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An effective and mild oxidative aromatization of isoxazolines and 2-pyrazolines by trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane promoted by ammonium iodide in water/MeCN

Akbar Mobinikhaledi, Kaveh Khosravi*, Samira Kazemi

Department of Chemistry, Faculty of Science, Arak University, Arak 38156-8-8349, Iran.

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ABSTRACT

In this work, trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane (DHPDMDO)/NH_4I has been used as, powerful, nearly green, effective and inexpensive oxidant for oxidative aromatization of isoxazolines and 2-pyrazolines to corresponding isoxazoles and 2-pyrazoles in the presence of catalytic amount of acetic acid at room temperature in water/MeCN. All products were obtained in high yields and good purity within short time by an easy work-up.

***Keywords**: Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane; Pyrazoles; Isoxazoles.*

1. Introduction

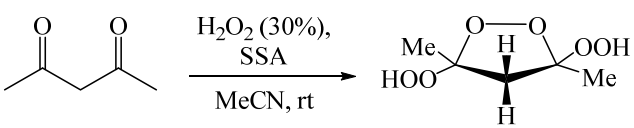
Five member heterocyclic compounds often play important roles in biologically active natural and synthetic medicines [1-2]. Among them, a number of isoxazoles and pyrazoles exhibit fluorescence features and can act as agrochemical herbicides, soil fungicides, pesticides and insecticides [3-4]. In addition, isoxazoles and pyrazoles are suitable synthetic intermediates capable of undergoing various transformations and transition-metal catalyzed cross-coupling reactions, such as Heck, Stille, Suzuki, Sonogashira and Negishi couplings [5]. Various efforts have been made previously for oxidation of isoxazolines and 2-pyrazolines that have used a variety of reagents including Pd/C/Acetic acid [6], carbon-activated oxygen [7], cobalt soap of fatty acids [8-10], lead tetraacetate [11], mercury or lead oxide [12], manganese dioxide [13], potassium permanganate [13-14], silver nitrate [15], iodobenzene diacetate [16], zirconium (IV) nitrate [17], nickel (II) peroxide [18], chromite (III) [19], N-bromosuccinimide (NBS) [20], manganese triacetate [21], sodium bicarbonate/dimethyl formamide [22], 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) [23], sodium carbonate/methanol [24], and tetrakispyridine nickel(II) dichromate [25]. Recently, gem-dihydroperoxides as the powerful organic peroxides have been used in organic chemistry [26]. As the importance of these peroxides, we have synthesized trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane as a powerful oxidant in organic reactions [27] (Scheme 1). In this work, we wish to report a simple and efficient procedure for oxidative aromatization of isoxazolines and 1,3,5-trisubstituted pyrazolines to the corresponding isoxazoles and pyrazoles respectively, using the DHPDMDO/NH_4I/HOAc system in water/MeCN at room temperature (Scheme 2).

*Corresponding author email: khosravi.kaveh@gmail.com
Tel.: +98 86 3417 3400; Fax: +98 86 3262 7339

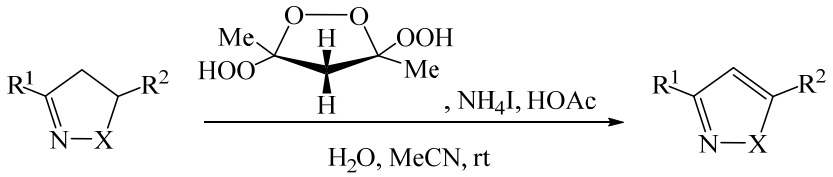
2. Experimental

2.1. General

Solvents, reagents, and chemical materials were obtained from Aldrich and Merck chemical companies and purified prior to use.



Scheme 1. Synthesis of trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO).



Scheme 2. Oxidative aromatization of 2-pyrazolines and isoxazolines

Nuclear magnetic resonance spectra were recorded on JEOL FX 90Q using tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a PerkinElmer GX FT IR spectrometer in KBr pellets. Elemental analyses were performed using a Perkin-Elmer 2400 series analyser. Melting points were measured on an SMPI apparatus. Caution: Although we did not encounter any problem with trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane, but all peroxides potentially explosive and should be handled with precautions, all reactions should be carried out behind a safety shield inside a fume hood and heating should be avoided.

2.2. Preparation of DHPDMDO

DHPDMDO has been synthesized and characterized according to the reported method (27b-g).

2.3. General experimental procedure for the oxidative aromatization of 2-pyrazolines, and isoxazolines

A mixture of 2-pyrazolines or isoxazolines (1 mmol), NH_4I (0.07 g, 0.5 mmol) and acetic acid (0.006 mL, 0.1 mmol) in water (3 mL) and MeCN (2 mL) is prepared. Then trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane (0.5 g, 0.3 mmol) was added to this mixture and stirred for appropriate time at room temperature. The progress of reaction was followed by TLC. After completion of the reaction, Na_2SO_3 1 M (1 ml) was added and stirred for 10 minutes. Then, water (15 ml) was added and the products were filtrated and dried as the pure products.

Selected spectral data

(E)-1-phenyl-5-styryl-3-(p-tolyl)-1H-pyrazole ***(2O)****:*

m.p.: 122-124°C. IR (KBr): $\bar{\nu}$ =3020, 3005, 2867, 1610, 1593, 1455, 1361, 1305, 1279, 1165, 1140, 1054, 867 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ= 2.33 (s, 3H), 6.60 (s, 1 H), 6.78-7.84 (m, 16 H) ppm. ^{13}C NMR (22.5 MHz, $CDCl_3$) δ= 19.4, 96.5, 120.8, 124.5, 124.7, 124.9, 125.6, 125.9, 126.8, 127.5, 128.1, 128.4, 128.9, 129.2, 129.6, 130.0, 130.3, 131.9, 132.4, 135.0, 137.0, 138.2, 142.5, 149.2.1 ppm. Found: C, 86.20; H, 5.81; N, 8.42, $C_{24}H_{20}N_2$, Reported: C, 85.68; H, 5.99; N, 8.33.

3. Results and Discussion

The reaction conditions (amount of oxidant, amount of NH_4I, HOAc and solvent) were optimized for 1,3,5-triphenyl-4,5-dihydro-1H-pyrazole as the model reaction (Table 1). As the results show, water/MeCN is the best solvent and also, the amount of oxidant (0.3 mmol) and NH_4I (0.1 mmol) was optimized. Also, it is notable that the addition of catalytic glacial acetic acid improved the yield and reduced the reaction time. Suggested mechanism is shown in Scheme 3. As shown in this scheme, the positive effect of HOAc is deduced from formation of IOAc that is more active than IOH. The formed I+ activates the nitrogen of imine group, then the acetate anion as a base eliminates the H+ and finally NH4I is reformed (Scheme 3). The results for several 2-pyrazolines and isoxazolines are shown in Table 2. Various 2-pyrazolines and isoxazolines with aromatic substituent that have both electron-withdrawing groups (Table 2, entries 2e, 2h, 2i, 2l, 2m, 2q, 2r, 2u, 2w, and 2x) and electron-donating groups (Table 2,entries 2b, 2c, 2d, 2g, 2h, 2n, 2o, 2p, 2t, and 2v) were oxidized to the corresponding pyrazoles and isoxazoles, respectively.

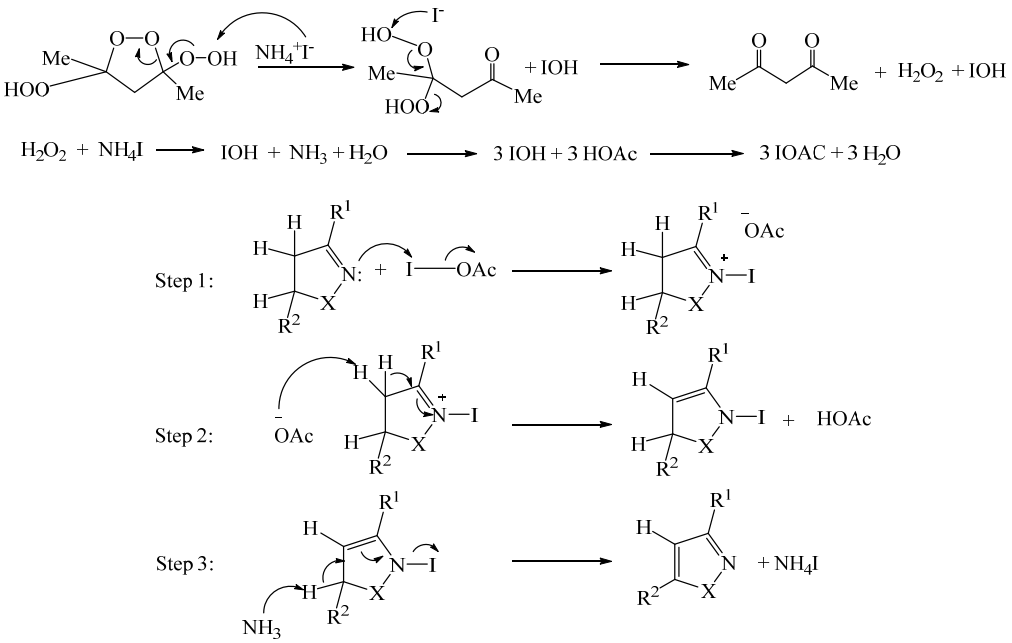
It seems that generally, steric effects of substituent groups increase the reaction time. Maximum of this steric effect was observed for naphtyl substitution (Table 2, entries 1d, 1e, 1d and 1g for pyrazoles and 1s, 1t, 1u, 1v, 1w and 1x for isoxazoles). Also, electron-withdrawing groups such as Cl or nitro substations increase reaction time rather than electron-realizing substations such as methoxy group. The obtained results by this method have been compared with other reported methods in Table 3. Due to the presented results, this method has shown a clear yield improvement. Furthermore, all reactions in this method need shorter reaction time than other reported methods. Therefore this method leads to a great improvement in reaction conditions and also high efficiency. Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane in comparing to other peroxides such as hydrogen peroxide, t-butyl hydrogen peroxide and urea-hydrogen peroxide has clearly advantages such as more oxidizing power, solubility in many organic solvents and water, solid physical state and mild reaction conditions.

Finally, from green chemistry aspect, it is noteworthy that, in all cases the products (isoxazoles and 2-pyrazoles) are isolated in neutral media with easy work up.

In addition, MeCN is used as a less toxic organic solvent. Also the probable produced acetyl acetone and NH_4I during the reaction, are soluble in water, so they can easily be separated from the reaction mixture.

4. Conclusions

In summary, trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane has been conveniently used as an oxidant in oxidation of various substituted isoxazolines and 2-pyrazolines. The reactions proceed under mild conditions at room temperature. This protocol may be considered as environmentally benign since no toxic catalyst is used in this method.



Scheme 3. Suggested mechanism for oxidative aromatization of 2-pyrazolines and isoxazolines.

Table 1. Optimization of reaction conditions for oxidation of 1,3,5-triphenyl-4,5-dihydro-1H-pyrazole (1 mmol).

Entry	Oxidant (mmol)	NH_4I (mmol)	HOAc (mmol)	Solvent	Time (min)	Yield (%)
1	0.3	-	-	MeCN	120	20
2	0.3	0.05	-	MeCN	120	50
3	0.3	0.1	-	MeCN	120	60
4	0.3	0.2	-	MeCN	120	60
5	0.3	0.5	-	MeCN	120	55
6	0.3	0.8	-	MeCN	120	40
7	0.3	0.1	0.05	MeCN	60	93
8	0.3	0.1	0.05	$CHCl_3$	120	45
9	0.3	0.1	0.05	CCl_4	120	50
10	0.3	0.1	0.05	THF	90	90
11	0.3	0.1	0.05	H_2O/MeCN	25	97
12	0.1	0.1	0.05	H_2O/MeCN	30	87
13	0.2	0.1	0.05	H_2O/MeCN	40	90
14	0.5	0.1	0.05	H_2O/MeCN	25	83
15	1	0.1	0.05	H_2O/MeCN	20	70

Table 2. Oxidative aromatization of 2-pyrazolines (1a-p) and isoxazolines (1q-x) to the corresponding pyrazoles (2a-p) and isoxazoles (2q-x) by DHPDMDO/NH_4I/HOAc system in water/MeCN at r.t.

Substrate[a]	Product	X	R^1	R^2	Time (min)	Yield (%)[b]	m.p. (˚C)		Ref.
							Found	Reported	
1a	2a	NC_6H_5	C_6H_4	C_6H_4	25	97	136-138	133-134	[30]
1b	2b	NC_6H_5	C_6H_4	4-$MeOC_6H_4$	30	92	78-80	79-80	[29]
1c	2c	NC_6H_5	4-$MeOC_6H_4$	C_6H_4	25	90	76-78	77-79	[41]
1d	2d	NC_6H_5	2-naphthyl	2-Me C_6H_4	60	88	146-148	148-150	[41]
1e	2e	NC_6H_5	2-naphthyl	4-ClC_6H_4	55	87	131-133	130-133	[41]
1f	2f	NC_6H_5	2-naphthyl	C_6H_4	50	89	70-72	67-70	[41]
1g	2g	NC_6H_5	2-naphthyl	2-MeC_6H_4	60	88	148-150	148-150	[29]
1h	2h	NC_6H_5	2-thienyl	4-ClC_6H_4	40	95	130-132	135-138	[42]
1i	2i	NC_6H_5	3-thienyl	4-ClC_6H_4	50	95	146-148	145-148	[42]
1j	2j	NC_6H_5	3-thienyl	4-$Me_2NC_6H_4$	65	92	118-120	120-123	[42]
1k	2k	NC_6H_5	4-MeC_6H_4	4-ClC_6H_4	45	94	96-98	93-95	[41]
1l	2l	NC_6H_5	C_6H_4	4-ClC_6H_4	30	94	113-115	114-115	[41]
1m	2m	NC_6H_5	C_6H_4	4-$NO_2C_6H_4$	55	92	142-144	144-146	[29]
1n	2n	NC_6H_5	4-$MeOC_6H_4$	3-MeC_6H_4	55	88	96-98	94-96	[29]
1o	2o	NC_6H_5	4-MeC_6H_4	2-styryl	70	88	122-124	New	-
1p	2p	NC_6H_5	4-$MeOC_6H_4$	4-ClC_6H_4	50	88	71-73	70-71	[29]
1q	2q	O	2-thienyl	4-ClC_6H_4	90	90	192-194	192-194	[43]
1r	2r	O	2-furyl	4-ClC_6H_4	100	82	122-124	124-125	[43]
1s	2s	O	2-naphthyl	2-thienyl	100	87	117-119	118-120	[43]
1t	2t	O	2-naphthyl	4-$MeOC_6H_4$	90	82	106-108	107-109	[43]
1u	2u	O	2-naphthyl	3-ClC_6H_4	85	78	91-93	90-92	[43]
1v	2v	O	2-naphthyl	2-styryl	110	95	164-166	165-167	[43]
1w	2w	O	2-naphthyl	2-ClC_6H_4	80	90	91-93	94-95	[43]
1x	2x	O	1-naphthyl	2-ClC_6H_4	90	95	66-68	64-65	[73]

[a]Isoxazolines and 2-pyrazolines were prepared according to the literature [44] and characterized by their elemental analysis and IR, ^{1}HNMR, ^{13}CNMR spectral and physical data.
[b]Isolated yields.

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Table 3. Comparing the present method with some other previously reported procedure for oxidation of 1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole.

Entry	Oxidant	Condition	Solvent	Time (h)	Yield (%)	Ref.
1	DHPDMDO/NH_4I/HOAc	r.t	H_2O/MeCN	0.41	97	This work
2	I_2O_5/KBr	r.t	H_2O	3.5	98	[28]
3	4-(p-Chloro)phenyl-1,3,4-triazole-3,5-dione	r.t	CH_2Cl_2	0.25	70	[29]
4	NHPI/$Co(OAc)_2/O_2$	Reflux	MeCN	4	99	[30]
5	*N*,*N*′-Dibromo-*N*,*N*′-1,2-ethanediylbis(p-toluenesulfonamide)	r.t	CCl_4	0.25	82	[31]
6	1,3-dibromo-5,5-dimethylhydantoin	r.t	CCl_4	0.5	90	[32]
7	Silica sulfuric acid-activated poly-1,3-dichloro-5-methyl-5(4'-vinylphenyl)hydantoin	r.t	EtOH	1	82	[33]
8	Silica- adsorbed benzyltriphenylphosphonium peroxymonosulfate	Reflux	MeCN	5	76	[34]
9	*N*,*N*′,*N*,*N*′-tetrabromo-benzene-1,3-disulfonylamide [TBBDA]	r.t	CCL_4	0.3	92	[35]
10	1,3-dichloro-5,5-dimethylhydantoin	r.t	AcOH	4	79	[36]
11	tris(4-bromophenyl)aminium (TBPA+)hexachloroantimonate	r.t	$CHCl_3$	0.5	91	[37]
12	Trichloroisocyanuric acid	r.t	CCl_4	0.75	85	[38]
13	$Zr(NO_3)_4$	r.t	AcOH	0.25	85	[39]
14	Pd/C	80	AcOH	6.5	86	[6]
15	I_2	r.t	AcOH	3-4	86	[40]
16	Molecular Oxygen Promoted by Activated Carbon	120	AcOH	2.5	91	[7]

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