Regioselectivity in the Alkylation of Ambident 2-Pyrimidinone Anions

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Selectivity in the alkylation of ambident anions is influenced by a number of factors such as the alkylating agent, the leaving group, the temperature, the counter-ion and the solvent.[1] We have previously shown that selective *N*-alkylation of ambident anions of 2-pyrimidinones can be achieved with hard electrophiles like α-halo ethers using *O*-stannylated or *O*-silylated pyrimidines.[2] We herein report high selectivity for *O*-alkylation of 2-pyrimidinones with hard electrophiles using cesium carbonate as the base in dimethylformamide (DMF).

The utility of cesium carbonate as a base in several alkylation reactions has been documented in the literature.[3] The selectivity in alkylations of ambident anions using cesium carbonate has, however, only briefly been mentioned.[4] In the alkylation of cytosine, the use of cesium carbonate gives more *N*-alkylation versus *O*-alkylation than does potassium carbonate.[4] This is the opposite of our findings for 5-halo-2-pyrimidinones (Table 1; entries 8 and 9, 12 and 15).

We find that reducing the hardness of the electrophile leads to increased alkylation of the softer part of the ambident anion, i.e., the N-atom (Table 1, compare entries 1, 17 and 18). The same effect is observed when the steric bulk close to the electrophilic carbon in the alkylating agent is reduced (Table 1, compare entries 1, 5 and 14). The importance of steric effects in the alkylation of 2-pyrimidinones has been pointed out.[5] The way the electrophile is introduced is also important. Rapid addition of neat electrophile (Method B) gives significantly more *N*-alkylated isomer than does the slow addition of the electrophile in solution (Method A; Table 1, compare entries 3 and 4, 9 and 10, 14 and 15). [Separate experiments indicate that the solvent (DMF) does *not* react with the electrophiles]. The halogen substituent in the pyrimidine ring, does not seem to influence the yield or the product distribution to any significant extent (Table 1, compare entries 15 and 16).

We have also compared cesium carbonate with other carbonates of the alkali metals, i.e. sodium, potassium and rubidium carbonate. Lithium carbonate is not included because it gave low yields (< 10 %) in the alkylation reactions. A significant difference between cesium carbonate and the other carbonates is observed (Table 1). The difference is, as indicated above, more pronounced when a solution of the electrophile is slowly added to the nucleophile than after rapid addition of the neat electrophile. A minor temperature effect was observed in the alkylation of **1b** with chloromethoxybenzene (**2a**) using sodium carbonate: at 60 °C the *O*:*N*-ratio was 60:40 whereas at 0 °C it was 57:43. In the corresponding reaction using cesium carbonate, no temperature effect was observed.

An effect of the different cations on the product distribution is clearly observed, which indicates that the anion is not completely free. The effect of the cesium cation can be explained by its large polarizability[6] hence soft character. The softer the cation the more closely it is associated with the softer part of the ambident anion, i.e., the N-atom, leaving the oxygen atom free to be alkylated.

Experimental

Mass spectra were recorded under electron impact conditions at 70 eV (EI). Isobutane or ammonia was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.). The ^{1}H NMR spectra were recorded at 200 MHz or 300 MHz and the ^{13}C NMR spectra at 50 MHz or 75 MHz. DMF was distilled from BaO.

Compounds available by literature methods. 5-Chloro-2(1*H*)-pyrimidinone (**1a**),[7] 5-bromo-2(1*H*)-pyrimidinone (**1b**),[7] chloromethyl phenyl ether (**2a**),[8a] chloromethyl benzyl ether (**2b**),[8b] allyl chloromethyl ether (**2d**),[8c] 5-chloro-1-phenoxymethyl-2(1*H*)-pyrimidinone (**4a**),[2a] 5-bromo-1-phenoxymethyl-2(1*H*)-pyrimidinone (**4b**),[2b] 1-benzyloxymethyl-5-bromo-2(1*H*)-pyrimidinone (**4c**),[2b] 1-benzyl-5-bromo-2(1*H*)-pyrimidinone (**4i**).[9]

General procedures for the alkylation of 5-halo-2-pyrimidinones **1**. *Method A.* The carbonate (2.5 mmol) was added to a solution of the 5-halo-2(1*H*)-pyrimidinone (2.5 mmol) in dry DMF (15 ml) under N_2. The mixture was heated for

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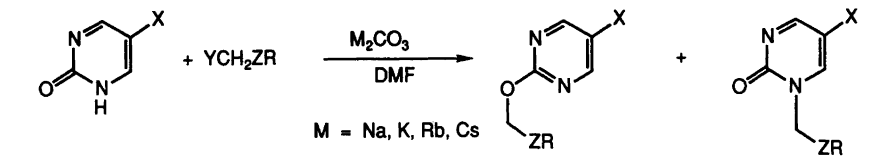

1

1a X = Cl
b X = Br

2

2a	Y = Cl	ZR = OPh
b	Y = Cl	ZR = OCH_2Ph
c	Y = Cl	ZR = OPivaloyl
d	Y = Cl	ZR = OAllyl
e	Y = Cl	ZR = SPh
f	Y = Br	ZR = Ph

3

3/4a	X = Cl	ZR = OPh
b	X = Br	ZR = OPh
c	X = Br	ZR = OCH_2Ph
d	X = Cl	ZR = OPivaloyl
e	X = Br	ZR = OPivaloyl
f	X = Cl	ZR = OAllyl
g	X = Br	ZR = OAllyl
h	X = Br	ZR = SPh
i	X = Br	ZR = Ph

4

Scheme 1.

10 min at 60 °C with vigorous stirring and then slowly cooled to 0 °C before the dropwise addition of the alkyl halide (2.75 mmol) in dry DMF (3 ml). The mixture was stirred at ambient temperature for 4 h before DMF was removed *in vacuo* at 35 °C. Chloroform (150 ml) was added and the mixture was stirred for 15 min before the insoluble salts were removed by filtration. The filtrate was washed with saturated aqueous sodium chloride (3 × 100 ml) and water (2 × 50 ml). The dried ($MgSO_4$) solution was evaporated and the product was purified by flash chromatography on silica gel.

Method B. The carbonate (2.5 mmol) was added to a solution of the 5-halo-2(1*H*)-pyrimidinone (2.5 mmol) in dry DMF (15 ml) under N_2. The mixture was heated for 10 min at 60 °C and then cooled to 0 °C before the neat alkyl halide (2.75 mmol) was added. The mixture was stirred at ambient temperature for 4 h before the DMF was removed at reduced pressure. Chloroform was added, and the solution was washed with saturated aqueous sodium chloride (5 ×). The dried ($MgSO_4$) solution was evaporated, and the product was purified by flash chromatography on silica gel using first hexane–ethyl acetate 6:1 then ethyl acetate for elution.

5-Chloro-2-phenoxymethoxypyrimidine (**3a**). The eluent was chloroform; m.p. 51 °C. Anal. $C_{11}H_9ClN_2O_2$: C, H. ^1H NMR ($CDCl_3$): δ 6.08 (OCH_2O), 7.04 (H-4', t, *J* 7.3 Hz), 7.14 (H-2', d, *J* 8.8 Hz), 7.30 (H-3', q, *J* 8.8 Hz, *J* 7.3 Hz), 8.50 (H-4, H-6, s). ^{13}C NMR ($CDCl_3$): δ 89.0 (OCH_2O), 116.4 (C-2'), 122.8 (C-4'), 125.3 (C-5), 129.6 (C-3'), 157.0 (C-1'), 157.7 (C-4, C-6), 162.2 (C-2). MS(EI):

Table 1. Alkylation of alkali-metal salts of 2-pyrimidinones **1**.

					Method A[a]		Method B[b]	
Entry	M	X	ZR	Yield[c] (%)	**3**[d] (%)	**4**[d] (%)	**3**[d] (%)	**4**[d] (%)
1	Cs	Cl	OPh	67–74	100	–[e,f]		
2	Na	Br	OPh	80	57	43		
3	Cs	Br	OPh	69–70	100	–[e,f]		
4	Cs	Br	OPh	80			67	33
5	Cs	Br	OCH_2Ph	67	88	12		
6	Cs	Cl	OPivaloyl	49[g]	95	5		
7	Na	Br	OPivaloyl	40–45[g]	48–50	50–52		
8	K	Br	OPivaloyl	64[g]	75	25		
9	Cs	Br	OPivaloyl	48–52[g]	100	–[e,f]		
10	Cs	Br	OPivaloyl	55[g]			74	26
11	Na	Cl	OAllyl	90			53	47
12	K	Cl	OAllyl	82			59	41
13	Rb	Cl	OAllyl	95			59	41
14	Cs	Cl	OAllyl	76	82	18		
15	Cs	Cl	OAllyl	76–83			70–71	29–30
16	Cs	Br	OAllyl	85–92			65–68	32–35
17	Cs	Br	SPh	58[f]	40	60		
18	Cs	Br	Ph	60[f]	–[e]	100		

[a] Slow addition of the electrophile in solution. [b] Rapid addition of the neat electrophile. [c] Isolated. [d] Relative yield estimated from the ^1H NMR spectra of the crude product. [e] The isomer could not be observed by ^1H NMR spectroscopy. [f] Several experiments. [g] The reaction was not complete.

238/236 (2/8, *M*), 207 (4), 145/143 (24/85), 118/116 (11/34), 116/114 (34/5), 107 (16), 77 (100).

5-Bromo-2-phenoxymethoxypyrimidine (**3b**). The eluent was chloroform; m.p. 52 °C. Anal. $C_{11}H_9BrN_2O_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 6.07 (OCH_2O), 7.04 (H-4′, t, *J* 7.3 Hz), 7.14 (H-2′, d, *J* 8.8 Hz), 7.30 (H-3′, q, *J* 8.8 Hz, *J* 7.3 Hz), 8.58 (H-4, H-6, s). ^{13}C NMR ($CDCl_3$): δ 88.9 (OCH_2O), 113.2 (C-5), 116.4 (C-2′), 122.8 (C-4′), 129.6 (C-3′), 157.0 (C-1′), 159.8 (C-4, C-6), 162.5 (C-2). MS(EI): 282/280 (13/14, *M*), 254/252 (2/2), 189/187 (97/100), 162/160 (16/19), 159/157 (13/13), 148/146 (1/1), 107 (34), 77 (93).

2-Benzyloxymethoxy-5-bromopyrimidine (**3c**). The eluent was ethyl acetate–hexane 3:2; m.p. 52 °C. Anal. $C_{12}H_{11}BrN_2O_2$. ^{1}H NMR ($CDCl_3$): δ 4.80 (CH_2Ph, s), 5.63 (OCH_2O), 7.3–7.4 (Ph, m), 8.56 (H-4, H-6, s). ^{13}C NMR ($CDCl_3$): δ 71.5 (CH_2Ph), 91.3 (OCH_2O), 112.6 (C-5), 127.9, 128.0, 128.5 (Ph), 137.0 (C-1′), 159.8 (C-4, C-6), 163.1 (C-2). MS(CI): 297/295 (98/100, *M* + 1), 268/266 (2/4), 267/265 (11/11), 194/192 (4/4), 190/188 (8/8), 177/175 (7/7), 108 (10), 91 (21).

5-Chloro-2-pivaloyloxymethoxypyrimidine (**3d**). The eluent was chloroform; white waxy substance; m.p. 39–40 °C. Anal. $C_{10}H_{13}ClN_2O_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.15 (3 × CH_3, s), 6.04 (OCH_2O), 8.46 (H-4, H-6, s). ^{13}C NMR ($CDCl_3$): δ 28.3 (3 × CH_3), 40.1 [$C(CH_3)_3$], 84.0 (OCH_2O), 125.8 (C-5), 157.5 (C-4, C-6), 161.9 (C-2), 176.7 (C=O).

5-Bromo-2-pivaloyloxymethoxypyrimidine (**3e**). The eluent was chloroform; white waxy substance; m.p. 49 °C. Anal. $C_{10}H_{13}BrN_2O_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.21 (3 × CH_3, s), 6.09 (OCH_2O), 8.59 (H-4, H-6, s). ^{13}C NMR ($CDCl_3$): δ 27.0 (3 × CH_3), 38.9 [$C(CH_3)_3$], 83.3 (OCH_2O), 113.7 (C-5), 160.3 (C-4, C-6), 162.8 (C-2), 177.6 (C=O). MS(EI): 290/288 (1/1, *M*), 260/258 (3/4), 245/243 (1/1), 189/187 (3/3), 177/175 (10/12), 162/160 (1/1), 159/157 (3/2), 57 (100).

5-Chloro-2-propenyloxymethoxypyrimidine (**3f**). Oily substance. Anal. $C_8H_9ClN_2O_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 4.28 (OCH_2, d, *J* 6 Hz), 5.19–5.35 (CH_2=, m), 5.61 (OCH_2O), 5.85–5.99 (CH=, m), 8.49 (H-4, H-6, s). ^{13}C NMR ($CDCl_3$): δ 70.4 (CH_2O), 91.0 (OCH_2O), 117.8 (CH_2=), 124.5 (C-5), 133.3 (CH=), 157.4 (C-4, C-6), 162.3 (C-2). MS(EI): 202/200 (0.1/0.4, *M*), 171 (11), 169 (35), 146 (26), 144 (79), 131 (11), 114 (28), 41 (100).

5-Bromo-2-propenyloxymethoxypyrimidine (**3g**). Oily substance. Anal. $C_8H_9BrN_2O_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 4.25 (OCH_2, d, *J* 6 Hz), 5.15–5.32 (CH_2=, m), 5.57 (OCH_2O), 5.78–5.96 (CH=, m), 8.53 (H-4, H-6, s). ^{13}C NMR ($CDCl_3$): δ 71.4 (CH_2O), 91.9 (OCH_2O), 113.1 (C-5), 118.4 (CH_2=), 133.8 (CH=), 159.8 (C-4, C-6), 162.9 (C-2). MS(CI): 247/245 (51/55, *M* + 1), 217 (59), 215 (65), 190 (38), 188 (39), 177 (57), 175 (58), 71 (100).

5-Bromo-2-phenylthiomethoxypyrimidine (**3h**). The eluent was dichloromethane; white waxy substance; m.p. 25 °C. Anal. $C_{11}H_9BrN_2OS$. ^{1}H NMR ($CDCl_3$): δ 5.76 (OCH_2S), 7.2–7.6 (Ph, m), 8.56 (H-4, H-6, s). ^{13}C NMR ($CDCl_3$): δ 72.8 (OCH_2S), 113.1 (C-5), 127.7, 129.4, 131.0 (SPh), 135.3 (C-1′), 160.1 (C-4, C-6), 163.1 (C-2). MS(EI): 298/296 (9/9, *M*), 189/187 (68/70), 177/175 (16/17), 162/160 (13/16), 134/132 (5/5), 123 (100), 122 (40), 109 (26).

5-Chloro-1-pivaloyloxymethyl-2(1H)-pyrimidinone (**4d**). M.p. 162 °C (CCl_4). ^{1}H NMR (acetone-d_6): δ 1.20 (3 × CH_3, s), 5.78 (NCH_2O), 8.30 (H-6, d, *J* 3 Hz), 8.57 (H-4, d, *J* 3 Hz). MS(EI): 244 (5, *M*), 143 (11), 131 (28), 85 (20), 57 (100).

5-Bromo-1-pivaloyloxymethyl-2(1H)-pyrimidinone (**4e**). M.p. 181 °C (EtOAc). Anal. $C_{10}H_{13}BrN_2O_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.22 (3 × CH_3, s), 5.78 (NCH_2O), 8.06 (H-6, d, *J* 3 Hz), 8.61 (H-4, d, *J* 3 Hz). ^{13}C NMR ($CDCl_3$): δ 26.9 (3 × CH_3), 39.0 [$C(CH_3)_3$], 72.2 (NCH_2O), 96.8 (C-5), 147.4 (C-6), 153.7 (C-2), 168.3 (C-4), 178.6 (C=O). MS(EI): 290/288 (4/4, *M*), 260/258 (4/4), 189/187 (6/6), 177/175 (18/18), 162/160 (2/3), 120/118 (2/2), 85 (24), 57 (100).

5-Bromo-1-propenyloxymethyl-2(1H)-pyrimidinone (**4g**). M.p. 110 °C. Anal. $C_8H_9BrN_2O_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 4.14 (OCH_2, d, *J* 6 Hz), 5.22–5.36 (CH_2=, m), 5.31 (NCH_2O), 5.77–5.93 (CH=, m), 7.93 (H-6, d, *J* 3.3 Hz), 8.56 (H-4, d, *J* 3.3 Hz). ^{13}C NMR ($CDCl_3$): δ 72.2 (OCH_2), 79.3 (NCH_2O), 97.8 (C-5), 119.3 (CH_2=), 133.0 (CH=), 145.5 (C-6), 154.4 (C-2), 167.4 (C-4). MS(CI): 247/245 (83/88, *M* + 1), 217 (62), 215 (68), 190 (31), 189 (21), 188 (36), 187 (17), 71 (100).

5-Bromo-1-phenylthiomethyl-2(1H)-pyrimidinone (**4h**). M.p. 189 °C (EtOAc). Anal. $C_{11}H_9BrN_2OS$. ^{1}H NMR ($C_2D_2Cl_4$): δ 5.12 (NCH_2S, s), 7.34 (H-6, d, *J* 3 Hz), 7.3–7.5 (Ph, m), 8.51 (H-4, d, *J* 3 Hz). ^{13}C NMR ($C_2D_2Cl_4$): δ 55.8 (NCH_2S), 96.5 (C-5), 129.3, 129.7 (C-3′, C-4′), 130.7 (C-1′), 133.4 (C-2′), 145.7 (C-6), 153.3 (C-2), 166.7 (C-4). MS(EI): 298/296 (12/12, *M*), 189/187 (98/100), 177/175 (15/16), 162/160 (17/18), 160/158 (18/2), 123 (36), 122 (40), 109 (27).

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