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The first report on the catalytic oxidation of urazoles to their corresponding triazolinediones via *in situ* catalytic generation of Br^+ using periodic acid or oxone®/KBr system

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Abstract

A combination of periodic acid or oxone® and a catalytic amount of KBr in the presence of few drops of water, were used for the catalytic oxidation of urazoles and bis-urazoles to their corresponding triazolinediones under mild and heterogeneous conditions with moderate to excellent yields.

Keywords: Urazoles; Bis-urazoles; Triazolinediones; Periodic acid; Oxone®; Potassium bromide; Catalytic oxidation; Heterogeneous conditions

The development of an efficient catalytic system for the selective organic transformation is currently one of the challenging tasks in synthetic organic chemistry [1]. In recent years, the search for environmentally benign chemical processes or methodologies has received much attention by chemists, due to their necessity on the conservation of the global ecosystem. The development of heterogeneous catalysts for fine chemical synthesis has become a major research area, as the potential advantages of these materials (simplified recovery and reusability; the potential for incorporation in continuous reactors and microreactors) over homogeneous systems can lead to novel environmentally benign chemical procedures both for academia and industry. From this viewpoint, catalytic oxidation is a valuable process because the use of stoichiometric reagents that are often toxic poses inherent limitations from both economical and environmental viewpoints regarding product purification and waste management [2].

4-Substituted-1,2,4-triazole-3,5-diones (TADs), have been used both as substrates and reagents in various organic reactions. For example they have been used in Diels–Alder, ene or [2 + 2] cycloadditions, dehydrogenation reactions, electrophilic aromatic substitution, condensation of dicarbonyl compounds, oxidation of alcohols to aldehydes and ketones [3]. Very recently aromatization of 1,4-dihydropyridines, pyrazolines and coupling of thiols with TADs were reported [4]. The unusual reactivity which makes TADs (**2** and **4**) of interest also makes them hard to prepare and purify. Although a variety of reagents are capable for efficient oxidations of urazoles (**1** and **3**) to TADs, this transformation is not easy because these compounds are very sensitive to the oxidizing agents and reaction conditions. In addition, most of the reported reagents produce by-products, which either destroy, or are difficult to remove from the sensitive triazolinediones [5–10].

Recently, that application of heterogeneous systems, for the above-mentioned oxidations has many advantages over their liquid phase counterparts such as simple experimental procedures, mild reaction conditions and the minimization of chemical wastes [11].

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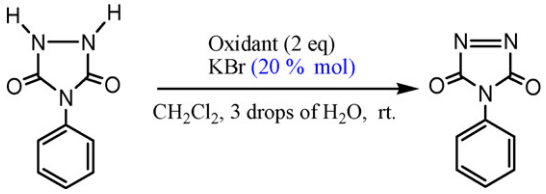
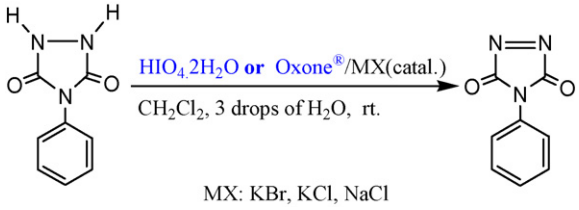


Scheme 1.



Scheme 2.

Solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal [12]. Also, wastes and by-products can be minimized or avoided by developing cleaner synthesis routes. On the other hand, reduction in the amount of liquid acid needed and/or simplification in handling procedures is required for risk reduction, economic advantage and environment protection [13]. Among solid acids, periodic acid [$HIO_4{\cdot}2H_2O$] and oxone® [$2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$] are commercially available as two inorganic acidic oxidizing reagents. There are several reports in the literature which demonstrate that periodic acid and oxone® are efficient oxidizing agents for the oxidation of various organic substrates [14].

In continuation of our studies using periodic acid [15], oxone® [16] and catalytic oxidation methods [2c,17] in organic transformations, we have been interested to find out a catalytic heterogeneous system for the oxidation of urazoles. In this context, we have found that a combination of periodic acid or oxone® and a catalytic amount of KBr in the presence of few drops of water, generate *in situ* Br^+ as an efficient oxidizing agent for the oxidation of urazoles and bis-urazoles to their corresponding triazolinediones.

To find the best catalytic reagent system, we studied a number of oxidizing reagents in a combination of KBr for the oxidation of urazoles (Scheme 1). As it can be seen in Table 1, the best results are referred to $HIO_4{\cdot}2H_2O$ or oxone®/KBr system.

In addition to KBr, we also used KCl and NaCl as the catalyst for the described system (Scheme 2) and the obtained results are depicted in Table 2. From results in Table 2 it is evident that KBr is more efficient than KCl or NaCl, and for this reason it has been chosen as the best catalyst for the oxidation of urazoles.

Table 1
Comparison between various oxidizing agents\KBr systems for the oxidation of 4-phenyl urazole

Oxidant	Time (h)	Yeilds (%)[a]
$Na_2S_2O_8$	1	–
$K_2S_2O_8$	1	–
$(NH_4)_2S_2O_8$	1	–
Oxone®	3[b]	–
Oxone®	0.25	90
$HIO_4{\cdot}2H_2O$	1[b]	–
$HIO_4{\cdot}2H_2O$	0.33	95
HIO_3	1.5	Sluggish
UHP [18a][c]	2	–
DABCO–DNODP [18b][c]	2	–
PVP–H_2O_2 [18c][c]	2	–
Sodium perborate [18d][c]	3	–

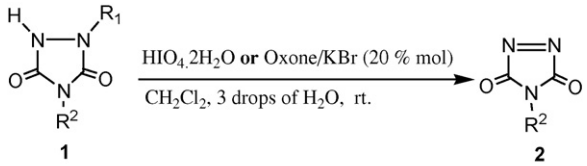
[a] Isolated yields.
[b] Without KBr.
[c] These reagents have been used for different functional group transformation. Please see their references.

Table 2
Comparison of various types of MX for the oxidation of 4-phenyl urazole

Oxidizer acid	MX	Time (min)	Yeilds (%)[a]
$HIO_4{\cdot}2H_2O$	NaCl	40	96
$HIO_4{\cdot}2H_2O$	KCl	60	95
$HIO_4{\cdot}2H_2O$ [16c]	Silica chloride	60	95
$HIO_4{\cdot}2H_2O$	KBr	20	95
$HIO_4{\cdot}2H_2O$	KBr[b]	20	–
$HIO_4{\cdot}2H_2O$	KBr[c]	120	90
Oxone®	NaCl	30	66
Oxone®	KCl	45	60
Oxone®	KBr	25	60
Oxone®	KBr[b]	25	–
Oxone®	KBr[c]	120	–

[a] Isolated yields.
[b] Solvent free.
[c] In the presence of 0.2 g wet SiO_2 (50%, w/w) instead of few drops water.

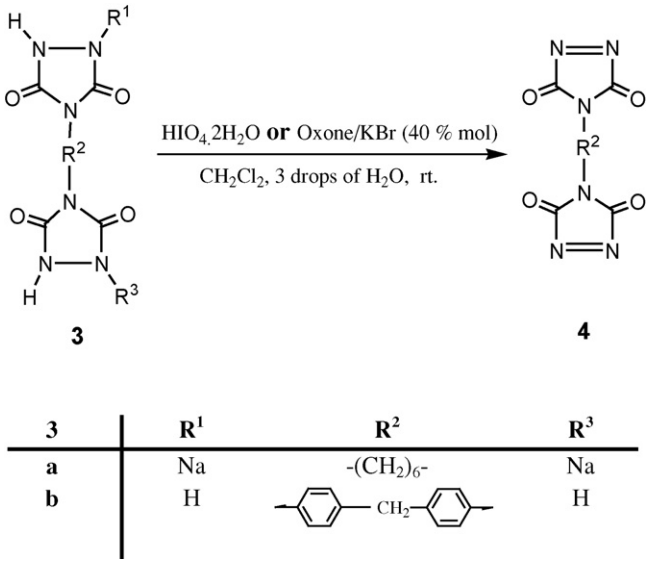
Thus, in this article we wish to report the first example of a catalytic method for the effective oxidation of urazoles (**1**) and bis-urazoles (**3**) to their corresponding triazolinediones (**2** and **4**) under mild and heterogeneous conditions (Schemes 3 and 4). A variety of urazoles (**1**) and bis-urazoles (**3**) were subjected to the oxidation reaction with a combination of periodic acid (**I**) or oxone® (**II**) with a catalytic amount of KBr in the presence of few drops of water. All oxidation reactions were performed under mild and completely heterogeneous conditions, at room temperature with good to excellent yields (Table 3).



1 **2**

1	R_1	R_2
a	H	Me
b	H	Et
c	Na	n-Pr
d	H	n-Bu
e	H	Cyclohexyl
f	H	Ph
g	H	4-Cl-C_6H_4-
h	H	3,4-Cl_2-C_6H_3-
i	H	4-NO_2-C_6H_4-

Scheme 3.

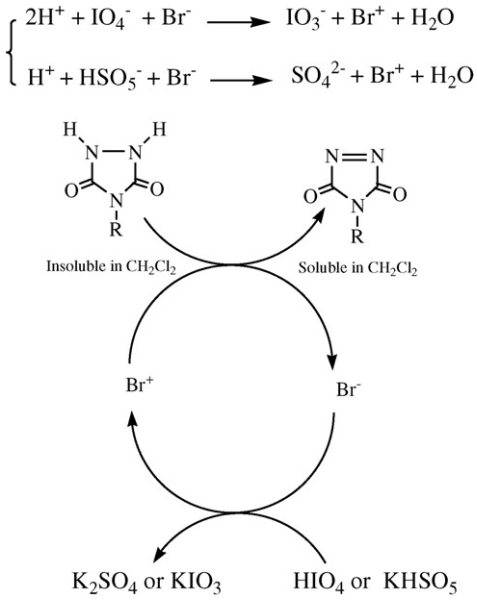


Scheme 4.

Table 3
Oxidation of urazoles (**1**) and bis-urazoles (**3**) to their corresponding triazolinediones (**2** and **4**) with $HIO_4{\cdot}2H_2O$ (**I**) or oxone® (**II**) in the presence of a catalytic amount of KBr and few drops of water in dichloromethane at room temperature.

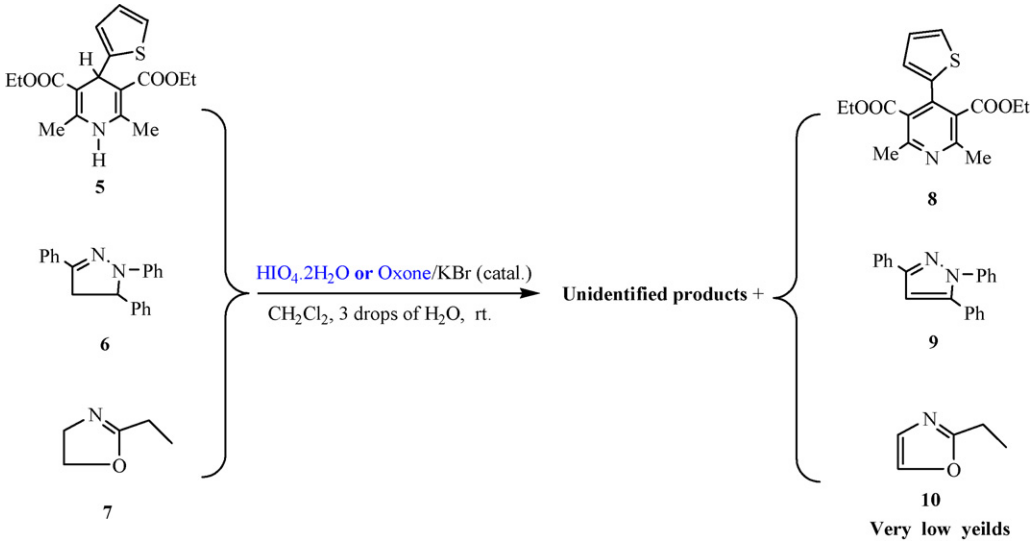
Substrat	Products	Reagent/substrate (mmol)		Time (min)		Yeilds (%)[a]	
		I	II	I	II	I	II
1a	**2a**	2	1.15	20	3	100[b]	100[b]
1b	**2b**	2	1.15	20	3	100[b]	100[b]
1c	**2c**	2	1.15	25	2	86	55
1d	**2d**	2	1.15	25	5	91	97
1e	**2e**	2	1.15	25	5	91	99
1f	**2f**	2	1.25	20	25	95	60
1g	**2g**	2	1.25	25	25	91	94
1h	**2h**	2	1.25	30	30	95	94
1i	**2i**	2	1.25	30	25	86	98
3a	**4a**	5	2.25	25	4	90	88
3b	**4b**	5	2.5	30	25	99	99

[a] Isolated yields.
[b] Conversion.



Scheme 5.

The present oxidation reaction can be readily carried out only by placing, periodic acid or oxone® with a catalytic amount of KBr, urazoles (**1**) or bis-urazoles (**3**), with CH_2Cl_2 as solvent, in the presence of few drops water in a reaction vessel under efficient stirring of the resulting heterogeneous mixture at room temperature. The triazolinediones (**2**) and bis-triazolinediones (**4**) are obtained by simple filtration and evaporation of the solvent. As mentioned above the oxidation reactions are heterogeneous because urazoles and bis-urazoles [(**1** and **3**) as white solids] are insoluble in dichloromethane whereas all of the triazolinediones and bis-triazolinediones [(**2** and **4**), as red and pink solids, respectively] are very soluble in dichloromethane. Therefore, the oxidation reaction has been performed via *in situ* generation of Br^+ (Scheme 5).



Scheme 6.

This new catalytic system acts as such as 1,3-dibromo-5,5-dimethylhydantoin (DBH) via in situ generation of Br^+[19].

In continuation of our studies on the chemistry of 1,4-dihydropyridines [20,4a] and 1,3,5-trisubstituted pyrazolines [21,4b] we were also interested to use the above reported system for the oxidation of 1,4-dihydropyridines (**5**), 1,3,5-trisubstituted pyrazolines (**6**) and 2-substituted oxazolines (**7**), but the reactions were sluggish and not practical. Several efforts for optimizing the reaction conditions failed and the yields of the desired products (i.e., pyridines (**8**), pyrazoles (**9**) or oxazole (**10**)) were very low among with some unidentified by-products (Scheme 6).

In conclusion, in this work the first catalytic method for the oxidation of urazoles and bis-urazoles has been reported. We suggest that this system could be used for the oxidation of a wide variety of urazole derivatives and similar functionalities under mild and safe conditions.

1. Experimental section

1.1. General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Yields refer to isolated pure products. The oxidation products were characterized by comparison of their spectral (IR, UV, ^{1}H NMR, and ^{13}C NMR) and physical data with authentic samples. Urazoles and bis-urazoles were synthesized via multi step synthesis according to our previously reported procedures [9,10].

2. Synthesis of 4-phenylurazole (1f) [9]

2.1. A typical procedure

2.1.1. Synthesis of ethyl carbazate

Into a 1000-ml three-necked round-bottomed flask were placed 100.20 g (2.0 mol) of hydrazine monohydrate (100%) and 236.26 g (243 ml, 2.0 mol) of diethylcarbonate. The mixture turned to milky solution. The flask was shaken vigorously to mix the two liquids. After about 2 min, the milky emulsion became warm. Shaking was continued until a clear solution was obtained (approximately 10 min). The flask was then fitted with a water-cooled condenser attached to a drying tube containing calcium chloride and heated at reflux for 4.5 h. After cooling, the clear solution was transferred to a 500 ml round-bottomed flask and distilled through a 15-cm vigreux column under reduce pressure. By-products were collected (18 mm Hg, 80 °C). Ethyl carbazate was obtained as a colorless liquid 179.95 g (87.0%) (Scheme 7).

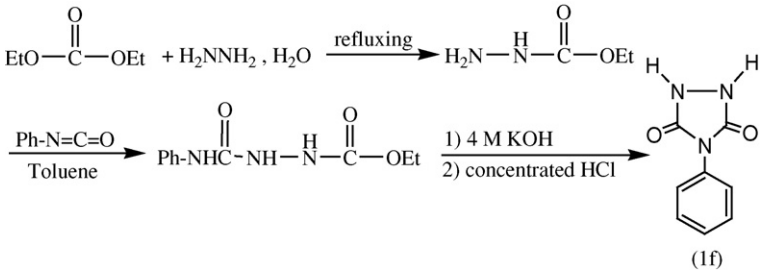
2.1.2. Synthesis of 1-ethoxycarbonyl-4-phenylsemicarbazide

A 1000-ml three-necked round-bottomed flask was used. It was equipped with a constant-pressure dropping funnel, a mechanical stirrer, and a reflux condenser fitted with a drying tube containing silica gel. Into it were charged 45.06 g (0.432 mol) of ethyl hydrazine carboxylate (ethyl carbazate) and 500 ml of toluene. The solution was cooled in an ice-water bath to about 10 °C, and the stirrer was started. To the solution was added dropwise 51.56 g (0.432 mol) of phenyl isocyanate over a period of 75 min. A white precipitate formed after about one-half of the isocyanate had been added. After the addition was complete, the ice bath was removed, and the mixture was stirred at room temperature for 2.5 h. Then it was heated by a heating mantle under reflux for 2 h. At the end of the refluxing period, the slurry mixture was allowed to cool to room temperature. The white solid was collected by suction filtration, then washed with 300 ml of toluene and then dried in a vacuum desiccator for 24 h, the yield was 92.57 g (96%) (Scheme 7).

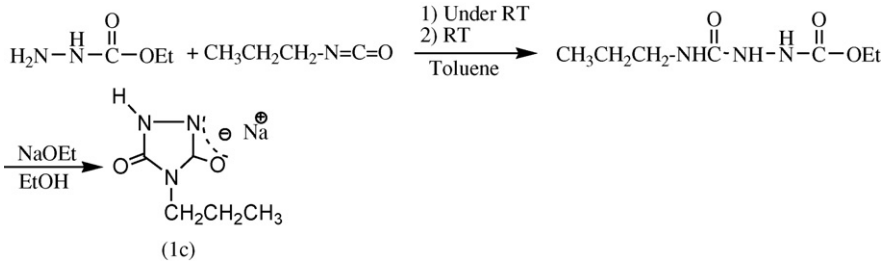
2.1.3. Synthesis of 4-phenylurazole

1-Ethoxycarbonyl-4-phenylsemicarbazide (44.60 g, 0.20 mol) was placed in a 500-ml Erlenmeyer flask, and 100 ml of 4 M KOH was added. The suspension was warmed on a hot plate and stirred by a magnetic stirrer for 1.5 h. Then 80 ml of 4 M KOH was added to ensure that the reaction had taken place to a large extent. The hot solution was filtered by suction filtration. The filtrate was cooled in an ice bath and then acidified with concentrated hydrochloric acid (about 53 ml). A white solid was precipitate, filtered, and then dried in a vacuum desiccator at room temperature; the yield was 35.38 g (100%) of product. Recrystallization from hot water (about 300 ml) yielded a white crystalline compound, mp 205–206 °C (Scheme 7).

IR (KBr): 3400 (w), 3100 (s, br), 1780 (sh), 2990 (m), 1680 (s), 1600 (w), 1495 (s), 1440 (s), 1290 (w), 1220 (m), 1115 (m), 1060 (w), 1030 (w), 1005 (w), 910 (w), 770 (s, br), 685 (w), 600 (m, br) (cm^{-1}).



Scheme 7.



Scheme 8.

^{1}H NMR (DMSO-d_6, TMS): δ 7.45 (m, 5H), 10.40 (s, br, 2H) [9].

3. Synthesis of 4-*n*-propylurazole sodium salt (1c) [10]

3.1. A typical procedure

In a 1000-ml three-necked round-bottle flask, which was equipped with a water-cooled condenser, a constant pressure dropping funnel and a mechanical stirrer, sodium metal (3.88 g, 0.1690 mol) was placed. To this metal absolute ethanol (300 ml) was added dropwise over a period of 60 mins. While magnetically being stirred, at the end of addition, a clear solution was obtained. 1-Ethoxycarbonyl-4-*n*-propyl semicarbazide (32.00 g, 0.1690 mol) was added to the resulting clear solution under reflux conditions. Upon addition, an orange and then a red solution was obtained. After 2 h slurry was formed which was refluxed for 54 h. The hot reaction mixture was filtered and the desired solid compound was isolated as a white solid 17.82 g (Scheme 8) [10]. Concentration of the filtered to about 30 ml afforded more material 6.12 g, yield: 23.94 g, 85.5%, mp 230 °C.

IR (KBr): 3480 (m, sh), 3400 (s), 3200 (s), 2990 (m), 2920 (m), 2880 (m), 1690 (s), 1620 (s, sh), 1590 (s), 1460 (s), 1420 (m), 1370 (m), 1260 (m), 1050 (m), 910 (w), 807 (s), 770 (w), 720 (w), 640 (m, br) (cm^{-1}).

^{1}H NMR (D_2O, DSS): δ 0.85 (t, 3H, J = 9.0 Hz), 1.63 (sextet, 2H, J = 7.5 Hz), 3.46 (t, 2H, J = 7.5 Hz) [10].

4. Oxidation of 4-phenyl urazole (1f) to 4-phenyl-1,2,4-triazoline-3,5-dione (2f)

4.1. A typical procedure

Compound **1f** (0.177 g, 1 mmol), periodic acid [**I** (0.456 g, 2 mmol)], KBr [(0.0238 g, 0.2 mmol)] and three drops of water were added in dichloromethane (10 ml) and the resulted suspension was vigorously stirred for 20 min. Then the reaction mixture filtered and washed with CH_2Cl_2 (2× 10 ml). The filtrate was dried over anhydrous Na_2SO_4 (3 g) and filtered off after appropriate time. Dichloromethane was removed by water bath (40–50 °C) [22] and simple distillation. The yield was 0.168 g (95%) of crystalline red solid (**2f**), mp. 168–175 °C [Ref. [11], mp 170–178 °C].

Note: For physical and spectral data for all of the reported compounds see reference [11a].

Acknowledgment

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[22] TADs compounds are sensitive to light, heat, alcohols, ethers, transition metals, and other nucleophiles. Also, they are very volatile so that, if the temperature rises over 50 °C in the course of removing of CH_2Cl_2, some TADs are removed with the solvent simultaneously. Therefore, the temperature must be controlled and dichloromethane is the best solvent for the synthesis of this class of compounds.