTAL

Melting points were determined by the electrothermal method in an open capillary tube and are uncorrected. The ir spectra are recorded in cm^{-1} and were acquired as potassium bromide pellets on a Buck scientific spectrophotometer. The ^1H nmr spectra were recorded on Bruker AC 300F nmr spectrometer using tetramethylsilane as the internal standard and chemical shift are expressed in ppm (δ). The mass spectra were recorded on LKB 9000 mass spectrometer. The purity of the compound was routinely checked by tlc using silica gel G and the spots were exposed to iodine vapor.

General Procedure for the Synthesis of 3-Substituted 2-Thioxo-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **3a-e**.

Method A.

A mixture of 2-amino-3-carbethoxy-4,6-dimethylpyridine **1** (0.01 mole, 1.94 g), the appropriate methyl-*N*-aryldithiocarbamate **2** (0.01 mole) and *N*,*N*-dimethylformamide (20 ml) was refluxed for 8-10 hours. The reaction mixture was cooled and poured onto the crushed ice. The solid thus obtained was

Table 4
IR and ^{1}H NMR Spectral Data for Compounds **6a-t**

No.	ir(potassium bromide) cm^{-1}	^{1}H nmr (δ ppm)
6a	1685, 1595, 1550, 855	2.57 (s, 3H, CH_3), 6.94 (s, 1H, Ar-H at C_6) 7.21-7.50 (m, 5H, Ar-H)
6b	1695, 1590, 1535, 1490	1.29-1.34 (t, J = 7.5, 3H, CH_3), 3.24-3.31 (q, J = 7.5, 2H, CH_2), 6.97(s, 1H, Ar-H at C_6) 7.28-7.58 (m, 5H, Ar-H)
6c	1687, 1593, 1565, 1490	0.94-0.98 (t, J = 7.4, 3H, CH_3), 1.60-1.72 (sextet, J = 7.5, 2H, CH_2), 3.20-3.26 (t, J = 7.5, 2H, CH_2), 7.0 (s, 1H, Ar-H at C_6), 7.25-7.52 (m, 5H, Ar-H)
6d	1686, 1593, 1551, 1494	0.86-0.90 (t, J = 7.5, 3H, CH_3), 1.37-1.47 (sextet, J = 7.3, 2H, CH_2), 1.59-1.70 (quintet, J = 7.1, 2H, CH_2), 3.25-3.32 (t, J = 7.5, 2H, CH_2), 6.98 (s, 1H, Ar-H at C_6), 7.22-7.42 (m, 5H, Ar-H)
6e	1685, 1597, 1545, 1495	4.57 (s, 2H, CH_2), 6.95 (s, 1H, Ar-H at C_6) 7.20-7.68 (m, 10H, Ar-H)
6f	1675, 1592, 1546, 856	2.60 (s, 3H, CH_3), 7.01 (s, 1H, Ar-H at C_6), 7.12-7.26 (m, 4H, Ar-H)
6g	1689, 1590, 1555, 1505	1.26-1.33 (t, J = 7.3, 3H, CH_3), 3.25-3.33 (q, J = 7.2, 2H, CH_2), 6.99 (s, 1H, Ar-H at C_6), 7.14-7.28 (m, 4H, Ar-H)
6h	1689, 1593, 1548, 1504	0.92-0.97 (t, J = 7.6, 3H, CH_3), 1.58-1.69 (sextet, J = 7.2, 2H, CH_2), 3.19-3.25(t, J = 7.5, 2H, CH_2), 6.93 (s, 1H, Ar-H at C_6), 7.17-7.25 (m, 4H, Ar-H)
6i	1690, 1590, 1535, 1490	0.88-0.93 (t, J = 7.4, 3H, CH_3), 1.38-1.49 (sextet, J = 7.3, 2H, CH_2), 1.61-1.71 (quintet, J = 7.1, 2H, CH_2), 3.29-3.35 (t, J = 7.5, 2H, CH_2), 6.97 (s, 1H, Ar-H at C_6), 7.15-7.29 (m, 4H, Ar-H)
6j	1682, 1596, 1547, 1507	4.59 (s, 2H, CH_2), 6.98 (s, 1H, Ar-H at C_6) 7.16-7.62 (m, 9H, Ar-H)
6k	1680, 1593, 1545, 854	2.59 (s, 3H, CH_3), 7.0 (s, 1H, Ar-H, at C_6), 7.19-7.51 (m, 4H, Ar-H)
6l	1686, 1594, 1548, 1490	1.25-1.32 (t, J = 7.2, 3H, CH_3), 3.24-3.32 (q, J = 7.5, 2H, CH_2), 6.96 (s, 1H, Ar-H, at C_6), 7.20-7.53 (m, 4H, Ar-H)
6m	1679, 1582, 1545, 1489	0.97-1.02 (t, J = 7.5, 3H, CH_3), 1.63-1.76 (sextet, J = 7.2, 2H, CH_2), 3.26-3.31 (t, J = 7.5, 2H, CH_2), 6.99 (s, 1H, Ar-H at C_6) 7.23-7.54 (m, 4H, Ar-H)
4n	1687, 1593, 1548, 1490	0.87-0.92 (t, J = 7.2, 3H, CH_3), 1.37-1.48 (sextet, J = 7.3, 2H, CH_2), 1.60-1.69 (quintet, J = 7.3, 2H, CH_2), 3.28-3.33 (t, J = 7.2, 2H, CH_2), 7.02 (s, 1H, Ar-H, at C_6), 7.22-7.53 (m, 4H, Ar-H)
4o	1687, 1594, 1547, 1490	4.58 (s, 2H, CH_2), 6.99 (s, 1H, Ar-H at C_6), 7.27-7.65 (m, 9H, Ar-H)
4p	1685, 1592, 1547, 858	2.61 (s, 3H, CH_3), 6.97 (s, 1H, Ar-H at C_6), 7.32-7.52 (m, 3H, Ar-H)
4q	1696, 1594, 1546, 1497	1.27-1.34 (t, J = 7.5, 3H, CH_3), 3.26-3.34 (q, J = 7.2, 2H, CH_2), 7.01 (s, 1H, Ar-H at C_6), 7.30-7.55 (m, 3H, Ar-H)
4r	1689, 1594, 1547, 1498	0.95-1.0 (t, J = 7.4, 3H, CH_3), 1.62-1.75 (sextet, J = 7.3, 2H, CH_2), 3.27-3.33 (t, J = 7.1, 2H, CH_2), 7.03 (s, 1H, Ar-H at C_6), 7.28-7.53 (m, 3H, Ar-H)
4s	1697, 1594, 1546, 1497	0.89-0.95 (t, J = 7.4, 3H, CH_3), 1.38-1.50 (sextet, J = 7.3, 2H, CH_2), 1.62-1.70 (quintet, J = 7.5, 2H, CH_2), 3.30-3.34 (t, J = 7.5, 2H, CH_2), 6.98 (s, 1H, Ar-H at C_6), 7.29-7.44 (m, 3H, Ar-H)
4t	1690, 1595, 1550, 1495	4.60 (s, 2H, CH_2), 7.0 (s, 1H, Ar-H at C_6), 7.35-7.70 (m, 8H, Ar-H)

Table 5
^{13}C NMR data of **6l & 6h** (δ value in DMSO-d_6, TMS as Internal Standard)

	6l	**6h**
C-2	164.53	164.95
C-4	161.47	161.81
C-4a	111.01	117.66
C-5	131.00	131.63
C-6	123.80	124.32
C-7	157.65	158.33
C-8a	160.28	161.60
C-5a	21.74	21.45
C-7a	24.45	22.32
C-3a	151.36	152.65
C-3d	134.86	162.49
C-3b,3f	131.54	131.15
C-3c,3e	129.64	131.04
C-2a	26.52	34.74
C-2b	13.86	25.16
C-2c	-	12.5

isolated by filtration, washed with water, dried and crystallized from glacial acetic acid.

Method B.

A mixture of 2-amino-3-carbethoxy-4,6-dimethylpyridine **1** (0.01 mole, 1.94 g), the appropriate isothiocyanate **4** (0.01 mole) and pyridine (10 ml) was refluxed in an oil bath for 12-14 hours. The reaction mixture was cooled, poured onto crushed ice and the precipitated solid was isolated by filtration, washed repeatedly with water followed by sodium bicarbonate solution (5% w/v) and finally with water. The dried crude product was crystallised from glacial acetic acid to give **3**.

General Procedure for the Synthesis of 3-Substituted 2-Alkylthio-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **6a-t**.

To a vigorously stirred mixture of 3-substituted 2-thioxo-5,7-dimethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one **3** (0.01 mole), tetra-*n*-butylammonium bromide (TBAB) (0.001 mole), aqueous 50%

sodium hydroxide (0.02 mole) and toluene (20 ml), was added the appropriate alkyl halide **5** (0.011 mole) dropwise. The reaction mixture was stirred at the temperature and time given in table 3. After completion of reaction (tlc), the toluene layer was washed with water, separated and dried over anhydrous magnesium sulfate. Toluene was removed *in vacuo* to obtain the crude solid product, which was washed with water, cold methanol, dried and crystallized from ethanol.

Acknowledgment.

We wish to thank Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow and Regional Sophisticated Instrumentation Centre, Chandigarh, India for nmr and mass spectra; Dishman Pharmaceuticals and Chemicals Ltd., Ahmedabad for providing Phase Transfer Catalyst and the Management of M. G. Science Institute, Ahmedabad for the facilities to carry out this work.

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