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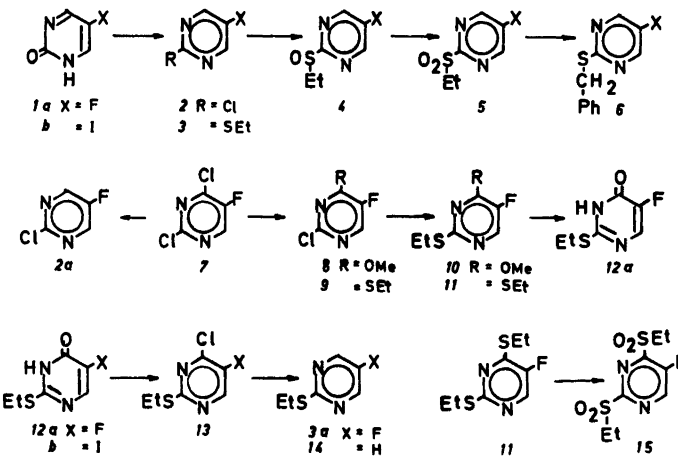
Chemoselectivity and Regioselectivity in Reactions of Pyrimidines

MICHEL GACEK and KJELL UNDHEIM

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

Selective nucleophilic substitution and hydrogenolysis reactions in pyrimidines are discussed. Stepwise oxidation reactions of pyrimidine sulfides and HPLC studies of these are reported.

Certain 2-alkylsulfinyl- and 2-alkylsulfonyl-5-halopyrimidines possess the important ability to inhibit cell proliferation, being especially active in the S-phase of the cell cyclus.[1] We herein describe some syntheses developed for the preparation of sulfines and sulfones within this class of inhibitors.



The target molecules, the sulfines *4* and the sulfones *5*, carry a 5-fluoro or a 5-iodo substituent; a starting material is the corresponding 5-halo-2(1*H*)-pyrimidinone *1*. We have reported a synthesis of the fluoro derivative *1a* from the corresponding uracil.[2] A different method has to be used for the iodo compound *1b*. Direct iodination in this series often leaves a lot to be desired,[3] but we herein report an efficient synthesis of *1b*; the reaction is carried out with sodium dichloroiodide in phosphate buffer at 60 °C. *1* was further converted into the 2-chloro compound *2* by means of phosphorus oxychloride, and then transformed into the 2-ethylsulfide *3* by means of potassium ethanethiolate.

The starting material for the preparation of *1a* is 5-fluorouracil which is further converted to *3a*. In an alternative route 5-fluorouracil is 2,4-dichlorinated to form compound *7*, which

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is subsequently substituted at C-4 by methoxide and thiolate reagents; the 4-position is slightly more reactive than the 2-position in pyrimidines and this difference is enhanced by the inductive effect of the 5-fluoro substituent. The products *8* and *9* are further reacted with potassium ethanethiolate in a selective manner, the new products being the sulfide *10* and *11*. The difference in the activation between C-2 and C-4 allows for selective nucleophilic displacements at C-4; controlled alkaline hydrolysis gives *12a* from either *10* or *11*. The corresponding 5-iodo compound *12b* was differently prepared, *viz.* from 2-ethylthio-4(1*H*)-pyrimidinone and sodium dichloroiodide. The chlorination of *12* to yield *13* was effected by the *in situ* prepared reagent from thionyl chloride and dimethylformamide; this reagent is a milder and more selective reagent than phosphorus oxychloride.[4] The 4-chloro substituent in *13a* is removed by hydrogenolysis over 5 % Pd–C under alkaline conditions, the product being *3a*. Under these reaction conditions, both the chloride and iodide substituents in *13b* were lost (*14*).

The different electronic activation of the positions in the dichloride *7* also allows for regioselective hydrogenolysis; with zinc dust in the two-phase system of benzene and aqueous ammonia the 4-chloro substituent is removed, the product being *2a*. Under these conditions 2,4-dichloro-5-iodopyrimidine suffers hydrogenolysis at both C-4 and C-5, the product being 2-chloropyrimidine.

m-Chloroperbenzoic acid (MCPBA) was chosen as the oxidizing agent. With the peracid at $\div 10$ °C the oxidation is controlled to the sulfoxide level *4*. At room temperature the sulfoxide is further oxidized to the corresponding sulfone *5*.

Iodo compounds are sensitive to oxidation. In the present case the iodine liberation was prevented by running the oxidations of *3b* and *4b* in the dark.

MCPBA was unsatisfactory for the oxidation of the bis-ethylsulfide *11*, presumably because the reaction is stepwise and therefore the first oxidized sulfide group will electronically deactivate the second group towards oxidation. Under stronger oxidizing conditions, which are also chosen so as to minimize the tendency for hydrolysis, however, the bis-sulfone *15* could be obtained; the reaction was effected by means of chlorine in an aqueous solution of *11*.

Both sulfinyl and sulfonyl substituents in activated pyrimidine positions can be displaced by nucleophiles, e.g. *5a* reacts readily with benzylsulfide *6*. Thus both the 2-chloro compounds *2* and the 2-sulfones *5* are suitable intermediates for the preparation of new sulfides and their oxidation products.

The sulfides *3* and their oxidation products *4* and *5* are well separated on HPLC analysis by isocratic elution on an ODS column with 50 % acetonitrile (Fig. 1). It is notable that the sulfoxides are eluated before the respective sulfones, the relative retention times being $SOR < SO_2R < SR$.

In ^{1}H NMR the pyrimidine protons for the sulfoxides and sulfones are almost equally deshielded in comparison with the sulfides; e.g. the chemical shifts for the pyrimidine protons in *3a*, *4a* and *5a* in deuteriochloroform were 8.35, 8.70, 8.73 ppm respectively.

EXPERIMENTAL

HPLC was run on a Waters analytical HPLC system equipped with a UV detector (254 and 280 nm) and a μBondapak C_{18} column (10 μm, 300×4 mm I.D.). The solvent was 50 % acetonitrile in water, and the flow rate was 1.3 ml/min ^{1}H NMR spectra were recorded at 60 MHz.

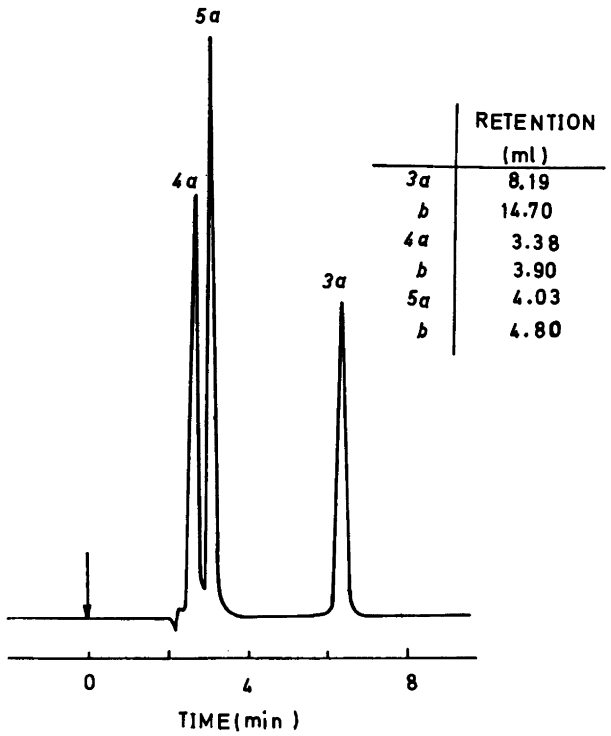

Fig. 1. Isocratic elution of 2-alkylthiopyrimidine derivatives from a μBondapak C_{18} column using 50 % acetonitrile in water (1.3 ml/min).

5-Fluoro-2(1H)-pyrimidinone 1a was prepared as described.[2] The crude product (6.0 g) in water (150 ml) was applied on an ion exchange column (Amberlite 400 in *OH* form; 120 g), the column washed successively with water, 2.5 % NH_4OH and water, and the title compound eluated with aqueous acetic acid (1 %); yield 5.4 g (90 %), m.p. 171–172 °C (EtOAc).

5-Iodo-2(1H)-pyrimidinone[3] 1b. Aqueous 3.55 M sodium dichloroiodide (10.1 ml; 36 mmol) was added to an aqueous solution (70 ml) of 2(1*H*)-pyrimidinone hydrochloride (4.0 g, 30 mmol) and sodium dihydrogen phosphate (60 mmol). The pH was thereby changed from 2.4 to 0.95. The mixture was slowly heated to 65 °C over 35 min, and kept at this temperature for 100 min. The title compound has started to crystallize out after *ca.* 1 h. The reaction mixture was left at 5 °C overnight before filtration. The product was washed with cold water containing a little sodium thiosulfate, dissolved in 1 M NaOH and reprecipitated by addition of acetic acid. The yield of the product was 5.0 g (75 %), purity 98 % (HPLC); m.p. >280 °C (dec.). Anal. $C_4H_3IN_2O$: C, H. ^1H NMR (TFA): δ 8.95 (H-4, H-6).

2-Chloro-5-fluoropyrimidine[5] 2a. Method A: From 5-fluoro-2(1*H*)-pyrimidinone and phosphorus oxychloride.[5]

Method B: Zinc dust (7 g) was added to the vigorously stirred two-phase system from 3 M aqueous ammonia saturated with ammonium chloride and a benzene solution (25 ml) of 2,4-dichloro-5-fluoropyrimidine[6] (24 mmol). The progress of the reaction was monitored by TLC (silica gel/iPr_2O). The benzene phase was collected after 30 h, the aqueous phase extracted with ether (5×40 ml), the combined organic solution washed with water and the solvent distilled off from the dried ($MgSO_4$) solution, leaving the title compound; yield 40 %. ^1H NMR ($CDCl_3$): δ 8.55 (H-4, H-6).

2-Chloro-5-iodopyrimidine 2b *was prepared from 1b* as described.[3]

2-Ethylthio-5-fluoropyrimidine[7] 3a. 2-Chloro-5-fluoropyrimidine (15 mmol) was added to a solution from ethanethiol (17 mmol) and potassium *tert*-butoxide in abs. ethanol (120 ml) and the mixture stirred at room temperature for 1 d before the solvent was distilled off. The residue was extracted with chloroform (100 ml), the chloroform solution shaken successively with water, 2 M NaOH (2×15 ml) and water, the dried ($MgSO_4$) solution evaporated and the residual material distilled; yield 76 % b.p. 94 °C/14 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.40 and 3.13 (EtS), 8.35 (H-4, H-6).

By hydrogenolysis of 13a: A mixture from 4-chloro-2-ethylthio-5-fluoropyrimidine (48 mmol) and 5 % Pd–C (2 g) in 0.7 M NaOH (165 ml) in a Parr apparatus was hydrogenated at 170 kPa and 20 °C 12 h. The catalyst was then removed by filtration and washed with dichloromethane. The filtrate was extracted with dichloromethane (4×40 ml), the combined organic solutions washed with water and dried ($MgSO_4$) before the solvent was distilled off and the residual material distilled as above; yield 78 %.

2-Ethylthio-5-iodopyrimidine 3b was prepared as above from *2b* in 82 % yield, m.p. 66 °C (2-PrOH). Anal. $C_6H_7IN_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.38 and 3.06 (EtS), 8.55 (H-4, H-6).

2-Ethanesulfinyl-5-fluoropyrimidine 4a. 85 % *m*-Chloroperbenzoic acid (1.5 mmol) was added to a solution of 2-ethylthio-5-fluoropyrimidine (1.5 mmol) in dichloromethane at −10 °C. The reaction mixture was kept at 0 °C until TLC monitoring (silica gel/EtOAc) showed the reaction to be complete (6 h). Thereafter the solution was successively shaken with aqueous sodium bisulfite and sodium bicarbonate and the dried ($MgSO_4$) solution evaporated. The residual material was distilled; yield 46 %, b.p. 132–134 °C/0.1 mmHg. Anal. $C_6H_7FN_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.26 and 3.13 (EtSO), 8.70 (H-6, H-4).

2-Ethanesulfinyl-5-iodopyrimidine 4b was prepared as above from *3b* keeping the reaction flask in the dark. The product which was isolated after 6 h, was purified by recrystallization from diisopropyl ether; yield 92 %, m.p. 96 °C. Anal. $C_6H_7IN_2OS$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.30 and 3.20 (EtSO), 9.03 (H-4, H-6).

2-Ethanesulfonyl-5-fluoropyrimidine[7] 5a. 85 % *m*-Chlorperbenzoic acid (3 mmol) was added to a solution of 2-ethanesulfinyl-5-fluoropyrimidine (2 mmol) in dichloromethane (80 ml) at 20 °C. The product was isolated as above; it crystallized slowly from diisopropyl ether at 0 °C; yield 79 %, m.p. 60–61 °C. Anal. $C_6H_7FN_2O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.43 and 3.54 ($EtSO_2$), 8.73 (H-4, H-6).

2-Ethanesulfonyl-5-iodopyrimidine 5b was prepared as above from *4b*. The reaction was run in the dark in order to avoid side-reactions caused by the iodine. TLC monitoring (silica gel/EtOAc) showed the reaction to be complete after 5 h at 20 °C. The solution was then shaken successively with saturated aqueous sodium bisulfite and sodium bicarbonate before the dried ($MgSO_4$) solution was evaporated. The residue was recrystallized from 2-propanol; yield 90 %, m.p. 138 °C. Anal. $C_6H_7IN_2O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.40 and 3.50 ($EtSO_2$), 9.08 (H-4, H-6).

2-Benzylthio-5-fluoropyrimidine 6. A mixture of 2-ethanesulfonyl-5-fluoropyrimidine (10 mmol) and potassium benzylthiolate (15 mmol) in 1,2-dimethoxyethane (75 ml) was stirred at 20 °C for 2 h before the mixture was filtered. The filtrate was evaporated, the residue extracted into diethyl ether which was successively shaken with 2 M NaOH and water before the dried ($MgSO_4$) solution was evaporated; yield 70 % (light petroleum), m.p. 39–41 °C. Anal. $C_{11}H_9FN_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 4.36 (SCH_2Ph), 7.23 (Ph), 8.33 (H-4, H-6).

2-Chloro-5-fluoro-4-methoxypyrimidine 8. 0.9 M Methanolic sodium methoxide was added dropwise with stirring to a solution of 2,4-dichloro-5-fluoropyrimidine[6] (54 mmol) in methanol (140 ml) at 0 °C. The mixture was stirred at 20 °C for 20 h, the methanol distilled off, the residue extracted with ether and the filtered ether solution evaporated to furnish an oily material which slowly crystallized on standing; yield 76 %, m.p. 30 °C (heptane at −10 °C). Anal. $C_5H_4ClFN_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 4.13 (OMe), 8.18 (H-6).

2-Chloro-4-ethylthio-5-fluoropyrimidine 9. A slurry from ethanethiol (88 mmol) and potassium *tert*-butoxide (88 mmol) in 1,2-dimethoxyethane (150 ml) was added dropwise with stirring at 0 °C to a solution of 2,4-dichloro-5-fluoropyrimidine[6] (88 mmol) in 1,2-dimethoxyethane (100 ml) during 35 min. The mixture was stirred at 20 °C for 36 h before filtration, the filtrate evaporated, the residue extracted with ether and the solution washed with water before the dried ($MgSO_4$) solution was evaporated to furnish the title

compound; yield 81 %, m.p. 47 °C (heptane). Anal. $C_6H_6ClFN_2S$: C, H. ^1H NMR ($CDCl_3$): δ 1.40 and 3.23 (SEt), 8.00 (H-6).

2-Ethylthio-5-fluoro-4-methoxypyrimidine 10. 2-Chloro-5-fluoro-4-methoxypyrimidine (91 mmol) was added gradually to a stirred slurry of potassium ethanethiolate (91 mmol) in 1,2-dimethoxyethane (300 ml). When the addition was completed, the temperature of the mixture was raised to 70 °C. The reaction mixture was kept at this temperature for 80 min before being worked up as above; yield 62 %, b.p. 104–107 °C/10 mmHg. Anal. $C_7H_9FN_2OS$: C, H. ^1H NMR ($CDCl_3$): δ 1.41 and 3.13 (SEt), 4.03 (OMe), 8.10 (H-6).

2,4-Diethylthio-5-fluoropyrimidine 11 was prepared under the above conditions from 2,4-dichloro-5-fluoropyrimidine (yield 52 %) or 2-chloro-4-ethylthio-5-fluoropyrimidine (yield 69 %) using two or one equivalents respectively of potassium ethanethiolate; b.p. 142–144 °C/14 mmHg. Anal. $C_8H_{11}FN_2S_2$: C, H. ^1H NMR ($CDCl_3$): δ 1.40 and 3.20 (SEt), 7.95 (H-6).

2-Ethylthio-5-fluoro-4(1H)-pyrimidinone[7,8] 12a. Method A: A suspension of 2-ethylthio-5-fluoro-4-methoxypyrimidine (31 mmol) in 2 M NaOH (120 ml) was heated under reflux for 26 h. The volume of the mixture was then reduced to *ca.* 50 ml at reduced pressure before extraction with ether. Acidification with acetic acid led to precipitation of the product; yield 84 %, m.p. 193–194 °C (H_2O). Anal. $C_6H_7FN_2OS$: C, H.

Method B; A suspension of 2,4-diethylthio-5-fluoropyrimidine in 2 M NaOH was heated under reflux for 3 d. The product was isolated as above; yield 69 %.

2-Ethylthio-5-iodo-4(1H)-pyrimidinone[9] 12b. 2-Ethylthio-4(1*H*)-pyrimidinone[10] (30 mmol) was dissolved in 2 M NaOH (42 ml) and dioxane (14 ml) and an aqueous solution of 3.55 M sodium dichloroiodide (20 ml) added dropwise with vigorous stirring. The pH was kept at *ca.* 9 by simultaneous additions of 2 M NaOH. When the addition was completed, the reaction mixture was heated at 60 °C for 10 min. The cold reaction mixture was acidified with acetic acid, the precipitate collected and redissolved in 2 M NaOH (20 ml). The sodium salt of the product was precipitated. The salt was dissolved in water and the solution acidified with acetic acid which precipitated the product; yield 48 %, m.p. 199–200 °C (2-PrOH). Anal. $C_6H_7IN_2OS$: C, H. ^1H NMR (DMSO-d_6): δ 1.30 and 3.10 (EtS), 8.16 (H-6).

4-Chloro-2-ethylthio-5-fluoropyrimidine[7] 13a. A mixture from 2-ethylthio-5-fluoro-4-(1*H*)-pyrimidinone (87 mmol) and DMF (0.9 ml) in thionyl chloride (33 ml) was heated under reflux for 3 h. The mixture was then evaporated to dryness, the residue triturated with ice-water (40 ml) and neutralized with sodium bicarbonate, the resultant mixture extracted with ether, the dried ($MgSO_4$) ether solution evaporated and the residue distilled; yield 78 %, b.p. 100–101 °C/12 mmHg. Anal. $C_6H_6ClFN_2S$: C, H. ^1H NMR ($CDCl_3$): δ 1.40 and 3.13 (EtS), 8.26 (H-6).

4-Chloro-2-ethylthio-5-iodopyrimidine[9] 13b was prepared from *12b* as above in 95 % yield, m.p. 67 °C (petroleum ether). Anal. $C_6H_6ClIN_2S$: C, H. ^1H NMR ($CDCl_3$): δ 1.36 and 3.12 (EtS), 8.63 (H-6).

2-Ethylthiopyrimidine[11] 14. A suspension of 2-ethylthio-4-chloro-5-iodopyrimidine (48 mmol) and 5 % Pd–C (2 g) in 0.7 M NaOH was hydrogenated at 170 kPa and 20 °C for 12 h. The catalyst was filtered off, the filtrate extracted with dichloromethane, the washed and dried solution evaporated and the residue distilled; yield 81 %, b.p. 106 °C/14 mmHg. ^1H NMR ($CDCl_3$): δ 1.38 and 3.16 (EtS), 6.89 (H-5), 8.44 (H-4, H-6).

2,4-Diethanesulfonyl-5-fluoropyrimidine 15. Chlorine gas was passed into a vigorously stirred suspension of 2,4-diethylthio-5-fluoropyrimidine (8.4 mmol) in ice-cold water (30 ml) for 5 min. The mixture was stirred at 0 °C for another 15 min before the addition of chlorine gas was repeated as above. After another 10 min the mixture was neutralized by addition of $NaHCO_3$, the product removed by filtration and washed with water. It was further purified by dissolution in DMF and the solution diluted with water when the product slowly crystallized out from the solution; yield 53 %, m.p. 132–134 °C. Anal. $C_8H_{11}FN_2O_4S_2$: C, H. ^1H NMR (DMSO-d_6): δ 1.30 and 3.61 ($EtSO_2$), 9.43 (H-6).

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