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Graphical Abstract

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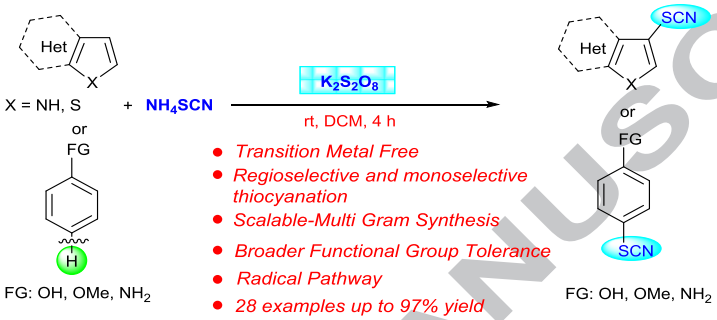

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Trimbak B. Mete, Tushar M. Khopade, Ramakrishna G. Bhat*

Department of Chemistry, Indian Institute of Science Education and Research (IISER), Pune, 411008, Maharashtra, India, E-mail: rgb@iiserpune.ac.in

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ABSTRACT

An expedient direct and regioselective thiocyanation of phenols, anilines and heterocycles is described. Transformation is realized via the direct C-H functionalization under transition metal free conditions at ambient temperature in excellent yields. Method proved to be monoselctive and variety of functional groups tolerated the reaction conditions. The practicality of the protocol is demonstrated in gram scale synthesis of a precursor of PPAR δ agonist in excellent yield.

1. Introduction

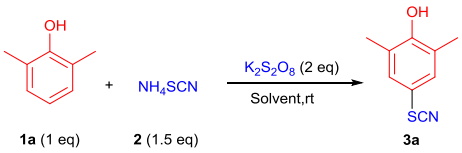
Organosulfur derivatives are very important class of compounds with biological importance. Hence, efforts have been devoted to synthesize organosulfur compounds by directly introducing the sulfur moieties into the organic scaffolds. Among these, direct thiocyanation of aromatic and heteroaromatics is one of the most important and convenient methods for carbon-sulfur bond formation. Many aryl thiocyanates exhibit potent biological and pharmacological activities and they are the building blocks of many biologically active heterocycles and agrochemicals.[1] Moreover, aryl thiocyantes are versatile precursors for making various useful organosulfur compounds such as thiols,[2] thioethers,[3] thioesters,[4] thiocarbamates,[5] disulfides,[6] sulfur containing heterocycles[7] and many pharamceuticals.[1a] Owing to the importance, efforts were made to access the thiocyanates by different methods.[8] Usually, thiocyanates are obtained by direct electrophilic thiocyanation of arenes or nucleophilic substitution reaction of the corresponding organic molecules. Even though some of these traditional methods contributed to the various synthetic transformations, however, use of toxic transition metal reagents, corrosive molecular halogen and halogen based reagents, harsher reaction conditions impede their wide utility. Certainly, these are the limiting factors for the successful and wider applications. Some of the reagents that have been explored for the thiocyanation under various conditions are antimony (V) chloride/lead (II) thiocyanate,[9] arylthallium bistrifluoroacetate/potassium thiocyanate,[10] $Zn(SCN)_2/Cl_2$,[11] ceric ammonium nitrate (CAN)/ammonium thiocyante,[8c] $Mn(OAc)_3$,[12] $Cu(SCN)_2/Cl_2$,[13] $NaSCN/Br_2$,[14]. These methods greatly rely either on the use of heavy and toxic transition metals, or on corrosive halogen and stronger oxidants. Use of these stoichiometric reagents, oxidants and in turn generation of a large amount of heavy metal waste is the real drawback of these methods. Most of these thiocyanation methods were focused on limited substrates, mostly on electron rich indoles and closely related *N*-bearing heterocycles which are of high reactivity. Some of these methods are also accompanied by low regio- and chemo-selectivity. In the recent years, efforts have been made to improvise these classic protocols using specialized reagents. Some of these methods are thiocyanation of aryl organometallic compounds,[15] copper promoted thiocyanation of aryl iodides,[16] direct cyanation of organosulfur compounds[17] thiocyanation of arylboronic acids.[18] However, these methods are not devoid of the use of transition metals or harsh reaction conditions and they generate metal waste in the process. Efforts have also been focused on the metal free and visible light promoted thiocyanation in an elegant way.[19] However, most of the protocols of thiocyanation available in the literature are executed on indoles, imidazoheterocycles and nitrogen containing activated heterocycles.[8a-g,12,19] Also, thiocyanation of aromatic amines and nitrogen heterocycles are reported to be facile. On the other hand, interestingly thiocyanation of phenols are less explored[20] and not studied extensively possibly due to its intrinsic electronic nature. Practical use of some of these available methods are seriously limited due to the use of toxic $Pb(SCN)_2$, molecular halogen, and formation of side products. Thiocyanation of phenols are not facile especially with electron withdrawing groups and have limited substrate scope. Practical, efficient and highly selective transition metal free transformations are gaining great importance for the last few years.[21] Synthetic organic chemists have been focusing on the approaches that are transition metal free in nature and they are increasingly becoming popular. Hence, efforts are being made for the transition metal free direct C-H functionalization of organic molecules. Phenol and heterocycle scaffolds are core to many bioactive molecules and

pharmaceuticals. In this regard, development of transition metal free, more efficient and practical protocol for the direct thiocyanation of diverse phenol, aniline and heterocycle derivatives is highly desirable. Herein, we report novel, practical and direct transition metal free regioselective thiocyanation of phenols, aromatic amines and heterocycles with inexpensive NH_4SCN under mild conditions. This method has several advantages such as broad substrate scope and transition metal free reaction condition.

Results and Discussions

At the outset of our investigation, we selected 2,6-dimethyl phenol **1a** and ammonium thiocyanate **2** as model substrates. In order to optimize the reaction conditions different oxidants, solvents, and conditions were explored. In presence of 2 equiv. of oxone in DCE at room temperature, reaction afforded trace amount of the expected product. Several solvents such as CH_3CN, THF, DCM were screened; however, reaction did not afford the expected product. Later, the reaction of **1a** and **2** in presence of $K_2S_2O_8$ in acetic acid at room temperature afforded the thiocyanated product **3a** in 70 % yield (entry 4).

Table 1 Optimization of the reaction conditions[a]



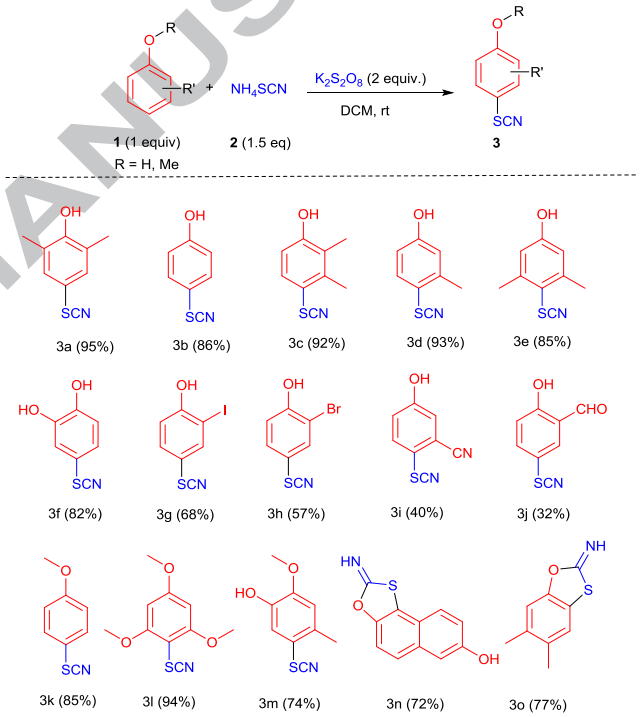
Entry	Oxidant[a]	Solvent	Time (h)	Yield[b] (%)
1	Oxone	DCM	12	trace
2	TBHP	DCM	12	NR
3	O_2	DCM	12	NR
4	$K_2S_2O_8$	Acetic	12	70
5	$K_2S_2O_8$	Acetonitril	12	85
6	**$K_2S_2O_8$**	**DCM**	**4**	**95**
7	$K_2S_2O_8$	DCE	4	93
8	$K_2S_2O_8$	THF	12	50
9	$K_2S_2O_8$	water	6	68
10	$K_2S_2O_8$	Methanol	12	73
11	$K_2S_2O_8$	1,4-	12	60
12	$K_2S_2O_8$	DMF	12	trace
13	$(NH_4)S_2O_8$	DCM	4	94
14	$Na_2S_2O_8$	DCM	4	93
15	No Reagent	DCM	12	NR

[a]Reaction conditions: **1a (**0.1 g**), 2** (1.5 equiv), Oxidant (2 equiv, 1.64 mmol), solvent (2 mL), rt (24 ^oC), 4 h, [b]Isolated yield

Reaction proceeded in acetonitrile affording **3a** in 85% yield. Gratifyingly, when solvent DCM was used, the reaction proceeded smoothly by affording **3a** in excellent yield (95%) in 4 hours at room temperature.

Notably, the reaction also proceeded in water yielding **3a** in 68%. DCM was found to be the best solvent after screening the reaction in few other solvents. Based on further investigation, we observed that both $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$ were effective for the direct thiocyanation of the **1a**. Further studies revealed that 2 equivalents of $K_2S_2O_8$ were crucial for the transformation and for the higher yield. However, we observed the incomplete conversion, when the amount of $K_2S_2O_8$ was reduced to 1-1.5 equivalents. Importantly, reaction did not work in the absence of oxidant $K_2S_2O_8$ (entry 15). The oxidants such as molecular oxygen and TBHP did not facilitate the reaction. With the optimized reaction conditions in hand, to generalize the methodology, the substrate scope of this metal free direct thiocyanation was investigated (Table 2).

Table 2 Direct Regioselective Thiocyanation of Phenol derivatives[a]



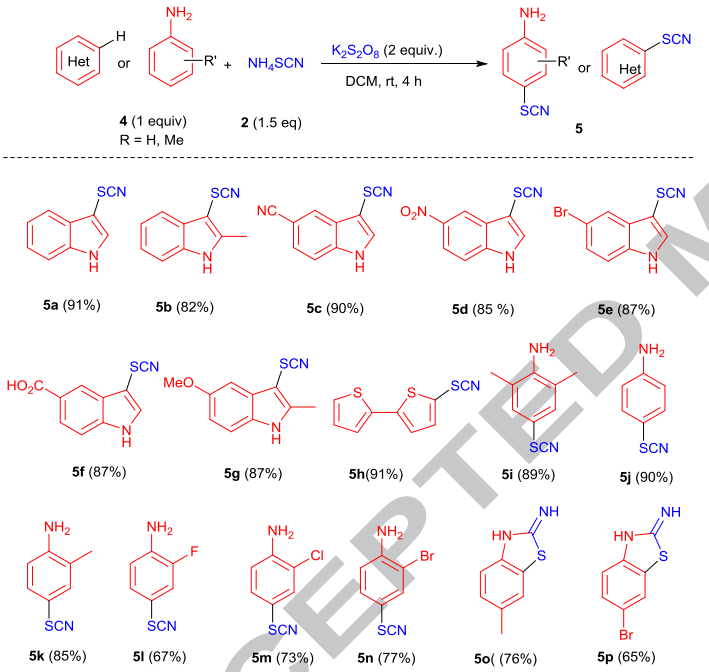
[a]Reaction conditions: Substituted phenols and Anisoles (0.1 mg). NH_4SCN (1.5 equiv), DCM, (2 mL), reaction time (4 h), Isolated yields after column chromatography given in brackets. rt (24 ^oC)

To our delight, various substrates underwent a facile direct and regioselective thiocyanation under optimized reaction conditions by affording the desired products in good to excellent yields.[22] Various phenol and anisole derivatives with electron donating and withdrawing groups reacted efficently under the optimized reaction conditions to afford the corresponding desired products (entry **3a-3m,** Table 2). It is noteworthy that direct thiocyanation exclusively occurred at the *para* position. The reaction found to be facile, monoselective and did not form any disubstituted products. Phenols bearing electron withdrawing groups such as iodo, bromo, cyano, aldehyde resulted in relatively lower yields of the corresponding products (**3g-3j**). However, cyano and aldehyde functional groups tolerated the reaction conditions. While the *o*-nitrophenol did not react under the optimized reaction condition. The thiocyanate functional group was confirmed by the characteristic IR absorption peak

(~2160 cm^{-1}) and ^{13}C NMR data. We did not observe the formation of any isothiocyanates. Reactions of naphthalene derivative (**1n**) and 3,4-dimethyl phenol (**1o**) under the reaction conditions resulted in the corresponding stable oxathioimines (**3n**, **3o**).

Encouraged by the success, we turned our attention towards the relatively more reactive anilines and heterocycles. Different indole derivatives (**4a-4g**) under the optimized conditions underwent direct C-3 thiocyanation easily in excellent yields (**5a-5g**, Table 3). Indoles bearing –CN, -NO_2, -Br groups reacted regioselectively to afford the corresponding thiocyanted products (**5c-5e**) in good to excellent yields. Notably, 2, 2'-bithiophene (**4h**) reacted with ease to afford the C-2 mono thiocyanated product **5h** in excellent yield. Later, we explored the reactivity of various aniline derivatives. All the aniline derivatives under the reaction conditions afforded thiocyanted products (**5i-5n**) in good to excellent yields.

Table 3 Direct and Regioselective Thiocyanation of Anilines and Heterocycles[a]

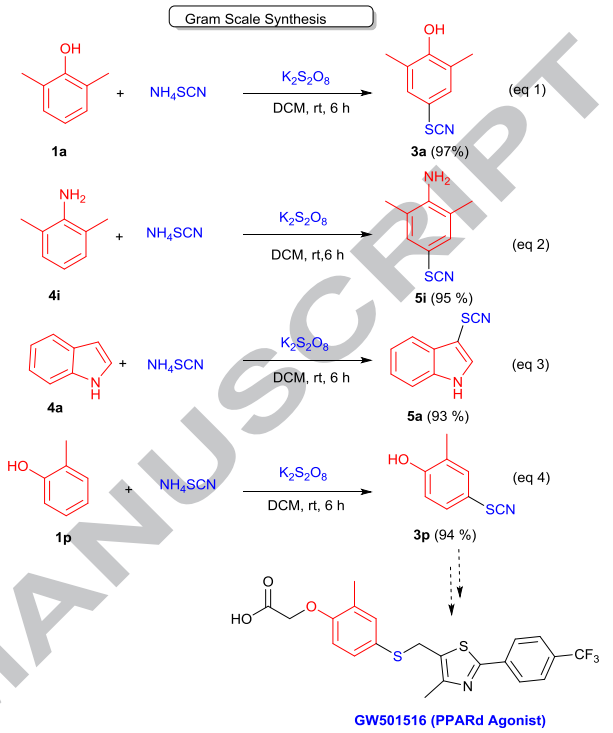


[a]Reaction conditions: Substituted Aromatic amines and Heterocycles (0.1 g). NH_4SCN (1.5 equiv), DCM, (2 mL), reaction time (4 h), rt (24 ^oC), Isolated yields after column chromatography given in brackets.

It is very important to note that direct thiocyanation was highly regioselective and occurred at *para* position. Substrates bearing electron withdrawing groups afforded the thiocyanated products in excellent yields. However, *para* substituted anilines resulted in the formation of the corresponding stable azathioimines (**5o, 5p**) via *ortho* thiocyanation.

In order to make this approach more practical and for the future development, we extended this method on gram scale (Scheme 1). 2,6-dimethyl phenol **1a**, 2,6-dimethyl aniline **4i** and indole **4a** afforded the corresponding thiocyanated products (**3a, 5i, 5a**, eq. 1-3) in excellent yields. GW501516 is a well known, most potent and selective peroxisome proliferator-activator receptor δ (PPARδ) agonist. Compound **3p** (Scheme 1), precursor of GW501516 was earlier synthesized using NaSCN and molecular bromine.[2] Using our protocol we synthesized compound **3p** under optimized reaction condition on a 3g scale in excellent yield (94%, eq 4). Easy, practical and metal free reaction conditions demonstrated the practical utility of this method for the direct thiocyanation.

Scheme 1 Thiocyanation on a Gram Scale[a]

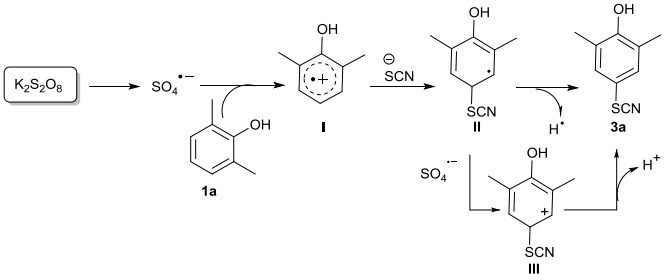


[a]Reaction conditions: Phenol, Aniline and Indole (2 g), $K_2S_2O_8$ (2 equiv), DCM (20 mL), rt (24 ^oC), time (6 h), 2-methyl phenol, **1p** (3 g, 30 mL)

In order to gain further insight into the mechanism, we treated the reaction mixture with the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl). The thiocyanation reaction did not proceed even after prolonged reaction time and this indicated that most likely free radical pathway might have been involved during the course of the reaction. $K_2S_2O_8$ is known to generate a strong, short-lived oxidant-sulphate radical anion ($SO_4^{\bullet-}$) easily. The sulphate radical anion (E^o = 2.6 V) is known to generate radical cation on interaction with the low ionization potential aromatics.[23]

In order to investigate further the formation of a radical cation intermediate, we carried out UV−Vis spectroscopy studies. We observed an intense UV absorption band in the visible region between 400 to 500 nm during the reaction of phenol **1a** with $K_2S_2O_8$ at rt (see supporting Information). This study strongly favours the formation of radical cation intermediate during the reaction and is in accordance with the previous literature findings.[24]

Scheme 2 Proposed Mechanism for the direct Thiocyanation



Based on these investigations and previous literature, the plausible mechanism is proposed (Scheme 2). Potassium persulphate would decompose to generate very strong oxidant sulphate radical anion ($SO_4^{\bullet-}$), which in turn oxidizes the aromatic compound to form radical cation intermediate **I**. Simultaneous nucleophilic addition of thiocyanate anion to the cation intermediate would lead to the formation of radical intermediate **II**. Ultimately the loss of hydrogen radical from **II** would afford the desired compound **3a**. Alternatively, further oxidation of the intermediate **II** will lead to the formation of cation intermediate **III**. Finally, the elimination of H^+ from this intermediate would afford the desired product **3a**.

Conclusions

In conclusion, we have demonstrated the transition-metal-free regioselective and monoselective direct thiocyantion of phenols, anilines and other aromatics under mild conditions. The use of commercially available and inexpensive $K_2S_2O_8$ has been explored for the thiocyantion in an efficient manner. Most importantly, this protocol proved to be scalable on a multi gram quantity. The desired products were obtained in good to excellent yields and a wide range of functional groups were tolerated. Initial understandings suggested that reaction proceeded via radical cation intermediate. This protocol presents a new and viable path to access thiocyanated aromatics and precursors of bioactive molecules.

Acknowledgments

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22. **General Procedure for the synthesis of Thiocyanatophenols, Thiocyanatoindoles and Thiocyanatoanilines:** In an oven dried round bottom flask containing a mixture of 2,6-dimethyl phenol **1a** (100 mg, 0.82 mmol), ammonium thiocyanate **2** (94 mg, 1.23 mmol) and potassium persulphate (443 mg, 1.64 mmol) in DCM (2 mL) were stirred for 4 h. Progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was filtered through sintered funnel containing silica and sodium sulphate. The Filtrate was concentrated under reduced pressure to afford the crude product **3a**. This was purified by column chromatography (EtOAc:Hexane) to furnish the pure compound **3a** as a white solid (139 mg, 95% yield). Similar procedure was used for the thiocyanation of anisoles, anilines and heterocycles.
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Highlights

- Transition metal free protocol
- Reaction is regioselective and monoselective in nature
- Scalable-Multi Gram Synthesis
- Radical pathway
- 28 examples up to 97% yield