Regiocontrolled Amination of Dichloropyrimidines in $LiClO_4$-Et_2O Solutions.

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Abstract: Aminolysis of 4,6-dichloro-2-methylpyrimidine 1 and 2-thiomethyl-4,6-dichloropyrimidine 2 using 5M LPDE yields exclusively C-4 amino substituted pyrimidines, no trace of di-substitution was detected. Yields were moderate to good (27 - 82%), and the C6-C1 could be replaced by a second amine substituent (sealed tube reaction), again in good yields (34 - 79%).

Introduction

There has been an increased interest in the literature lately with regard to the synthesis of selectively substituted pyrimidine analogues; Chen *et al.* reported the synthesis of amino substituted pyrimidines and triazines in an attempt to delineate key structural features for inhibition of corticotropin releasing hormone (1); Botta *et al.* reported the direct nucleophilic C-4 hydroxyl substitution on 2-methoxy- and 2-methylthio-4(3H)-pyrimidones (2); and Xie and co-workers in the stereocontrolled synthesis of β-2'-deoxypyrimidine nucleosides (3).

We recently required a rapid and versatile method for the synthesis of a range of 4,6-amino-substituted pyrimidine analogues for an ongoing study within our group (Figure 1). As our intention was to develop a be versatile synthesis amenable to robotic based solution phase synthesis we wished to use readily available materials and were possible avoid tedious chromatographic separations.

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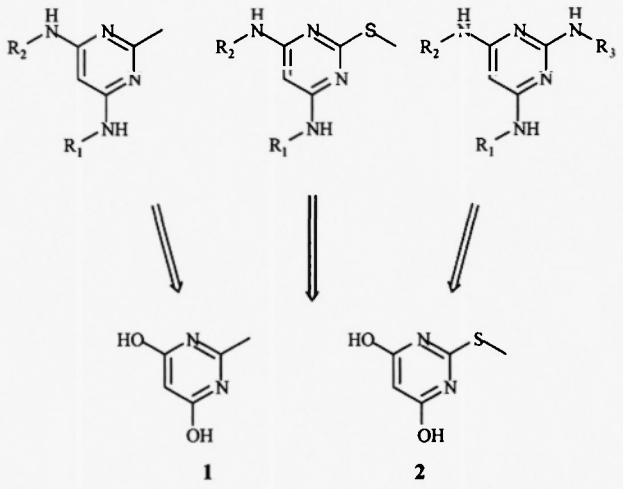
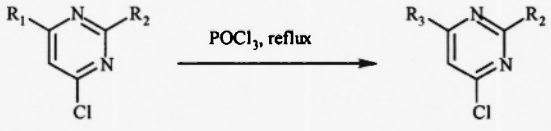


Figure 1. Synthetic targets, with a variety of potential amino substituent patterns

Results and Discussion

It has been shown previously, in the development of potent and selective adenosine agonists, that the mercaptomethyl moiety can be replaced by an amino group (sealed tube 110°C, EtOH, NHR_2) (4). Thus we originally believed it would be possible to mercaptomethyl group by aminolysis, followed by treatment with NaH and a variety of amines would generate our target compounds. Accordingly hydroxypyrimidines 1 and 2 were chlorinated with $POCl_3$ according to the method of Henze (5) (Scheme 1, compounds 3 and 4) in excellent yields (79% and 88% respectively) (6).

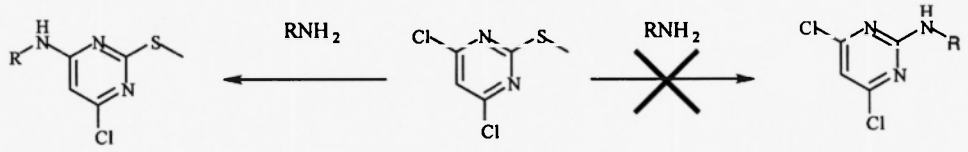


1 R_1 = OH; R_2 = CH_3 **3** R_1 = Cl; R_2 = CH_3 79%
2 R_1 = OH; R_2 = SCH_3 **4** R_1 = Cl; R_2 = SCH_3 88%

Scheme 1

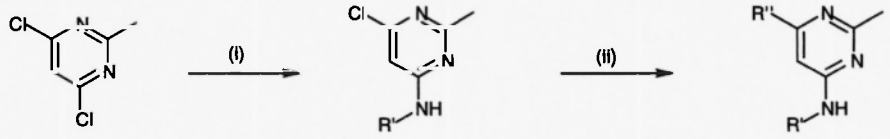
We then directed our attention towards the methylmercapto analogue 4 in the expectation of displacing the methylmercapto group with a variety of amines, however unlike the previous adenosine analogues no displacement was

observed. Instead we observed the selective displacement of the C-4 chlorine (scheme 2).



Scheme 2

As part of a separate project running within our group we have been exploring the use of 5M of lithium perchlorate in diethylether (LPDE) as a solvent system for the synthesis of cantharidin analogues. It occurred to us that LPDE mixture might mimic the effect of high pressure and allow our aminolysis reactions to proceed at room temperature (7). To the best of our knowledge LPDE mixtures have not previously been used in this manner (Scheme 3).

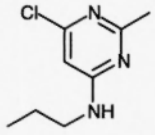
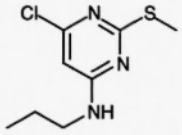
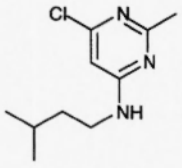
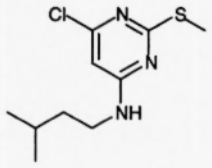
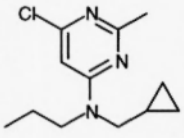
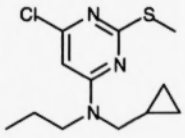
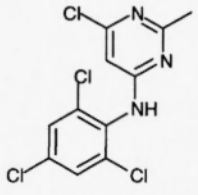
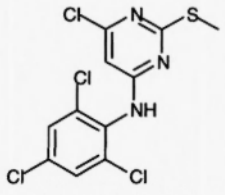


Scheme 3. Reagents and Conditions: (i) R'_2NH, 5M LPDE, rt, 16h; (ii); R''_2NH, sealed tube, 160°C, 24 h.

Typically, 3 (250 mg, 1.5 mmol) was dissolved in scrupulously anhydrous LPDE (5 mL) along with propylamine (1.26 mL, 10 equiv.), stirred at room temperature overnight (16 h, 20°C), followed by extractive work-up gave, in all instances mono-substituted products in moderate to good yields (Table I, entries: 1-8) (8).

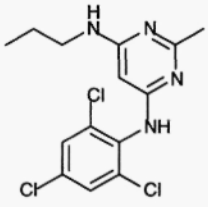
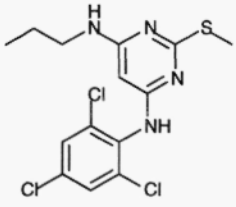
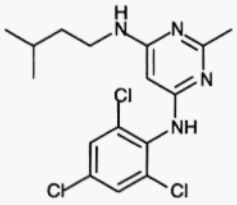
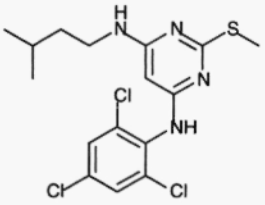
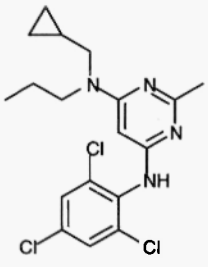
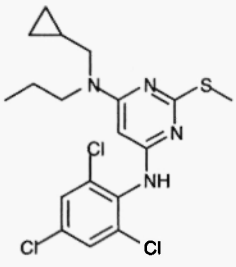
The final chlorine was then readily substituted with a range of amines by simply heating the amine and pyrimidine in a sealed tube at 160 ºC, with moderate yields (9).

Table I. Aminolysis of dichloropyrimidines 3 and 4.

Entry	Compound	Yield (%)	Entry	Compound	Yield (%)
1		57	5		61
2		38	6		61
3		50	7		27
4		82	8		60

In conclusion, 5M LPDE aminolysis of chlorinated pyrimidines proceeds with greater regio-control than the corresponding sealed tube procedure, and than that of any literature procedure that we are aware of, allowing the facile synthesis of the mono-aminated species.

Table II. Substitution of remaining chlorine atom by amines under the influence of pressure.

Entry	Compound	Yield (%)	Entry	Compound	Yield (%)
1		47	4		55
2		34	5		78
3		79	6		47

Acknowledgments

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References and Notes

1. C. Chen, R. Dagnino Jr, E. B. De Souza, D. E. Grigoriadis, C. Q. Huang, K. -I. Kim, Z. Liu, T. Moran, T. R. Webb, J. P. Whitten, Y. F. Xie, J. R. McCarthy, J. Med. Chem. 39, 4358 (1996).
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4. S. A. Poulsen, R. J. Quinn, J. Med. Chem. 39, 4156 (1996) and references cited therein.
5. H. R. Henze, W. J. Clegg, C. W. Smart, J. Org. Chem., 17, 1320 (1952).
6. Typical synthesis of chlorinated pyrimidines: **4,6-Dichloro-2-methylpyrimidine**
4,6-Dihydroxy-2-methylpyrimidine (5.0g, 40 mmol) was refluxed with $POCl_3$ (30 mL, 15 eq) for three hours, cooled to room temperature, the reaction mixture was slowly added dropwise to vigorously stirred ice water (200 mL) in a salt-ice bath (note: rapid addition leads to significantly lower yields). The yellow solid formed was collected by vacuum filtration (3.40 g). The filtrate was extracted with ethyl acetate (2x70 mL). The extract was washed with saturated NaCl (30 mL), dried over $MgSO_4$ and evaporated *in vacuo* to give an additional 1.72g of light brown solid. Recrystallising in ethyl acetate gave a light brown solid. Total yield 5.12 g, 79 %, MP. 48-49°C. ^1H NMR: 2.75 (s, 3H), 7.25 (s, 1H); ^{13}C NMR: 26.25, 118.97, 162.17, 170.39.
7. G Jenner, R. Bensalem, Tetrahedron, 53, 4637 (1997); A. Kumar, J. Org. Chem., 59, 4612 (1994).
8. Typical synthesis of monoaminated pyrimidines: **4-Chloro-2-methyl-6-(N-propylamino)pyrimidine**. 4,6-Dichloro-2-methylpyrimidine 3 (250mg, 1.5 mmol) was dissolved in 5mL of 5M LPDE. Propylamine (1.26 mL, 10 eq) was added and the sealed vessel was stirred for 24 hours. The solution was extracted with ether (3x30 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. This material was sufficiently pure for subsequent reactions. Analytical sample, the yellow solid was purified by flash chromatography with 15:85 ethyl acetate : n-hexanes and gave the product as an off-white solid. Yield 160 mg, 57 %, MP. 69-70°C. ^1H NMR: 0.82 (t, 3H), 1.48 (q, 2H), 2.31 (s, 3H), 3.08 (br s, 2H, $-CH_2-NH-$), 5.72 (br s, 1H), 6.10 (s, 1H); ^{13}C NMR: 11.79, 22.77, 26.06, 43.69, 97.92, 159.95, 164.02, 168.42.
9. Typical procedure for sealed tube reactions: **2-Methyl-4-(N-propylamino)-6-(2`,4`,6`-trichloroanilino)pyrimidine.** A solution of 4-Chloro-2-methyl-6-(2`,4`,6`-trichloroanilino)pyrimidine (150 mg, 0.46 mmol) in THF (10 mL) was added to a pressure vessel with propylamine (0.39 mL, 10 eq). The vessel was flushed with nitrogen, sealed and stirred at 160°C for 24 hours. The solvent was removed *in vacuo* to give a brown solid. The product was purified by flash chromatography with 1:4 ethyl acetate-hexanes to give a pale yellow solid. Yield 75 mg, 47 %, MP. 156-158°C. ^1H NMR: 0.85 (t, 3H), 1.48 (sex, 2H), 2.12 (s, 3H), 1.95 (q, 2H), 4.73 (s, 1H), 5.29 (br s, 1H), 7.38 (s, 2H); ^{13}C NMR: 12.06, 22.95, 25.73, 43.90, 78.75, 129.33, 133.44, 133.57, 136.02, 161.97, 164.07, 167.12.

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