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I₂-Catalyzed Oxidative C(sp³)-H/S-H Coupling: Utilizing Alkanes and Mercaptans as the Nucleophiles

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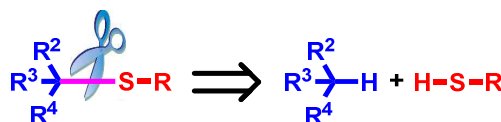
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By using alkanes and mercaptans as the nucleophiles, di-tert-butyl peroxide (DTBP) as the oxidant, I₂-catalyzed oxidative C(sp³)-H/S-H coupling was achieved. This protocol provided a novel process to construct C(sp³)-S bond from commercially available hydrocarbons and mercaptans.

C-S bonds are key structures of many nature products and functional molecules which exhibit different biological activities, hence much attention has been paid to the formation of C-S bond through coupling reactions¹. Classically, coupling reactions of organic halides/organic boronic acid with mercaptans in the presence of bases and catalysts was employed to form C-S bonds². Oxidative coupling between RH and R'H, which shortens the synthesis route due to the elimination of pre-activation of C-H or X-H bonds, has attracted much attention during the past decades³. Although transition-metal-catalyzed C(sp²)-H and C(sp)-H functionalization were the major force in this field⁴, they were seldom utilized to perform oxidative coupling with S-H bonds⁵ due to the strong poisoning effect of mercaptans. Moreover, up to now, only isolated reports focus on oxidative C(sp³)-H/S-H coupling⁶. Thus, it is still highly desirable to explore the C-S bond formation utilizing C(sp³)-H bonds and mercaptans as the nucleophiles.

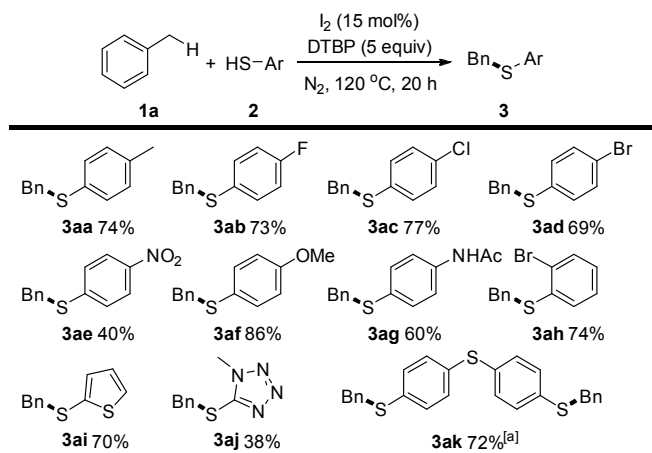
C(sp³)-H bonds existed extensively in the nature, and most of which were of alkanes. Thus it is a pivotal task to realize the functionalization of the abundant C(sp³)-H bonds of alkanes. However, they are difficult to be activated in reactions, which may be ascribe to their nonpolarity, which weakened the interaction between the bonds and other species such as transition metals. Consequently, to date, only few reports have described oxidative coupling utilizing simple alkanes in highly selective manner⁷ although they are always easy accessible. Therefore, it is still a crucial but challenging task to achieve the oxidative coupling of the C(sp³)-H bonds of simple alkanes. Moreover, there is no report focused on the oxidative C-H/S-H coupling of C(sp³)-H bonds between simple alkanes and mercaptans, so such topic of C(sp³)-H functionalization would provide a new way to construct C(sp³)-S bonds (Scheme 1).

Scheme 1. New way for C(sp³)-S bond construction

In consequence of the strong coordination of the mercaptans to the transition metals, and the use of metal limited the further application of the protocols in industry and pharmacy. We initiated the investigation with a metal-free protocol⁸. Recently, iodide catalysts are gaining more attention among the oxidative coupling reactions⁹. Moreover, compared with transition metals, iodide catalysts might exhibit weaker interaction with mercaptans. Thus, this serious of catalysts were picked out to catalyze the oxidative C(sp³)-H/S-H coupling. To figure out the best condition, 4-methyl thiophenol **2a** was employed to react with toluene **1a**. After a series of condition optimization, I₂ and DTBP were selected to be the catalyst and the oxidant respectively (see supporting information, Table S1). The detailed condition was: **1a** (4 mL), **2a** (0.3 mmol), DTBP (1.5 mmol), I₂ (0.045 mmol) at 120 °C for 20 h under N₂. The corresponding sulfide was obtained in the yield of 74% under the optimized condition (Scheme 2, **3aa**)¹⁰.

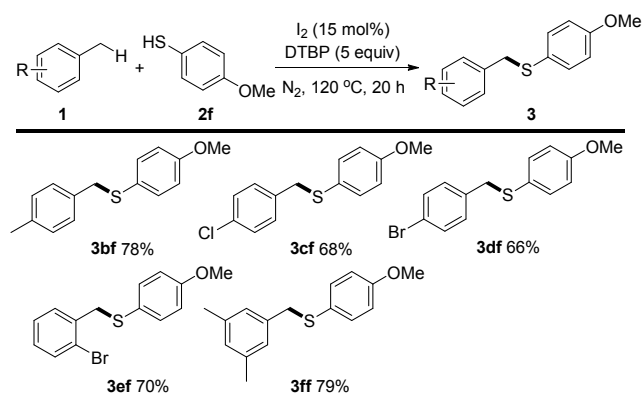
Then we began to investigate the substrate scope of the reaction. First, various aryl mercaptans were examined to react with toluene **1a** under optimized condition. Electron-rich thiophenols performed the benzylation smoothly and good yields were obtained (Scheme 2, **3aa**, **3af**, **3ag**). The electron-deficient thiophenol, however, exhibited lower activity than the electron-rich ones (Scheme 2, **3ae**). The halo-substituted thiophenols, which allowed further functionalization, were tolerated (Scheme 2, **3ab**, **3ac**, **3ad**, **3ah**). The steric hindrance effect was not obvious in the reactions of thiophenols bearing *o*-Br and *p*-Br group (Scheme 2, **3ad**, **3ah**). It was noteworthy that both electron-rich and electron-deficient heterocyclic mercaptans were also suitable for this transformation (Scheme 2, **3ai**, **3aj**). Moreover, 4-mercapto-phenyl sulfide **2k**, a substrate bearing two mercapto group, also react with toluene with good selectivity that only dibenzylated product was

obtained (Scheme 2, **3ak**). Unfortunately, only trace amount of product were detected when aliphatic mercaptans were employed to couple with toluene, which might result from the over-oxidation of the relatively unstable aliphatic mercaptans.



Scheme 2. I_2 -promoted oxidative $C(sp^3)$ -H/S-H coupling of toluene with aryl mercaptans. Reaction conditions: **1a** (4 mL), **2** (0.3 mmol), DTBP (1.5 mmol), I_2 (0.045 mmol) at 120 °C for 20 h under N_2 . Yields shown are of isolated products. Bn = benzyl. [a] **2k** (0.15 mmol).

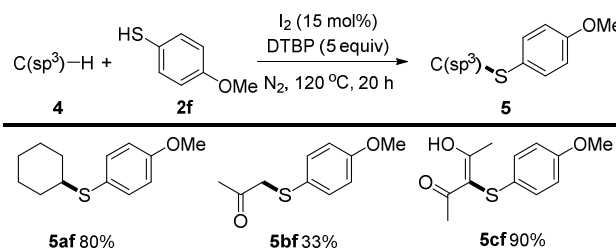
Inspired by the encouraging results, the reactivity of methyl arenes was further investigated. 4-methoxy-thiophenol **2f** was selected to react with various methyl arenes due to the easier isolation of the products. The methyl arenes bearing multiple methyls, which enriched the electron density of the arene slightly, exhibited good activity (Scheme 3, **3bf**, **3ff**). However, methyl arenes bearing electron-deficient group such as Cl and Br group exhibited lower activity in the reaction (Scheme 3, **3cf**, **3df**, **3ef**). Steric effect was also not observed since the *o*-Br and *p*-Br toluenes showed similar activity (Scheme 3, **3df**, **3ef**).



Scheme 3. I_2 -promoted oxidative $C(sp^3)$ -H/S-H coupling of various methyl arenes with 4-methoxy-thiophenol. Reaction conditions: **1** (4 mL), **2f** (0.3 mmol), DTBP (1.5 mmol), I_2 (0.045 mmol) at 120 °C for 20 h under N_2 . Yields shown are of isolated products.

Since the bond dissociation energy (BDE) of toluene $C(sp^3)$ -H bond (89 kcal/mol¹¹) was low among the $C(sp^3)$ -H bonds, cyclohexane, another alkane with relatively low $C(sp^3)$ -H bond energy (96 kcal/mol¹²), was tested utilizing the standard condition. To our delight, the corresponding phenyl alkyl sulfide was obtained in the yield of 80% (Scheme 4, **5af**). Moreover, the BDE of $C(sp^3)$ -H bond of acetone was 95

kcal/mol¹³, and as the result, acetone, the most simple ketone, can also perform the $C(sp^3)$ -H/S-H coupling as predicted with lower yield (Scheme 4, **5bf**). With the C-H bond of acetone activated, acetylacetone reacted with 4-methoxy-thiophenol smoothly and the yield rose to 90% (Scheme 4, **5cf**).



Scheme 4. I_2 -promoted oxidative $C(sp^3)$ -H/S-H coupling of various $C(sp^3)$ -H source with 4-methoxy-thiophenol. Reaction conditions: **4** (4 mL), **2f** (0.3 mmol), DTBP (1.5 mmol), I_2 (0.045 mmol) at 120 °C for 20 h under N_2 . Yields shown are of isolated products.

Furthermore, we wanted to gain some mechanistic insights of this oxidative coupling of alkane $C(sp^3)$ -H bonds with aryl mercaptans. Control experiments were carried out firstly. When I_2 was excluded from the system, the yield of sulfide lowered slightly [Scheme 5, eq(1)]. Which indicated that I_2 was involved among the transformation. Then, benzyl iodide was employed to react with 4-methylthiophenol (see supporting information, Scheme S1) and only 30% of the aryl alkyl sulfide was obtained. This result suggested that the iodization/substitution procedure may not be the main access led to the formation of product.

Then *in situ* IR was selected to monitor the reaction between toluene and 4-methylthiophenol to figure out the role of I_2 . We can see that 4-methyl-thiophenol consumed within 3 minutes accompanying the generation of 4-methylphenyl disulfide (see supporting information, Figure S1). The sampling experiment revealed that the disulfide generated very fast with the yield of 79% (Figure 1, disulfide with I_2), and the product did not form until the fully consumption of mercaptans (Figure 1, product with I_2). Slower generation of the disulfide and lower yield of the product were observed when I_2 was taken away from the system (Figure 1, disulfide and product without I_2). Therefore, we drew the inference that the disulfides may be the intermediate of the reaction, and I_2 may act as accelerator of the generation of disulfide¹⁴. The accelerated dimerization might prevent the side reactions of mercaptans, which may result to the slight promotion of the yield. Another control experiment showed that disulfide exhibited similar activity compared with mercaptan [Scheme 5, eq(2)], which further confirmed the deduction.

In view of the previous reports employed methyl arenes as the benzyl source and DTBP as the oxidant, a single electron transfer (SET) process led to the generation of benzyl radical might be one step among the reaction^{7d, 15}. Therefore, a radical-trapping experiment was carried out using butylated hydroxytoluene (BHT) as the radical trapper. As predicted, the coupling reaction was suppressed by BHT [Scheme 5, eq(3)]. Thus we believed that a radical process was involved among the reaction.

Then, to further confirm our speculation, electron paramagnetic resonance (EPR) experiments were carried out. A complicated spectrum was recorded when 5,5-dimethyl-1-pyrroline N-oxide (DMPO) was added to the reaction of toluene and DTBP [Figure 2(a)]. Moreover, with I_2 or both I_2

and 4-methylphenyl disulfide added to above system, similar radical signal was recorded [Figure 2(b, c)]. This result excluded I_2 and disulfide from the radical signal source. When toluene was replaced by cyclohexane, a different signal was recorded [Figure 2(d)], which indicated that the radical signal was related to the $C(sp^3)$ -H bonds, and thus the $C(sp^3)$ radical generated from the $C(sp^3)$ -H bonds may be the intermediate of the reaction.

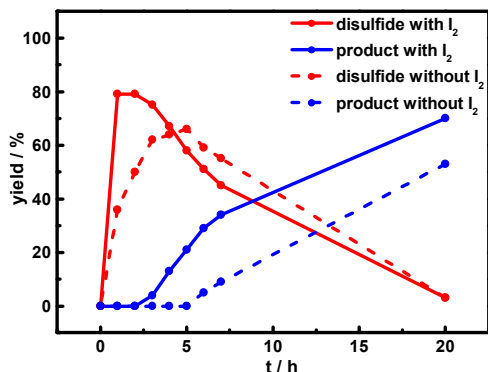
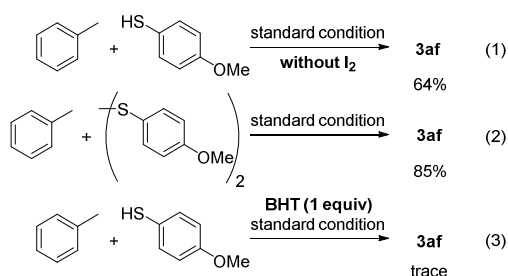


Figure 1. The sampling experiment of reaction mixture of 1a (4 mL), 2a (0.3 mmol), DTBP (1.5 mmol) at 120 °C with and without I_2 respectively.



Scheme 5. Control experiments and Radical trapping experiment

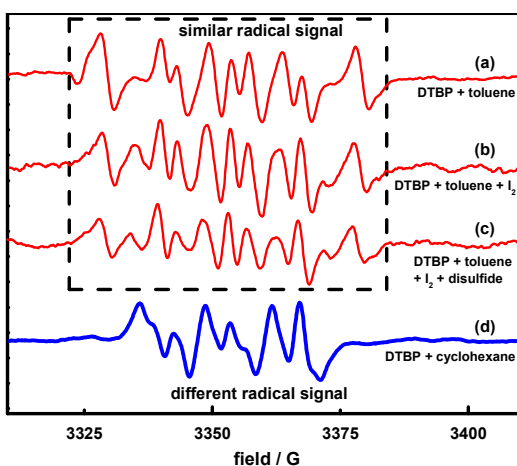
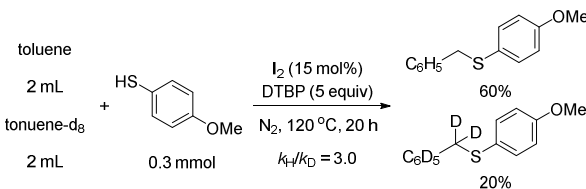


Figure 2. The electron paramagnetic resonance (EPR) spectra (X band, 9.4GHz, RT) of (a) reaction mixture of DTBP (1.5 mmol) in toluene (2 mL) at 120 °C for 5 h with the addition of DMPO; (b) Reaction mixture of DTBP (1.5 mmol) and I_2 (0.045 mmol) in toluene (2 mL) at 120 °C for 5 h with the addition of DMPO; (c) Reaction mixture of DTBP (1.5 mmol), I_2 (0.045 mmol) and 4-methylphenyl disulfide (0.2 mmol) in toluene (2 mL) at 120 °C for 5 h with the addition of DMPO; (d) Reaction mixture of DTBP in cyclohexane (2 mL) at 120 °C for 5 h with the addition of DMPO.

Furthermore, an intermolecular kinetic isotopic effect (KIE) experiment was carried out, and a noteworthy KIE was observed with the $k_H/k_D = 3.0$ (Scheme 6). This result indicated that the $C(sp^3)$ -H bond activation might be involved in the rate determining step.



Scheme 6. KIE experiment

Based on the experiment results and literature precedent, a plausible mechanism was proposed. Initially, an oxidative dimerization of aryl mercaptans took place quickly to give corresponding disulfide with the I_2 as the catalyst and DTBP as the oxidant. The homocoupling of the sulfur radical, which generated from the S-H bond abstraction by tert-butoxy radical, were believed to be the route¹⁴. The tert-butoxy radical could also abstracted hydrogen from methyl arene to obtained benzyl radical with a lower rate that it did not occur before the completely consumption of the mercaptan. This step was also considered to be the rate determining step (RDS). Afterward, there are two possible pathways. Similar to organic peroxides, the disulfide might act as a sulfur radical pool that it release the sulfur radical slowly through homolysis¹⁶. And the sulfur radical couple with the benzyl radical to afford the product. Another possibility is that radical-substitution occurred between benzyl radical and disulfide^{6b, 10, 17} to give the product and the sulfur radical, which dimerized quickly to regenerate the disulfide.

In summary, we have established an oxidative $C(sp^3)$ -H/S-H coupling of alkanes with mercaptans to afford aryl alkyl sulfides with the employment of cheap and nontoxic I_2 and DTBP in moderate to good yields. This proposal provided a novel process to construct $C(sp^3)$ -S bond using alkanes and mercaptans directly, which eliminate the pre-functionalization of the starting materials and might encourage the further application. The mechanism study suggested that the disulfides were the intermediate and the $C(sp^3)$ -H bond cleavage was the rate-determining step of the transformation.

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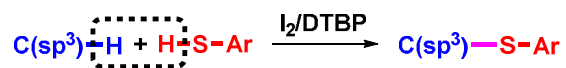
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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x

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19 examples, up to 90%

The C(sp³)-S bond formation was achieved utilizing C(sp³)-H and S-H as the nucleophiles. Methyl arenes, cycloalkanes and aliphatic ketones exhibited reactivity for this transformation. Mechanism study revealed that C(sp³) radical and disulfide were the intermediates of the reaction.