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Alkylated 2- and 4-Thiouracils. Syntheses and HPLC Separations

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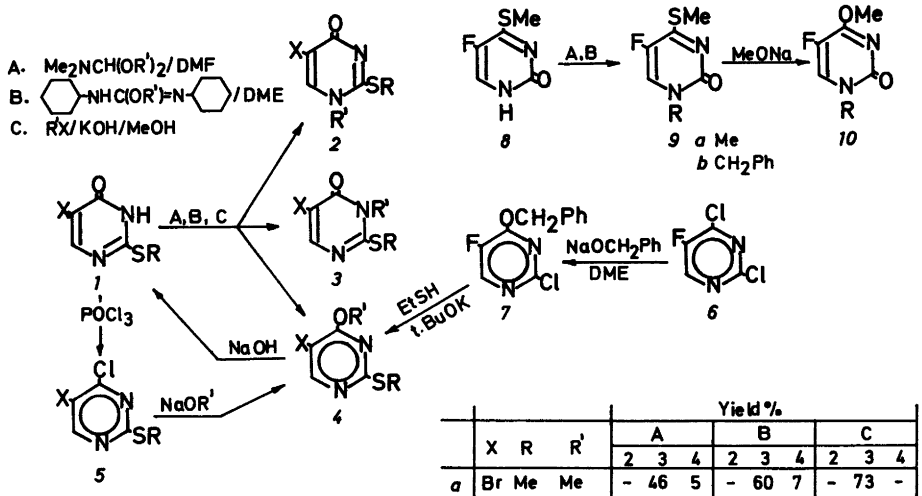
Alkylation of thiouracils using *N,N*-dimethylformamide acetals and *N,N'*-dicyclohexyl-*O*-alkylisoureas have been compared for yields and isomer formation with alkylations using alkyl halides. Isomer formation can be analyzed by TLC on RP-18 gel or the isomers are readily analyzed and separated by reverse-phase HPLC, the order of elution being the *N*(1)-, the *N*(3)- and the *O*-alkylated isomer.

From our studies of regioselective transformations of pyrimidines which eventually will lead us to selected target molecules for cytostatic studies,[1] we herein report on the use of less conventional reactants for alkylations of heterocycles, *viz. N,N*-dimethylformamide acetals[2,3] and *N,N'*-dicyclohexyl-*O*-alkylisoureas.[4,5] The thiated uracils used as substrates in these studies do in thermselves possess biological activities.[6,7] The alkylations with the above reactants were compared for yields and isomer formation with the conventional alkyl halide alkylation (Scheme 1). The alkylthiouracils *1* can react on either *N*(1) or *N*(3) or on the oxygen atom, whereas the thioether sulfur atom will not react under the conditions chosen for the reactions. Reference compounds for identification of *O*-alkylated isomers were prepared by selective nucleophilic displacement of the 4-substituent in suitably 2,4-disubstituted pyrimidines. Thus the 4-chloro substituent is the more reactive in 2,4-dichloro-5-fluoropyrimidine *6* and is replaced by sodium benzyl alcoholate to give *7;* the 2-chlorine substituent was subsequently replaced by sodium ethanethiolate to furnish *4b*. Alternatively, starting from a



	X	R	R'	Yield % A 2	A 3	A 4	B 2	B 3	B 4	C 2	C 3	C 4
a	Br	Me	Me	-	46	5	-	60	7	-	73	-
b	F	Et	$PhCH_2$	-	-	7	-	43	43	41	12	12
c	H	Me	Me	-	58	20	-	52	20	-	64	-
d	H	Me	$PhCH_2$	-	-	-	-	30	40	39	15	7

Scheme 1.

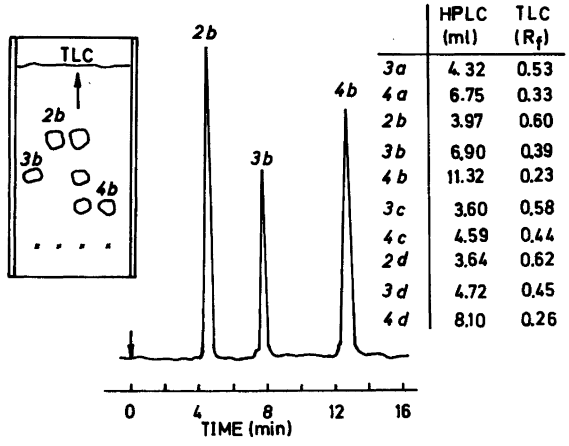
0302-4369/82/010015-04$02.50

2-alkylthio-4-pyrimidinone *1*, the oxygen function is replaced by a chlorine substituent using phosphorous oxychloride *5*, and the latter reacted further with an alkoxide to yield *4*. The conditions of the reaction are decisive for thioether replacement; treatment of the 4-thiomethyl uracil *9* with sodium methoxide furnished the 1-alkyl-4-*O*-methyl uracil *10*.

The dimethylacetal of *N*,*N*-dimethylformamide in its reactions with uracils, thymines and nucleosides has been reported to give high yields of exclusively *N*-methylated products.[2,3] In its reactions with the thiouracils, however, a significant degree of *O*-alkylation was observed (*4a*, *4c*; Scheme 1). The dibenzyl acetal was much less reactive and the product isolated (7 %) from the reaction with the 5-fluorouracil was the *O*-benzylated isomer *4b* (Scheme 1). The *O*-alkyl isourea reagents, however, gave superior yields of products. The *N*(3)-methyl derivative (*3a*, *3c*) was the major product, and the *O*-methyl isomer (*4a*, *4c*) was the minor product from the reaction with the *O*-methyl isourea. From the *O*-benzylisourea reagent, *N*(3)- and *O*-alkylation were of similar importance. Dimethoxyethane is a good solvent for this reaction since the reactants and the products are soluble. In the comparative reactions using methyl iodide, exclusive *N*(3)-methylation (*3a*, *3c*) resulted, whereas benzyl bromide furnished all three isomers, the *N*(1)-isomer (*2b*, *2d*) being the major product, presumably because of steric effects. In the isomeric series of *1*, *i.e.* in the 2-pyrimidinone series, only one compound, *viz.* 4-methylthio-5-fluoropyrimidin-2-one *8* was studied. The latter has both nitrogen atoms directly attached to the oxo function; on treatment with the acetal and isourea reagents exclusively *N*(1)-alkylated products were obtained from the reaction (*9a*, *9b*). Similarly the reaction with methyl iodide gave only the *N*(1)-methylated isomer *9a*.[8]

Reverse-phase HPLC has been found very convenient and useful in the analyses and preparative separations of the various alkylated isomers (Fig. 1). Previously we have reported that *N*-substituted 2-pyrimidinones have shorter retention times than their *O*-substituted isomers.[1] The same pattern is retained in the thiouracil series. But more important is the finding that the *N*(1)- and *N*(3)-alkylated isomers are readily separable, the order of elution being the *N*(1)-, the *N*(3)- and the *O*-isomer (Fig. 1). Furthermore, TLC on RP-18 gel shows the same relative mobilities (Fig. 1).

In ^{1}H NMR the deshielding of *H*-6 appears to be different in the three series; δ 8.15–9.4 for the *O*-isomer, δ 7.7–8.0 for the *N*(3)-isomer and δ *ca.* 7.4 for the *N*(1)-isomer. A similar scale is observed for the benzyl protons; δ *ca.* 5.2 for the *N*(3)-isomer and δ 5.05 for the *N*(1)-isomer. The *CO*-absorption in IR also differs for the *N*(1)- and *N*(3)-isomers, being in the regions 1630–1660 cm^{-1}, and 1670–1690 cm^{-1}, respectively. The fragmentations of the isomers on mass spectrometry are similar and related to the behaviour of alkoxy-, alkylthio- and *N*-alkyluracils.[9–12]



	HPLC (ml)	TLC (R_f)
3a	4.32	0.53
4a	6.75	0.33
2b	3.97	0.60
3b	6.90	0.39
4b	11.32	0.23
3c	3.60	0.58
4c	4.59	0.44
2d	3.64	0.62
3d	4.72	0.45
4d	8.10	0.26

Fig. 1. HPLC retention volumes (ml) on μBondapak C_{18} column and TLC R_f-values on RP-18 (Merck) using 70 % MeCN aq.

EXPERIMENTAL

TLC was run on Merck Silica gel 60 F_{254} using (a) EtOAc or (b) iPr_2O, or on Merck RP-18 using 70 % MeCN in water. HPLC was run on a Waters HPLC system equipped with a UV monitor (260 mm) and a μBondapak C_{18} column (10 μm, 30 cm × 4 mm I.D.). The solvent was 70 % MeCN in water, and the flow rate was 0.9 ml/min. Preparative separations were carried out on Waters PrepLC/System 500 equipped with a PrepPak 500/C_{18} column.

The mass spectra were recorded on MM 70–70F VG Micromass spectrometer at 70 eV. The data are reported as MS [70 eV; m/z (% rel. int.)]

2-Methylthio-5-bromopyrimidin-4-one[13] 1a. Bromine (20 mmol) was added dropwise over 10 min. to a solution of 2-methylthiopyrimidin-4-one[13] (20 mmol) and NaBr (40 mmol) in dioxan (8 ml) and 1 M KOH (32 ml) at room temperature. The reaction mixture was heated at 70 °C for 1 h, cooled to room temperature and water (40 ml) added. The product was precipitated on acidification with acetic acid; yield 75 %, m.p. 245 °C (EtOH). ^{1}H NMR (DMSO-d_6): δ 2.53 (SMe), 8.16 (H–6). MS: 222/220 (99/100, M), 176/174 (25/27), 175/173 (26/21), 150/148 (8/15), 149/147 (17/24), 141 (62), 113 (27).

2-Ethylthio-5-fluoropyrimidin-4-one[14] 1b. A suspension of 2-ethylthio-4-benzyloxy-5-fluoropyrimidine (19 mmol) in 2 M NaOH (70 ml) was heated under reflux for 26 h. The resultant solution was concentrated to *ca.* half of its volume and acidified with acetic acid, which precipitated the product; yield 70%, m.p. 193–194 °C (H_2O). ^{1}H NMR (TFA): δ 1.56 and 3.50 (SEt), 8.03 (H–6). MS 174 (78, M), 159 (32), 146 (38), 141 (82), 130 (7), 114 (47), 88 (100), 87 (47).

Alkylation of 2-alkylthiopyrimidin-4-ones. Method A. A solution of the 2-alkylthiopyrimidin-4-one (6.5 mmol) and *N,N*-dimethylformamide dimethyl or dibenzyl acetal (15 mmol) in DMF (25 ml) was heated at 80 °C for 6 h. The reaction mixture was then evaporated, the residue was dissolved in the minimum volume of DMF and the solution applied onto a Waters PrepPak 500/C_{18} column which was eluted (100 ml/min) with 70 % MeCN aq. The order of elution was the *N*(1)-isomer, the *N*(3)-isomer and the *O*-isomer.

Method B. A solution of the 2-alkylthiopyrimidin-4-one (6.2 mmol) and *N,N'*-dicyclohexyl-*O*-methyl[15] or *O*-benzyl isourea[16] (7.5 mmol) in dimethoxyethane (60 ml) was heated under reflux for 70 min. The dicyclohexylurea formed was then filtered off, the filtrate evaporated to dryness and the residue chromatographed on Waters PrepPak 500/C_{18} column as above.

Method C: The alkyl halide (8.6 mmol) was added to a solution prepared from the 2-alkylthiopyrimidin-4-one (8.6 mmol) in 0.57 M methanolic KOH (15 ml), and the resultant solution heated under reflux for 3 h. The solvent was then removed at reduced pressure, the residue extracted with DMF and the DMF solution chromatographed as above.

1-Benzyl-2-ethylthio-5-fluoropyrimidin-4-one 2b. M.p. 118–119 °C (iPrOH). Anal. $C_{13}H_{13}FN_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.36 and 3.23 (Et), 5.05 (CH_2), 7.30 (Ph), 7.36 (H–6). IR (KBr): 1642 cm^{-1} (CO). MS: 264 (6, M), 236 (13), 235 (4), 203 (10), 173 (12), 148 (5), 91 (100).

1-Benzyl-2-methylthiopyrimidin-4-one 2d. M.p. 176–177 °C (iPrOH). Anal. $C_{12}H_{12}N_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.53 (SMe), 5.05 (CH_2), 5.91 (H–5), 7.28 (Ph), 7.39 (H–6). IR (KBr): 1630 cm^{-1} (CO). MS: 232 (25), 217 (7), 185 (9), 158 (12), 141 (9), 130 (6), 104 (8), 91 (100).

2-Methylthio-3-methyl-5-bromopyrimidin-4-one 3a. M.p. 130 °C (iPrOH). Anal. $C_6H_7BrN_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.56 (SMe), 3.56 (NMe), 8.00 (H–6). IR (KBr): 1681 (CO). MS: 236/234 (35/34, M), 221/219 (4/5), 190 (30), 189 (100), 188 (21), 187 (21), 160 (8), 155 (6), 118 (13).

2-Ethylthio-3-benzyl-5-fluoropyrimidin-4-one 3b. M.p. 46 °C (light petroleum). Anal. $C_{13}H_{13}FN_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.32 and 3.16 (Et), 5.28 (CH_2), 7.13 (Ph), 7.75 (H–6). IR (KBr): 1690 cm^{-1} (CO). MS: 264 (19, M), 236 (5), 235 (17), 203 (12), 176 (10), 173 (21), 130 (25), 118 (6).

2-Methylthio-3-methylpyrimidin-4-one[17] 3c. M.p. 126–127 °C (H_2O). ^{1}H NMR ($CDCl_3$): δ 2.56 (SMe), 3.50 (NMe), 6.13 (H–5), 7.66 (H–6). IR (KBr): 1670 cm^{-1} (CO). MS: 156 (32), 141 (7), 123 (6), 112 (9), 111 (100), 110 (25), 109 (68), 82 (20), 81 (29).

2-Methylthio-3-benzylpyrimidin-4-one 3d. M.p. 97 °C (iPrOH). Anal. $C_{12}H_{12}N_2OS$: C, H. ^{1}H NMR ($CHCl_3$): δ 2.50 (SMe), 5.26 (CH_2), 6.23 (H–5), 7.26 (Ph), 7.72 (H–6). IR (KBr): 1680 cm^{-1} (CO). MS: 232 (66), 217 (13), 199 (3), 185 (13), 158 (21), 148 (11), 141 (10), 112 (37).

2-Methylthio-4-methoxy-5-bromopyrimidine 4a. 2-Methylthio-4-chloro-5-bromopyrimidine[18] (11 mmol) was added gradually to methanolic 0.43 M NaOMe (30 ml) and the reaction mixture stirred at room temperature for 20 h. The solvent was then evaporated, the residue extracted with ether, the ether solution washed with water, and the dried ($MgSO_4$) solution evaporated, to leave the product; yield 91 %, m.p. 86 °C (light petroleum). Anal. $C_6H_7BrN_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.53 (SMe), 4.06 (OMe), 8.30 (H–6). MS: 236/234 (25/24, M), 235/233 (5/2), 221/219 (17/16), 191/189 (3/3), 190/188 (11/11), 149/147 (3/4), 118 (4), 109 (7), 32 (100).

2-Methylthio-4-methoxypyrimidine 4c was prepared as *4a* above from 2-methylthio-4-chloro-

pyrimidine[19] in 84 % yield, m.p. 35 °C (n-heptane). Anal. $C_6H_8N_2OS$: C, H. ^1H NMR ($CDCl_3$): δ 2.53 (SMe), 3.93 (OMe), 6.30 (H−5), 8.13 (H−6). MS: 156 (100, M), 141 (34), 125 (3), 111 (10), 110 (55), 109 (4), 95 (17), 82 (10).

2-Ethylthio-4-benzyloxy-5-fluoropyrimidine 4b. 2-Chloro-4-benzyloxy-5-fluoropyrimidine (12.3 mmol) was added to a mixture from ethanethiol (12.3 mmol) and t-BuOK (12.3 mmol) in dimethoxyethane (100 ml). The reaction mixture was heated under reflux for 2 h and then worked up as above; yield 89 %, b.p. 128−130 °C/0.01 mmHg, m.p. 36 °C. Anal. $C_{13}H_{13}FN_2OS$: C, H. ^1H NMR ($CDCl_3$): δ 1.37 and 3.10 (Et), 5.46 (CH_2), 7.38 (Ph), 8.13 (H−6). MS: 264 (4, M), 236 (2), 235 (4), 203 (3), 173 (12), 130 (3), 118 (3), 91 (100).

2-Methylthio-4-benzyloxypyrimidine 4d. 2-Methylthio-4-chloropyrimidine (29.3 mmol) was added to a mixture from benzyl alcohol (29.3 mmol) and t-BuOK (29.3 mmol) in dimethoxyethane (100 ml) and the mixture heated under reflux for 1 h. Work-up as above gave 73 % yield, b.p. 116−118 °C/0.01 mmHg. Anal. $C_{12}H_{12}N_2OS$: C, H. ^1H NMR ($CDCl_3$): δ 2.52 (SMe), 5.35 (CH_2), 6.37 (H−5), 7.30 (Ph), 8.13 (H−6). MS: 232 (28, M), 217 (3), 185 (5), 160 (7), 158 (5), 141 (7), 126 (18), 91 (100).

2-Chloro-4-benzyloxy-5-fluoropyrimidine 7. Sodium benzyl alcoholate (2.02 M) in benzyl alcohol (10 ml) was added dropwise to an ice-cold solution of 2,4-dichloro-5-fluoropyrimidine[20] (20.2 mmol) in dimethoxyethane (50 ml). After the addition was completed, the mixture was stirred at room temperature for 2 days. The solvent was evaporated, the residue extracted with ether, and the washed (H_2O) and dried ($MgSO_4$) solution evaporated to yield the product; yield 71 %, m.p. 109 °C (heptane). Anal. $C_{11}H_8ClFN_2O$: C, H. ^1H NMR ($CDCl_3$): δ 5.50 (CH_2), 7.40 (Ph), 8.10 (H−6).

1-Methyl-4-methylthio-5-fluoropyrimidin-2-one 9a[8] by alkylation of 4-methylthio-5-fluoropyrimidin-2-one;[21] yield 70 % by Method A and 82 % by Method B, m.p. 154 °C. MS: 174 (100, M), 173 (2), 159 (79), 144 (3), 141 (2), 129 (2), 118 (4), 116 (4), 100 (7).

1-Benzyl-4-methylthio-5-fluoropyrimidin-2-one 9b by alkylation of 4-methylthio-5-fluoropyrimidin-2-one; yield 48 % by Method A and 68 % by Method B, m.p. 177−170 °C (iPrOH) Anal. $C_{12}H_{11}FN_2OS$: C, H. ^1H NMR ($CDCl_3$): δ 2.56 (SMe), 5.00 (CH_2), 7.23 (H−6), 7.31 (Ph). IR (KBr): 1660 cm^{-1} (CO). MS: 250 (34, M), 249 (3), 235 (6), 203 (2), 192 (2), 144 (4), 91 (100).

1-Methyl-4-methoxy-5-fluoropyrimidin-2-one[22] 10a. A solution of 1-methyl-4-methylthio-5-fluoropyrimidin-2-one (3.3 mmol) in methanolic 0.26 M NaOMe (25 ml) was kept at room temperature for 24 h. The solvent was then evaporated, the residue extracted with chloroform, and the washed (H_2O) and dried ($MgSO_4$) chloroform solution evaporated to leave the product; yield 58 %. ^1H NMR ($CDCl_3$): δ 3.48 (NMe), 4.05 (OMe), 7.53 (H−6). MS: 158 (100, M), 157 (18), 143 (18), 130 (4), 129 (11), 128 (18), 127 (4), 114 (5), 102 (6), 101 (11), 100 (82).

1-Benzyl-4-methoxy-5-fluoropyrimidin-2-one 10b was prepared as *10a* above from 1-benzyl-4-methylthio-5-fluoropyrimidin-2-one in 51 % yield, m.p. 132−134 °C (EtOAc). Anal. $C_{12}H_{11}FN_2O_2$: C, H. ^1H NMR ($CDCl_3$): δ 4.01 (OMe), 5.00 (NCH_2), 7.30 (Ph), 7.36 (H−6). IR (KBr): 1645 cm^{-1} (CO). MS: 234 (27), 219 (8), 176 (11), 142 (2), 129 (2), 128 (10), 114 (2), 91 (100).

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