A Brief on Thiocyanation of N-Activated Arenes and N-Bearing Heteroaromatic Compounds

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Received 17 September 2012 / Accepted 20 October 2012

Abstract: Methods for the thiocyanation of N-activated arenes (arylamines and anilines) and N-bearing heteroaromatic compounds (indoles, indolines, pyrroles, carbazoles, quinolines, isatins and oxindoles) have been discussed in this article. The general procedure which has been reported is using an oxidant/thiocyanation agent system. Based on oxidant type the methods classified on 6 parts. At the end the mechanistic aspects of the route have been discussed.

Keywords: Thiocyanation, Indoles, Anilines, Pyrroles

Introduction

Aryl thiocyanates are the versatile and valuable class of organic compounds. Thiocyanate motif is potential in organic and bioorganic chemistry. Besides this reality, the notability of thiocyanates can be considered from other aspects. First, it is very significant because of its ability to transform to various sulfur-bearing functional groups such as sulfides, thioesters, thiophenols, cyanothiolates which lead to thionitrile synthesis, thiosulfonates (thiotosylates), thiols and S-acetates and thiocarbamates. Second, it is a key intermediate for the synthesis of heterocyclic compounds such as thiazoles and thiazinones, which are precursors of agrichemicals (for example wood preservative), dyes and drugs. Third, combination of this motif with other substrates yields the other chemicals, as the cross-coupling desulfurization of aryl thiocyanates also used as a cyanide-free source for the cyanation of arylboronic acids to nitriles.

Most of the mentioned application of the thiocyanate moiety have been observed when it is used as a functional group on N-bearing (hetero) arene compounds. Also thiocyanate group can be hold on other chemicals (ketones, alkenes and etc.) but the N-bearing chemicals with thiocyanate motif have excessive key applications. Nitrogen occurs in all living organisms, primarily in amino acids and thus proteins and in the nucleic acids (DNA and RNA). It is a defining component of alkaloids and is used in key ingredients of industrial fertilizers. So because of wide range application of N-bearing thiocyanated chemicals, we are interested in centralization of this review article on thiocyanating processes of N-arenes and N-heteroaromatics compounds. In most cases these compounds contain medicinal and pharmaceutical properties. For example, Pezzalla et al. reported that some
3-thiocyanatoindoles\textsuperscript{6} which converted to 3-indolylthiols has anti-allergy\textsuperscript{14} capacity and can be used as HIV-treating\textsuperscript{15} and anti-angina\textsuperscript{15} agents (Scheme 1).

\[
\text{R= H, CO}_2\text{Me} \quad \text{(a) SmI}_2, \text{Ac}_2\text{O, overnight} \quad \text{(b) Phosphate buffer, acidic work-up} \quad \text{74-78\%}
\]

\textbf{Scheme 1. Preparation of 3-indolylthiols with pharmaceutical properties}

\textit{Thiocyanation procedure}

The general procedure for thiocyanation of organic compounds is dissolving a thiocyanic acid salt (MSCN, M= k, Na, NH\textsubscript{4}) in appropriate solvent, mixing with substrate and adding an oxidant drop wise\textsuperscript{16}. The literatures which have reported this reaction in the presence of various oxidants can be classed as 6 parts: halogens, halides, haloacids and halogen-bearing organics; imides and amides; supported oxidant systems; inorganic and organic salts; azo compounds and miscellaneous reagents. As an evolution, the instrumental electrochemical methods also have been utilized for this purpose. In continue we will focus on each group in literatures.

\textit{Halogens, halides, haloacids and halogen-bearing organics oxidants}

The first reports of thiocyanation of N-arenes is due to anilines in the presence of combined systems of NaSCN/Br\textsubscript{2}\textsuperscript{17}, dichlorourerea/NH\textsubscript{4}SCN\textsuperscript{18}, Cu(SCN)\textsubscript{2}/Cl\textsubscript{2}\textsuperscript{19}, (SCN)\textsubscript{2}/Cl\textsubscript{2}\textsuperscript{20-21}, Zn(SCN)\textsubscript{2}/Cl\textsubscript{2}\textsuperscript{22} and Zn(SCN)\textsubscript{2}\textsuperscript{23}. In all these methods p-thiocyanated anilines were the sole main products.

The first reports of pyrrole thiocyanation is in the presence of Cu(SCN)\textsubscript{2}/Cl\textsubscript{2}\textsuperscript{19} and Zn(SCN)\textsubscript{2}/Cl\textsubscript{2}\textsuperscript{22}. In these literatures, only mono 2-thiocyanated pyrrole obtained. The resonance theory\textsuperscript{23} and molecular orbital calculations\textsuperscript{24} indicate that the electrophonic reagents attack preferentially to 2-position rather than 3-position of pyrrole ring. Mattesson et al. reported that thiocyanogen dimer in methanol at -70 °C gave the 3-thiocyanatopyrrole\textsuperscript{25}.

An interesting and the first pathway for indole thiocyanation have been reported by Grant et al. in the presence of Br\textsubscript{2}/KSCN system. They pretended that attempts for purification of obtained 3-thiocyanato indole on alumina converted the product to 3-indolyl-disulfide\textsuperscript{26} (Scheme 2).

\[
\text{(a) Br}_2, \text{KSCN, -60 C to rt, CH}_2\text{OH} \quad \text{(b) purification on alumina with CH}_2\text{Cl}_2/\text{cyclohexane} \quad \text{2}
\]

\textbf{Scheme 2. Thiocyanation of indole}

Waters explained that lower energy level of transition state in indole thiocyanation which depends on its aromaticity yields thiocyanation in 3-position\textsuperscript{27}. Later the NMR assignments plus the chemical evidence confirmed this phenomenon\textsuperscript{28}. 
Our consideration for thiocyanation of quinolines in publications, bounded just to one case. Maggiolo and co-workers\textsuperscript{29} reported that under the Br\textsubscript{2}/KSCN system, thiocyanation of quinoline, its 3-amino 2-methyl and 4-methyl derivatives failed. Addition of strong electron-donating groups (for example hydroxyl) on the pyridine ring of the quinoline yielded 3-thicyanato products\textsuperscript{29}. In the case of pyridine and pyrimidine ring as another N-heteroaromatics the only report is in the presence of Br\textsubscript{2}/NaSCN in methanol at 0 °C. The procedure is successful if electron-donating groups are presented in 2-position of pyridine and 2-, 4- and 6-position of pyrimidines\textsuperscript{29} (Scheme 3).

![Scheme 3](image)

Scheme 3. Thiocyanation of quinolines, pyridines and pyrimidines

Pilyugin et al. reported a modified Br\textsubscript{2}/NH\textsubscript{4}SCN system in acetic acid media for \textit{p}-thiocyanation of 2-nitroaniline\textsuperscript{30}. Anhydrous FeCl\textsubscript{3}/NH\textsubscript{4}SCN has been utilized for thiocyanation of arylamines, indoles, \textit{N}-alkyloxindoles and isatins\textsuperscript{31}. Thiocyanation of oxindoles and isatins takes place in 5-position. It seemed this method is the first report of isatin thiocyanation. It is memorable that accounts for preparation of 5-thiocyanato isatins are rare.

HIO\textsubscript{3}/NH\textsubscript{4}SCN also converted arylamines and indoles to their corresponding 3- and \textit{p}-thiocyanated derivatives. Among different aniline derivatives which are used in this procedure, only \textit{p}-bromoaniline undergoes cyclization\textsuperscript{32} (Scheme 4).

![Scheme 4](image)

Scheme 4. In situ cyclization of of \textit{p}-bromoaniline for formation of 2-thicyanato-4-bromoaniline

In 2004 Yadav and co-workers\textsuperscript{3} recommended I\textsubscript{2}/NH\textsubscript{4}SCN for thiocyanation of indoles, anilines, \textit{N}-alkyloxindoles and pyrrole. Under this system mono-2-thiocyanato and bis-2,5-dithiocyanatopyrrole were generated. It is significant to mention that among very few route for thiocyanation of oxindoles in publications it is the first one (Scheme 5).

![Scheme 5](image)

Scheme 5. Thiocyanation of oxindoles
Thiocyanated indoles, anilines and pyrroles have been accomplished in the presence of I$_2$/NH$_4$SCN system. The reaction media achieved mono-thiocyanated correspondence of pyrrole and diphenylamine$^{33}$. Aqueous H$_5$IO$_6$/KSCN and aqueous HCl/H$_2$O$_2$/KSCN was a prosperous reagent for thiocyanation of indoles, pyrroles, anilines and also indolines. This report is one of the two papers which thiocyanated indoline successfully$^{34}$. Reaction of (dichloroiodo)benzene/NH$_4$SCN or Zn(SCN)$_2$ was used for thiocyanation of anilines$^{35}$. Poly(4-diacetoxyiodo)styrene (PDAIS)/NH$_4$SCN$^{36}$ was also used for thiocyanation of indoles and anilines. o-Iodoxybenzoicacid (IBX)/NH$_4$SCN suggested by Yadav for thiocyanation of indoles, arylamines and pyrroles$^{37}$.

In 2008 Yadav et al.$^{38}$ claimed that Selectfluor$^{TM}$/NH$_4$SCN catalyzed efficiently the electrophilic thiocyanation of indoles, pyrrole, anilines and carbazoles to produce the corresponding 3-indolyl, 2-pyrrolyl, 4-carbazolyl and $p$-anilines thiocyanates, respectively. While many of reported procedures failed to produce thiocyanates from azaindole, it is the only performed way for preparation of 3-thiocyaantoazaindole (Scheme 6).

![Scheme 6. Thiocyanation of azaindole](image)

**Scheme 6.** Thiocyanation of azaindole

Tricholoroisocyanuric acid (TCCA)/NH$_4$SCN/wet SiO$_2$$^{39}$ fulfilled thiocyanation of indoles and pyrroles. In this method thiocyanation of 3-cyanoindole and 4-methylanilne were infeasible. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)/NH$_4$SCN have been recommended as a benefit system for thiocyanation of indoles, carbazole, pyrrole and arylamines at room temperature and under reflux condition$^{40}$ and also under ultrasonic waves$^{41}$. In both conditions in the case of pyrrole and diphenylamine mono- and bis-thiocyanated products were obtained. Diacetoxyiodobenzen (DIB)/NH$_4$SCN thiocyanated indoles and anilines$^{42}$.

**Imides and amides as oxidant**

In 1995 Toste et al.$^{43}$ introduced N-bromosuccinimide (NBS)/NaSCN system for thiocyanation of some anilines and special indoles. This mixture leads to in situ generation of N-thiocyanatosuccinimide (NTS). It is the unique report for bis-thiocyanation of indoels$^{43}$ (Scheme 7).

![Scheme 7. Bis–thiocyanation of indoles](image)

**Scheme 7.** Bis–thiocyanation of indoles
N-haloamides and imides also used for this reaction. N-bromoamides and imides (CH$_3$CONHBr, C$_6$H$_5$CONHBr and N-bromophthalimide)/NH$_4$SCN/Chloramine-T$^{44}$ and also bromosulphonamides/KSCN$^{45}$ used for thiocyanation of anilines.

**Supported oxidants**

Recently organic chemists have been interested in supported reagents because of their heterogeneity and reusability properties. In our subject manner silica vanadic acid (vanadium oxytrichloride which is supported on silica)/KSCN/aqueous H$_2$O$_2$ \(^{46}\) and aqueous silica sulfuric acid (SSA)/urea hydrogen peroxide (UHP)/KSCN and also silica boronosulfuric acid (SBSA)/H$_2$O$_2$/KSCN$^{47}$ have been used by Khazaie et al. for mono thiocyaantion of indoles, anilines and pyrroels. Supported methanesulfonic acid on alumina, Al$_2$O$_3$/MeSO$_3$H (AMA)/NH$_4$SCN has been reported by Hosseini-Sarvari et al. for indole thiocyanation in solvent-free media$^{48}$.

**Inorganic and organic salts as oxidant**

NABrO$_3$/NH$_4$SCN$^{49}$ and Mn(OAc)$_2$/NH$_4$SCN$^{50}$ achieved thiocyanated indoles and electron-rich N-arenes. Thiocyanated indoles, anilines and pyrrole have gained in the presence of ceric ammonium nitrate (CAN)/NH$_4$SCN system. Besides the mono-thiocyanato products diphenylamine and pyrrole has given insignificant amounts of bis-thiocyanato adducts$^{31}$. Potassium perxy monosulfate (Oxone)/NH$_4$SCN thiocyanated indoles, pyrrole, carbozoles and arylamines$^{52}$.

**Azo compounds**

Diethylazodicarboxylate (DEAD)/NH$_4$SCN$^{53}$ and 2,2-azobenzothiazole/NH$_4$SCN$^{54}$ used for thiocyanation of anilines, indoles and pyrroles. Under both conditions very little amount of bis-thiocyaanto pyrrole obtained.

**Miscellaneous oxidant systems**

In a patent, concentrated sulfuric acid/NH$_4$SCN performed p-thiocyanation of anilines$^{55}$. Montmorillonite K-10 clay/NH$_4$SCN heated up to 80 °C used for thiocyanation of indoles and carbozoles. Attempts for thiocyanation of 3-methylindole (skatole) in 2- position failed and dimerization of the substrate occurred$^{56}$ (Scheme 8).

![Scheme 8. Dimerization of skatole instead of 2-thiocyanation](image)

$p$-Toluene sulfonic acid ($p$-TSA)/NH$_4$SCN has been introduced by Das et al. for thiocyanation of indoles$^{57}$. Recently, Khazaei and co-workers$^{58}$ presented aqueous citric acid/KSCN/H$_2$O$_2$ system as an organocatalyst for thiocyanation of anilines, indoles and pyrroles. This system was the first lucrative effort for preparation of 5-thiocyanatoindoline (Scheme 9).

![Scheme 9. Thiocyanation of indoline](image)
Boromethylsulfonium bromide (BDMS) as an example of ionic liquid in the presence of NH₄SCN also used for thiocyanation of N-activated arenes, indoles and pyrroles.

Microwave assisted thiocyanation of indoles and anilines have been reported by acidic alumina/NH₄SCN system in solvent-free condition. Amberlyst-15 as a cation-exchange resin/NH₄SCN utilized for thiocyanation of pyrroles, indoles and anilines.

**Electrochemical thiocyanation**
The electrochemical thiocyanation of indole has been reported by Misra for the first time. Anodic thiocyanation (LiClO₄, CH₃CN, Pt, 0.9 V vs. SCE) by NaSCN of 2-substituted indoles yields 3-thiocyanato product but 3-substituted indoles caused isothiocyanation at indole -2-position rather than expected thiocyanation.

It is interesting to mention that isothiocyanato functional group is biologically active. The reaction of this motif with imidazoles or thiols can be employed successfully in design of opioid receptor affinity labels.

The yield of electrochemical thiocyanation of anilines by NH₄SCN in acidic media (formic acid) is very low because the formylation which occurs in the amino group that converts the substrate to its formamide prior to thiocyanation (Scheme 10).

![Scheme 10. Electrochemical thiocyanation](image)

**Mechanistic aspects of the procedure**
The thiocyanation procedure can be done by electrophilic (polar), radical or charge transfer (CT-Complex) mechanism. The first mechanistic aspects of thiocyanation procedure has been suggested by Kaufmann and co-workers in the presence of Cu(SCN)₂/Cl₂ system. They claimed that the thiocyanogen dimer ((SCN)₂) is existed in the reaction media and in combination with chlorine as an oxidizing agent, the S-S bond of the thiocyanogen polarized to generate a positive charge on one of the sulfur atom in the form of thiocyaanto chloride to allow an electrophilic attack of the N-bearing aromatic compound (Scheme 11). It is noteworthy to mention that thiocyanogen dimer discovered by Söderbäck in 1919 for the first time.

![Scheme 11. Generation of thiocyanate nucleophile](image)

An overview on all the mechanisms that suggested up to now, shows that thiocyanogen is an important dimer in the mechanistic study of this procedure. Generation of thiocyanogen dimer is a symbol of electrophilic (polar) mechanism. The electrochemical thiocyanation also defined by thiocyanogen formation. Karade reported that PhI(OAc)₂ (DIB) undergoes a ligand-exchange by the initial nucleophilic attack of thiocyanate ion which will form an intermediate that lead to form unstable thiocyanogen which is required for aromatic electrophilic reaction (Scheme 12).
The exact mechanistic explanation also reported for PDAIS/H$_2$O$_2$/NH$_4$SCN system by Wu et al.$^{36}$ The idea of thiocyanogen presentation as an intermediate reported by Kayzi et al. by N-haloamides and imides/NH$_4$SCN$^{44}$.

In some cases thiocyanogen has not mentioned as a key intermediate and another polar mechanism have been reported which showed presentation of SCN. One of them has been suggested by Toste and co-workers by in situ generation of N-thiocyanatosuccinimide (NTS) as thicyanating agent$^{13}$ (Scheme 13).

![Scheme 13. Generation of NTS](image)

Similar protocol reported for azo compounds$^{53}$, silica vanadic acid$^{46}$, heterogeneous SSA/UHP and SBSA/H$_2$O$_2$ systems$^{47}$, N-bromosulphonamides$^{45}$ and (IBX)/NH$_4$SCN$^{37}$. The radical mechanism has been reported by Wu et al. for the first time$^{52}$ (Scheme 14).

![Scheme 14. Radical mechanism of thiocyanation](image)

The redox potential of oxone and indole were estimated to be +0.325 v and –1.050 v, yet NH$_4$SCN exhibited no redox potential. So oxone oxidized indole rather than ammonium thiocyanate to yield indole cation-radical which stabilized by resonance effect. Nucleophilic attack of thiocyanate ion at the 3-position of cation-radical and 3-H absorption of hydroxyl radical generated from oxone during reduction$^{68}$, affected the 3-thiocyanatoindole. This radical mechanism have been reported by Pan et al. for Mn(OAc)$_2$/NH$_4$SCN system$^{50}$. The charge-transfer mechanism (CT-complex or π-complex formation) also suggested by Memarian et al. in the thiocyanation by DDQ/NH$_4$SCN system$^{40-41}$ (Scheme 15).

![Scheme 15. Charge-transfer complex mechanism in thiocyanation](image)
Conclusion

Thiocyanated N-activated arenes and N-bearing aromatics has physiological and pharmacituel properties. They are also special motifs in organic chemistry that can be transformed to other sulfur functionalities. Direct settling of this functional need a thiocyanationg agent/oxidant system. Although special electrochemical methods are free from oxidant. The manuscript is a brief review about the methods for thicyanation within a mechanistic literature survey of the procedures.

References