RING TRANSFORMATION OF 1,2,6-THIADIAZINE 1,1-DIOXIDES INTO PYRAZOLES. A CONVENIENT SYNTHESIS OF N-ALKYSULFAMIDES

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Abstract - Conversion of thia diazines into pyrazoles by the action of hydrazine represents a new example of ring transformation and provides a new entry into N-methylsulfamide. The latter has been used to prepare an N-methyl-3,5-diaminothiadiazine which cannot be obtained by direct alkylation.

For many years, there has been considerable interest in ring transformations caused by the action of nucleophiles on heterocyclic compounds. We now wish to report conversion of N-substituted 1,2,6-thiadiazine-1,1-dioxides into pyrazoles by reaction with hydrazine. When N-methylthiadiazines are used, this reaction has an additional interest since it provides a very convenient synthesis of N-methylsulfamide, a valuable key intermediate for many heterocycles containing the N-SO₂-N moiety. The general synthesis of N-alkylsulfamides involves reaction of sulfamide and alkylamines but with methylamine this procedure does not work. Reaction of 2,3,5-trimethyl-1,2,6-thiadiazine-1,1-dioxide (1a) prepared according to Scheme 1, with hydrazine in water afforded N-methylsulfamide (mp 63-65°C Lit. 63-64°C) and 3,5-dimethylpyrazole in good yields.
The reaction proceeded in a very clean and smooth manner and the compounds were easily separated by crystallization. Other thiadiazines were used and the results are gathered in Table 1: 3,4,5-Trimethylpyrazole was obtained from 2,3,4,5-tetramethyl-1,2,6-thiadiazine 1,1-dioxide \( \text{Ib} \), prepared in a similar way to \( \text{Ia} \) whilst 2-phenylethyl-3,5-dimethyl-1,2,6-thiadiazine-1,1-dioxide \( \text{Ic} \) afforded N-phenylethylsulfamide and 3,5-dimethylpyrazole. This reaction was only performed in order to check the general scope of the method, since thiadiazine \( \text{Ic} \) was synthesized from N-phenylethylsulfamide and 2,4-pentanedione.

\[ \text{TABLE 1} \]

<table>
<thead>
<tr>
<th>R(_1)</th>
<th>R(_2)</th>
<th>%yield in sulfamide</th>
<th>%yield in pyrazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Me</td>
<td>H</td>
<td>95</td>
<td>89</td>
</tr>
<tr>
<td>b) Me</td>
<td>Me</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>c) CH(_2)CH(_2)Ph</td>
<td>H</td>
<td>67</td>
<td>59</td>
</tr>
</tbody>
</table>

The probable mechanism involved is depicted in Scheme 2. A similar mechanism has been postulated for the conversion of pyrimidines into pyrazoles by the action of hydrazine\(^7\).

Scheme 2
The structures of the pyrazoles were established by comparison with authentic samples. Since no recent reports have dealt with N-methylsulfamide its nmr spectra have been recorded: $^1$H nmr (300 MHz) (DMSO-d$_6$) $\delta$: 6.46 (s, NH$_2$), 6.28 (d, J=3.4 Hz, NH), 2.50 (d, J=3.5 Hz, CH$_3$); (acetone-d$_6$) $\delta$: 5.81 (s, NH$_2$), 5.50 (bs, NH), 2.68 (d, J=5.3 Hz, CH$_3$). $^{13}$C nmr (75 MHz) (DMSO-d$_6$) $\delta$: 28.7 (q, J=137.7 Hz, CH$_3$).

Finally, the synthetic usefulness of N-methylsulfamide is exemplified in the preparation of 2-methyl-3,5-diamino-1,2,6-thiadiazine-1,1-dioxide (2). The parent compound, 3,5-diamino-2H-1,2,6-thiadiazine-1,1-dioxide (3) is the starting material of many [6+6] and [6+5] fused thiadiazine derivatives. Direct methylation of this compound afforded C-mono- and C,N-dimethyl derivatives but the N-methyl derivative 2 could not be isolated. This compound can easily be obtained from N-methylsulfamide and malononitrile in dimethoxyethane (Scheme 3).

General procedure for conversion of 1,2,6-thiadiazines 1,1-dioxides into pyrazoles: An equimolar mixture of the thiadiazine and hydrazine hydrate in water (50-100 ml) was refluxed for 2h. After cooling, the precipitate (pyrazole) was collected by filtration and solvent evaporated under reduced pressure to afford the corresponding sulfamide.

ACKNOWLEDGEMENTS
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REFERENCES
6. 2-Phenylethyl-3,5-dimethyl-1,2,6-thiadiazine-1,1-dioxide \( \mathbf{1c} \): A solution of phenylethylsulfamide (2g, 0.01 mol) and 2,4-pentanedione (1g, 0.01 mol) in ethanol (50 ml) was saturated with hydrogen chloride. The reaction mixture was refluxed for 4 h, the solvent evaporated in vacuo and the residue recrystallized from methanol to give 2.3 g (88%) of \( \mathbf{1c} \), mp 185-186°C. Uv (MeOH) \( \lambda_{\text{nm}}(\epsilon) \): 217 (28001, 323 (41001; ir (nujol) \( \nu \text{cm}^{-1} \): 1320, 1180 (SO\(_2\)); \( ^1\)H nmr (DMSO-d\(_6\)) \( \delta \): 7.4 (m, 5H, Ar-H), 5.9 (s, 1H, H-4), 4.1 (t, J=6 Hz, 2H, N-CH\(_2\)), 3.1 (t, J=6 Hz, 2H, CH\(_2\)), 2.2 (s, 3H, CH\(_3\)-3), 2.1 (s, 3H, CH\(_3\)-5). C\(_{13}\)H\(_8\)N\(_2\)O\(_2\)S requires: C, 59.09; H, 6.06; N, 10.60; S, 12.12. Found: C, 59.31; H, 6.11; N, 10.64; S, 12.36.


12. 2-Methyl-3,5-diamino-1,2,6-thiadiazine-1,1-dioxide \( \mathbf{2} \): A solution of malononitrile (3g, 0.045 mol) and methylsulfamide (5g, 0.045 mol) in dimethoxyethane (30 ml) was saturated with hydrogen chloride for 15 min. The solid was collected by filtration and dissolved in a saturated solution of sodium bicarbonate. After cooling, a crystalline white precipitate appeared which was recrystallized from ethanol to give 2 g (26%) of \( \mathbf{2} \), mp 175-177°C, Uv (MeOH) \( \lambda_{\text{nm}}(\epsilon) \): 205 (7500), 225 (6200), 265 (13950). Ir (nujol) \( \nu \text{cm}^{-1} \): 1330, 1180 (SO\(_2\)). \( ^1\)H nmr (DMSO-d\(_6\)) \( \delta \): 6.8 (s, 2H, NH\(_2\)), 6.5 (s, 2H, NH\(_2\)), 4.6 (s, 1H, H-4) 3.1 (s, 3H, CH\(_3\)). C\(_4\)H\(_8\)N\(_4\)O\(_2\)S requires: C, 27.27; H, 4.54; N, 31.81; S, 18.18. Found: C, 27.56; H, 4.61; N, 32.01; S, 18.01.


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