SYNTHECOFOE THVENO[3,2-d][1,2,3]THIADIAZoLEs.
NEW MECHANISTIC ASPECTS OF THE HURD-MORI REACTION

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Abstract - The synthesis of new thieno[3,2-d][1,2,3]thiadiazole derivatives is described. A modified reaction mechanism of the Hurd-Mori reaction is presented showing better agreement with the obtained results.

In recent years 1,2,3-thiadiazoles have attracted some attention for pharmaceutical use as well as precursors for highly reactive intermediates (e.g. thioketenes and alkynethiolate salts). In the course of our studies towards the synthesis of various types of new annelated 1,2,3-thiadiazoles, we were interested in methyl thieno[3,2-d][1,2,3]thiadiazolecarboxylates as new potential plant activators. For the construction of the parent ring system two synthetic approaches are reported in the literature: the first one is the cyclization by diazotation of 3-amino-2-thio-substituted thiophenes (path A in Scheme 1), the second one (path B in Scheme 1) is the annelation via the Hurd-Mori reaction.

In our first attempts to build-up the unknown methyl thieno[3,2-d][1,2,3]thiadiazole-5-carboxylate (4) we started with the diazotation approach first. The reaction sequence started with the synthesis of the 4-nitro-5-phenylmethylthio-substituted thiophene (2) which was obtained from methyl 5-chloro-4-nitrothiophene-2-carboxylate (1) by nucleophilic substitution. This nitro compound was then reduced with iron
powder in acetic acid to the amine (3). The diazotation with sodium nitrite was carried out according to a protocol published by Gewald et al. However, after chromatographic purification the target compound (4) was isolated in only 15% yield (Scheme 2).

As a consequence of this disappointing result we continued our synthetic work with the Hurd-Mori reaction: Thus, methyl tetrahydro-4-oxothiophene-2-carboxylate (5) (easily prepared from dimethyl tetrahydro-4-oxothiophene-2,3-dicarboxylate (13) by hydrolysis, decarboxylation and esterification) was converted with 4-toluenesulfonylhydrazine to the hydrazone (6), which was obtained as a mixture of the E- and Z-isomers in a ratio of 45:55. The cyclization of 6 with an excess of SOCl₂ under standard conditions yielded a 1:2.6-mixture of the 1,2,3-thiadiazoles (7) and (8) beside traces of 4 as well as tosyl chloride instead of 4-toluene sulfonic acid as described by Ohno et al. The 5,6-dihydrothienothiadiazole (8) was identified using the NMR data tabulated in Table I and by its successful DDQ-oxidation to 4. (Scheme 3)
When we compare this product distribution with the cyclization of the tosylhydrazone (9) which was already investigated by Rovira et al.\textsuperscript{11} we can see that in both cases [3,2-\(d\)]-annelation is preferred by 3:1 to the [3,4-\(d\)]-annelation (Scheme 4). This can be explained with the electronic influence of the sulfur atom to the regioselectivity of the Hurd-Mori reaction.\textsuperscript{12} However, the presence of the ester functionality effects the aromatization of the [3,4-\(d\)] isomer (7) but decreases the aromatization tendency of the [3,2-\(d\)]-isomers (8:4 = 2.6:0.15 vs. 11:12 = 2:1).

\begin{center}
\begin{tikzpicture}[xscale=1.5,yscale=1.5]
\node at (0,0) {\includegraphics[width=0.8\linewidth]{Scheme_4.png}};
\end{tikzpicture}
\end{center}

\textit{trans}-Dimethyl tetrahydro-4-oxothiophene-2,3-dicarboxylate (13)\textsuperscript{9} was condensed with 4-tolueno-sulfonylhydrazone to the corresponding hydrazone, which appears completely in its tautomeric form (14). In the next step 14 was treated with an excess of SOCl\(_2\) in CH\(_2\)Cl\(_2\) at room temperature for 17 h. After working up the reaction mixture we isolated again tosyl chloride and a 3:2 mixture of 15 and the \textit{trans}-dihydro product (16). (Scheme 5) The formation of tosyl chloride and 16 is in disagreement with the mechanism suggested by Ohno et al.\textsuperscript{6} Our attempt to increase the amount of 15 by stirring the isolated mixture of 15 and 16 with SOCl\(_2\) in CH\(_2\)Cl\(_2\) failed. So we had an experimental evidence that the formation of the full aromatized product (15) must be a result of the cyclization sequence and not of a subsequent reaction, e.g. oxidation by air, dehydrogenation or some addition-elimination reactions.

\begin{center}
\begin{tikzpicture}[xscale=1.5,yscale=1.5]
\node at (0,0) {\includegraphics[width=0.8\linewidth]{Scheme_5.png}};
\end{tikzpicture}
\end{center}
A mechanistic model of the Hurd-Mori reaction which explains the influence of the ester group on the aromatization of the [3,4-\(d\)]-isomer as well as the formation of tosyl chloride as a by-product is shown in Scheme 6. The first intermediate is the \(N\)-tosyldihydrothiadiazole \(S\)-oxide (17)\(^{13}\) which undergoes a Pummerer-like rearrangement to the \(N\)-tosylthiadiazolium chloride (18) with \(\text{SOCl}_2\). In the case \(R=H\), 18 affords the thiadiazole (10) just by elimination of tosyl chloride, however, when \(R=\text{CO}_{2}\text{Me}\) elimination of \(\text{HCl}\) is favored. Electrophilic attack of \(\text{SOCl}_2\) on the the push-pull-substituted double bond then leads to the sulfinyl chloride (20) which forms 7 via elimination of tosyl chloride, \(\text{HCl}\), and sulfur oxide.

Finally, we would like to suggest a model, which can probably explain the formation of the thieno[3,2-\(d\)] [1,2,3]thiadiazoles (15) and (12) beside 16 and 11. In Scheme 7 we have outlined the mechanism exemplified for the reaction of 14.

The first intermediate is again the \(N\)-tosyldihydrothiadiazole \(S\)-oxide (21) which undergoes a Pummerer-like rearrangement to 22. This intermediate can either eliminate tosyl chloride forming the dihydrothienothiadiazole (16) or \(\text{HCl}\) forming the thiocarbonyl ylide intermediate (23) which is stabilized due to the push-pull substituents providing a charge stabilization.\(^{14}\)

The formation of thiocarbonyl ylides under reaction conditions of the Pummerer-rearrangement is well known and used for the synthesis of thieno[3,4-\(c\)]thiophenes.\(^{15}\) Thiocarbonyl ylide (23) can again react with \(\text{SOCl}_2\) in a 1,3-addition forming the sulfinyl chloride (24) which forms 25 via a syn-elimination.\(^{16}\) The last step is the loss of tosyl chloride leading to 15.
Table 1: Spectroscopic Properties of Thieno[3,2-][1,2,3]thiadiazoles (4-16) in (CDCl₃):

<table>
<thead>
<tr>
<th>Compd</th>
<th>¹H NMR</th>
<th>¹³C NMR</th>
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<tbody>
<tr>
<td>4</td>
<td>4.00 (s, 3H, OMe), 8.45 (s, 1H, H-6)</td>
<td>52.9 (q, OMe), 122.3 (d, C-6), 141.4 (s, C-5), 149.1 (s, C-3a), 161.6 (s, CO), 168.1 (s, C-6a)</td>
</tr>
<tr>
<td>7</td>
<td>4.00 (s, 3H, OMe), 8.55 (s, 1H, H-4)</td>
<td>52.8 (q, OMe), 114.5 (s, C-6a), 122.2 (d, C-4), 144.0 (s, C-6), 161.1 (s, C-6a), 169.3 (s, CO)</td>
</tr>
<tr>
<td>8</td>
<td>3.70 (ABX, J=16 Hz, J=9 Hz, 1H, H-6A), 3.80 (s, 3H, OMe), 3.95 (ABX, J=16 Hz, J=6 Hz, 1H, H-6B), 5.25 (ABX, J=9 Hz, J=6 Hz, 1H, H-5)</td>
<td>28.3 (t, C-6), 52.8 (q, OMe), 58.0 (d, C-5), 151.2 (s, C-3a), 165.6 (s, C-6a), 169.7 (s, CO)</td>
</tr>
<tr>
<td>15</td>
<td>3.95 (s, 3H, OMe), 4.05 (s, 3H, OMe)</td>
<td>53.2 (q, OMe), 53.4 (q, OMe), 127.3 (s, C-6), 139.8 (s, C-5*), 147.8 (s, C-3a*), 160.3 (s, CO), 162.4 (s, CO), 165.5 (s, C-6a)</td>
</tr>
<tr>
<td>16</td>
<td>3.83 (s, 3H, OMe), 3.87 (s, 3H, OMe), 5.08 (d, J=6 Hz, 1H, H-6), 5.68 (d, J=6 Hz, 1H, H-5),</td>
<td>46.0 (d, C-6), 53.4 (q, OMe), 53.5 (q, OMe), 60.7 (d, C-5), 152.4 (s, C-3a), 162.0 (s, C-6a), 168.9 (s, CO), 169.1 (s, CO)</td>
</tr>
</tbody>
</table>
EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and are not corrected. All column chromatographic purifications were accomplished on silica gel 60 (Merck).

NMR spectra were recorded on a Bruker AC 200 FT-NMR spectrometer and are expressed in δ-values (ppm) downfield to TMS used as internal standard. Significant ¹H NMR data are tabulated in the following order: δ, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; b, broad), coupling constant(s) in Hz, number of protons, and assignments.

Methyl 4-Nitro-5-[(phenylmethyl)thio]thiophene-2-carboxylate (2):

A solution of 14.59 g (65.8 mmol) methyl 5-chloro-4-nitrothiophene-2-carboxylate (1) in 50 mL of dry DMF was dropped into a cooled solution of 8.18 g (65.8 mmol) phenylmethylmercaptan and 18.19 g (131.6 mmol) K₂CO₃ in 20 mL of DMF. After stirring for 5 h at rt the reaction mixture was poured on ice. The precipitate was filtered, washed with cold MeOH, and dried in vacuo to obtain 19.2 g (94%) yellow crystals. An analytical sample was prepared by recrystallization from diisopropyl ether, mp 151-152°C; ¹H NMR (CDCl₃): δ = 3.91 (s, 3H, COOCH₃), 4.30 (s, 2H, SCH₂), 7.35-7.50 (m, 5H, aromH), 8.22 (s, 1H, H-3); ¹³C-NMR (CDCl₃): δ = 39.9 (t, SCH₂), 52.7 (q, COOCH₃), 127.8 (d, C-3), 128.4 (d, C-4'), 128.9 (d, C-3'), 129.1 (d, C-2'), 133.3 (s, C-2), 141.3 (s, C-1'), 145.7 (s, C-4), 154.1 (s, C-5), 160.5 (s, COOCH₃). Anal. Calcd for C₁₃H₁₁NO₂S: C, 50.47; H, 3.58; N, 4.53 Found: C, 50.55; H, 3.38; N, 4.50.

Methyl 4-Amino-5-[phenylmethylthio]thiophene-2-carboxylate (3):

A cooled solution of 10.00 g (32.32 mmol) of nitrothiophene (2) in 50 mL of AcOH was treated with 10.83 g (193.9 mmol) of Fe-powder in small portions. After stirring for 4 h at 5°C the reaction mixture was poured in water. The aqueous solution was neutralized with NaHCO₃ and extracted twice with ether. The organic layer was dried over Na₂SO₄ to obtain 7.43 g (81%) of beige crystals, mp 60-62°C; ¹H NMR (CDCl₃): δ = 3.45 (br s, 2H, NH₂), 3.85 (s, 5H, SCH₂ + COOCH₃), 7.10-7.20 (m, 5H, aromH), 7.20-7.30 (m, 4H, arom.H + H-3); ¹³C-NMR (CDCl₃): δ = 42.2 (t, SCH₂), 52.1 (q, COOCH₃), 111.9 (s, C-5), 124.6 (d, C-3), 127.3 (d, C-4'), 128.5 (d, C-3'), 128.8 (d, C-2'), 133.8 (s, C-2), 137.7 (s, C-1'), 150.1 (d, C-4), 162.0 (s, COOCH₃). Anal. Calcd for C₁₃H₁₃NO₂S₂: C, 55.47; H, 3.58; N, 4.53 Found: C, 55.50; H, 3.38; N, 4.49.

Methyl Thieno[3,2-d][1,2,3]thiadiazole-5-carboxylate (4):

A solution of 1.23 g (17.9 mmol) of NaN₂O₄ in 10 mL of water was dropped slowly in a cooled suspension of 5.00 g (17.9 mmol) of aminothiophene (3) in 70 mL of AcOH and 25 mL conc. HCl. After stirring for 90 min at 0°C the green, homogeneous solution was poured in water. The aqueous phase was neutralized with NaHCO₃ and extracted with ether. The organic layer was dried over Na₂SO₄ and evaporated to dryness. After chromatographic purification on 150 g silica gel using light petroleum and ethyl acetate (20:1) as the eluent and recrystallization from diisopropyl ether 0.55 g (72%) of beige crystals were

**General Procedure for the Preparation of the Hydrazones (6) and (14):**
A solution of the ketone (5 or 13) and one equiv. of 4-toluenesulfonylhydrazine in dry MeOH (2 mL/mmole of ketone) was stirred for 4 h at rt. The precipitate was filtered, washed with cold MeOH, and dried in vacuo. An analytical sample was prepared by recrystallization from MeOH.

(E)/(Z)-Methyl Tetrahydro-4-[2-[4-methylphenylsulfonyl]-2-hydrazinyl-l-ylidene]thiophene-2-carboxylate (6): This compound was obtained as colorless crystals (83%), mp 171-173°C; ¹H NMR (CDCl₃): δ = 2.41 (s, 3H, CH₃), 2.50-3.10 (m, 2H, H-3a+H-3b), 3.40-3.75 (m, 2H, H-Sa+H-5b+OCH₃), 3.80-4.05 (m, 1H, H-2). The NMR spectrum shows the presence of methylene protons at δ 3.40-3.75 ppm, which are characteristic of the thiophene ring. The presence of two sets of methylene protons at δ 2.41 ppm indicates the presence of two different isomers, (E) and (Z).

**Dimethyl 2,5-Dihydro-4-[4-methylphenylsulfonyl]hydrazothiophene-2,3-dicarboxylate (14):**
This compound was obtained as colorless crystals (85%), mp 169-172°C; ¹H NMR (CDCl₃): δ = 2.50 (s, 3H, CH₃), 3.68 (s, 3H, COOCH₃), 3.75 (s, 3H, COOCH₃), 4.05 (s, 2H, H-5a+H-5b), 4.69-4.73 (m, 1H, H-2), 6.45 (br s, 1H, NH), 7.40 (d, 2H, J=8 Hz, H-3'+H-5'), 7.78 (d, 2H, J=8 Hz, H-2'+H-6'). The NMR spectrum shows the presence of two sets of methylene protons at δ 3.40-3.75 ppm, which are characteristic of the thiophene ring. The presence of two sets of methylene protons at δ 2.50 ppm indicates the presence of two different isomers, (E) and (Z).

**Methyl Thieno[3,4-d][1,2,3]thiadiazole-6-carboxylate (7) and methyl 5,6-dihydrothieno[3,2-d][1,2,3]thiadiazole-5-carboxylate (8):**
A solution of 1.00 g (3.04 mmol) of 6 in 20 mL of dry CH₂Cl₂ was treated with 4.5 mL (62 mmol) of SOCl₂ in one portion. After stirring for 17 h at rt the mixture was concentrated in vacuo. The oily residue was chromatographed on 50 g silica gel using light petroleum and ethyl acetate (10:1) as the eluent to obtain 0.12 g (20%) of 7 (colorless crystals) and 0.32 g (50%) of 8 (pale yellow liquid which darkens within a few hours), respectively. An analytically pure sample of 7 was prepared by crystallization from diisopropyl ether, mp 104-106°C. Anal. Calcd for C₆H₄N₂O₄S₂: C, 35.99; H, 2.01; N, 13.99. Found: C, 36.21; H, 2.20; N, 13.99.

**Aromatization of 8 to 4 with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ):**
A solution of 150 mg (0.74 mmol) of 8 and 336 mg (1.48 mmol) of DDQ in 20 mL of dry benzene was heated under reflux for 10 days. After evaporating the solvent the residue was chromatographed on 20 g of silica gel using light petroleum and ethyl acetate (15:1) as the eluent to obtain 90 mg (60%) of 4.
Dimethyl Thieno[3,2-d][1,2,3]thiadiazole-5,6-dicarboxylate (15):
A solution of 3.50 g (9.10 mmol) of 14 in 50 mL of dry CH₂Cl₂ was treated with 13.2 mL (182 mmol) of SOCl₂ in one portion. After stirring for 17 h at rt the mixture was concentrated in vacuo. The oily residue was chromatographed on 120 g of silica gel using light petroleum and ethyl acetate (3:1) as the eluent to obtain a 3:2 mixture of 15 and 16 in 65% yield. An analytically pure sample of 15 (0.40 g, 17%) was prepared by recrystallization from THF, mp 127-129°C. Anal. Calcd for C₈H₆N₂O₄S₂: C, 37.20; H, 2.34; N, 10.85. Found: C, 37.46; H, 2.34; N, 11.01.

REFERENCES

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