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COMMUNICATION

Iodine-catalyzed Efficient 2-Arylsulfanylphenol Formation from Thiols and Cyclohexanones

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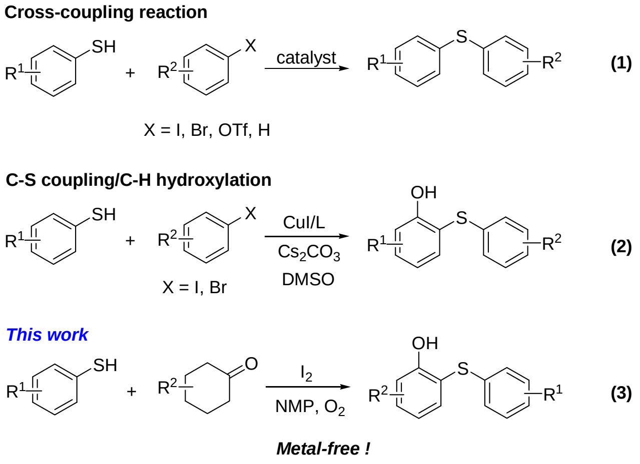
A novel method for formation of 2-arylsulfanylphenols from thiols and cyclohexanones is described. Iodine was used as effective catalyst for this kind of transformation. Cyclohexanones were used as phenol source via dehydrogenation and tautomerization reaction.

Aryl thioethers are important organosulfur compounds and widely exist in natural products, functional materials and pharmaceuticals.[1] Consequently, development of efficient methods for facile construction of aryl thioethers has stimulated considerable interest. In the past decade, the cross-coupling of aryl halides (or triflates) with thiols has become one of the most powerful methods for the construction of C-S bonds.[2] Various transition-metals such as palladium,[3] copper,[4] nickel,[5] cobalt,[6] indium[7] and iron[8] were used as efficient catalyst for aryl thioethers (Scheme 1, eq 1). In recent years, the direct conversion of C-H bonds into C-S bonds has arisen as an efficient alternative approach. Aryl thioethers could be synthesized by electrophilic substitution of arenes (especially electron-rich (hetero)arenes) with sulfenylating agents such as thiols,[9] disulfides,[10] sulfonyl chlorides[11] and sulfonyl hydrazides.[12]

As an important type of aryl thioethers, 2-phenylthiophenol and its derivatives can be used as the glycine transporter-1 (GlyT-1) inhibitors.[13] The conventional methods for the synthesis of these important compounds mainly involve the metal-catalyzed cross-coupling of thiols with 2-halophenols. Copper,[14] nickel,[15] and nano-$CuFe_2O_4$[16] were successfully employed as catalysts for this type of reaction. In addition, 1,2-diaryldisulfanes also could be used as sulfur sources for preparation of 2-(aryl)thiophenols.[17] Kumar and co-workers developed a transition-metal-free method for the synthesis 2-(aryl)thiophenols from diaryl disulfides and phenols using potassium persulfate in trifluoroacetic acid.[18] Dehydrogenation of 2-(aryl)thio cyclohexanones could afford an alternative approach to 2-arylthiophenols. However, 2-(aryl)thio cyclohexanones are not commercially available and excess bromine or strong base is required in this transformation, which seriously limited its application.[19] Deprotection of the corresponding methoxy compounds provided a multi-step procedure for 2-(aryl)thiophenols.[20] In 2010, Pan and co-workers reported an efficient protocol for the preparation of 2-(arylthio)phenols via copper(I)-catalyzed tandem transformation of C-S coupling/C-H functionalization (Scheme 1, eq 2).[21] Although various methods have been discovered for 2-(arylthio)phenols, development of general and efficient methods from readily available starting materials is highly desirable. Cyclohexanones are cheap, stable, readily available and easy to handle. Recently, the Stahl group found that these compounds can be dehydrogenated under palladium catalyzed reaction conditions to afford the corresponding phenols or cyclohexenones using molecular oxygen as hydrogen acceptor.[22] We and others successfully used cyclohexanones as aryl sources for C-N[23] and C-O bonds[24] formation. Based on this, we envisaged that 2-arylsulfanylphenols might be prepared from commercially available cyclohexanones and thiols via tandem transformation of C-S coupling/dehydrogenation/tautomerization. Herein, we describe an iodine-catalyzed efficient 2-arylsulfanylphenol formation from thiols and cyclohexanones under metal-free conditions using oxygen as the hydrogen acceptor (Scheme 1, eq 3).



Scheme 1 Various methods for C-S bond formation.

Our study was initiated using equal amount of cyclohexanone **1a** and 4-methylbenzenethiol **2a** as starting materials to detemine the optimized reaction conditions (Table 1). The desired product **3a** was observed in trace amount when the reaction was carried out in NMP at 150 °C under oxygen in the absence of any additives (entry 1). Subsequently, various iodide-containing additives were investigated under similar reaction conditions (entries 2-5). Cyclohexanone **1a** could smoothly react with 4-methylbenzenethiol **2a** to give the desired product in

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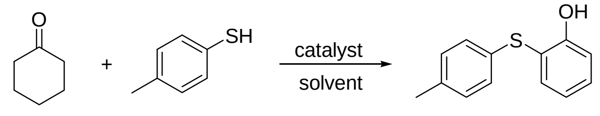
observable yield. Among the addtives investigated, iodine showed the best efficiency to give the corresponding product in 54% yield (entry 5). It's necessary to use 20 mol% of iodine to get satisfactory yield. The reaction yield decreased to 40% when 10 mol % iodine was used (entry 6). Except NMP, other solvents were also tested and failed to provide more favorable outcomes (entries 7-10). No product was observed when the reaction was carried out in toluene or diglyme. The ratio of **1a** to **2a** had an obvious influence on the reaction yield (entries 11 and 12). The reaction yield could be improved to 70% when 2 equiv of cyclohexanone was used. The reaction temperature played an important role in this kind of transformation. The reaction yield could be further improved to 80% by increasing the reaction temperature to 160 °C (entry 13). Lower yield was observed when the reaction was carried out under air atmosphere (entry 14) and no product was obtained under argon (entry 15). This means molecular oxygen acted as an efficient oxidant to accept hydrogen generated from cyclohexanone dehydrogenation step.

Table 1 Optimization of the reaction conditions[a]



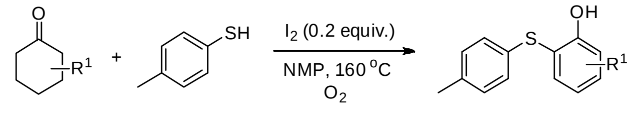
1a **2a** **3a**

Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1		NMP	150	trace
2	KI (0.2 eq)	NMP	150	15
3	NIS (0.2 eq)	NMP	150	34
4	ICl (0.2 eq)	NMP	150	49
5	I_2 (0.2 eq)	NMP	150	54
6	I_2 (0.1 eq)	NMP	150	40
7	I_2 (0.2 eq)	DMF	150	10
8	I_2 (0.2 eq)	toluene	150	0
9	I_2 (0.2 eq)	diglyme	150	0
10	I_2 (0.2 eq)	DMSO	150	19
11[c]	I_2 (0.2 eq)	NMP	150	59
12[d]	I_2 (0.2 eq)	NMP	150	70
13[d]	**I_2 (0.2 eq)**	**NMP**	**160**	**80**
14[d,e]	I_2 (0.2eq)	NMP	160	67
15[d,f]	I_2 (0.2eq)	NMP	160	0

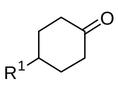
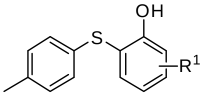
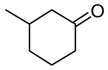
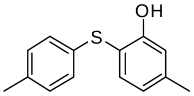
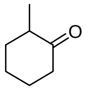
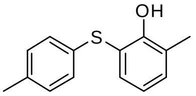
[a] conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent (2.0 mL) under oxygen unless otherwise noted. [b] GC yield based on **2a** using dodecane as internal standard. [c] **2a** (1.0 mmol). [d] **1a** (1.0 mmol). [e] Under air. [f] Under argon.

With the optimized reaction conditions in hand, the substrate scope with respect to cyclohexanones was explored (Table 2). Cyclohexanones bearing an alkyl substituent at the *para* position were able to smoothly couple with **2a** to give the corresponding products in good yields (entries 2-5). When 4-phenylcyclohexanone (**1f**) was employed to react with **2a,** 3-(*p*-tolylthio)-[1,1'-biphenyl]-4-ol (**3f**) was obtained in 80% yield (entry 6). To our delight, functional groups, such as ester and acetamido were well tolerated in this reaction (entries 7 and 8). The influence of the methyl substituent on the cyclohexanone moiety was also evaluated. The position of the substituents on the cyclohexanone ring profoundly affected the reaction yield. When 3-methylcyclohexanone (**1i**) was used, the desired product **3i** was obtained in 67% yield (entry 9). However, **3j** was observed in only 40% yield when 2-methylcyclohexanone (**1j**) was used (entry 10).

Table 2 Reaction of 4-methylbenzenethiol (**2a**) with cyclohexanones[a]



1 **2a** **3**

Entry	Cyclohexanone		Product		Yield (%)[b]
					
1	R^1 = H	**1a**	**3a**		75
2	R^1 = Me	**1b**	**3b**		70
3	R^1 = Et	**1c**	**3c**		72
4	R^1 = *n*-pentyl	**1d**	**3d**		75
5	R^1 = *tert*-pentyl	**1e**	**3e**		71
6	R^1 = Ph	**1f**	**3f**		80
7	R^1 = CH_3CONH	**1g**	**3g**		62
8	R^1 = $CO_2C_2H_5$	**1h**	**3h**		61
9		**1i**		**3i**	67
10		**1j**		**3j**	40

[a] Conditions: **1** (1.0 mmol), **2a** (0.5 mmol), I_2 (0.1 mmol), NMP (2.0 mL), 160 °C, 20 h, under oxygen. [b] Isolated yield based on **2a**.

To further examine the scope and limitation of the reaction, we tested various thiols for this kind of reaction (Table 3). The results demonstrated that thiols bearing electron-donating groups on the aryl ring could couple with cyclohexanone to give the desired products in moderate to good yields (entries 1–3). Functional groups such as acetamido, hydroxyl, fluoro, chloro and bromo were well tolerated under the optimal reaction conditions (entries 4–8). It should be noted that no cleavage of the C-Br thiol bond was observed. When naphthalene-2-thiol (**2j**) was reacted with **1a**, the target product **3s** was furnished in 67% yield (entry 9). To our delight, aliphatic thiols such as cyclohexanethiol (**2k**) also could react with **1a** to give the product

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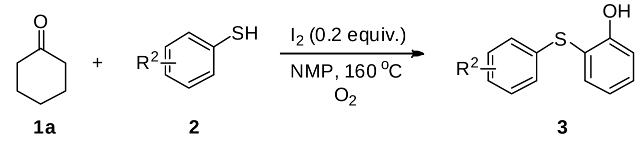
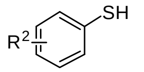
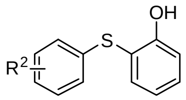
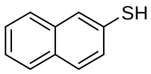
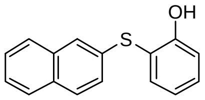
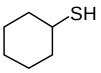
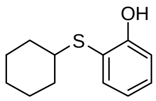
3t in 50% yield (entry 10).

To elucidate the mechanism, some control experiments were carried out (Scheme 2). 1,2-di-*p*-Tolyldisulfane (**4a**) was formed as the major products when the reaction of cyclohexanone (**1a**) with 4-methylbenzenethiol (**2a**) was stopped in 2 h under the optimized reaction conditions. 2-(*p*-Tolylthio) cyclohexanone (**5a**) and the desired product **3a** were obtained in 14% and 8% yields as determined by GC method (Scheme 2, **a**). In the absence of **1a** and iodine catalyst, **4a** was formed in 80% yield in 0.5 h (Scheme 2, **b**). Treatment of **4a** with **1a** under the standard reaction conditions in 2 h afforded the desired product **3a** in 39% yield together with 2-(*p*-tolylthio) cyclohexanone (**5a**) in 10% yield (Scheme 2, **c**). **5a** could further convert into the corresponding product **3a** in 78% yield via dehydrogenation and tautomerization (Scheme 2, **d**).

Table 3 Reaction of cyclohexanone (**1a**) with thiols[a]

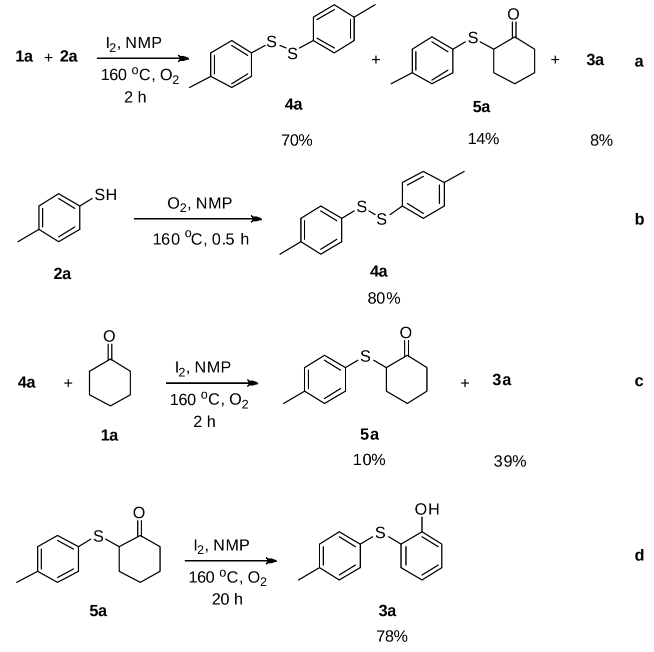


Entry	Thiol		Product		Yield (%)[b]
					
1	R = 2-Me	**2b**	**3k**		60
2	R = 3-Me	**2c**	**3l**		64
3	R = 4-OCH_3	**2d**	**3m**		52
4	R = 4-$NHCOCH_3$	**2e**	**3n**		72
5	R = 4-OH	**2f**	**3o**		81
6	R = 4-F	**2g**	**3p**		70
7	R = 4-Cl	**2h**	**3q**		62
8	R = 4-Br	**2i**	**3r**		71
9		**2j**		**3s**	61
10		**2k**		**3t**	50

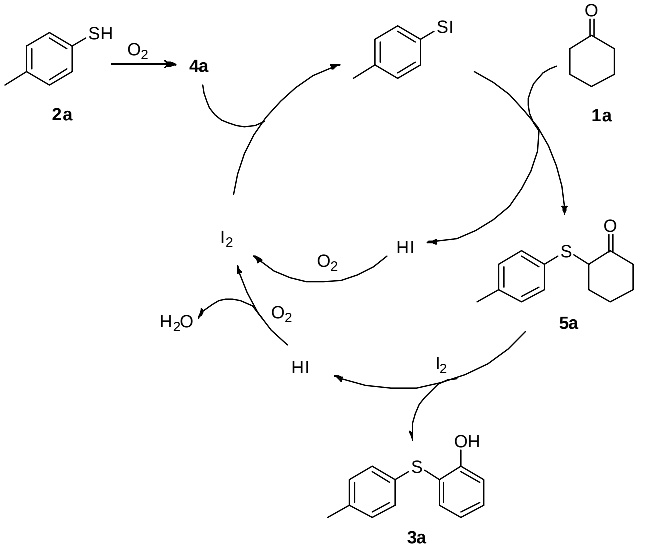
[a] Conditions: **1a** (1.0 mmol), **2** (0.5 mmol), I_2 (0.1 mmol), NMP (2.0 mL), 160 °C, 20 h, under oxygen. [b] Isolated yield based on **2**.

Based on these observations, a plausible mechanism was proposed as outlined in Scheme 3. Initially, oxidation of 4-methylbenzenethiol **(2a)** under oxygen affords disulfide **4a**. Reaction of **4a** with I_2 to form an electrophilic species 4-Me-PhSI,[25] which can couple with cyclohexanone (**1a**) to generate an intermediate 2-thio cyclohexanone **(5a)** and HI. Subsequent dehydrogenation and tautomerization of **5a** provides the target product **3a** promoted by iodine catalyst.[19a] Meanwhile, HI can be oxidized into I_2 by oxygen, thus closing the catalytic cycle.

In summary, we have developed a novel iodine-promoted approach for the synthesis of 2-arylsulfanylphenols using cyclohexanones as phenol source under metal-free conditions. Catalytic amount of iodine was used as catalyst and molecule oxygen was used as hydrogen acceptor in this transformation. Functional groups such as fluoro, chloro, bromo, hydroxyl, acetamido and ester were all well tolerated under the optimized reaction conditions. The C-S bond formation, dehydrogenation and tautomerization were realized in one-pot without any metal-catalyst. Since cyclohexanones and thiols are readily available starting materials, this method can afford an efficient and environmentally benign approach for 2-arylsulfanylphenols. The scope, mechanism and synthetic applications of this reaction are under investigation.



Scheme 2 Control experiments.



Scheme 3 Proposed mechanism.

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Notes and references

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