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Iodine-Mediated Synthesis of Methylthio-Substituted Catechols from Cyclohexanones

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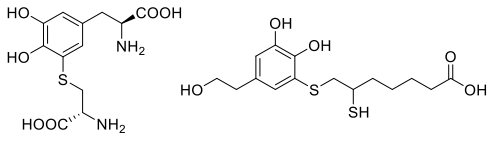
Abstract. A novel and efficient I_2-mediated direct synthesis of methylthio-substituted catechols from cyclohexanones was developed. Various cyclohexanones underwent oxygenation, methylthiolation, and dehydrogenative aromatization in one pot in moderate to good yields. DMSO was utilized as the solvent, oxygen source, and methylthiolation agent. A possible reaction mechanism is proposed.

Keywords: catechol; cyclohexanone; methylthiolation; one pot reaction; synthetic methods

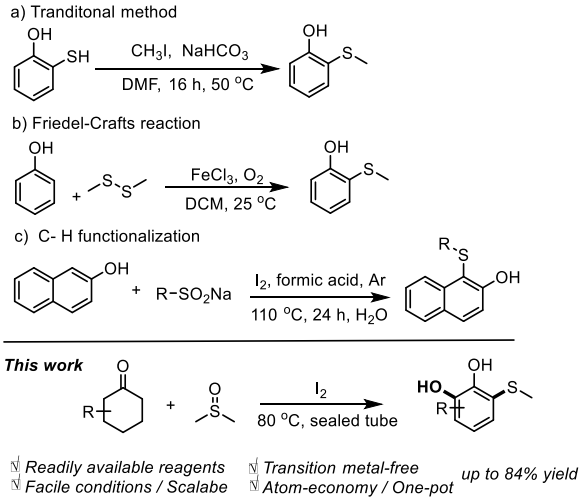
Thioethers and their derivatives are ubiquitous functionalities in pharmaceuticals and agrochemicals (Figure 1).[1] Among them, aryl methyl sulfides, especially sulfanylphenols, are high-value compounds with important biological activities.[2] Aryl methyl sulfides are useful substrates for C-C cross-coupling reactions[3] and also versatile precursors for sulfoxides,[4] arenes, and thiols.[5] Additionally, phenols are key building blocks in organic synthesis.[6]



5-*S*-cysteinyldopa 5-*S*-lipoylhydroxytyrosol

Figure 1. Bioactive molecules with alkylthio-substituted catechol motif.

There are only a limited number of efficient and environmentally friendly methods to form C-S bonds at the *ortho* position of phenols. The traditional approaches utilize methylation of 2-sulfanylphenol (Scheme 1a).[7] The substrates need to be pre-synthesized and the selectivity was poor. Takaki and co-workers reported an alternative method. They found that 2-sulfanylphenols could be synthesized by sulfanylation of phenols under an oxygen atmosphere using the toxic reagent MeSSMe and a stoichiometric amount of $FeCl_3$ (Scheme 1b).[8] Mixtures of *ortho*- and *para*-substituted thioethers of phenols were obtained under Friedel-Crafts conditions. Recently Xiao reported the synthesis of aryl sulfides from sodium sulfinates and phenols under aqueous conditions (Scheme 1c).[9]



Scheme 1. Strategies for the synthesis of 2-sulfanylphenols.

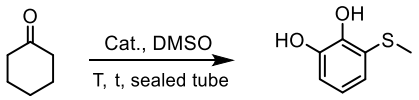
Dimethyl sulfoxide (DMSO) is a readily available and less toxic polar solvent. It has also been widely used as oxidant in well-known name reactions such as the Kornblum reaction[10] and Swern oxidation.[11] Besides, in the past decades, DMSO was reported as a useful building block for the synthesis of many organic motifs.[12] DMSO could serve as the source in methylthiolation,[12a-d] sulfonylation,[12e] formylation,[12f] and even as methylene source.[12g] Using the I_2/DMSO system for the synthesis of

complex compounds has attracted considerable attention from the synthetic community. Our group has been dedicated to research for realizing the high-value transformation of bulk chemicals. We previously reported the difunctionalization of styrene with alcohols, ketones, and nitriles to provide complex products only in one step.[13] Recently, functionalization of readily available bulk chemical cyclohexanones attracts our attention. Jiao reported the conversion of cyclohexanones into catechols using I_2/DMSO.[14] It is worth noting that only catechols were obtained in their work without methylthio substitutions. Herein, we wish to report that cyclohexanones can be transformed to methylthio-substituted catechols under facile, economical, and transition metal-free conditions. We speculated that methylthiolation promoted by in situ generated DMS in the oxidation step, followed by dehydrogenation and aromatization with I_2 and DMSO afforded this novel conversion. In this study, by means of controlled experiments and intermediates trapping experiments, the mechanism of this transformation was confirmed. To the best of our knowledge, this is the first report of the conversion of cyclohexanones into methylthio-substituted catechols in one pot.

We commenced our investigation with cyclohexanone **1a** as the model substrate for the optimization studies (Table 1). A series of iodide containing catalysts were examined. Unfortunately, KI, NBu_4I, CuI, and CuI_2 exhibit no reactivity. I_2 was proven to be the optimal catalyst for this transformation (entries 1-5). When I_2 was reduced to 10 mol%, only trace amount of product was observed (entry 6). We found that 59% of the product yield was achieved when 1.0 equiv of I_2 was utilized (entries 7-8). However, when the amount of I_2 was increased to 1.2 equiv, the yield of **2a** could not be further improved (entry 9). Testing to find the optimal reaction temperature revealed that the reaction temperature was very crucial for this transformation. 80 °C was identified as the optimal reaction temperature. Reactions ran at temperatures below or above 80 °C resulted in decreased product yields (entries 10-13). To our delight, when the reaction time was prolonged to 24 h at 80 °C, product **2a** was isolated with a yield of 84% (entries 14-16). It is worth mentioning that the product yield was not improved when the reaction was performed under N_2 atmosphere (entry 17). When an extra 1.0 equiv of DMS was added to the reaction system, the yield of **2a** was improved from 84% to the 86%. Under the conditions of entry 7, but with extra DMS added, the yield of **2a** improved significantly from 35% to 54%. The results show that an extra amount of DMS could be beneficial to the reaction (entries 18 and 19).

With the optimal reaction conditions in hands, a wide range of cyclohexanones were converted to the corresponding methylthio-substituted catechols (Table 2). An array of monosubstituted cyclohexanone at *para* position with alkyl substituents (such as Me-, Et-, Pr-, *t*-Bu-, amyl- and *t*-amyl-) were found to provide the desired products **2b**-**2g** in favorable yields. More sterically hindered alkyl groups tend to give lower reaction yields (**2b** *VS* **2g**).

Table 1. Optimization of the reaction conditions.[a]

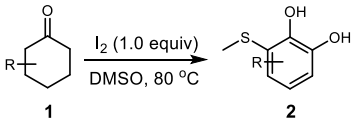


1 2

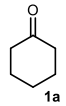
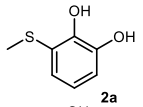
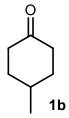
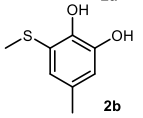
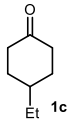
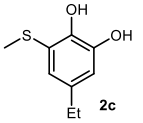
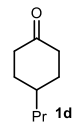
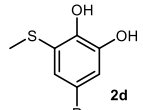
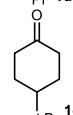
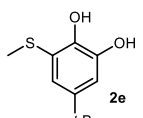
Entry	cat.(equiv)	temp(°C)	time(h)	Yield[b](%)
1	I_2 (0.2)	80	8	21
2	KI (0.2)	80	8	N.R.
3	NBu_4I (0.2)	80	8	N.R.
4	CuI (0.2)	80	8	N.R.
5	CuI_2 (0.2)	80	8	N.R.
6	I_2 (0.1)	80	8	Trace
7	I_2 (0.5)	80	8	35
8	I_2 (1.0)	80	8	59
9	I_2 (1.2)	80	8	51
10	I_2 (1.0)	40	8	11
11	I_2 (1.0)	60	8	55
12	I_2 (1.0)	100	8	44
13	I_2 (1.0)	120	8	Trace
14	I_2 (1.0)	80	4	45
15	I_2 (1.0)	80	12	71
16	I_2 (1.0)	80	24	84
17[c]	I_2 (1.0)	80	24	81
18[d]	I_2 (1.0)	80	24	86
19[d]	I_2 (0.5)	80	12	54

[a] Reaction conditions: cyclohexanone **1** (1.0 mmol, 1.0 equiv), DMSO (2.0 mL) in sealed tube.
[b] Isolated yields.
[c] Under N_2 atmosphere.
[d] 1.0 equiv of DMS was added.

Table 2. Substrate scope for the transformation of cyclohexanone.[a]



1 2

Entry	1	2	Yield [%][b]
1	 1a	 2a	84 (86[c])
2	 1b	 2b	75
3	 Et 1c	 Et 2c	72
4	 Pr 1d	 Pr 2d	71
5	 *t*-Bu 1e	 *t*-Bu 2e	70

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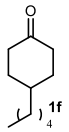
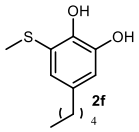
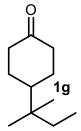
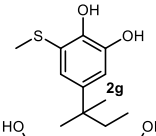
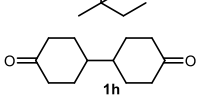
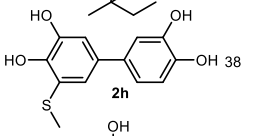
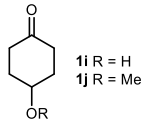
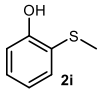
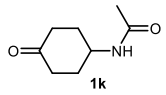
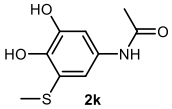
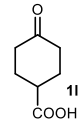
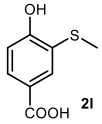
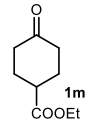
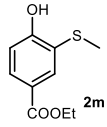
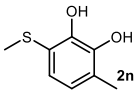
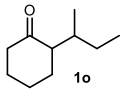
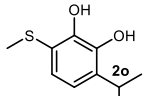
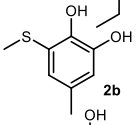
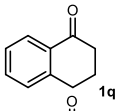
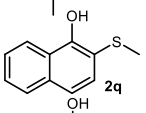
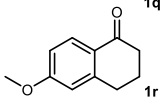
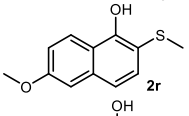
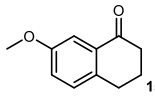
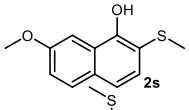
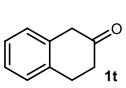
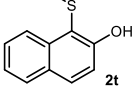
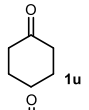
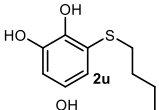
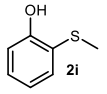
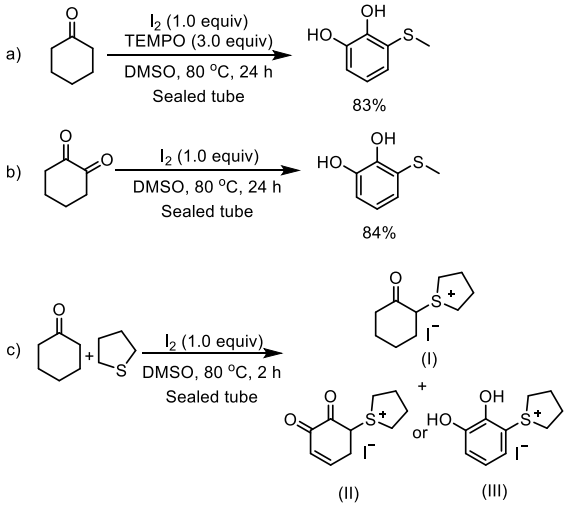
Entry	1	2	Yield [%][b]
6			67
7			65
8			38
9 10			R = H, 39% R = Me, 41%
11			0
12			12
13			21
14			28
15			42 56[c]
16			36 47[c]
17			39 52[c]
18			43
19			37
20			0
21			52
22			53

[a] Reaction conditions: cyclohexanones **1** (1.0 mmol), I_2 (1.0 mmol, 1.0 equiv), and DMSO (2.0 mL), in sealed tube, at 80 °C for 24 h.
[b] Isolated yield.
[c] 1.0 equiv of DMS was added.

When 4,4'- bicyclohexanone was used as the substrate, **2h** was obtained instead of 4,4'-bimethylthiocatechol. We speculated that the amount of I_2 was insufficient. When **1i** was used as starting material, **2i** was obtained in 39% yield, whereas cyclohexanone **1j** gave the same product in 41% yield. Unfortunately, the amide group was not tolerated under the optimal conditions, and therefore product **2k** was not obtained. Cyclohexanones bearing a carboxyl or an ester group could give the corresponding products (**2l**, **2m**) and the major side product is the catechols without methylthiolation. The *ortho*-substituted cyclohexanone **1n** and **1o** generated the desired compounds **2n** and **2o** in 28% and 42% yield, separately. Using 3-methylcyclohexanone as starting material, **2b** was obtained in 36% yield. Additionally, α-tetralone and its derivatives provided the corresponding methylthiolated naphthol **2q**-**2s** in 37% - 43% yield. However, β-tetralone was transformed into 1-iodonaphthalen-2-ol instead of **2t**. When *n*-butyl sulfoxide (*n*-BuSO*n*-Bu) was used as solvent, butylthiocatechol **2u** was isolated in 52% yield. And when cyclohex-2-en-1-one **1v** was used as starting material, **2i** was obtained in 53% yield. By adding extra 1.0 equiv of DMS to the reaction system, the yields of the products were improved (entries 15-17).

To gain further insight of the mechanism, some mechanistic studies were designed and performed (Scheme 2). First, 3.0 equiv of radical inhibitor tetramethylpiperidin-1-oxyl (TEMPO) was introduced to the reaction system under standard conditions. As expected, there was no significant yield loss, which excluded the free-radical reaction pathway (Scheme 2a). When cyclohexane-1,2-dione was used as the starting material, methylthio-substituted catechol was isolated with a yield of 84%, suggesting that cyclohexane-1,2-dione could be the intermediate of this reaction (Scheme 2b).

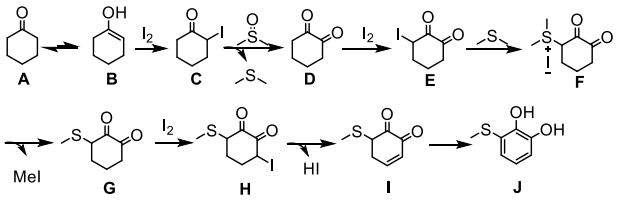


Scheme 2. Mechanistic Studies.

To further verify the mechanism, 1.0 equiv of tetrahydrothiophene was introduced to the reaction. After 2 hours, the reaction mixture was tested by ESI-HRMS, a few intermediates were detected including (I) and (II) and (III) (other intermediates were included

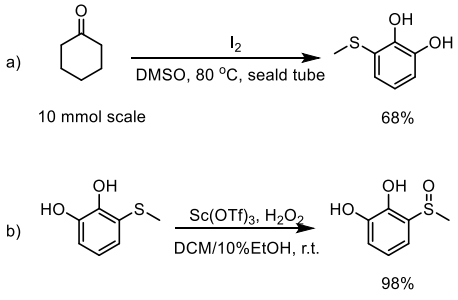
in Supporting Information) (Scheme 2c). (I) suggested that the 2-iodocyclohexanone was generated from cyclohexanone and I_2. (II) and (III) suggested that 1,2-cyclohexanedione and the aromatization process was involved.

Based on our experimental results and the previous literature reports,[14] a plausible mechanism was proposed for the reaction. Although the mechanism is not completely understood yet, we believe what occurs is as follows (Scheme 3). First, electrophilic iodization of cyclohexanone occurs, promoted by the iodine catalyst, to form 2-iodocyclohexanone **C**. Then, Kornblum oxidation takes place to generate the 1,2-cyclohexanedione **D** and DMS, followed by further α - iodization to give intermediate **E**. Followed by the reaction of DMS with **E** to provide intermediate **F**. After the loss of MeI, **G** undergoes iodization to generate intermediate **H**. Lastly, HI elimination and aromatization produces the methylthio-substituted catechol product.



Scheme 3. Possible Mechanistic Pathways.

To further utilize the methylthio-substituted catechol, a gram scale reaction was performed, which resulted in 16% reduction of our original yield (Scheme 4a). Sulfoxides are important precursors in the synthesis of various chemical and biological active molecules.[4b,15] Hence, we treated the methylthio-substituted catechol **2a** with H_2O_2 (30% in water) and $Sc(OTf)_3$, due to information collected from literature,[4d] and the methylsulfinyl-substituted catechol was obtained in 98% yield (Scheme 4b).



Scheme 4. Gram scale reaction and oxidation reaction.

In summary, we have developed a convenient I_2 – mediated synthesis of methylthio-substituted catechols via oxygenation, methylthiolation, dehydrogenation, and aromatization processes. Readily available DMSO was used as the oxidant, oxygen source, and methylthiolation source, as well as solvent. Various cyclohexanones were smoothly converted to the corresponding products in moderate to good yields. Our new method also provides an efficient way to produce sulfanylphenols. Further studies regarding the detailed mechanism and the synthetic applications are currently underway in our laboratory.

Experimental Section

Unless otherwise specified, all commercially available reagents were purchased from chemical suppliers without further purification. ^{1}H NMR (400 MHz or 300 MHz) and ^{13}C NMR (100 MHz or 75 MHz) spectra were recorded in $CDCl_3$ or DMSO-d^6. High-resolution mass spectra (HRMS) were obtained by ESI or EI. Column chromatography was performed on silica gel (200-300 mesh). All products were characterized by comparison of ^{1}H NMR, ^{13}C NMR, and HRMS.

Typical Experimental Procedure for Synthesis of Methylthio-Substituted Catechols from Cyclohexanones:

In a sealed tube with magnetic stir bar was charged with I_2 (1.0 equiv), DMSO (2.0 mL) and cyclohexanone (1.0 mmol). Then the tube was sealed with Teflon cape and heated at 80 °C for 24 h. After completion of the reaction, the reaction mixture was quenched with 4 mL $Na_2S_2O_3$ (10% in water), then extracted with ethyl acetate (10 mL) 3 times The combined organic phase was washed with brine and then concentrated by a rotary evaporator. The residue was purified by column chromatography on silica gel (200−300 mesh) using petroleum ether and ethyl acetate as eluent to provide the desired product (**2a-2v**).

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COMMUNICATION

Iodine-Mediated Synthesis of Methylthio-substituted Catechols from Cyclohexanones

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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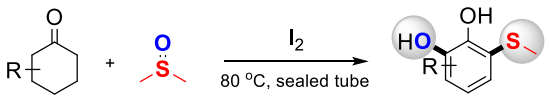

☑ *Readily available reagents* ☑ *Transition metal-free*
☑ *Facile conditions / Scalabe* ☑ *Atom-economy / One-pot*
up to 84% yield