Tetrahedron Letters,Vol.26,No.50,pp 6155-6158,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

1,2,5-THIADIAZOLE-1-OXIDES, IV, RING TRANSFORMATION TO 1,2,3,5-THIATRIAZOLE- AND 1,2,4,6-THIATRIAZENE-1-OXIDE

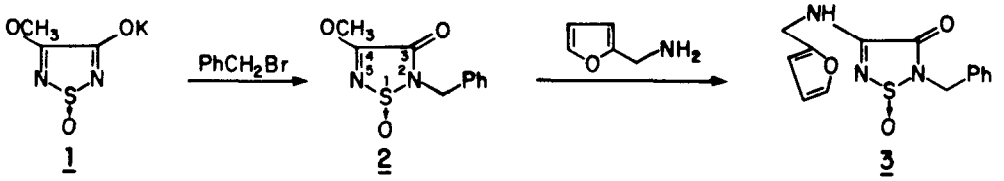
Sandor Karady*, Joseph S. Amato, Robert A. Reamer
and Leonard M. Weinstock

Process Research Department
Merck Sharp & Dohme Research Laboratories
Rahway, New Jersey 07065

Summary: 2-Alkyl-1,2,5-thiadiazole-3-one-1-oxides were converted to 1,2,3,5-thiatriazole-1-oxides and 1,2,4,6-thiatriazene-1-oxides. The postulated intermediate of these rearrangements, a sulfinylamine, was isolated.

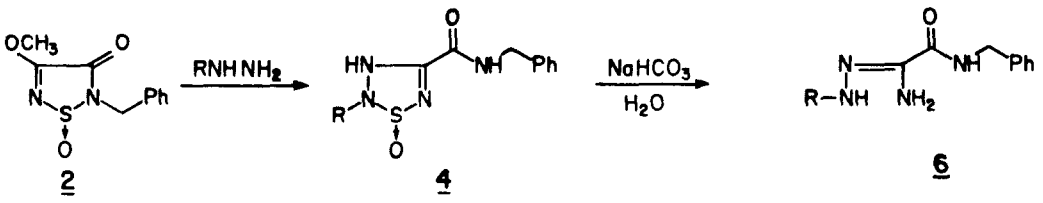
In the previous papers in this series we described the synthesis, basic chemistry[1] and a study of the inversion barrier[2] of 1,2,5-thiadiazole-1-oxides. Pharmacological activity associated with this unusual sulfoxide has also been reported[3]. In this and the subsequent paper we describe a unique property of this ring system: its propensity to rearrange to other heterocyclic systems.

As reported earlier[(1)], the N-alkyl derivatives 2, obtained by alkylation of the corresponding alcoholate 1, undergo smooth displacement with nitrogen nucleophiles to produce stable amino derivatives, e.g. 3, in good yield.



1 2 3

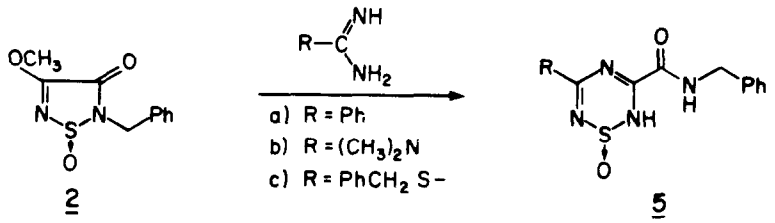
In contrast to this, bifunctional nucleophiles cause a complete rearrangement of the system exemplified by the reaction with substituted hydrazines which initiates a conversion to the little known thiatriazole oxides 4[4,5].



a, R = Ph
b, R = CH_3

The reactions were carried out by stirring the solution of the reagents overnight at room temperature. In this manner the phenyl analog 4a was prepared in 47% yield, by filtration of the precipitated crystals from the chilled reaction mixture (CH_3CN). Similarly, the methyl derivative 4 b was obtained in 30% yield by removal of the solvent (MeOH) and crystallization from CH_3CN. The thiatriazole oxides are nicely crystalline, stable compounds, but on hydrolysis with aqueous sodium bicarbonate (reflux, 10 min) the sulfur was removed and 6 was obtained in good yield.

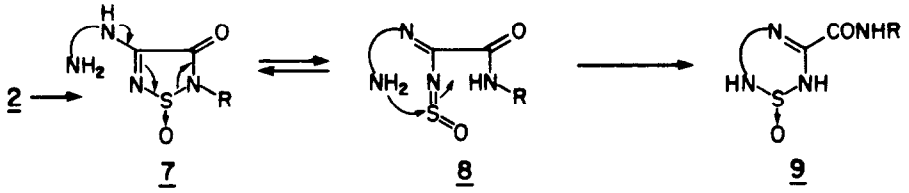
In an analogous ring transformation with amidine type binucleophiles, 1,2,4,6-thiatriazene oxides 5[6] were obtained in fair yield.



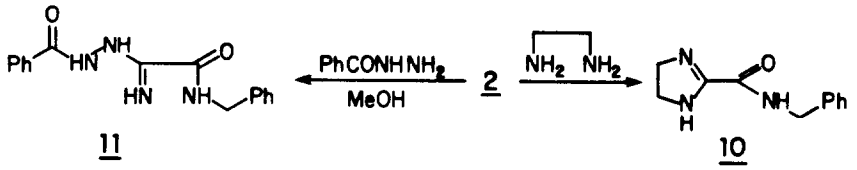
a) R = Ph
b) R = $(CH_3)_2N$
c) R = $PhCH_2S$-

These reactions were conducted in a methanol solution at room temperature overnight. When the reagents were hydrochloride salts, an equivalent of sodium methoxide was used for neutralization. Thus, 5a was obtained in 40% yield by reaction with benzamidine hydrochloride. After the solvent was evaporated, the residue was partitioned between water and ethyl acetate and the product was crystallized from benzene/cyclohexane. Thiatriazene 5b was prepared similarly in 45% yield (crystallization from ethanol). When 2 was allowed to react with 2-benzyl-2-thiopseudourea, 5c precipitated from the reaction mixture in 35% yield. The generality of these rearrangements was demonstrated by the preparation of a large number of alkyl and aryl substituted analogs of 4 and 5.

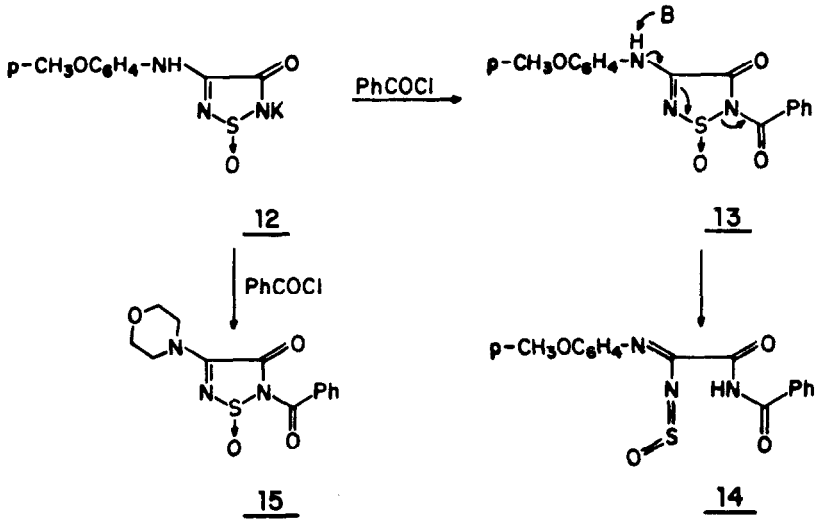
These rearrangments are visualized as proceeding through: a) displacement of the methoxy group (2 → 7); b) ring opening initiated by the NH group leading to the sulfinylamine[7] 8 in an equilibrium fashion and c) ring closure by nucleophilic addition of the second amino function to the electrophilic sulfinylamine (8 → 9).



Clearly, an NH group attached to the 4-position and a suitably placed second nucleophile are required for this rearrangement. Therefore reaction with 1,2-dimethylhydrazine or benzoyl hydrazide did not yield analogous products. Furthermore, reaction with ethylenediamine, where the analogous rearrangement would require a 7-membered ring closure, yielded imidazoline 10. The postulated sulfinylamine intermediate 8 could not be detected in these



these rearrangements, probably because of its low concentration in the equilibrium 7 ⇄ 8. The position of the equilibrium can be influenced by the nature of the ring substituents, i.e., electron withdrawing groups at the 2-position should facilitate the breaking of the N-S bond. By systematic change of substituents, analogs have been found which exist completely in the ring open form. For example, benzoylation of 12 yielded the stable crystalline sulfinylamine 14. In contrast with this, morpholino derivative 15 produced by an analogous process exists in the thiadiazole form.



The isolation of sulfinylamine 14 is direct evidence for the ring-opening 7 → 8 and lends strong support for the mechanism depicted above (7 ⇄ 8 → 9). In the accompanying paper a further generalization of this mode of ring transformation will be demonstrated.

Acknowledgements:

We are grateful to Dr. Arthur A. Patchett for useful discussion and Mr. Jack Smith for mass spectra.

References and Notes

1. S. Karady, J. S. Amato, D. Dortmund and L. M. Weinstock, Heterocycles, 1981, 16, 1561 and 1565.

2. J. Amato, S. Karady, R. A. Reamer, H. B. Schlegel, J. P. Springer and L. M. Weinstock, J. Am. Chem. Soc., 1982, 104, 1375.

3. W. C. Lumma, Jr., et al., J. Med. Chem., 1982, 25, 207. A. A. Algieri, G. M. Luke, R. T. Standridge, M. Brown, R. A. Partyka, R. R. Crenshaw, ibid, 1982, 25, 210.

4. H. Reimlinger, J. J. M. Vandewalle and W. R. F. Lingier, Chem. Ber., 1970, 103, 1934 and H. Reimlinger, W. R. F. Lingier and J. J. M. Vandewalle, Chem. Ber., 1971, 104, 639.

5. Satisfactory C,H,N and S analysis and spectral data (NMR,IR,UV and mass) were obtained on all intermediates. Melting points are uncorrected. Diagnostic data are summarized as follows: 4b: mp 126-128°C; MS m/z 252 (M+); ^{1}H NMR ($CDCl_3$) δ 3.3(s,3H,N-CH_3), 4.5 (d,2H, J=6Hz, $PhCH_2$), 7.35(s,5H,Ph), 9.8(s,1H,NH); 5C: mp 168-170°C; MS m/z 372 (M+), 356(M^+-O); ^{13}C NMR ($CDCl_3$, internal TMS) δ_c 33.5 (CH_2-S), 42.7 ($PhCH_2$), 146.3 (NHCO), 158.7 (N=C-C=O), 162.1 (N=C-S); 14: IR (cm^{-1}, Nujol) 1715,1650,1625,1300,1175; MS m/z 357 (M+), 196 (M^+ - $MeOC_6H_4N$=C-N=S=O); ^{13}C NMR (DMSO-d_6) δ_c 153.5 (NHC=O), 156.2 (N=C-NSO), 167.4 (NHCO-Ar).

6. For review see: A. Lawson and R. B. Tinker, Chem. Rev., 1970, 70, 594.

7. For review see: "Organic Compounds of Sulfur, Selenium and Tellurium." (Specialist Periodical Reports) The Chemical Society, London, Vol. 2, 1973, p. 336-338., Vol. 4, 1977, p. 105.

(Received in USA 8 February 1983)