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SYNTHESIS OF A PYRIMIDINE BY ELIMINATION OF NITROGEN FROM A TRIAZOLO[4,5-*D*]PYRIMIDINE

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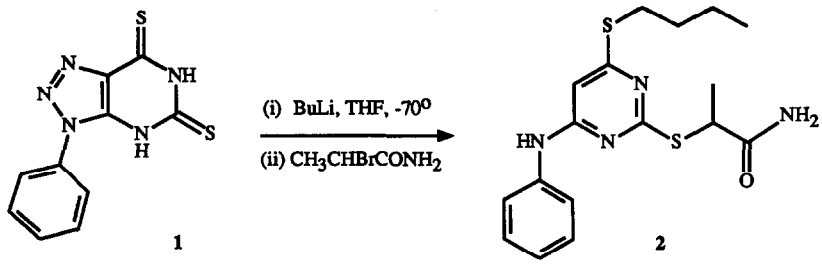
Summary. Treatment of 3-phenyl-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dithione with butyl lithium and an alkylating agent afforded a bis-alkylated pyrimidine, incorporating one butyl side chain.

We have recently proposed a model of the adenosine A1 and A2 receptors that defines the receptors as having three binding domains; a hydrophobic binding domain, an aromatic binding domain and a ribose binding domain.[1] The aromatic binding domain is described by a conserved 6 membered ring. We now report the synthesis of a six membered ring heterocyclic compound, 4-(n-butylthio)-6-(phenylamino)-2-propionamidylthiopyrimidine by elimination of nitrogen from a triazolopyrimidine. This appears to be the first monocyclic heterocyclic compound to exhibit binding to the adenosine receptor.

Treatment of 3-phenyl-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dithione (**1**)[2] in THF at -70° with n-butyllithium (3.0 equiv, hexane, 5 min) followed by 2-bromopropionamide (2.0 equiv in THF, over 20 min) and stirring for a further 45 min at -70° gave complete reaction (tlc analysis:- hexane - ethyl acetate 1:1). Quenching with water, extractive workup, silica gel flash chromatography (ethyl acetate - hexane 1:1) and recrystallization from ethyl acetate aforded **2** in 30% yield.[3] The product contained only one amide side chain, one methyl doublet at δ 1.56 in the ^{1}H NMR and a carbonyl and methine signals at δ 175.3 and 41.6 respectively in the ^{13}C NMR. The presence of a butyl side chain was apparent from both ^{1}H and ^{13}C NMR which showed signals for three methylenes and one methyl, the chain was apparently attached to a heteroatom as methylene signals occured at δ 3.06 in the ^{1}H and δ 31.3 in the ^{13}C NMR. Mass spectral analysis showed a base peak at 362 which together with the spectroscopic data indicated a formula of $C_{17}H_{22}N_4OS_2$. The loss of nitrogen from the precursor triazolopyrimidine was confirmed by a X-ray crystallographic analysis (**Figure 1**). Crystal/refinement data: -$C_{17}H_{22}N_4OS_2$, M = 362.6, Triclinic, space group $P\bar{1}$, a = 11.184(5), b = 10.066(11), c = 9.509(5)Å, α = 86.55(7), β = 68.61(3), γ = 68.40(7)°, V = 923 Å^3. D_c (Z = 2) = 1.30g cm^{-3}. $F(000)$ = 384. Monochromatic MoK_α radiation, λ = 0.71069Å, closely twinned crystal *ca* 0.2mm, μ_{Mo} = 2.5cm^{-1}, no absorption or extinction corrections. $2\theta_{max}$ = 45°, N_{indept}= 2414, N_{obs} = 1567; R_F = 0.064, R_W = 0.069 (statistical weights). Anisotropic thermal parameter refinement for non-hydrogen atoms; $(x,y,z,U_{iso})_H$ constrained at estimated values in full matrix least squares refinement.[4] The refinement model is consistent with the spectroscopic evidence.



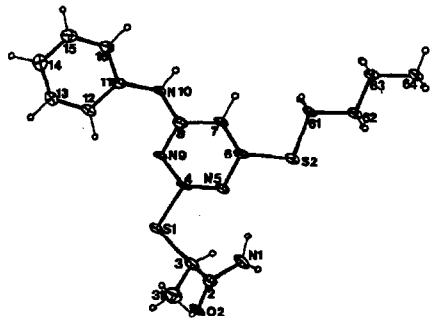


Figure 1 Projection of a single molecule normal to the central ring plane; 20% thermal ellipsoids are shown for the non-hydrogen atoms. Hydrogen atoms have arbitary radii of 0.1Å.

Table 1. Non-hydrogen atom coordinates

Atom	x	y	z
S(1)	0.1628(2)	0.8670(2)	0.3302(2)
S(2)	0.3758(2)	0.5368(2)	- 0.1736(6)
N(1)	0.3912(6)	0.9056(6)	- 0.0072(7)
C(2)	0.2973(7)	1.0026(7)	0.1089(7)
O(2)	0.3259(5)	1.0975(4)	0.1521(5)
C(3)	0.1609(7)	0.9870(6)	0.1822(7)
C(31)	0.0413(8)	1.1288(8)	0.2451(9)
C(4)	0.2216(6)	0.6959(6)	0.2344(7)
N(5)	0.2716(5)	0.6831(5)	0.0847(6)
C(6)	0.3112(7)	0.5464(6)	0.0231(7)
C(61)	0.4265(7)	0.3498(6)	- 0.2275(8)
C(62)	0.4927(7)	0.3281(6)	- 0.3987(7)
C(63)	0.5284(7)	0.1726(7)	- 0.4535(8)
C(64)	0.5927(9)	0.1487(8)	- 0.6252(9)
C(7)	0.2956(7)	0.4391(6)	0.1095(7)
C(8)	0.2433(6)	0.4666(6)	0.2675(7)
N(9)	0.2062(5)	0.5989(5)	0.3320(6)
N(10)	0.2298(5)	0.3591(5)	0.3559(6)
C(11)	0.1759(6)	0.3551(6)	0.5111(7)
C(12)	0.1234(7)	0.4727(7)	0.6184(8)
C(13)	0.0727(8)	0.4538(7)	0.7679(8)
C(14)	0.0673(8)	0.3267(8)	0.8204(8)
C(15)	0.1188(8)	0.2117(7)	0.7150(8)
C(16)	0.1701(7)	0.2271(7)	0.5659(8)

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References and Notes

1. R. J. Quinn, M. J. Dooley, A. Escher, F. A. Harden and H. Jayasuriya, *Nucleosides and Nucleotides*, in press
2. prepared following the method of A. Albert, C. I. Lin and I. Perkins, *J. Chem. Soc.*, 210 (1977).
3. Spectral data for **2**: m.p.: 142.7- 143.1°C; 1H-NMR (250MHz, $CDCl_3$): δ 0.91 (t, J 7.5 Hz, 3H, CH_3), 1.42 (sextet, 2H, CH_2); 1.56 (d, J 7.5Hz, 3H, CH_3); 1.61 (quintet, 2H, CH_2); 3.06 (ABX_2 system J_{AB} 13.1 Hz, J_{AX} 7.2Hz , J_{BX} 7.2Hz , δ_A 3.1, δ_B 3.01, 2H); 4.37 (q, J 7.5Hz, 1H, C-H); 5.75 (br s, 1H, amide N-H); 6.31 (s, 1H, C-H); 7.06 (br s, 1H, amide N-H); 7.17-7.41 (m, 5H, aromatic H); 7.52 (br s, 1H, N-H); 13C NMR ($CDCl_3$): δ 13.49 (CH_3), 16.34 (CH_3), 21.81 (CH_2), 29.29 (CH_2), 31.29 (CH_2), 41.55 (C-H), 95.66 (C-H), 123.01 (C2', C6'), 125.51 (C4'), 129.63 (C3', C5'), 137.67 (C1'), 159.62 (C), 169.32 (C), 170.00 (C), 175.27 (C=0); I.R. 3340 (N-H broad), 3180, 3230 (N-H), 2970, 2960, 2940, 1680, 1620, 1550, 1540 cm-1; UV (methanol): λ_{max} = 252, 305 nm (e = 26780, 16380), base shift: λ_{max}252, 306 nm; acid shift: λ_{max} 248, 311 nm.
4. Tables of structure factor amplitudes, thermal and hydrogen parameters and molecular geometries have been deposited at the Cambridge Crystallographic Centre.

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