Phosphoramides, XIX [1]
Phosphorus Pentoxide Amine Hydrochloride Reagents in the Synthesis of 3-Amino-1,2-benzisothiazole-1,1-dioxides and 3-Aminothieno[3,4-d]isothiazole-1,1-dioxides

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Phosphorus Pentoxide Amine Hydrochloride Reagents, Saccharin, 3-Amino-1,2-benzisothiazole-1,1-dioxides, 3-Aminothieno[3,4-d]isothiazole-1,1-dioxides

3-Amino-1,2-benzisothiazole-1,1-dioxides (2b-n) have been prepared by heating saccharin (1) and the hydrochlorides of primary and secondary aliphatic amines with phosphorus pentoxide and N,N-dimethylcyclohexylamine at 240 °C. 3-Aminothieno[3,4-d]isothiazole-1,1-dioxides (6a-c) were similarly prepared from thieno[3,4-d]isothiazole-3(2H)-one-1,1-dioxide (5).

31P NMR spectra were obtained of reaction mixtures and reagents. Biological screening of 2 is discussed.

In an earlier work it was reported that saccharin (1) when heated at 225 °C in hexamethylphosphoric triamide (HMPT) produced 3-dimethylamino-1,2-benzisothiazole-1,1-dioxide (21) [2]. Later studies showed that HMPT, phenyl phosphorodiamidates [3] and phosphorus pentoxide/amine reagents [4] and phosphorus pentoxide amine hydrochloride reagents [5, 6] afforded similar reactions and therefore they can all be classified as phosphoric amide reagents.

3-Amino-1,2-benzisothiazole-1,1-dioxides (2) are readily prepared from 3-chlorobenzisothiazole-1,1-dioxide [7] which is prepared from saccharin and PCl5 [8] or SOCl2 in dimethylformamide [9].

Kutlu [10] showed that heating of saccharin in strongly basic amines usually produced 2 in low yields. No report was given for low boiling amines. This prompted us to find out whether 2 was produced, when saccharin was reacted with the easily available P2O5/amine hydrochloride reagents.

Results and Discussion

The reaction of saccharin (1) with P2O5 and amine hydrochlorides in N,N-dimethylcyclohexylamine usually produced the corresponding 3-aminobenzi- 

The reaction of saccharin with P2O5 and ammonium chloride in N,N-dimethylcyclohexylamine at 240 °C for 2 h 'H NMR and MS showed that a mixture of the 3-amino and 3-methylamino-1,2-benzisothiazole-1,1-dioxides was obtained. The reaction was therefore repeated with quinoline as the tertiary amine component of the reagent and the desired product 2a was obtained in low yield (13%).

In our hands the reaction of saccharin with the phosphorus pentoxide tert-butylammonium chloride reagent afforded a mixture similar to that obtained with ammonium chloride. That means dealkylation of the tert-butyl group takes place followed by a partial methylation reaction. Side reactions due to the methylating power of N,N-dimethylcyclohexylamine have been observed on previous occasions [6, 13].

The P2O5 reagent mixture is believed to phosphorylate saccharin on the oxygen atom to give 3.

The phosphate group is then a good leaving group in a nucleophilic aromatic substitution reaction of 3 with amines.

The viscous reaction mixtures were readily soluble in CHCl3, which made 31P NMR possible. From
Table. Synthesis of 3-amino-1,2-benzisothiazoles-1,1-dioxides.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>Lit. m.p. [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>H</td>
<td>H</td>
<td>13</td>
<td>310-312 (acetone)</td>
<td>314 [7]</td>
</tr>
<tr>
<td>2b</td>
<td>H</td>
<td>CH₃</td>
<td>73</td>
<td>304-306 (EtOH)</td>
<td>303 [7]</td>
</tr>
<tr>
<td>2c</td>
<td>H</td>
<td>CH₂CH₃</td>
<td>74</td>
<td>286-288 (MeOH)</td>
<td>286 [7]</td>
</tr>
<tr>
<td>2d</td>
<td>H</td>
<td>CH₃CH₂CH₃</td>
<td>88</td>
<td>220-221 (EtOH/H₂O)</td>
<td>223-224 [11]</td>
</tr>
<tr>
<td>2e</td>
<td>H</td>
<td>CH(CH₃)₂</td>
<td>71</td>
<td>254-255 (EtOH)</td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>H</td>
<td>CH₂CH₂CH₂CH₃</td>
<td>84</td>
<td>182-183 (MeOH)</td>
<td>185-185.5 [11]</td>
</tr>
<tr>
<td>2g</td>
<td>H</td>
<td>CH₂CH₂CH₃</td>
<td>83</td>
<td>218-219 (MeOH)</td>
<td></td>
</tr>
<tr>
<td>2h</td>
<td>H</td>
<td>CH(CH₃)CH₂CH₃</td>
<td>75</td>
<td>210-212 (EtOH)</td>
<td></td>
</tr>
<tr>
<td>2i</td>
<td>H</td>
<td>cyclopropyl</td>
<td>32</td>
<td>290-292 (EtOH)</td>
<td></td>
</tr>
<tr>
<td>2j</td>
<td>H</td>
<td>cyclopentyl</td>
<td>84</td>
<td>246-248 (EtOH)</td>
<td></td>
</tr>
<tr>
<td>2k</td>
<td>H</td>
<td>cyclohexyl</td>
<td>74</td>
<td>238-260 (CH₃CN)</td>
<td>258 [7]</td>
</tr>
<tr>
<td>2l</td>
<td>CH₃</td>
<td>CH₃</td>
<td>84</td>
<td>302-304 (CH₃CN)</td>
<td>301 [12]</td>
</tr>
<tr>
<td>2m</td>
<td>-CH₂CH₂OCH₂CH₂-</td>
<td>70</td>
<td>231-233 (MeOH/CH₃CN)</td>
<td>251 [7]</td>
<td></td>
</tr>
<tr>
<td>2n</td>
<td>-CH₂-</td>
<td>(CH₂)₅-</td>
<td>79</td>
<td>210-212 (CH₃CN)</td>
<td>211 [7]</td>
</tr>
</tbody>
</table>

* Quinoline (35 ml) was used instead of C₆H₁₁N(CH₃)₂ (35 ml).

among many signals we were only able to identify the trimetaphosphate ion. A ³¹P NMR spectrum was also obtained of the reagent made from P₂O₅, propylammonium chloride and N,N-dimethylcyclohexylamine, but shortly after mixing and heating at 240 °C only the trimetaphosphate ion could be identified in the mixture of phosphate ions. When heating of the reagent was continued for 40 min at 240 °C, the reagent mixture changed into a mixture of the trimetaphosphate ion and 4, which is seen from the hydrogen noise decoupled ³¹P NMR spectrum in Fig. 1. The H₃PO₄ present in the spectrum solely results from the reference H₃PO₄. In the non decoupled spectrum the triplet at 9.8 ppm changed into a multiplet due to couplings to the hydrogen atoms, while the doublet at 23.0 ppm was unchanged. After heating at 240 °C for 40 min the reagent mixture was stable and a similar spectrum was obtained after 2 h of heating.

To extend the scope of the reaction, the thieno analogue of saccharin, thieno[3,4-d]isothiazol-3(2H)-one-1,1-dioxide (5) which has recently been prepared by Hromatka [14] was synthesised and subjected to the P₂O₅/amine hydrochloride reagent.

Fig. 1. ¹H noise decoupled ³¹P NMR spectrum of the P₂O₅-CH₂CH₂CH₂NH₂Cl-C₆H₁₁N(CH₃)₂ reagent in CDCl₃ after heating at 240 °C for 40 min.
3-Aminothieno[3,4-d]isothiazole-1,1-dioxides (6) were then produced in 31–61% yield. The yields were lower than for saccharin. The 3-amino-1,2-benzisothiazole-1,1-dioxides with the exception of 2i were tested against P 388 lymphocytic leukemia but no activity was indicated [15]. In biological systems phosphorylation (e.g. by ATP or phosphoenolpyruvate) of saccharin to give 3 is quite conceivable. Amino-1,2-benzisothiazole-1,1-dioxides (2) may then be formed in reactions with naturally occurring amines. Fortunately, our findings indicate that 2 are biologically inactive substances which is on the same line as previously found. Ashby et al. did not find any positive response in the Ames assay for these compounds [16].

Experimental

1H NMR spectra were recorded on a JEOL JWM-PMX 60 spectrometer. Mass spectra were obtained on a Varian MAT 311 A and a Varian MAT CA 7 A. IR spectra were recorded on a Perkin Elmer Model 457 and microanalyses were performed by the NOVO Microanalytical Laboratory, Bagsværk, Denmark.

Amine hydrochlorides were prepared by adding the amine dropwise to 1.5 equivalents of an ice cooled 6 M HCl with stirring. The dry hydrochloride was obtained by stripping off the excess HCl.

3-Amino-1,2-benzisothiazole-1,1-dioxides (2)

General procedure

A mixture of saccharin (1) (9.2 g, 0.05 mol), amine hydrochloride (0.2 mol), P2O5 (15 g, 0.106 mol) and N,N-dimethylcyclohexylamine (35 ml) was heated with stirring on an oil bath at 240 °C for 2 h. The reaction mixture was then poured into ice and the reaction cake allowed to dissolve. The mixture was filtered and the precipitated slightly colored crystals were recrystallized from the solvents given in the Table.

3-Isopropylamino-1,2-benzisothiazole-1,1-dioxide (2e)

1H NMR (CF3COOH) δ (ppm): 1.50 (6H, d, J = 6 Hz); 4.28 (1H, m); 7.83–8.40 (4H, m), 8.60 (1H, broad s).

IR (KBr) ν (cm⁻¹): 3324, 1620, 1282, 1158.

Mass, m/e (%) = 224 (M⁺, 65), 223(60), 103(56), 102(100), 58(53).

Analysis for C11H12N2O2S

Calcd C 53.55 H 5.39 N 12.41,

Found C 53.63 H 5.47 N 12.27.

3-sec-Butylamino-1,2-benzisothiazole-1,1-dioxide (2h)

1H NMR (CF3COOH) δ (ppm): 1.05 (3H, t, J = 7 Hz); 1.48 (3H, d, J = 6 Hz); 1.83 (2H, m); 4.12 (1H, m); 7.73–8.33 (4H, m); 8.53 (1H broad s).

IR (KBr) ν (cm⁻¹): 3318, 1620, 1285, 1159.

Mass, m/e (%) = 238 (M⁺, 27), 209(54), 183(100).

Analysis for C11H14N2O2S

Calcd C 55.44 H 5.92 N 11.76,

Found C 55.24 H 5.97 N 11.72.

3-Cyclopropylamino-1,2-benzisothiazole-1,1-dioxide (2i)

1H NMR (CF3COOH) δ (ppm): 1.17 (4H, m); 3.18 (1H, broad s); 7.90–8.33 (4H, m); 9.40 (1H, broad d).

IR (KBr) ν (cm⁻¹): 3320, 1615, 1282, 1159.

Mass, m/e (%) = 202 (M⁺, 2), 183(100), 103(96).

Analysis for C10H10N2O2S

Calcd C 54.04 H 4.53 N 12.60,

Found C 53.42 H 4.55 N 12.59.

3-Aminothieno[3,4-d]isothiazole-1,1-dioxides (6)

General procedure

A mixture of thieno[3,4-d]isothiazol-3(2H)one-1,1-dioxide (5) (0.01 mol, 1.89 g) [17], amine hydrochloride (0.04 mol) P2O5 (0.021 mol, 3 g) and N,N-dimethylcyclohexylamine (7 ml) was heated on an oil bath at 180 °C for 30–70 min. The reaction mixture was then poured into ice and the reaction cake allowed to dissolve. The mixture was filtered and the precipitated slightly colored crystals were recrystallized from the solvents given in the Table.

3-Isobutylamino-1,2-benzisothiazole-1,1-dioxide (2g)

1H NMR (CF3COOH) δ (ppm): 1.08 (6H, d, J = 7 Hz); 2.08 (1H, m); 3.58 (2H, t, J = 7 Hz); 7.83–8.37 (4H, m); 8.91 (1H, broad s).

IR (KBr) ν (cm⁻¹): 3307, 1620, 1282, 1152.

Mass, m/e (%) = 224 (M⁺, 10), 223(60), 103(56), 102(100), 58(53).

Analysis for C11H14N2O2S

Calcd C 55.44 H 5.92 N 11.76,

Found C 55.33 H 5.93 N 11.86.

3-Cyclopentylamino-1,2-benzisothiazole-1,1-dioxide (2j)

1H NMR (CF3COOH) δ (ppm): 1.9 (8H, m); 4.43 (1H, m); 7.83–8.43 (4H, m); 8.77 (1H, broad d, J = 7 Hz).

IR (KBr) ν (cm⁻¹): 3325, 1614, 1278, 1155.

Mass, m/e (%) = 250(M⁺, 11), 183(100).

Analysis for C12H14N2O2S

Calcd C 57.58 H 5.64 N 11.19,

Found C 57.51 H 5.62 N 11.25.

3-Amino-thieno[3,4-d]isothiazole-1,1-dioxides (6)

General procedure

A mixture of thieno[3,4-d]isothiazol-3(2H)one-1,1-dioxide (5) (0.01 mol, 1.89 g) [17], amine hydrochloride (0.04 mol) P2O5 (0.021 mol, 3 g) and N,N-dimethylcyclohexylamine (7 ml) was heated on an oil bath at 180 °C for 30–70 min. The reaction mixture was then poured into ice and the reaction cake allowed to dissolve. The mixture was filtered and the precipitate was recrystallized.
3-Propylaminothieno[3,4-d]isothiazole-1,1-dioxide (6a)

Reaction time 30 min. Yield 1.1 g (48%), m.p. 202–203 °C (EtOH).

$^1$H NMR (CF$_3$COOH) δ (ppm): 1.06 (3H, t, $J = 7$ Hz); 1.88 (2H, sext., $J = 7$ Hz); 3.67, 2H, q, $J = 7$ Hz), 8.25 (1H, d, $J = 2.5$ Hz), 8.53 (1H, d, $J = 2.5$ Hz), 9.23 (1H, broad s).

IR (KBr) ν (cm$^{-1}$): 3312, 1619, 1305, 1170.

Mass, m/e (%) = 230(M+, 77), 172(100), 124(66), 109(61), 64(52).

Analysis for C$_{9}$H$_{10}$N$_{2}$O$_{2}$S$_{2}$

Calcd C 41.72 H 4.38 N 12.16,
Found C 42.08 H 4.38 N 11.95.

3-Isobutylaminothieno [3,4-d]isothiazole-1,1-dioxide (6b)

Reaction time 70 min. Yield 1.5 g (61%), m.p. 194–195 °C (EtOH).

$^1$H NMR (CF$_3$COOH) δ (ppm): 1.08 (6H, d, $J = 6.5$ Hz); 2.05 (1H, m); 3.50 (2H, t, $J = 6.5$ Hz); 8.25 (1H, d, $J = 2.4$ Hz); 8.53 (1H, d, $J = 2.4$ Hz); 8.95 (1H, broad s).

IR (KBr) ν (cm$^{-1}$): 3302, 1618, 1305, 1171.

Mass, m/e (%) = 244(M+, 22), 189(100), 172(95), 109(59), 56(69).

Analysis for C$_9$H$_{12}$O$_2$S$_2$

Calcd C 44.24 H 4.95 N 11.47,
Found C 44.16 H 4.95 N 11.38.

3-sec-Butylaminothieno[3,4-d]isothiazole-1,1-dioxide (6c)

Reaction time 40 min. Yield 0.75 g (31%), m.p. 216–218 °C (EtOH).

$^1$H NMR (CF$_3$COOH) δ (ppm): 1.03 (3H, t, $J = 7$ Hz); 1.45 (3H, d, $J = 6.5$ Hz); 3.77 (1H, m); 8.24 (1H, d, $J = 2.4$ Hz); 8.55 (1H, d, $J = 2.4$ Hz); 8.95 (1H, broad s).

IR (KBr) ν (cm$^{-1}$): 3300, 1610, 1303, 1172.

Mass, m/e (%) = 244(M+, 37), 215(56), 189(83), 172(100), 64(55), 56(55).

Analysis for C$_{9}$H$_{12}$N$_{2}$O$_{2}$S$_{2}$

Calcd C 44.24 H 4.95 N 11.47,
Found C 44.49 H 4.89 N 11.22.