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SYNTHESIS OF 1,2,4,6-THIATRIAZINE 1,1-DIOXIDES. PART III

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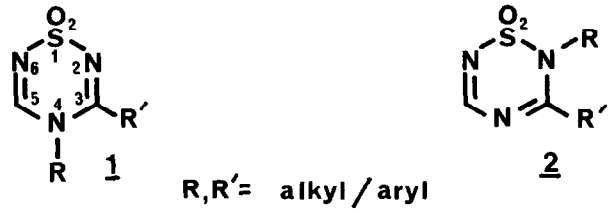
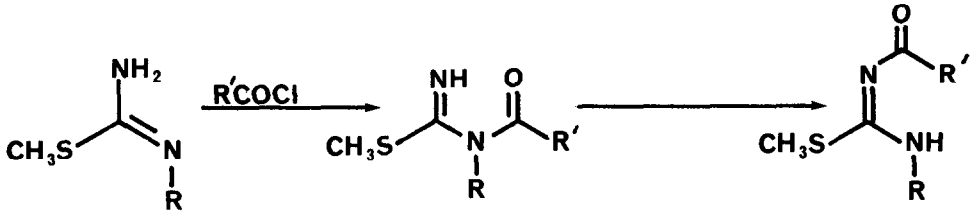
Abstract: Novel 1,2,4,6-thiatriazine 1,1-dioxides substituted at either the 2 or 4 ring nitrogen atom have been prepared by cyclizing sulfamido-iso(thio)urea derivatives.

We have recently reported methods for preparing the three possible isomeric forms of ring N-substituted 3,5-diamino-1,2,4,6-thiatriazine 1,1-dioxides [1,2]. We now wish to present some of the synthetic routes we have developed which give access to the 3-alkyl/aryl derivatives 1 and 2 of this ring system, and which complement and extend our procedure.



Our first approach to the 4-substituted isomer 1 required the preparation of the N-acyl isothioureas 4. Acylation of N-phenyl isothiourea 3a had been reported to give a single isomer 4a, which rapidly isomerized to 5a on warming [3].



3a R = Phenyl
3b R = Me

4a R = Phenyl, R′ = Me
4b R = Me, R′ = Phenyl
4c R′ = R = Me

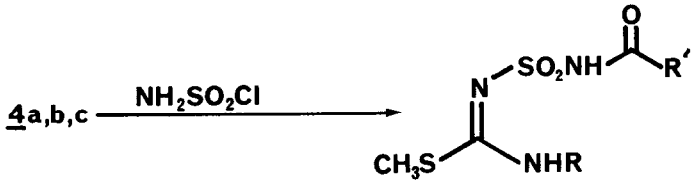
5a R = Phenyl, R′ = Me
5b R = Me, R′ = Phenyl
5c R′ = R = Me

We confirmed this report and similarly showed that N-methyl isothiourea 3b reacts with acetyl or benzoyl chloride (-20°C, THF, Et_3N, 15 min.) to give predominantly the analogous compounds 4b or 4c together with traces of the corresponding isomer 5b or 5c.

Compounds 4b and 4c were obtained as colourless oils[4,5] in yields of 55 and 65% respectively after chromatographic purification (silica gel, ether). If the acylations were carried out at room temperature, approximately equal amounts of isomers 4 and 5 were formed. Pure samples of 5b (mp 63-5°C) and 5c (mp 53°C) were obtained in this way after chromatography and recrystallization from ether-pentane. Both 5b and 5c were characterized from the expected nmr couplings (J = 5.23 Hz for 5b and J = 3.23 Hz for 5c in $CDCl_3$) between the N-methyl hydrogens and adjacent N-H, although for 5c the coupling was only observable at -30°C.

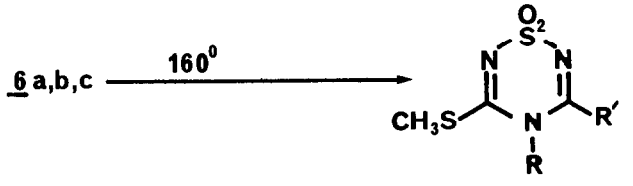
In contrast to the N-phenyl isothiourea 4a (mp 81-5°C), the N-methyl analogues 4b and 4c did not isomerize to 5b and 5c on heating (neat, 150°C, 10 min.) and were recovered unchanged.

Reaction of the N-acyl isothioureas 4 with aminosulfonyl chloride[7] (CH_3CN, 0°C, Et_3N, 30 min.) gave the sulfamide derivatives 6 in which ^1H nmr spectroscopy indicated that acyl group migration onto the sulfamide nitrogen had occurred[8]. In this way 6a (mp 154-6°C, N-H resonances at 9.00 and 9.93 ppm) was obtained in 90% yield, 6b (mp 152-3°C, N-CH_3 doublet at 3.18 ppm) in 91% yield[9], and 6c (mp 117-134°C, N-CH_3 doublet at 3.04 ppm) in 84% yield.



6a R = Phenyl R' = CH_3
6b R = CH_3 R' = Phenyl
6c R = R' = CH_3

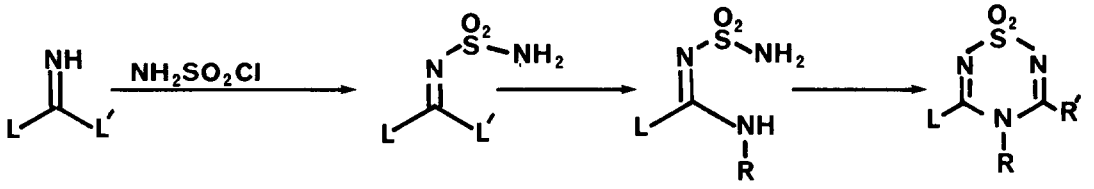
Base catalyzed cyclization[8] of compounds 6 to give the thiatriazines 7 could not be achieved because of the acidity of the acyl sulfamide hydrogen which was abstracted by base to give a stable and unreactive sulfamido anion. Cyclization was realised by heating in an inert solvent (160°C, diglyme) to give 7a (mp 298-300°C, 14%), 7b (mp 190-2°C, 21%), and 7c (mp 210-212°C, 64%).



7a R = Phenyl, R' = CH_3
7b R = CH_3, R' = Phenyl
7c R = R' = CH_3

Because of the low yields of thiatriazines 7 obtained from the above cyclization procedure, we investigated a second approach to these compounds. Imidocarbonates 8a[10] and 8b[11] were reacted with aminosulfonyl chloride (CH_2Cl_2, 20°C, Et_3N, 30 min.) to give the sulfamide derivatives 9a (mp 125-6°C, 60%) and 9b (mp 166-8°C, 37%).

Reaction with one equivalent of a primary amine (THF, 20°C, 30 min.) provided the isoureas 10a (mp 109-110°C, 86%), 10b (mp 141-2°C and 146-7°C, 86%), and 10c (mp 169-170°C, 87%) which could readily be cyclized by refluxing in acetonitrile with trimethyl orthoacetate (2 equivalents) to give 11a (mp 278-292°C (dec.), 46%), and 7c (mp 210°C, 50%), or with trimethyl orthoformate to give 11b (mp 166-170°C, 95%), and 11c (mp 259-260°C, 81%).



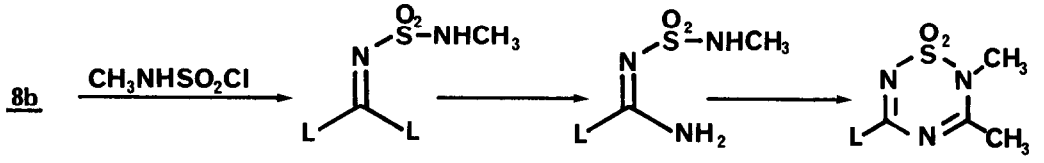
8a L = CH_3S, L' = PhS
8b L = L' = 2-$NO_2C_6H_4O$

9a, b

10a L = CH_3S, R = H
10b L = CH_3S, R = CH_3
10c L = $2NO_2C_6H_4O$, R = C_2H_5

11a L = CH_3S, R = H, R' = CH_3
11b L = CH_3S, R = R' = H
11c L = 2-$NO_2C_6H_4O$, R = C_2H_5, R' = H

The isomeric 2-methyl thiatriazines 2 were prepared using a sequence of reactions analogous to those described above. For example, reaction of 8b with methylaminosulfonyl chloride[12] (CH_2Cl_2, Et_3N, 20°C, 30 min.) gave sulfamide 12 (mp 171-2°C, 82%) which was treated with one equivalent of ammonia (THF, 0°C, 30 min.) to give the isourea 13 (mp 150-1°C, 85%). Cyclization of 13 using 3 equivalents of methylorthoacetate in refluxing acetonitrile (18 hours) gave the 2,3-dimethyl thiatriazine 14 (mp 212-214°C, 54%) after evaporation of the solvent and recrystallization from acetone.



12 **13** **14**

L = 2-$NO_2C_6H_4O$

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References and Notes

[1] J.D. Michael, P.M. Rees and B.C. Ross, Tet. Letters, 26(8), 1101 (1985).

[2] S.J. Cousins, B.C. Ross, G.N. Maw and J.D. Michael, Tet. Letters, 26(8), 1105 (1985).

[3] H.L. Wheeler, Am. Chem. J., 27, 270 (1902).

[4] A crystalline sample of 4c HI was prepared by bubbling dry HI through an ethereal solution of 4c and recrystallizing the precipitate from ethanol/ether, mp 155-6°C (see note 5 below).

[5] Pure 4c.HI could also be prepared by the method of A.E. Dixon and J. Hawthorne, J. Chem. Soc., 91, 132 (1907). They prepared the N-phenyl-N-acetyl thiourea corresponding to 4a by acetylation and rearrangement of N-phenylthiourea. We adapted this procedure starting from N-methyl thiourea which was reacted with acetyl chloride in acetone to give S-acetyl-N-methylisothiourea-HCl (100%, mp 96-102°C). This was rearranged by treatment with Et_3N in acetonitrile at 20°C to give N-acetyl-N-methyl thiourea (84%, mp 110-112°C). Reaction of the thiourea with methyl iodide (2 equivalents) in acetonitrile (20°C, 18 hours) gave 4c.HI (89%, mp 155-6°C) which was uncontaminated by any of the isomeric form 5c.

[6] ^{1}H nmr spectral data (250 MHz) at 20°C in ppm:

4b ($CDCl_3$) 2.23 (3H, s), 3.32 (3H, s), 7.30 (5H, m).
4c ($CDCl_3$) 2.24 (3H, s), 2.40 (3H, s), 3.24 (3H, s).
5b ($CDCl_3$) 2.62 (3H, s), 3.04 (3H, d), 7.43 (3H, m), 8.17 (2H, m).
5c ($CDCl_3$) 2.15 (3H, s), 2.47 (3H, s), 2.97 (3H, s).
6a ($CDCl_3$) 2.17 (3H, s), 2.36 (3H, s), 7.39 (5H, m), 9.00 (1H, s), 9.93 (1H, s).
6b ($CDCl_3$) 2.45 (3H, s), 3.18 (3H, d), 7.63 (3H, m), 7.95 (1H, d), 8.75 (1H, d), 9.36(1H,s)
6c ($CDCl_3$) 2.23 (3H, s), 2.42 (3H, s), 3.04 (3H, d), 8.43 (1H, br.s), 9.35 (1H, br.s).
7a (DMSO-d_6) 1.90 (3H, s), 2.31 (3H, s), 7.64 (5H, m).
7b ($CDCl_3$) 2.58 (3H, s), 3.42 (3H, s), 7.56 (5H, m).
7c (DMSO-d_6) 2.36 (3H, s), 2.43 (3H, s), 3.32 (3H, s).
9a ($CDCl_3$) 2.35 (3H, s), 7.53 (5H, s). 9b (DMSO-d_6) 7.32-8.32 (8H, m).
10b (DMSO-d_6) 2.35 (3H, s), 2.90 (3H, s).
10c (DMSO-D_6) 1.23 (3H, t), 3.44 (2H, m), 7.46-8.18 (4H, m).
11a (CD_3CN) 2.16 (3H, s), 2.49 (3H, s).
11b (DMSO-d_6) 1.39 (3H, t), 4.05 (2H, q), 7.66-8.31 (4H, m), 8.35 (1H, s).
11c (CD_3CN) 2.49 (3H, s), 7.63 (1H, s). 12 (DMSO-d_6) 2.50 (3H, d), 7.22-8.32 (8H, m).
13 (DMSO-d_6) 2.32 (3H, d), 6.67 (1H, q), 7.40 (1H, s), 7.48-8.17 (4H, m), 8.81 (1H, s).
14 ($CDCl_3$) 2.49 (3H, s), 3.57 (3H, s), 7.33-8.19 (4H, m).

[7] R. Appel and G. Berger, Chem. Ber., 91, 1339 (1958).

[8] Migration of a carbonyl group on treatment with aqueous base has been observed in a similar compound: R.-D. Acker, G. Hamprecht and E. Hadicke, Angew. Chem. Int. Ed., 20, 884 (1981).

[9] This compound was also prepared directly by reacting benzoylamino sulfonyl chloride (german Patent 931,225 (1952) Hoechst) with the dithioimidocarbonate 8a, and treating the resulting (32%) sulfamide with one equivalent of methylamine to give 6b (53%) with identical tlc, nmr, and mp to material obtained from 4b.

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

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

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