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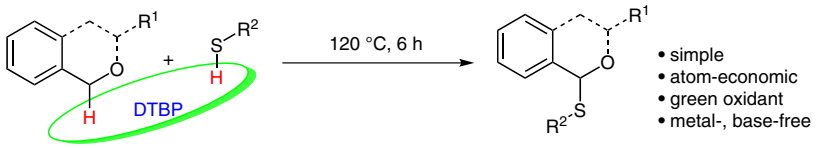
Facile Approach for C(sp³)–H Bond Thioetherification of Isochroman

Jie Feng
Guoping Lu
Meifang Lv
Chun Cai*

Chemical Engineering College, Nanjing University of Science & Technology, 200 Xiaolingwei, Nanjing 210094, P. R. of China
c.cai@mail.njust.edu.cn



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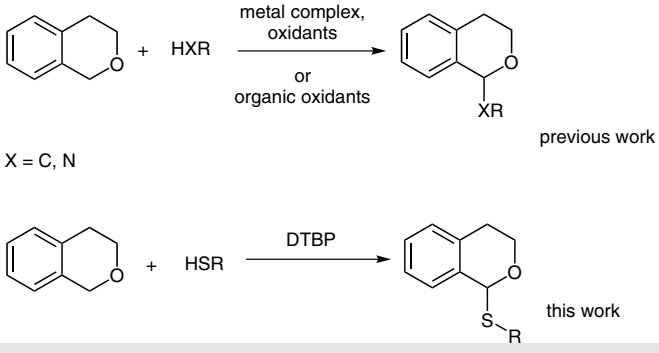
Abstract An unprecedented C–S formation protocol via the direct oxidative C(sp³)–H bond thioesterification of isochroman under metal-free conditions was developed. A series of isochroman derivatives could be afforded efficiently by the green, simple, and atom-economical method.

Key words C–S coupling, thioetherification, peroxides, dehydrogenation, isochroman

The direct C–H functionalization path is now being extensively investigated because of its atom economics and the environmental sustainability.[1] One such strategy, cross-dehydrogenative coupling, the CDC protocol, is of immense importance as it has been successfully employed to access a diverse array of C–C and C–heteroatom bonds, by functionalizing C–H bonds of all types (sp, sp², sp³).[2] Among all types C–H bonds activation paths via CDC, the functionalizations of inert C(sp³)–H bond have received special research attention.[3] In the past few years, the breakthrough achievements in this area mainly include C(sp³)–H bond functionalization of cycloalkanes or benzylic C(sp³)–H bonds,[4] C(sp³)–H bond functionalization with the assistance of a chelating group,[5] and the functionalization of C(sp³)–H bond adjacent to heteroatoms.[6]

Herein, we are primarily interested in investigating the activation of C(sp³)–H bond of benzyl ethers such as isochroman. Isochroman derivatives usually exhibit various potential pharmaceutical activities[7] and may serve as important building blocks in synthetic chemistry.[8] As the benzyl C–H bond adjacent to oxygen atom, direct C–H bond adjacent to oxygen atom and benzyl C–H bond exist simultaneously in the isochroman ring, it is interesting and challenging for researching selective C(sp³)–H bond functionalization of isochroman.

Screening of reference revealed that studies on the metal-catalyzed or noncatalytic C–C bond formations at the C(1) position of isochroman via C(sp³)–H bond activation have been widely reported (Scheme 1).[9] However, fewer reports deal with the CDC-mediated carbon–heteratom bond formation, especially C–S bond formation.[10]



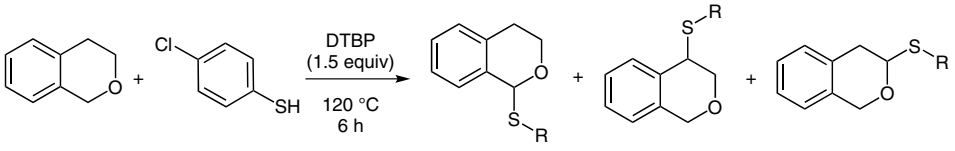
Scheme 1 Thioetherification of isochromans

Sulfur-containing compounds represent a class of important synthetic intermediates and excellent building blocks for chemical biology.[11] Traditional C–S bond-formation protocols, whether organocatalytic C–S bond forming[12] or transition-metal-catalyzed C–S bond formation,[13] usually need prefunctionalization of the substrate which means more chemical wastes and less atom economy. Gratefully, the emergence of the CDC method provides an alternative method to synthesize thioether compounds. Recently, C–S formation of disulfide and symmetric aliphatic ether has already been achieved with DTBP as oxidant.[14] In particular, the reactions under metal-free conditions are more appreciable in the sulfur-containing pharmaceutical synthesis.

Encouraged by that, we report here the straightforward and convenient CDC protocol for the syntheses of thioethers through the direct oxidative cross-couplings of isochroman with thiophenol (thiol) in the absence of metal catalysts.

The initial choice of reaction conditions was focused on using isochroman and 4-chlorobenzenethiol as substrates with DTBP as an oxidant. The desired product was observed with the mentioned reagents stirred at 100 °C. Inspired by this result, we examined other oxidants in a quest to improve the yield. Among all other oxidant candidates, such as TBHP (5–6 M in decane), $K_2S_2O_8$, TBP, and BPO, DTBP was found to be the most effective oxidant (Table 1, entries 1–5). Further checking the oxidants equivalent revealed that adding more oxidants was conductive to improve the yield (Table 1, entry 6), but when three or more equivalents of DTBP were added, the yield dropped in adverse (Table 1, entry 7). Next, we screened the reaction temperature. To our delight, the product yield could further be improved when the reaction was heated up to 120 °C. Under this temperature, the coupling reacted efficiently (within 6 h). Extension of reaction time may lead to more nasty byproducts (Table 1, entry 9). It was encouraging that the C–S coupling showed excellent selectivity throughout these conditions. There is a slight decrease of the selectivity when conducting the reaction in a higher temperature (Table 1, entry 10). Furthermore, it is worth to note that the air conditions do not show significant inhibition to the reaction, but when the reaction was performed under O_2 atmosphere, the lower yield was obtained with more isochroman-1-one formed.

Table 1 Screening for Optimal Conditions[a]



3a **3a'** **3a''**

R = ClC_6H_4

Entry	Oxidants (equiv)	Time (h)	Temp (°C)	Yield of **3a**/**3a'**/**3a''**[b]
1	DTBP[c] (1.5)	6	120	81/0/1
2	DTBP (1)	6	100	33/0/0
3	$K_2S_2O_8$ (1)	6	100	0/0/0
4	TBHP[d] (1)	6	100	25/0/0
5	BPO[e] (1)	6	100	3/0/0
6	DTBP (2)	6	100	66/0/0
7	DTBP (3)	6	100	59/1/1
8	DTBP (1.5)	6	110	72/0/1
9	DTBP (1.5)	24	120	56/2/3
10	DTBP (1.5)	6	130	68/3/4
11[f]	DTBP (1.5)	6	120	78/1/1 (3)[h]
12[g]	DTBP (1.5)	6	120	43/1/1 (23)[h]

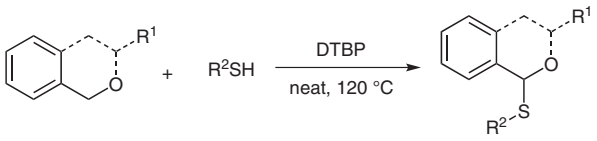
[a] Reaction conditions: 4-chlorobenzenethiol (1.5 mmol), isochroman (1 mmol), DTBP (1.5 mmol), 120 °C, 6 h.
[b] The yield was determined by ^{1}H NMR of crude products.
[c] DTBP = di-*tert*-butyl peroxide.
[d] TBHP = *tert*-butyl hydroperoxide.
[e] BPO = benzoyl peroxide.
[f] The reaction was conducted in the air.
[g] The reaction was conducted in oxygen atomosphere.
[h] The yield of 3,4-dihydronaphthalen-1(2*H*)-one.

Having established the standard reaction conditions, the oxidative thioetherification was then implemented on cross-couplings between isochroman and substituted thiophenols.[16] As can be seen in Table 2, the present methodology was applicable to diverse thiophenols (Table 2, entries 1–6, 8, and 11). Comparatively, the electron-withdrawing substrates showed higher yields than the electron-donating ones, especially when 4-(*tert*-butyl)thiophenol was used, more disulfide was obtained instead of the thioether (Table 2, entry 5). *ortho*-Substituted thiophenol gave an inferior product yield to that of *para*- or *meta*-substituted thiophenols (Table 2, entries 2, 6, and 8) due to the steric effect. In case of 4-bromothiophenol, the C–Br bond cleavage preferentially occurred with a mixture of aryl thioether obtained.

This protocol was also applied to heterocyclic thiophenol {benzo[*d*]thiazole-2-thiol}. Interestingly, an open-ring process occurred during the CDC protocol with the unexpected product 2-{2-[(benzo[*d*]thiazol-2-ylthio)methyl]phenyl}acetaldehyde obtained in good yields instead of the aimed C–S coupling products (Table 2, entry 17). Next, we checked alkyl thiols. Along with the aimed products, a collection of byproducts (the C–H activation adjacent to the sulfur atom could also occur) was also formed which can hardly be separated with the main products (Table 2, entries 10 and 12). Finally, open-chain benzyl ethers were investigated. Like isochroman, benzyl ethers, such as benzyl methyl ether, afforded the corresponding coupling products in good yields (Table 2, entries 13 and 14). But the coupling between benzyl methyl ether and 4-fluorobenzenethiol is an exception with 'dithiother' **3p′** obtained.

To demonstrate the general applicability of this method, cyclic benzylic ethers bearing similar isochroman structure, such as 1,3-dihydroisobenzofuran, isochroman-4-one were then checked respectively. Moderate yield of the thioether **3r** (Table 3, entry 1) could be obtained under the standard conditions. Interestingly, small amount of the open-ring product **3s** (Table 3, entry 1) was also produced. Adding more DTBP and extending the reaction time could lead to more product **3s** (Table 3, entry 2). Notably, this method may have potential usage in total synthesis[15] (provide alternative access to the unique *ortho*-bifunctionalized structure). Like isochroman, isochroman-4-one could also furnish this C–S coupling, but the presence of the carbonyl group put a negative effect on the product yield with the thioether **3t** (Table 3, entry 5) formed in the yield of 30%. Moreover, we tried some other ethers which do not contain a benzylic structure. Dioxane, tetrahydrofuran, and tetrahydro-2*H*-pyran could couple with thiophenol smoothly, but the linear ethers (diethyl ether) gave low yields. Also the rigid 2,3-dihydrobenzo[1,4]dioxine showed less reactivity even with extension of the reaction time.

Table 2 Scope of the Oxidative C–S Formation[a]



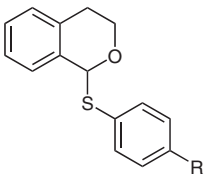
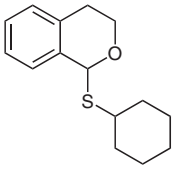
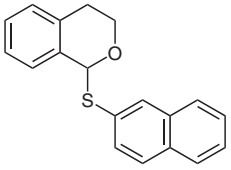
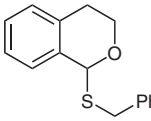
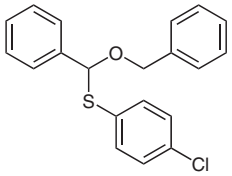
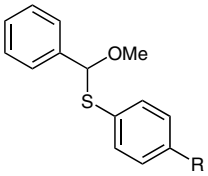
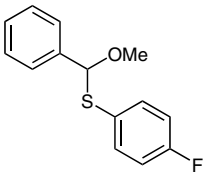
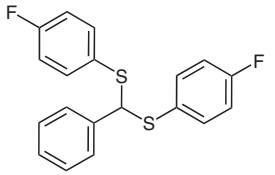
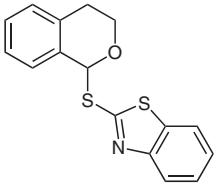
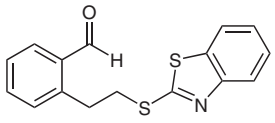
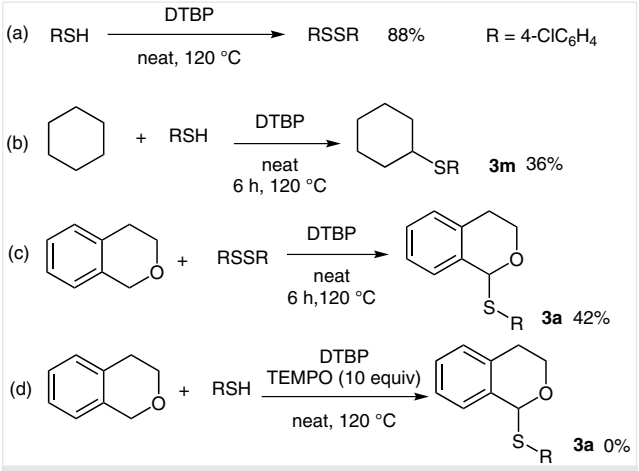
Entry	Product			Yield (%)[b]
1		R = 4-Cl	**3a**	77
2		R = 4-Me	**3b**	75
3		R = 4-F	**3c**	80
4		R = 4-OMe	**3d**	68
5		R = 4-*t*-Bu	**3e**	4[c] (80[d])
6		R = 2-Me	**3f**	16[c] (76[d])
7		R = 2-Cl	**3g**	trace
8		R = 3-Me	**3h**	78
9		R = 4-Br	**3i**	0 (56[e])
10			**3j**	30[c]
11			**3k**	70
12			**3l**	35[c]
13			**3m**	80
14		R = 4-Me	**3n**	81
15		R = 4-Cl	**3o**	84
16			**3p**	0

Table 2 (continued)

Entry	Product		Yield (%)[b]
17		**3p′**	52
		**3q**	0
		**3q′**	75

[a] Reaction conditions: thiophenol or thiol (1.5 mmol), isochroman or benzylic ether (1 mmol), DTBP (1.5 mmol), 120 °C, 6 h.
[b] Isolated yield.
[c] The yield of was determined by GC–MS as the difficulty in separation.
[d] The yield of disulfide.
[e] Total yield of aryl thioether mixture.

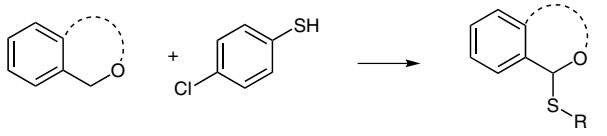
To further investigate the details of the mechanism for this convenient oxidative thioesterification of isochroman with thiophenol or thiols, a series of controlled experiments was carried out (Scheme 2).

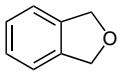
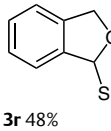
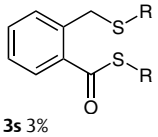
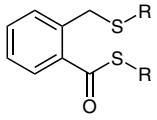
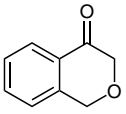
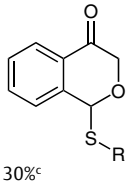
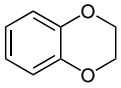
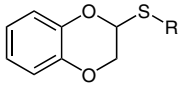
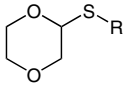
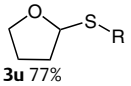
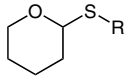


Scheme 2 Controlled experiments for the CDC C–S coupling

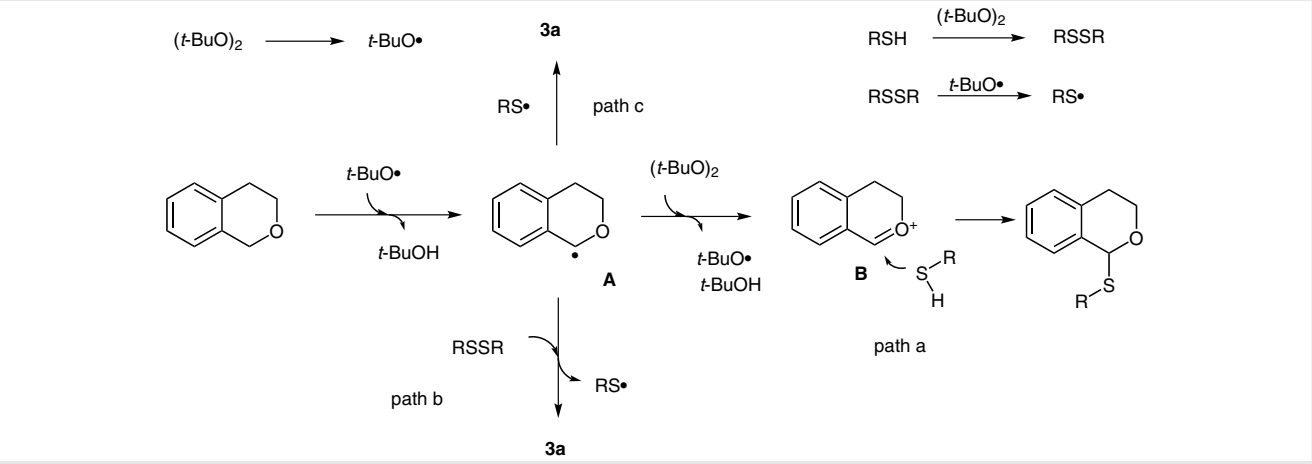
In the presence of DTBP, thiophenols could easily convert into disulfide, but the disulfide could also couple with isochroman in spite of the lower reactivity (Scheme 2, line c). As similar CDC protocols commonly involve radical mechanisms, excess TEMPO was then added as a radical inhibitor. As expected, no desired product was observed. Therefore the present coupling may follow the radical mechanism. Also we conducted the reaction with 4-chlorobenzenethiol and cyclohexane under the standard conditions which indicated that unactivated C–H bond cleavage

Table 3 Oxidative C–S Formation of Cyclic Ethers[a]



Entry	Substrates	Conditions	Product and yield (%)[b]
1		DTBP (1.5 equiv), 120 °C, 6 h	 **3r** 48%
			 **3s** 3%
2		DTBP (3 equiv), 120 °C, 16 h	 **3s** 23%
3		DTBP (1.5 equiv), 120 °C, 6 h	 30%[c]
4		DTBP (3 equiv), 120 °C, 24 h	 trace
5		DTBP (1.5 equiv), 120 °C, 6 h	 **3t** 85%
6		DTBP (1.5 equiv), 120 °C, 6 h	 **3u** 77%
7		DTBP (1.5 equiv), 120 °C, 6 h	 **3v** 70%
8	Et_2O	DTBP (1.5 equiv), 120 °C, 6 h	**3w** 5%[c]

[a] R = ClC_6H_4.
[b] Isolated yield.
[c] by GC–MS.



Scheme 3 Proposed mechanism for the for the CDC C–S coupling

could occur to form a cyclohexane radical which was captured by the disulfide or thiophenol. However, the reactivity showed the significant difference between benzylic ethers and unbenzylic ethers, and almost all the substrates tested showed excellent C(1) selectivity between the C–H bonds at different positions of isochroman. It can be concluded that the intermediate A (Scheme 3) owns higher reactivity than other potential radical intermediate.

Based on the above experiments and reported literatures, the plausible reaction mechanism is shown in Scheme 3. DTBP decomposed into the *tert*-butoxyl radical at first under heated conditions. Hydrogen abstraction of the C–H bond adjacent to an oxygen atom produced intermediate **A**. After that, intermediate **A** was further oxidized to intermediate **B**. Thiol coupled with intermediate **B**, thereafter gave the desired product. Alternatively, the radical intermediate **A** may directly react with disulfide to give the product **3a** and release thiyl radical. Of course, it is also possible two radicals (intermediate **A** and thiyl radical) quenched to form the desired product. Considering that thiophenol showed higher yield than disulfide in comparable time, path a was preferred.

In summary, an unprecedented C–S formation based on the direct oxidative cross-couplings of isochroman derivatives with thiophenol or thiols in the absence of a transition metal has been developed. The major advantages of this method include the use of DTBP as the green oxidant without utilizing any other additives added, thus this simple and atom-economic route can be conducted in an environment-friendly way.

References and Notes

(1) For selected reviews or books on transition-metal-catalyzed C–H functionalization, see: (a) Yu, J.-Q.; Shi, Z.-J. *C-H Activation*; Springer: Berlin, **2010**. (b) Sun, C. L.; Li, B. J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (c) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (d) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886.

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(16) **General Procedure for the Oxidative C–S Formation**

A sealed tube was charged with isochroman (or benzylic ether; 1 mmol), DTBP (1.5 mmol), thiol (or thiophenol; 1.5 mmol). The reaction mixture was stirred at 120 °C for 6 h. The reaction mixture was then cooled to obtain a brown liquid. The organic solutions could be purified directly by column chromatography on silica gel to give the pure product (hexane–EtOAc, 20:1).

1-[(4-Chlorophenyl)thio]isochromane 3a

Colorless oil; yield: 212 mg (77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.3 Hz, 2 H), 7.40–7.30 (m, 3 H), 7.28–7.21 (m, 2 H), 7.20–7.11 (m, 1 H), 6.49 (s, 1 H), 4.55 (td, *J* = 11.5, 3.3 Hz, 1 H), 4.03 (dd, *J* = 11.3, 6.2 Hz, 1 H), 3.20–3.09 (m, 1 H), 2.72 (dd, *J* = 16.5, 2.4 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 133.56, 132.90, 132.48, 132.27, 131.64, 128.06, 127.89, 126.93, 126.13, 125.16, 85.06, 76.39, 76.14, 75.89, 57.36, 26.75. Anal. Calcd for $C_{15}H_{13}ClOS$: C, 65.09; H, 4.73. Found: C, 64.88; H, 4.64. ESI-MS: *m*/*z* = 276.