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Co(II)-catalyzed regioselective clean and smooth synthesis of 2-(aryl/alkyl-thio)phenols *via* sp^2 C—H bond activation

Abed Rostami[a,b], Vahid Khakyzadeh[c,*], Mohammad Ali Zolfigol[a,*], Amin Rostami[d]

[a] Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan 65167, Iran
[b] Kurdistan University of Medical Science, Sanandaj, Iran
[c] Faculty of Science, Department of Chemistry, K. N. Toosi University of Technology, P.O. Box 15875-4416, Tehran, Iran
[d] Department of Chemistry, Faculty of Science, University of Kurdistan, 66177-15175, Sanandaj, Iran

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ABSTRACT

The first example of a smooth, practical and useful strategy for the preparation of *ortho*-aryl/alkyl sulfenyl phenols by using the reaction of aryl/alkyl thiols with phenols in the presence cobalt as catalyst, and with the assistance of acetic anhydride as directing group *via* C—H bond activation, was developed. Described method enables to form selectively C—S bond without any ligand, oxidant, and aryl/alkyl halide under mild conditions.

Introduction

Discovering novel organic methodologies are always an important and main concern for chemists over the world [1]. In recent years, a selective 'inert' C—H bond activation/subsequent functionalization, is a challenging theme in many laboratories to furnish more versatile synthetic compounds and consider as a potent strategy for integrating small molecules to reach complex structures [2]. However, such C—H bond activations usually, suffer from critical challenges such as intrinsic reactivity and selectivity as well as a big part of them is conducted under harsh conditions [3]. In this regard, the directing groups perform a significant task because they can guide the specific "inert" C—H bond toward activation [4]. Owing to the unique place of sulfur, as a vital element, in living cells, decoration of new sulfur-containing compounds is a noted importance in organic synthesis, particularly, because of their extensive presence in medicines and natural products [5].

Among sulfur-containing compounds, 2-(aryl/alkyl-thio) phenols consider as notable skeletal motifs because of their therapeutic value in the treatment of cancer, HIV, heart disease, allergies, and obesity (Chart 1) [6a–c]. They have been broadly used in the creation of natural products and also drugs, such as flavonoid derivative **F1**, and essential intermediate **F2** as potent inhibitor for aldosterone synthase inhibitor (ASI) [6d–f]. On this matter, regioselective and direct C—S bond formation via C—H bond activation, as one of the most powerful protocols, has attracted considerable attention [7].

As a glance to the typical preparation of the aryl sulfides, they have synthesized by the reaction of aryl halides [8], phenolic esters [9], aryl boronic acid [10], triphenyl tin chloride [11] and nitro arenes [12] with S-containing nucleophiles in the presence of transition metal catalysts. Another method involves the cross-coupling diary disulfides with aryl halides or coupling partners in the presence of rhodium [13], copper [14] and nickel [15] metals.

To the best of our knowledge, C—H bond activation of aromatic compounds by transition metal catalyst under mild conditions is still the research target especially in halide-free processes [16] and literature survey shows that not only a few reports are available for sulfenylation of aryl 2-naphthols [17] but also direct synthesizing of 2-(aryl/alkyl-thio)phenol via sp^2 C—H bond activation and then subsequent C—S bond formation is rare and highly desirable. Through documented methods, up-to-date, (Scheme 1), in 2010, Pan and coworkers described a copper (I)-catalyzed tandem transformation of C—S coupling/C—H functionalization method through reaction of thiophenol derivatives with aryl halides for the preparation of 2-(aryl)thiophenols (path I) [18]. After that, Deng et al. introduced coupling of thiols and cyclohexanones via a dehydrogenation and tautomerization reaction by employing of Iodine as a catalyst (path II) [19] and, very recently Wang and Shi presented a copper-catalyzed tandem thiophenol hydroxylation subsequent S-arylation using aryl boronic acids (path III) [20]. Accordingly, it is urgent to recognize new synthetic methods in this case.

As the part of our continuing efforts for the C—S bond formation and the synthesis of aryl sulfides [21], as well as considering that employing directing groups could be simply used in such directed C—H bond activation we postulated that free-phenols could be feasible as a starting material and by connecting directing group on its hydroxy group, the

* Corresponding authors.
E-mail addresses: v.khakyzadeh@kntu.ac.ir (V. Khakyzadeh), zolfi@basu.ac.ir (M.A. Zolfigol).

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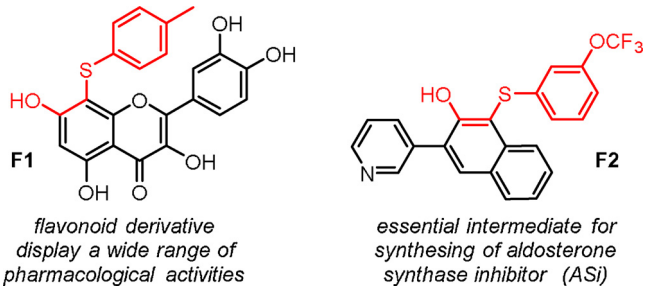
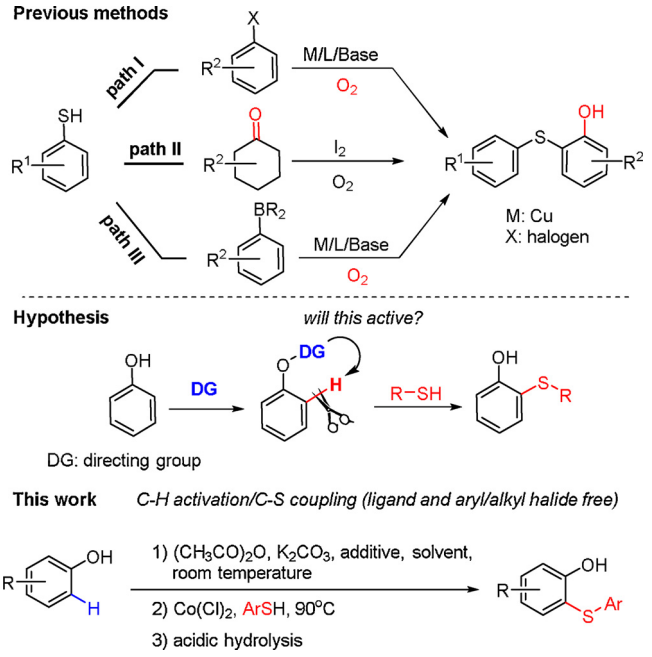


Chart 1. Selected examples of 2-(aryl/alkyl-thio) phenol derivatives in natural products and medicines.

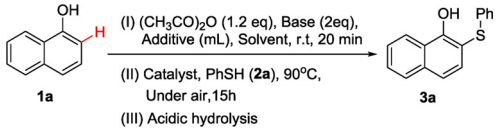


Scheme 1. Possible approach for ortho-functionalization of phenols, our hypothesis, and work.

desired C—H activation could take place and let to selective C—S bond formation (hypothesis). Herein we disclose the successful and selective synthesis of alkyl/aryl sulfenyl-phenols through cobalt catalyzed C—H bond activation/functionalization of phenols with thiols in the presence of acetic anhydride as directing group under ligand and additive-free conditions (Scheme 1, this work).

Our initial efforts were focused on finding an efficient catalytic system using 1-naphthol (1a), thiophenol (2a), and acetic anhydride as model substrates (Table 1). Using 10 mol% $Cu(OAc)_2$ as a catalyst and K_2CO_3 in dimethyl sulfoxide (DMSO) solvent gave the desired product in 40% yield (entry 1). Surprisingly, no improvement was observed with employing $Pd(OAc)_2$ and $Ru(Cl)_3$ as catalysts and desired products produced in only 15 and 45% yields, respectively (entries 2 and 3). Fe and Ni were also examined as other metal catalysts in this reaction, and moderate yields were detected for iron and trace yield in case of the Ni catalyst (entries 4–6). A sharp progress was seen by switching the catalyst to $Co(Cl)_2$ (entries 7–9) and the best efficiency for reaching to the corresponding product 3a was viewed in the presence of K_2CO_3, 75% yield. Almost same yields were obtained by other base sources (entries 8 and 9). To our delight, a series of ionic liquids were investigated as phase transfer materials and led to a better result (entry 10, 94%). Dimethylformamide (DMF), was also utilized in the present of TBAC; the desired product was obtained in poor, 38%, yield (entry 11). Cobalt chloride as the catalyst and acetic anhydride as directing group is both necessary, and no yields were observed when the reaction

Table 1
Catalyst, base, additive and solvent screening table.[a]



Entry	Catalyst	Solvent[b]	Base	Additive	Yield[c] (%)
1	$Cu(OAc)_2$	DMSO	K_2CO_3	–	40
2	$Pd(OAc)_2$	DMSO	K_2CO_3	–	15
3	$Ru(Cl)_3$	DMSO	K_2CO_3	–	45
4	$Fe(Cl)_3$	DMSO	K_2CO_3	–	47
5	$Fe(Cl)_3$[d]	DMSO	K_2CO_3	–	55
6	$Ni(Cl)_2$	DMSO	K_2CO_3	–	9
7	$Co(Cl)_2$	DMSO	K_2CO_3	–	75
8	$Co(Cl)_2$	DMSO	Cs_2CO_3	–	70
9	$Co(Cl)_2$	DMSO	NaO^tBu	–	72
10	$Co(Cl)_2$	DMSO	K_2CO_3	TBAC	94
11	$Co(Cl)_2$	DMF	K_2CO_3	TBAC	38
12	$Co(Cl)_2$	DMSO	K_2CO_3	TBAC	0 [e]
13	––	DMSO	K_2CO_3	TBAC	0 [f]
14	$Co(Cl)_2$	DMSO	K_2CO_3	TBAC	19 [g]

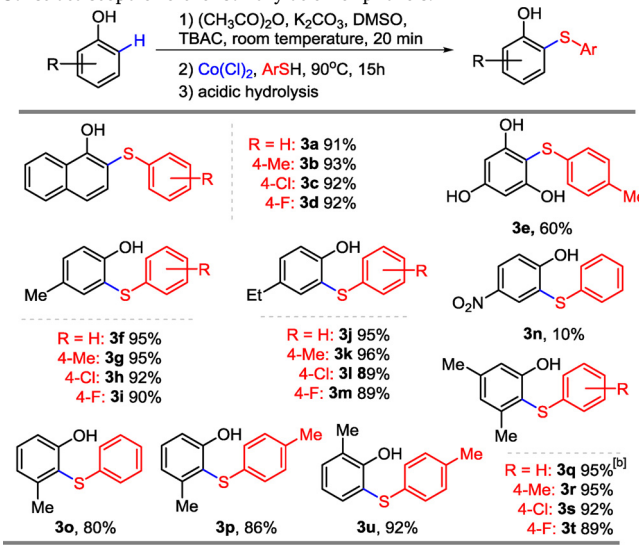
[a] Condition: At first; **1a** (1 mmol), $(CH_3CO)_2O$ (1.2 mmol), base (2 mmol), additive (0.5 mL) and solvent (2.0 mL) mixed together for 20 min at room temperature then, **2a** (1.2 mmol) and catalyst (10 mol%) added to the flask at 90 °C for15 h, under air atmosphere. Finally, product was obtained by acidic hydrolysis. [b] all solvents were dried. [c] GC yield. [d] $Fe(Cl)_3 \times 6H_2O$. [e] Without acetic anhydride. [f] Without catalyst. [g] Under argon. TBAC = Tributylmethylammonium chloride. More details are in supporting information.

was performed in the absence either one (entries 12 and 13) also the desired product did not obtain when the reaction was carried out under an argon atmosphere (entry 14).

To demonstrate the utility of this method, with the optimized conditions in hand, various aryl thiols and phenols were chosen to establish the scope, limitations, and generality of this protocol (Table 2).

Initial investigations were performed on the coupling of 2-Naphthol with free/substituted thiophenol derivatives. Electron-donating and halogen substituted thiophenol were suitable substrates (3a-d) and coupled smoothly in good to excellent yields. The moderate yield (60%)

Table 2
Substrate scope of ortho- sulfenylation of phenols.[a]



[a] Reaction Condition: ROH (1 mmol), $(CH_3CO)_2O$ (1.2 mmol), ArSH (1.2 mmol), K_2CO_3 (2 mmol), DMSO (2.0 mL), TBAC (0.5 mL), Catalyst (10 mol %), under air. [b] Isolated Yield.

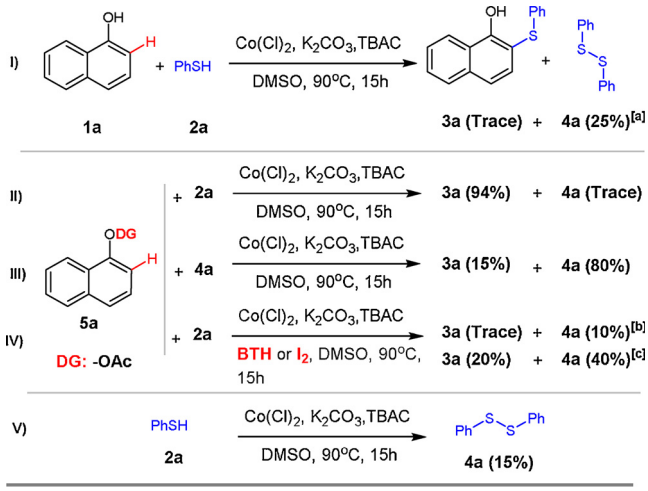
was obtained when benzene-1,3,5-triol was employed, probably because of multiple reaction sites (3e). Next, the coupling of para substituted phenols (para methyl and para ethyl) with different monosubstituted thiophenols were tested (3f-m) and well tolerated in this study. A strong electron withdrawing group (–NO_2) on para position of phenol suppressed coupling reaction (3n, 10%). Interestingly, good to excellent yields (80–92%) and selectivity were obtained by using of ortho or meta-substituted phenols, and only C—H activation on 2-position of the hydroxy group was observed, in contrary to steric effects (3o-p, 3u). Moreover, dimethyl substituted phenols smoothly participated in coupling with several thiophenols and furnished corresponding products in excellent yields (3q-t).

Generally, phenols with electron-rich groups were efficiently produced the desired product in high yields, but we found that phenols containing electron withdrawing groups (—NO_2, —CN, —CHO) are not fit for this transformation.

To show the more synthetic applicability of defined system and also ability to discriminate between C—H bonds, the sulfunylation of 2-naphthol, benzene rings fused to phenol, were investigated and the possibility of synthesis of aryl/alkyl sulfenylphenols using the reaction of aryl/alkyl thiols with 2-naphthol was examined under optimized reaction conditions (Table 3).

The results in Table 3 demonstrate that most of the thiols tested underwent smooth transformations to afford the corresponding 1-aryl/alky sulfenyl naphthol in good to excellent yields (83–93%) with high selectivity (> 80% in position 1 and < 10% in positon 3 of 2-naphthol). Not only free thiophenol but also electron-donating (–CH_3) and halogen (–F, –Cl, –Br) substituted thiophenols were well tolerated and known as suitable substrates by smoothly coupling in the reaction and giving good to excellent yields (4ba-4be). After that desired product was obtained in 90% yield when naphthalene-1-thiol employed as another partner in coupling reaction (4bf). Aliphatic thiols including benzyl mercaptan, 1-octanethiol, and cyclohexanthiol as sulfenylating agents were also performed successfully under present reaction conditions (4bg-4bi), showing the high potential of the system for further investigations. Our experimentations on scope indicated that the presence of an electron donating/withdrawing groups on the benzene ring of thiols did not prevent the smooth formation of the expected products.

To gain an understanding the reaction mechanism, we conducted a good range of experiments to explore the roles of directing group, catalyst and other aspects of the reaction (Scheme 2). Under the standard condition without the addition of acetic anhydride, 1-naphthol (1a) not converted to the corresponding product (3a), leaving the starting material intact and disulfide (4a) obtained in 25% yield (Scheme 2I). The reaction of naphthalen-1-yl acetate, 5a, (instead of the 1-naphthol/acetic anhydride system) with thiophenol (2a) in the

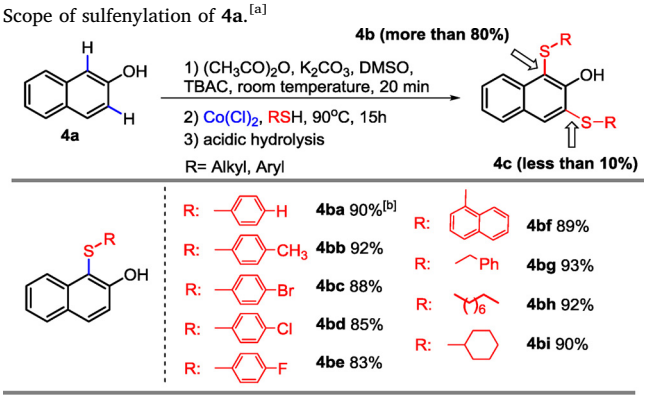


Scheme 2. Chemoselective control experiments.
[a] All yields are GC yields. [b] In the precence of butylated hydroxytoluene (BHT). [c] In the precence of Iodine.

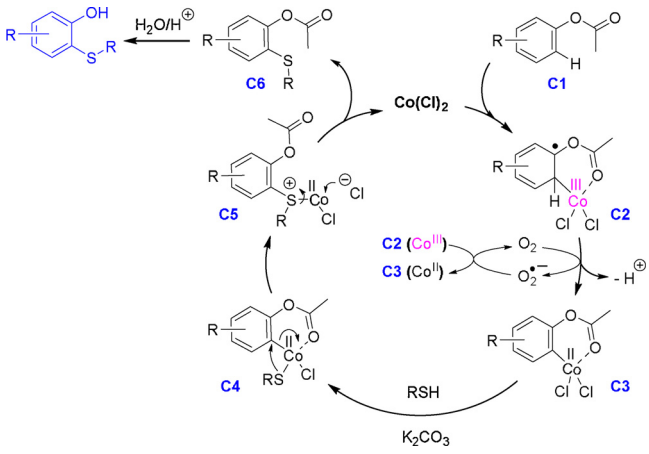
reaction, desired product (3a) obtained in 94% yield (Scheme 2II). Employing disulfide (4a) instead of thiophenol (2a), the product 3a was formed in only 15% yield under the standard reaction conditions (Scheme 2III). The model reaction was also studied in the presence of Iodine and Butylated Hydroxytoluene (BHT) as the common radical scavengers. From the taken results, trace yield for BTH and 20% in case of I_2, it can, therefore, be concluded that reaction pathway is sensitive to radical scavengers (Scheme 2IV). Additionally, in a control experiment in the absence of phenol substrates, thiophenol (2a) underwent dimerization to afford disulfide (4a) in 15% yield (V).

Based on the above experimental results, a plausible reaction pathway for the reaction of thiols with phenols in the presence of acetic anhydride as directing group and cobalt catalyst has been presented in Scheme 3. It is hypothesized that phenol reacts with acetic anhydride to produce phenolic ester **C1**. Then, cobalt is coordinated to oxygenate atom leading to a directed ortho-metalation by a radical pathway and provide the key intermediate **C2** which is cobalt (III) intermediate. Since cobalt (III) complexes are very kinetically inert [22], we imagine that oxygen molecule can be responsible for re-aromatization of ring and reactivating cobalt by reducing of cobalt (III) to cobalt (II) in an internal cyclic pathway to produce **C3**. In continue, the intermediate **C4** generate by reaction of sulfur source with cobalt (II), then **C5** form by an internal immigration. Finally, protected desired product results from regeneration of $CoCl_2$ and can easily deprotected by an acidic hydrolysis strategy.

Table 3
Scope of sulfenylation of **4a**.[a]



[a] Reaction Condition: ROH (1 mmol), $(CH_3CO)_2O$ (1.2 mmol), ArSH (1.2 mmol), K_2CO_3 (2 mmol), DMSO (2.0 mL), TBAC (0.5 mL), Catalyst (10 mol %), under air. [b] Isolated Yield.



Scheme 3. Proposed mechanism for the sulfunylation of phenols.

Conclusions

In conclusion, we have developed a novel, simple, effective and practical method for exclusively synthesizing of the 2-arylsulfanylphenols from phenols, under ligand and halide-free conditions. The process was catalyzed by a catalytic amount of cobalt chloride and was performed through C−H activation/functionalization of phenols with aryl/alkyl thiols. The presence of acetic anhydride, as a directing group, was essential. This method affords a powerful alternative approach for the synthesis of biologically important scaffolds or intermediates from free phenols. We believed that the current work can open up a new and promising insight for designing and synthesis of various kinds of sulfides. Further investigation of this protocol is currently underway in our group.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mcat.2018.04.020.

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