Article

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# Metal-free Regioselective Mono Cyanation of Hydroxy-, Alkoxy- and Benzyloxyarenes by Potassium Thiocyanate and Silica Sulfuric Acid as a Cyanating Agent

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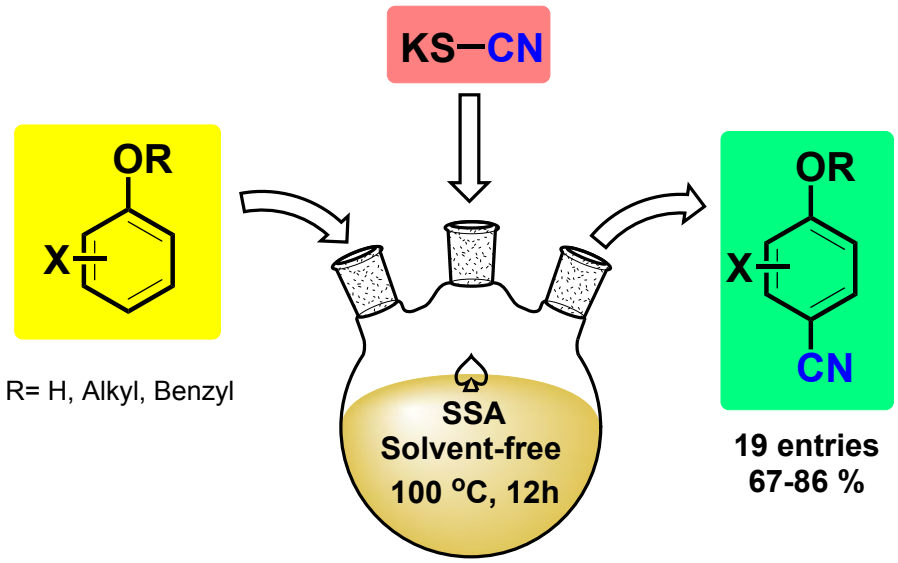



## Abstract

A novel and efficient metal- and solvent-free regioselective *para* C-H cyanation of hydroxy-, alkoxy- and benzyloxyarene derivatives have been introduced with using non-toxic potassium thiocyanate as a cyanating reagent in the presence of silica sulfuric acid (SSA). The desired products are obtained in good to high yields without any toxic byproducts.

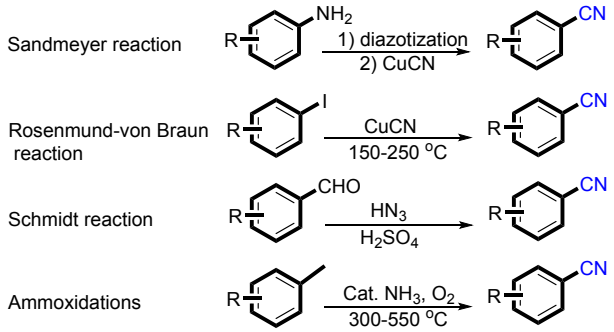
**Keywords:** Cyanation, C-H functionalization, Silica sulfuric acid(SSA), Potassium thiocyanate (KSCN), Metal-free.

## Introduction

Benzonitriles (cyanoarenes) constitute key components of various commercial compounds such as versatile building blocks in the synthesis of natural products,[1] polymers,[2] pharmaceuticals,[3] herbicides,[4] pesticides[5] and dyes.[6] These nitrile-containing bioactive molecules have been shown to treat a broad spectrum of ailments, such as depression, breast cancer, anti-HIV, and Parkinson's disease.[7] For instance, etravirine, periciazine, fadrozole, letrozole and citalopram are well-known drugs containing an aromatic nitrile scaffold.[6b, 7] They have also served as the intermediates for many synthetic targets and can be easily transformed into a various important functionalized products, such as alcohols, amines, amides, imines, aldehydes, ketones, benzoic acid derivatives, esters and heterocyclic compounds (tetrazoles, triazoles, oxazoles, thiazoles, etc).[8] As a result, much effort has been devoted to the development of various effective methods for the introduction of a cyanide functionality into aromatic compounds.[1-9]

Classical methods of introducing a cyano group into aromatic rings require pre-functionalized arenes as precursors (Scheme 1), such as diazonium salts (Sandmeyer reaction),[10] aryl halides (Rosenmund-von Braun reaction),[11] aldehydes (Schmidt reaction),[12] toluenes (by ammoxidations),[13] and many others.[14]

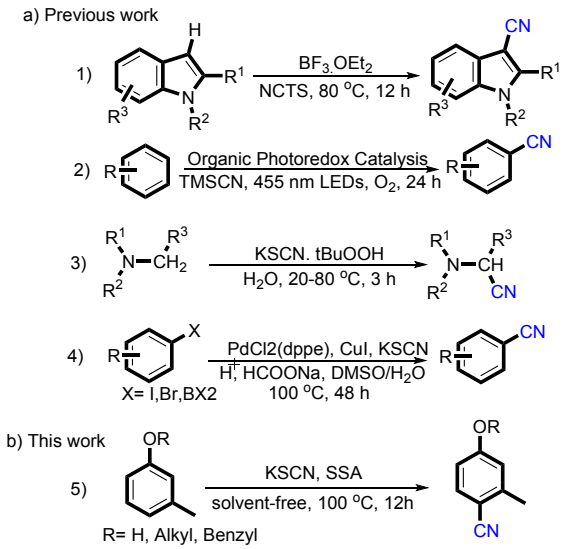
These methods suffer some important disadvantages such as consuming uses an excessive amount of hazardous cyanating reagents, limited substrate scope, elevated temperatures, high-pressure conditions, multistep organic transformations and production of large amounts of heavy metal waste.[10-14]




**Scheme 1.** Traditional methods for the synthesis of benzonitriles.

In the past decade, significant progress has been made in the development of methods to access aryl nitriles directly by the transition-metal-catalyzed cross-coupling (Pd,[15] Cu,[16] Ni,[17] Co,[18] Ru,[19] Rh,[20] Zn [21] and Ir [22]) of aryl-X compounds [X = I, Br, Cl, $CH_3SO_3$-, -CON(R)$_2$, -OCONMe$_2$, -OCO*t*-Bu, -COOH, B(OH)$_2$ and H].[15-23] Although these reactions are reliable for the synthesis of aryl nitriles by many cyanating agents, which are metal cyanides, such as CuCN,[20c] KCN,[16d] NaCN,[16c] Zn(CN)$_2$,[15b, 15e, 17a] $K_4[Fe(CN)_6]$,[15a] and trimethylsilyl cyanide (TMSCN),[15d] aryl(cyano)-iodonium Triflates.[24] but the generation of hazardous hydrogen cyanide gas and stoichiometric amounts of metal-containing waste are serious limiting factors in their applications. Although several practical methods for the synthesis of aryl nitriles with nonmetallic cyanating agents [*N*-cyano-*N*-phenyl-ptoluene sulfonamide (NCTS),[16a, 18, 19a, 20, 21] aminoacetonitriles,[17b] acetonitrile,[16b] acetone cyanohydrin,[15c] *tert*-butyl isocyanide,[20d] *N*,*N*-dimethylformamide,[15d, 16e] DMSO/$NH_4HCO_3$ [15e] and hexamethylenetetramine[15d] have been developed but cyanation reactions that are employing organic cyanating agents remain in their infancy in synthetic chemistry.[25] Nonetheless, general problems in these reactions are using expensive aryl halides, high catalyst loading due to the cyanide poisoning, need to excess amounts of additives (generally metal salts), and lack of generality and versatility.

Therefore, the development of new, safe and more environmentally friendly cyanation methods (metal-free methods) with less toxic cyanide sources on a broad substrate scope remains an extremely attractive but challenging task for organic chemists. In 2011, Jianbo Wang has demonstrated the successful direct cyanation of indoles and pyrroles with NCTS as the non-metal cyanation reagent in the presence of $BF_3$-$OEt_2$ as Lewis acid (Scheme 2, reaction 1) [26] and also, in 2017 Nicewicz introduced a new method for the direct C-H cyanation of arenes *via* organic photoredox catalysis reaction and TMSCN as a cyanide source (Scheme 2, reaction 2).[27] Moreover, as a safe cyanide source, potassium thiocyanate was applied for the oxidative α-cyanation of tertiary amines (Scheme 2, reaction 3) [28] and also cyanation of aryl halides in the presence of Pd and Cu as catalyst (Scheme 2, reaction 4).[29]




**Scheme 2.** Different approaches to the synthesis of cyano-arene Derivatives.

After the successful efforts in the employs thiocyanate salts as the green and affordable cyanide sources in recent years,[28-30] herein, we wish to report a novel and efficient regioselective *para* C-H cyanation of hydroxy-, alkoxy- and benzyloxy of arene derivatives with potassium thiocyanate, as nontoxic cyanide source, and silica sulfuric acid (SSA) as a novel cyanating agent under a metal-free condition (Scheme 2, reaction 5).

## Results and discussion

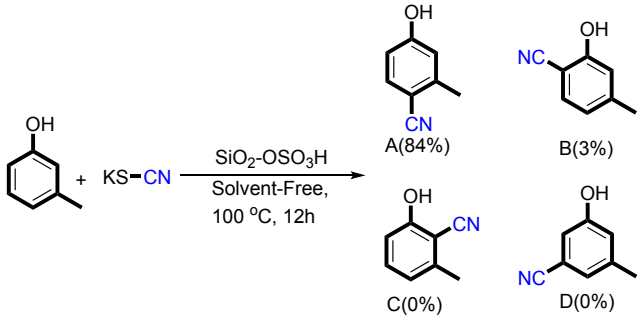
Initially, for finding of the optimized parameters of cyanation reaction, the reaction of *m*-cresol with potassium thiocyanate in the presence of silica sulfuric acid was chosen as a model reaction and then the effect of solvent, temperature, and molar ratio SSA: *m*-cresol: KSCN were studied, which their results are summarized in Table 1. According to these data, using 2:1:2 molar ratios of SSA, *m*-cresol and potassium thiocyanate under a solvent-free condition at 100 $^{o}$C gives the highest yield of 4-hydroxy-2-methylbenzonitrile after 12 h (Table 1, entry **7**). Performing the reaction in a longer reaction time (Table 1, entry 10), higher temperature (Table 1, entry **9**) and using the higher amount of potassium thiocyanate and SSA in related to KSCN (Table 1, entry **8**) does not show any improvement in the efficiency of model reaction. As it is clear from Table 1, the reaction is not preceded efficiently in any type of solvents studied (Table 1, entries **15-19**).

**Table 1.** Optimization of the reaction parameters of *m*-cresol with potassium thiocyanate in the presence of SSA.

| Entry | Molar ratio SSA:m-Cresol :KSCN | Solvent | T ($^{o}$C) | *t* (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | 1:1:1 | -- | rt | 12 | 0 |
| 2 | 1:1:1 | -- | 60 | 12 | 51 |
| 3 | 1:1:1 | -- | 100 | 12 | 63 |
| 4 | 1.5:1:1.5 | -- | 100 | 12 | 68 |
| 5 | 1:1:1.5 | -- | 100 | 12 | 62 |
| 6 | 1.5:1:1 | -- | 100 | 12 | 61 |
| 7 | 2:1:2 | -- | 100 | 12 | 84 |
| 8 | 3:1:3 | -- | 100 | 12 | 83 |
| 9 | 2:1:2 | -- | 130 | 12 | 77 |
| 10 | 2:1:2 | -- | 100 | 24 | 78 |
| 11 | 2:1:2 | $CH_3CN$ | Reflux | 12 | 40 |
| 12 | 2:1:2 | $CH_3CO_2Et$ | Reflux | 12 | 43 |
| 13 | 2:1:2 | $CHCl_3$ | Reflux | 12 | 38 |
| 14 | 2:1:2 | $CH_2Cl_2$ | Reflux | 12 | 36 |
| 15 | 2:1:2 | $CH_3Cl$ | Reflux | 12 | 37 |
| 16 | 2:1:2 | Toluene | Reflux | 12 | 0 |
| 17 | 2:1:2 | PEG200 | Reflux | 12 | 41 |
| 18 | 2:1:2 | DMSO | Reflux | 12 | 0 |
| 19 | 2:1:2 | DMF | Reflux | 12 | 0 |

[a] Isolated yield.

A closer look to the model reaction mixture under the optimized conditions by gas chromatography (GC) technique appeared also the formation of 2-hydroxy-4-methylbenzonitrile (**B**) as a by-product in only 3% yield (Scheme 3).




**Scheme 3.** Selective cyanation of *m*-cresol.

The crystal structure of 4-hydroxy-2-methylbenzonitrile (**A**) was further determined by X-ray crystallography. This compound is crystallized in the monoclinic crystal system *C*2/*c* space group. The molecular structure, shown in Figure 1, confirms that the C-N group is located in the *para* position in relation to phenyl O-H group. The intermolecular hydrogen bonding interaction (O···N 2.849(2) Å) stabilizes the molecular conformation. All the crystallographic data for the molecule, hydrogen-bond geometry, containing bond distances, angles and torsion angles are listed in the supporting information.

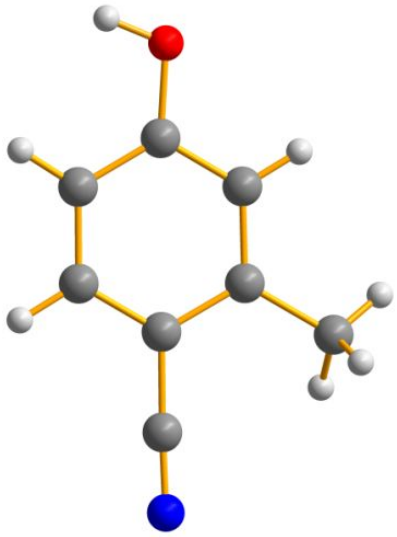


**Figure 1.** Molecular structure for 4-hydroxy-2-methylbenzonitrile.

This excellent regioselectivity is in agreement with previous reports [27, 31, 32] where the bromination of anisole and the cyanation of multi-substituted benzenes have been reported. Although the origin of this regioselectivity is not clear at the moment, it seems the steric effect may be a reason.[31b, 33] In the next step, the effect of Brønsted acids such as HCl, $H_2SO_4$, $CCl_3COOH$, $HClO_4$, $CF_3COOH$, $SiO_2$-$HClO_4$, $ClSO_3H$, *p*-TSA, polyphosphoric acid (PPA) and 4-dodecylbenzenesulfonic acid (DBSA) were also explored on the model reaction. On the basis of the results, which are presented in Table 2, the desired product is not produced in the presence of HCl, $H_2SO_4$, $CCl_3COOH$, $HClO_4$, $SiO_2$-$HClO_4$, *p*-TSA, PPA and DBSA but the model reaction provides the desired product to some extent in the presence of $CF_3COOH$ and $ClSO_3H$ after 12 hours at 100 °C although not as well as SSA. Also, employment of the other thiocyanate salts in the place of potassium thiocyanate dose not resulted in higher efficiency of the cyanation reaction (Table 2, entries **12** and **13**).

**Table 2.** Comparison among efficiency of sodium and ammonium thiocyanates with potassium thiocyanate and some Brönsted acids with SSA.[a]

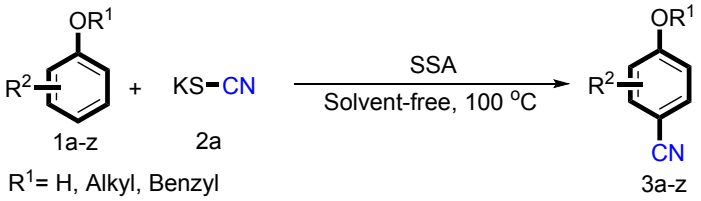
| Entry | Catalyst | Cyanate salt | Yield (%)[b] |
|---|---|---|---|
| 1 | HCl (37%) | KSCN | 0 |
| 2 | $H_2SO_4$ (98%) | KSCN | 0 |
| 3 | $CCl_3COOH$ | KSCN | 0 |
| 4 | $HClO_4$ | KSCN | 0 |
| 5 | $SiO_2$-HClO4 | KSCN | 0 |
| 6 | DBSA | KSCN | 0 |
| 7 | p-TSA | KSCN | 0 |
| 8 | PPA | KSCN | 0 |
| 9 | $SiO_2$ | KSCN | 0 |
| 10 | $SiO_2$+$CF_3COOH$ | KSCN | 39 |
| 11 | SSA | KSCN | 84 |
| 12 | SSA | NaSCN | 74 |
| 13 | SSA | NH4SCN | 70 |

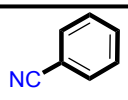
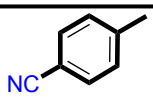
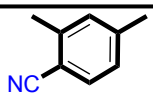
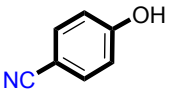
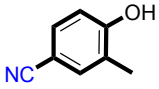
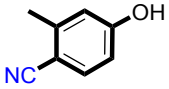
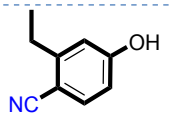
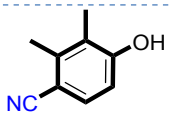
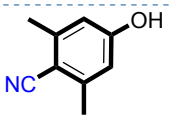
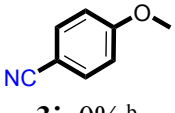
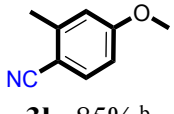
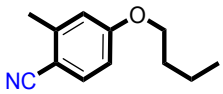
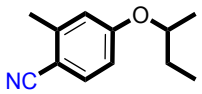
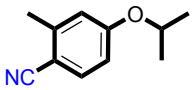
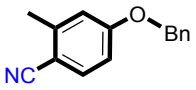
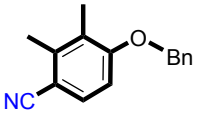
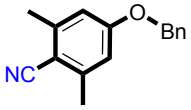
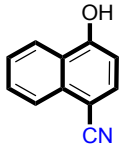
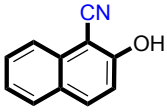
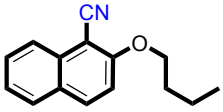
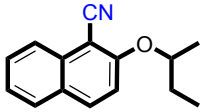
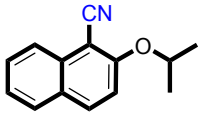
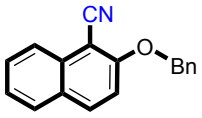
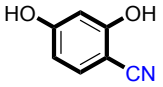
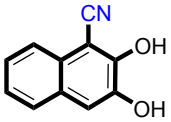
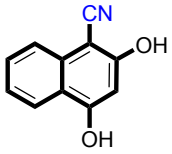
[a] Reaction condition: *m*-cresol (1 mmol), MSCN (2 mmol), acid (2 mmol), 100 °C, 12 h.
[b] Isolated yields

With the optimized results in hand, various phenols and phenyl ether are treated with potassium thiocyanate salt in the presence of SSA at 100 °C to determine efficiency, scope, versatility and

regioselectivity of the method for one pot and solvent-free synthesis of the related aryl cyanides, which their results are shown in Table 3.

**Table 3**. Cyanation of phenols and alkyl aryl ethers by potassium thiocyanate salt in the presence of SSA.[a]




| | | | | | |
|---|---|---|---|---|---|
|  **3a**, 0% [b] |  **3b**, 0% [b] |  **3c**, 0% [b] |  **3d**, 0% [b] |  **3e**, 0% [b] |  **3f**, 84% [b] |
|  **3g**, 80% [b] |  **3h**, 83% [b] |  **3i**, 77% [b] |  **3j**, 0% [b] |  **3k**, 85% [b] | |
|  **3l**, 80% [b] |  **3m**, 77% [b] |  **3n**, 78% [b] |  **3o**, 80% [b] |  **3p**, 78% [b] | |
|  **3q**, 72% [b] |  **3r**, 0% [b] |  **3s**, 86% [b] |  **3t**, 74% [b] |  **3u**, 69% [b] | |
|  **3v**, 67% [b] |  **3w**, 71% [b] |  **3x**, 76% [b] |  **3y**, 80% [b] |  **3z**, 83% [b] | |

[a] Reaction conditions: Phenol or alkyl aryl ethers (1 mmol), KSCN(2 mmol), SSA (2 mmol, 0.8 g), 100 °C and 12 h.

[b] Isolated yields.

Cyanation of benzene (Table 3, entry **3a**), toluene (Table 3, entry **3b**), *m*-xylene (Table 3, entry **3c**), phenol (Table 3, entry **3d**), *o*-cresol (Table 3, entry **3e**), and anisole (Table 3, entry **3j**) are not

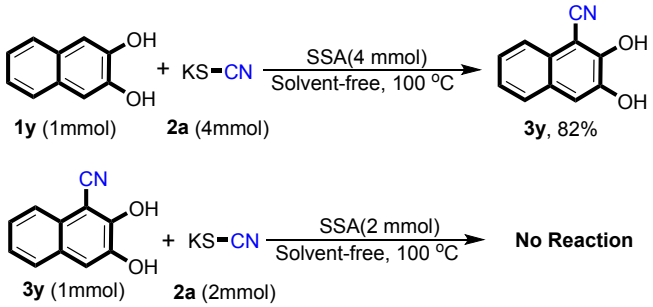
proceeded under the optimized condition after 24 hours at 100 °C. But, when *m*-cresol is checked against the cyanation reaction in the presence of potassium thiocyanate under the optimized condition, the corresponding nitrile derivative is formed in 84% yield after 12 hours (Table 3, entry **3f**).

These results encourage us to check the other *m*-cresols against the cyanation reaction, the reaction with KSCN in the presence of SSA at 100 °C under a solvent-free condition. These experiments are conducted to the corresponding nitrile derivatives in 77-84% yields (Table 3, entries **3g-3i**). Although, anisole does not undergo the cyanation reaction *m*-methyl anisole and the other *m*-tolyl alkyl ethers carry out this reaction under the optimized reaction conditions and the desired products are produced in high yields after 12 hours (Table 3, entries **3k-3o**). Conversely, cyanation of *para*-methyl substituted phenol and alkyl aryl ethers, such as 1-((3,4-dimethylphenoxy) methyl) benzene, 3,4-dimethylphenol and 4-methoxy toluene, are difficult to achieve and do not give the desired products. The above-mentioned reactions appear that the presence of alkyl group in meta-position of hydroxyl and alkoxy group is necessary for performing the cyanation reaction.

α-Naphthol, the same as phenol does not undergo the cyanation reaction but cyanation of 2-naphthol is led to the desired nitrile product in 86% yield after 12 hours (Table 3, entries **3r-3s**). When the corresponding 2-alkoxynaphthalenes are treated with potassium thiocyanate in the presence of SSA at 100 °C, it provides the related cyano product in 67-74% yields (Table 3, entries **3t-3w**), which are lower than their alkoxybenzenes that might be because of the considerable steric effect in *ipso* position of 2-alkoxynaphthalene. In addition, benzene-1,3-diol, naphthalene-2,3-diol and naphthalene-1,3-diol were also employed and fortunately, the related cyanation reaction proceeds as well as 2-naphthol and *m*-cresol (Table 3, entries **3x-3z**).

The cyanation of thiophenols and their thioether derivatives, such as 3-methylbenzenethiol and methyl-*m*-tolyl sulfide, and also *N*, *N*-dimethylaniline, as an aniline derivative, do not occur at all. Reactive heterocyclic aromatic compounds like furan, thiophene, *N*- methylpyrrole and *N*-methylindole are also unreactive towards this reaction.

In the next step, for showing monoselective ability of KSCN/SSA, two experiments are designed. In the first experiment, 1 mmol of naphthalene-2,3-diol, which there are two same positions for cyanation, are reacted with 4 mmol potassium thiocyanate under the optimized reaction condition and only 2,3-dihydroxy-1-naphthonitrile are produced and the related 1,4-dicyano derivative of 2,3-dihtdroxynaphthalene is not detected in the reaction mixture by TLC monitoring. In the second experiment, 1 mmol 2,3-dihydroxy-1-naphthonitrile was treated with 2 mmol potassium thiocyanate and SSA under the optimized reaction condition for 12 h but 2,3-dihydroxynaphthalene-1,4-dicarbonitrile is not detected in the reaction mixture (Scheme 4).




**Scheme 4.** Study of mono selective cyanation of naphthalene-2,3-diol.

To determine recyclability of SSA after completion of the cyanation of 3-methylphenol, SSA is removed from the mixture by filtration. Then it is washed with hot toluene for 2 h in a Soxhlet apparatus to remove the adsorbed unconsumed starting materials on the surface of SSA and then dried in a vacuum oven at 100 °C. The recovered SSA is reused in the next run. According to the results summarized in Figure 2, the efficiency of SSA remains over four runs without significant loss of activity.

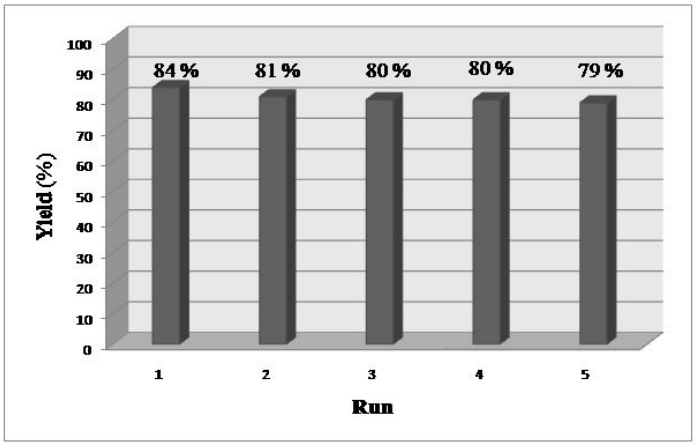



**Figure 2.** Study of reusability SSA in cyanation of 3-methylphenol.

According to the color change of SSA from white to yellow after the first run (Figure 3) it was decided to do CHNS analysis on the fresh SSA and the used SSA. These results, as shown in Table 4, reveal the existence of more sulfur content in the recovered catalyst.

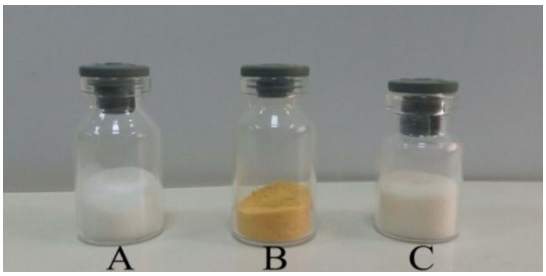


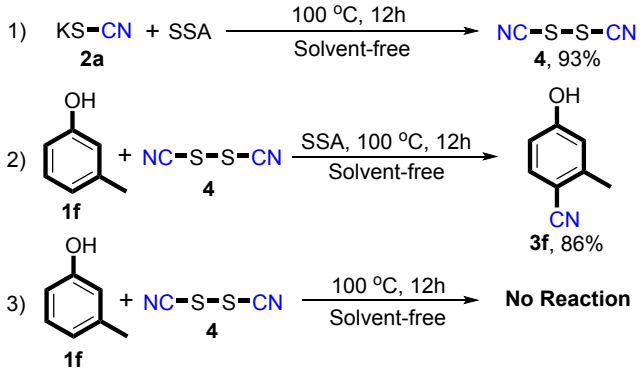

**Figure 3.** The color of SSA before (A) and after the reaction (B) and after recovery process (C).

**Table 4.** CHNS analysis of SSA samples.

| **Type of SSA** | C(%) | H(%) | N(%) | S(%) |
|---|---|---|---|---|
| SSA(Fresh) | 0.0 | 2.14 | 0.0 | 5.11 |
| SSA(First Used) | 0.0 | 2.25 | 0.0 | 7.16 |

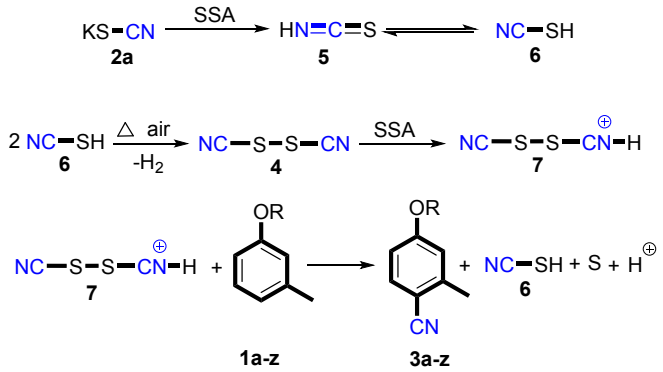
For looking deeply at the cyanation reaction, at the first, KSCN was treated with SSA. After completion of the reaction, the product (thiocyanogen) was isolated and purified (Scheme 5, reaction 1). Then, *m*-cresol was mixed with thiocyanogen in the presence of SSA at 100 $^{o}$C under

a solvent-free condition. After 12 h stirring and purification of the mixture, 4-hydroxy-2-methylbenzonitrile was obtained (Scheme 5, reaction 2). The repetition of this reaction in the absence of SSA has not resulted in 4-hydroxy-2-methylbenzonitrile after 12h (Scheme 5, reaction 3). These findings appear that the presence of simultaneous SSA and thiocyanogen is necessary for carrying out the reaction.




**Scheme 5.** Investigation of the reaction pathway.

Although for proposing a precise mechanism there is still more data to get, based on all of the reported information in the literature [34] and the above-mentioned results, the following plausible mechanism pathway can be suggested for the formation of benzonitriles derivatives (Scheme 6). In the first step, isothiocyanic acid (**5**) will produce by the protonation of potassium thiocyanate (**2a**) with SSA, which is in equilibrium with thiocyanic acid (**6**). A self-oxidative coupling of thiocyanic acid (**6**) is led to thiocyanogen (**4**) under atmosphere condition. In the next step, thiocyanogen undergoes the protonation reaction in the presence of SSA and forms **7** that is converted to the desired products (**3a-z**) through an electrophilic aromatic substitution.




**Scheme 6.** The suggested mechanism for the regioselective *para*-cyanation of hydroxy and alkoxy arenes with potassium thiocyanate in the presence of silica sulfuric acid.

In summary, we have developed a novel and efficient metal-free regioselective *para* C-H cyanation of electron-rich phenyl rings with employment of potassium thiocyanate and SSA as the cyanating reagent. The use of inexpensive chemicals, less toxic cyanide source, mild reaction conditions, high regioselectivity and good to high yield of products make this approach one of the most attractive and practical methods for cyanation of hydroxy and alkoxyarenes.

**Experimental:**

**General:**

Chemicals were obtained from Sigma-Aldrich and Merck. Column chromatography was performed using silica gel from Macherey-Nagel (60 M, 0.04–0.063 mm). The products were characterized by comparison of their spectral and physical data such as NMR, FT-IR, MS, CHNS and melting point with available literature data. $^{1}H$ and $^{13}C$ NMR data were recorded in DMSO on a 250 MHz Bruker avance DPX 250MHz instrument with $Me_4Si$ or solvent resonance as the internal standard, spectrometer at r.t. Chemical shifts are reported relative to residual DMSO ($\delta$ = 3.35 ppm $^{1}H$, $\delta$ =39.42 ppm for $^{13}C$). Fourier transforms infrared (FTIR) spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. The C, H, N and S elemental analyses were

carried out by the using a Thermofinigan Flash EA-1112 CHNSO rapid elemental analyzer. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Melting points were recorded by Electrothermal 9100. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos.

**General procedure for preparation of silica sulfuric acid (SSA):**[35]

At the first step for drying the silica gel (60-120 mesh), it was placed in the oven at 400 $^{o}$C for 6 hours. Then, dry Silica gel (60.0 g) was taken in two necked round bottom flask. Chloro sulfonic acid (23.3 g, 0.2 mol) was added dropwise and gradually during 60 minutes. Rapidly generated HCl gas was neutralized by NaOH solution. Once the addition was over, the reaction mixture was shaken for another 30 minutes to provide silica sulfuric acid (76.0 g) as a white solid. The amount of chlorosulfonic loaded on silica gel was determined by acid-base titration method. For this purpose, 0.1 g of silica sulfuric acid was added to 10mL of deionized water and stirred for 30 min at room temperature. Then, this mixture was titrated by 25.0 mL of NaOH (0.01 M). Therefore, the amount of chlorosulfonic acid loaded in 0.1g of silica sulfuric acid is equal to 2.5mmol (or 25mmol in 1g of SSA).

**General procedure for regioselective para-cyanation of hydroxy-, alkoxy- and benzyloxy arenes (3f-3z):**

To a mixture of potassium thiocyanate (1.0 mmol) and a hydroxy-or alkoxy arene (1.0 mmol) was added $SiO_2$-$OSO_3H$ (0.8 g, 20 mmol). Then, the mixture was heated and stirred at 100 $^{o}$C in oil bath under solvent-free solid-state conditions for 12 h. The reaction was monitored by TLC. After completion of reaction, ethyl acetate (3 × 10 mL) was added and the mixture was filtered. The solvent (EtOAc) was removed under reduced pressure and the product was purified by column

chromatography on silica gel (petroleum ether and ethyl acetate, 8:2) and characterized. The isolated pure products were obtained in excellent to moderate yields.

**4-Hydroxy-2-methylbenzonitrile (3f):** Brown crystals (0.1119 gr, 84% yield), mp = 139-140 $^{o}$C. IR (KBr), ῡ(cm$^{-1}$): 3305, 3194, 2914, 2226, 1624, 1304, 1233, 881. $^{1}$H NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 2.34, (s, 3H), 6.67-6.75 (m, 2H), 7.51 (d, J = 7.5 Hz, 1H), 10.45 (s, 1H. OH). $^{13}$C{$^{1}$H} NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 19.9 ($CH_3$), 101.6 (C), 113.8 (CH), 117.0 (CH), 118.6 (C), 134.3 (CH), 143.6 (C), 161.3 (C). Anal. Calcd for $C_8H_7NO$: C, 72.16; H, 5.30; N, 10.52%. Found: C, 72.12; H, 5.31; N, 10.57%.

**2-Ethyl-4-hydroxybenzonitrile (3g):** Brown crystals (0.1176 gr, 80% yield), mp = 74-75 $^{o}$C. IR (KBr), ῡ(cm$^{-1}$): 3260, 3191, 2926, 2230, 1599, 1591, 1293, 888, 823, 654. $^{1}$H NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 1.15 (t, J = 7.5 Hz, 3H), 2.65 (q, J = 7.5 Hz, 2H), 6.69-6.78 (m, 2H), 7.53 (d, J = 7.5 Hz, 1H), 10.53 (s, 1H. OH). $^{13}$C{$^{1}$H} NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 14.8 ($CH_3$), 27.0 ($CH_2$), 100.7 (C), 114.0 (CH), 115.6 (CH), 118.5 (C), 134.6 (CH), 149.6 (C), 161.6 (C). Anal. Calcd for $C_9H_9NO$: C, 73.45; H, 6.16; N, 9.52%. Found: C, 73.41; H, 6.11; N, 9.57%.

**4-Hydroxy-2,3-dimethylbenzonitrile (3h):** Yellow crystals (0.1220 gr, 83% yield), mp = 132-134 $^{o}$C. IR (KBr), ῡ(cm$^{-1}$): 3274, 3164, 2928, 2230, 1598, 1585, 1291, 824, 789, 653. $^{1}$H NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 2.05, (s, 3H), 2.33, (s, 3H), 6.76 (d, J = 8.25 Hz, 1H), 7.38 (d, J = 8.25 Hz, 1H), 10.40 (s, 1H. OH). $^{13}$C{$^{1}$H} NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 11.5 ($CH_3$), 17.9 ($CH_3$), 102.0 (C), 113.1 (CH), 119.4 (C), 124.1 (C), 131.1(CH), 141.4 (C), 159.2 (C). Anal. Calcd for $C_9H_9NO$: C, 73.45; H, 6.16; N, 9.52%. Found: C, 73.42; H, 6.11; N, 9.57%.

**4-Hydroxy-2,6-dimethylbenzonitrile (3i):** Yellow crystals (0.1114 gr, 77% yield), mp = 175-177 $^{o}$C. IR (KBr), ῡ(cm$^{-1}$): 3267, 3158, 2929, 2230, 1598, 1584, 1292, 824, 790, 654. $^{1}$H NMR (250

MHz, 298K, DMSO-$d_6$), δ (ppm): 2.05 (s, 6H), 7.39 (s, 2H), 10.47 (s, 1H, OH). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 19.6 ($CH_3$), 102.0 (C), 113.1 (CH), 119.4 (C), 141.4 (C), 159.16 (C). Anal. Calcd for $C_9H_9NO$: C, 73.45; H, 6.16; N, 9.52%. Found: C, 73.40; H, 6.12; N, 9.59%.

**4-Methoxy-2-methylbenzonitrile (3k):** Yellow crystals (0.1250 gr, 85% yield), mp = 51-52 °C. IR (KBr), ῡ($cm^{-1}$): 3058, 3027, 2918, 2219, 1605, 1250, 852, 821. $^1H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 2.37, (s, 3H), 3.76, (s, 3H), 6.84 (d, J = 7.50 Hz, 1H), 6.92 (s, 1H), 7.59 (d, J = 7.50 Hz, 1H). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 19.9 ($CH_3$), 55.4 ($CH_3$), 103.3 (C), 112.4 (CH), 115.6 (CH), 118.3 (C), 134.19 (CH), 143.6 (C), 162.4 (C). Anal. Calcd for $C_9H_9NO$: C, 73.45; H, 6.16; N, 9.52%. Found: C, 73.41; H, 6.11; N, 9.57%.

**4-Butoxy-2-methylbenzonitrile (3l):** Yellow liquid (0.1512 gr, 80% yield), mp = 137-138 °C. IR (KBr), ῡ($cm^{-1}$): 3090, 3077, 2961, 2221, 1605, 1251, 1113, 869, 821. $^1H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 0.86 (t, J = 7.5 Hz, 3H), 1.28 (m, 2H), 1.47 (m, 2H), 2.20 (s, 3H), 3.87 (t, J = 5.0 Hz, 2H), 6.84 (d, J = 7.50 Hz, 1H), 7.00 (s, 1H), 7.59 (d, J = 7.50 Hz, 1H). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 13.5 ($CH_3$), 18.5 ($CH_3$), 26.4 ($CH_2$), 30.7 ($CH_2$), 62.9 ($CH_2$), 103.2 (C), 112.2 (CH), 115.8 (CH), 118.3 (C), 134.0 (CH), 143.6 (C), 162.6 (C). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40%. Found: C, 76.11; H, 7.96; N, 7.44%.

**4-*sec*-Butoxy-2-methylbenzonitrile (3m):** White crystals (0.1455 gr, 77% yield), mp = 137-138 °C. IR (KBr), ῡ($cm^{-1}$):3253, 3185, 2968, 2219, 1604, 1498, 1251, 869. $^1H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 0.56 (t, J = 7.5 Hz, 3H), 0.82 (d, J = 6.3 Hz, 3H), 1.10-1.28 (m, 2H), 2.09, (s, 3H), 4.24, (sex, J = 6.3 Hz, 1H), 6.59 (d, J = 7.50 Hz, 1H), 6.65 (s, 1H), 7.41 (d, J = 7.50 Hz, 1H). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 9.5 ($CH_3$), 19.6 ($CH_3$), 25.9 ($CH_2$), 28.5 ($CH_3$), 70.5 (CH), 100.9 (C), 114.2 (CH), 115.8 (CH), 118.8 (C), 134.8 (CH), 149.9 (C), 161.8 (C). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40%. Found: C, 76.10; H, 7.94; N, 7.47%.

**4-*iso*-Propoxy-2-methylbenzonitrile (3n):** White crystals (0.1365 gr, 78% yield), mp = 137-138 $^{o}$C. IR (KBr), ῡ(cm$^{-1}$): 3059, 3029, 2926, 2222, 1605, 1497, 1475, 1250, 869. $^{1}$H NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 1.24 (d, J = 6.3 Hz, 6H), 2.06 (s, 3H), 3.79 (hep, J = 7.50 Hz, 1H), 6.90 (d, J = 7.50 Hz, 1H), 7.00 (s, 1H), 7.65 (d, J = 7.50 Hz, 1H). $^{13}$C{$^{1}$H} NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 10.9 ($CH_3$), 20.5 ($CH_3$), 61.0 (CH), 103.8 (C), 113.0 (CH), 116.1 (CH), 118.8 (C), 134.6 (CH), 144.2 (C), 163.0 (C). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%. Found: C, 75.35; H, 7.72; N, 8.07%.

**4-(Benzyloxy)-2-methylbenzonitrile (3o):** White crystals (0.1784 gr, 80% yield), mp = 137-138 $^{o}$C. IR (KBr), ῡ(cm$^{-1}$): 3026, 2917, 2228, 1602, 1589, 1494, , 1277, 728, 698. $^{1}$H NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 2.34 (s, 3H), 5.15 (s, 2H), 6.68 (d, J = 7.50 Hz, 1H), 6.75 (s, 1H), 7.22 (m, 5H), 7.51 (d, J = 7.50 Hz, 1H). $^{13}$C{$^{1}$H} NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 20.4 ($CH_3$), 68.4 ($CH_2$), 102.1 (C), 114.3 (CH), 117.5 (CH), 119.2 (C), 127.4 (CH), 128.1 (CH), 128.6 (CH), 134.8 (CH), 135.3 (C), 144.1 (C), 161.6 (C). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27%. Found: C, 80.64; H, 5.85; N, 6.32%.

**4-(Benzyloxy)-2,3-dimethylbenzonitrile (3p):** White crystals (0.1849 gr, 78% yield), mp = 137-138 $^{o}$C. IR (KBr), ῡ(cm$^{-1}$): 3167, 2957, 2231, 1598, 1584, 1291, 824, 790. $^{1}$H NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 2.05, (s, 3H), 2.33, (s, 3H), 5.29, (s, 2H), 6.76, (d, J = 7. 5 Hz, 1H), 7.09, (m, 5H), 7.37 (d, J = 7.5 Hz, 1H). $^{13}$C{$^{1}$H} NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 11.5 ($CH_3$), 17.9 ($CH_3$), 71.0 ($CH_2$), 102.0 (C), 113.10 (CH), 120.6 (C), 124.1 (CH), 125.6 (CH), 126.9 (CH), 129.2 (C), 131.1 (CH), 137.7 (C), 142.4 (C), 159.2 (C). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90%. Found: C, 80.95; H, 6.34; N, 5.94%.

**4-(Benzyloxy)-2,6-dimethylbenzonitrile (3q):** White crystals (0.1706 gr, 72% yield), mp = 137-138 $^{o}$C. IR (KBr), ῡ(cm$^{-1}$): 3060, 3026, 2917, 2228, 1599, 1581, 1291, 821, 792. $^{1}$H NMR (250

MHz, 298K, DMSO-$d_6$), δ (ppm): 2.05, (s, 6H), 5.30, (s, 2H), 6.79, (s, 2H), 7.36, (m, 5H). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 20.1 ($CH_3$), 67.3 ($CH_2$), 102.5 (C), 113.7 (CH), 119.9 (C), 127.5 (CH), 128.4 (CH), 129.8 (CH), 138.2 (C), 142.0 (C), 159.7 (C). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90%. Found: C, 80.94; H, 6.35; N, 5.93%.

**2-Hydroxynaphthalene-1-carbonitrile (3s):** Brown crystals (0.1453 gr, 86% yield), mp = 156-158 °C. IR (KBr), ῡ($cm^{-1}$): 3188, 2227, 1627, 1578, 1516, 1505, 1440, 1287, 968, 822, 776. $^1H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 6.96, (d, J = 7. 5 Hz, 1H), 7.61, (m, 1H), 7.74, (m, 1H), 7.97, (m, 2H), 8.25 (d, J = 8.00 Hz, 1H), 11.48 (s, 1H. OH). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 91.0 (C), 116.0 (C), 117.6 (CH), 122.6 (CH), 124.6 (CH), 126.9 (C), 128.8 (CH), 129.0 (CH), 132.9 (C), 135.1 (CH), 161.2 (C). Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.28%. Found: C, 78.03; H, 4.12; N, 8.32%.

**2-Butoxynaphthalene-1-carbonitrile (3t):** White crystals (0.1665 gr, 74% yield), mp = 137-138 °C. IR (KBr), ῡ($cm^{-1}$):3163, 2943, 2147, 1617, 1595, 1504, 1460, 1440, 1334, 1271, 1234, 1060 1020, 826, 808, 773. $^1H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 0.63 (t, J = 7. 5 Hz, 3H), 1.06 (m, 2H), 1.35 (m, 2H), 4.01 (t, J = 7. 5 Hz, 2H), 6.97 (d, J = 8.00 Hz, 1H), 7.62 (m, 1H), 7.74 (m, 1H), 7.97 (t, J = 8.00 Hz, 2H), 8.25 (d, J = 8.00 Hz, 1H). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 13.5 ($CH_3$), 18.5 ($CH_2$), 30.2 ($CH_2$), 65.2 ($CH_2$), 102.4 (C), 116.0 (CH), 117.6 (C), 122.6 (CH), 124.3 (CH), 126.9 (C), 128.8 (CH), 129.2 (CH), 132.9 (C), 135.1 (CH), 161.2 (C). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 79.92; H, 6.67; N, 6.26%.

**2-*sec*-Butoxynaphthalene-1-carbonitrile (3u):** White crystals (0.1552 gr, 69% yield), mp = 137-138 °C. IR (KBr), ῡ($cm^{-1}$): 3066, 2958, 2920, 2146, 1621, 1594, 1505, 1460, 1273, 1238, 1059, 825, 808, 462. $^1H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 0.56 (t, J = 7. 5 Hz, 3H), 0.76 (d, J = 7. 5 Hz, 3H), 1.06 (qun, J = 7. 5 Hz, 2H), 3.23 (sex, J = 7. 5 Hz, 1H), 6.95 (d, J = 7. 5 Hz, 1H),

7.62 (m, 1H), 7.76 (m, 1H), 7.99 (m, 2H), 8.25 (d, J = 8.00 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 9.7 ($CH_3$), 19.0 ($CH_2$), 28.2 ($CH_3$), 70.6 (CH), 100.4(C), 115.2 (CH), 116.8 (CH), 121.8 (CH), 123.5 (C), 126.1 (C), 127.9 (CH), 128.2 (CH), 132.0 (C), 134.2 (CH), 160.4 (C). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22%. Found: C, 79.91; H, 6.66; N, 6.27%.

**2-*iso*-Propoxynaphthalene-1-carbonitrile (3v):** White crystals (0.1414 gr, 67% yield), mp = 137-138 °C. IR (KBr), ῡ($cm^{-1}$): 3064, 2968, 2957, 2146, 1621, 1594, 1505, 1459, 1269, 1249, 1059, 826, 808, 465. $^{1}H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 1.20 (d, J = 7. 5 Hz, 6H), 3.30 (hep, J = 7. 5 Hz, 1H), 6.96 (d, J = 7. 5 Hz, 1H), 7.54 (m, 1H), 7.84 (m, 1H), 7.97 (m, 2H), 8.30 (d, J = 8.00 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 21.7 ($CH_3$), 72.8 (CH), 101.4 (C), 116.0 (C), 117.6 (CH), 122.6 (CH), 124.3 (CH), 126.9 (C), 128.8 (CH), 129.0 (CH), 132.9 (C), 135.1 (CH), 161.2 (C). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63%. Found: C, 79.53; H, 6.15; N, 6.69%.

**2-(Benzyloxy) naphthalene-1-carbonitrile (3w):** White crystals (0.1839 gr, 71% yield), mp = 154-156 °C. IR (KBr), ῡ($cm^{-1}$): 3029, 2930, 2350, 1627, 1599, 1452, 1258, 1218, 1018, 839, 696. $^{1}H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 4.27, (s, 2H), 6.95, (d, J = 7. 5 Hz, 1H), 7.37, (m, 5H), 7.63, (m, 1H), 7.77, (m, 1H), 7.96, (m, 2H), 8.24 (d, J = 8.00 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 57.0 ($CH_2$), 93.1 (C), 116.0 (C), 117.6 (CH), 118.8 (CH), 118.9 (CH), 121.6 (CH), 122.6 (CH), 124.3 (CH), 126.9 (C), 128.8 (CH), 129.0 (CH), 132.9 (C), 135.1 (CH), 144.0 (C), 161.2 (C). Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40%. Found: C, 83.32; H, 5.01; N, 5.44%.

**2,4-Dihydroxybenzonitrile (3x):** White crystals (0.1026 gr, 76% yield), mp = 178-180 °C.

IR (KBr), ῡ($cm^{-1}$): 3029, 2930, 2350, 1627, 1599, 1452, 1258, 1218, 1018, 839, 819, 696. $^{1}H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 6.78 (s, 1H), 6.84 (d, J = 7. 5 Hz, 1H), 7.54 (d, J = 7. 5 Hz,

1H), 10.06 (s, 1H, OH), 10.40 (s, 1H, OH). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 92.4 (C), 101.6 (C), 109.7 (CH), 116.5 (CH), 129.5 (C), 135.4 (CH), 160.3 (C), 162.4 (C). Anal. Calcd for $C_7H_5NO_2$: C, 62.22; H, 3.73; N, 10.37%. Found: C, 62.20; H, 3.74; N, 10.42%.

**2,3-Dihydroxy-1-naphthonitrile (3y):** Brown crystals (0.1480 gr, 80% yield), mp = 164-165 °C. IR (KBr), ῡ($cm^{-1}$): 3059, 3029, 2930, 2350, 1627, 1599, 1452, 1258, 1218, 1018, 839, 819, 696. $^1H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 6.52 (s, 1H), 7.80 (m, 1H), 7.96 (m, 1H), 8.20 (d, J = 8.00 Hz, 1H), 8.62 (d, J = 8.00 Hz, 1H), 10.08 (s, 1H, OH), 10.41 (s, 1H, OH). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 90.9 (C), 95.6 (C), 115.9 (CH), 117.8 (CH), 123.2 (CH), 124.4 (C), 128.6 (CH), 129.3 (CH), 142.9 (C), 160.3 (C), 162.2 (C). Anal. Calcd for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56%. Found: C, 71.32; H, 3.78; N, 7.59%.

**2,4-Dihydroxy-1-naphthonitrile (3z):** Brown crystals (0.1536 gr, 83% yield), mp = 183-185 °C. IR (KBr), ῡ($cm^{-1}$): 3059, 3029, 2930, 2350, 1627, 1599, 1452, 1258, 1218, 1018, 839, 725. $^1H$ NMR (250 MHz, 298K, DMSO-$d_6$), δ (ppm): 6.83 (s, 1H), 7.70 (m, 1H), 7.85 (m, 1H), 8.10 (d, J = 8.00 Hz, 1H), 8.52 (d, J = 8.00 Hz, 1H), 10.05 (s, 1H, OH), 10.64 (s, 1H, OH). $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δ (ppm): 90.4 (C), 99.7 (C), 108.5 (CH), 112.3 (CH), 119.2 (CH), 120.0 (CH), 127.2 (C), 133.1 (CH), 140.2 (C), 160.0 (C), 161.7 (C). Anal. Calcd for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56%. Found: C, 71.30; H, 3.80; N, 7.60%.

**Thiocyanogen:** Yellow crystals, mp = 171-173 °C. IR (KBr), ῡ($cm^{-1}$): 2050, 1021, 748, 485. $^{13}C\{^1H\}$ NMR (63 MHz, 298K, DMSO-$d_6$), δppm; 129.6 (C). MS: Calcd *m/z* 116, Found 116. Anal. Calcd for $C_2N_2S_2$: C, 20.68; N, 24.12; S, 55.20%. Found: C, 20.67; N, 24.27; S, 55.06%.

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**Supporting Information:**

Copies of IR, $^{1}H$ NMR, $^{13}C$ NMR spectra and elemental analysis for all compounds **3a-3z**, Crystallographic data of compound **3f** (CIF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

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