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Syntheses and Reactions of Some 5-Vinyl- and 5-Ethynylpyrimidines

TORE BENNECHE and KJELL UNDHEIM

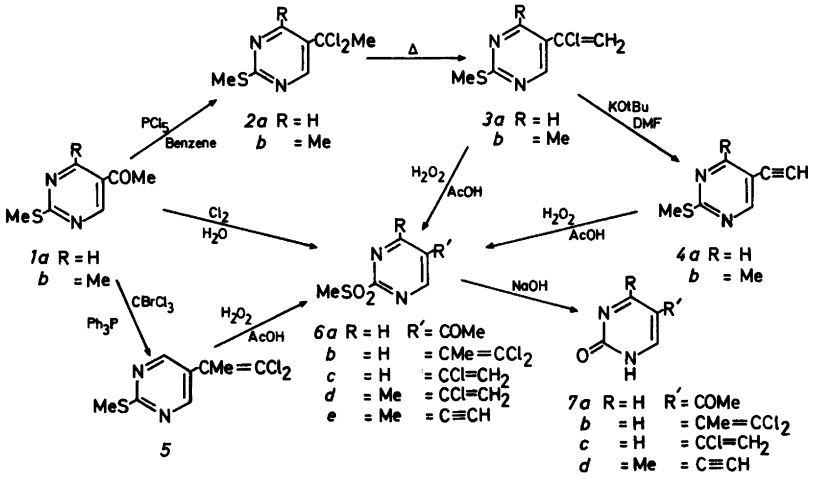
Department of Chemistry, University of Oslo, Oslo 3, Norway

5-β,β-Dichlorovinyl- and 5-α-chlorovinylpyrimidines have been prepared from 5-acetyl-2-methylthiopyrimidines. HCl elimination from the 5-α-chlorovinyl derivatives yields the 5-ethynyl analogues. Peracid or chlorine oxidation of the sulfides yields the sulfones which may be hydrolyzed to the corresponding lactams. The reaction paths are discussed.

Certain 2-alkylsulfonyl-5-substituted pyrimidines possess the ability to inhibit cell proliferation.[1] In this report we describe studies on 2-methylsulfonylpyrimidines carrying unsaturated substituents in the 5-position, in particular vinyl and ethynyl groups.

As starting materials for the syntheses were chosen 5-acyl pyrimidines since simple routes to the preparation of 5-acyl-2-thiopyrimidines are available.[2,3] Furthermore, 5-acylpyrimidines have been converted to olefins by Wittig type reactions,[4] or 5-ketones to α-chlorolefins by treatment with phosphorus pentachloride [5] or by phosphorus oxychloride.[6] We have found that the 5-acetyl derivatives *1* can be converted into the desired 5-α-chlorovinyl derivatives *3* using phosphorus pentachloride in benzene (Scheme 1). Under these conditions replacement of the 2-methylthio substituent was avoided.

The crude reaction product from the phosphorus pentachloride reaction was a mixture (*ca.* 1:1) of the 5-(1,1-dichloroethyl)pyrimidine *2* (^{1}H NMR) and the 5-(1-chlorovinyl)pyrimidine *3*. The former is the intermediate product in the reaction which subsequently eliminates hydrogen



Scheme 1.

0302-4369/83 $2.50

chloride. Elimination went essentially to completion when the mixture was distilled slowly; on rapid distillation both products codistilled. Addition of catalytic amounts of aluminium tribromide before distillation, however, gave the pure vinyl product *3*. The distillate from the 4-methyl homologue *1b* also contained the HCl salt of the base; combination of the base and the gaseous HCl was not observed for *3a*. This may reflect the effect of the 4-methyl substituent on the basicity.

The synthesis of the β,β-dichlorovinyl derivative *5* was initially attempted in the Wittig manner using the phosphorus ylide dichloromethylentriphenylphosphorane generated *in situ* from triphenylphosphine in carbon tetrachloride.[7] The product, however, consisted of a mixture (3:2) of the dichlorovinyl derivative *5* and the α-chlorovinyl derivatives *3a*. Formation of α-chlorolefins have also previously been observed in attempted Wittig reactions with triphenylphosphine in tetrachloromethane, and this course of the reaction has been rationalized by initial formation of dichlorotriphenylphosphorane which reacted further with the ketone.[8] Better yields and cleaner products are claimed by the use of bromotrichloromethane instead of tetrachloromethane.[9] This modification, when applied to the reaction of *1a*, gave 72 % yield of *5*. In addition there was a little of the corresponding monobromo analogue, 5-(2-bromo-2-chloro-1-methylvinyl)-2-methylthiopyrimidine (MS). The latter was readily removed on recrystallization.

A strong base is required for elimination of HCl from the α-chlorovinyl derivative *3* to form the acetylene *4*; potassium *tert*-butoxide in DMF caused the reaction to proceed at room temperature without affecting the 2-methylthio substituent. When attempting the reaction with potassium hydroxide in ethanol, addition products of ethanol to the triple bond were seen together with the desired 5-ethynyl compound.

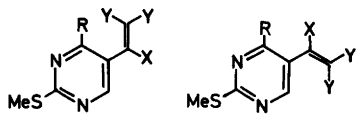
There was a significant difference in the rate of elimination of HCl from *3a* and *3b*; the reaction of *3b* was complete after 4 h at room temperature, whereas only 40 % of the 4-methyl derivative *3a* had reacted after 15 h.

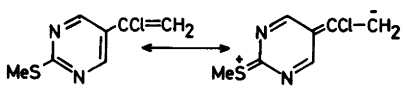
The long-wave absorption of the 4-methyl derivative *3b* is at lower wavelength (MeOH, 264 nm) than for *3a* (278 nm) and its absorptivity is less. This suggests that the non-bonded interaction from the methyl group (*8*, R=Me, X=Cl and Y=H) causes the vinyl group to twist out of the plane of the pyrimidine and thereby reduces resonance interaction with the pyrimidine ring. The electron donating resonance interaction from the *para* methylthio group (*9*) is therefore reduced in *3b* as compared with *3a*. The elimination reaction probably proceeds by an ElcB-type mechanism because of the electron attracting properties of the pyrimidine, the use of a strong base and the relatively poor leaving properties of the chloride ion. The incipient carbanion on the β-carbon of the vinyl group is more destabilized by the electronic effects of the methylthio group in *3a* than in *3b* in accordance with the relative rates of elimination.

The sulfones of the 5-vinyl and 5-ethynyl derivatives were prepared from the respective sulfides using peracetic acid generated *in situ* from 30 % hydrogen peroxide and acetic acid. Under these experimental conditions the unsaturated 5-substituents are deactivated towards oxidation and selective formation of the sulfones was experienced. The 5-acetyl derivative *1a* reacted differently, presumably because the relatively long reaction time (24 h) led to solvolysis of the 2-substituent or reaction on the acetyl function. By using chlorine in aqueous solution as oxidizing agent,[10] the reaction time could be shortened (30 min) and *1a* was converted to its sulfone *6a* in good yield. In ^{1}H NMR the oxidation of a sulfide to a sulfone is seen by a downfield shift of *ca.* 0.8 ppm for the signals of the methyl protons.

The sulfonyl group, in an activated azine position, is readily displaced by nucleophiles. Such sulfones may, therefore, in part exert their biological activity by substitution at the sulfonyl-attached carbon atom by a hydroxy, amino or thiol group at some essential biological site. Tested as inhibitors of cell proliferation,[1] the sulfones *6* were found to possess strong toxic properties.

The relative ease of the displacement of the sulfonyl group of the sulfones *6* is shown by hydrolysis in 0.5 M sodium hydroxide at room temperature. The activation from the acetyl group in *6a* resulted in an almost immediate transformation of *6a* to the corresponding lactam *7a*. *6a* was also hydrolyzed to *7a* under neutral conditions. The reaction time for the β,β-dichlorovinyl derivative *6b* was more than 6 h, whereas the hydrolysis of the α-chlorovinyl de-





Scheme 2.

rivatives *6c* and *6d* was complete in the course of 10–15 min. As opposed to *6a*, *6c* was not hydrolyzed under neutral conditions (5 days, room temperature). The relatively low rate of hydrolysis of the dichloride *6b* is attributed to the conformational preferences of the vinyl group. In the two conformations where the vinyl group lies in the plane of the pyrimidine ring (*8*, R=H, X=Me and Y=Cl) there is a serious non-bonded interaction between an α-methyl or a β-chloro substituent of the vinyl group with the 4- and 6-substituents of the pyrimidine. The vinyl group is, therefore, twisted out of the pyrimidine plane and will have less influence on the electronic properties leading to sulfonyl displacement than if it had been coplanar.

The hydrolytic reaction of the 4-methyl derivative *6d* also led to complete elimination of HCl to give the 5-ethynyl lactam *7d*, whereas no HCl elimination in the hydrolysis of *6c* was observed. The different nature of the products from the hydrolysis of *6c* and *6d* must be attributed to the influence of the 4-methyl group, which may be mainly steric in nature. The experimental findings are then rationalized by assuming initial elimination of HCl from the 4-methyl derivative *6d* with subsequent hydrolysis of the 2-substituent. In contrast, in *6c* the sulfonyl group is initially displaced to give the lactam *7c*. In alkaline solution the latter is negatively charged as a sodium salt, and the negative charge of the pyrimidine ring protects the α-chlorovinyl group against the elimination reaction.

EXPERIMENTAL

5-(1-Chlorovinyl)-2-methylthiopyrimidine 3a. Phosphorus pentachloride (6.2 g, 30 mmol) was added to a solution of 5-acetyl-2-methylthiopyrimidine [3] (3.30 g, 20 mmol) in dry benzene (100 ml). The mixture was refluxed for 3 h before the cooled solution was poured into ice and water (150 ml). The aqueous phase was neutralized with sodium carbonate and extracted with benzene. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was distilled under reduced pressure with a catalytic amount of aluminium tribromide; b.p. 96 °C/0.01 mmHg. The product was recrystallized from light petroleum; yield: 2.1 g (56 %), m.p. 73–75 °C. Anal. $C_7H_7ClN_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.57 (MeS), 5.58 and 5.82 (J 2 Hz, vinyl), 8.72 (H-4, H-6). IR (KBr): 1615 (vinyl), 1580 and 1530 cm^{-1} (pyrimidine). MS [70 eV; *m/z* (% rel.int.)]: 188/186 (35/100, M), 185(20), 151(20), 140(31), 105(33), 86(15), 51(30).

5-(1-Chlorovinyl)-4-methyl-2-methylthiopyrimidine 3b was prepared as *3a* above from 5-acetyl-4-methyl-2-methylthiopyrimidine [2] in 59 % yield, b.p. 129–131 °C/0.2 mmHg. Anal. $C_8H_9ClN_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.55 (Me-4 and MeS), 5.45 and 5.72 (J 1.5 Hz, vinyl), 8.33 (H–6). IR (KBr): 1630 (vinyl), 1570/1530 cm^{-1} (pyrimidine). MS [70 eV; *m/z* (% rel.int.)]: 202/200 (36/100, M), 199(19), 165(21), 154(30), 119(23).

5-Ethynyl-2-methylthiopyrimidine 4a. 1 M potassium *tert*-butoxide (7 ml) was added to a solution of 5-(1-chlorovinyl)-2-methylthiopyrimidine (1.40 g, 6.3 mmol) in DMF (25 ml) over 5 min. The mixture was stirred at room temperature for 48 h before the solvent was distilled off. The residue was triturated with water and extracted into chloroform. The dried solution ($MgSO_4$) was evaporated and the residue sublimed at 30 °C/90 mmHg; yield 8 %, m.p. 46–47 °C. Anal. $C_7H_6N_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.55 (MeS), 3.30 (CH), 8.55 (H–4, H–6). IR (KBr): 3280 (CH), 2120 (C≡C), 1590/1530 cm^{-1} (pyrimidine). MS [70 eV: *m/z* (% rel.int.)]: 150 (100, M), 105(19), 104(31), 77(18), 73(25).

5-Ethynyl-4-methyl-2-methylthiopyrimidine 4b. 1 M potassium *tert*-butoxide (7 ml) was added to a solution of 5-(1-chlorovinyl)-4-methyl-2-methylthiopyrimidine (1.00 g, 5 mmol) in DMF (20 ml) over 10 min. The mixture was stirred at room temperature for 4 h before the solvent was distilled off. The residue was triturated with water and extracted into chloroform. The dried solution ($MgSO_4$) was evaporated and the residue purified on a silica column (silica gel 60, 70–230 mesh, chloroform); yield: 0.70 g (85 %), m.p. 75–76 °C. Anal $C_8H_8N_2S$: C, H. ^{1}H NMR

($CDCl_3$): δ 2.57 (MeS, Me-4) 3.47 (CH), 8.46 (H–6). IR (KBr): 3390 (CH), 2100 (C≡C), 1570/1520 cm $^{-1}$ (pyrimidine). MS [70 eV; *m/z* (% rel.int.)]: 164 (100, M), 163(24), 119(11), 118(44), 77(10), 64(22), 63(19).

5-(2,2-Dichloro-1-methylvinyl)-2-methylthiopyrimidine 5. Bromotrichloromethane (15 ml, 150 mmol) was added to a mixture of 5-acetyl-2-methylthiopyrimidine [3] (1.10 g, 6.5 mmol) and triphenylphosphine (4.00 g, 15 mmol) in dry benzene (15 ml). The mixture was stirred for 2 h at 50 °C under N_2 before the solvent was distilled off. The residue was dissolved in acetone (20 ml) and ether added (300 ml). The solution was filtered and the filtrate evaporated. The residue was dissolved in ether (30 ml), filtered and the filtrate evaporated. The residual material was sublimed at 60–70 °C/0.03 mmHg; yield 1.10 g (72 %), m.p. 61–62 °C. Anal. $C_8H_8Cl_2N_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.20 (CH_3C=) 2.57 (MeS), 8.47 (H–4, H–6). IR (KBr): 1590/1530 cm $^{-1}$ (pyrimidine). MS [70 eV; *m/z* (% rel.int.)]: 238/236/234 (12/66/100,M), 233(29), 191(12), 190(18), 188(27), 153(40), 99(24).

5-Acetyl-2-methylsulfonylpyrimidine 6a. Chlorine was slowly bubbled through a suspension of 5-acetyl-2-methylthiopyrimidine (0.48 g, 2.9 mmol) in water (30 ml) for 30 min at 5 °C. The mixture was neutralized with potassium carbonate and extracted into chloroform. The dried solution ($MgSO_4$) was evaporated and the residue recrystallized from ethanol; yield 0.49 g (84 %), m.p. 132–134 °C. Anal. $C_7H_8N_2O_3S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.72 (CH_3CO), 3.36 ($MeSO_2$), 9.35 (H–4, H–6). IR (KBr): 1700 (CO), 1580/1560 (pyrimidine), 1310/1140 cm $^{-1}$ (sulfone). MS [70 eV; *m/z* (% rel.int.)]: 200 (18,M), 185(11), 137(29), 136(21), 123(28), 121(47), 95(22), 43(100).

Oxidation of the sulfides 3a–5 *with 30 % hydrogen peroxide.* Hydrogen peroxide (30 %, 8 ml) was added to a solution of the sulfide (12 mmol) in acetic acid (25 ml). The mixture was stirred for 2 h and left overnight. The solution was concentrated to ⅓ of its original volume before water (50 ml) was added, and the solution extractred with chloroform (3×50 ml). The extract was washed with a saturated solution of aqueous sodium carbonate and dried ($MgSO_4$). The solvent was distilled off and the residue recrystallized.

5-(2,2-Dichloro-1-methylvinyl)-2-methylsulfonylpyrimidine 6b. Yield: 66 %, m.p. 134–135 °C (MeOH). Anal. $C_8H_8Cl_2N_2O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.18 (CH_3–C=), 3.37 ($MeSO_2$), 8.86 (H–4, H–6). IR (KBr): 1550 (pyrimidine), 1310/1130 cm $^{-1}$ (sulfone). MS [70 eV; *m/z* (% rel.int.)]: 270/268/266 (5/39/56,M), 231(15), 205(24), 204(18), 203(37), 189(34), 187(54), 171(31), 169(100), 168(52).

5-(1-Chlorovinyl)-2-methylsulfonylpyrimidine 6c. Yield: 50 %, m.p. 111–114 °C (MeOH). Anal. $C_7H_7ClN_2O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 3.37 ($MeSO_2$), 5.88 and 6.10 (*J* 2.5 Hz, vinyl), 8.85 (H–4, H–6). IR (KBr): 1610 (C=CH_2), 1560/1550 (pyrimidine), 1310/1130 cm $^{-1}$ (sulfone). MS [70 eV; *m/z* (% rel.int.)]: 220/218 (6/16, M), 157(33), 155(100), 141(26), 139(74), 112(31), 100(13), 87(25).

5-(1-Chlorovinyl)-4-methyl-2-methylsulfonylpyrimidine 6d. Yield: 54 %, m.p. 67–68 °C (CCl_4/light petroleum). Anal. $C_8H_9ClN_2O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.75 (Me–4), 3.34 ($MeSO_2$), 5.62 and 5.92 (*J* 2 Hz, vinyl), 8.74 (H–6). IR (KBr): 1630 (vinyl), 1560/1540 (pyrimidine), 1310/1130 cm $^{-1}$ (sulfone). MS [70 eV; *m/z* (% rel.int.)]: 234/232 (19/53,M). 171(32), 170(27), 169(100), 168(32), 155(32), 153(99), 135(75), 126(50), 118(44), 99(38).

5-Ethynyl-4-methyl-2-methylsulfonylpyrimidine 6e. Yield: 26 %, m.p. 97–98 °C (CCl_4/light pertroleum). Anal. $C_8H_8N_2O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.78 (Me–4), 3.35 ($MeSO_2$), 3.79 (CH), 8.85 (H–6). IR (KBr): 3250 (CH), 2120 (C≡C), 1310/1140 cm $^{-1}$ (sulfone). MS [70 eV; *m/z* (% rel.int.)]: 196 (14,M), 181(8), 153(10), 134(61), 132(23), 117(100), 106(25), 90(60).

Hydrolysis of the sulfones 6 *with 0.5 M sodium hydroxide.* A mixture of the sulfone (2.5 mmol) and 0.5 M sodium hydroxide (25 ml) was stirred at room temperature till the sulfone had disappeared (TLC). The reaction times were 5 min (*6a*), 18 h (*6b*), 15 min (*6c*) and 10 min (*6d*). The solution was acidified (pH 5) with 1 M hydrogen chloride and extracted with ethyl acetate. The extract was dried ($MgSO_4$), evaporated and the residue sublimed.

5-Acetyl-2-pyrimidinone 7a was sublimed at 140–150 °C/0.03 mmHg; yield 29 %, m.p. 169–171 °C. ^{1}H NMR (DMSO-d_6): δ 2.38 (CH_3CO), 8.74 (H–4, H–6). IR (KBr): 2900–2600 (NH), 1730/1670/1630 cm $^{-1}$ (CO). MS [70 eV; *m/z* (% rel. int.)]: 138 (74,M), 123(100), 96(60), 95(32), 68(15), 53(22), 43(46). High resolution of M: found 138.0429, calc. for $C_6H_6N_2O_2$: 138.0429.

5-(2,2-Dichloro-1-methylvinyl)-2-pyrimidinone 7b. The title compound precipitated upon acidifying in 77 % yield, m.p. 228–229 °C (MeOH). Anal. $C_7H_6Cl_2N_2O$: C, H. ^{1}H NMR (DMSO-d_6): δ 2.12 (Me), 8.33 (H–4, H–6). IR (KBr): 1735 cm $^{-1}$ (CO). MS [70 eV; *m/z* (% rel.int.)]: 208/206/204 (5/30/46,M), 171(32), 169(100), 106(12), 99(10), 63(10).

5-(1-Chlorovinyl)-2-pyrimidinone 7c was sublimed at 110–120 °C/0.03 mmHg; yield: 62 %, m.p. 130–140 °C (decomp.). ^{1}H NMR (DMSO-

d_6): δ 5.44 and 6.01 (J 2.5 Hz, vinyl), 8.56 (H–4, H–6). IR (KBr): 3100–2700 (NH), 1660–1640 cm^{-1} (CO). MS [70 eV; m/z (% rel.int.)]: 158/156 (18/58,M), 155(15), 137(9), 121(100), 101(14), 93(18), 66(17), 51(34). High resolution of M: found 156.0086, calc. for $C_6H_5ClN_2O$: 156.0089.

5-Ethynyl-4-methyl-2-pyrimidinone 7d was sublimed at 130–140 °C/0.01–0.03 mmHg; yield 66 %, m.p. 180 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 2.34 (Me–4), 4.34 (CH), 8.31 (H–6). IR (KBr): 3250 (CH), 3080–2600 (NH), 1690 cm^{-1} (CO). MS [70 eV; m/z (% rel. int.)]: 134 (100,M), 107(30), 106(27), 79(14), 64(28), 50(37). High resolution of M: found 134.0473, calc. for $C_7H_6N_2O$: 134.0480.

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