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 thiatriazines. The structure proof of these compounds is the subject of this paper.

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

2-Aminothiazoline reacted with CSI to afford 50% yield of a single adduct, mp 218-221°C, IR (nujol); 1705 (C=O), 1350 and 1175 (SO2) cm⁻¹; m/e 207 (M⁺), 164 (M⁺-NHCO).

\[
\begin{align*}
\text{NH}_2 & \quad \text{CSI} \\
1 & \quad \text{or} \\
& \quad 2
\end{align*}
\]

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

\[
\begin{align*}
\text{NH}_2 & \quad \text{CH}_3\text{NCO} \\
1 & \quad 4, 5
\end{align*}
\]

Reaction of 1 in CH₃CN 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⁺-NHCH₂), 102 (M⁺-CH₂NCO). Structures 4 and 5 were assigned on the basis of the ¹H NMR chemical shifts of the ring CH₂-N groups. Yamamoto prepared thioureas 6 and 7 by unambiguous routes and pointed out that the ring substituted isomer 7 has the CH₂-N resonance at lower field. In our case, 5 showed the lower field shift, which substantiates the assignment shown.
H NMR data (CDCl₃)

<table>
<thead>
<tr>
<th></th>
<th>CH₂N</th>
<th>CH₂S</th>
<th>N-CH₃</th>
</tr>
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<tbody>
<tr>
<td>4 (60 MHz)</td>
<td>3.98 m</td>
<td>3.30 m</td>
<td>2.86 d, J=5 Hz</td>
</tr>
<tr>
<td>5 (60 MHz)</td>
<td>4.30 t, J=7 Hz</td>
<td>3.17 t, J=7 Hz</td>
<td>2.86 d, J=5 Hz</td>
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<tr>
<td>6 (100 MHz)</td>
<td>4.13 t, J=7 Hz</td>
<td>3.16 t, J=7 Hz</td>
<td>3.15 d, J=5 Hz</td>
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<tr>
<td>7 (100 MHz)</td>
<td>4.87 t, J=7 Hz</td>
<td>3.19 t, J=7 Hz</td>
<td>3.18 d, J=5 Hz</td>
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</table>

Ring closure of 5 with SOCl₂ in pyridine afforded compound 8 in 68% yield [mp 74-75⁰, IR (CHCl₃) 1705, 1580 cm⁻¹; ¹H NMR (CDCl₃) : 3.2 (s, CH₃N), 3.3 (t, J = 8 Hz, S-CH₂), 4.35 (m, NCH₂)]. This was oxidized with m-chloroperbenzoic acid in CH₂Cl₂ to 9 in 30% yield [mp 143-144⁰; IR (CHCl₃) 1725, 1600 cm⁻¹; ¹H NMR (DMSO-d₆) : 3.1 (s, CH₃-N), 3.5 (t, J = 8 Hz, CH₂S), 4.3 (t, J = 8 Hz, CH₂N)]. The same product was obtained by the methylation of 2 with CH₃I and ethyldiisopropylamine in CH₂CN for 3 days. This sequence of reactions (1→5→2) 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 preferentially³.
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⁺-SCH₃), 241 (M⁺-SO₂NCO)].

Phenyl analog 13 was obtained in 22% yield from 12 by the usual procedure and purification by extraction into NaHCO₃ solution and precipitation with HCl, mp 208°-210° dec; m/e 271 (M⁺), 228 (M⁺-HNCO), 164 (M⁺-SO₂HNCO).

From these data it is not clear whether the correct structure is 13 or the other possible regioisomer in which the position of SO₂ 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.

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⁺-C₆H₅ClF), 143 (M⁺-C₃H₂N₂O₂S₂); ¹³C NMR (DMSO-d₆) δc 165.6 (C₅), 147.9 (C₃), 31.4 (C₄) ppm. The proton coupled ¹³C spectrum showed coupling between the N-CH₃ 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), ¹³C NMR (DMSO-d₆), 169.7 (C₄), 152.2 (C₆), 149.6 (C₂, 3JC₂-CH₃ = 3 Hz)] probably formed by reaction of 14 with two moles of CSI and elimination of ClSO₂NH₂.

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 thiourea 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 thiourea 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


2. All new compounds gave correct C, H, N and S analyses. Only diagnostic spectral data are listed in the text.


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