HETEROCYCLES FROM CHLOROSULFONYL ISOCYANATE II. REACTION WITH ISOTHIOUREAS

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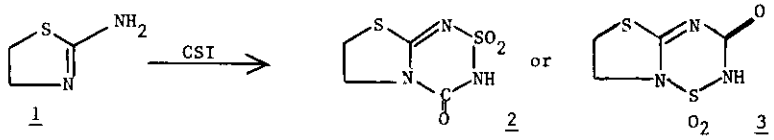
Abstract - 2-Aminothiazoline and open chain isothioureas react with CSI to afford substituted thiatriazenes. The structure proof of these compounds is the subject of this paper.

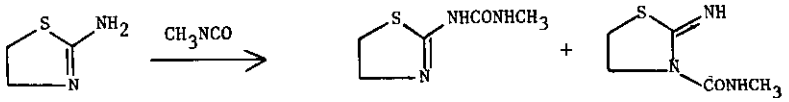
A preceding publication[1] described the cyclization of 2-aminopyridines with chlorosulfonyl isocyanate (CSI). In this paper we would like to show that isothioureas also react with CSI in an analogous fashion.

2-Aminothiazoline 1 reacted with CSI to afford 50% yield of a single adduct,[2] mp 218-221°, IR (nujol); 1705 (C=O), 1350 and 1175 (SO_2) cm^{-1}; m/e 207 (M^+), 164 (M^+-NHCO).



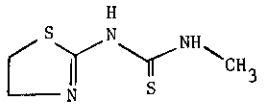
1 2 3

In order to distinguish between regio-isomers 2 and 3 an unequivocal synthesis was devised for this system.



1 4 5

Reaction of 1 in CH_3CN at 0°C with methyl isocyanate gave two isomeric products 4 (crystallized from the reaction mixture in 13% yield) and 5 (isolated by chromatography in 66% yield). It appears that 4 is the thermodynamically more stable product because on heating at 70°C for 4 hrs in DMSO, the mixture was converted to 4. Both isomers had the expected composition and mass spec. fragmentation: m/e 159 (M^+), 129 (M^+-$NHCH_3$), 102 (M^+-CH_3NCO). Structures 4 and 5 were assigned on the basis of the ^1H NMR chemical shifts of the ring CH_2-N groups. Yamamoto[3] prepared thioureas 6 and 7 by unambiguous routes and pointed out that the ring substituted isomer 7 has the CH_2-N resonance at lower field. In our case, 5 showed the lower field shift, which substantiates the assignment shown.



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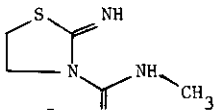

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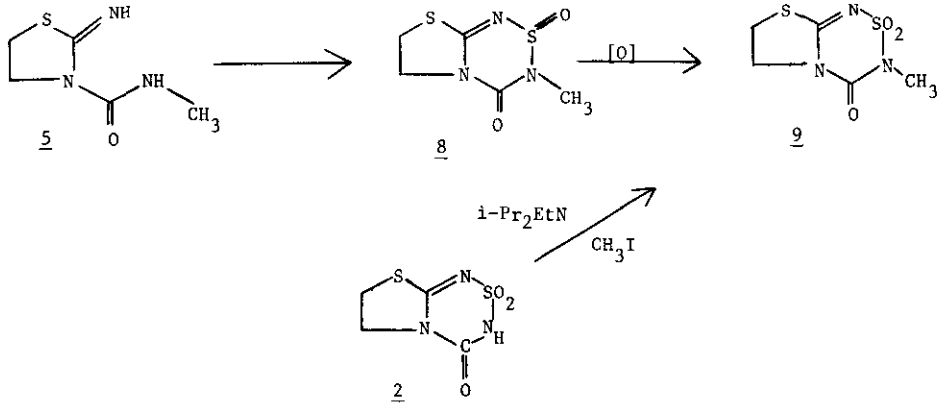
^{1}H NMR data ($CDCl_3$)

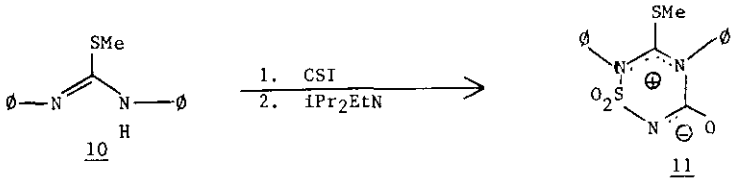
	CH_2N	CH_2S	$N-CH_3$
4 (60 MHz)	3.98 m	3.30 m	2.86 d, J=5 Hz
5 (60 MHz)	4.30 t, J=7 Hz	3.17 t, J=7 Hz	2.86 d, J=5 Hz
6 (100 MHz)[3]	4.13 t, J=7 Hz	3.36 t, J=7 Hz	3.16 d, J=5 Hz
7 (100 MHz)[3]	4.87 t, J=7 Hz	3.19 t, J=7 Hz	3.18 d, J=5 Hz



5 8 9 2

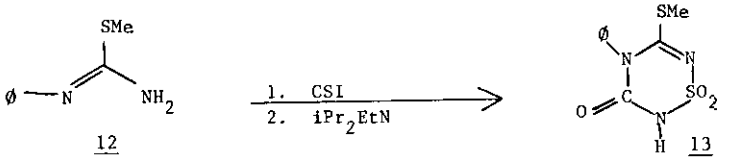
Ring closure of 5 with $SOCl_2$ in pyridine afforded compound 8 in 68% yield [mp 74-75°, IR ($CHCl_3$) 1705, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) : 3.2 (s, CH_3N), 3.3 (t, J = 8 Hz, S-CH_2), 4.35 (m, NCH_2)]. This was oxidized with m-chloroperbenzoic acid in CH_2Cl_2 to 9 in 30% yield [mp 143-144°; IR ($CHCl_3$) 1725, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6) 3.1 (s, CH_3-N), 3.5 (t, J = 8 Hz, CH_2S), 4.3 (t, J = 8 Hz, CH_2N)]. The same product was obtained by the methylation of 2 with CH_3I and ethyldiisopropylamine in CH_3CN for 3 days. This sequence of reactions (1 → 5 → 9) established that the structure of the reaction product of 1 and CSI was 2 and not 3, indicating that CSI reacted analogously to other isocyanates and attacked the ring nitrogen preferentially[3].

Open chain isothioureas reacted in a similar fashion. Diphenyl analog 10 was converted to the heterocyclic betain 11 in 40% yield [mp 150° dec; IR (nujol) 1720, 1375, 1175 cm^{-1} ; m/e 347 (M^+), 300 (M^+-SCH_3), 241 (M^+-SO_2NCO)].



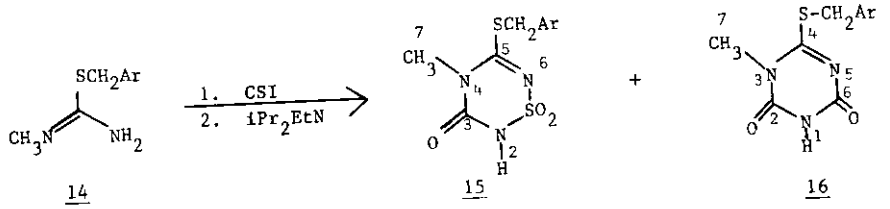
10 11

Phenyl analog 13 was obtained in 22% yield from 12 by the usual procedure and purification by extraction into $NaHCO_3$ solution and precipitation with HCl, mp 208°-210° dec; m/e 271 (M^+), 228 (M^+-HNCO), 164 (M^+-SO_2HNCO).



12 13

From these data it is not clear whether the correct structure is 13 or the other possible regioisomer in which the position of SO_2 and CO exchanged. In the case of 15, however, a definitive structural assignment was possible. Compound 15 was the major product of the reaction of 14 with CSI. It was separated from the second component 16 by chromatography.



14 15 16

Ar = 2-chloro-6-fluorophenyl

The structural assignment of 15 was based on the following data: mp 178-182°, m/e 337 (M^+), 302 (M^+-Cl), 194 ($M^+-C_7H_5ClF$), 143 ($M^+-C_3H_4N_3O_3S_2$); ^{13}C NMR (DMSO-d_6) δ_c 165.6 (C_5), 147.9 (C_3), 31.4 (C_7) ppm. The proton coupled ^{13}C spectrum showed coupling between the N-CH_3 and CO (3 bond pathway J = 3 Hz) confirming that 15 was the regio-isomer formed.

The other product 16 [mp 255-258°, m/e 301 (M^+), 266 (M^+-Cl), ^{13}C NMR (DMSO d_6), 169.7 (C_4), 152.2 (C_6), 149.6 (C_2, $^3J_{C_2-CH_3}$ = 3 Hz)] probably formed by reaction of 14 with two moles of CSI and elimination of $ClSO_2NH_2$.

The experimental procedure used for these reactions is the following: an equimolar amount of CSI was added dropwise to an ice cold solution of the thiouronium compound in acetonitrile. After 30 minutes an equivalent of ethyldiisopropylamine was added dropwise and the reaction mixture was allowed to stand at room temperature overnight. Usually the product precipitated from the reaction mixture but if this failed to occur the mixture was poured on dilute HCl and the product was isolated by extraction with EtOAc.

It appears the described mode of cyclization of CSI with thioureido compounds is a general reaction. The chemical reactivity of this heterocyclic system will be the subject of a future publication.

†Deceased August 12, 1978.

REFERENCES

1. S. Karady, J. S. Amato, D. Dortmund, A. A. Patchett, R. A. Reamer, R. J. Tull and L. M. Weinstock, HETEROCYCLES, 1979, 815.
2. All new compounds gave correct C, H, N and S analyses. Only diagnostic spectral data are listed in the text.
3. Y. Yamamoto, R. Yoda and M. Matsumura, Chem. Pharm. Bull., (Japan), 1975, 23, 2134.

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