2-Stannyloxypyrimidines in Regioselective Alkylation Reactions

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2(1*H*)-Pyrimidinones are readily *O*-stannylated by reaction with bis(tributyltin) oxide. The stannylated products are converted into 1-alkyl-2(1*H*)-pyrimidinones on treatment with alkylating agents. With palladium(0) catalysis, allyl acetate becomes a specific *N*-alkylating agent.

Alkylation of 5-halo- and 5-phenylsulfenyl-2-(1*H*)-pyrimidinones under basic conditions with α-halo ethers and α-halo sulfides, which are relatively hard electrophiles, gives in most cases a mixture of the *O*- and *N*-alkylated isomers.[1–3] When the physical characteristics of the isomers are dominated by strong lipophilic or hydrophilic properties of the side-chain, chromatographic separations may be difficult to achieve. It was therefore desirable to develop methods for the preparation of each isomer. We report a specific synthesis of the *N*-alkylated isomers, which are of special interest to us since we have found that certain *N*-alkylated 2-pyrimidinones affect the cell-cycle during mitosis and possess reversible metaphase-arresting properties. The *O*-isomers, however, are inactive in this respect.[4]

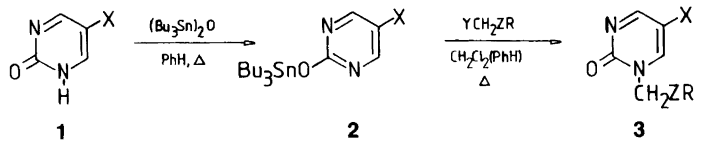
We have previously reported on selective *N*-alkylation using the silyl derivatives 5-halo-2-trimethylsilyloxypyrimidines as intermediates. The yields, however, were only moderate and the reactants had to be heated together at 120 °C without solvent for the reaction to proceed at acceptable rates.[1] We now report that *O*-stannylated 5-halo- and 5-phenylsulfenyl-2(1*H*)-pyrimidinones react readily with α-halo ethers and α-halo sulfides in a specific manner to yield the *N*-alkylated product. It has previously been reported that stannylated uracils can be *N*-alkylated.[5] Frequently, however, we find that 2(1*H*)-pyrimidinones and the corresponding uracils differ in chemical properties because the 4-hydroxy group in uracils makes the latter more nucleophilic than 2(1*H*)-pyrimidinones. In the present comparison it is pointed out that stannylated uracils are alkylated at ambient temperature whereas heating is required for the alkylation of the corresponding 2(1*H*)-pyrimidinones.

The stannylation method is especially useful for the alkylation of 5-iodo-2(1*H*)-pyrimidinone (Scheme 1), since the usual alkylation reaction using the NEt_3/CH_2Cl_2-system gives poor yields, and the *t*-BuOK/DMF-system gives the *O*-alkylated isomer as the major product.

From Table 1 it is seen that the nature of the 5-substituent in the pyrimidinone has little influence on the reaction and that dichloromethane and benzene are both useful solvents.

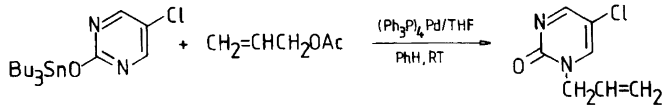
The *O*-stannylated pyrimidinone can be isolated and stored in a normal dry atmosphere for weeks without any significant decomposition, whereas *O*-trimethylsilylated-5-halopyrimidinones have to be handled in an inert atmosphere and should be used shortly after their preparation.

The high reactivity of the *O*-stannylated pyrimidinones is also demonstrated in the reaction of the 5-chloro derivative **2a** with allyl acetate using Pd(0) catalysis; no reaction takes place without the catalyst. To effect the formation of the exocyclic C–N bond in **4** (yield 68 %), the reaction conditions were chosen to be similar to those reported for the selective *C*-alkylation of enol stannanes under the influence of palladium(0) catalysis.[6]



1 **2** **3**

X=Cl, Br, I, SPh Z=O,S



Scheme 1. **2a** **4**

Experimental

The ^{1}H NMR spectra were recorded at 60 MHz. The mass spectra under electron impact conditions were recorded at 70 eV ionizing energy. Isobutane was used for chemical ionizing mass spectra (CI); the spectra are presented as *m/z* (% rel. int.).

Preparation of 2-tributylstannyloxy-5-halo- and 5-phenylsulfenylpyrimidines (**2**). Bis(tributyl)tin oxide (0.5 mmol) was added to a suspension of 5-chloro-,[7] 5-bromo-,[8] 5-iodo-[1] or 5-phenylthio-2-(1*H*)-pyrimidinone[9] (1 mmol) in benzene. The mixture was heated under reflux for 2 h using a Dean-Stark trap. The solvent was evaporated and the product recrystallized from benzene.

2-Tributylstannyloxy-5-chloropyrimidine (**2a**). The yield of **2a** was 72%; m.p. 122°C. Anal. $C_{16}H_{29}ClN_2OSn$: C,H. ^{1}H NMR ($CDCl_3$): δ 0.5–1.9 (3 × Bu), 8.33 (2H, H-4, 6). MS(CI): 423/421 (23/64, *M*+H), 420 (23), 419 (43), 417 (21), 363 (22), 361 (15), 291 (55), 289 (42), 287 (24), 133 (65), 131 (100).

2-Tributylstannyloxy-5-bromopyrimidine (**2b**).

Table 1. Alkylations of 2-tributylstannyloxypyrimidines.

Product	X	Y	Z	R	Solvent[a]	Reflux time/h	Yield/%
3a	Cl	Cl	O	CH_2Ph	A	3	64
					B	12[b]/1	64
3b	Br	Cl	O	CH_2Ph	B	3	85
3c	I	Cl	O	CH_2Ph	A	3	67
					B	12[b]/1	70
3d	SPh	Cl	O	CH_2Ph	A	4	58
					B	6	55
3e	Br	Cl	O	Ph	B	6	51
					B	48	58
3f	I	Cl	O	Ph	B	3	55
3g	SPh	Cl	O	Ph	B	12	58
3h	Br	Br	S	C_6H_4-Cl-*p*	B	12	80
3i	I	Br	S	Ph	B	6	68
3j	SPh	Br	S	C_6H_4-Cl-*p*	B	12	72

[a]A = Benzene, B = dichloromethane. [b]At ambient temperature.

The yield of **2b** was 81 %; m.p. 126 °C. Anal. $C_{16}H_{29}BrN_2OSn$: C,H. ^1H NMR ($CDCl_3$): δ 0.7–1.8 (3 × Bu), 8.33 (2H, H-4, 6). MS(CI): 467/465 (62/95, *M*+H), 464 (38), 462 (17), 463 (65), 461 (24), 409 (23), 407 (37), 405 (23), 291 (100), 290 (34), 289 (75), 288 (27), 287 (43), 177/175 (44/49).

2-Tributylstannyloxy-5-iodopyrimidine (**2c**). The yield of **2c** was 72 %; m.p. 129 °C. Anal. $C_{16}H_{29}IN_2OSn$: C,H. ^1H NMR ($CDCl_3$): δ 0.6–2.0 (3 × Bu), 8.43 (2H, H-4, 6). MS(CI) 513 (12, *M*+H), 511 (10), 361 (11), 295 (10), 291 (61), 290 (20), 289 (44), 288 (18), 287 (28), 233 (100), 97 (98).

2-Tributylstannyloxy-5-phenylsulfenylpyrimidine (**2d**). The yield of **2d** was 68 %; m.p. 128 °C. Anal. $C_{22}H_{34}N_2OSSn$: C,H. ^1H NMR ($CDCl_3$): δ 0.6–1.8 (3 × Bu), 7.26 (S–Ph), 8.36 (2H, H-4, 6). MS(CI): 495 (100, *M*+H), 493 (75),, 492 (30), 491 (40), 437 (37), 436 (14), 435 (26), 433 (14), 281 (33), 290 (11), 289 (24), 288 (9), 287 (14), 205 (37).

Preparation of 1-substituted 5-halo- and 5-phenylsulfenyl-2(1H)-pyrimidinones (**3**) *without isolation of* **2**. The reaction mixture containing the 2-tributylstannyloxy-5-halo- or -5-phenylsulfenylpyrimidine (**2**), prepared as described above, was either treated with the alkylating agent (1 mmol) directly, or the solvent was distilled off and the residue redissolved in dichloromethane (25 ml) before addition of the alkylating agent. The mixture was then stirred at ambient temperature or heated under reflux as given in Table 1. The solvent was evaporated and the residue triturated with hexane and cold diethyl ether. Normally, the product which remained was the pure compound **3**. If TLC showed the presence of unreacted 2(1*H*)-pyrimidinone, the latter was removed by dissolving the residue in dichloromethane and extracting this solution with 1 M NaOH. The organic solution was then washed with aq. NaCl and the dried ($MgSO_4$) solution evaporated.

When the intermediate 2-tributylstannyloxypyrimidine was isolated and later alkylated, the conditions were chosen as described for the alkylation in the direct process.

1-Benzyloxymethyl-5-chloro-2(1H)-pyrimidinone (**3a**). M.p. 122 °C (EtOAc). Anal. $C_{12}H_{11}ClN_2O_2$: C,H. ^1H NMR ($CDCl_3$): δ 4.71 (CH_2Ph), 5.42 (CH_2N), 7.4 (Ph), 7.74 (H-6, d, J = 3 Hz), 8.53 (H-4, d, J = 3 Hz). MS(CI): 251/249 (11/7, *M*+H), 223 (17), 221 (53), 144 (7), 91 (100).

1-Benzyloxymethyl-5-bromo-2(1H)-pyrimidinone (**3b**). M.p. 134 °C. Anal. $C_{12}H_{11}BrN_2O_2$: C,H. ^1H NMR ($CDCl_3$): δ 4.55 (CH_2Ph), 5.25 (CH_2N), 7.1–7.2 (Ph), 7.74 (H-6, d, J = 3 Hz), 8.42 (H-4, d, J = 3 Hz). MS(CI): 297/295 (98/100, *M*+H), 267/265 (75/78), 217 (14), 190/188 (17/18), 91 (61).

1-Benzyloxymethyl-5-iodo-2(1H)-pyrimidinone (**3c**). M.p. 182 °C. Anal. $C_{12}H_{11}IN_2O_2$: C,H. ^1H NMR (DMSO-d_6/$CDCl_3$): δ4.75 (CH_2Ph), 5.42 (CH_2N), 7.43 (Ph), 8.43 (H-6, d, J = 3 Hz), 8.68 (H-4, d, J = 3Hz). MS(CI): 343 (100, *M*+H), 314 (8), 313 (16), 235 (20), 217 (7), 187 (3), 91 (35).

1-Benzyloxymethyl-5-phenylsulfenyl-2(1H)-pyrimidinone (**3d**). M.p. 132 °C. (EtOAc). Anal. $C_{18}H_{16}N_2O_2S$: C,H. ^1H NMR ($CDCl_3$): δ 4.70 (CH_2Ph), 5.24 (CH_2N), 7.2–7.5 (2 × Ph), 8.00 (H-6, d, J = 3 Hz), 8.63 (H-4, d, J = 3 Hz). MS: 324 (3, *M*), 252 (12), 251 (15), 218 (32), 91 (100).

5-Bromo-1-phenoxymethyl-2(1H)-pyrimidinone (**3e**). M.p. 158 °C. Anal. $C_{11}H_9BrN_2O_2$: C,H. ^1H NMR ($CDCl_3$): δ 5.86 (CH_2N), 6.8–7.5 (Ph), 7.98 (H-6, d, J = 3 Hz), 8.61 (H-4, d, J = 3 Hz). MS: 282/280 (11/10, *M*), 189/187 (16/18), 162/160 (16/18), 109 (51), 94 (100), 80 (28), 77 (31).

5-Iodo-1-phenoxymethyl-2(1H)-pyrimidinone (**3f**). M.p. 188 °C. Anal. $C_{11}H_9IN_2O_2$: C,H. ^1H NMR ($CDCl_3$): δ 5.89 (CH_2N), 6.9–7.6 (Ph), 8.07 (H-6, d, J = 3 Hz), 8.70 (H-4, d, J = 3 Hz). MS: 328 (17, *M*), 235 (100), 109 (43), 108 (58), 94 (27), 80 (41), 77 (21).

1-Phenoxymethyl-5-phenylsulfenyl-2(1H)-pyrimidinone (**3g**). M.p. 85 °C. Anal. $C_{17}H_{14}N_2O_2S$: C,H. ^1H NMR ($CDCl_3$): δ 5.90 (CH_2N), 6.8–7.6 (2 × Ph), 8.08 (H-6, d, J = 3 Hz), 8.67 (H-4, d, J = 3 Hz). MS: 310 (43, *M*), 218 (20), 217 (100), 189 (16), 188 (96), 147 (18), 110 (30), 109 (78), 94 (74), 77 (54).

5-Bromo-1-(4-chlorophenylsulfenyl)methyl-2(1H)-pyrimidinone (**3h**). M.p. 210 °C. Anal. $C_{11}H_8BrClN_2OS$: C,H. ^1H NMR (DMSO-d_6): δ

5.25 (CH_2N), 7.3–7.6 (Ar), 8.21 (H-6, d, J = 3 Hz), 8.62 (H-4, d, J = 3 Hz). MS: 334/332/330 (2/7/5, *M*), 189/187 (96/100), 177/175 (14/14), 162/160 (18/20), 108 (39), 80 (33).

5-Iodo-1-phenylsulfenylmethyl-2(1H)-pyrimidinone (**3i**). M.p. 203 °C. Anal. $C_{11}H_9IN_2OS$: C,H. ^{1}H NMR (DMSO-d_6/$CDCl_3$): δ 5.30 (CH_2N), 7.50 (Ph), 8.00 (H-6, d, J = 3 Hz), 8.61 (H-4, d, J = 3 Hz). MS(CI): 345 (73, M+H), 344 (8), 237 (7), 235 (11), 219 (19), 123 (100).

1-(4-Chlorophenylsulfenyl)methyl-5-phenylsulfenyl-2(1H)-pyrimidinone (**3j**). M.p. 160 °C. Anal. $C_{17}H_{13}ClN_2OS_2$: C,H. ^{1}H NMR ($CDCl_3$): δ 5.15 (CH_2N), 7.1–7.4 (2 × Ph),7.49 (H-6, d, J = 3 Hz), 8.60 (H-4, d, J = 3 Hz). MS: 362/360 (10/21, *M*), 218 (15), 217 (100), 205 (11), 204 (32), 189 (12), 188 (96), 147 (22), 110 (15), 109 (89), 108 (27).

Preparation of 1-allyl-5-chloro-2(1H)-pyrimidinone (**4**). A mixture of 5-chloro-2(1*H*)-pyrimidinone (0.39 g, 3 mmol) and bis(tributyltin) oxide (0.76 ml, 1.5 mmol) in benzene (25 ml) was heated under reflux using a Dean-Stark trap for 2 h. The mixture was cooled to ambient temperature, allyl acetate (0.36 ml, 3.3 mmol) and tetrakis(triphenylphosphine)palladium (0.15 mmol in THF) were added, and the mixture was stirred under nitrogen at ambient temperature for 18 h. The solvent was then evaporated and the crude product purified by flash chromatography (SiO_2; CH_2Cl_2/MeOH 95:5); yield 0.35 g (68 %). The product was identical with an authentic sample.[10]

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