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 (DHPOMDO) 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

Organic chemistry

SUBJECT CLASSIFICATION

Organic chemistry
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 thionitrides [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-OPPh2) [10], I2O5 [11], 2-iodobenzoic acid [12], Br2/KSCN (only for indoles) [13], ceric ammonium nitrate (CAN) [14], trichloroisocyanuric acid/ammonium thiocyanate/wet SiO2 [15], and silica boron sulfonic acid (SBSA/ KSCN/ H2O2 [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 H2O2 is low for many purposes and requires activation by different catalytic systems [18]. Activation of H2O2 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 sulfides [36], selective halogenation of aromatic compounds [37], epoxidation of α,β-unsaturated ketones [38], oxidative conversion of aldehydes, amines, alcohols and halo- 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 CDCl3 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 H2O2 under the catalytic effect of SnCl2·2H2O as described (Scheme 1).

\[
\text{Scheme 1. Synthesis of trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane catalyzed by SnCl2·2H2O}
\]

To a solution of acetylacetone (100 mg, 1 mmol) in CH3CN (5 mL) was added SnCl2·2H2O (45 mg, 0.2 mmol) and the resulting mixture was stirred for 5 min at room temperature. Then, aqueous 30% H2O2 (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 MgSO4 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 Na2SO4. 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 13C 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](image)

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 13C 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, CH3Cl, H2O, Et2O, AcOH and CH3CN 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 CH3CN 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 wi...
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$_3$CN 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].
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     | \(\text{NH}_2\) | \(\text{NH}_2\) | 10         | 93              | 97-99   | 97     |
| b     | \(\text{NH}_2\) \(\text{CH}_3\) | \(\text{NH}_2\) \(\text{SCN}\) | 5          | 95              | 60-62   | 62-64  |
| c     | \(\text{NH}_2\) \(\text{CH}_3\) | No reaction | 60         | 0               | -       | -      |
| d     | \(\text{NH}_2\) \(\text{Cl}\) | No reaction | 60         | 0               | -       | -      |
| e     | \(\text{NH}_2\) \(\text{OMe}\) | No reaction | 60         | 0               | -       | -      |
| f     | \(\text{NH}_2\) \(\text{NO}_2\) | \(\text{NH}_2\) \(\text{NO}_2\) | 90         | 80              | 110-112 | 113    |
| g     | \(\text{NH}_2\) \(\text{F}\) | \(\text{NH}_2\) \(\text{F}\) | 40         | 92              | liquid  | liquid |
| h     | \(\text{Cl}\) \(\text{NH}_2\) \(\text{Cl}\) | \(\text{Cl}\) \(\text{NH}_2\) \(\text{Cl}\) | 50         | 80              | liquid  | liquid |
| i     | \(\text{NH}_2\) \(\text{CF}_3\) | \(\text{NH}_2\) \(\text{CF}_3\) | 50         | 87              | 144-148 | 148-150|
| j     | \(\text{NH}_2\) \(\text{CF}_3\) | \(\text{NH}_2\) \(\text{CF}_3\) | 50         | 85              | 98-100  | 97-99  |
k \[ \begin{array}{c} \text{H}_3\text{C}\text{NCH}_3 \quad \text{H}_3\text{C}\text{NCH}_3 \\ \text{SCN} \quad \text{SCN} \end{array} \] 3 96 71-74 72-73

l \[ \begin{array}{c} \text{H}_3\text{C}\text{NCH}_3 \quad \text{H}_3\text{C}\text{NCH}_3 \\ \text{SCN} \quad \text{SCN} \end{array} \] 5 92 81-83 84

m \[ \begin{array}{c} \text{H}_2\text{C}_2\text{NCH}_3 \quad \text{H}_2\text{C}_2\text{NCH}_3 \\ \text{SCN} \quad \text{SCN} \end{array} \] 3 94 liquid liquid

n \[ \begin{array}{c} \text{Br} \quad \text{Br} \\ \text{NH}_2 \quad \text{NH}_2 \\ \text{NH}_2 \quad \text{NH}_2 \\ \text{SCN} \quad \text{SCN} \end{array} \] 45 82 - -

o \[ \begin{array}{c} \text{Cl} \quad \text{Cl} \\ \text{NH}_2 \quad \text{NH}_2 \\ \text{NH}_2 \quad \text{NH}_2 \\ \text{SCN} \quad \text{SCN} \end{array} \] 45 87 - -

p \[ \begin{array}{c} \text{H}_2\text{NH} \quad \text{H}_2\text{NH} \\ \text{SCN} \quad \text{SCN} \end{array} \] 5 92 191-193 191-194

q \[ \begin{array}{c} \text{H}_2\text{NH} \quad \text{H}_2\text{NH} \\ \text{SCN} \quad \text{SCN} \end{array} \] 2 98 70-72 71-73

r \[ \begin{array}{c} \text{H}_2\text{NH} \quad \text{H}_2\text{NH} \\ \text{SCN} \quad \text{SCN} \end{array} \] 1 96 98-101 99-101

s \[ \begin{array}{c} \text{H}_2\text{NH} \quad \text{H}_2\text{NH} \\ \text{SCN} \quad \text{SCN} \end{array} \] 1 96 80-83 83-84

t \[ \begin{array}{c} \text{Br} \quad \text{Br} \\ \text{SCN} \quad \text{SCN} \end{array} \] 4 95 119-123 127-129

u \[ \begin{array}{c} \text{Cl} \quad \text{Cl} \\ \text{NCO} \quad \text{NCO} \\ \text{O} \quad \text{O} \\ \text{NCO} \quad \text{NCO} \\ \text{O} \quad \text{O} \end{array} \] 5 92 198-201 201-202

v \[ \begin{array}{c} \text{Cl} \quad \text{Cl} \\ \text{O} \quad \text{O} \end{array} \] No reaction 60 0 - -

*Condition: substrate (1 mmol), oxidant 1 (1 mmol), NaSCN (1.1 mmol), CH₂CN (3 mL), r.t.
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.

![Scheme 3](image)

**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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