1,2,4-Triazines. 5. Regioselective N2-Amination of 3-Methylthio-1,2,4-triazin-5(2*H*)-ones. A New Efficient Synthesis of [1,2,4]Triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-one (1)

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A regioselective synthesis of 2-amino-1,2,4-triazinones (**3a-b**) is reported, by reaction of 3-methylthio-1,2,4-triazinones (**1a-b**) with *O*-(2,4-dinitrophenyl)hydroxylamine (**2**), as an amino transfer agent. A spectroscopic study and an unequivocal synthesis of 2-amino-4-methyl-6-phenyl-1,2,4-triazinone (**8a**) has shown the site of amination to be N2 of the 1,2,4,-triazinone ring. Subsequent reaction of 2-amino-1,2,4-triazinone (**3b**) with ammonium hydroxide, followed by ring closure with formic acid provided [1,2,4]triazolo[2,3-*b*][1,2,4]triazin-7 (1*H*)-one (**10**).

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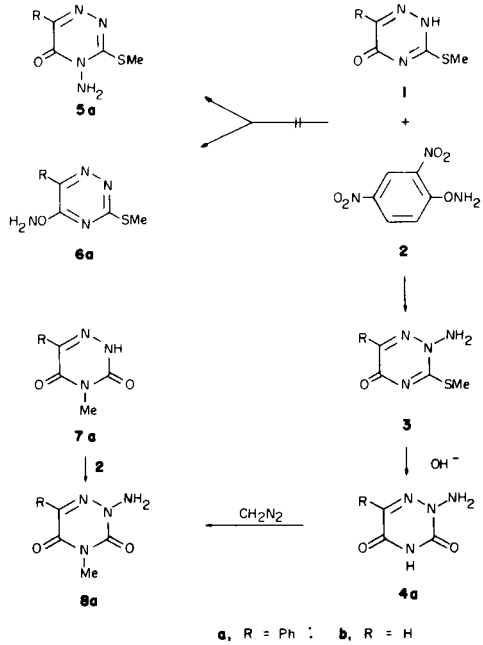
The recent report (2) of a new method for the preparation of [1,2,4]triazolo[1,2,4]triazine heterocycles, in particular [1,2,4]triazolo[2,3-*b*][1,2,4]triazines prompts us to describe a new procedure which we have recently found successful. Our procedure involves the key intermediate preparation of 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones (**3a-b**), this being produced by regioselective N2-amination (3) of 3-methylthio-1,2,4-triazin-5(2*H*)-ones (**1a-b**) (4) with an aminating agent (5) such as *O*-(2,4-dinitrophenyl)-hydroxylamine (**2**). The transformation of 2-amino-3-methylthio-1,2,4-triazinone (**3b**) to [1,2,4]triazolo[2,3-*b*][1,2,4]triazin-7(1*H*)-one (**10**) was accomplished by converting **3b** to 2,3-diamino-1,2,4-triazin-5(2*H*)-one (**9**), followed by ring closure with formic acid.

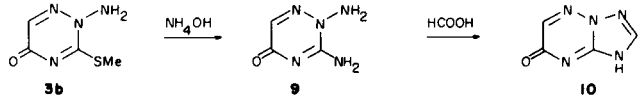
Scheme I



The reaction of 3-methylthio-6-phenyl-1,2,4-triazinone (**1a**) (4) with **2** in the presence of *n*-butyllithium in tetrahydrofuran at room temperature afforded only one product after chromatography. Compound **3a** (7a) has the expected molecular formular, $C_{10}H_{10}N_4OS$. The ^1H nmr spectrum of **3a** exhibited a singlet at δ 6.67 presumably due to an amino group because it was extinguished by addition of deuterium oxide. This indicated that an amino group was introduced into **1a**. Theoretically, there should be three possibilities for amination, *i.e.*, either N2, N4, or O5 (**3a, 5a** and **6a**).

The structure of **3a** was elucidated on the basis of spectroscopic and chemical studies. The fact that **3a** was different from the known 3-methylthio-4-amino-6-phenyl-1,2,4-triazin-5(4*H*)-one (**5a**) (6) in every respect tested (melting point, mixture melting point, and infrared spectrum), clearly established that no N4-amination took place. The possibility of O5-amination to give 6-phenyl-1,2,4-triazine (**6a**) was ruled out because of an infrared signal at 1620 cm^{-1} presumably due to the carbonyl group.

Scheme II

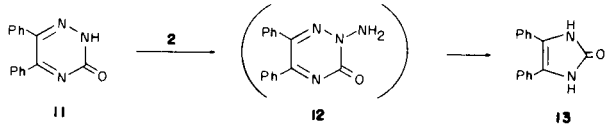


Treatment of **3a** with 1.1 equivalents of sodium hydroxide under reflux for 1 hour provided 1,2,4-triazindione (**4a**) (7b) in 63% yield after neutralization with glacial acetic acid. An excess of basic media (more than 1.3 equivalents) and prolonged reaction time (longer that 2 hours) resulted in decomposition of **4a**. Attempted hydrolysis of **3a** with 18% hydrochloric acid gave a complex mixture from which none of the desired 1,2,4-triazindione (**4a**) could be isolated. The reaction of ethereal diazomethane

with **4a** gave in a nearly quantitative yield a monomethylated 1,2,4-triazindione, which was identical, in all respects (melting point, mixture melting point, and infrared spectrum), with 2-amino-4-methyl-6-phenyl-1,2,4-triazindione (**8a**) (7c) prepared by the reaction of **2** on 4-methyl-6-phenyl-1,2,4-triazinone (**7a**) (4) (Scheme I). We can now unequivocally state that amination of **1a** with **2** in basic condition proceeds regioselectively to give the N2 aminated 1,2,4-triazinone (**3a**). Likewise, 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-one (**3b**) (7d) was also prepared under similar condition as described above.

The synthesis of unsubstituted [1,2,4]triazolo[2,3-*b*]-[1,2,4]triazinone (**10**) was achieved by a two step sequence starting with **3b** (Scheme II). Treatment of **3b** with 18% ammonium hydroxide in a sealed tube at 100° gave 2,3-diamino-1,2,4-triazinone (**9**) (7e) in 86% yield after recrystallization. Ring closure of **9** was accomplished using excess formic acid under reflux for 8 hours to furnish the desired [1,2,4]triazolo[2,3-*b*][1,2,4]triazinone (**10**) (7f) in 89% yield. That ring cyclization had occured was established by the appearance of a sharp singlet for H-2 at δ 8.14 in the ^{1}H nmr spectrum.

In conclusion, this study represents the first example of the synthesis of 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones and a synthetic route for the [1,2,4]triazolo[2,3-*b*]-[1,2,4]triazin-7(1*H*)-one. We believe that 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones now readily available, are highly promising as synthetic intermediates of the fused [1,2,4]triazine heterocycles.



REFERENCES AND NOTES

(1) For part **4**, see Y. Nakayama, Y. Sanemitsu, H. Yoshioka and A. Nishinaga, *Tetrahedron Letters*, **23**, 2499 (1982).

(2) J. Daunis and H. Lopez, *J. Org. Chem.*, **42**, 1018 (1977).

(3) Attempted N2-Amination of 5,6-diphenyl-1,2,4-triazin-3(2*H*)-one (**11**) with aminating agents such as hydroxylamine-*O*-sulphonic acid and *O*-(2,4-dinitrophenyl)hydroxylamine (**2**) was reported to lead to the formation of 4,5-diphenylimidazolin-2-one (**13**) in a new ring contraction reaction. 2-Amino-triazinone was proposed as the intermediate (**12**) but it was not isolated; see C. W. Rees and A. A. Sale, *J. Chem. Soc., Chem. Commun.*, 531 (1971); *J. Chem. Soc., Perkin Trans. 1*, 545 (1973).

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(7) All new compounds gave satisfactory microanalytical data and demonstrated the following properties: (a) **3a**, 62%, mp 221-222°; ir (potassium bromide): 1620 (C=O) cm^{-1}; pmr (DMSO-d_6): δ 2.47 (s, 3H, SCH_3), 6.67 (s, 2H, NH_2). 7.30-8.30 (m, 5H, arom). (b) **4a**, 63%, mp 169-170°; ir (potassium bromide): 1680 and 1720 (two C=O) cm^{-1}; pmr (DMSO-d_6): δ 5.75-5.95 (br s, 2H, NH_2), 7.30-8.10 (m, 5H, arom), 12.15-12.65 (br s, 1H, NH). (c) **8a**, 89% from **4a** and 47% from **7a**, mp 118-119°; ir (potassium bromide): 1640 and 1700 (two C=O) cm^{-1}; pmr (DMSO-d_6): δ 3.35 (s, 3H, CH_3), 4.90-5.50 (br s, 2H, NH_2), 7.20-8.20 (m, 5H, arom). (d) **3b**, 35%, mp 215-216°; ir (potassium bromide): 1620 (C=O) cm^{-1}; pmr (DMSO-d_6): δ 2.30 (s, 3H, SCH_3), 6.51 (s, 2H, NH_2), 7.48 (s, 1H, H6). (e) **9**, 86%, mp 278-279°; ir (potassium bromide): 1660 (C=O) cm^{-1}; pmr (DMSO-d_6): δ 6.01 (br s, 2H, N-NH_2), 7.07 (s, 1H, H6), 6.90-7.20 (br s, 2H, NH_2). (f) **10**, 89%, mp 213-214°; ir (potassium bromide): 1570 (C=O) cm^{-1}; pmr (DMSO-d_6): δ 7.85 (s, 1H, H6), 7.60 -8.20 (br s, 1H, NH), 8.14 (s, 1H, H2).