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# Metal-free sequential dual oxidative amination of C($sp^3$)–H bonds: A direct approach to benzothiadiazine 1,1-dioxide derivatives

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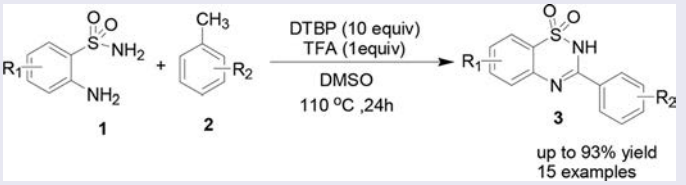
**ABSTRACT**

An efficient and metal-free Di-*tert*-butyl peroxide (DTBP)-promoted dual oxidative amination annulation of 2-amino arylsulfonamide with methylarene has been developed. This protocol provides straightforward access to benzothiadiazine 1,1-dioxide derivatives without using prefunctionalized substrates in good to excellent yields with good functional group tolerance.

**GRAPHICAL ABSTRACT**

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**KEYWORDS**
2-Amino arylsulfonamide; benzothiadiazine 1,1-dioxide; metal free; oxidative amination

## Introduction

Benzothidiazine-1,1-dioxides are a class of important fused heterocyclic scaffolds that exhibit a wide range of biological and pharmacological activities, including diuretic,[1] antihypertensive,[2] KATP channel activators,[3] and anticancer activities.[4] In connection with this, numerous methods have been developed for the synthesis of benzothidiazine-1,1-dioxide ring system. The typical procedures are the reactions of *o*-aminobenzene sulfonamide with either carboxylic acid derivatives under harsh conditions[5] or aldehydes[6] with subsequent oxidation using strong oxidants. An alternative approach to the 1,2,4-benzothiadiazine-1,1-dioxide ring is based on transition metal catalyzed reactions, for example, Yang et al.[7] developed an efficient method for the synthesis of 1,2,4-benzothiadiazine through iron-catalyzed cascade coupling reactions of *o*-bromobenzenesulfonamide with amidine hydrochlorides. Cherepakha et al.[8a] reported a facile approach to 1,2,4-benzothiadiazine-1,1-dioxides through Cu(I)-catalyzed intramolecular cyclization of *o*-bromoarylsulfonylated amidines, in addition, the same

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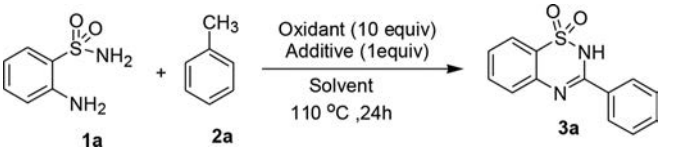
Supplemental data (detailed experimental procedures, characterization data, and copies of $^1$H and $^{13}$C NMR spectra for all of the products **3a–n**) can be accessed on the publisher's website.

author developed a facile approach to hetaryl-annulated 1,2,4-thiadiazine-1,1-dioxides through a reaction of hetaryl-sulfonyl chlorides with amidines under mild noncatalytic conditions.[8b] Recently, benzyl alcohols as acylating reagents were also used for preparation of 1,2,4-benzothiadiazine-1,1-dioxide through ruthenium-catalyzed hydrogen transfer reaction.[9] Very recently, a transition-metal-free, $K_2S_2O_8$-mediated intramolecular oxidative nitrogenation of C($sp^3$)–H in *N*-aryl benzylic amines followed by oxidation at the benzylic center has been developed for the synthesis of benzothidiazine-1,1-dioxide ring.[10] It was worth to mention that all synthetic routes mentioned above depended on the use of functional groups in the substrates.

In recent years, direct oxidative C($sp^2$)–H/N–H coupling reaction has received tremendous attraction, and great progress was made in the synthesis of *N*-heterocycles.[11] However, C($sp^3$)–H, which are naturally more abundant, still face great challenges in C–N bond formation. Recently, the C–N bond formation through C($sp^3$)–H activation has been the focus of recent interest,[12] and various methodologies were developed, including transition metal catalyzed,[13] iodide salt catalyzed,[14] and hypervalent iodine-mediated[15] benzylic C($sp^3$)–H amination. Very recently, Li reported an elegant metal-free approach for the synthesis of *o*-aryl quinazolinones through dual benzylic C($sp^3$)–H bond amination, using *o*-amino benzamides and methylarenes as the accessible starting materials.[16] Encouraged by the above results, and in the continuation of our research in C–H

**Table 1.** Optimization of the reaction conditions.[a]




| Entry | Oxidant[b] | Additive | Solvent | Yield (%)[c] |
|---|---|---|---|---|
| 1 | Benzoquinone | $CF_3COOH$ | DMSO | 0 |
| 2 | $H_2O_2$ | $CF_3COOH$ | DMSO | Trace |
| 3 | BPO | $CF_3COOH$ | DMSO | Trace |
| 4 | TBHP | $CF_3COOH$ | DMSO | 23 |
| 5 | $KIO_3$ | $CF_3COOH$ | DMSO | 26 |
| 6 | DTBP | $CF_3COOH$ | DMSO | 93 |
| 7 | DTBP | TsOH | DMSO | 76 |
| 8 | DTBP | $H_3PO_4$ | DMSO | 65 |
| 9 | DTBP | $KH_2PO_4$ | DMSO | 52 |
| 10 | DTBP | $CH_3COOH$ | DMSO | 85 |
| 11[d] | DTBP | $CF_3COOH$ | DMSO | 37 |
| 12[e] | DTBP | $CF_3COOH$ | DMSO | 51 |
| 13 | DTBP | $CF_3COOH$ | Toluene | 15 |
| 14 | DTBP | $CF_3COOH$ | $CH_3CN$ | 19 |
| 15 | DTBP | $CF_3COOH$ | 1,4-Dioxane | 17 |
| 16 | DTBP | $CF_3COOH$ | $H_2O$ | Trace |
| 17[f] | DTBP | $CF_3COOH$ | DMSO | 56 |
| 18[g] | DTBP | $CF_3COOH$ | DMSO | 78 |
| 19 | DTBP | \ | DMSO | 32 |

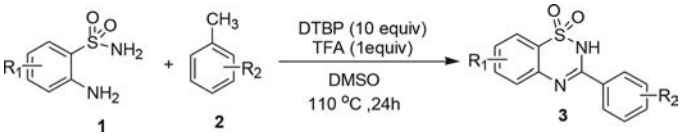
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (8 mmol), oxidant (2 mmol), additive (0.2 mmol), DMSO (1 mL), 110 °C, 24 h.
[b]$H_2O_2$: 30% $H_2O_2$ in water, TBHP: 70% *t*-BuOOH in water, BPO: $(PhCOO)_2$, TBPB: PhCOO*t*-Bu.
[c]Isolated yield.
[d]5 equiv. of DTBP relative to **1a**.
[e]2 equiv. of $CF_3COOH$ relative to **1a**.
[f]30 equiv. of toluene relative to **1a**.
[g]50 equiv. of toluene relative to **1a**.

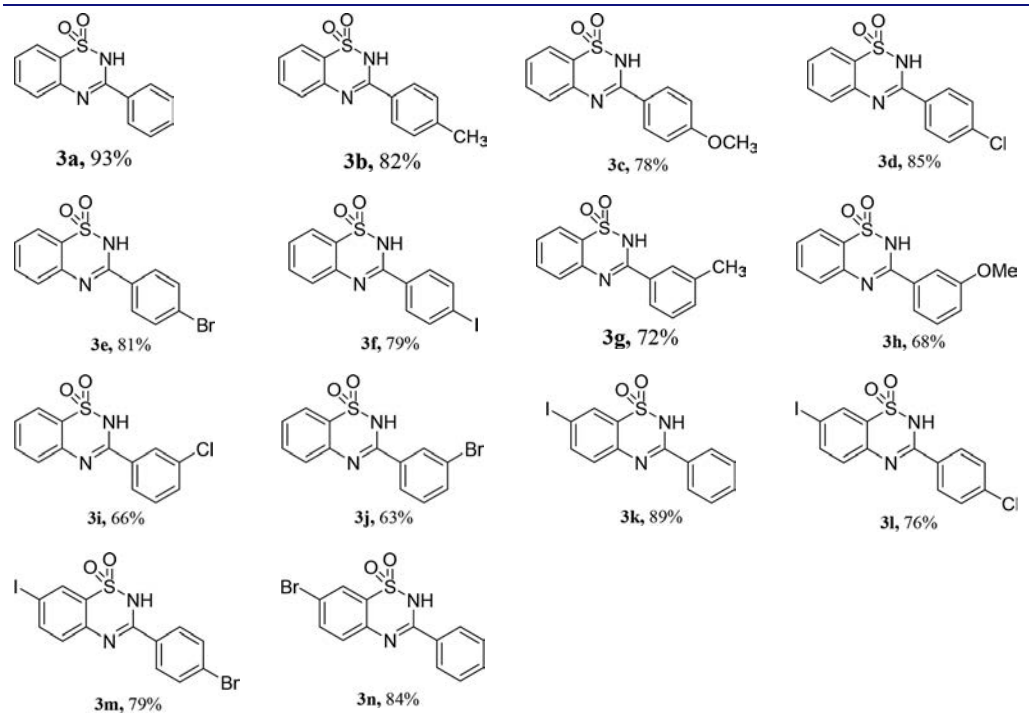
activation,[17] we envisaged whether *o*-aminobenzene sulfonamide and methylarenes were used as substrates for the synthesis of 1,2,4-benzothiadiazine-1,1-dioxides. To certify our purpose, herein, we would like to report our recent efforts toward the synthesis of benzothiadiazine-1,1-dioxide derivatives through metal-free sequential dual oxidative amination of C($sp^3$)–H bonds.

## Results and discussion

To verify our hypothesis, our study began with a model reaction of *o*-aminobenzene sulfonamide (**1a**), 40 equiv. of toluene **2a** and 1 equiv. of $CF_3COOH$ as the additive in the presence of 10 equiv. of various oxidants (Table 1). We first examined benzoquinone as oxidant; in DMSO at 110 °C for 24 h, none of the desired **3a** was detected (Table 1, entry 1). When using $H_2O_2$ and BPO: $(PhCOO)_2$, only trace amount of product **3a** was obtained (Table 1, entries 2, 3). Other oxidants such as TBHP and $KIO_3$ afforded the desired product in moderate yield (Table 1, entries 4, 5). To our delight, **3a** was obtained in excellent yield when using di-*tert*-butyl peroxide (DTBP) as an oxidant (93%, Table 1,

**Table 2.** Substrate scope for the reaction of **1** with methylarenes **2**.[a,b]




[a]Reaction conditions: **1** (0.2 mmol), **2** (8 mmol), DTBP (2 mmol), $CH_3COOH$ (0.2 mmol), DMSO (1 mL), 110 °C, 24 h.
[b]Isolated yield.

entry 6). In addition, various additives were also examined using DTBP as oxidant; we found that organic acid such as *p*-toluenesulfonic acid (TsOH) as additive can afford 76% yield (Table 1, entry 7) and inorganic acids such as $H_3PO_4$ and $NaH_2PO_4$ offer the desired product in 65 and 52%, respectively (Table 1, entry 8, 9). Significantly, $CH_3COOH$ was also able to work in this transformation, affording the desired product in 85% yield (Table 1, entry 10). Furthermore, the amount of DTBP was also optimized, reducing the amount of DTBP to 5 equiv. obviously decreased the yield of **3a** (Table 1, entry 11). Interestingly, only 51% yield was obtained when the amount of $CF_3COOH$ was increased to 2 equiv. (Table 1, entry 12). Various solvents were also examined, and DMSO was turned out to be the best choice still (Table 1, entries 13–16). The yields dropped after varying the amount of toluene **2a** (Table 1, entries 17, 18). Finally, we found that only 32% yield of **3a** was obtained in the absence of $CF_3COOH$, (Table 1, entry 19). Therefore, the optimal conditions are those described in entry 6.

Under the optimal reaction conditions, we investigated the substrate scope of intermolecular annulation of **1** with methylarenes **2**. First, we performed the generality of this methodology with different methylarenes (Table 2). Most of the toluenes **2** with electron-donating and -withdrawing substituents were found to be suitable reaction partners with **1** to provide the corresponding benzothidiazine-1,1-dioxide derivatives in good to excellent yields. For example, *p*-methyl- and *p*-methoxy-substituted toluenes were successfully converted and gave the corresponding products in 82, 78% yields, respectively (**3b, 3c**). Halogen-substituted toluenes such as *p*-chloro, *p*-bromo, and *p*-iodo can be reacted as well the desired products were isolated in 73–85% yields (**3d–f**). Furthermore, *m*-substituted methylarenes **2** can also generate the corresponding products in good yields. For example, *m*-methyl, *m*-methoxyl, *m*-chloro, and *m*-bromo gave the corresponding products **3g–j** in 63–72% yields. Remarkably, halogen groups substituted at the aromatic ring of **1**, such as bromo and even iodo, were all well tolerated and afforded the desired products in high to excellent yields (**3k–n**), which provided the possibility for further functionalization. However the steric hindrance played a key role in the present reaction, an attempt to use *o*-substituted methylarenes **2** failed to afford the desired products.

## Conclusion

In summary, we have developed an efficient and practical methodology for the synthesis of *o*-aryl benzothidiazine-1,1-dioxides derivatives. The present protocol is based on a metal-free sequential oxidative animation of benzylic C($sp^3$)–H bonds in the present of DTBP/TFA, using 2-aminobenzene sulfonamide and methylarenes as the accessible starting materials, this novel protocol shows some distinguished characteristics, such as the lack of any expensive transition metals, excellent functional group tolerance, and a broad substrate scope. Further applications of the oxidative C–H aminations for the synthesis of other heterocycles are going on in our laboratory.

## Experimental

All reactions were performed in air. Chemicals were purchased from Aldrich, Acros, or Alfa Asar, and, unless otherwise noted, were used without further purification. Flash chromatography was performed on silica gel (silica gel, 200–300 mesh). $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker 400 MHz and Bruker 100 MHz spectrometers

with DMSO as the solvent. High-resolution mass spectral data were recorded on Bruker APEX IV Fourier transform ion cyclotron resonance mass spectrometer using ESI. **1b–c** was prepared according to the literature.[18]

## Typical experimental procedure

A flask equipped a magnetic stirring bar was charged with *o*-amino arylsulfonamide **1** (0.2 mmol), methylarenes **2** (8 mmol), DTBP (2 mmol), and DMSO (1 mL). The reaction mixture was stirred under a nitrogen atmosphere at 110 °C for 24 h. The reaction mixture was cooled to room temperature; the reaction mixture was extracted with diethyl ether (5 × 3 mL). The combined extracts were washed with brine and dried over $MgSO_4$, and the crude product was purified by flash column chromatography on silica gel with petroleum ether/EtOAc as the eluent to give the desired product **3**.

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