Syntheses of 5-Alkenylpyrimidines by Organotin Reactions

Jessie Sandosham, Tore Benneche, Bjørg Siw Møller and Kjell Undheim

Department of Chemistry, University of Oslo, N-0315 Oslo 3, Norway

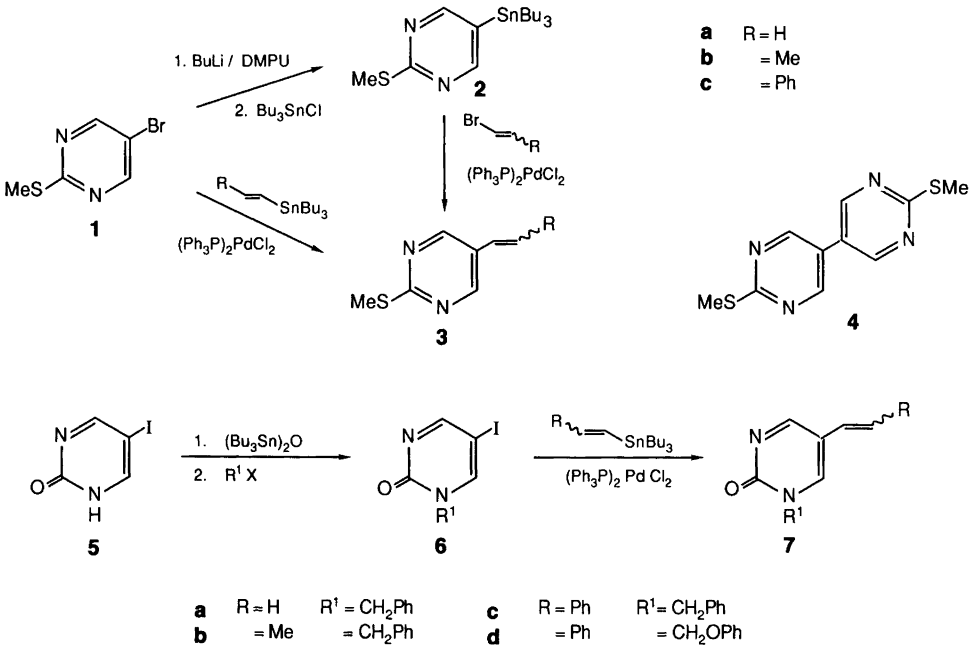
Sandosham, J., Benneche, T., Møller, B. S. and Undheim, K., 1988. Syntheses of 5-Alkenylpyrimidines by Organotin Reactions. – Acta Chem. Scand., Ser. B 42: 455–461.

5-Stannylpyrimidines can be prepared from the corresponding bromides by lithiation at −95 °C and quenching with tributylstannyl chloride. The 5-stannyl-pyrimidine is used in Pd-catalyzed coupling reactions with vinyl bromides. The opposite reaction sequence, i.e. Pd-catalyzed coupling between 5-halopyrimidines and vinyltin derivatives, is also described. Alternatively, the 5-vinylpyrimidines have been obtained by dehydrohalogenation with cesium fluoride and by a modified Wittig reaction. 2-Methylthiopyrimidines are transformed into the 2-methoxy derivatives or 2-pyrimidinones using chloramine-T (CAT) in a simple one-pot synthesis.

5-Vinyluracils are structurally similar to biologically important pyrimidines, and therefore considerable efforts have been made in the synthesis of these compounds.[1] Little has, however, been reported on the 5-alkenylation of non-uracil substituted pyrimidines.[2] We have previously described a synthesis of 2-substituted 5-halovinylpyrimidines,[3] and we now report on the syntheses of 5-β-alkylvinyl and 5-β-arylvinyl derivatives. We also describe a new method for the transformation of a 2-methylthiopyrimidine into a 2-methoxypyrimidine or a 2-pyrimidinone.

Palladium-catalyzed coupling reactions with aryltin compounds are well known in the literature.[4] By analogy, we have studied the 5-tributylstannylpyrimidine **2** in Pd-catalyzed coupling with bromovinyl compounds. 2-Methylthio-5-tributylstannylpyrimidine (**2**) was prepared by lithiation of 5-bromo-2-methylthiopyrimidine (**1**) and quenching with tributyltin chloride. Low temperature (−95 °C) and one equiv. of *N,N*-dimethylpropyleneurea (DMPU) was used in order to obtain a clean reaction (Scheme 1). The 5-tributylstannylpyrimidine **2** is stable at ambient temperature, and can be purified by column chromatography or by distillation. Reaction of the 5-tributylstannylpyrimidine **2** with β-bromostyrene or propenyl bromide in the presence of 3 mol % bis(triphenylphosphine)palladium dichloride gave the corresponding 5-alkenylpyrimidines in good yields with dichloroethane as solvent. Using THF as solvent, propenyl bromide produced both the dimer **4** and the 5-propenylpyrimidine. Vinyl bromide yielded the dimer **4** as the major product in both 1,2-dichloroethane and THF, even though a large excess of the bromide was used.

The carbon–carbon bond formation in the 5-position has also been achieved using the opposite reaction sequence. Although Pd-catalyzed coupling reactions between aryl halides and alkenyltin compounds are well known in the literature,[5] few examples of the corresponding reaction with heterocyclic halides are known.[6] We have found that the 5-bromopyrimidines **1** and **8** (Schemes 1 and 2) can be coupled to alkenyl synthons in good yields using bis(triphenylphosphine)palladium dichloride (2 mol %) as catalyst. With vinyltributyltin a better yield of the 5-vinylpyrimidine was obtained when the amount of catalyst was increased (5 mol %). Aryl iodides are usually more reactive than bromides in Pd-catalyzed coupling reactions with organotin compounds.[7] Thus, in the reaction of the 5-iodopyrimidinone **6a** with vinyltributyltin and 2 mol % of catalyst, 60 % of the corresponding 5-vinylpyrimidinone **7a** was formed. The pyrimidinones **6** also reacted well with the other vinyltin reagents.



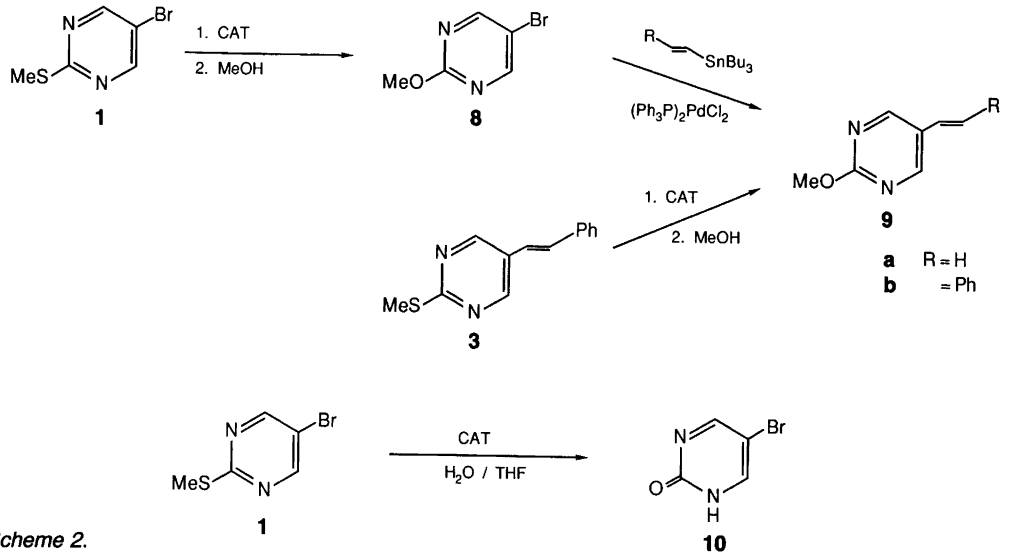
Scheme 1.

Transformation of an alkylthio substituent into an alkoxy substituent in an activated pyrimidine position can be affected with the appropriate alcohol under strongly basic conditions,[8] or by a two-step procedure in which the alkylthio group is oxidized before alcoholysis.[9] We have found that 2-methylthiopyrimidines can be transformed into 2-methoxypyrimidines by treatment with chloramine-T (CAT) in methanol under acidic conditions followed by hydrolysis with a 2 M sodium hydroxide solution. The 2-methoxypyrimidines can be extracted or filtered from the solution in good yields (Scheme 2). Invariably, in these reactions a small amount (5–7 %) of the 2-methylthio starting material was isolated. A close investigation of the reaction mixture by TLC before treatment with NaOH showed that all starting material had been consumed. This may provide some insight into the mechanism of this reaction.

When methanol was replaced by water in the CAT reaction the corresponding hydroxy compound was formed, as shown in the reaction with 5-bromo-2-methylthiopyrimidine (**1**) leading to 5-bromo-2(1*H*)-pyrimidinone (**10**) (Scheme 3).

An alternative preparation of 5-vinylpyrimidines involved a reduction and elimination reaction sequence with the 5-acetylpyrimidine **11**, which was obtained from cyclization reactions.[9] Sodium borohydride reaction and thionyl chloride treatment gave first the hydroxy derivative **12** and then the chloride **13**. Treatment of the latter with strong base such as potassium *tert*-butoxide in DMF resulted in a mixture of products from which the 5-vinyl derivative **3a** was isolated in 14 % yield. **3a** was prepared from the chloride **13** in 66 % yield using cesium fluoride in DMF. The application of the latter reagent was suggested by reports which have shown that the "naked" fluoride anion is useful in many types of dehydrohalogenation reactions, and that reactions of this type often give better yields than the treatment of the halides with conventional bases.[10] The main by-product in the above reaction was the fluoride **14**. The ratio between the vinyl derivative **3a** and the latter (**14**) was the same (ca. 4:1) regardless of the reaction time (8 h or 24 h at 100 °C). This indicates that dehydrohalogenation occurs from the chloride **13** and not from the fluoride **14**.

The first step in the second reaction sequence was to convert the 5-formyl group into a vinyl

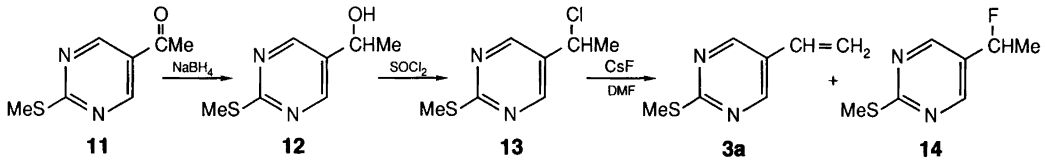


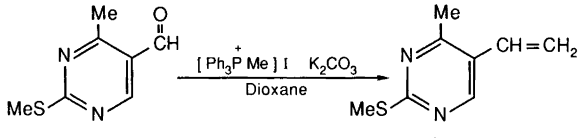
Scheme 2.

group. The Wittig reaction with methyl(triphenyl)phosphonium iodide and the strong base sodium methylsulfinylmethide in dimethylsulfoxide (DMSO) was unsatisfactory, which is not unexpected in view of the acidity of the hydrogens attached to the activated 4-methyl substituent. Compound **16**, however, was obtained in 60% yield by a modification of the recently described solid-liquid transfer process in Wittig reactions;[11] the formyl compound **15** was treated with methyl (triphenyl)phosphonium iodide and potassium carbonate in dioxane.

Experimental

^{1}H NMR spectra were recorded at 60 MHz or at 300 MHz, and ^{13}C NMR spectra at 75 MHz. The mass spectra were recorded at 70 eV ionizing energy. Isobutane was used for chemical ionization (CI). The MS spectra are presented as *m/z* (% rel. int.). THF used in the organometallic reactions was dried by distillation over metallic sodium/benzophenone. Dichloromethane was distilled over calcium hydride and 1,2-dichloroethane over phosphorus pentoxide.





Scheme 3.

2-Methylthio-5-tributylstannylpyrimidine (**2**). 5-Bromo-2-methylthio-pyrimidine[12] (10.25 g, 50 mmol) was dissolved in dry THF (120 ml); the solution was cooled to below −95 °C and stirred under N_2 before adding butyllithium (57 mmol, 1.5 M in hexane) slowly such that the temperature remained below −95 °C. After 10 min, DMPU (6.4 g, 50 mmol) was added and the reaction mixture stirred for a further 1 h, while maintaining a constant temperature. Tributyltin chloride (18.5 g, 55 mmol) in THF (50 ml) was then introduced gradually. The reaction mixture was warmed to 0 °C overnight, 10 % NH_4Cl (500 ml) solution was added, and the mixture was extracted with diethyl ether, dried ($MgSO_4$) and purified on a silica column with 1,2-dichloroethane as eluent. Distillation gave 14.5 g (70 %) of product (b.p. 130 °C/0.001 mmHg). Anal. $C_{17}H_{32}N_2SSn$. C, H. ^{1}H NMR ($CDCl_3$): δ 0.84–1.60 (Bu), 2.57 (SMe), 8.50 (2H, H-4, H-6). ^{13}C NMR ($CDCl_3$): δ 9.8, 13.8, 14.0, 27.3, 29.0, 127.1, 163.4, 172.4. MS(CI): 417 (100), 416 (41, *M*), 415 (76), 414 (31), 413 (44), 359 (31), 358 (11), 357 (22), 303 (6), 291 (11), 289 (9).

Synthesis of 5-alkenylpyrimidines by palladium-catalyzed coupling of 5-tributylstannylpyrimidines with vinyl bromides:

2-Methylthio-5-vinylpyrimidine (**3a**). 2-Methylthio-5-tributylstannylpyrimidine (2.08 g, 5 mmol), vinyl bromide (1.5 ml, 15 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.105 g, 0.15 mmol) and THF (5 ml) were heated together under reflux in a sealed tube under N_2 for 4 h. After cooling, the reaction mixture was diluted with diethyl ether and treated with aqueous potassium fluoride, the precipitated tributyltin fluoride was filtered off, and the filtrate was dried ($MgSO_4$), evaporated and purified on a silica column with hexane/ethyl acetate (1:1) as eluent to give 0.22 g (28 %) of the desired product **3a** and 0.35 g (56 %) of the dimer **4**. M.p. 48–49 °C. Anal. $C_7H_8N_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.53 (CH_3S), 5.37 (1H, dd, *J* 11 Hz, *J* < 1 Hz), 5.78 (1H, dd, *J* 18 Hz, *J* < 1 Hz), 6.63 (1H, dd, *J* 18 Hz, *J* 11 Hz), 8.52 (2H, H-4, H-6). ^{13}C NMR ($CDCl_3$): δ 14.0, 116.3, 125.9, 129.9, 154.4, 171.4. MS: 152 (100, *M*), 151 (25), 107 (11), 106 (37), 105 (19), 80 (13).

Bis-5,5'-(2,2'-methylthiopyrimidine) (**4**). M.p. 212 °C, lit.[17] 209–212 °C. Anal. $C_{10}H_{10}N_4S_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.65 (CH_3S), 8.8 (2H, H-4, H-6). MS: 252 (12), 250 (100, *M*), 217 (19), 162 (5), 150 (6), 132 (8), 130 (6), 106 (10), 104 (18).

2-Methylthio-5-propenylpyrimidine (**3b**). 2-Methylthio-5-tributylstannylpyrimidine (2.07 g, 5 mmol), 1-bromopropene (1 ml, 10 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.118 g, 0.168 mmol) were dissolved in 5 ml of dry, freshly distilled 1,2-dichloroethane and the solution heated under reflux under N_2 overnight. Work-up as for **3a**, above. The crude product was purified on a silica column with dichloromethane as eluent to give 0.74 g (89 %) of the title compound, m.p. 0 °C. Anal. $C_8H_{10}N_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.89 (CH_3C), dd, *J* 7.5 Hz, *J* 2.3 Hz), 2.58 (CH_3S), 5.9–6.0 (1H m), 6.2–6.3 (1H, m), 8.47 (2H, H-4, H-6). ^{13}C NMR ($CDCl_3$): δ 14.1, 14.7, 122.7, 126.1, 130.3, 156.6, 170.0. MS: 166 (100, *M*), 165 (23), 121 (8), 120 (28), 119 (14), 105 (20), 94 (12), 66 (22).

2-Methylthio-5-β-styrylpyrimidine (**3c**). 2-Methylthio-5-tributylstannylpyrimidine (2.07 g, 5 mmol), β-bromostyrene (1.46 g, 8 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.118 g, 0.168 mmol) were dissolved in 5 ml of freshly distilled 1,2-dichloroethane and the solution heated under reflux under N_2 for 4 h. The reaction mixture was cooled, diluted with light petroleum and treated with potassium fluoride in methanol. The precipitated tributyltin fluoride was filtered off, and the filtrate was evaporated to give a mixture of the title compound **3c** and the dimer **4**, which were separated on a silica column using hexane/ethyl acetate (1:1) as eluent; yield 1.22 g (71 %) of the title compound **3c** and 0.15 g (24 %) of the dimer **4**. **3c**: M.p. 140 °C (EtOH). Anal. $C_{13}H_{12}N_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.56 (CH_3S), 6.85 (1H, d, *J* 16 Hz), 7.06 (1H, d, *J* 16 Hz), 7.25–7.46 (Ph), 8.58 (2H, H-4, H-6). ^{13}C NMR ($CDCl_3$): δ 14.4, 121.3, 126.1, 126.8, 128.4, 128.8, 130.8, 136.4, 154.5, 171.0. MS: 228 (100, *M*), 195 (9), 181 (24), 156 (24), 154 (11), 141 (11), 129 (11), 128 (23), 127 (19).

General procedure for the synthesis of 5-alkenylpyrimidines by palladium-catalyzed coupling of 5-bromo-2-substituted pyrimidines with vinyltin reagents: The vinyltin reagent (1.16 mmol) was

added to a mixture of the 5-bromo-2-substituted pyrimidine (1.06 mmol) and bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol) in dry, freshly distilled 1,2-dichloroethane (2.5 ml), and the mixture was heated under reflux under N_2 until the reaction was complete as shown by TLC. The reaction mixture was cooled, diluted with 1,2-dichloroethane or diethylether and treated with a saturated aqueous solution of potassium fluoride (10 ml), and the precipitated tributyltin fluoride was filtered off. The filtrate was washed with water, dried ($MgSO_4$), evaporated and purified on a silica column.

2-Methylthio-5-vinylpyrimidine (**3a**). Compound **3a** was obtained in 69 % yield from vinyltributyltin,[13] 5-bromo-2-methylthiopyrimidine and bis(triphenylphosphine)palladium(II) dichloride (5 mol %) after reflux for 17 h. After cooling, the reaction mixture was diluted with diethyl ether. Eluent: pentane/ethyl acetate (5:1). Physical data are given above.

2-Methylthio-5-β-styrylpyrimidine (**3c**). Compound **3c** was obtained in 58 % yield from β-styryltributyltin[14] and 5-bromo-2-methylthiopyrimidine (**1**) after reflux for 7 h. Eluent: chloroform. Physical data are given above.

2-Methoxy-5-vinylpyrimidine (**9a**). Compound **9a** was obtained in 53 % yield from vinyltributyltin,[13] 5-bromo-2-methoxypyrimidine (**8**) and bis(triphenylphosphine)palladium(II) dichloride (5 mol %) after reflux for 2 h. After cooling, the reaction mixture was diluted with diethyl ether. Eluent: pentane/ethyl acetate (5:1). B.p. 30 °C/0.015 mmHg. ^{1}H NMR ($CDCl_3$): δ 4.02 (CH_3O), 5.32 (1H, dd, *J* 11 Hz, *J* < 1 Hz), 5.74 (1H, dd, *J* 18 Hz, *J* < 1 Hz), 6.63 (1H, dd, *J* 18 Hz, *J* 11 Hz), 8.57 (2H, H-4, H-6). MS: 136 (100, *M*), 135 (47), 121 (1), 107 (54), 106 (77), 105 (50), 94 (7), 80 (34), 79 (14), 66 (17).

2-Methoxy-5-β-styrylpyrimidine (**9b**). Compound **9b** was obtained in 81 % yield from β-styryltributyltin[14] and 5-bromo-2-methoxypyrimidine (**8**) after reflux for 2 h; eluent: chloroform; al. $C_{13}H_{12}N_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 4.0 (CH_3O), 6.92 (1H, d, *J* 17 Hz), 7.11 (1H, d, *J* 17 Hz), 7.2–7.5 (Ph), 8.65 (2H, H-4, H-6). ^{13}C NMR ($CDCl_3$): δ 55.4, 121.1, 125.0, 126.5, 128.2, 128.8, 136.4, 157.0, 164.0. MS: 212 (50, *M*), 211 (35), 183 (12), 181 (10), 156 (17), 128 (11), 127 (14), 115 (16).

1-Benzyl-5-iodo-2(1H)-pyrimidinone[15] (**6a**). Bis (tributyltin) oxide (1.49 g, 2.50 mmol) in benzene was added dropwise with stirring under N_2 to a solution of 5-iodo-2(1*H*)-pyrimidinone[16] (1.10 g, 5.00 mmol) in dry benzene (25 ml). The mixture was heated under reflux for 1 h with a Dean-Stark trap and cooled to ambient temperature before adding benzyl bromide (0.86 g, 5.00 mmol). The reaction mixture was heated under reflux for 6 h and left to stand overnight at 5 °C. The precipitated product was filtered off, washed with diethyl ether and recrystallized from ethyl acetate; yield 1.25 g (80 %), m.p. 221–222 °C, lit.[15] 220 °C.

General procedure for the synthesis of 5-alkenyl-2(1H)-pyrimidinones (**7**) *by palladium-catalyzed coupling of 1-alkyl-5-iodo 2(1H)-pyrimidinones with vinyltin reagents:* The vinyltin reagent (1.76 mmol) in 1,2-dichloroethane (0.5 ml) was added to a mixture of 1-alkyl-5-iodo-2(1-*H*)-pyrimidinone[20] (1.60 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.032 mmol) in dry freshly distilled 1,2-dichloroethane (4.5 ml), and the mixture was heated under reflux under N_2 until the reaction was complete. The cold reaction mixture was concentrated and washed with pentane. The crude product was purified on a silica gel column using ethyl acetate for elution.

1-Benzyl-5-vinyl-2(1H)-pyrimidinone (**7a**). Compound **7a** was obtained in 60 % yield from vinyltributyltin[13] and 1-benzyl-5-iodo-2(1*H*)-pyrimidinone (**6a**) after reflux for 3.5 h; m.p. 130–131 °C. Anal. $C_{13}H_{12}N_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 5.14 (CH_2Ph), 5.23 (1H, dd, *J* 11 Hz, *J* < 1 Hz), 5.57 (1H, dd, *J* 18 Hz, *J* < 1 Hz), 6.43 (1H, dd, *J* 18 Hz, *J* 11 Hz), 7.3–7.5 (Ph), 7.67 (h-6, d, *J* 3 Hz), 8.89 (H-4, d, *J* 3 Hz). MS: 212 (29, *M*), 183 (2), 170 (2), 157 (7), 121 (8), 106 (4), 91 (100), 89 (5).

1-Benzyl-5-propenyl-2(1H)-pyrimidinone (**7b**). Compound **7b** was obtained in 60 % yield from propenyltributyltin[14] and 1-benzyl-5-iodo-2(1*H*)-pyrimidinone (**6a**) after reflux for 2.5 h; m.p. 111–112 °C. Anal: $C_{14}H_{14}N_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.73 (CH_3C, dd, *J* 7.1 Hz, *J* 1.7 Hz), 5.12 (CH_2Ph), 5.7–5.8 (1H, m), 6.0–7.1 (1H, m),

7.3–7.4 (Ph), 7.59 (H-6, d, *J* 3 Hz), 8.56 (H-4, d, *J* 3 Hz). ^{13}C NMR ($CDCl_3$): δ 14.2, 53.7, 114.8, 120.9, 128.1, 128.4, 128.9, 134.7, 145.2, 155.2, 166.3. MS: 226 (25, *M*), 211 (4), 197 (3), 184 (3), 171 (7), 135 (23), 91 (100).

1-Benzyl-5-β-styryl-2(1H)-pyrimidinone (**7c**). Compound **7c** was obtained from β-styryltributyltin[14] and 1-benzyl-5-iodo-2(1*H*)-pyrimidinone (**6a**) in 80% yield after reflux for 1 h; m.p. 205 °C. Anal. $C_{19}H_{16}N_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 5.14 (CH_2Ph), 6.69 (1H, d, *J* 17 Hz), 6.88 (1H, d, *J* 17 Hz), 7.2–7.4 (Ph), 7.64 (H-6, d, *J* 3 Hz), 8.89 (H-4, d, *J* 3 Hz). ^{13}C NMR ($CDCl_3$): δ 53.9, 145.3, 119.6, 126.1, 127.9, 128.1, 128.4, 128.5, 128.6, 129.0, 134.5, 136.0, 155.6, 143.6, 163.6. MS: 289 (12), 288 (54, *M*), 259 (12), 246 (4), 233 (5), 198 (10), 197 (74), 115 (16), 91 (100).

1-Phenoxymethyl-5-β-styryl-2(1H)-pyrimidinone (**7d**). Compound **7d** was obtained from β-styryltributyltin[14] and 1-phenoxymethyl-5-iodo-2(1*H*)-pyrimidinone[20] in 55% yield after reflux for 1 h; m.p. 182–183 °C. Anal. $C_{19}H_{16}N_2O_2$: C, H. ^{1}H NMR ($CDcl_3$): δ 5.95 (CH_2O), 6.8–7.5 (m, styryl, Ph), 7.93 (H-6, d, *J* 3 Hz), 8.98 (H-4, d, *J* 3 Hz). MS: 304 (47, *M*), 211 (46), 197 (14), 183 (4), 182 (17), 154 (4), 141 (8), 127 (8), 91 (100).

Synthesis of 2-methoxypyrimidines from the corresponding 2-methylthiopyrimidine by treatment with CAT in methanol:

5-Bromo-2-methoxypyrimidine[12] (**8**). 5-Bromo-2-methylthiopyrimidine[12] (3.06 g, 15 mmol), CAT (5.8 g, 20 mmol), acetic acid (2 ml), and methanol (65 ml) were heated at 50 °C for 2 h. The reaction mixture was concentrated and 2 M NaOH was added to pH 12, for a further 2 h and then acidified with acetic acid. The crude product was extracted into chloroform, and the solution was dried ($MgSO_4$) and evaporated. The residue was sublimed and the sublimate purified on a silica column with chloroform/ethyl acetate (3:1) to give 2.0 g (72%) of the title compound; m.p. 90 °C. Anal. $C_5H_5N_2BrO$: C, H. ^{1}H NMR ($CDCl_3$): δ 4.00 (OMe), 8.54 (2H, H-4, H-6). ^{13}C NMR ($CDCl_3$): δ 55.2, 111.6, 159.2, 163.9.

2-Methoxy-5-β-styrylpyrimidine (**9**). 2-Methylthio-5-β-styrylpyrimidine (**3c**) (0.22 g, 0.96 mmol), CAT (0.56 g, 1.9 mmol), acetic acid (0.2 ml) and methanol (7 ml) were heated under reflux overnight; the mixture was then cooled, concentrated and treated with 2 M NaOH until basic. The precipitate formed was filtered off, washed with water and recrystallized from 2-propanol to give 0.18 g (90% yield). Physical data are given above.

5-Bromo-2(1H)-pyrimidinone (**10**). CAT (0.41 g, 1.5 mmol) was added to a mixture of 5-bromo-2-methylthiopyrimidine[12] (205 mg, 1.04 mmol) and acetic acid (0.1 ml) in THF (2 ml) and water (3 ml). The mixture was stirred for 30 min at 70 °C, cooled; 2 M NaOH (3 ml) was added, and the mixture was then stirred for a further 30 min at ambient temperature before being acidified with acetic acid. The mixture was kept at 5 °C overnight. The precipitate was washed with water, acetone and diethyl ether; yield 130 mg (74%). The product was identical with an authentic sample.[18]

Synthesis of 5-vinylpyrimidines from 5-acylpyrimidines:

5-(1-Hydroxyethyl)-2-methylthiopyrimidine (**12**). Sodium borohydride (0.17 g, 4.6 mmol) was added to a mixture of 5-acetyl-2-methylthiopyrimidine[9] (0.96 g, 5.7 mmol) in 2-propanol (35 ml). The mixture was stirred for 30 min at ambient temperature, after which water (35 ml) was added and the mixture neutralized (1 M HCl). The product was extracted into chloroform, and the dried solution ($MgSO_4$) was evaporated to give the title compound as an oil. Anal. $C_7H_{10}N_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.48 (CH_3CH, d, *J* 7 Hz), 2.55 (CH_3S), 4.87 (CH_3CH, q, *J* 7 hz), 8.50 (2H, H-4, H-6). MS: 170 (100, *M*); 168 (36), 155 (48), 153 (18), 152 (13), 124 (19), 122 (9).

5-(1-Chloroethyl)-2-methylthiopyrimidine (**13**). Thionyl chloride (1.5 ml, 21 mmol) was added to a solution of 5-(1-hydroxyethyl)-2-methylthiopyrimidine (0.80 g, 4.7 mmol) in dioxane (10 ml). The mixture was heated under reflux for 1 h, and the solvent was then distilled off and diethyl ether added. The solution was washed with water, dried ($MgSO_4$), evaporated and the product distilled; yield 0.55 g (62%), b.p. 90–91 °C/0.1

mmHg. Anal. $C_7H_9ClN_2S$: C, H. ^1H NMR ($CDCl_3$): δ 1.85 (CH_3CH), d, *J* 7 Hz), 2.55 (CH_3S), 5.05 (CH_3CH, q, *J* 7 Hz). MS: 190/188 (15/40, *M*), 154 (13), 153 (100), 152 (35), 151 (9), 107 (9), 106 (14), 105 (8).

Reaction of 5-(1-chloroethyl)-2-methylthiopyrimidine (**13**) *with cesium fluoride.* A mixture of 5-(1-chloroethyl)-2-methylthiopyrimidine (0.19 g, 1 mmol) and dried cesium fluoride[19] (0.46 g, 3 mmol) in dry DMF was heated under N_2 at 100 °C for 8 h. Water was then added and the product extracted into diethyl ether. The solution was washed well with water, dried ($MgSO_4$) and evaporated to give a mixture (0.14 g) of **3a** and **14** (below). The products were separated by column chromatography [Al_2O_3, activity II; light petroleum/chloroform (3:1)].

2-Methylthio-5-vinylpyrimidine (**3a**) was eluted first; yield 100 mg (66 %), m.p. 48–49 °C. Anal. $C_7H_8N_2S$: C, H. Physical data are given above.

5-(1-Fluoroethyl)-2-methylthiopyrimidine (**14**) was the second elution product; yield 30 mg (17 %), oil. ^1H NMR ($CDCl_3$): δ 1.67 (CH_3CHF, *J* 6 Hz, $^2J_{HF}$; 24 Hz), 2.75 (CH_3S), 3.98 (CH_3CHF, *J* 6 Hz, $^3J_{HF}$ 48 Hz). MS: 172 (100, *M*) 171 (22), 157 (11), 152 (7), 127 (8), 126 (51), 110 (6), 80 (14).

4-Methyl-2-methylthio-5-vinylpyrimidine (**16**). 5-Formyl-4-methyl-2-methylthiopyrimidine[9] (0.33 g, 2 mmol) was added to a mixture of methyl(triphenyl)phosphonium iodide (0.79 g, 2 mmol) and potassium carbonate (0.35 g, 2 mmol) in dioxane (5 ml) containing water (0.03 ml). The mixture was heated at 100 °C for 4.5 h, after which the solvent was distilled off. The product was extracted into ether and the solution was washed with water (3×), dried ($MgSO_4$) and evaporated. The residue was sublimed and purified on a silica column ($CHCl_3$); yield 0.20 g (60 %), m.p. 40–41 °C. Anal. $C_8H_{10}N_2S$; C, H. ^1H NMR ($CDCl_3$): δ 5.37 (1H, dd, *J* 11 Hz, $J < 1$ Hz), 6.70 (1H, dd, *J* 18 Hz, *J* 11 Hz). MS: 166 (100, *M*), 165 (25), 149 (51), 121 (11), 120 (53), 119 (16), 105 (31), 94 (9).

References

1. (a) Evans, C. H., Jones, A. S. and Walker, R. T. *Tetrahedron 29* (1973) 1611; (b) Fissekis, J. D. and Sweet, F. *J. Org. Chem. 38* (1973) 264; (c) Fissekis, J. D. and Sweet, F. *J. Org. Chem. 38* (1973) 1963; (d) Jones, A. S., Stephenson, G. P. and Walker, R. T. *Nucleic Acids Res. 1* (1974) 105; (e) Sharma, R. A. and Bobek, M. *J. Org. Chem. 40* (1975) 2377; (f) Arai, I. and Doyle Daves, G., Jr. *J. Heterocycl. Chem. 15* (1978) 351.
2. (a) Feit, B. A. and Teuerstein, A. *J. Heterocycl. Chem. 11* (1974) 295; (b) Kvita, V. *Synthesis 786* (1986).
3. Benneche, T. and Undheim, K. *Acta Chem. Scand., Ser. B 37* (1983) 235.
4. Stille, J. K. *Angew. Chem. Int. Ed. Engl. 25* (1986) 508 and references therein.
5. (a) McKean, D. R., Parrinello, G., Renaldo, A. F. and Stille, J. K. *J. Org. Chem. 52* (1987) 422 and references therein; (b) Beletskaya, I. P. *J. Organomet. Chem. 250* (1983) 551 and references therein.
6. (a) Kosugi, M., Koshiba, M., Atoh, A., Sano, H. and Migita, T. *Bull. Chem. Soc. Jpn. 59* (1986) 677; (b) Solberg, J. and Undheim, K. *Acta Chem. Scand., Ser. B 41* (1982) 712.
7. Tunney, S. E. and Stille, J. K. *J. Org. Chem. 52* (1987) 748.
8. Brown, D. J. *The Pyrimidines,* Wiley Interscience, New York 1962, p. 247; *Ibid.* Suppl. I (1970) p. 179; *Ibid.* Suppl. II (1985) p. 244f.
9. Benneche, T. and Undheim, K. *Acta Chem. Scand., Ser. B 36* (1982) 529.
10. (a) Ono, N. *Bull. Chem. Soc. Jpn. 44* (1971) 1369; (b) Hayami, J., Ono, N. and Kaji, A. *Bull. Chem. Soc. Jpn. 44* (1971) 1628; (c) Naso, F. and Ronzini, L. *J. Chem. Soc., Perkin Trans 1* (1974) 340; (d) Chollet, A., Hagenbuch, J. P. and Vogel, P. *Helv. Chim. Acta 62* (1979) 511.
11. Le Bigot, Y., Delmas, M. and Gaset, A. *Synth. Commun. 12* (1982) 107.
12. Brown, D. J. and Foster, R. V. *Aust. J. Chem. 19* (1966) 2321.
13. Seyferth, D. and Stone, F. G. A. *J. Am. Chem. Soc. 79* (1957) 515.
14. Labadie, J. W. and Stille, J. K. *J. Am. Chem. Soc. 105* (1983) 6129.
15. Rise, F., Rømming, C. and Undheim, K. *Acta Chem. Scand., Ser. B 39* (1985) 459.
16. Gacek, M. and Undheim, K. *Acta Chem. Scand., Ser. B 39* (1985) 691.
17. Pater, R. *J. Heterocycl. Chem. 8* (1971) 743.
18. Crosby, D. G. and Berthold, R. V. *J. Org. Chem. 25* (1960) 1916.
19. Yakobson, G. G. and Akhmetova, N. E. *Synthesis* (1983) 169.
20. Keilen, G., Benneche, T. and Undheim, K. *Acta Chem. Scand., Ser. B 41* (1987) 577.

Received January 25, 1988.