Synthesis and Reactivity of Tetrahydroimidazo [1,5-b][1,2,4]oxadiazol-2(1H)-thiones

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1,3-Dipolar cycloaddition of imidazoline 3-oxides 1 with methylisothiocyanate proceeds regio- and diastereoselectively to give tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1H)-thiones 3 in high yields. The cis configuration of the adducts was proved by our double cis elimination test as well as by NOESY experiments. Adducts 3a-c undergo ring opening at reflux in acetonitrile to give imidazoles while 3d-e undergo retro dipolar cycloaddition to give the starting nitrones 1d-e. The imidazooxadiazol-2-thiones 3a-e were treated with concentrated HCl in ethanol at 50 °C to give the corresponding 4H-[1,2,4]oxadiazole-5-thione only in cases in which the substituent at C-6 is an aryl.

Key Words: Imidazoline 3-oxides, 1,3-Dipolar cycloaddition, Tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1H)-thiones, 4H-[1,2,4]oxadiazole-5-thione.

Introduction

A number of works either on cycloadditions or incorporating cycloadditions have appeared in recent years.1,3-Dipolar cycloadditions of nitrones, with a variety of dipolarophiles, are important in the synthesis of 5-membered heterocyclic compounds.1-4 Aryl and alkylisothiocyanates also act as dipolarophiles with respect to C=N bonds but in some cases cycloaddition may occur at C=S in the reaction with different nitrones.4 While nitrones undergo cycloaddition to the C=N double bond of phenylisothiocyanates to give the corresponding oxadiazole-5-thiones, in reactions with substituted phenylisothiocyanates and benzoylisothiocyanate addition to the C=S double bond predominates.5-6 The cycloaddition reactions with alkylisothiocyanates are analogous to the reaction with arylisothiocyanates.6 The reaction of acyclic nitrones with isothiocyanates was shown to give mainly oxadiazolidin-5-thiones.7 We have shown the 1,3-dipolar cycloaddition reactions of cyclic nitrones 1 with dipolarophiles as arylisocyanates,8-9 styrene,10 DMAD,11,12 and β-pinene13 to proceed regio- and, in the case of chiral nitrones, diastereoselectively. When heated, the adducts from isocyanates and styrene undergo retro 1,3-dipolar cycloaddition, while the adducts from DMAD and β-pinene give the corresponding imidazoles. The most interesting feature of the adducts from isocyanate,14 DMAD11,12 and chiral nitrones 1 was their different behavior in the presence of secondary

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and tertiary amines. A quite reliable chemical way, double cis elimination, was developed for determination of the relative configuration of the carbons 3a and 6 in the tetrahydroimidazooxadiazol-2-ones, and tetrahydroimidazoisoazolines.\textsuperscript{11–12,14} Recently, we reported our preliminary results\textsuperscript{15} on the 1,3-dipolar cycloaddition of nitrones 1 and methylisothiocyanate and the ring opening reactions of the adducts formed. Here we report in detail the reaction of cyclic nitrones 1 with a 4-fold excess of methylisothiocyanate in acetonitrile, method A, and with twenty fold excess of the dipolarophile without solvent, method B, to give a new class of tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1\textsubscript{H})-thiones 3. Methylisothiocyanate was shown to react regio- and diastereoselectively with nitrones 1d-e. The configuration of their adducts 3d-e was confirmed as cis by our double cis elimination test\textsuperscript{11–12,14} as well as by a NOESY experiment. The behaviour of adducts 3 in a warm solution and the condensed phase, and the reactions of 3 with secondary and tertiary amines are reported. An interesting rearrangement of C-6 substituted adducts 3 in the presence of HCl to give 4H-[1,2,4]oxadiazole-5-thione and its possible mechanism are also discussed.

Results and Discussion

Cyclic nitrones 1 were refluxed in acetonitrile in the presence of phenylisothiocyanate for 48 h but no conversion to the corresponding imidazooxadiazol-2-thiones was observed; the nitrones were recovered unchanged. This was in contrast with the reaction of the same nitrones with arylisocyanates, in which the reaction proceeds in high yields to give the corresponding imidazooxadiazol-2-ones.\textsuperscript{14} However, nitrones 1 gave the corresponding oxadiazol-2-thiones, method A, in low yields when refluxed in acetonitrile for 4 h in the presence of a 4-fold excess of methylisothiocyanate. The yields of 3 and unreacted 1 are given in the Table. Prolonging the reaction time did not improve the yields, instead lower or no yields were obtained after 48 and 64 h respectively. In the latter cases the main product formed was the corresponding imidazole. High yields were achieved by performing the reaction using the dipolarophile as a solvent, method B (see Table 1). When 12 mmolar acetonitrile solutions of 3a-c were refluxed for 17 h, a quantitative conversion to imidazole 4a-c was observed. The analogous experiment revealed that 36 h reflux of 12 mmolar acetonitrile solution of 3d-e led mainly to imidazole 4d-e while the more dilute solution (2 mM) led to the corresponding nitrone 1d-e after 72 h in 80% yield. However, the 2 mmolar solution of 3c did not give the corresponding nitrone 1c; it gave the corresponding 4c. The ring opening of 3a-e when concentrated solutions are used to give imidazoles and the retro dipolar cycloaddition of C-6 phenyl substituted adducts to give nitrones 1 when diluted solutions are used is unique behaviour among the tetrahydroimidazo adducts reported in our earlier studies.\textsuperscript{8–13} The structures of compounds 3 were established on the basis of their IR, \textsuperscript{1}H, and \textsuperscript{13}C NMR spectra and elemental analysis. The absence of absorption in the 1510-1650 cm\textsuperscript{−1} region of the IR spectra of compounds 3 was indicative of the regioisomer arising from the addition to the C=N double bond. Alternative addition to the C=S bond should give an exocyclic imine having a C=N stretching vibration in the mentioned region.\textsuperscript{6} Characteristic patterns of adducts 3a-c are the 2 proton AB systems at 3.73 (\textit{J}_{\text{AB}} = 10.8 \text{ Hz}) and 4.72 ppm (\textit{J}_{\text{AB}} = 10.8 \text{ Hz}) assigned to C-4 and C-6 methylenes. The AB system for C-4 protons of 3d-e appears at nearly 4.20 ppm and the singlet for the C-6 proton has δ 5.92 and 6.02 for 3d and 3e respectively. These chemical shifts are in good agreement with those for the same protons in the adducts obtained from the same imidazoline 3-oxides and phenylisocyanate where the cis relation of the phenyls at C-3a and C-6 was
deduced from NOE and double cis elimination amine test experiments. The thiocarbonyl carbon’s shifts in the $^{13}$C NMR spectra of compounds 3 are at δ 183 ppm approximately.

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\begin{align*}
\text{Scheme 1} \\
\text{Table 1. Tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1H)-thiones 3, imidazoles 4 and oxadiazolethione 5.}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Yields of 3</th>
<th>Meth. A</th>
<th>R</th>
<th>R'</th>
<th>mp of 3 (°C)</th>
<th>Yields of 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>15 (80)$^a$</td>
<td>65</td>
<td>4-MeC$_6$H$_4$</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td>b</td>
<td>22 (70)</td>
<td>70</td>
<td>4-MeOC$_6$H$_4$</td>
<td>H</td>
<td>4-MeOC$_6$H$_4$</td>
</tr>
<tr>
<td>c</td>
<td>15 (80)</td>
<td>70</td>
<td>4-MeOC$_6$H$_4$</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td>d</td>
<td>30 (65)</td>
<td>90</td>
<td>4-MeOC$_6$H$_4$</td>
<td>Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>e</td>
<td>20 (70)</td>
<td>95</td>
<td>4-MeC$_6$H$_4$</td>
<td>Ph</td>
<td>Ph</td>
</tr>
</tbody>
</table>

$^a$The yields of the recovered 1.$^b$Thermal ring opening was performed at temperatures of 118, 165, 90, 150, 143 °C for 3a, 3b, 3c, 3d, and 3e respectively under vacuum (1.3 x 10$^{-3}$ mm Hg) for 10 min.

We assume that due to steric hindrance the dipolarophile should attack nitrones 1d-e from the opposite side of the phenyl at C-2. This results in cis 3a,6-diphenylimidazooxadiazol-2-thiones 3d-e, which is the case in all of the tetrahydroimidazo adducts reported.$^{8-13}$

The reaction of 3d with aniline (1:2 molar ratio) in ethanol at reflux for 24 h gave the corresponding nitrone 1 and N-methyl-N-phenylurea. This is in agreement with the reaction of arylisocyanate adducts with aniline where the products were also nitrone 1 and the corresponding N,N-diary lurea.

Thermal treatment of adducts 3 in the condensed phase under vacuum at the temperatures given in the Table led to the formation of corresponding imidazoles in high yields. The same reaction with the adducts of nitrones 1 with arylisocyanates led to the formation of corresponding nitrones.$^8,^9$ The reflux of compounds 3a-e at the concentration mentioned above in acetonitrile for 48 h gave the same imidazoles as in the condensed phase reaction, while the reflux of the diluted solution of 3d-e led to the formation of nitrones 1d-e. It is clear from these experiments that the reaction between methylisothiocyanate and nitrones 1 is a reversible process and in more concentrated solutions it seems that the isothiocyanate formed catalyzes the elimination of methylthiocarbamic acid to give the corresponding imidazole, while in low concentrations the retro reaction is favored, probably due to the consumption of the isothiocyanate in a hydrolysis reaction (water from the moisture of the acetonitrile).
Adducts 3a-c are converted to the corresponding 4 within 30-40 min in the presence of diethyl- or triethylamine in refluxing acetonitrile. Adducts 3d-e were refluxed for 4 h with an excess of diethylamine expecting a double cis elimination as in the cases of DMAD and isocyanate\textsuperscript{14} adducts. This was the case; imidazole 4 was the only product formed. However, the same adducts remained unchanged, as did the cis DMAD\textsuperscript{11-12} adducts. The cis structure was confirmed by X-ray analysis, under the same conditions as when triethylamine was used. cis Arylisocyanate adducts also gave no elimination but underwent retro cycloaddition when treated with triethylamine for a long time.\textsuperscript{14}

Some selected NOESY correlations for 3e are given in the figure below. Methyls protons are in clear relation with the part of the AB system at C-4. This proton, in turn, gives a cross peak with the protons of the p-tolyl ring. The proton at C-6 also gives a cross peak with the protons of the aryl at N-5. All these give a reliable base for the assignment of the cis configuration for compounds 3d-e.

Figure. Selected NOESY correlations for 3e.

Compound 3a with R\textsuperscript{1} = H slowly gives the corresponding imidazole when heated gently on a water bath in ethanol in the presence of 37% HCl while 3c remains unchanged.\textsuperscript{16} However, at the same reaction conditions adducts 3d-e having R\textsuperscript{1} = Ar were identified to give 4H-[1,2,4]oxadiazole-5-thione 5 and 4H-[1,2,4]oxadiazole-5-one 6. The probable mechanism of the reaction is outlined in Scheme 2. Protonation of adduct 3 at the bridgehead nitrogen leads to the formation of an ammonium species 7, which undergoes retro 1,3-dipolar cycloaddition to give the corresponding azomethine ylide 8 and oxadiazol-5-thione 5. To the best of our knowledge this is the first example of acid induced rearrangement of tetrahydroimidazooxadiazol-5-thiones.

Scheme 2
Azomethine ylide formation was deduced from its hydrolysis products, namely the aldehyde and the corresponding amine. Thus the method described serves as an alternative cycloaddition way of obtaining oxadiazol-5-thiones by the reaction of N-substituted amide oximes with ethyl chloroformate and thiophosgene.\textsuperscript{17−18}

Compound 6 was isolated in 36 and 35\% yields from the reaction mixtures of 3d and 3e, respectively. Compound 6 should arise from the rearrangement of the hydrolyzed products of 3d and 3e since attempts to hydrolyze isolated compound 5 in ethanol in the presence of 37\% HCl for 40 h did not give any 6. Compound 6 was treated with P\textsubscript{2}S\textsubscript{5} in xylene to give quantitative amounts of compound 5.

**Experimental**

Melting points were recorded on an Electrothermal Digital melting point apparatus. IR spectra were recorded on a Mattson 1000 FTIR. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a Bruker Dpx 400 MHz spectrometer. All spectra were taken in deuteriochloroform with a little DMSO-d\textsubscript{6}. Freshly prepared imidazoline 3-oxides\textsuperscript{19−21} were used after recrystallization from either ethanol or acetone.

**Tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1\textit{H})-thiones 3a-e; General procedure. Method A-** To a suspension of imidazoline 3-oxide 1 (2 mmol) in acetonitrile (10 mL) was added methylisothiocyanate (8 mmol) and the mixture was refluxed for 4 h. The solvent and the excess of isothiocyanate were removed under vacuum. The residue was subjected to column chromatography using silica gel as an adsorbent and ethyl acetate petroleum ether (1:3) as an eluent. Further purification was performed by recrystallization from ethanol.

**Method B-** A mixture of imidazoline 3-oxide 1 (2 mmol) and methylisothiocyanate (20 mmol) was heated for 2 h at 80 °C. Excess isothiocyanate was removed under vacuum and the residue was dissolved in ethanol under heating and was left to crystallize at room temperature. The formed white crystals were separated by filtration and dried under vacuum.

3-Methyl-3a-phenyl-5-p-tolyl-tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1\textit{H})-thione (3a) IR (KBr) No absorption corresponding to $\nu_{C=N}$; \textsuperscript{1}H NMR (CDCl\textsubscript{3} and DMSO-d\textsubscript{6}) $\delta$ ppm 2.27 (3H, s), 3.0 (3H, s), 3.46 (1H, d, $J = 10.7$), 4.2 (1H, d, $J = 10.78$), 4.36 (1H, d, $J = 10.7$), 5.07 (1H, d, $J = 10.78$), 6.68 (2H, d, $J = 7.7$), 7.05 (2H, d, $J = 7.6$), 7.43-7.54 (5H, m). \textsuperscript{13}C NMR (CDCl\textsubscript{3} and DMSO-d\textsubscript{6}) $\delta$ ppm 20.11; 31.04; 53.94; 75.46; 93.46; 115.02; 126.44; 128.64; 129.16; 129.46; 129.49; 135.51; 142.68; 182.42.

Calcd. for C\textsubscript{18}H\textsubscript{19}N\textsubscript{3}OS C, 66.43; H, 5.88; N, 12.91; S, 9.85. Found C, 66.84; H, 6.31; N, 12.67; S, 9.47.

3-Methyl-3a,5-di(4-methoxyphenyl)-tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1\textit{H})-thione (3b) IR (KBr) No absorption corresponding to $\nu_{C=N}$; \textsuperscript{1}H NMR (CDCl\textsubscript{3} and DMSO-d\textsubscript{6}) $\delta$ ppm 2.96 (3H, s), 3.33 (1H, d, $J = 10.7$), 3.73 (3H, s), 3.82 (3H, s), 4.08 (1H, d, $J = 10.9$), 4.43 (1H, d, $J = 10.7$), 5.06 (1H, d, $J = 10.9$), 6.79 (4H, s), 6.94 (2H, d, $J = 7.9$), 7.46 (2H, d, $J = 7.9$). \textsuperscript{13}C NMR (CDCl\textsubscript{3} and DMSO-d\textsubscript{6}) $\delta$ ppm 30.96; 54.70; 75.98; 54.87; 54.92; 93.61; 113.93; 114.33; 116.58; 127.56; 128.04; 139.12; 153.52; 160.16; 182.05.

Calcd. for C\textsubscript{19}H\textsubscript{21}N\textsubscript{3}O\textsubscript{3}S C, 61.44; H, 5.70; N, 11.31; S, 8.63. Found C, 60.95; H, 5.27; N, 11.16; S, 8.34.

3-Methyl-3a-phenyl-5-(4-methoxyphenyl)-tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1\textit{H})-thione (3c) No absorption corresponding to $\nu_{C=N}$; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) $\delta$ ppm 2.93 (3H, s), 3.40 (1H, d, $J$...
3-Methyl-3a,6-diphenyl-5-(4-methoxyphenyl)-tetrahydroimidazo[1,5-b][1,2,4]oxadiazol-2(1H)-thione (3d) No absorption corresponding to \(\text{C}=\text{N}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) ppm 3.0 (3H, s), 3.7 (3H, s), 4.21 (1H, d, \(J\) = 11), 4.29 (1H, d, \(J\) = 11), 6.02 (1H, s), 6.56 (2H, d, \(J\) = 7.9), 6.98 (2H, d, \(J\) = 7.8), 7.19-7.24 (3H, m), 7.31-7.42 (7H, m). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) ppm 20.86; 31.94; 54.68; 87.18; 92.82; 114.77; 126.97; 127.70; 128.90; 129.94; 129.05; 129.35; 130.04; 130.36; 135.96; 136.99; 143.25; 183.58.

Calcd. for \(C_{24}H_{23}N_3O_2S\) C, 71.79; H, 5.77; N, 10.46; S, 7.99. Found C, 70.97; H, 5.41; N, 10.29; S, 7.61.

Thermal ring opening of compounds 3a-e. Imidazooxadiazol-2-thiones 3 (0.1 mmol) were heated in a vacuum oven under vacuum (1.3 x 10\(^{-3}\) mm Hg) at 90-165 °C for 10 min. The imidazole formed was extracted with hexane (3 x 2 mL). The combined extracts were concentrated and left to crystallize.

Reaction of 3a-e with secondary amines. To a solution of 3 (0.3 mmol) in acetonitrile (13 mL) was added diethylamine (8 mL) and the mixture was refluxed at stirring for 3 h. The solvent was evaporated and the residue recrystallized to give the corresponding imidazole 4.

Reaction with tertiary amines. To a solution of 3 (0.3 mmol) in acetonitrile (13 mL) was added triethylamine (8 mL) and the mixture refluxed at stirring for 3h. The solvent was evaporated and the residue recrystallized to give the corresponding imidazole 4 in the cases of 3a-c and the unreacted adducts 3 in the cases of 3d-e.

The reaction of 3d-e with HCl. To a suspension of 3 (0.15 mmol) in ethanol (20 mL) was added HCl (0.13 mL, 37%) and the mixture heated at 50 °C on a water bath for 25 h. The solvent was removed and the residue extracted with dichloromethane (3 x 15 mL). The combined extracts were dried over anhydrous Na\(_2\)SO\(_4\), filtered and the solvent removed under vacuum. The products isolated by recrystallization or column chromatography were the corresponding 4-Methyl-3-phenyl-4H-[1,2,4]oxadiazole-5-thione, mp 117-118 °C; lit\(^{18}\) mp 119-120 and 4-Methyl-3-phenyl-4H-[1,2,4]oxadiazole-5-one, lit\(^{22}\) mp 119-120 °C.

Reaction with HClO\(_4\). To a solution of 3a (0.100 g, 0.25 mmol) in CH\(_2\)Cl\(_2\) (4 mL) was added 70% HClO\(_4\) (4mL) and the mixture stirred at room temperature for 40 min. The mixture was basified with ammonia and the organic phase was separated, dried and filtered and the organic solvent evaporated. The residue was recrystallized from petroleum ether to give the corresponding imidazole 4a. Yield 92% .
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References

16. Compound 3a gives imidazole in 58% yield when heated in the presence of HCl for 39 h. 30% of 3a was recovered unchanged. 3c was treated at the same reaction conditions for 10 h and no conversion to any product was observed.