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2(6)-ALKYL-3,5-DIAMINO-1,2,4,6-THIATRIAZINE 1,1-DIOXIDES. PART 1

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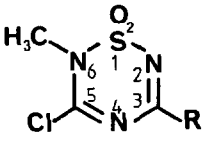
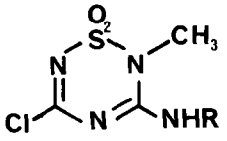
Abstract: New methods for the synthesis of 1,2,4,6-thiatriazine 1,1-dioxides are reported which allow for the first time selective preparation of either the 2-alkyl or 6-alkyl isomers 1 and 2.

The thiatriazine ring system has attracted interest since the discovery that certain 6-alkyl derivatives possess potent and selective herbicidal activity[1]. Access to these compounds, however, has been limited mainly to one synthetic route which only provides the 6-alkyl derivatives, such as 1a and 1b[2 3 4]. We have recently shown that some 4-alkyl-3,5-diamino-thiatriazines[5] are powerful histamine H_2-antagonists[6]. As part of our program to discover new histamine antagonists we have developed methods for the synthesis of novel 6-methyl thiatriazines and the corresponding 2-methyl isomers 2, which we now wish to report.



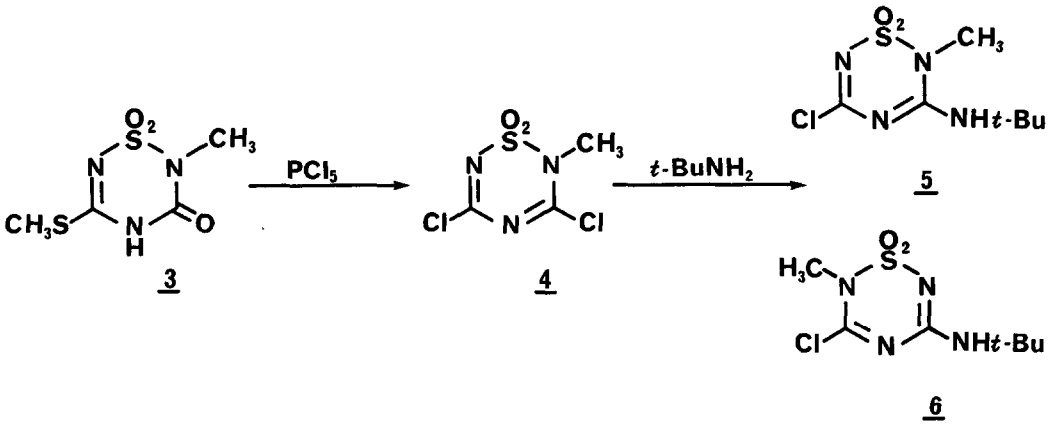
1a R=CH_3
1b R=$(CH_3)_2N$



2 R=Alkyl

Our synthetic strategy was to obtain thiatriazine systems having displaceable groups at the 3 (and 5) position(s) in order to allow the addition of various primary or secondary amines by nucleophilic substitution. Reaction of the previously reported thiatriazine-3-one 3[2] with PCl_5 ($POCl_3$, reflux, 18 hours) gave the highly reactive 3,5-dichlorothiatriazine 4 (mp 79°C, 73%). Treatment of this compound with 2 equivalents of t-butylamine (dry ether, 20°C, 15 minutes) gave a mixture of isomers 5 (mp 145-147°C) and 6 (mp 153-154°C) in a ratio of 2:1 (total yield 60%). Lowering the reaction temperature to -50°C changed the ratio of isomers obtained to 5:1 without altering the total yield.

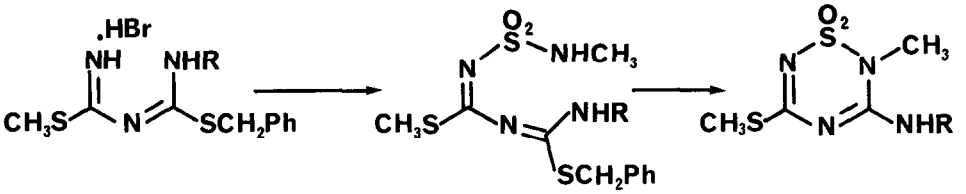
This shows the greater reactivity of the 3 position of the ring toward nucleophilic attack in spite of the steric interference which the approaching nucleophile must encounter at this site.



3 4 5 6

Isomers 5 and 6 were easily separated by fractional crystallization from dry ether. Structures could not conclusively be assigned on the basis of spectroscopic data[7], although a small long range coupling (J = 0.46Hz in $CDCl_3$) between the 2-methyl and adjacent NH was observed for isomer 5 but not for isomer 6.

A specific synthesis of isomer 5 was accomplished by treating di-isothiobiuret 7b[8] with methylaminosulfonyl chloride[9] (CH_2Cl_2, 20°C, 2.5 equivalents Et_3N) and cyclizing the intermediate 8b in refluxing acetonitrile (3 hours) to give thiatriazine 9b (mp 163-165°C, 89%). Chlorinolysis of the methylthio group of 9b (CH_2Cl_2, excess Cl_2, 30 minutes, 20°C) gave a chlorothiatriazine (83%) with identical melting point, nmr, and tlc characteristics to isomer 5.

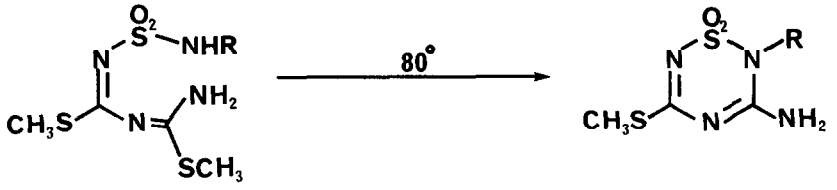


7a R=CH_3 8a R=CH_3 9a R=CH_3

7b R=t-Bu 8b R=t-Bu 9b R=t-Bu

The same reaction sequence was used to prepare compound 9a (mp 189°C), but interestingly the yield of 9a was only 40% compared with the higher yield of 9b. This may reflect an additional driving force given to the cyclization of 8b by release of steric strain between the neighbouring t-butyl and S-benzyl groups when benzyl mercaptan is displaced.

This cyclization is also subject to strong steric inhibition as shown by the observation that compound 10a[10] could be converted by refluxing acetonitrile to 11a (mp 282-283°C) in greater than 90% yield. Where R = isopropyl the yield of the expected derivative 11b (mp 228-230°C) was only 6% after 15 hours in refluxing acetonitrile, and where R = t-butyl only decomposition products were observed.



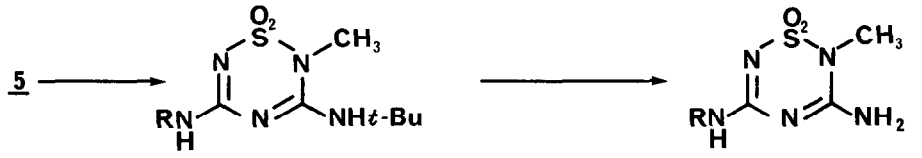
10a R = CH_3

10b R = *i*-Pr

11a R = CH_3

11b R = *i*-Pr

Chlorothiatriazines 5 and 6 react readily with primary and secondary amines as well as ammonia to give 3,5-diaminothiatriazines. For example, 5 may be reacted with ethylamine (2 equivalents, 20°C, dry ether, 15 minutes) to give 12a (mp 174-175°C, 68%). The ^1H nmr spectra of this and other t-butylaminothiatriazines show splitting of all the alkyl substituents on the ring[7], indicating that each of these derivatives exists in two stable conformations due to restricted rotation of the alkyl amino groups.



12a R = Et

12b R = H

13 R = H

Reaction of 5 with excess anhydrous ammonia (MeCN, 20°C, 1 hour) gave 12b (mp 217°C, 91%) which was treated with trifluoroacetic acid (72°C, 8 hours) to give the diaminothiatriazine 13 (R = H, mp 302°C, 70%). Compound 13 could also be obtained from 6 by the same sequence of reactions.

Acknowledgement: We wish to thank Dr. I. Ismail for providing all nmr spectral data and Mr. G. Hunt for his valuable technical assistance.

References

[1] G. Hamprecht, K.-H. Konig and G. Stubenrauch, Angew. Chemie Int. Ed., 20, 151-164 (1981).

[2] ICI, Ger. Patent 2,508,832 (1975).

[3] BASF, Ger. Patent 3,134,143 (1983).

[4] BASF, Ger. Patent 2,943,703 (1981).

[5] See following paper in this journal.

[6] Hoechst UK Ltd., Brit. Patent 2.129,426A (1984).

[7] ^{1}H nmr spectral data (250 MHz) in ppm for compounds:

4 ($CDCl_3$) 3.70 (3H, s).
5 ($CDCl_3$) 1.52 (9H, s), 3.36 (3H, s).
6 ($CDCl_3$) 1.44 (9H, s), 3.38 (3H, s).
9a (acetone-d_6) 2.42 (3H, s), 3.02 (3H, d), 3.35 (3H, s).
9b (acetone-d_6) 1.50 (9H, s), 2.36 (3H, s), 3.30 (3H, s).
11a (DMSO-d_6) 2.33 (3H, s), 3.23 (3H, s), 8.26 (2H, br.S).
11b (DMSO-d_6) 1.44 (6H, d), 2.32 (3H, s), 4.54 (1H, m).
12a (DMSO-d_6) 1.05 (3H, m), 1.41 (9H, d), 3.07-3.27 (2H, m), 3.18 (3H, d), 6.36 (1H, d), 7.54 (1H, 2 triplets).
12b (DMSO-d_6) 1.41 (9H, s), 3.18 (3H, s), 6.35 (1H, s), 7.05 (2H, d).

^{13}C nmr spectral data (62.89 MHz) in ppm for compounds:

5 (DMSO) 28.44 (t-Bumethyls), 29.56 (N2-Me), 54.85 (t-Bu tertiary C), 154.63 (C3), 160.09 (C5).
9b (DMSO) 28.49 (t-Bu methyls), 28.90 (N2-Me), 45.49 (SMe), 53.90 (t-Bu tertiary C), 153.64 (C3), 174.58 (C5).
12b (DMSO) 28.17 (N2-Me), 28.65 (t-Bumethyls), 52.78 (t-Bu tertiary C), 154.82 (C3), 159.56 (C5).
13 (DMSO) 28.19 (N2-Me), 157.80 (C3), 160.19 (C5).

[8] Compound 7b HBr (mp 153-156°C) was obtained by reacting S-methyl isothiourea with t-butylisothiocyanate to give 1-t-butyl-4-methyl dithiobiuret (mp 133, 17%) which was Salkylated using benzyl bromide to give 7b HBr (77%). Similarly 7a.HBr (mp 152°C) was obtained from S-methyl isothiourea and methyl isothiocyanate followed by benzyl bromide alkylation in 58% overall yield. See F.H.S. Curd, D.G. Davey, D.N. Richardson, R.B. Ashworth, J. Chem. Soc. 1739 (1949).

[9] J.A. Kloek, K.L. Leschinsky, J. Org. Chem. 41, 4028 (1976).

[10] Compounds of formula 10 were prepared by reacting the appropriate alkylaminosulfonyl chloride with dimethyl di-isothiobiuret (H. Eilingfield, H. Scheuermann, Chem. Ber. 100, 1874 (1967)) according to the same procedure used for compounds 8.

[11] All final products and key intermediates gave correct high resolution mass spectral or CHN elemental analysis.

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