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

Ahmad Khoramabadi-zad,*[a] Azam Shiri,[a] Mohammad Ali Zolfigol,[a] Shadpour Mallakpour[b]

[a] Faculty of Chemistry, Bu-Ali Sina University, P.O. Box 6517838683, Hamadan, Iran

[b] Organic Polymer Chemistry Research Laboratory, College of Chemistry, Isfahan University of Technology, Isfahan 84156, Iran
Fax +98(31)18257407; E-mail: khoram@basu.ac.ir

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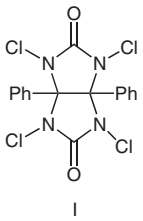
Abstract: Iodogen is employed as an efficient oxidizing agent for the conversion of urazoles and bis-urazoles into the corresponding 1,2,4-triazoles in good to excellent yields under mild heterogeneous conditions at room temperature.

Key words: iodogen, oxidations, chloroamides, glycolurils

1,3,4,6-Tetrachloro-3a,6a-diphenylglycoluril, also known as iodogen (**I**), was first used by Fraker and Speck in 1978 for the radioiodination of proteins and cell membranes,[1] and this procedure is still widely used for this purpose.[2–6] Iodogen (Figure 1) is a mild oxidizing agent and is as effective as enzymatic methods for the iodination of externally exposed residues, and is comparable with chloramine-T for general protein iodination. In addition, iodogen being a mild reagent results in limited oxidative damage and retained cell viability.[7–11]



I

Figure 1 The structure of iodogen (**I**)

Di- and tetrachloroglycolurils were found to have good bactericidal activity against test organisms. Chloroglycolurils, prepared using chlorine gas,[1,12–15] generally have greater thermal stability than other known chloroamides which makes them very useful as impregnating agents for clothing. Furthermore, as they contain a high percentage of active chlorine, they are useful as neutralizing agents or as antivesicants for mustard gas and other vesicants. Chlorinated glycolurils have been proposed as the source of chlorine for swimming pool sanitation and sewage treatment.[1]

4-Substituted-1,2,4-triazole-3,5-diones (TADs) are well known for their high reactivity in both thermal and photochemical reactions, due to the presence of both carbonyl and azo moieties in the molecule. They can undergo self-reactions leading to deazadimers[16] and polymers.[17] Volanschi and coworkers have investigated the electrochemical behavior and redox reactivity of several 4-substituted 1,2,4-triazole-3,5-diones.[18] TADs have been used both as substrates and reagents in various organic reactions including [2+2] cycloadditions,[19] dehydrogenation,[20] electrophilic aromatic substitution,[21] condensation of dicarbonyl compounds,[22] and oxidation of alcohols to aldehydes and ketones.[16,23] The varied reactivity of TADs makes them interesting compounds, however, they can be difficult to prepare and purify. It is interesting to note that 4-phenyl-3*H*-1,2,4-triazole-3,5-dione (**2e**) is an extremely reactive dienophile and enophile.[24]

All the known methods for the preparation of 1,2,4-triazole-3,5-diones involve oxidation of the corresponding urazoles. Although a number of reagents are available for the efficient oxidation of urazoles into TADs, this transformation is not straightforward due to their high sensitivity to the oxidizing agents and the reaction conditions. In addition, most of the reported reagents produce by-products, which either decompose the sensitive 1,2,4-triazole-3,5-dione, or are difficult to remove from the reaction product. Furthermore, the products are sensitive to light, heat, alcohols, ethers, transition metals and several nucleophiles. Another major drawback is the use of reagents which are highly toxic or impose serious disposal problems, or both.[25] The use of *N*-chloro- and *N*-bromo-containing oxidizing agents have also been reported, but without optimizing the reaction times or the amount of oxidizing agent required.[26]

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 (diphenylglycoluril which is insoluble in dichloromethane). Despite its advantages, there has been limited application of **I** in organic synthesis. We have thus investigated iodogen as a mild reagent for the oxidation of urazoles **1** and bis-urazoles **3** under heterogeneous conditions (Scheme 1). Iodogen can be easily prepared from diphenylglycoluril.[27] 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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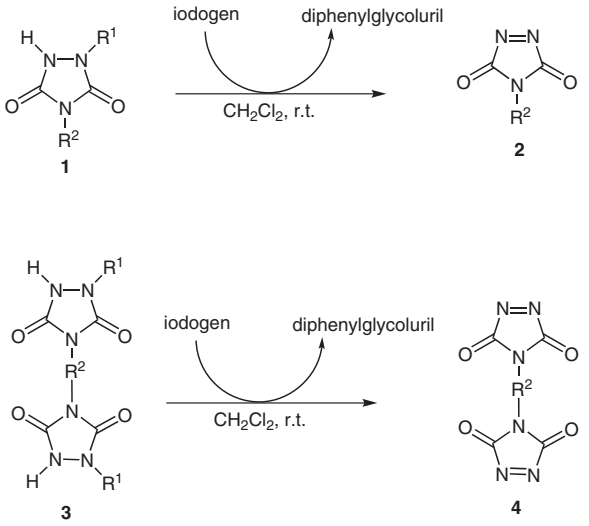
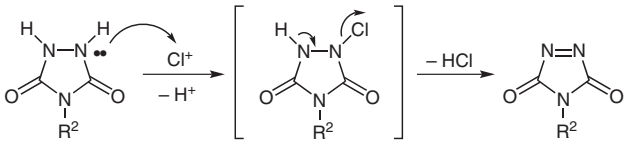


Scheme 1 Synthesis of 1,2,4-triazole-3,5-diones **2** and **4**

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).



Scheme 2 A plausible mechanism for the iodogen-mediated oxidation of urazoles or bis-urazoles into the corresponding 1,2,4-triazole-3,5-diones

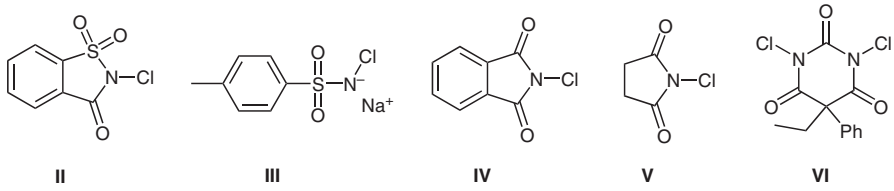


Figure 2 Structures of the *N*-chloro-based oxidizing agents **II–VI**

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[a]

Entry	Urazole	Product[b]	R^1	R^2	Iodogen (mmol)	Time (h)	Yield (%)[c]	Mp (°C) Found	Lit.
1	**1a**	**2a**	H	Me	1.0	2.5	100[d]	98–99	97–98[26a]
2	**1b**	**2b**	H	Et	0.5	0.66	100[d]	53–55	54–55[26a]
3	**1c**	**2c**	Na^+	*n*-Pr	0.45	1	89	41–44	40–42[26a]
4	**1d**	**2d**	H	*c*-Hex	0.5	0.33	92	95–96	95–97[26a]
5	**1e**	**2e**	H	Ph	0.5	1	96	169–170	171–175[26a]
6	**1f**	**2f**	H	4-ClC_6H_4	0.5	1.5	91	130–133	132–135[26a]
7	**1g**	**2g**	H	3,4-$Cl_2C_6H_3$	0.5	1.25	94	113–115	111–113[26a]
8	**1h**	**2h**	H	4-$O_2NC_6H_4$	1.0	2.5	90	125–127	125–126[26a]
9	**1i**	**2i**	H	4-$MeOC_6H_4$	0.5	1.25	96	87–90	89–93[28]
10	**1j**	**2j**	H	4-*t*-BuC_6H_4	0.5	0.58	95	122–127	122–126[28]
11	**3a**	**4a**	Na^+	$(CH_2)_6$	1.0	2	93	144–150	145–150[26a]
12	**3b**	**4b**	H	$C_6H_4CH_2C_6H_4$	2.0	2.5	87	183 (dec.)	180–185 (dec.)[26a]

[a] Reaction in CH_2Cl_2 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.[26a,28] NMR spectroscopic data are provided for representative compounds.

4-Phenyl-3*H*-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_2Cl_2 (10 mL) was stirred at r.t. for 1 h. The reaction mixture was filtered and the solvent evaporated[29] to give **2e** as a red, crystalline solid; yield: 0.167 g (96%).

^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.5 (s, 5 H, ArH).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 124.3, 129.6, 129.9, 158.0.

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

^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.3 (s, 3 H, CH_3).

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

^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.3 (t, *J* = 7.0 Hz, 3 H, CH_3), 3.7 (q, *J* = 7.0 Hz, 2 H, CH_2).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 12.7, 36.7, 159.2.

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

^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.4 (s, 4 H, ArH).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 125.1, 128.1, 130.3, 135.6, 157.8.

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

^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.9–8.4 (m, 4 H, ArH).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 124.0, 125.4, 135.1, 147.7, 157.8.

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

^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.9 (s, 3 H, OCH_3), 7.0–7.4 (m, 4 H, ArH).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 55.6, 115.2, 125.6, 126.0, 158.0, 160.2.

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

^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.3 (s, 9 H, CH_3), 7.2–7.5 (m, 4 H, ArH).

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

^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.3–1.6 (m, 8 H), 3.6 (t, *J* = 7.0 Hz, 4 H).

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 25.5, 27.0, 41.1, 159.2.

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