Synthesis of substituted 2,2'- and 4,4'-bithiazoles in various solvents

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Some tetra substituted derivatives of 2,2'- and 4,4'-bithiazoles have been synthesized and characterized in various solvents.

Bleomycines are a family of compounds that have potent tumour killing properties which have given them an important role in cancer chemotherapy. The bleomycin molecule has two main structural compounds, a bithiazole component which partially intercalates into the DNA helix, parting the strands as well as pyrmidine and imidazole structures which are iron and oxygen forming and active complex capable of releasing damaging oxidants in close proximity to the polynucleotide chain of DNA.

Rhodium(III) complexes with bithiazoles have also been reported to be used in the cyclic photoproduction of hydrogen from water. Bithiazoles with different substitutions at 2,2', 2,4', 4,5', 4,4' and 5,5' have been reported.

The synthesis of substituted 2,2' and 4,4'-bithiazoles is an interesting area in organic chemistry. Studies in the last decade have revealed that a number of organic reactions proceed more rapidly in aqueous solutions than in organic solvents. Use of water as solvent has obvious environmental and economic advantages relative to other solvents.

In this regard we wish to report the synthesis of some derivatives of 2,2'- and 4,4'-bithiazoles with different methods (Scheme I). Table I shows a set of various 2,2' and 4,4'-bithiazoles which were synthesized.

Experimental Section

All melting points are uncorrected. 1H NMR spectra were recorded on Brucker AC-80 (80 MHz) spectrometer in CDCl3 (chemical shifts in δ, ppm). IR(KBr) spectra on FT-IR Unicam Mattson 1000 spectrophotometer and mass spectra on Varian Matt. CH5 spectrometer. Chemicals were purchased from Merck, Aldrich, Fluka and Riedel Dehaen AG chemical companies and were used without further purification. All products were identified by their mp, IR, 1H NMR and Mass spectral data. All yields refer to pure isolated products.

**Synthesis of 4,4' and 5,5'-tetramethyl-2,2'-bithiazole.** Dithioxamide (6.00g, 0.05 mole) was added into 100 mL of water. Then the solution was added to a two necked flask that contains 4-chloro-2-butanone (10.70g, 0.10 mole) under magnetic stirring. The mixture was refluxed for 18 hr. The progress of the reaction was monitored by TLC. After the reaction was complete the reaction mixture was cooled to room temperature and the product isolated by steam distillation and purified by recrystallization from chloroform to furnish yellow purple solid, yield 5.80g.

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>Reaction period (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>CH3</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>2a</td>
<td>C6H5</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>1b</td>
<td>CH3</td>
<td>24</td>
<td>52</td>
</tr>
</tbody>
</table>

*Yields refer to pure the isolated products.

Note

![Scheme I](image-url)
NOTES

Synthesis of 4,4' and 5,5'-tetraphenyl-2,2'-bithiazole. Dithioxamide (6.00g, 0.05 mole) was added into 200 mL of abs. ethanol. Then this solution was added into a two necked flask that contains desyl bromide (27.50g, 0.10 mole) under magnetic stirring. The mixture was refluxed for 18 hr. The progress of the reaction was monitored by TLC. After the reaction was complete the reaction mixture was cooled to room temperature and the solid product filtered through a sintered glass. It was recrystallized from benzene to furnish yellow purple solid, yield 5.70g (24%); mp, 228-29 °C; IR(KBr): 3100, 1600, 1476, 1390, 1300, 870, 761, 700 cm⁻¹. ¹H NMR(CDC13): δ 7.60-7.20 (m), Mass, (M), 472, (100%); (M+1), 473, (25.1%); 236, (19.5%); 210, (15.7%); 178, (21.3%); and 165, (47.2%).

Synthesis of 2,2' and 5,5'-tetramethyl-4,4'-bithiazole. Thioacetamide (15.00g, 0.2 mole) and n-buthanol (200 mL) was added into a two necked flask. Then 2,5-dibromo-3,4-hexane-dione (27.20g 0.10 mole) was added into the flask under magnetic stirring. The mixture was refluxed for 24 hr. The progress of the reaction was monitored by TLC. After the reaction was complete the reaction mixture was cooled to room temperature, neutralized with sodium carbonate and then the product isolated by steam distillation. Drying of product with sodium acetate yielded 11.7g of yellow red crystals (24%); mp, 76-79 °C; IR(KBr): 3100, 1600, 1476, 1390, 1300, 870, 761, 700 cm⁻¹. ¹H NMR(CDC13): δ 2.74 (s), 2.51 (s); Mass, (M), 224, (100%); (M+1), 225, (13.4%); 226, (7.8%); 182, (44.9%); 150, (42.7%); 149, (23.0%); 82, (23.6%) and 59, (47.2%).

References
1 Hay J, Shahzeidi S & Laurent G, Archives of Toxicology, 65, 1991, 81.