Phase-Transfer Catalysis; I. *S*-Methylation of 1-Aryl-4,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidines

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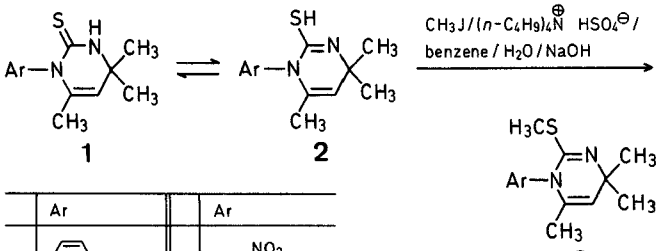
Phase-transfer catalysis has been used for alkylation of ambident anions in preference to conventional methods because of its experimental simplicity, superior regioselectivity, and high yields[1-4]. 1-Aryl-4,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidines **(1)** are easy to prepare[5,6] and are capable of forming ambident anions of the type N—C—S. The thiones **1** are physiologically active and the thioethers **3** have potential industrial use[7]. As a part of our study on restricted rotation about single bonds by the dynamic N.M.R. technique[8], we were interested in some of these thiones and thioethers which exhibit a high barrier to rotation about the aryl-nitrogen bond[9]. Alkylation of the pyrimidinethiones **1** with alkyl halides and base did not proceed well and we report here a clean and almost quantitative preparation of *S*-methylated (and a few *S*-benzylated) compounds **3** under phase-transfer conditions.

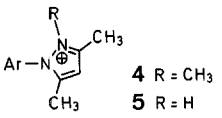


1 **2** **3**

	Ar		Ar
a		f	NO_2
b	Cl	g	CH_3, O_2N
c	CH_3	h	COOH
d	OCH_3	i	
e	O_2N		

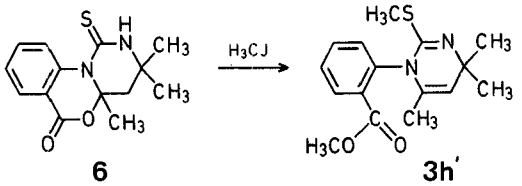
According to their spectral data, the 2-thioxo-1,2,3,4-tetrahydropyrimidines **1** which have previously been described as mercapto compounds **2**[5,6] appear to exist solely in the thione form **1**. The U.V. spectrum shows peaks around $\lambda_{max} = 265$ nm ($\varepsilon = 20000$) which are characteristic of cyclic thioureas[10,11] and the I.R. spectrum shows the NH stretching frequency at $\nu = 3400$ cm^{-1}. In the N.M.R. spectra, the signal of the NH proton appears at $\delta \approx 7.0$ (br. s) and the signal of the C-atom of the C=S group appears at $\delta = 176.5$ ppm[7]. The thiones **1** used in this study are high-melting solids whereas the *S*-methylation products are either liquids or low-melting solids which are completely homogeneous on T.L.C. and G.L.C. Their structure as thioethers is shown by the following observations:

- The U.V. spectra of the methylation products are entirely different from those of the starting thiones **1** and of the thiourea chromophore.
- In the I.R. spectrum, the methylation products show a strong band at $\nu = 1600$ cm^{-1} which is absent in the spectra of the thiones **1** and which is possibly due to the C=N double bond in the thioethers **3**.
- In the ^{1}H-N.M.R. spectrum of the methylation products, a new methyl signal appears at $\delta = 2.20$–2.28 ppm and in the ^{13}C-N.M.R. spectrum the signal at $\delta = 15.1$ ppm is characteristic of the S—CH_3 group. The C-2 peak at $\delta = 150.0$–150.4 ppm is also in agreement with the thioether structure[7].
- The mass spectra are not diagnostic here but the absence of the fragment **4** arising out of a loss of 4-CH_3 and the C=S moiety (a lower homologue, fragment **5** is observed in the thiones) is in distinct favour of the thioether structure **3**.



4 R = CH_3
5 R = H

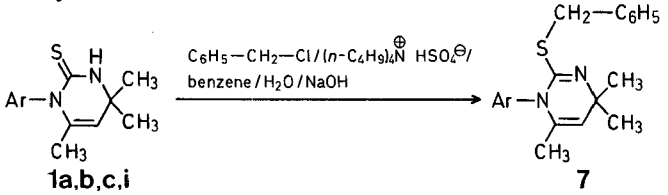
The *o*-carboxy derivative **1h** prepared from anthranilic acid proved to be a lactone (**6**; see spectral data in Table 1). However, on methylation lactone **6** was converted into the thioether **3h'** with simultaneous esterification of the carboxy group under the phase-transfer conditions employed[12].



6 **3h'**

Some of the thiones and thioethers with bulky *o*-substituents on the aromatic ring and the 1-naphthyl derivatives **1i** and **3i** were expected to have hindered rotation around the aryl-nitrogen bond, giving rise to geminal non-equivalence of the C-4 methyl groups. However, in the ^{1}H-N.M.R. spectrum only the *o*-nitro derivative **1f** (and to a smaller extent, the *o*-methoxy derivative **1d**) these two methyl groups gave two singlets ($\delta = 1.37$ and 1.44 ppm, $\Delta\nu = 6$ Hz) of equal intensity which coalesced at 150 °C giving a value of 95 kJ/mol as the free energy of activation[8] for the conformational inversion. None of the methyl thioethers showed any such splitting. Apparently, the 4-methyl groups are situated too far from the aromatic ring in most of these compounds to be affected by the differential ring anisotropy.

Four thiones **(1a, b, c, i)** were benzylated under the same phase transfer conditions using benzyl chloride in place of methyl iodide.



1a,b,c,i **7**

As expected, the ^{1}H-N.M.R. spectrum of the benzylation products **7a, b** showed a sharp singlet at $\delta = 4.12$ ppm for the two benzylic protons and that of compounds **7c, i** showed an AB quartet centered at $\delta = 4.05$ ppm for the two benzylic protons. The results of variable temperature ^{1}H-N.M.R. spectrometry of these and analogous compounds will be reported in a subsequent communication.

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1-Aryl-4,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidines (1); General Procedure[5,6]:

Concentrated hydrochloric acid (0.11 mol) is added dropwise to a mixture of aromatic amine (0.1 mol), 4-methylpent-3-en-2-one (0.1 mol), ammonium thiocyanate (0.1 mol), and water (25 ml) stirred vigorously at 25 °C for 0.5 h. The mixture is then refluxed for 3 h when a buff coloured crystalline precipitate appears, which is filtered, washed with water (2 × 50 ml), and dried. The products are purified by several recrystallizations from aqueous ethanol.

***S*-Methylation or *S*-Benzylation of Compounds 1; General Procedure:**

Methyl iodide or benzyl chloride (2 mmol) is added dropwise to a vigorously stirred mixture of benzene (15 ml), 50% aqueous sodium hydroxide (15 ml), thione **1** (1 mmol), and tetrabutylammonium hydrogen sulphate (100 mg, 0.3 mmol). Stirring at ambient temperature is continued for 2 h, and the mixture then diluted with cold water (50 ml). The benzene layer is separated, the aqueous layer extracted with benzene (1 × 20 ml), the total benzene extract washed with water (2 × 30 ml), and dried with magnesium sulphate. The benzene is re-

Table 1. 1-Aryl-4,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidines (**1**)

1	Yield [%]	m.p. [°C]	Molecular formula[a]	U.V. (C_2H_5OH)[b] λ_{max} [nm]	I.R. ($CHCl_3$)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[d] δ [ppm]
a	90	187°	$C_{13}H_{16}N_2S$ (232.4)	262, 268	3375	1.38 (s, 6H, 4-CH_3); 1.50 (s, 3-H, 6-CH_3); 4.83 (s, 1H, 5-H); 6.90 (bs, 1H, NH)[e]; 7.2–7.5 (m, 5H_{arom})
b	90	188°	$C_{13}H_{15}ClN_2S$ (266.8)	262, 268	3400	1.37 (s, 6-H, 4-CH_3); 1.52 (s, 3H, 6-CH_3); 4.88 (s, 1H, 5-H); 6.95 (bs, 1H, NH)[e]; 7.25–7.50 (AB q, 4H_{arom})
c	85	203°	202°[5]	265	3410	1.37 (s, 6H, 4-CH_3); 1.43 (s, 3H, 6-CH_3); 2.27 (s, 3H, Ar—CH_3); 4.90 (s, 1H, 5-H); 7.00 (bs, 1H, NH)[e]; 7.3 (m, 4H_{arom})
d	60	190°	$C_{14}H_{18}N_2OS$ (262.4)	262, 268	3410	1.37, 1.40 (2s, 6H, 4-CH_3); 1.47 (s, 3H, 6-CH_3); 3.87 (s, 3H, OCH_3); 4.83 (s, 1H, 5-H); 6.9–7.25 (m, NH^e + 4H_{arom})
e	90	201°	201°[6]	262, 268	3425	1.38 (s, 6H, 4-CH_3); 1.50 (s, 3H, 6-CH_3); 4.90 (s, 1H, 5-H); 7.44 (d, 2H_{arom}, J = 8 Hz); 7.70 (s, 1H, NH)[e]; 8.25 (d, 2H_{arom}, J = 8 Hz)
f	80	213°	$C_{13}H_{15}N_3O_2S$ (277.4)	255	3400	1.37, 1.43 (2s, 6H, 4-CH_3); 1.55 (s, 3H, 6-CH_3); 4.91 (s, 1H, 5-H); 6.90 (bs, 1H, NH)[e]; 7.4–8.2 (m, 4H_{arom})
g	78	204°	$C_{14}H_{17}N_3O_2S$ (291.4)	262, 268	3370	1.40 (s, 6H, 4-CH_3); 1.48 (s, 3H, 6-CH_3); 2.40 (s, 3H, Ar—CH_3); 4.95 (s, 1H, 5-H); 7.15 (bs, 1H, NH)[e]; 7.5 (m, 1H_{arom}); 8.18 (m, 2H_{arom})
h (as **6**)	65	188°	$C_{14}H_{16}N_2O_2S$ (276.4)	260, 268	3400, 1735	1.40 (s, 3H, 4-CH_3); 1.49 (s, 3H, 4-CH_3); 1.60 (s, 6-CH_3); 2.45 (AB q, 2H, 5-H_2, J = 15 Hz); 7.3–8.3 (m, 4H_{arom})
i	90	214°	216°[5]	262, 268	3400	1.43 (s, 6H, 4-CH_3); 1.50 (s, 3H, 6-CH_3); 4.93 (s, 1H, 5-H); 7.05 (bs, 1H, NH)[e]; 7.58 (m, 4H_{arom}); 7.9 (m, 3H_{arom})

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.25; H, ±0.20; N, ±0.30; S, ±0.35.
[b] The spectra were taken on a Cary 17 D spectrometer.
[c] The spectra were taken on a Perkin-Elmer 237 B spectrometer.
[d] The spectra were recorded on a Varian EM 390 spectrometer at 90 MHz.
[e] Exchangeable with D_2O.

Table 2. *S*-Methylation of 1-Aryl-4,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidines (**1**)

Product **3**	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[b] δ [ppm]
a	96	—	$C_{14}H_{18}N_2S$ (246.4)	1600	1.30 (s, 6H, 4-CH_3); 1.50 (s, 3H, 6-CH_3); 2.28 (s, 3H, SCH_3); 4.57 (s, 1H, 5-H); 7.25–7.6 (m, 5H_{arom})
b	93	51–54°	$C_{14}H_{17}ClN_2S$ (280.8)	1600	1.23 (s, 6H, 4-CH_3); 1.43 (s, 3H, 6-CH_3); 2.25 (s, 3H, SCH_3); 4.57 (s, 1H, 5-H); 7.30 (AB q, 4H_{arom})
c	92	—	$C_{15}H_{20}N_2S$ (260.4)	1600	1.27 (s, 6H, 4-CH_3); 1.40 (s, 3H, 6-CH_3); 2.27 (s, 6H, Ar—CH_3 + SCH_3); 4.53 (s, 1H, 5-H); 7.3 (m, 4H_{arom})
d	90	—	$C_{15}H_{20}N_2OS$ (276.4)	1600	1.27 (s, 6H, 4-CH_3); 1.43 (s, 3H, 6-CH_3); 2.27 (s, 3H, SCH_3); 3.87 (s, 3H, OCH_3); 4.53 (s, 1H, 5-H); 6.9–7.5 (m, 4H_{arom})
e[c]	~50			1600	
f	94	72–74°	$C_{14}H_{17}N_3O_2S$ (291.4)	1600	1.28 (s, 6H, 4-CH_3); 1.47 (s, 3H, 6-CH_3); 2.27 (s, 3H, SCH_3); 4.60 (s, 1H, 5-H); 7.3–7.7 (m, 3H_{arom}); 8.1 (m, 1H_{arom})
g	96	—	$C_{15}H_{19}N_3O_2S$ (305.4)	1605	1.30 (s, 6H, 4-CH_3); 1.40 (s, 3H, 6-CH_3); 2.26 (s, 3H, SCH_3); 2.40 (s, 3H, Ar—CH_3); 4.60 (s, 1H, 5-H); 7.5 (m, 1H_{arom}); 8.18 (s + d, 2H_{arom})
h[d]	88	—	$C_{16}H_{20}N_2O_2S$ (304.4)	1600, 1725	1.27 (s, 6H, 4-CH_3); 1.40 (s, 3H, 6-CH_3); 2.25 (s, 3H, SCH_3); 3.91 (s, 3H, $COOCH_3$); 4.53 (s, 1H, 5-H); 7.6 (m, 3H_{arom}); 8.1 (m, 1H_{arom})
i	92	83–85°	$C_{18}H_{20}N_2S$ (296.5)	1600	1.36 (s, 6H, 4-CH_3); 1.40 (s, 3H, 6-CH_3); 2.20 (s, 3H, SCH_3); 4.62 (s, 1H, 5-H); 7.58 (m, 4H_{arom}); 7.9 (m, 3H_{arom})

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.25; H, ±0.25; N, ±0.30; S, ±0.35.
[b] The spectra were recorded on a Varian EM 390 spectrometer at 90 MHz.
[c] Product **3e** contained an unidentified impurity.
[d] From methylation of lactone **6**.

Table 3. *S*-Benzylation of 1-Aryl-4,4,6-trimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidines (**1**)

Product **7**	Yield [%]	Supl. p. [°C]/torr	Molecular formula[a]	I.R. ($CHCl_3$)[b] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[c] δ [ppm]
a	86	130°/0.1	$C_{20}H_{22}N_2S$ (322.5)	1600	1.32 (s, 6H, 4-CH_3); 1.43 (s, 3H, 6-CH_3); 4.20 (s, 2H, $C_6H_5CH_2$—); 4.60 (br. s, 1H, 5-H); 7.1–7.7 (m, 10H_{arom})
b	90	138°/0.1	$C_{20}H_{21}ClN_2S$ (356.9)	1600	1.28 (s, 6H, 4-CH_3); 1.40 (s, 3H, 6-CH_3); 4.12 (s, 2H, $C_6H_5CH_2$—); 4.55 (s, 1H, 5-H); 7.1–7.5 (m, 9H_{arom})
c	85	142°/0.1	$C_{21}H_{24}N_2S$ (336.6)	1600	1.25, 1.29 (2s, 6H, 4-CH_3); 1.35 (s, 3H, 6-CH_3); 2.16 (s, 3-H, Ar—CH_3); 4.00–4.28 (AB q, 2H, J = 14 Hz, $C_6H_5CH_2$—); 4.52 (s, 1H, 5-H); 7.1–7.5 (m, 9H_{arom})
i	88	180°/0.1	$C_{24}H_{24}N_2S$ (372.6)	1600	1.33, 1.37 (2s, 6H, 4-CH_3); 1.40 (s, 3H, 6-CH_3); 3.93–4.27 (AB q, 2H, J = 13.5 Hz, $C_6H_5CH_2$—); 4.58 (s, 1H, 5-H); 7.1–8.1 (m, 12H_{arom})

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.50; H, ±0.35; N, ±0.40; S, ±0.5.
[b] The spectra were taken on a Perkin-Elmer 237 B spectrometer.
[c] The spectra were recorded on a Varian EM 390 spectrometer at 90 MHz.

Table 4. ^{13}C-N.M.R. Spectra[a] of the Thione **1a** and Thioethers **3a** and **3b**; δ [ppm]

Compound	C-2	C-4	C-5	C-6	4-CH_3	6-CH_3	SCH_3	C-1′	C-2′	C-3′	C-4′
1a	176.5	51.8	109.55	131.8	30.7	20.1	—	140.8	128.3	129.4	127.75
3a	150.4	53.8	106.6	132.2	32.7	19.4	15.1	139.3	128.5	130.9	128.4
3b	150.0	53.95	107.2	132.2	32.8	19.5	15.1	137.9	129.0	130.3	134.5

[a] Recorded on a JEOL FX spectrometer at 20 MHz.

moved in vacuo and the residue sublimed at 110–130 °C/0.1 torr; purity of the sublimed products: 98–100% [T.L.C. on silica gel, ethyl acetate/benzene (1/4) as eluent; G.L.C. (15% FAPP, 150–160 °C)]. The solid products **3** and **7** are recrystallized from ether/petroleum ether.

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