

A NEW SYNTHESIS OF 2-AMINO-2-THIAZOLINES  
(2-AMINODIHYDRO-1,3-THIAZOLES)

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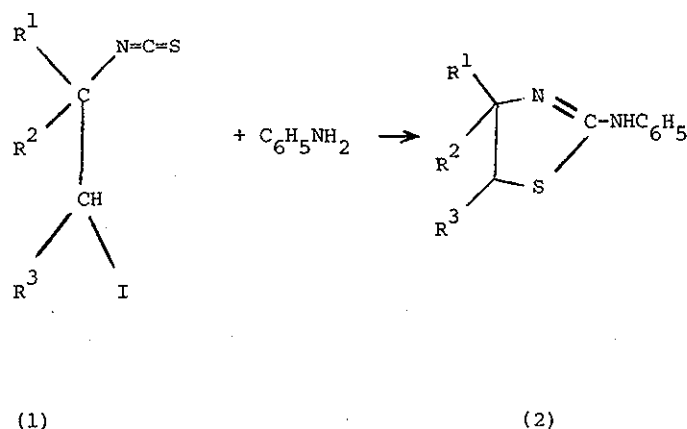
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2-Phenylamino-2-thiazolines are readily prepared under mild conditions by the reaction of aniline with vic-iodoisoithiocyanates. Ammonia, and primary and secondary alkylamines each give clean reactions with trans-1-iodo-2-isothiocyanatocyclohexane but not with 2-iodo-1-phenyl-1-isothiocyanatoethane.

2-Amino-2-thiazolines have usually been prepared by heating a 2-haloalkylamine with a thiocyanate,<sup>1</sup> by treating a 2-hydroxyethylamine with an organic isothiocyanate,<sup>1,2</sup> or by the reaction of an allylthiourea with a mineral acid.<sup>1</sup> Other preparations include the brief acid hydrolysis of acetalylthiocarbamides,<sup>3</sup> the isomerisation of 1-aziridinethiocarboxanilides with acids<sup>4</sup> or nucleophiles,<sup>5</sup> the reaction of 2,3-dibromo-1-isothiocyanatopropane with an amine,<sup>6</sup> and the cyclisation of 2-(2-aminoethyl)thio-pseudoureas.<sup>7</sup>

Recently we reported methods for the preparation of vicinal-iodothiocyantes and iodoisothiocyanates from alkenes.<sup>8</sup> For the reaction of iodine—potassium thiocyanate with an alkene the use of chloroform as solvent resulted in high yields of products and the rate of addition was accelerated in the presence of a phase-transfer catalyst.<sup>9</sup> We have now found that the ratio of isothiocyanate to thiocyanate in the preparation using iodine—thallium(I) thiocyanate, increases in

the presence of boron trifluoride etherate thereby making the former derivatives more readily available for synthesis. Their conversion into 2-thiazolidinones has already been described.<sup>10</sup> We now report a simple one-step method for preparing 2-phenylamino-2-thiazolines from vicinal-iodoisoithiocyanates. Thus, reaction of the iodoisoithiocyanates (1a-f) with aniline (ca. 2 molar equivs.) in anhydrous ether at room temperature in the dark followed by p.l.c. of the product in chloroform led to the heterocyclic products (2a-f) as indicated in the Table.



- (a)  $R^1 = H, R^2 - R^3 = - (CH_2)_4 -$  (cis)  
 (b)  $R^1, R^2, R^3 = 5\alpha\text{-androst-2,3-ano}$   
 (c)  $R^1 = R^3 = H, R^2 = C_6H_5$   
 (d)  $R^1 = H, R^2 = C_6H_5, R^3 = CH_3$   
 (e)  $R^1 = CH_3, R^2 = C_6H_5, R^3 = H$   
 (f)  $R^1 = R^2 = R^3 = \text{indano (1'-N)}$

Table: 2-Phenylamino-2-thiazoline derivatives

| Substrate (mmol) | Aniline (mmol) | Product         | Reaction time (h) | Yield (%) <sup>a</sup> | M.p. (°C)                   |
|------------------|----------------|-----------------|-------------------|------------------------|-----------------------------|
| 1a               | (0.31)         | 2a              | 72                | 84                     | 133-134 <sup>b</sup>        |
| 1b <sup>c</sup>  | (0.25)         | 2b <sup>d</sup> | 94                | 57                     | 235-236<br>178 <sup>e</sup> |
| 1c               | (0.23)         | 2c              | 22                | 59                     | 154-155                     |
| 1d               | (0.20)         | 2d              | 22                | 67                     | 155-156                     |
| 1e               | (0.24)         | 2e              | 168               | 62                     | 80-81 <sup>f</sup>          |
| 1f               | (0.22)         | 2f              | 24                | 83                     | 197-198                     |

a Yields after p.l.c.

b With sintering at 120°.

c A mixture of 3α-iodo-2β-isothiocyanato-5α-androstane and 2β-iodo-3α-isothiocyanato-5α-androstane (ca. 7:1) which was inseparable after multiple p.l.c. (hexane—chloroform, 2:1).

d A 6.1:1 mixture of isomeric (2'β-N, 3'β-S) and (2'α-S, 3'α-N)-2-phenylamino-2-thiazolines which were separated by p.l.c. (CHCl<sub>3</sub>).

e The minor product which sintered at 163°.

f With sintering at ca. 72°.

When trans-1-iodo-2-isothiocyanatocyclohexane (1a) was treated with an excess of anhydrous ammonia in place of aniline at ca. -33° it gave a thiourea which readily cyclized at room temperature and more so in refluxing chloroform, to give cis-cyclohexano-2-amino-2-thiazoline hydroiodide (68%), m.p. 175-176°. Attempts to extend the reaction to 2-iodo-1-phenyl-1-isothiocyanatoethane (1c) gave a complex mixture of products. However reaction of 1c with n-pentylamine gave a 56% yield of 4-phenyl-2-pentylamino-2-thiazoline. The reaction appeared to have general application since reaction of 1a with n-pentylamine gave a 94% yield of cis-cyclohexano-2-pentylamino-2-thiazoline, m.p. 64-65°, while reaction of 1a with the secondary amine, di-n-butylamine gave a 78% yield of cis-cyclohexano-2-di-n-butylamino-2-thiazoline.

The reactions with aniline are noteworthy since Hassner and co-workers<sup>11</sup> have reported that the reaction of vicinal-iodoisocyanates with aniline give only phenyl ureas. Formation of the 2-amino-2-thiazolines in the present case probably results from the greater reactivity of the intermediate thioureas.

All products obtained above were characterised by <sup>1</sup>H n.m.r., i.r., m.s., and elemental analysis. In all cases, the i.r. spectra (CHCl<sub>3</sub>) showed bands at ca.  $\nu_{\text{max}}$ . 1595 (s), 1640 (s), 3150 (m, br), and 3400 cm<sup>-1</sup> (m).

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