THE SYNTHESIS AND AMINOLYSIS OF SOME 4-CHLORO-2-(SUBSTITUTED)THIOPYRIMIDINES

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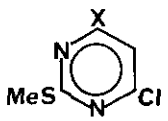
Abstract - Some 2-methylthio,2-methylsulphinyl and 2-methylsulphonyl-4-chloropyrimidines have been prepared. In each case which was studied except one the chloride ion was that which was preferentially displaced by diethylamine. The pseudo first order rate constant for each reaction was determined the results showing that oxidation of the 2-methylthio group greatly enhances the rate of displacement of the 4-chloro group.

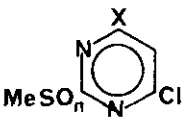
Methylthiopyrimidines are readily prepared and may be easily converted into the corresponding methylsulphinyl or methylsulphonyl derivatives using m-chloroperoxybenzoic acid.[1,2,3] These compounds, despite their potential usefulness as intermediates, seem to have been comparatively little studied. Although methylsulphonyl derivatives of a number of nitrogen heterocycles have been shown[4,5] to be about 40 to 100 times more reactive towards methoxide ion than the corresponding chloro compounds, in the case of the pyrimidines the methylsulphinyl and methylsulphonyl derivatives have been reported to be little more reactive than the corresponding chloropyrimidines although $>10^5$ times more reactive than the methylthio derivatives.[2]

A 4-chloropyrimidine usually has been considered to be more reactive than the corresponding 2-isomer although this has been shown to be not always the case in aminolysis.[4] We are interested in the synthesis of sulphur substituted pyrimidines, in their use as potential intermediates, and in their reactions and wish to report our studies of the aminolysis of some such compounds.

The methylthio compounds 1a, b, c and 2a were made by standard methods and the methylsulphonyl derivatives 2c, 3b and 3d were made by oxidising these with more than two equivalents of m-chloroperoxybenzoic acid. The methylsulphinyl compounds 2b, 3a and 3c were made using 1.2 equivalents of the peroxy acid. The reactions were carried out in dichloromethane or chloroform except for the synthesis of 3d which was carried out in dimethylformamide as the methylsulphinyl compound 3c precipitated readily from dichloromethane.

The pseudo first order rate constants for the displacement of the 4-chloro substituent of compounds 1a, c, 2a, b, c, 3a and 3b were measured by reacting them with a large excess (ten equivalents) of diethylamine in deuterochloroform solution and by following the change in ^1H nmr spectrum with time.





1(a) X = H

(b) X = NH_2

(c) X = $NHCOCH_3$

2(a) X = MeS

(b) X = MeSO

(c) X = $MeSO_2$

3(a) X = H , n = 1

(b) X = H , n = 2

(c) X = NH_2, n = 1

(d) X = NH_2, n = 2

Compounds 1b, 3c and 3d were insufficiently soluble in such a solution and these reactions were carried out in d_6-dimethylsulphoxide solution. In order to compare the effect of changing the solvent on the reaction rate, compounds 1a and 1c were studied in both solvents. The rates in dimethylsulphoxide were about ten times those in chloroform solution. Because of the considerable differences in the rates of reaction as the methylthio group was changed to the oxidised derivative the reaction temperature for each reaction had to be changed to give comparable and conveniently measurable rates. The results are shown in the Table.

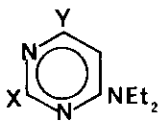
Compound number	Solvent	Temperature (°C)	Rate (S^{-1})
1a	d_6DMSO	35	1.74×10^{-4}
1a	$CDCl_3$	36	1.33×10^{-5}
3a	"	-31	3.60×10^{-5}
3b	"	-31	1.29×10^{-4}
2a	"	35	1.13×10^{-4}
2b	"	-30	1.80×10^{-4}
2c	"	-30	1.29×10^{-4}
1c	"	36	9.87×10^{-7}
1c	d_6DMSO	36	5.04×10^{-5}
1b	"	36	1.02×10^{-5}
3c	"	58	2.37×10^{-5}) *
3d	"	58	4.42×10^{-5})

* more than one product formed

Table. Rates of reaction of the 4-chloropyrimidines with diethylamine.

In all cases but two (3c and 3d) only one product was formed which was that resulting from displacement of the 4-chloro subsituent. The structures of the products were confirmed by ^1H nmr and mass

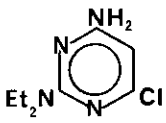
spectroscopy and in three cases preparative reactions were carried out, products 4a, b and 4c being obtained and fully characterised.



4(a) X = MeS, Y=H

(b) X = $MeSO_2$, Y=H

(c) X = $MeSO_2$, Y=NH_2



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In the case of 3d two products were formed the major product being the expected product 4c with the second product being the result of displacement of the 2-methylsulphonyl group to give 5 (product ratio approximately 4:1). However, the reaction of 3c gave 4-amino-6-chloro-2-diethylaminopyrimidine 5 as the major product (>60%) with at least two other products being formed in the reaction but with no evidence for the product resulting from displacement of the 4-chloro group.

Thus it seems that the substitution of a 4-chloro group is generally preferred to the substitution of a 2-methylsulphinyl or 2-methylsulphonyl group in the reaction of such compounds with diethylamine, and that the conversion of the methylthio group to the oxidised derivatives greatly increases the ease of this substitution. The introduction of a 5-bromo group further increases the rate of aminolysis of the 4-chloro group without directing attack to the 2-$MeSO_2$ group, but the presence of a 6-amino group decreases the ease of attack at the 4-chloro group and aids displacement of the 2-$MeSO_n$ group.

This work represents part of an extensive programme which we hope will provide data such that substituent groups may be chosen with the view to directing substitution at a required position and that the site of nucleophilic attack in the pyrimidine series may be predicted.

EXPERIMENTAL SECTION

All mps are uncorrected. ^1H nmr spectra are recorded with δ in ppm relative to Me_4Si using deuterochloroform as solvent, except where stated otherwise.

4-Chloro-2-methylsulphonylpyrimidine (3b)

4-Chloro-2-methylthiopyrimidine (1.0g) was dissolved in chloroform (5 ml) and m-chloroperoxybenzoic acid (4.0g, 2.2 equivs.) in chloroform (4.0 ml) was added slowly, with stirring. The reaction mixture was set aside for 24 h and was then washed with saturated sodium bicarbonate solution (2 x 30 ml) and water. The chloroform layer was dried (magnesium sulphate) and the solvent was removed to yield a white crystalline solid (67%), recrystallised from ether, of the 2-methylsulphonylpyrimidine, mp 87-89°C.(Found: C,31.4; H,2.6; N,13.7%. $C_5H_5ClN_2O_2S$ requires C,31.2; H,2.6;

N,14.5%). M^+192(^{35}Cl molecular ion). ^{1}H nmr 3.35(s,2-$MeSO_2$), 7.60(d,5-H), 8.85(d,6-H).

5-Bromo-4-chloro-2-methylsulphonylpyrimidine(2c)(90%)

mp 102-106°C(from dichloromethane:light petroleum) was obtained similarly but using dichloromethane as solvent. (Found: C,22.2; H,1.5; N,10.3%.$C_5H_4BrClN_2O_2S$ requires C,22.2; H,1.5, N,10.3%). ^{1}H nmr 3.35(s,2-$MeSO_2$), 9.00(s,6-H).

Using the above method but using 1.2 equivalents of m-chloroperoxybenzoic acid gave:

5-Bromo-4-chloro-2-methylsulphinylpyrimidine(2b)(92%)

mp 95-97°C (from ether).(Found:C,23.5; H,1.5; N,10.9%. $C_5H_4BrClN_2OS$ requires C,23.4; H,1.6; N,10.9%) ^{1}H nmr 2.99(s,2-MeSO), 8.98(s,6-H).

4-Chloro-2-methylsulphinylpyrimidine(3a)(95%) (oil at room temp).

M^+176(^{35}Cl molecular ion). ^{1}H nmr 2.95(s,2-MeSO), 7.45(d,5-H), 8.80(d,6-H).

4-Amino-6-chloro-2-methylsulphinylpyrimidine (3c)(90%)

mp 255-257°C (from ethanol).(Found:C,31.5; H,3.2; N,21.7%. $C_5H_6ClN_3OS$ requires C,31.3;H,3.1;N,21.9%) M^+191(^{35}molecular ion). ^{1}H nmr 3.30(s,2-MeSO), 6.50(s,5-H).

4-Amino-6-chloro-2-methylsulphonylpyrimidine (3d)

4-Amino-6-chloro-2-methylthiopyrimidine (1.0g) was dissolved in dimethylformamide (5 ml) and m-chloroperoxybenzoic acid (2.5g) in dimethylformamide (5 ml) was added with stirring. The reaction mixture was allowed to stir for two days then a further portion of the peroxy acid (1.25g) in dimethylformamide (5 ml) was added. After a further two days the reaction mixture was poured into ice-water (50g) and the precipitate was collected. The solid was triturated with saturated sodium bicarbonate solution, was collected, and was then recrystallised from ethanol to give the methylsulphonylpyrimidine (50%) mp 235-237°C. (Found: C,28.8;H,2.8; N,20.4%.$C_5H_6ClN_3O_2S$ requires C,28.9;H,2.9;N,20.2%). M^+207(^{35}molecular ion). ^{1}H nmr(d_6DMSO)3.25(s,MeSO),6.65(s,5-H).

4-Acetylamino-6-chloro-2-methylthiopyrimidine(1c)

4-Amino-6-chloro-2-methylthiopyrimidine (1.0g) and sodium acetate trihydrate (0.8g) were refluxed in acetic anhydride (10 ml) for 1¼ h. The reaction mixture was cooled and saturated sodium bicarbonate solution was added to give pH 7. The reaction mixture was extracted with dichloromethane (3 x 20 ml) and this extract was then washed with water and dried (magnesium sulphate). Removal of the solvent gave the acetylaminopyrimidine (52%) as pale yellow crystals mp 193-194°C(from dichloromethane:hexane). (Found: C,38.7;H,3.6;N,19.3%. $C_6H_8ClN_3OS$ requires C,38.6;H,3.7;N,19.3%). M^+217(^{35}Cl molecular ion). ^{1}H nmr 2.20(s,4-MeCONH),2.50(s,2-MeS),7.85 (s,5-H).

4-Diethylamino-2-methylthiopyrimidine(4a)

4-Chloro-2-methylthiopyrimidine (0.5g) and diethylamine (2.3g) were dissolved in chloroform (15 ml) and allowed to stand at room temperature for two weeks. The reaction mixture was washed

with water (3 x 20 ml), dried, and then evaporated to leave a solid residue which was recrystallised from ether:pentane to give colourless crystals (72%) mp 61-63°C. (Found: C,55.6;N,7.9;N,21.7%. $C_9H_{15}N_3S$ requires C,54.8;H,7.7;N,21.3%). M^+197. ^{1}H nmr 1.20(t,CH_3CH_2N), 2.50(s,2-MeS),3.50 (q,CH_3CH_2N),6.05(d,5-H),7.95(d,6-H).

4-Diethylamino-2-methylsulphonylpyrimidine (4b)

4-Chloro-2-Methylsylphonylpyrimidine (200 mg) and diethylamine (800 mg) were dissolved in chloroform (10 ml) and stirred at room temperature for 5 min. The reaction mixture was then washed with water (3 x 20 ml), dried (magnesium sulphate), and evaporated to give a light brown oil which was chromatographed (silica, ether) to give a colourless oil (65%). (Found: C,46.6; H,6.8;N,17.8%. $C_9H_{15}N_3O_2S$ requires C,47.1;H,6.6;N,18.3%). M^+229. ^{1}H nmr 1.20(t,CH_3CH_2N),3.25(s, 2-$MeSO_2$),3.55(q,CH_3CH_2N), 6.45(d,5-H), 8.20(d,6-H).

A similar reaction gave 4-diethylamino-2-methylsulphinylpyrimidine (25%) as a colourless oil purified by chromatography (silica, ethyl acetate). M^+213. ^{1}H nmr 1.20(t,CH_3CH_2N),2.85(s,2-MeSO), 3.55(q,CH_3CH_2N), 6.40(d,5-H), 8.20(d,6-H).

4-Amino-6-diethylamino-2-methylsulphonylpyrimidine (4c)

4-Amino-6-chloro-2-methylsulphonylpyrimidine (103 mg) and diethylamine (370 mg) were dissolved in dimethylsulphoxide (2 ml) and were heated in a sealed bottle at 65°C for 16 h. The reaction mixture was cooled and was then poured into water. The yellow crystals (76%) were collected and recrystallised from aqueous dimethylsulphoxide. mp 176-178°C. (Found: C,44.4; H,6.6; N,22.9%. $C_9H_{10}N_4O_2S$ requires C,44.3; H,6.6; N,22.9%). M^+244. ^{1}H nmr (d_6-DMSO)1.10(t,CH_3CH_2N), 3.20(s,2-$MeSO_2$), 3.40(q,CH_3CH_2N), 5.55(s,5-H).

(The minor product, about 10%, was shown by TLC, ^{1}H nmr and mass spectrum, to be compound 5).

A similar reaction using 4-amino-6-chloro-2-methylsulphinylpyrimidine (101 mg) and diethylamine (390 mg) in dimethylsulphoxide (4 ml) gave white needles of 4-amino-6-chloro-2-diethylamino-pyrimidine (5)(30%, isolated yield), mp 112-114°C (from aqueous dimethylsulphoxide)(lit.[6] 124-125°C, from benzene). (Found: C,48.0; H,6.5;, N.27.5%. $C_8H_{13}ClN_4$ requires C,47.9; H,6.5;, N.27.9%). M^+200 (^{35}Cl molecular ion). ^{1}H nmr 1.15(t,CH_3CH_2H), 3.55(q,CH_3CH_2N), 5.70(s,5-H).

(Extraction of the filtrate with dichloromethane and TLC examination of the extract showed at least two other compounds in addition to the major product but ^{1}H nmr and mass spectra showed no evidence for the presence of 4-amino-6-diethylamino-2-methylsulphinylpyrimidine).

Kinetic experiments

All kinetic experiments were carried out using a Jeol R32 nmr spectrometer with variable temperature probe.

The pyrimidine, together with diethylamine (10 equivalents), were dissolved in deuterochloroform or deuterodimethylsulphoxide and the rates of reaction were followed by measuring the integrals

of the 5 and/or 6 hydrogens of the pyrimidine ring of the starting materials and products as a function of time. The temperature of the experiments were chosen to give rates which could be easily measured in a reasonable time. The pseudo first order rate constant was obtained from the slope of the plot of log $\left(\frac{SM}{(SM+P)}\right)$ + 1 versus time where SM and P are the integrated areas of the appropriate hydrogens in the starting material and product respectively. Each reaction gave good straight line plots and the identity of each product was confirmed by ^{1}H nmr and by mass spectra.

REFERENCES

1. D.J. Brown, "The Pyrimidines", Wiley-Interscience, New York and London, 1962; "The Pyrimidines, Supplement I", 1970.
2. D.J. Brown and P.W. Ford, J.Chem.Soc.(C), 1967, 568.
3. D.T. Hurst, Aust.J.Chem., 1983, 36, 1477.
4. G.B. Barlin and D.J. Brown in "Topics in Heterocyclic Chemistry", Ed. R.N. Castle, Wiley-Interscience, New York, 1969, p.122.
5. G.B. Barlin and W.V. Brown, J.Chem.Soc.(C), 1967, 2473.
6. Y. Nitta, K.Okui and K. Ito, Chem.Pharm.Bull., 1965, 13, 557.

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