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Efficient thiocyanation of phenols and anilines in the $CeBr_3/H_2O_2$ system

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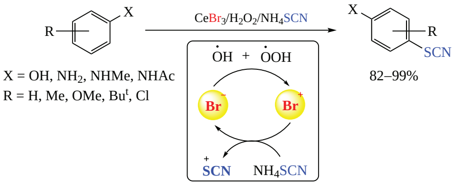
An efficient electrophilic thiocyanation of phenols and anilines in the $CeBr_3/H_2O_2$ system has been developed. The system $CeBr_3/H_2O_2$ generates reactive brominating species which would react with NH_4SCN to deliver the active SCN cations *in situ*. The Br^- anion can be further oxidized to Br^+, thereby furnishing the catalytic cycle.

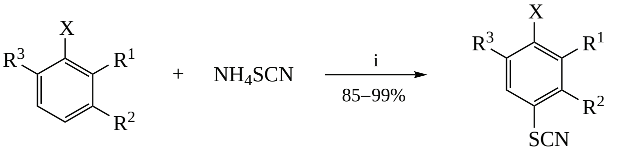


Keywords: thiocyanation, phenols, anilines, $CeBr_3/H_2O_2$ system, reactive brominating species, Fenton-like chemistry.

Thiocyanation of aromatic compounds is of significant importance since thiocyano compounds have found wide applications in medicinal chemistry.[1] Thiocyano group also can be easily converted to other organosulfur groups.[2] In past decades, various thiocyanation methodologies have been developed.[3–15] However, these procedures usually suffer from the drawbacks such as the use of toxic transition metal or acidic catalysts, excess oxidants, and harsh reaction conditions.

Recently, some new electrophilic thiocyanating reagents[16–18] and synthetic methodologies[19–21] have been reported. Nevertheless, these electrophilic thiocyanating reagents are expensive and should be preliminarily prepared. In contrast, electrophilic thiocyanation using *in situ* formed *N*-thiocyanato-succinimide is undoubtedly the fastest and cost-optimal approach. However, equivalents of *N*-halosuccinimides (NCS or NBS) were required, thereby leading to low atom economy.

Just recently, Tong group developed a new and green Fenton-like process comprising $CeBr_3/H_2O_2$ system.[22–25] The reactive brominating species can be generated under neutral conditions at room temperature. Inspired by their contributions, we envisioned that the *in situ* generated reactive brominating species Br^+ could react with inorganic thiocyanate salt to generate SCN cations. Herein, we report an efficient electrophilic thiocyanation of phenols and anilines employing $CeBr_3/H_2O_2$ system.



1a–n **2a–n**

a X = OH, $R^1 = R^2 = R^3$ = H
b X = OH, R^1 = Me, $R^2 = R^3$ = H
c X = OH, R^1 = MeO, $R^2 = R^3$ = H
d X = OH, R^1 = Bu^t, $R^2 = R^3$ = H
e X = OH, R^1 = Cl, $R^2 = R^3$ = H
f X = OH, $R^1 = R^3$ = H, R^2 = Me
g X = OH, $R^1 = R^3$ = H, R^2 = MeO
h X = NH_2, $R^1 = R^2 = R^3$ = H
i X = NH_2, R^1 = Me, $R^2 = R^3$ = H
j X = NH_2, R^1 = MeO, $R^2 = R^3$ = H
k X = NH_2, $R^1 = R^3$ = H, R^2 = Me
l X = NH_2, $R^1 = R^3$ = Me, R^2 = H
m X = NHMe, $R^1 = R^2 = R^3$ = H
n X = NHAc, $R^1 = R^2 = R^3$ = H

Scheme 1 *Reagents and conditions*: i, substrate **1** (0.5 mmol), NH_4SCN (1.5 mmol), $CeBr_3$ (0.1 mmol), H_2O_2 (30% aq. solution, 1.75 mmol), EtOAc (2 ml), 2 h, room temperature.

Phenol **1a** and ammonium thiocyanate were selected as the model substrates to optimize the reaction conditions (Scheme 1, Table 1). Different solvents were initially surveyed. Reaction in THF afforded low yield of 4-thiocyanatophenol **2a** (entry 1). Switching the solvent to some others (entries 2–7) provided

Table 1 Optimization of reaction conditions for conversion of phenol **1a** into 4-thiocyanatophenol **2a**.[a]

Entry	Solvent	MBr_n (equiv.)	NH_4SCN (equiv.)	H_2O_2 (equiv.)	t/h	Yield of **2a** (%)[b]
1	CH_2Cl_2	$CeBr_3$ (0.1)	2	2.5	6	69
2	THF	$CeBr_3$ (0.1)	2	2.5	6	30
3	MeCN	$CeBr_3$ (0.1)	2	2.5	6	70
4	EtOAc	$CeBr_3$ (0.1)	2	2.5	6	74
5	DMF	$CeBr_3$ (0.1)	2	2.5	6	48
6	$(F_3C)_2CHOH$	$CeBr_3$ (0.1)	2	2.5	6	65
7	MeOH	$CeBr_3$ (0.1)	2	2.5	6	55
8	EtOAc	$CeBr_3$ (0.15)	2	2.5	2	83
9	EtOAc	$CeBr_3$ (0.2)	2	2.5	2	92
10	EtOAc	$CeBr_3$ (0.2)	3	2.5	2	95
11	EtOAc	$CeBr_3$ (0.2)	3	3.5	2	99
12	EtOAc	$CeBr_3$ (0.2)	3	3.5	2	94[c], 91[d]
13	EtOAc	$FeBr_3$ (0.2)	3	3.5	2	73
14	EtOAc	$FeBr_2$ (0.2)	3	3.5	2	90

[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv.), NH_4SCN, $CeBr_3$, H_2O_2, solvent (2 ml), air, room temperature. [b] Isolated yield. [c] NaSCN was used. [d] KSCN was used.

[†] *General procedure for the synthesis of* **2a–n**. A solution of phenol **1a–g** or aniline **1h–n** (0.5 mmol, 1 equiv.), $CeBr_3$ (0.1 mmol, 0.2 equiv.) and ammonium thiocyanate (1.5 mmol, 3 equiv.) in EtOAc (2 ml) was cooled to 0 °C. Then 30 % H_2O_2 (3.5 equiv.) was added dropwise in 30 min. After completion, the mixture was stirred for more 2 h at room temperature (TLC control). The residue was extracted with ethyl acetate (3 × 5 ml) and washed with water. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate to afford the pure desired product **2a–n**. Compounds **5** and **6** were synthesized using the same procedure.

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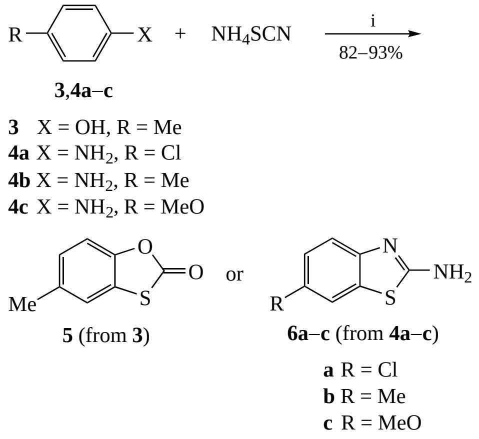


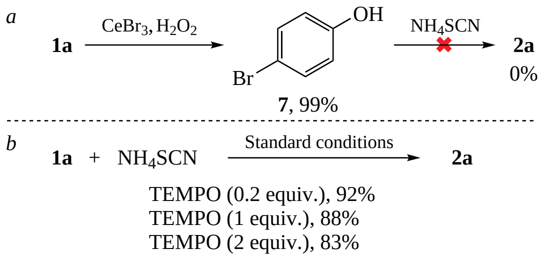
Scheme 2 *Reagents and optimized conditions*: i, substrate **3**,**4** (0.5 mmol), NH_4SCN (1.5 mmol), $CeBr_3$ (0.1 mmol), H_2O_2 (30% aq. solution, 1.75 mmol), EtOAc (2 ml), 2 h, room temperature.

moderate to good yields, while the use of EtOAc gave the best result (74% yield, entry 4). The amounts of $CeBr_3$, NH_4SCN and hydrogen peroxide were also evaluated (entries 8–11). Generally, increase in the amount of these reagents significantly promotes the reaction. Nearly quantitative yield was obtained with the combination $CeBr_3/NH_4SCN/H_2O_2$ (0.2 : 3 : 3.5 molar ratio) within 2 h at room temperature. A slight decrease in the product yield was observed when NH_4SCN was replaced by NaSCN or KSCN (entry 12). Other metal bromides such as $FeBr_3$ and $FeBr_2$ were also tried (entries 13 and 14); however, lower yields were obtained (73 and 90%, respectively).

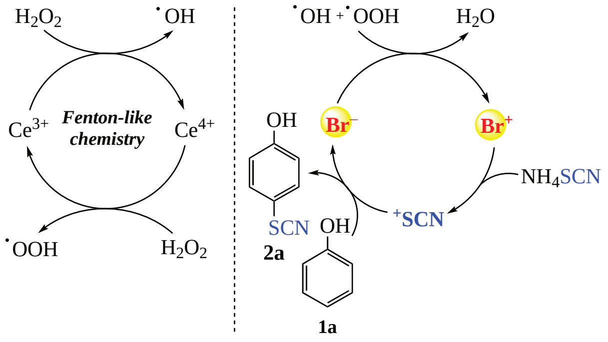
With the optimized reaction conditions in hand, a series of phenols **1b**–**g** was examined (Scheme 1).[†] Phenols with different groups such as methyl, *tert*-butyl, chloro and methoxyl at *ortho*- and *meta*-positions underwent the reaction smoothly to afford the corresponding products **2b**–**g** in excellent yields (85–99%), with the thiocyanation occurring exclusively at the *para*-position. 2-Chlorophenol **1e** also showed good activity, giving the desired product **2e** in 85% yield. The optimized reaction conditions were also suitable for the thiocyanation of anilines **1h**–**m** and acetanilide **1n** to deliver products **2h**–**n** in excellent yields.

Interestingly, when *para*-substituted phenol **3** and anilines **4a**–**c** were employed, benzo[*d*][1,3]oxathiol-2-one **5** and benzo[*d*]thiazol-2-amines **6a**–**c** were obtained as the major products in good to excellent yields. The *ortho*-thiocyanation occurred at the first step, and the attack of hydroxy group onto the thiocyanato one followed by hydrolysis afforded benzo[*d*][1,3]oxathiol-2-one **5**. Similarly, the reaction between amino and thiocyanato groups provided formation benzo[*d*]thiazol-2-amines **6a**–**c** (Scheme 2).

Some control experiments were carried out. When H_2O_2 was added to the reaction mixture, the color turned brown, this might be the result of generation of bromine or other reactive brominating species.[22] Treatment of phenol **1a** with $CeBr_3/H_2O_2$ system provided 4-bromophenol **7** in quantitative yield. However, no reaction took place between compound **7** and ammonium thiocyanate. This result ruled out the possibility that the product was formed through nucleophilic substitution reaction [Scheme 3(*a*)]. Then, different equivalents of TEMPO were added to the reaction mixture and the reactions were not inhibited [Scheme 3(*b*)]. All these results suggested that this reaction was more likely to proceed *via* an electrophilic thiocyanation pathway.



Scheme 3



Scheme 4

Based on the above results and previous report,[22] a mechanism is proposed (Scheme 4). Initially, reactive oxygen species $HO^\bullet$ and $HOO^\bullet$ were generated from the reaction $CeBr_3$ with H_2O_2 (Fenton-like chemical process). The bromide ion (Br^-) was then oxidized by these reactive oxygen species to release reactive brominating species Br^+ (may be a mixture of HOBr, Br_2, *etc.*), which would react with NH_4SCN to generated SCN cations *in situ*. Then, electrophilic thiocyanation of phenol **1** (or aniline) provided product **2**, along with regeneration of bromide ion for further oxidation.

In summary, an efficient electrophilic thiocyanation of phenols and anilines in the $CeBr_3/H_2O_2$ system has been developed. This system generates reactive brominating species, which react with NH_4SCN to deliver SCN cations *in situ*. The Br^- can be further oxidized to Br^+, thereby furnishing the catalytic cycle. All the starting materials are cheap and readily available. The reaction conditions are green and mild, providing the thiocyanated products in good to excellent yields in short reaction times.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.01.037.

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