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Regioselective and facile oxidative thiocyanation of anilines and indoles with trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane

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ABSTRACT

Oxidative potential of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPODMDO) has been explored in the facile thiocyanation of anilines and indoles through the efficient and *in situ* generation of SCN^+ ion from sodium thiocyanate. The reactions proceed with regioselectivity under mild conditions at room temperature to afford the respective thiocyanate derivatives in excellent yields and low reaction times.

Keywords

Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane; DHPODMDO; sodium thiocyanate; thiocyanation; anilines; indoles.

Academic Discipline And Sub-Disciplines

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1. INTRODUCTION

Organic thiocyanates are well-documented and important industrial compounds [**1**]. These compounds have played important roles in the synthesis of organic compounds and various pharmaceutically important products [**2**]. The compounds containing thiocyanate group are considered as versatile intermediates in which the thiocyanate group can be readily transferred into different functional groups such as sulfides [**3**], thiocarbamates [**4**] and thionitriles [**5**]. For this reason, there is significant interest in the development of new and more convenient synthetic approaches to thiocyanate containing compounds including aromatic derivatives [**6**].

Several methods have been reviewed in the literature for thiocyanation of aromatic and heteroaromatic systems including cross-coupling reaction of arylboronic acids with different reagents such as KSCN [**7**], sodium perborate [**8**], diethyl azodicarboxylate [**9**], Imidazolium-based phosphinite ionic liquid (IL-$OPPh_2$) [**10**], I_2O_5 [**11**], 2-iodobenzoic acid [**12**], Br_2/KSCN (only for indoles) [**13**], ceric ammonium nitrate (CAN) [**14**], trichloroisocyanuric acid/ammonium thiocyanate/wet SiO_2 [**15**], and silica boron sulfonic acid (SBSA/ KSCN/ H_2O_2 [**16**]. However, many of these methods are subject to certain drawbacks such as the use of costly explosive and/or toxic reagents, long reaction times, low yields, and tedious work-up [**17**]. Among the reagents employed, hydrogen peroxide is considered as environmentally benign oxidant since it produces water as the only by-product in its reactions. Nevertheless, the oxidative power of H_2O_2 is low for many purposes and requires activation by different catalytic systems [**18**]. Activation of H_2O_2 has been achieved by different acid catalysts such as AcOH [**19**], TBHP/PTSA [**20**], and also by various transition metal-based catalysts [**21,22**]. Therefore, development of more effective and benign approaches for thiocyanation of different organic compounds including anilines and related compounds such as indoles appears as important experimental challenge. Recently, *gem*-dihydroperoxides have received considerable interest as high potent oxidants for various organic transformations [**23-30**]. Following our ongoing research on the synthesis of *gem*-dihydroperoxides [**31-34**], and their applications in a variety of organic conversions including oxidation of alcohols to ketones [**35**], selective sulfoxidation of sufides [**36**], selective halogenation of aromatic compounds [**37**], epoxidation of α,β-unsaturated ketones [**38**], oxidative conversion of aldehydes, amines, alcohols and halides to nitriles [**39**], ultrasound-accelerated selective oxidation of primary aromatic amines to azoxy derivatives [**40**], and synthesis of benzimidazoles and benzothiazoles [**41**], herein, we were encouraged to study the oxidative potential of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO) for thiocyanation of anilines and their related heterocyclic compounds such as indoles.

2. EXPERIMENTAL

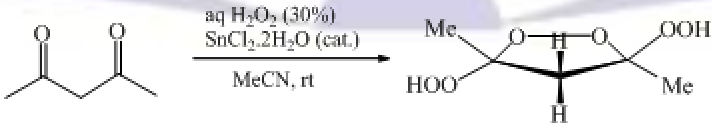
2.1 Material and instruments

Chemicals were purchased from Merck chemical company and used without further purification. FT-IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets). The NMR spectra were recorded on a JEOL FX 90 MHz spectrometer in $CDCl_3$ or DMSO-d6 solutions using TMS as internal standard. Melting points were determined in open capillary tubes with a Stuart SMP3 apparatus and were uncorrected.

Caution: Although we did not encounter any problem with *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane, it is potentially explosive and should be handled with precautions; all reactions should be carried out behind a safety shield inside a fume hood and transition metal salts or heating should be avoided.

2.2 Preparation of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO)

Following our previously reported procedure [**37**], this compound was prepared from acetyl acetone upon treatment with 30% aqueous H_2O_2 under the catalytic effect of $SnCl_2.2H_2O$ as described (Scheme 1).



Scheme 1. Synthesis of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane catalyzed by $SnCl_2.2H_2O$

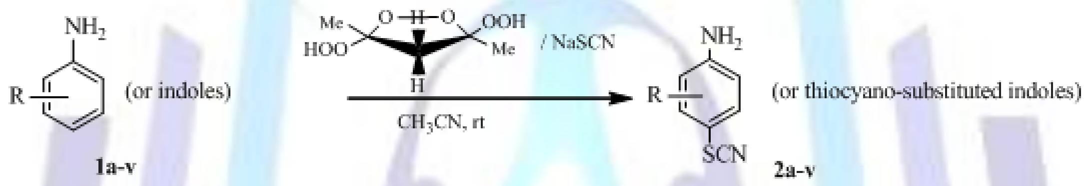
To a solution of acetylacetone (100 mg, 1 mmol) in CH_3CN (5 mL) was added $SnCl_2.2H_2O$ (45 mg, 0.2 mmol) and the resulting mixture was stirred for 5 min at room temperature. Then, aqueous 30% H_2O_2 (5 mmol) was added to the reaction mixture and let to stir for 12h at room temperature. After completion of the reaction as monitored by TLC,distilled water (15 mL) was added and the product was extracted with ethylacetate (2×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to leave almost pure white crystalline product in 85% yield (140 mg); mp 98-100 ˚C.

2.3 General procedure for synthesis of thiocyanate derivatives

To a solution of aniline (or indole) **1** (1 mmol), sodium thiocyanate (89 mg, 1.1 mmol), and catalytic amount of glacial acetic acid (2 drops) in acetonitrile (3 mL), was added *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (166 mg, 1 mmol). The resulting mixture was allowed to stir at room temperature for an appropriate time (Table 2). After completion of the reaction as monitored by TLC, the reaction mixture was diluted with distilled water (10 mL) and the product was extracted in chloroform (3 × 5 mL). The combined organic layer was washed with water (2 × 5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave almost pure products. Structures of the known products were established on the basis of their physical and spectroscopic (IR, ^1H NMR, and ^{13}C NMR) data that were consistent with those previously reported [**16, 42**].

3. RESULTS AND DISCUSSION

In continuation of our previous reports on the synthesis [**31-34**], and applications of dihydroperoxides as versatile and potent oxidants for various transformations [**35-41**], we were encouraged to investigate the hitherto unexplored oxidative potential of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO) in thiocyanation of aromatic and heteroaromatic compounds. Herein, we wish to report, for the first time, the convenient application of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane as an efficient oxidant for *in situ* generation of thiocyanate ion (SCN^+) from sodium thiocyanate which undergoes regioselective electrophilic substitution with anilines **1a-p** and indoles **1q-v** to produce the respective thiocyanate derivatives **2** in high to excellent yields (Table 2, Scheme 2).



Scheme 2. Oxidative thiocyanation of anilines and indoles with NaSCN using *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane as the oxidant

In the present method, NaSCN has been used as the source of HOSCN which is produced upon the initial degradation of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane with NaSCN. The reactions proceed rapidly under mild conditions at room temperature in acetonitrile to afford the corresponding thiocyanated aromatic products in high to excellent yields. The experimental data resulted from the reactions are summarized in Table 1. The products were characterized based on their physical and spectral (IR, ^1H NMR and ^{13}C NMR) analysis and compared with the reported data [**16,42**].

To establish the reaction conditions, we preliminarily studied the model reaction of indole **1q** with NaSCN using *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane at room temperature. The effects of solvent and the oxidant loading on the reaction were studied using different solvents such as *n*-hexane, CH_2Cl_2, H_2O, Et_2O, AcOH and CH_3CN with various molar ratios of the oxidant DHDMDO (Table 1). As seen in Table 1, the best results in terms of the yield and reaction time were obtained when AcOH and CH_3CN were used as the solvents with using equimolar amount of the oxidant (entries 5 and 6). However, due to the probable acetylation and protonation of the amino group by acetic acid in anilines that may result in the reduction of their reactivity, thiocyanation reactions were preferably conducted in acetonitrile as the solvent of choice. The partial protonation of amino group with acetic acid can also increase the solubility of the products in aqueous layer and render their separation more difficult in the course of work up. In addition, the optimum amount of the oxidant used in this reaction was found to be one equimolar when activated with a catalytic amount (two drops) of acetic acid. It is noticed that, using lower amount of the oxidant brings about unfavorable changes in the yield and reaction time (entry 7). Moreover, no improving effect on the yield was observed with using higher amounts of the oxidant (entry 8). It is noteworthy that, when the reaction was carried out using 30% H_2O_2 as the oxidant, only a very low yield of the expected product was obtained with longer reaction time (entry 9). It should be noted that, the reaction was conducted at room temperature since heating the reaction mixture to higher temperatures can cause explosion of the oxidant. The role of the oxidant used in this reaction was substantiated by conducting the reaction in the absence of the oxidant that left the starting indole untouched after a long reaction time (entry 10).

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Table 1. Screening the conditions of thiocyanition reaction of indole with DHPDMDO/NaSCN at r.t.[a]

Entry	Solvent	Oxidant (mmol)	Time (min)	Yield (%)[b]
1	*n*-Hexane	1	60	10
2	CH_2Cl_2	1	40	65
3	H_2O	1	90	trace
4	EtOH	1	90	trace
5	CH_3COOH	1	50	94
6	CH_3CN	1	2	98
7	CH_3CN	0.5	20	35
8	CH_3CN	2	2	95
9[c]	CH_3CN	1	50	25
10	CH_3CN	0	120	0

[a] Conditions: indole (1 mmol), NaSCN (1.1 mmol), solvent (3 mL), r.t.

[b] Isolated yield.

[c] H_2O_2 (30%) is used as the oxidant.

To explore the scope of the reaction, we extended the model reaction to a series of differently substituted anilines **1a-p** and indoles **1q-v** under the aforementioned optimized conditions (DHPDMDO one equimolar, CH_3CN as solvent, r.t.). The results obtained are summarized in Table 2. In general, all the reactions proceeded very smoothly at room temperature to provide the thiocyanated products **2a-v** in high to excellent yields (80-98%). As shown in Table 2, the anilines and indoles carrying electron-donating groups react more readily compared with those carrying electron-withdrawing groups. It is noticed that, under the present conditions the reactions occur *para*-selectively. In consequence, the *para*-substituted anilines remained unreacted in this reaction (entries c-e). These observations are also supported by other reports [**9,10,43-45**].

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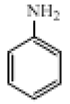
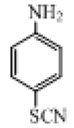
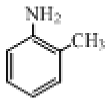
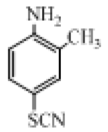
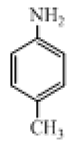
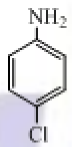
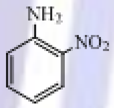
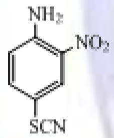
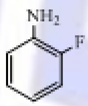
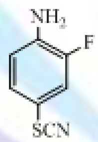
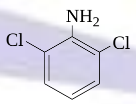
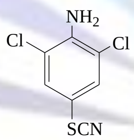
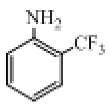
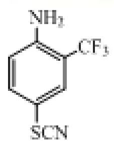
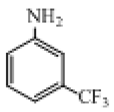
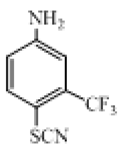
Table 2. Thiocyanation of anilines and related heterocyclic compounds with NaSCN using the oxidant *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane at room temperature.[a]

Entry	Substrate **1**	Product **2**	Time (min)	Yield (%)[b]	Mp (ºC)	
					Found	Reported [16,42]
a			10	93	97-99	97
b			5	95	60-62	62-64
c		No reaction	60	0	-	-
d		No reaction	60	0	-	-
e		No reaction	60	0	-	-
f			90	80	110-112	113
g			40	92	liquid	liquid
h			50	80	liquid	liquid
i			50	87	144-148	148-150
j			50	85	98-100	97-99

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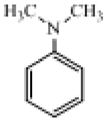
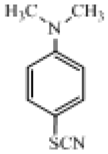
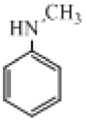
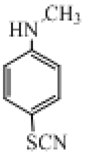
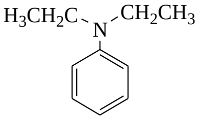
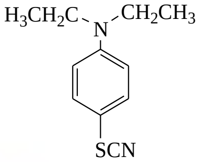
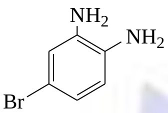
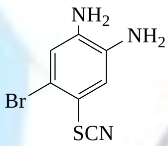
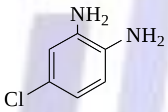
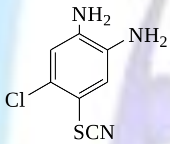
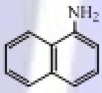
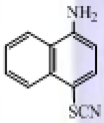
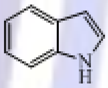
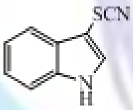
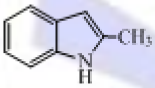
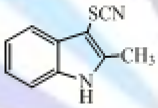
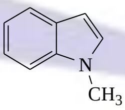
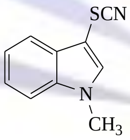
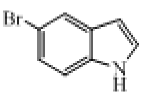
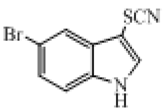
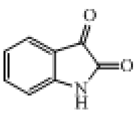
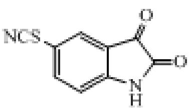
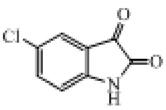
k			3	96	71-74	72-73
l			5	92	81-83	84
m			3	94	liquid	liquid
n			45	82	-	-
o			45	87	-	-
p			5	92	191-193	191-194
q			2	98	70-72	71-73
r			1	96	98-101	99-101
s			1	96	80-83	83-84
t			4	95	119-123	127-129
u			5	92	198-201	201-202
v		No reaction	60	0	-	-

[a] Condition: substrate (1 mmol), oxidant **1** (1 mmol), NaSCN (1.1 mmol), CH_3CN (3 mL), r.t.

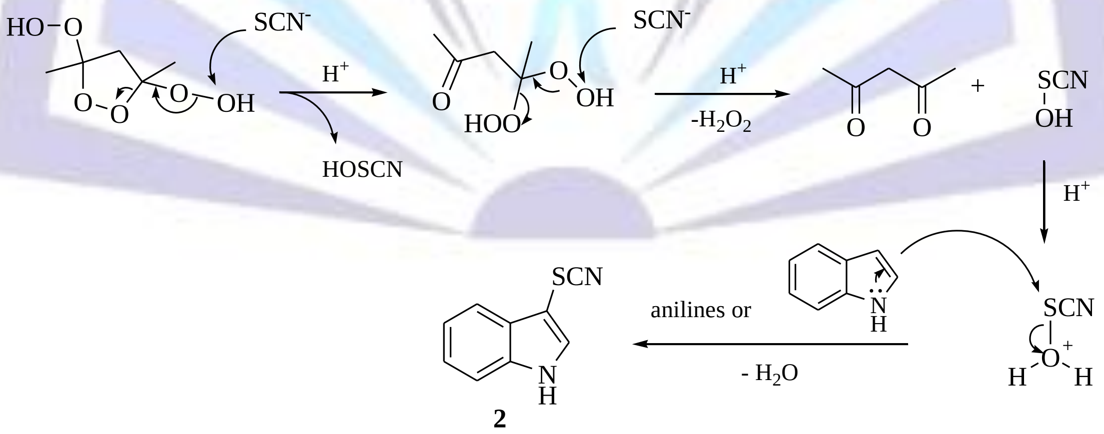
[a] Isolated yield.

As mentioned before, most of the methods reported in the literature for thiocyanation of organic compounds suffer from certain drawbacks such as long reaction times, requirement for high reaction temperatures or ultrasonic irradiation, low yield, and use of explosive and/or toxic reagents. While, the reactions involved in the present method proceed very smoothly under mild conditions at room temperature. Our procedure may be considered as environmentally friendly since no additional catalyst is necessary for activation of the reactions and the oxidant used in this method is regarded as non-polluting reagent. As summarized in Table 3, the preference of the present method in terms of the reaction time and yield is revealed in comparison with a number of other methods reported in the literature based on the model reaction with indole.

Table 3. Comparison of the present method with some previously reported procedures based on the model thiocyanation of indole.

Entry	Reaction conditions	Time (min)	Yield (%)	Ref.
1	(DHPDMDO)/NaSCN/r.t.	2	98	Present work
2	Acidic Alumina/NH_4SCN/Microwave	5	85	[46]
3	SMBI/NH_4SCN	360	80	[47]
4	SBSA/UHP/KSCN	10	90	[16]
5	$NaBO_3$/NH_4SCN	15	95	[8]
6	*p*-TSA/NH_4SCN	45	88	[42]
7	Potassium Peroxymonosulfate	43	98	[11]
8	I_2	50	85	[2]

A probable mechanism to explain the conversion of anilines and indole derivatives into corresponding thiocyano-substituted products **2a-v** with NaSCN using *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane as the oxidant is depicted in Scheme 3. As shown in this scheme, it is likely that the reactions take place preliminarily with *in situ* generation of SCN^+ ion in two successive degradation steps upon the effect of SCN^- anion on *trans*-3,5-dihydroperoxy-3,5- dimethyl-1,2-dioxolane. Subsequently, the regioselective electrophilic substitution of indoles (or anilines) with protonated HOSCN proceeds to afford the respective products **2**.



Scheme 3. Proposed mechanism for thiocyanation of anilines or indoles with NaSCN using the oxidant DHPDMDO.

CONCLUSIONS

In summary, the oxidative potential of *trans*-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane for *in situ* generation of SCN^+ ion with NaSCN has been explored. Subsequently, SCN^+ ion acts as a powerful electrophile in regioselective substitution reaction with anilines and indoles to afford the respective thiocyanated products in quantitative yields. All the reactions proceed efficiently and smoothly under mild conditions at room temperature. High regioselectivity, improved yields and reaction times, simple work up, absence of toxic catalyst in the reactions, and avoidance of polluting and hazardous reagents are the main merits of the present protocol.

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