α-Halo Sulfides in the Alkylation of 2-Pyrimidinones

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When α-halo sulfides are reacted with ambident 2-pyrimidinones, the major product is due to *N*-alkylation, the minor product to *O*-alkylation. *N*-Alkylation is favoured by the presence of a tertiary amine in a solvent of low dielectric constant and also by a change of the α-halo sulfide substituent from chlorine to iodine. Complete selectivity can be achieved. The course of the reaction is rationalized in terms of the HSAB-principle.

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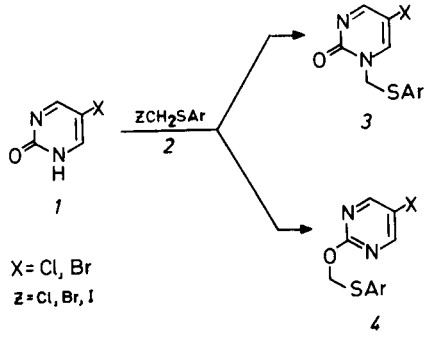
N-Substituted 5-halo-2(1*H*)-pyrimidinones have been found to affect the cell cycle during mitosis by possessing reversible metaphase arresting properties [1]. Such compounds are of potential interest in biology for synchronization of cell division. A major route for their preparation involves alkylation of the appropriately substituted pyrimidinone as the final step in the reaction sequence. As a consequence, we have been involved in studies of chemoselectivity and regioselectivity in the alkylation reactions of the ambident anion of 2-pyrimidinones [2,3].

In ambident systems the principal factors controlling the site of alkylation are the structure of the alkylating agent, the nature of the solvent, the nature of the counterion, the nature of the leaving group and the temperature [4]. In the reactions of the ambident 2-pyrimidinone system, the structure of the alkylating agent seems to be the most important factor for controlling the relative yield of *O*- and *N*-alkylated products [2,4b]. Thus the *N*/*O*-alkylation ratio is hardly affected by the nature of the counterion or the solvent when methyl or ethyl iodide, or allyl or benzyl bromide were the alkylating agents [2]. There is a relative increase in *O*-alkylation when α-halo ethers are used for the alkylation and the selectivity is sensitive to changes in the nature of the counter-ion as well as to the solvent [3]. This report describes studies using α-halo sulfides in alkylation reactions. The latter is a softer electrophile than the corresponding ether reagent, and hence a different *N*/*O*-alkylation ratio was to be expected.



The reactions were run under the same two sets of conditions for comparisons. In Method A the reaction between the pyrimidinone **1** and the alkylating agent **2** was effected by potassium *t*-butoxide in DMF; in Method B there was used triethylamine in dichloromethane. The *N*/*O*-alkylation ratios are given in the table as relative percentage yield of the *N*-alkyl isomer **3**. The *N*/*O*-alkylation ratio observed presumably results from kinetic control. Support for this view is provided by the failure of the isomer **3** or **4** to undergo any transalkylation under the conditions of their formation and the presence of an α-halo sulfide reagent.

The Table shows that the change of experimental conditions from potassium *t*-butoxide in DMF (Method A) to triethylamine in dichloromethane (Method B) clearly promotes *N*-alkylation and in some cases the *N*-alkyl isomer was the only product. This finding is in accordance with the empirical rule which teaches that a decrease in the polarity of the aprotic solvent disfavours alkylation at the centre with the highest electron density [5], which is the electronegative oxygen atom. The change of the counterion from potassium to triethylammonium may also be important. According to the HSAB-principle [6], the hard potassium ion must be assumed to be well solvated by DMF. The partly deshielded oxygen atom, which constitutes the harder part of the ambident pyrimidine system, can compete successfully with the softer part (*N*) for the alkylating agent. In dichloromethane, however, the ammonium nitrogen of the added base will form an ion pair with the pyrimidine anion [7]; the ion pair is between the relatively hard ammonium nitrogen and oxygen atoms. The oxygen is thereby shielded which should favour attack by the electrophile at the relatively soft pyrimidine nitrogen centre.

The reactivity of the α-halo sulfides in dichloromethane follows the usual pattern for S_N2 substitution, *viz.* I > Br > Cl. The nature of the leaving group in **2** also affects the *N*/*O*-alkylation ratio (Table), iodide causing the highest *N*-alkylation. The electronic nature of the substituents in the phenyl ring in **2** is not sufficiently transmitted to its electrophilic centre to affect the isomer ratio significantly.

Table

Alkylations of 5-Halo-2(1*H*)-pyrimidinones by α-Halo Sulfides

Mixture **3** and **4**	X	Z	Ar	Method [a]	Turnover [b] (%)	Yield [c] (%)	Relative yield [d] of **3** (%)
a	Cl	Cl	4-ClC_6H_4	A		72	63
a		Br	4-ClC_6H_4	A		73	65
a		I	4-ClC_6H_4	A		83	68
a		Cl	4-ClC_6H_4	B	39		83
a		Br	4-ClC_6H_4	B	85		90
a		I	4-ClC_6H_4	B	82		95
b	Cl	Br	4-FC_6H_4	A		59	65
b	Cl	Br	4-FC_6H_4	B	83		83
c	Br	Br	4-FC_6H_4	A		70	64
d	Cl	I	4-Cl-Pyrimidin-2-yl	A		84	74
d	Cl	I	4-Cl-Pyrimidin-2-yl	B		67	100
e	Cl	Cl	3-MeC_6H_4	A		64	58
e		Br	3-MeC_6H_4	A		90	65
e		I	3-MeC_6H_4	A		67	63
e		Cl	3-MeC_6H_4	B	47		82
e		Br	3-MeC_6H_4	B		77	87
e		I	3-MeC_6H_4	B	>95		94
f	Br	Cl	3-MeC_6H_4	A		67	60
g	Cl	Cl	4-$MeOC_6H_4$	A		87	58
g	Cl	Cl	4-$MeOC_6H_4$	B	46		83
g	Cl	I	4-$MeOC_6H_4$	B	>95		100

[a] Method A: *t*-BuOK/DMF at 60° for 3 hours. Method B: triethylamine/dichloromethane at 40° for 24 hours. [b] Yield estimated by ^1H nmr when the reaction was stopped after 3 hours. [c] Yield of isolated material from the reaction. [d] The relative yield estimated from the ^1H nmr spectra of the crude product, the precision being ±4%.

These results can be rationalized in terms of symbiotic stabilization of the transition state. The latter expresses stabilization due to flocking of ligands of the same hardness or softness on the same acceptor atom [8]. Since the nitrogen atom is the softer part of the ambident pyrimidine anion, an increase in the softness of the leaving group in **2** would also be expected to favour *N*-alkylation.

In DMF the isomer ratios are little affected by the nature of the leaving group. Due to a large increase in the dielectric constant from dichloromethane (ϵ = 9.08) [9] to DMF (ϵ = 36.71) [10] this may in part be associated with a change in the reaction mechanism from S_N2 over to an S_N1 mechanism due to better stabilization of charge separation.

α-Halo sulfides are softer alkylating agents then their α-halo ether analogues and would be expected to give a higher relative yield of *N*-alkylated product. Accordingly **1** (X = Cl) was found to react with **2** (Z = Cl) in DMF to furnish the *N*-alkyl isomer **3a** in 60% relative yield whereas the relative yield was 40% using the α-halo ether analogue; in dichloromethane with triethylamine as base the difference in relative yield was small.

The isomers **3** and **4** are readily distinguished by the ^1H nmr spectra; the pyrimidine protons in **4** appear as a singlet due to symmetry whereas in **3** the H-4 proton is more deshielded than H-6 [11].

EXPERIMENTAL

The ^1H nmr spectra were recorded at 60 MHz. The mass spectra are presented as ms [70 eV, m/z (% relative intensity)].

α-Halo Sulfides **2**.

The α-chloro and α-bromo sulfides were prepared as reported [12]. The α-iodo sulfides were prepared from the corresponding α-chloro sulfides by the Finkelstein reaction [13].

Procedure for Alkylation of **1**.

Method A.

Potassium *t*-butoxide (5.0 mmoles) was added to a solution of 5-halo-2(1*H*)-pyrimidinone (5.0 mmoles) in dry DMF (50 ml). The mixture was stirred at room temperature for 20 minutes before the α-halo sulfide (5.0 mmoles) was added. The resultant mixture was stirred at 60° for 3 hours. The solvent was then removed at reduced pressure, the residue extracted with chloroform (100 ml), the chloroform solution washed with water (3

×), and the dried (magnesium sulfate) solution evaporated. The residual product was an almost pure mixture of the *N*- and *O*-alkylated isomers **3** and **4**. The isomers differ by their solubility in ether, the *O*-alkylated isomer **4** being the more soluble. Extraction of the crude product with ether removes largely the *O*-alkyl isomer **4**. The *N*-alkyl isomer is further purified by recrystallization, whereas the *O*-alkyl isomer is purified by chromatography on a silica gel column using chloroform.

Method B.

Triethylamine (5.0 mmoles) was added to a suspension of the 5-halo-2(1*H*)-pyrimidinone (5.0 mmoles) in dry dichloromethane (50 ml). The mixture was stirred at room temperature for 10 minutes before the α-halo sulfide (5.0 mmoles) was added, the mixture was stirred at 40° for 24 hours, chloroform (50 ml) was then added to the cold mixture which was subsequently washed with water (3 ×) and worked up as above.

5-Chloro-1-(4-chlorophenylsulfenyl)methyl-2(1*H*)-pyrimidinone (**3a**).

This compound had mp 191° (acetone); ^{1}H nmr (deuteriochloroform): δ 5.25 (CH_2), 7.35 (Ph), 8.20 (H-6, $J_{4,6}$ = 4 Hz), 8.50 (H-4); ir (potassium bromide): 1660 cm^{-1} (CO); ms: 286 (4, M), 157 (11), 156 (11), 145 (33), 143 (100), 116 (27).

Anal. Calcd. for $C_{11}H_8Cl_2N_2OS$: C, 46.00; H, 2.81. Found: C, 45.90; H, 2.78.

5-Chloro-1-(4-fluorophenylsulfenyl)methyl-2(1*H*)-pyrimidinone (**3b**).

This compound had mp 179° (methanol/water/2-propanol); ^{1}H nmr (hexadeuteriodimethylsulfoxide): δ 5.25 (CH_2), 6.9-7.7 (Ph), 8.07 (H-6, $J_{4,6}$ = 4 Hz), 8.53 (H-4); ms: 272/270 (2/4, M), 145 (32), 143 (100).

Anal. Calcd. for $C_{11}H_8ClFN_2OS$: C, 48.81; H, 2.98. Found: C, 48.54; H, 3.08.

5-Bromo-1-(4-fluorophenylsulfenyl)methyl-2(1*H*)-pyrimidinone (**3c**).

This compound had mp 206° (methanol/acetic acid); ^{1}H nmr (trifluoroacetic acid): δ 5.47 (CH_2), 7.0-7.7 (Ph), 8.30 (H-6, $J_{4,6}$ = 3 Hz), 8.90 (H-4); ir (potassium bromide): 1660 cm^{-1} (CO); ms: 316/314 (6/5, M), 187 (100), 189 (98).

Anal. Calcd. for $C_{11}H_8BrFN_2OS$: C, 41.92; H, 2.56. Found: C, 42.06; H, 2.62.

5-Chloro-1-(5-chloropyrimidin-2-ylsulfenyl)methyl-2(1*H*)-pyrimidinone (**3d**).

This compound had mp 210° (acetone); ^{1}H nmr (deuteriochloroform): δ 5.56 (CH_2), 8.29 (H-6, $J_{4,6}$ = 3 Hz), 8.57 (H-4), 8.62 (H-4', H-6'); ir (potassium bromide): 1670 cm^{-1} (CO); ms: 288 (20, M), 159 (23), 149 (40), 147 (100), 143 (73).

Anal. Calcd. for $C_9H_6Cl_2N_4OS$: C, 37.38; H, 2.10. Found: C, 37.59; H, 2.07.

5-Chloro-1-(3-tolylsulfenyl)methyl-2(1*H*)-pyrimidinone (**3e**).

This compound had mp 134° (2-propanol/ethanol); ^{1}H nmr (hexadeuteriodimethylsulfoxide): δ 2.27 (Me), 5.22 (CH_2), 7.17 (Ph), 8.00 (H-6, $J_{4,6}$ = 4 Hz), 8.56 (H-4); ir (potassium bromide): 1660 cm^{-1} (CO); ms: 268/266 (2/6, M), 145 (32), 143 (100).

Anal. Calcd. for $C_{12}H_{11}ClN_2OS$: C, 54.03; H, 4.16. Found: C, 53.73; H, 4.25.

5-Bromo-1-(3-tolylsulfenyl)methyl-2(1*H*)-pyrimidinone (**3f**).

This compound had mp 164° (methanol); ^{1}H nmr (hexadeuteriodimethylsulfoxide): δ 2.30 (Me), 5.23 (CH_2), 7.20 (Ph), 8.03 (H-6, $J_{4,6}$ = 4 Hz), 8.57 (H-4); ir (potassium bromide): 1660 cm^{-1} (CO); ms: 312/210 (4/4, M), 189 (95), 187 (100).

Anal. Calcd. for $C_{12}H_{11}BrN_2OS$: C, 46.32; H, 3.56. Found: C, 46.46; H, 3.62.

5-Chloro-1-(4-methoxyphenylsulfenyl)methyl-2(1*H*)-pyrimidinone (**3g**).

This compound had mp 140° (methanol); ^{1}H nmr (hexadeuteriodimethylsulfoxide): δ 3.77 (OMe), 5.12 (CH_2), 6.8-7.4 (Ph), 7.90 (H-6, $J_{4,6}$ = 4 Hz), 8.56 (H-4); ir (potassium bromide): 1660 cm^{-1} (CO); ms: 284/282 (2/5, M), 145 (33), 143 (100).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2S$: C, 50.97; H, 3.93. Found: C, 51.13; H, 3.85.

5-Chloro-2-(4-chlorophenylsulfenyl)methyloxypyrimidine (**4a**).

This compound had mp 68° (ether/ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 5.52 (CH_2), 7.35 (Ph), 8.68 (H-4, H-6); ms: 286 (13, M), 159 (36), 158 (11), 157 (100), 156 (11), 145 (26), 143 (81), 131 (12).

Anal. Calcd. for $C_{11}H_8Cl_2N_2OS$: C, 46.00; H, 2.81. Found: C, 45.98; H, 2.79.

5-Chloro-2-(4-fluorophenylsulfenyl)methyloxypyrimidine (**4b**).

This compound was obtained as non-crystalline material; ^{1}H nmr (deuteriochloroform): δ 5.69 (CH_2), 6.8-7.3 (Ph), 8.44 (H-4, H-6); ms: 272/270 (3/9, M), 141 (100).

Anal. Calcd. for $C_{11}H_8ClFN_2OS$: C, 48.81; H, 2.98. Found: C, 48.71; H, 3.19.

5-Bromo-2-(4-fluorophenylsulfenyl)methyloxypyrimidine (**4c**).

This compound had mp 38° (ether/ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 5.67 (CH_2), 6.7-6.8 (H-4, H-6); ms: 316/314 (4/4, M), 141 (100).

Anal. Calcd. for $C_{11}H_8BrFN_2OS$: C, 41.92; H, 2.56. Found: C, 42.15; H, 2.63.

5-Chloro-2-(5-chloropyrimidin-2-ylsulfenyl)methyloxypyrimidine (**4d**).

This compound had mp 128° (methanol); ^{1}H nmr (deuteriochloroform): δ 6.15 (CH_2), 8.48 (H-4, H-6), 8.51 (H-4', H-6'); ms: 288 (5, M), 161 (37), 160 (28), 159 (100), 158 (51), 149 (23), 147 (61).

Anal. Calcd. for $C_9H_6Cl_2N_4OS$: C, 37.38; H, 2.10. Found: C, 37.56; H, 2.18.

5-Chloro-2-(3-tolylsulfenyl)methyloxypyrimidine (**4e**).

This compound was obtained as non-crystalline material; ^{1}H nmr (deuteriochloroform): δ 2.31 (Me), 5.72 (CH_2), 6.9-7.4 (Ph), 8.43 (H-4, H-6); ms: 268/266 (4/11, M), 137 (100).

Anal. Calcd. for $C_{12}H_{11}ClN_2OS$: C, 54.03; H, 4.16. Found: C, 54.50; H, 4.32.

5-Bromo-2-(3-tolylsulfenyl)methoxypyrimidine (**4f**).

This compound was obtained as non-crystalline material; ^{1}H nmr (deuteriochloroform): δ 3.30 (Me), 5.73 (CH_2), 7.0-7.4 (Ph), 8.53 (H-4, H-6); ms: 312/310 (4/4, M), 137 (100).

Anal. Calcd. for $C_{12}H_{11}BrN_2OS$: C, 46.32; H, 3.56. Found: C, 46.41; H, 3.59.

5-Chloro-2-(4-methoxyphenylsulfenyl)methyloxypyrimidine (**4g**).

This compound had mp 58° (ether/ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 3.80 (OMe), 5.63 (CH_2), 6.7-7.5 (Ph), 8.43 (H-4, H-6); ms: 284/282 (8/21, M), 153 (100).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2S$: C, 50.97; H, 3.93. Found: C, 51.22; H, 3.90.

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