Iodogen: A Novel Reagent for the Oxidation of Urazoles under Heterogeneous Conditions

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Abstract: Iodogen is employed as an efficient oxidizing agent for the conversion of urazoles and bis-urazoles into the corresponding 1,2,4-triazole-3,5-diones with the stability of iodogen and simple work-up procedure make it a safe and convenient source of chlorine in comparison to chlorine gas, which is a highly toxic oxidizing agent. During the reaction, iodogen is transformed into an environmentally benign and easily removable by-product (diphenyglycoluril which is insoluble in dichloromethane). Despite its advantages, there has been limited application of iodogen in organic synthesis. We have thus investigated iodogen as a mild reagent for the oxidation of urazoles and bis-urazoles under heterogeneous conditions (Scheme 1). Iodogen can be easily prepared from diphenyglycoluril. The oxidation reactions are heterogeneous as the solid substrates 1 and 3 are insoluble in the reaction solvent (dichloromethane) whereas the products 2 and 4 are soluble in dichloromethane.

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It should be noted that with the exception of iodogen as the oxidizing agent, attempts to oxidize urazoles using other active N-chloro reagents such as N-chlorosaccharin (II), chloramine-T (III), N-chlorophthalimide (IV) and N-chlorosuccinimide (V) failed (Figure 2). In the case of N,N'-dichlorophenobarbital (VI), urazoles were oxidized into the corresponding 1,2,4-triazole-3,5-diones, however, we were unable to isolate the products due to their high sensitivity.

Herein, we report a simple and inexpensive method for the efficient oxidation of various urazoles 1 and bis-urazoles 3 into the corresponding 1,2,4-triazole-3,5-diones 2 and 4 under optimized heterogeneous conditions using iodogen (I) (Table 1).

A plausible mechanism for this reaction involves in situ generated chlorine cations acting as the oxidizing species. Subsequent elimination of hydrogen chloride then yields the 1,2,4-triazole-3,5-dione (Scheme 2).

Table 1: Oxidation of Urazoles 1 and Bis-Urazoles 3 into the Corresponding 1,2,4-Triazole-3,5-diones 2 and 4 Using Iodogen*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Urazole</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>Iodogen (mmol)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Mp (°C) Found</th>
<th>Lit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>H</td>
<td>Me</td>
<td>1.0</td>
<td>2.5</td>
<td>100</td>
<td>98–99</td>
<td>97–98²⁶⁶a</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>H</td>
<td>Et</td>
<td>0.5</td>
<td>0.66</td>
<td>100</td>
<td>53–55</td>
<td>54–55²⁶⁶a</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>Na⁺</td>
<td>n-Pr</td>
<td>0.45</td>
<td>1</td>
<td>89</td>
<td>41–44</td>
<td>40–42²⁶⁶a</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d</td>
<td>H</td>
<td>c-Hex</td>
<td>0.5</td>
<td>0.33</td>
<td>92</td>
<td>95–96</td>
<td>95–97²⁶⁶a</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>2e</td>
<td>H</td>
<td>Ph</td>
<td>0.5</td>
<td>1</td>
<td>96</td>
<td>169–170</td>
<td>171–175²⁶⁶a</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2f</td>
<td>H</td>
<td>4-ClC₆H₄</td>
<td>0.5</td>
<td>1.5</td>
<td>91</td>
<td>130–133</td>
<td>132–135²⁶⁶a</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>2g</td>
<td>H</td>
<td>3,4-Cl₂C₆H₄</td>
<td>0.5</td>
<td>1.25</td>
<td>94</td>
<td>113–115</td>
<td>111–113²⁶⁶a</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>2h</td>
<td>H</td>
<td>4-O₂NC₆H₄</td>
<td>1.0</td>
<td>2.5</td>
<td>90</td>
<td>125–127</td>
<td>125–126²⁶⁶a</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>2i</td>
<td>H</td>
<td>4-MeOCC₆H₄</td>
<td>0.5</td>
<td>1.25</td>
<td>95</td>
<td>87–90</td>
<td>89–93²⁸⁸</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>2j</td>
<td>H</td>
<td>4-t-BuC₆H₄</td>
<td>0.5</td>
<td>0.58</td>
<td>95</td>
<td>122–127</td>
<td>122–126²⁸</td>
</tr>
<tr>
<td>11</td>
<td>3a</td>
<td>4a</td>
<td>Na⁺</td>
<td>(CH₃)₃</td>
<td>1.0</td>
<td>2</td>
<td>93</td>
<td>144–150</td>
<td>145–150²⁶⁶a</td>
</tr>
<tr>
<td>12</td>
<td>3b</td>
<td>4b</td>
<td>H</td>
<td>C₆H₅CH₂C₆H₄</td>
<td>2.0</td>
<td>2.5</td>
<td>87</td>
<td>183 (dec.)</td>
<td>180–185 (dec.)²⁶⁶a</td>
</tr>
</tbody>
</table>

*a Reaction in CH₂Cl₂ at r.t.

b The products are known and their spectra and physical data are reported in the literature.

c Yield of isolated product.

d % Conversion, as these compounds are very volatile.
In conclusion, we have described iodogen (I) as a novel reagent for the efficient and practical oxidation of urazoles and bis-urazoles under heterogeneous conditions. This system could be used for the oxidation of a range of urazoles under mild and safe conditions.

Chemicals were purchased from Fluka, Merck and Aldrich. Melting points were measured using a Stuart Scientific SMP3 apparatus and are uncorrected. The $^1$H NMR (90 MHz) and $^{13}$C NMR (22.5 MHz) spectra were recorded in CDCl$_3$ using a Jeol FX90Q spectrometer. The oxidation products were characterized by comparison of their spectral (IR, $^1$H and $^{13}$C NMR) and physical data with authentic samples prepared by reported procedures. NMR spectroscopic data are provided for representative compounds.

4-Phenyl-1H-1,2,4-triazole-3,5-dione (2e); Typical Procedure
A mixture of 4-phenylurazole (1e) (0.176 g, 1 mmol) and iodogen (I) (0.216 g, 0.5 mmol) in CH$_2$Cl$_2$ (10 mL) was stirred at r.t. for 1 h. The reaction mixture was filtered and the solvent evaporated to give 2e as a red, crystalline solid; yield: 0.167 g (96%).

$^1$H NMR (90 MHz, CDCl$_3$): $\delta$ = 7.5 (s, 5 H, ArH).

$^{13}$C NMR (22.5 MHz, CDCl$_3$): $\delta$ = 124.3, 126.9, 129.9, 158.0.

4-Methyl-1H-1,2,4-triazole-3,5-dione (2a)
Pink crystals.

$^1$H NMR (90 MHz, CDCl$_3$): $\delta$ = 3.3 (s, 3 H, CH$_3$).

4-Butylphenyl-1H-1,2,4-triazole-3,5-dione (2b)
Pink crystals.

$^1$H NMR (90 MHz, CDCl$_3$): $\delta$ = 1.3 (t, J = 7.0 Hz, 2 H, CH$_2$).

$^13$C NMR (22.5 MHz, CDCl$_3$): $\delta$ = 12.7, 36.7, 159.2.

4-(4-Chlorophenyl)-1H-1,2,4-triazole-3,5-dione (2f)
Red crystals.

$^1$H NMR (90 MHz, CDCl$_3$): $\delta$ = 7.4 (s, 4 H, ArH).

$^{13}$C NMR (22.5 MHz, CDCl$_3$): $\delta$ = 125.1, 128.1, 130.3, 135.6, 157.8.

4-(4-Nitrophenyl)-1H-1,2,4-triazole-3,5-dione (2h)
Red crystals.

$^1$H NMR (90 MHz, CDCl$_3$): $\delta$ = 7.9–8.4 (m, 4 H, ArH).

$^{13}$C NMR (22.5 MHz, CDCl$_3$): $\delta$ = 124.0, 125.4, 135.1, 147.7, 157.8.

4-(4-Methoxyphenyl)-1H-1,2,4-triazole-3,5-dione (2i)
Dark-red crystals.

$^1$H NMR (90 MHz, CDCl$_3$): $\delta$ = 3.9 (s, 3 H, OCH$_3$), 7.0–7.4 (m, 4 H, ArH).

$^{13}$C NMR (22.5 MHz, CDCl$_3$): $\delta$ = 55.6, 115.2, 125.6, 158.0, 160.2.

4-(4-Ethylphenyl)-1H-1,2,4-triazole-3,5-dione (2j)
Red crystals.

$^1$H NMR (90 MHz, CDCl$_3$): $\delta$ = 1.3 (s, 9 H, CH$_3$), 7.2–7.5 (m, 4 H, ArH).

4,4'-Hexane-1,6-diylbis(1H-1,2,4-triazole-3,5-dione) (4a)
Pink crystals.

$^1$H NMR (90 MHz, CDCl$_3$): $\delta$ = 1.3–1.6 (m, 8 H), 3.6 (t, J = 7.0 Hz, 4 H).

$^{13}$C NMR (22.5 MHz, CDCl$_3$): $\delta$ = 25.5, 27.0, 41.1, 159.2.

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References


(29) As the product 4-substituted-3H-1,2,4-triazole-3,5-diones are very volatile, it is important that the temperature be maintained below 50 °C during evaporation of the solvent to prevent loss of material.