

α -Haloalkyl Ethers in Alkylations of 2-Pyrimidinones

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The ambident 5-halopyrimidin-2-one anion with potassium as counterion in DMF is preferentially *O*-alkylated using the relatively hard α -chloroalkyl ether electrophiles. As ammonium salts in dichloromethane or by the use of KF-alumina in DME the preference is for *N*-alkylation. TMS ethers of the pyrimidinones are exclusively *N*-alkylated.

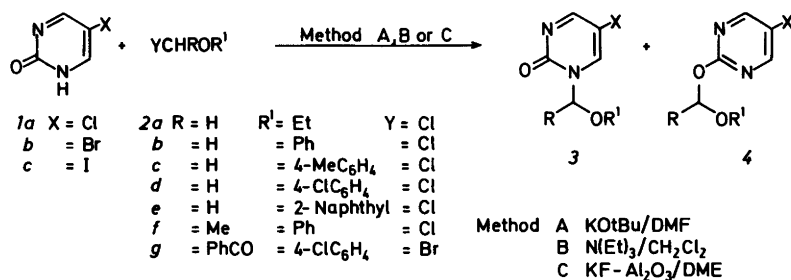
Anions of 5-halopyrimidin-2-ones are ambident and can thus in principle be either *O*- or *N*-alkylated. The preferential site of reaction seems to depend on factors such as the structure of the alkylating agent, the solvent used in the reaction, the nature of the counterion, the nature of the leaving group and on the temperature used.¹ In our previous report on alkylation reactions of this system, simple halides like methyl iodide, allyl bromide and benzyl bromide were studied in which case the *N*-substituted pyrimidines were obtained almost exclusively.² These reagents have a rather soft carbon where the substitution occurs, and hence the softer part of the ambident system (*N*) is preferentially alkylated. An increasing amount of *O*-alkylation of the ambident system is to be expected when

the reacting carbon of the alkylating agent is made harder. This would appear to be the case when the alkylating agent is an α -halo ether. We herein report such studies.

The *N*- β -oxa-alkyl products **3** coming out of these reactions are also of special interest since we have found that *N*-substituted 5-halopyrimidin-2-ones affect the cell cycle during mitosis by possessing reversible metaphase arresting properties.³

The 5-halopyrimidin-2-ones were available by literature methods.⁴ There was, however, the need for an improved synthesis of the 5-iodo analogue *1c*. It has been found that the latter can conveniently be prepared from 2-pyrimidinone using iodine monochloride under acidic conditions.

Various methods were studied for the alkylation with α -halo ethers (Scheme 1). In *N,N*-dimethylformamide (DMF), potassium was used as the counterion of the pyrimidinone. (Method A); the major product from the reaction was the *O*-alkylated isomer (Table 1). Presumably the hard potassium ion is well solvated by DMF so that the harder part of the ambident pyrimidine system (*O*) can compete successfully with the



Scheme 1.

Table 1. Alkylations of 5-halopyrimidin-2-ones using α -chloro ethers.

	X	R	R'	Method ^a	mmol <i>I</i> and 2	Yield (%) ^b	3:4 ^c
3a/4a	Cl	H	Et	B ^d	10	74	2:1
3b/4b	Cl	H	Ph	B	5	85	3:1
3b/4b	Cl	H	Ph	C	— ^e	48	3:1
3c/4c	Cl	H	4-MeC ₆ H ₄	A ^d	2	80	2:3
3c/4c	Cl	H	4-MeC ₆ H ₄	B ^d	10	76	3:1
3c/4c	Cl	H	4-MeC ₆ H ₄	C	— ^e	66	7:2
3d/4d	Cl	H	4-ClC ₆ H ₄	A ^d	20 ^f	70 ^g	2:3
3d/4d	Cl	H	4-ClC ₆ H ₄	B	6	91	4:1
3e/4e	Br	H	4-ClC ₆ H ₄	A	5	70	2:3
3e/4e	Br	H	4-ClC ₆ H ₄	C	— ^e	53	3:1
3f/4f	I	H	4-ClC ₆ H ₄	A ^h	5	87	3:5
3f/4f	I	H	4-ClC ₆ H ₄	B	10	56	4:1
3g/4g	Cl	H	2-naphthyl	B ^d	5	86	4:1
3h/4h	Cl	Me	Ph	B ^d	4.5	76	3:2
3i/4i	Cl	PhCO	4-ClC ₆ H ₄	B ^{d,i}	5	77	8:1

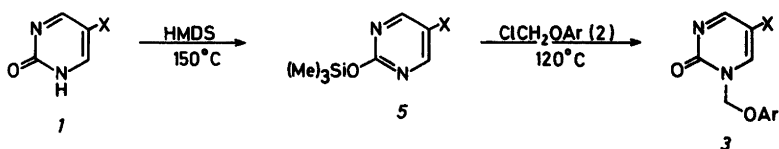
^a Method A: KOtBu/DMF (3c/4c: RT, 3 h; 3d/4d: RT, 1/2 h and 60 °C, 1/2 h; 3e/4e: 60 °C, 4 h; 3f/4f: RT, 3 1/2 h). Method B: N(Et)₃/CH₂Cl₂ (3a/4a: RT, 1 h; 3b/4b–3d/4d: RT, 24 h; 3f/4f: reflux 3 h and RT, 24 h; 3g/4g–3i/4i: RT, 24 h). Method C: KF/Al₂O₃ (RT, 4 d); ^b crude product; ^c estimated from ¹H NMR spectrum of the crude product; ^d the hydrochloride of *I* was used with 2 equivalents of base; ^e 2 mmol of *I* and 2.5 mmol of 2. ^f 20 mmol of *I* and 23 mmol of 2; ^g 74 % yield when the free base of *I* was used; ^h the potassium salt of *I* was premade; ⁱ the α -bromo ether was used as alkylating agent.

softer part (*N*) for the alkylating agent. Preferential *O*-alkylation also agrees with the empirical rule which states that the more electronegative atom is preferentially alkylated when the anion is "free".^{1a} When triethylamine was used as the base for the pyrimidinone in DMF, the *O*:*N*-alkylated isomer was ca. 1:1.

The α -haloalkyl ethers are reactive alkylating agents. Less polar solvents can therefore be used in the reaction provided the reactants can be solubilized. The pyrimidinones *I* constitute a solubility problem. Quaternary alkylammonium salts are popular for solvation of substances of low solubility in solvents with low polarity.⁵ We find that addition of triethylamine to 5-chloropyrimidin-2-one in dichloromethane results in full dissolution. The solubility of the ion pair⁶ between triethylamine and the 5-chloro-, the 5-bromo- and the 5-iodo-2-pyrimidinone decreased with increase in the size of the halogen but the solubility is sufficient in all cases for the alkylation to be carried out (Method B). The more basic secondary alkylamines are known to react slowly with dichloromethane and even tertiary amines of low steric hindrance such as trimethylamine are attacked.^{7,8}

The main product from the reaction is the *N*-alkylated isomer (Table 1); the ammonium nitrogen is apparently closer associated with the *O*-atom of the ambident system in dichloromethane than in DMF thereby favouring *N*-alkylation. It should also be pointed out, however, that anionic oxygen nucleophiles in dichloromethane have been reported to possess low nucleophilicity.⁹ When 3 or 4 was stirred together with α -haloalkyl ether in dichloromethane at room temperature for 2 days simulating the reaction condition for the formation of the former, no transalkylation was observed showing that the product isomer ratios result from kinetic control.

Organic synthesis using reagents adsorbed on insoluble inorganic supports is gaining importance;¹⁰ thus alumina has been used to promote the hydrogen-bond assisted reactions of potassium fluoride,^{11,12} and it has been claimed that this system is an effective reagent in selective *N*-alkylations of carboxamides, lactams and other *N*-heterocycles.¹² This reagent in 1,2-dimethoxyethane (DME) (Method C) applied to the pyrimidinones *I*, however, resulted in partial *O*-alkylation, the *N*:*O*-alkyl isomer ratio being similar to



Scheme 2.

that of Method B but the reaction was slow and the yields were inferior.

The silyl variant of the Hilbert-Johnson method, as used in the synthesis of pyrimidine nucleosides,¹³ has been applied to simple alkylations of uracils.¹⁴ Adapted for the pyrimidinones 1 the silyl ethers 5 were readily prepared using hexamethyldisilazane (HMDS). The alkylation in refluxing dichloromethane was slow resulting in low yield; better yields were obtained when the reactants were heated together at 120 °C in the absence of a solvent (Scheme 2). Only the *N*-alkylated isomers were obtained. The low reactivity is attributed to low nucleophilicity of the nuclear nitrogens. Nucleophilicity and basicity are interrelated, and it has been shown that the reactivity of heteroaromatic *O*-trimethylsilyl lactims decreases with decreasing pK_a values of the corresponding methoxy lactims.¹⁵ The pK_a value -0.77 for 5-bromo-2-methoxypyrimidine¹⁶ therefore explains why the silyl ethers 5 react sluggishly. On the other hand, Table 2 shows that the yield in the alkylation increases with increase in the size of the 5-halogen which we attribute to a gradual decrease in the electronegativity which results in an increase in the pK_a of the molecule.

For the preparative synthesis of *N*-alkylated pyrimidinones Method B is favoured because of good yields; the *N*- and *O*-alkyl isomers are readily separated since the *O*-alkyl isomer is less polar than the *N*-isomer which allows for selective solvent extraction, or separation by fractional crystallization or chromatography.

EXPERIMENTAL

The mass spectra are reported as MS [70 eV; (% rel. int.)].

5-Iodopyrimidin-2-one 1c as potassium salt. An aqueous solution of iodine monochloride stabilized with sodium chloride (3.67 M, 8.30 ml, 30 mmol) was added to 2-pyrimidinone hydrochloride (3.30 g, 25 mmol) in water (20 ml). The mixture was heated at 60 °C for 1 h, cooled and kept in the refrigerator overnight. The solid material was collected, washed with water, acetone and ether before dissolving in warm 5 M potassium hydroxide (15 ml). The title compound precipitated on cooling and was washed with a little cold ethanol and ether; yield 2.30 g (35 %). Anal. $C_4H_2IN_2KO$: C, H.

α -Halo ethers 2b–2f were prepared as recently described.¹⁷

2-Bromo-2-(4-chlorophenoxy)-1-phenylethanone 2g. A mixture of 2-(4-chlorophenoxy)-1-phenylethanone¹⁸ (4.2 g, 17 mmol) and *N*-bromosuccinimide (4.0 g, 22 mmol) with a catalytic amount of α,α' -azoisobutyronitrile in tetrachloromethane (50 ml) were heated under reflux for 3 h. The mixture was filtered and the solid washed with tetrachloromethane and ether. The filtrate was evaporated and the residue recrystallized from light petroleum; yield 2.6 g (47 %), m.p. 120 °C. 1H NMR ($CDCl_3$): δ 6.9–7.7 (m, 8 H) 8.0–8.3 (m, 2 H).

Formation of 3 and 4 by alkylation of 1.
Method A. Potassium *t*-butoxide (2.0 mmol) in dry DMF (5 ml) was added to a solution of 5-halopyrimidin-2-one (2.0 mmol) in dry DMF (20 ml). The mixture was stirred at room temperature for 10 min before the α -halo ether (2.0

Table 2. Alkylations of 5-halo-2-trimethylsilyloxy pyrimidines using α -chloroalkyl ethers.

	X	Ar	mmol 5	mmol 2	Time (min)	Yield (%)
3c	Cl	4-MeC ₆ H ₄	3.0	2.5	15	48
3d	Cl	4-ClC ₆ H ₄	4.2	3.8	60	27
3e	Br	4-ClC ₆ H ₄	6.7	6.0	30	37
3f	I	4-ClC ₆ H ₄	2.3	2.3	15	60

mmol) was added. The resultant mixture was stirred at room temperature or at 60 °C (time given in Table 1) before the solvent was removed at reduced pressure. The residue was triturated with water, extracted into chloroform, washed with water (5 x), dried (MgSO₄) and evaporated. The residual product was a mixture of the *N*- and *O*-alkylated isomer. For analysis the isomers were separated by their different solubility in ether, the *O*-isomer being the more soluble. The *N*-isomer was recrystallized and the *O*-isomer purified on a silica column (chloroform).

Method B. Triethylamine (10 mmol) was added to a suspension of the 5-halopyrimidin-2-one (10 mmol) in dry dichloromethane (50 ml). The mixture was stirred for 10 min at room temperature before the α -halo ether (10 mmol) in dry dichloromethane (15 ml) was added dropwise over 10 min. The mixture was stirred at room temperature for 24 h before the solvent was distilled off. The residue was washed with water, extracted into chloroform and worked up as above.

Method C. A mixture of the 5-halopyrimidin-2-one (2.0 mmol), the α -halo ether (2.5 mmol) and KF·Al₂O₃ (Type B)¹¹ (6.0 mmol) was stirred together in dry 1,2-dimethoxyethane (20 ml) for 4 days before chloroform (60 ml) was added and the mixture filtered, washed with water and worked up as above.

Formation of 3 by alkylation of 5. The 5-halo-2-trimethylsilyloxy pyrimidine 5 and the α -chloro ether 2 were heated together at 120 °C (time given in Table 2). Chloroform was added and the mixture heated under reflux for 30 min. The cooled solution was filtered and evaporated. The residue was extracted into chloroform, filtered, evaporated and recrystallized.

Physical data for the compounds 3 and 4 are as follows:

5-Chloro-1-(ethoxy)methylpyrimidin-2-one 3a. M.p. 89 °C (ether). Anal. C₉H₇ClN₂O₂: C, H. ¹H NMR (CDCl₃): δ 1.15 and 3.67 (Et), 5.30 (-CH₂O-), 8.22 and 8.53 (H-4 and H-6, respectively, *J* 3 Hz). IR (KBr): 1680 cm⁻¹ (CO). MS: 188 (1, M), 146 (15), 144 (45), 131 (13), 130 (11), 116 (12), 102 (19), 59 (100).

5-Chloro-2-(ethoxy)methoxy pyrimidin-2-one 4a. Oil. ¹H NMR (CDCl₃): δ 1.22 and 3.80 (Et), 5.55 (-CH₂O-), 8.42 (H-4 and H-6).

5-Chloro-1-(phenoxy)methylpyrimidin-2-one 3b. M.p. 146 °C. (Chrom.) Anal. C₁₁H₉ClN₂O₂: C, H. ¹H NMR (CDCl₃): δ 5.92 (CH₂), 6.8–7.4 (Ph), 7.80 and 8.43 (H-4 and H-6, respectively, *J* 3 Hz). IR (KBr): 1660 cm⁻¹ (CO). MS: 236 (7, M), 145 (32), 143 (100), 116 (31), 94 (6), 77 (18).

5-Chloro-1-(4-tolylloxy)methylpyrimidin-2-one 3c. M.p. 186 °C (acetone). Anal. C₁₂H₁₁ClN₂O₂:

C, H. ¹H NMR (CDCl₃): δ 2.25 (Me), 5.74 (CH₂), 6.8–7.3 (Ph), 7.80 and 8.50 (H-4 and H-6, respectively, *J* 3 Hz). IR (KBr): 1680 cm⁻¹ (CO). MS: 250 (7, M), 145 (31), 143 (100) 116 (28).

5-Chloro-2-(4-tolylloxy)methoxy pyrimidine 4c. M.p. 72 °C (MeOH). Anal. C₁₂H₁₁ClN₂O₂: C, H. ¹H NMR (CDCl₃): δ 2.25 (Me), 6.00 (CH₂), 6.8–7.3 (Ph), 8.45 (H-4 and H-6). IR (KBr): 1560 cm⁻¹ (pyrimidine). MS: 250 (15, M), 145 (31), 143 (100), 121 (15), 116 (23).

5-Chloro-1-(4-chlorophenoxy)methylpyrimidin-2-one 3d. M.p. 163 °C (CHCl₃/light petroleum). Anal. C₁₁H₈Cl₂N₂O₂: C, H. ¹H NMR (DMSO-*d*₆): δ 5.78 (CH₂), 7.0–7.4 (Ph), 8.64 and 8.71 (H-4 and H-6, respectively, *J* 4 Hz). IR (KBr): 1670 cm⁻¹ (CO). MS: 274/272/270 (1/6/9, M), 145 (62), 113 (100).

5-Chloro-2-(4-chlorophenoxy)methoxy pyrimidine 4d. M.p. 91 °C (MeOH). Anal. C₁₁H₈Cl₂N₂O₂: C, H. ¹H NMR (CDCl₃): δ 6.00 (CH₂), 6.9–7.3 (Ph), 8.45 (H-4 and H-6). IR (KBr): 1560 cm⁻¹ (pyrimidine). MS: 274/272/270 (1/6/10, M), 145 (36), 143 (100).

5-Bromo-1-(4-chlorophenoxy)methylpyrimidin-2-one 3e. M.p. 200 °C (acetone). Anal. C₁₁H₈BrClN₂O₂: C, H. ¹H NMR (DMSO-*d*₆, CDCl₃): δ 5.81 (CH₂), 7.0–7.3 (Ph), 8.49 and 8.60 (H-4 and H-6, respectively, *J* 3 Hz). IR (KBr): 1660 cm⁻¹ (CO). MS: 316/314 (6/5, M), 189 (96), 187 (100), 162 (16), 160 (17).

5-Bromo-2-(4-chlorophenoxy)methoxy pyrimidine 4e. M.p. 102 °C (MeOH). Anal. C₁₁H₈BrClN₂O₂: C, H. ¹H NMR (CDCl₃): δ 6.00 (CH₂), 6.9–7.4 (Ph), 8.52 (H-4 and H-6). IR (KBr): 1570 and 1560 cm⁻¹ (pyrimidine). MS: 316/314 (14/13, M), 189 (90), 187 (100), 162 (16), 160 (20).

1-(4-Chlorophenoxy)methyl-5-iodopyrimidin-2-one 3f. M.p. 216 °C (EtOAc). Anal. C₁₁H₈ClIN₂O₂: C, H. ¹H NMR (DMSO-*d*₆/CDCl₃): δ 5.85 (CH₂), 6.9–7.5 (Ph), 8.68 and 8.82 (H-4 and H-6, respectively, *J* 3 Hz). IR (KBr): 1650 cm⁻¹ (CO). MS: 362 (37, M), 235 (100), 222 (6), 108 (22).

2-(4-Chlorophenoxy)methoxy-5-iodopyrimidine 4f. M.p. 106 °C (MeOH). Anal. C₁₁H₈ClIN₂O₂: C, H. ¹H NMR (CDCl₃): δ 6.00 (CH₂), 6.9–7.3 (Ph), 8.70 (H-4 and H-6). MS: 362 (16, M), 235 (100), 205 (20), 108 (70).

5-Chloro-1-(2-naphthylloxy)methylpyrimidin-2-one 3g. M.p. 168 °C (acetone). Anal. C₁₅H₁₁ClN₂O₂: C, H. ¹H NMR (CDCl₃): δ 5.82 (CH₂), 7.0–7.9 (naphthyl and H-6), 8.45 (H-4, *J* 3 Hz). IR (KBr): 1660 cm⁻¹ (CO). MS: 288/286 (5/15, M), 145 (32), 143 (100), 116 (22), 115 (16).

5-Chloro-2-(2-naphthylloxy)methoxy pyrimidine 4g. M.p. 81 °C (MeOH). Anal. C₁₅H₁₁ClN₂O₂:

C, H. $^1\text{H NMR}$ (CDCl_3): δ 6.11 (CH_2), 7.0–7.7 (naphtyl), 8.40 (H-4 and H-6). MS: 288/286 (13/40, M), 157 (15), 156 (22), 145 (32), 144 (13), 143 (100), 127 (46).

5-Chloro-1-(1-phenoxy)ethylpyrimidin-2-one 3h. M.p. 92°C (CH_2Cl_2 /light petroleum). Anal. $\text{C}_{12}\text{H}_{11}\text{ClN}_2\text{O}_2$: C, H. $^1\text{H NMR}$ (CDCl_3): δ 1.72 (CH_3 , J 5 Hz), 6.4–7.3 (Ph and CH), 7.79 and 8.40, (H-4 and H-6, respectively, J 3 Hz). IR (KBr): 1665 cm^{-1} (CO). MS: 250 (1, M), 159 (30), 157 (100), 121 (23), 77 (30), 65 (17).

5-Chloro-2-(1-phenoxy)ethoxypyrimidine 4h. Oil. $^1\text{H NMR}$ (CDCl_3): δ 1.72 (CH_3 , J 5 Hz), 6.5–7.4 (Ph and CH); 8.41 (H-4 and H-6). MS: 250 (4, M), 159 (33), 157 (100), 131 (63), 121 (65), 94 (72), 77 (90).

1-[Benzoyl(4-chlorophenoxy)]methyl-5-chloropyrimidin-2-one 3i. M.p. 144°C (CCl_4). Anal. $\text{C}_{18}\text{H}_{12}\text{Cl}_2\text{O}_3\text{N}_2$: C, H. $^1\text{H NMR}$ (CDCl_3): 6.8–8.0 (11 H), 8.51 (H-6, J 3 Hz). IR (KBr): 1710 and 1665 cm^{-1} (CO). MS: 374 (14, M), 269 (15), 247 (22), 201 (22), 199 (70), 105 (100).

2-[Benzoyl(4-chlorophenoxy)]methoxy-5-chloropyrimidine 4i. M.p. 116°C . Anal. $\text{C}_{18}\text{H}_{12}\text{Cl}_2\text{O}_3\text{N}_2$: C, H. $^1\text{H NMR}$ (CDCl_3): 6.9–8.2 (10 H), 8.37 (H-4 and H-6). MS: 374 (2, M), 271 (65), 269 (100), 199 (15), 116 (30), 105 (53), 77 (47).

5-Halo-2-trimethylsilyloxyypyrimidines 5 were made using hexamethyldisilazane. ^{13}C 5-Chloro-2-trimethylsilyloxyypyrimidine; yield 83 %, b.p. $90^\circ\text{C}/8\text{--}9\text{ mmHg}$. 5-Bromo-2-trimethylsilyloxyypyrimidine; yield 61 %, b.p. $62^\circ\text{C}/0.01\text{ mmHg}$. 5-Iodo-2-trimethylsilyloxyypyrimidine; yield 77 %, b.p. $65\text{--}69^\circ\text{C}/0.01\text{ mmHg}$.

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