Tetrahedron Letters,Vol.26,No.8,pp 1105-1108,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

SYNTHESIS OF 4-ALKYL-3,5-DIAMINO-1,2,4,6-THIATRIAZINE 1,1-DIOXIDES. PART II

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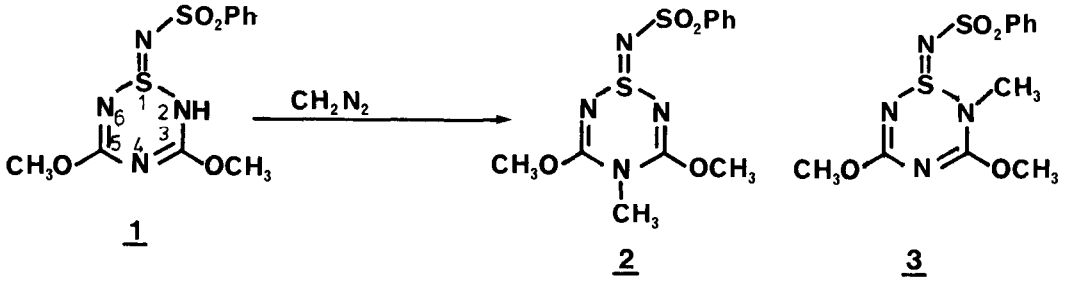
Abstract: 4-Alkyl-1,2,4,6-thiatriazine-1-oxides and dioxides have been prepared using a variety of new methods and their structures determined by ^{13}C nmr analysis.

As part of a program to discover new histamine H_2-antagonists[1], we required versatile new methods for preparing 4-alkyl-1,2,4,6-thiatriazine 1-oxides and dioxides. We now wish to report several synthetic methods we have used to prepare these compounds[2].

Only one example of a 4-alkyl-1,2,4,6-thiatriazine derivative has been reported in the literature[3]. This was prepared by methylation of 1-phenylsulfonylimino-3,5-dimethoxy-1,2,4,6-thiatriazine 1 with diazomethane to give one major product, which was assigned structure 2, and a minor component thought to be the isomer 3, although these structures were not rigorously proved. Related heterocycles, including a number of benzothiadiazine-1,1-dioxides, have been alkylated using a variety of alkylating agents. In most cases alkylation was reported to occur predominantly at the N-4 position[4].



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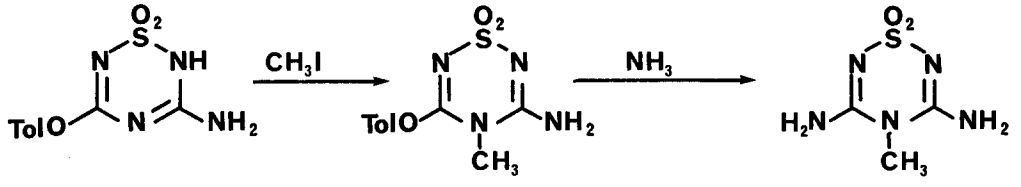
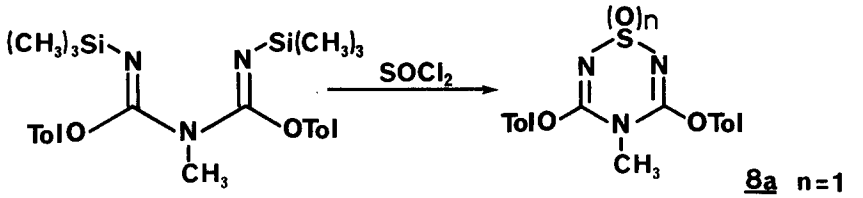
One approach which we adopted was based on this chemistry and used the previously reported thiatriazine 4 prepared from sulfamide and tolycyanate[5]. Methylation of this compound (1 equiv. $NaOCH_3$, MeCN; then MeI, 80°C, 3 hours) gave a mixture of isomers from which the major component 5 was separated by chromatography (mp 278-280°C, 23%). In order to confirm the position of alkylation this compound was treated with ammonia (MeCN, 45°C, 24 hours) to give the 3,5-diamino derivative 6 (mp 325-328°C, 85%).

^{13}C nmr showed the presence of only two resonances, one of which could be attributed to the methyl group (33.22 ppm) and the other (153.91 ppm) to the two ring carbon atoms of the symmetrical 4-methyl thiatriazine 6[6].



4 5 6

Due to the difficult separation of isomers and the low yields associated with the above route, a second approach to the synthesis of the N4-methyl thiatriazine 6 was investigated. Cyclization of the previously described bis-trimethylsilyl di-isobiuret 7[7] with thionyl chloride (CH_2Cl_2, 0°C, 1 hour) to give the S-oxide 8a (mp 232-233°C, 58%) followed by oxidation (m-$ClC_6H_4CO_3H$, $CHCl_3$, 20°C) gave the 3,5-bistolyl-4-methyl-1,2,4,6-thiatriazine 1,1-dioxide 8b (mp 290-291°C, 85%). Treatment of 8b with excess ammonia (MeCN, 35°C, 16 hours) gave compound 6 (98%) identical to the material prepared by our earlier procedure.



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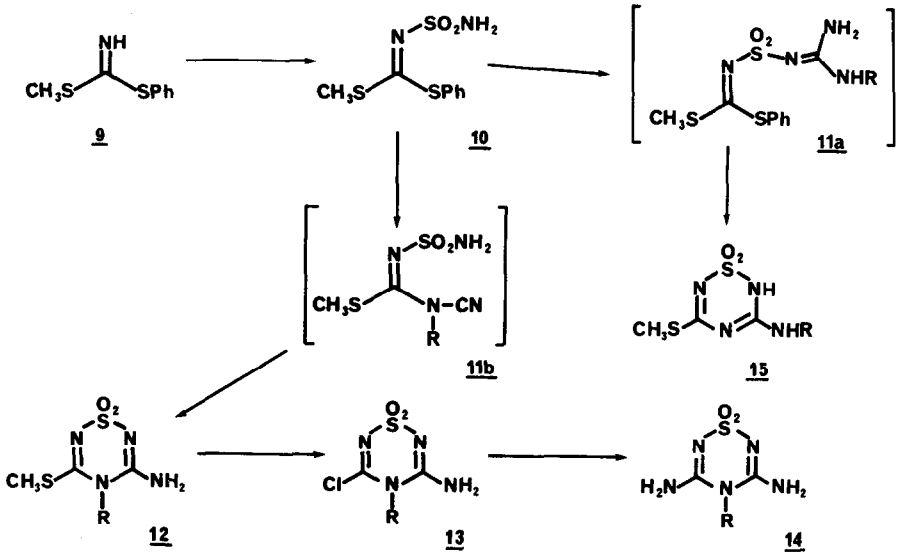
Cyclization of 7 could not be achieved with sulfuryl chloride and no product could be isolated pure from the attempted reaction.

The above method was, unfortunately, not of general synthetic utility for preparing other 4-alkyl thiatriazines because of the difficulty of preparing the required higher alkyl di-isobiurets. A more general route to these compounds was achieved by reacting the dithio-imidocarbonate 9[8] with sulfamoyl chloride [9](benzene, 20°C, Et_3N, 90 min) to give the sulfamide derivative 10 (mp 125-126°C, 60%). Treatment of 10 with one equivalent of NaH (dry THF, 0°C, 30 min) followed by reaction with an alkylcyanamide RNHCN [10](0° to 20°C, 18 hours) gave the 4-alkyl thiatriazine 12 (see table).

	R	Yield %	MPt °C
12a	Et	35	267-70
12b	*n*-Pr	29	217-18
12c	*n*-Bu	45	-
12d	CH_2Ph	62	264-65
12e	*i*-Pr	0	-
14a	Et	95	295-98
14b	*n*-Pr	95	-

In order to confirm that 12 was the desired 4-alkyl thiatriazine, it was converted to the 3,5-diamino derivative 14. As before ^{13}C nmr showed the symmetrical substitution pattern expected for the 4-alkyl isomer 14[11].

Direct conversion of 12 to 14 with ammonia was not possible, but chlorinolysis[2] of the methylthio group of 12 gave the 5-chlorothiatriazine 13 which reacted readily with excess anhydrous ammonia (MeCN, 20°C, 30 min) to provide 14.



Reaction of the sodium salt of 10 with the alkylcyanamide could proceed by two different mechanisms; the sulfamido anion of 10 attacking the nitrile group to give 11a, or proton exchange between the sulfamido anion and alkylcyanamide to give the cyanamide anion which then displaces thiophenol to give 11b. Intermediate 11a could cyclize in two ways, one of which would give compound 15. Intermediate 11b could only cyclize to the 4-alkyl compound 12. As we have found only 12 as the cyclized product from these reactions, 11b is suggested as the intermediate in this reaction sequence[12].

A variety of complex primary amines have been reacted with the chloro and phenoxy thiatriazines described below, leading to a number of highly active histamine H_2-antagonists. Details of this work will be published elsewhere.

Acknowledgement: We wish to thank Dr. I. Ismail for providing the ^{13}C nmr spectral data.

References and Notes

1 Hoechst U.K. Ltd., Brit. Patent 2,129,426A (1984).

2 See Part I, the preceeding paper in this journal.

3 E. Fischer, G. Rembarz and M. Teller, J. Prakt. Chem. 324 (6) 920 (1982).

4 I.C.I., Ger. Patent 2,508,832 (1975); H.L. Yale and J.T. Sheehan, J. Org. Chem., 26, 4315 (1961); G.C. Novello, S.C. Bell, E.L.A. Abrams, C. Ziegler and J.M. Sprague, J. Org. Chem., 25, 970 (1960).

5 Bayer, Ger. Patent 2,026,625 (1971).

6 The unsymmetrical 2-methyl isomer was prepared as described in the preceeding paper in this journal. ^{13}C nmr of this isomer clearly differentiated between the two ring carbons at C3 (157.80 ppm) and C5 (160.19 ppm).

7 D. Martin, K. Witke, P. Reich and K. Nadolski, Chem. Ber., 101, 3185 (1968).

8 W-D. Habicher and R. Mayer, Z. Chem., 8, 459 (1968).

9 R. Appel and G. Berger, Chem. Ber. 91, 1339 (1958).

10 A.D. Ainsley, F.H.S. Curd and F.L. Rose, J. Chem. Soc. 98 (1949).

11 ^{13}C nmr spectral data (62.89 MHz) in ppm for compounds:

5 (DMSO) 20.37 (aromatic-Me), 32.05 (N4-Me), 121.49 (Ph), 129.93 (Ph), 135.93 (Ph), 148.19 (Ph), 152.70 (C3), 154.17 (C5).
6 (DMSO) 33.22 (N4-Me), 153.91 (C3-C5).
12d (DMSO) 14.80 (SMe), 48.80 (N4-CH_2), 125.59 (Ph), 127.62 (Ph), 128.70 (Ph), 134.38 (Ph), 152.24 (C3), 164.45 (C5).
14a (DMSO) 13.23 (Me), 39.39 (N4-CH_2), 152.46 (C3-C5).
14b (DMSO) 9.0 (Me), 19.6 (CH_2), 44.4 (N4-CH_2), 151.8 (C3-C5).

12 Sterically hindered alkyl cyanamides such as isopropyl or t-butyl cyanamide fail to give cyclized products, and material isolated from these reactions shows an infra red absorption peak at 2200 cm^{-1} indicating the open structure 11b.

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

(Received in UK 7 December 1984)