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Di-*tert*-butyl Peroxide-Mediated Radical C(sp^2/sp^3)−S Bond Cleavage and Group-Transfer Cyclization

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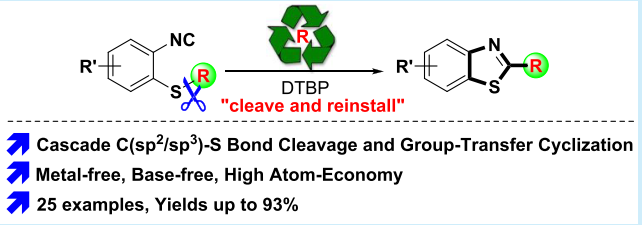
Supporting Information

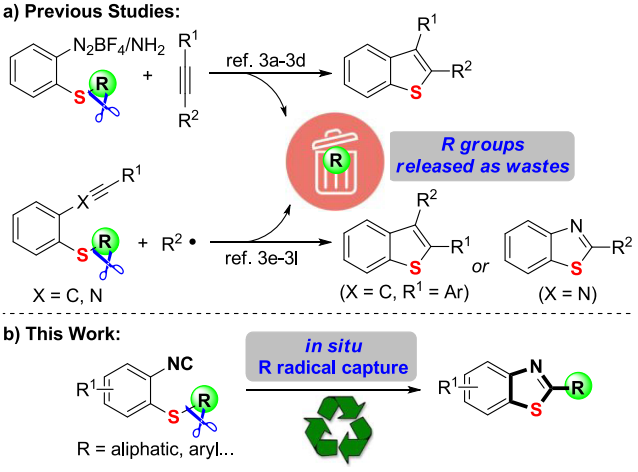
ABSTRACT: A novel strategy of cascade radical C(sp^2/sp^3)−S bond cleavage and group-transfer cyclization is disclosed. Triggered by alkyl radicals, varieties of 2-isocyanoaryl thioethers containing aliphatic, aryl, and heteroaromatic groups can be cleaved and precisely reinstalled to give benzothiazole derivatives. Mechanistic studies reveal that the cascade reaction undertakes an intermolecular pathway, and the inner radical sources (R radicals) exhibit high priority over those of methyl radical origin from di-*tert*-butyl peroxide.



Benzothiophene and benzothiazole derivatives prevalently exist in functional molecules applied in biology, pharmacy, material science, and catalysis.[1] To this end, synthetic endeavors have been extensively explored in building these sulfur-containing five-membered cores in recent decades.[2] Among these strategies, cascade radical cyclizations of thioanisole derivatives are usually more privileged than transition-metal-catalyzed electrophilic/coupling cyclizations because most of these methods feature metal-free, high regioselectivity, mild reaction conditions and easily accessible substrates.[3] For an elegant study, in 2012, the König group revealed the first photocatalytic C(sp^3)−S bond cleavage of *o*-methyl-thioarene-diazonium salts and performed intramolecular cyclization with alkynes to furnish benzothiophene derivatives.[3b] Later on, many achievements were devoted to establishing diverse intramolecular cyclizations of thioethers via inner or outer radical initiated cleavage (Scheme 1a). In 2018, our group reported a radical cyclization of 2-isocyanoarylthio-ethers using a sulfur atom as an imidoyl radical acceptor, where varieties of radical initiators and R groups were systematically investigated.[3h]

However, for all of these previously listed studies, the R groups (methyl, ethyl, benzyl, and phenyl) were released as waste no matter what they were transformed into while being quenched, with only one exception. In 2019, Wu and coworkers developed a radical relay strategy using sodium metabisulfite to trap the cleaved methyl radical and thus generate a methylsulfonyl radical, which subsequently underwent cyclization with alkynes and thioanisole to afford 3-methylsulfonylbenzothiophenes.[3j] It should be noted that sodium methylsulfinate was applied as a key radical initiator, and the methyl radical from di-*tert*-butyl peroxide (DTBP) was evidenced to be much less effective. Moreover, this strategy succeeded only with the methyl group; while being expanded to ethyl group, just 30% yield of the desired product was isolated.

Scheme 1. (a) Reported Radical Cascade Reactions of Thioether Derivatives and (b) This Work



In view of green and sustainable chemistry and inspired by the strategy of group-transfer radical cyclization,[4] we conceived that an intramolecular group transfer of the R group will provide a highly atom-economical strategy in this chemistry, although challenges lie in at least two aspects: (1) It is quite clear that a radical initiator, either internal or external, is necessary, but it will definitely compete with the R group-transfer pathway. (2) Although aliphatic groups, in particular, for methyl, have been intensively studied, the cleavage of bulky

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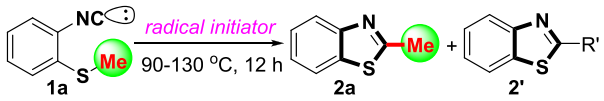
alkyl or aryl R groups other than benzyl and phenyl are never reported owing to their negative effects on the radical cleavage.[3e,i,k,l] As the ongoing work of our efforts on heteroatom chemistry and radical cascade reactions,[2g,3h,5] herein we wish to disclose an unprecedented strategy of cascade C(sp^2/sp^3)−S bond cleavage and group-transfer cyclization to access benzothiazole derivatives.

The study commenced with (2-isocyanophenyl)(methyl) sulfane (**1a**) at 110 °C under a nitrogen atmosphere to define the optimal reaction conditions, as summarized in Table 1.

Table 1. Optimization of the Reaction Conditions[a]



entry	radical precursors	temperature (°C)	solvent	yield (**2a**/**2′** (%))[b]
1	DTBP	110	MeCN	33/−
2	DTBP	110	DMF	N.R./−
3	DTBP	110	DMSO	N.R./−
4	DTBP	110	CH_3NO_2	trace/−
5	DTBP	110	toluene	43/−
6	DTBP	110	PhF	78/−
7	DTBP	110	PhCl	61/−
8	DTBP	110	$PhCF_3$	75/−
9	TBHP	110	PhF	52/−
10	DCP	110	PhF	60/−
11	TBPB	110	PhF	32/−
12	AIBN	110	PhF	19/18[c]
13	LPO	110	PhF	26/17[d]
14	BPO	110	PhF	<10
15	$K_2S_2O_8$	110	PhF	N.R.
16	30% H_2O_2	110	PhF	N.R.
17	DTBP	90	PhF	trace
18	**DTBP**	**130**	**PhF**	**93**
19[e]	DTBP	130	PhF	23
20[f]	DTBP	130	PhF	41
21		110	PhF	N.R.

[a]Reaction conditions: **1a** (0.3 mmol), radical precursor (3.0 equiv., 0.90 mmol), solvent (2.0 mL) at 110 °C under N_2 for 12 h. N.R. = no reaction. [b]Isolated yields. [c]R′ = isobutyronitrile. [d]R′ = undecyl. [e]DTBP (0.5 equiv). [f]DTBP (1.0 equiv).

Because DTBP has been reported as a privileged radical precursor that could release a *t*-BuO radical[6] or a Me radical,[7] we directly used DTBP in this cascade reaction as a radical initiator. To our delight, a group-transfer product, 2-methylbenzothiazole (**2a**), was produced in 33% yield after 12 h using acetonitrile as the solvent (entry 1). We first screened a series of solvents on the efficiency of this reaction and found that reactions in polar aprotic solvents, such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and CH_3NO_2, turned out to be sluggish (entries 2−4). On the contrary, nonpolar solvents of toluene, fluorobenzene, chlorobenzene, and benzotrifluoride were helpful to the reaction efficiency, among which PhF was found to be the best choice to give **2a** in a moderate yield of 78% (entries 5−8).

Next, the appropriate usage of radical initiators was more crucial to the transformation. As listed in entries 9−13, radical precursors, such as *tert*-butyl hydroperoxide (TBHP), dicumyl peroxide (DCP), *tert*-butyl peroxybenzoate (TBPB), azodiisobutyronitrile (AIBN), and lauroyl peroxide (LPO), were able to render the group-transfer process, albeit exhibiting less efficiency than DTBP. We note that when it came to AIBN and LPO, emulative byproducts **2′** appeared (entries 12, 13), except for the production of **2a**. The competitive pathway could be ascribed to the participation of alkyl radicals (R′ = isobutyronitrile or undecyl) other than methyl, but from another point of view, the production of **2a** under the current conditions indicated a success methyl transfer. In sharp contrast, no alkyl radical precursors, including benzoyl peroxide (BPO), potassium persulfate, and hydrogen peroxide, could trigger the reactions, leaving most of the starting materials untouched. In addition, the cascade process was found to be quite sensitive to the reaction temperature and the dosage of DTBP (entries 17−21). Meanwhile, the combination of 3 equiv of DTBP and a temperature of 130 °C afforded the final product in 93% yield (entry 18). It is noteworthy that side reactions of hydrogen-atom abstraction or radical couplings should lead to the dramatic concentration decrease in the methyl radical, and thus an excess amount of DTBP is necessary to render high reaction efficiency. Some metal catalysts were screened with a catalytic amount of DTBP. Nevertheless, the addition of metal catalysts, including silver, copper, iron, cobalt, nickel, and magnesium complexes, dramatically diminished the reaction efficiency. (See the details in the SI.) The above observations collectively suggested that the factors of the alkyl radical initiator, the solvent, and the reaction temperature play vital roles in achieving an efficient C(sp^3)−S bond cleavage and group-transfer process.

Given that it is well known that DTBP produces a methyl radical upon heating, the methyl source of 2-methylbenzothiazole (**2a**) might be confusing. It was worth figuring it out in this stage because this would offer a preliminary understanding of the reaction mechanism, thus providing guidelines on the expansion of the substrate scope. Under the optimized conditions, deuterated-**1a** (**1a-D$_3$**) preceded the cascade reaction to furnish mixed products of deuterated-**2a** (**2a-D$_3$**) and **2a** in a ratio of 3.4:1 (see the details in the Supporting Information), indicating that the major methyl group comes from the substrate itself instead of DTBP. Moreover, as shown in Figure 1, the CD_3 and CH_3 radicals independently originated from **1a-D$_3$**, and DTBP, as well as benzothiazole fragments, could be fully trapped by *N*,*N*-diallyl-4-methylbenzenesulfonamide. The HR−MS analysis of the reaction mixtures clearly showed that the CD_3 radical dominates the reaction pathway, which also supports the priority of group-transfer cyclization triggered by the CD_3 radical over that of the methyl radical. In this sense, the feasibility of other thioethers bearing alkyl or aryl substitutions would be predictable.

Afterward, the aromatic substitution of isocyanides and the scope of thioethers were examined, and the results are summarized in Scheme 2. A series of isocyanides that bear electron-rich (5-methyl, 5-methoxy) and electron-deficient (5-methyl-sulfonyl) aromatic moieties reacted well, initiated by DTBP to afford 2,6-disubstituted benzothiazoles (**2b**, **2c**, **2g**). Halide substituents such as F, Cl, and Br on the four- or five-positions of the phenyl rings performed smoothly, furnishing the corresponding products in moderate to good yield (**2d−f**, **2h−i**, 57−80%).

To probe the group-transfer capability of R groups on the sulfur atom, a variety of 2-isocyanoaryl thioethers containing

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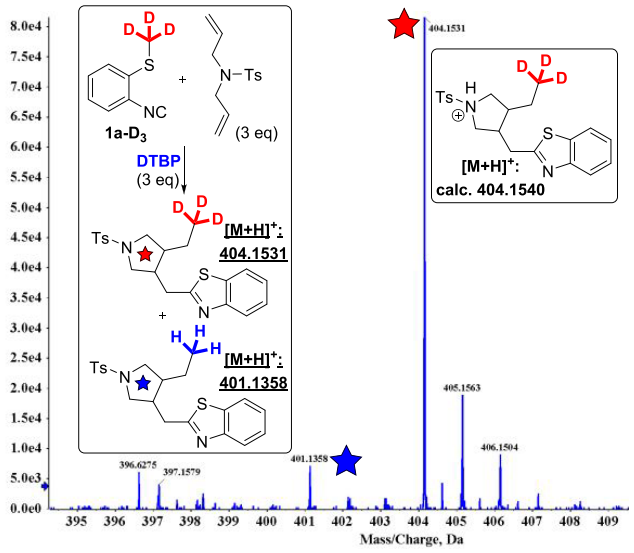
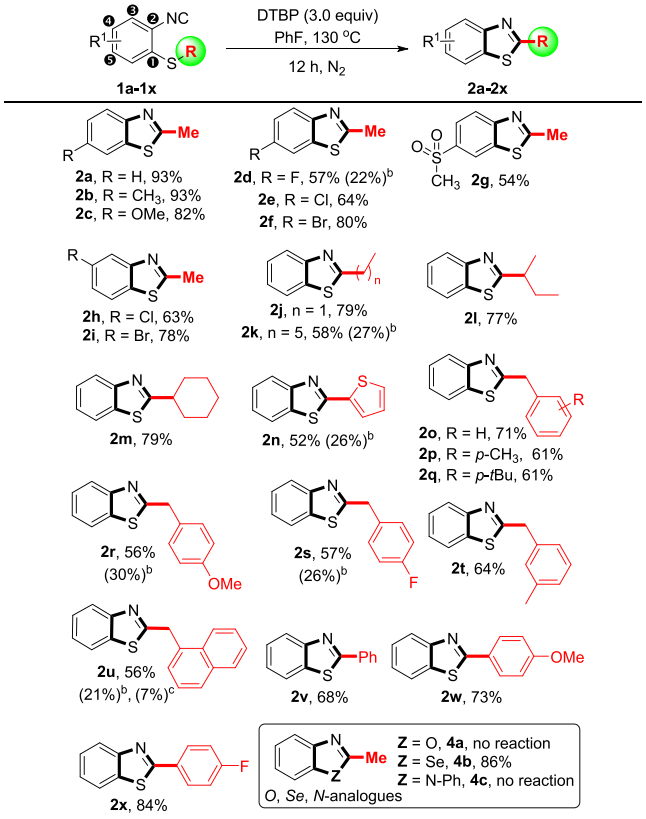


Figure 1. Trapping of CD_3 and CH_3 radicals.

Scheme 2. Scope of the 2-Isocyanoaryl Thioethers[a]

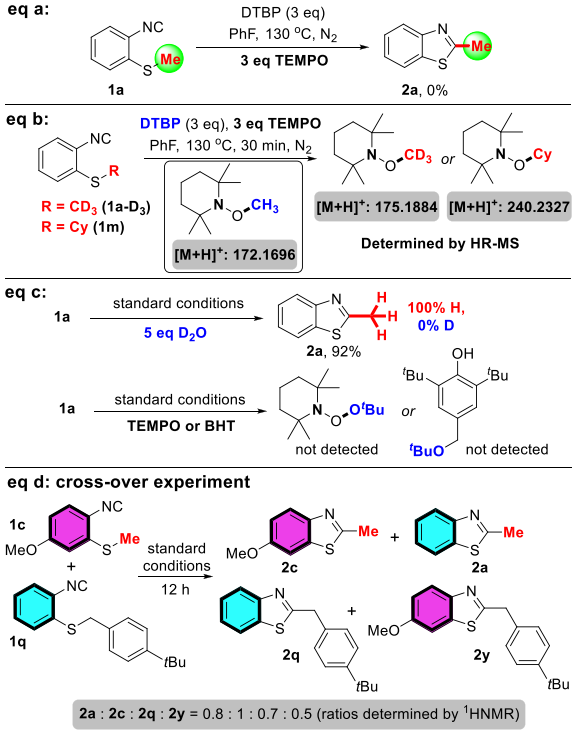


[a]Reaction conditions: **1a** (0.25 mmol), DTBP (3.0 equiv), 2 mL of PhF, 130 °C, 12 h. [b]Recovery percentage of the starting materials. [c]Yield of 1,2-di(naphthalen-1-yl)ethane (**3**).

alkyl, benzyl, and aryl groups were synthesized and applied for this transformation. All of them were efficiently cleaved and cyclized to give the desired products **2j**–**x** in moderate to good yield, regardless of their electronic properties. In general, alkyl -substituted ones (**1j**, **1l**, and **1m**) underwent the C(sp^3)–S bond cleavage rather smoothly to deliver 2-alkylbenzothiazoles in a good yield of 77–79%, albeit with an exception for hexyl (**2k**, 58% yield). This phenomenon might be a result of the blocking effect of the long flexible chain. Interestingly, the substrate with the 2-thienyl group was compatible with this protocol and delivered 2-(thiophen-2-yl)benzo[*d*]thiazole (**2n**) in 52% yield. To the best of our knowledge, this might be the first case of radical heteroaromatic C(sp^2)–S bond cleavage. Substituted benzyl thioethers were also reliable substrates yielding **2o**–**t** in range of 57–71%, although the efficacies were impaired to some extent. Notice that the naphthalen-1-ylmethyl group was precisely cleaved and reinstalled to produce **2u** in an acceptable yield, and in this case, homocoupling of the 1-naphthyl-methylene radical to 1,2-di(naphthalen-1-yl)ethane (**3**) was isolated in 7% yield as a major byproduct. Bulky aromatic substitutions have been recognized to dramatically diminish the reaction efficiency;[3e,i,k,l,8] however, we were pleased to find that phenyl and other ones bearing methoxy or fluoro groups (**2v**–**x**) exhibit competitive yields with alkyl substitutions. Analogues of O, Se, and N were also tested, yet only the selenium derivative was viable to this strategy, with 86% yield of **4b** obtained.

To gain more insights into the reaction mechanism, we performed several control experiments (Scheme 3). A radical

Scheme 3. Mechanistic Studies



inhibition experiment with 3 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) entirely stopped the reaction (eq a), therefore suggesting a radical pathway. Besides, upon utilizing deuterated **1a** and **1m**, the CD_3, cyclohexyl, and CH_3 radicals could be captured by TEMPO monitored by HR–MS in the early stage (eq b), and the methyl derivative was found to be a major product owing to dealing with excess DTBP. We note that the *t*-BuO radical has been explained to initiate certain reactions, most often in the hydrogen abstraction step.[6] Nevertheless, the H/D exchange and radical trapping experiments ruled out the probable participation of the *t*-BuO radical in subsequent steps (eq c). Crossover experiments of **1c** and

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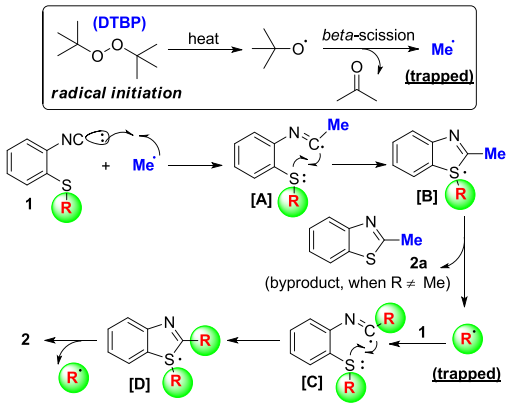
1q under the standard conditions were monitored using ^{1}H NMR. The spectrum displayed four components, assigned to **2a**, **2c**, **2q**, and **2y**, respectively, in ratios of 0.8:1:0.7:0.5 (eq d; see the details in the SI), which strongly indicated that the reaction involves an intermolecular process. More interestingly, the ratios provide a regularity in which once the benzothiazole moiety is installed with an electron-rich group (−OMe), the cleavage and transfer efficiency of the bulky benzyl group will be significantly diminished (**2c** vs **2y**).

On the basis of our observations and literature reports,[3h,7,9] a plausible mechanism is outlined in Scheme 4. Initially, the

Scheme 4. Proposed Mechanism



homolytic dissociation of DTBP upon heating affords a *tert*-butyl oxide radical, then undergoes *β*-scission to deliver a methyl radical, spontaneously releasing acetone. The resulting methyl radical attacks the terminal carbon of isocyano moiety (**1**) to give an imidoyl radical [A], and this intermediate cyclizes with the −SR moiety to produce 2-methylbenzothiazole (**2a**) along with the release of R radical. When the R group is not equal to methyl, **2a** will be deemed as a byproduct (usually in a yield <5%), which frequently accompanies other final products. Notably, once the R radical is generated, it will take over the reaction pathway to repeat a similar process through intermediates [C] and [D] to finalize the final product (**2**).

In conclusion, we have disclosed a novel strategy for di-*tert*-butyl peroxide-mediated radical C(sp^2/sp^3)−S bond cleavage and group-transfer cyclization. This strategy achieves the cascade reaction of 2-isocyanoarylthioethers, with varieties of aliphatic, aryl, and heteroaromatic groups being precisely cleaved and reinstalled, rendering two-substituted benzothiazoles in moderate to excellent yield. Mechanistic studies indicate that the reactions follow an intermolecular pathway, and the intramolecular radical sources (R groups) react with high priority over those of methyl radical origin from DTBP. The further application of this strategy to other transformations is currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02837.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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