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TBHP-mediated oxidative thiolation of an sp^3 C–H bond adjacent to a nitrogen atom in an amide†

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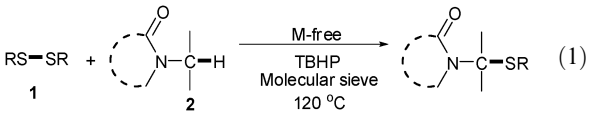
The first example of molecular sieve-promoted TBHP-mediated direct oxidative thiolation of an sp^3 C–H bond adjacent to a nitrogen atom with disulfides under metal-free conditions, which allows for preparation of numerous S,N-containing compounds, is presented. Moreover, diverse benzothiazoles and a fipronil analog can be synthesized through this strategy.

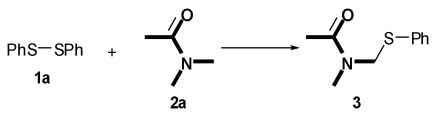
The development of catalytic reactions using an sp^3 C–H bond cleavage (activation) strategy is a challenging and powerful technology for preparing diverse compounds from simpler starting materials.[1–9] Recently, considerable efforts were devoted to this field; particularly to the construction of numerous C–C bonds *via* metal-catalyzed oxidative functionalization of an sp^3 C–H bond adjacent to a heteroatom (often nitrogen or oxygen).[1–4] This strategy allows introduction of diverse functional groups, including indole, benzofuran, alkyne, alkene, cyano, enol ether and pre-functionalized sp^3 carbon, to the carbon adjacent to a nitrogen atom[3,5] or an oxygen atom.[4,6] Despite a significant achievement in the C–C bond formation by the sp^3 C–H bond oxidative functionalization process, the carbon–heteroatom bond formation using a similar strategy[8] receives less attention.[6c,9] Moreover, in these transformations many required one or two metal catalysts,[1–8] and rare focused on metal-free oxidative functionalization of an sp^3 C–H bond.[4b,9] To the best of our knowledge, there is no example on metal-free functionalization of an sp^3 C–H bond adjacent to a heteroatom for the carbon–heteroatom bond construction.

Sulfur-containing compounds are valuable synthetic intermediates as well as important structural units in many naturally occurring and bioactive compounds.[10] In recent years, formation of metal-catalyzed intermolecular or intramolecular C–S bonds through an sp^2 C–H activation has become an alternative and intriguing strategy to sulfides.[11] However, the cleavage of an sp^3 C–H bond leading to the C–S bond formation is unexplored. We report here on the first realization of the C–S bond-formation by TBHP (*tert*-butyl hydroperoxide)-mediated oxidative thiolation of an sp^3 C–H bond adjacent to a nitrogen atom in an amide without the aid of metals (eqn (1)).



Our study begins with the reaction of diphenyldisulfide (**1a**) with DMA (*N*,*N*-dimethylacetamide) (**2a**) and oxidant under heating conditions (Table 1).[12] While no reaction was observed using a DDQ oxidizing reagent (entry 1), the reaction in the presence of TBHP afforded the target product **3** in 77% yield (entry 2). Screening revealed that the reaction temperature affected the reaction: 78% yield at 150 °C (entry 3) and 41% yield at 100 °C (entry 4). We found that 1.2 mmol TBHP gave identical results to those of 0.8 mmol TBHP (entry 5), but 0.4 mmol TBHP lowered the yield slightly (entry 6). Gratifyingly, molecular sieves could improve the reaction: the yield of **3** was enhanced to 86% in 100 mg molecular sieves (entry 7). Among the different amounts of DMF examined, it turned out that good

Table 1 Screening optimal conditions[a]



Entry	Oxidant (mmol)	Additive (mg)	T/°C	Isolated yield (%)
1	DDQ (0.8)	—	120	0
2	TBHP (0.8)	—	120	77
3	TBHP (0.8)	—	150	78
4	TBHP (0.8)	—	100	41
5	TBHP (1.2)	—	120	78
6	TBHP (0.4)	—	120	72
7	TBHP (0.8)	4 Å MS (100)	120	86
8[b]	TBHP (0.8)	4 Å MS (100)	120	71
9[c]	TBHP (0.8)	4 Å MS (100)	120	87
10[d]	TBHP (0.8)	4 Å MS (100)	120	87
11[e]	TBHP (0.8)	4 Å MS (100)	120	51
12[f]	TBHP (0.8)	—	120	85

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 mL, 21.5 mmol), and oxidant for 12 h. TBHP (70% in water solution). 4 Å MS = 4 Å molecular sieve. [b] **2a** (1 mL, 10.8 mmol). [c] **2a** (3 mL, 31.3 mmol). [d] In the dark. [e] K_2CO_3 (0.8 mmol) was added. [f] K_2CO_3 (0.1 mmol) was added.

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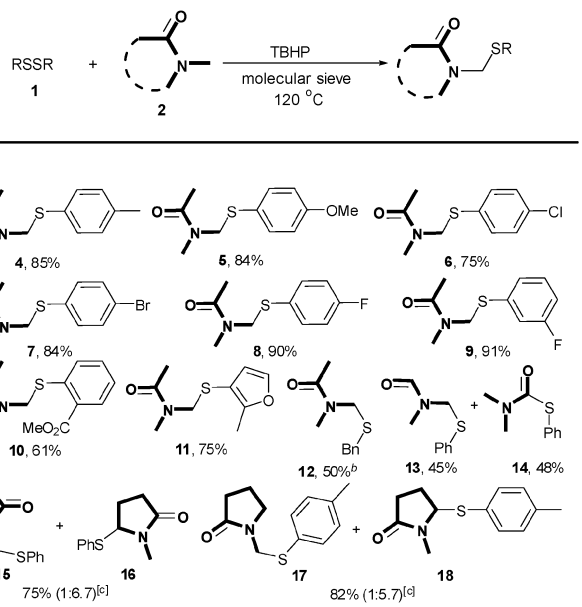
results were obtained in 2 mL or 3 mL DMF (entries 7–9). The reaction was not affected in the dark (entry 10). While 0.8 mmol of K_2CO_3 reduced the yield to 51% (entry 11), satisfactory results were obtained using 0.1 mmol K_2CO_3 without molecular sieves (entry 12). It is noteworthy that no reaction is observed when 5 mol% CuBr or $FeCl_3$ was added.[12] Thus, we deduce that molecular sieves may play the role of a weak base to promote the reaction by adjusting the pH value of reaction solution.

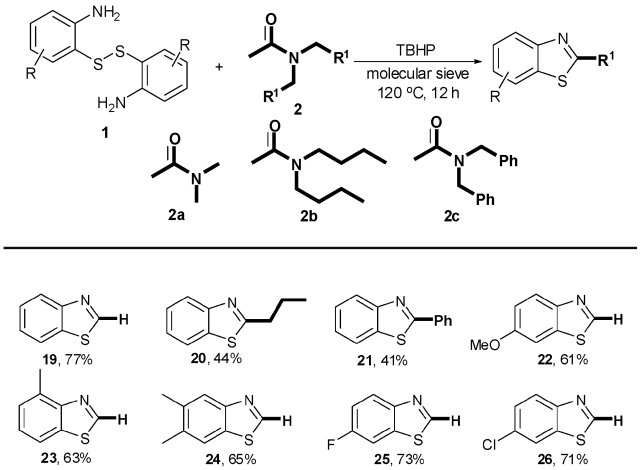
With the optimal reaction conditions in hand, the scope of both disulfides and amides was explored (Table 2). The results demonstrated that diaryl disulfides **1**, bearing either electron-withdrawing or electron-donating groups on the aromatic ring, were perfectly tolerated (products **4–10**). For example, bromo-substituted disulfide smoothly underwent the reaction with DMA (**2a**), TBHP and molecular sieves to afford the corresponding product **7** in 84% yield. Disulfide with an ester group was also suitable, providing product **10** in 61% yield. To our delight, a heteroaryl disulfide displayed high reactivity leading to the target product **11** in 75% yield. We found that product **12** was isolated from an aliphatic disulfide in moderate yield after prolonging the reaction time. To our surprise, DMF (*N*,*N*-dimethylformamide) reacted with diphenyldisulfide (**1a**) to selectively give two products, *N*-methyl-*N*-(phenylthiomethyl)formamide (**13**) and *S*-phenyl dimethylcarbamothioate (**14**), in 45% and 48% yields, respectively. It is noteworthy that the selectivity toward the CH_2 group adjacent to a nitrogen atom in the ring is superior to that toward the *N*-Me group for 1-methylpyrrolidin-2-one (products **15–18**).[3a] For instance, treatment of 1-methylpyrrolidin-2-one with disulfide **1a** and TBHP afforded products **15** and **16** in 75% total yield with the 1 : 6.7 ratio. However, 1-methylpyrrolidine was unsuitable for the reaction.

Table 2 Thiolation of an sp^3 C–H bond adjacent to a nitrogen atom[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (2 mL), TBHP (0.8 mmol, 70% in water solution) and 4 Å molecular sieve (100 mg) at 120 °C for 12 h. [b] For 20 h. [c] The ratio given in parentheses was determined by ^{1}H NMR spectra.

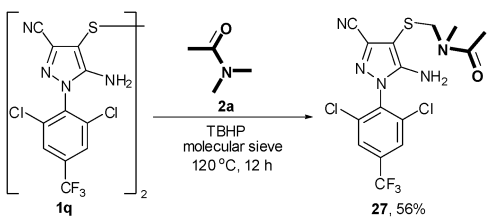
Table 3 TBHP-mediated synthesis of benzothiazoles[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (2 mL), TBHP (0.8 mmol, 70% in water solution) and 4 Å molecular sieve (100 mg) at 120 °C for 12 h.

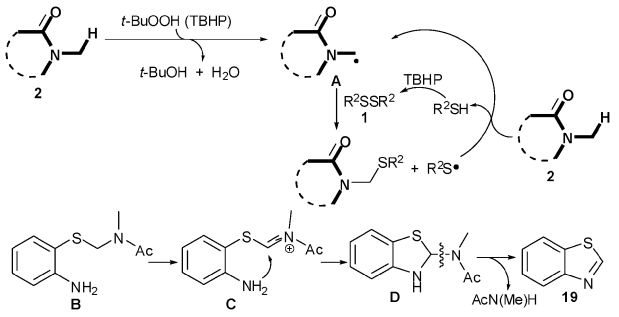
As shown in Table 3, applications of this thiolation reaction in benzothiazoles synthesis were investigated because benzothiazoles are very important compounds for pharmaceuticals and materials industries.[13] The results demonstrated that this thiolation reaction could be used for the synthesis of benzothiazoles through the formation of two bonds: a C–S bond and a C–N bond. We found that three amides **2a–2c** were treated with 2,2′-disulfanediyldianiline, TBHP and molecular sieves smoothly leading to the corresponding 2-substituted benzothiazoles **19–21** in moderate yields. To our delight, the standard conditions were consistent with numerous 2,2′-disulfanediyldianilines with MeO, Me, F, or Cl groups on the aryl ring (products **22–26**).

Significantly, a new fipronil analog **27** was readily prepared by this sp^3 C–H functionalization strategy in good yields (eqn (2)).[14,15] This successful S–S bond cleavage of pyrazole disulfide followed by the sp^3 C–S bond formation would be significant for pesticide and drug design.[16]



(2)

Notably, the reaction of disulfide **1a** with amide **2a** could not take place in the presence of the radical inhibitors, 1,1-diphenylethylene or TEMPO, suggesting that the present reaction proceeds *via* a free radical process.[7] Therefore, a possible mechanism as outlined in Scheme 1 was proposed.[1–9] Initially, the reaction of TBHP with substrate **2** affords intermediate **A**, followed by reaction with R^2SSR^2 **1**, which gives the target product and the $R^2S^\bullet$ free radical intermediate. The $R^2S^\bullet$ free radical intermediate undergoes the reaction with substrate **2** resulting in the target product and RSH. RSH is readily converted to R^2SSR^2 in the presence of TBHP. In the synthesis of benzothiazoles, intermediate **A** reacts with



Scheme 1 Possible mechanism.

2,2′-disulfanediyldianilines to give intermediate **B**, followed by oxidation to afford the iminium ion **C**. Subsequently, intermediate **C** undergoes a nucleophilic attack process to yield intermediate **D**. Finally, cleavage of the C–N bond in intermediate **D** gives the corresponding benzothiazoles.

In summary, we have described the first example of direct oxidative thiolation of an sp^3 C–H bond adjacent to a nitrogen atom under metal-free conditions. This thiolation method is valuable for preparing numerous S,N-containing compounds. It is noteworthy that these S,N-containing compounds with sweet-scented smell will be a good guideline for the new spices discovery.[17] Moreover, diverse benzothiazoles and a fipronil analog can be synthesized through the present TBHP-oxidative thiolation of an sp^3 C–H bond process.[13,14]

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