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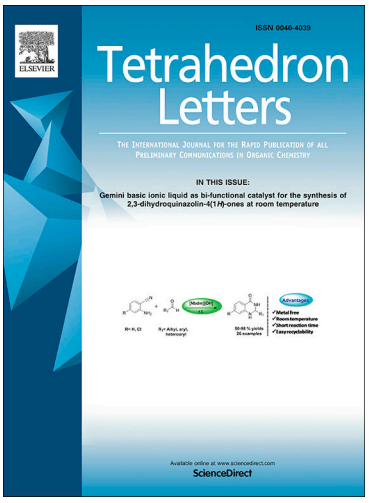

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NCS/TBHP promoted C2 Arylation of Benzothiazoles with Aldehydes in DMSO

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ABSTRACT

A *N*-chlorosuccinimide catalyzed oxidative synthesis of 2-aryl benzothiazole from benzothiazoles and aryl aldehydes using *tert*-butyl peroxybenzoate as an oxidant in dimethyl sulfoxide (DMSO) has been developed in moderate to good yields. Solvent DMSO as a strong Lewis base plays an efficient role in the reaction. Various substrates were tolerated under optimized conditions affording the arylated products in 12–94% yields for 28 examples. Additionally, acylated benzothiazoles were produced with 4 examples.

Keywords:
Benzothiazoles
Aldehydes
Arylation
NCS/TBHP

Introduction

2-Aryl benzothiazoles have been well known with various pharmaceutical applications, such as benzothiazole amphiphile (BAM)[1] and benzazole scaffold (ThT, [^{3}H]PIB, BFC)[2] related to the Alzheimer's disease, chloronitrobenzamide (CNB) for Human African Trypanosomiasis (HAT) antiparasitics,[3] 2-(3,4-Dimethoxyphenyl)-5-fluorobenzothiazole (GW 610) possessing antitumor activity[4] (**Fig. 1**)

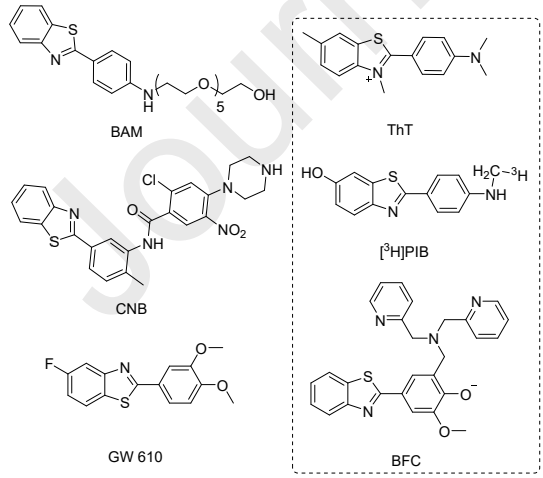
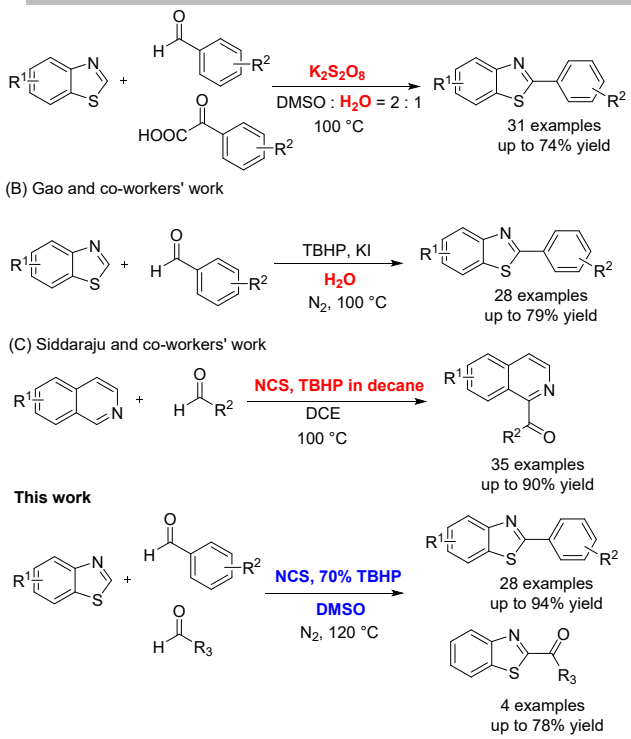


Fig. 1. Pharmaceutical applications of 2-aryl benzothiazole derivatives.

Therefore, development of efficient synthetic strategies for 2-aryl benzothiazoles has received much attention. Traditional methods for their syntheses mostly depend on condensation of 2-aminothiophenols,[5-6] 2-haloanilides,[7] 2-halonitroarene,[8] thiophenols,[9] and intramolecular cyclization of thiobenzanilides,[10] which are used as precursors to synthesize 2-substituted benzothiazoles. Besides, transition-metal catalyzed arylation of benzothiazole with aryl halides,[11] aryl boronic acids,[12] organosilanes,[13] sodium sulfinats,[14] aldehydes,[15] benzylic alcohols,[15d] phenylacetic acids[16] are also effective routes for their construction. However, these methods need prefunctionalized reactants which are costly and not easily available,[17] and complete removal of trace amounts of the residual heavy metals from the desired products remains costly and challenging.[18] Alternatively, 2-aryl benzothiazoles can also be developed through multi-component oxidative annulation including various sulfur source, such as elemental sulfur[19] and NH_4SCN.[20] Therefore, it is of great importance to develop efficient methods to construct 2-aryl benzothiazoles from simple starting materials under transition-metal free condition. In 2012, Tan and co-workers reported a $K_2S_2O_8$-catalyzed arylation of benzothiazoles with aryl aldehydes or glyoxylic acids, which are known to form aldehydes at a relative elevated temperature (**Scheme 1**A).[21] It has been reported that the peroxydisulfate ion ($S_2O_8^{2-}$) is the most powerful oxidant among other peroxygen families of compounds.[22] Thus, the strong oxidant $K_2S_2O_8$ seriously limit the utility of such method in organic synthesis requiring selectivity. Two year later, Cui and co-workers published a KI-catalyzed arylation of benzothiazoles with aldehydes in H_2O (**Scheme 1**B).[17] Interestingly, H_2O is essential in both works mentioned above and the yields decreased dramatically while H_2O was removed (Tan's work) or the organic solvent such as acetonitrile (MeCN) or dimethyl sulfoxide (DMSO) was added (Cui's work). As Cui reported, the homogeneous solution was not suitable for this method.[17] However, a lot of works have been reported that DMSO was an optimized solvent for synthesis of 2-aryl benzothiazoles initiated not only by organic catalyst[9] but also by inorganic catalyst,[13] even mediated by a very similar catalyst

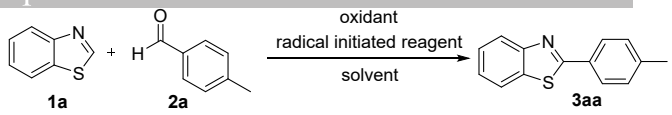


Scheme 1. Reactions between heteroarenes and aldehydes.

system.[19a] Accordingly, we envisioned that MeCN or DMSO as aprotic solvents might play significant roles in the reaction. In addition, *N*-chlorosuccinimide (NCS) was a useful radical initiator that has been used in several organic synthetic pre-activation processes.[23] Among these methods, Siddaraju and Prabhu described that NCS could promote *tert*-butyl peroxybenzoate (TBHP) to form a hydroxyl radical and a *tert*-butoxyl radical, which abstracts the hydrogen from the benzaldehyde to form an acyl radical followed by synthesis of acylated heteroarenes (**Scheme 2C**).[23] Inspired by this work, we envisioned that NCS may also promote the oxidative coupling of benzothiazoles with benzaldehydes in the presence of TBHP to produce 2-aryl benzothiazoles *via* a similar initial radical step. Herein, we wish to report our study in detail.

Results and discussion

We commenced our investigation by choosing benzothiazole (**1a**) with 4-methylbenzaldehyde (**2a**) as model substrates mediated by 5.5 M TBHP solution in decane and NCS in DMSO at 120 °C for 6.5 h (**Table 1**). To our delight, the arylated benzothiazoles **3aa** was obtained in 33% yield. Next, we screened various solvents. When another polar aprotic solvent MeCN was tested as the solvent, the desired product was observed in 14% yield (**Table 1**, entry 2). However, the target product was not obtained when polar protic solvent H_2O as the solvent (**Table 1**, entry 3). Besides, the reaction using non-polar aprotic solvent *N,N*-dimethylformamide (DCE) also provided product in 19% yield simultaneously (**Table 1**, Entry 4). These results show that protic solvent inhibited the reaction, on the contrary, aprotic solvents could promote the reaction. Among them, DMSO as one of the aprotic solvents was superior as we expected (**Table 1**, entry 1). Thus, we speculated that DMSO as a strong Lewis base plays an efficient role in the reaction,[24] for example, there might be hydrogen bonds between substrates and DMSO and that could be beneficial to the H-atom-transfer (HAT) in the reaction. In addition, other oxidants, such as DTBP and H_2O_2 aqueous solution, were useless under the condition (**Table 1**, entries 5 and 6), and the case with NBS did not afford any target product (**Table 1**, entry 7). Also, we changed the amount of oxidant and additive, but poorer yields were obtained in all these cases (**Table 1**, entries 9–11). Furthermore, the yield declined with different degree when the reaction temperature was decreased to 110 °C or increased to 140 °C (**Table 1**, entries 12–13). And a reasonable increase in the yield of the product **3a** was observed when the reaction time was increased from 6.5 h to 12 h (**Table 1**, entry 14). Further investigation suggested that the atmosphere was very important for this reaction. Performing the reaction under N_2 atmosphere resulted in 11% further enhancement in the yield (**Table 1**, entry 15). And no product was observed in the absence of TBHP (**Table 1**, entry 16). Thus, the reaction was generally completed within 12 h at 120 °C under N_2 atmosphere using 5.5 M TBHP solution in decane (2 eq.) and NCS (30 mol %) (**Table 1**, entry 15). Besides, to demonstrate the scalability of the method, we performed a gram-scale reaction of **1a** (15 mmol) with **2a** (10 mmol) (**Table 1**, entry 17). Gratifyingly, the efficiency of this method was not obviously affected, and the target product **3aa** was obtained in 51% yield.

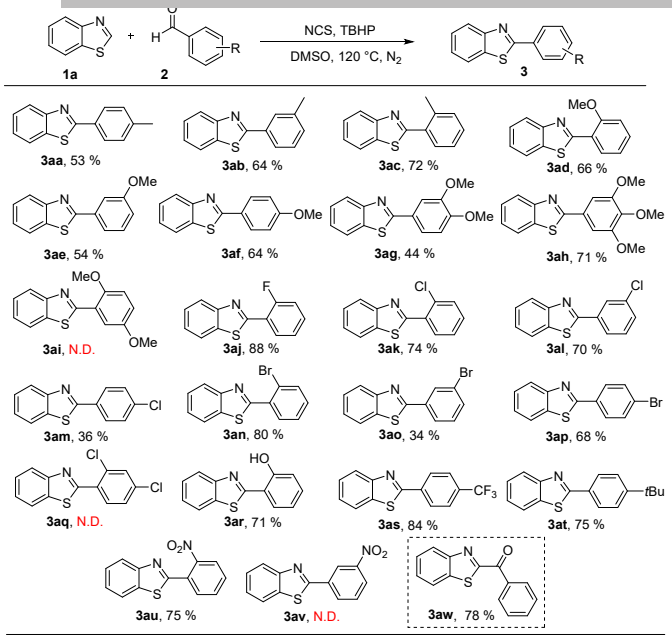


Entry	Oxidant (eq.)	Additive (mol %)	Solvent (mL)	Yield (%)[b]
1	TBHP (2)	NCS (30)	DMSO	33
2	TBHP (2)	NCS (30)	MeCN	14
3	TBHP (2)	NCS (30)	H_2O	N.D.
4	TBHP (2)	NCS (30)	DCE	19
5	DTBP (2)	NCS (30)	DMSO	N.D.
6	aq H_2O_2 (2)	NCS (30)	DMSO	N.D.
7	TBHP (2)	NBS (30)	DMSO	N.D.
8	TBHP (1)	NCS (30)	DMSO	12
9	TBHP (3)	NCS (30)	DMSO	27
10	TBHP (2)	NCS (20)	DMSO	15
11	TBHP (2)	NCS (40)	DMSO	23
12	TBHP (2)	NCS (30)	DMSO	7[c]
13	TBHP (2)	NCS (30)	DMSO	29[d]
14	TBHP (2)	NCS (30)	DMSO	42[e]
15	**TBHP (2)**	**NCS (30)**	**DMSO**	**53[e,f]**
16	none	NCS (30)	DMSO	N.D.[e,f]
17	TBHP (2)	NCS (30)	DMSO	51[e,f,g]

[a]Reaction conditions: **1a** (1.5 eq., 0.56 mmol), **2a** (0.37 mmol), oxidant (0.74 mmol), additive (0.11 mmol) in solvent (0.5 mL) at 120 °C for 6.5 h. [b]isolated yield. [c]reaction conducted at 110 °C. [d]reaction conducted at 140 °C. [e]for 12 h. [f]under N_2 atmosphere. [g]gram-scale reaction. N.D. = not detected, DCE = 1,2-dichloroethane, DTBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, TBAB = *tetra*-n-butylammonium bromide, TBAI = *tetra*-n-butylammonium iodide.

With these optimized conditions in hand, we examined the scope of substrates. As shown in **Table 2**, the reactions with benzaldehydes bearing a -Me or -OMe at their *ortho*-, *meta*- and *para*- positions gave the corresponding arylated products in 53-72 % yield (**Table 2**, **3aa-3af**). Besides, 3,4-dimethoxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde also afforded the target products in 44% and 71% yield, respectively (**Table 2**, **3ag-3ah**), but no desired product was observed with 2,5-dimethoxybenzaldehyde (**Table 2**, **3ai**). The halogenated

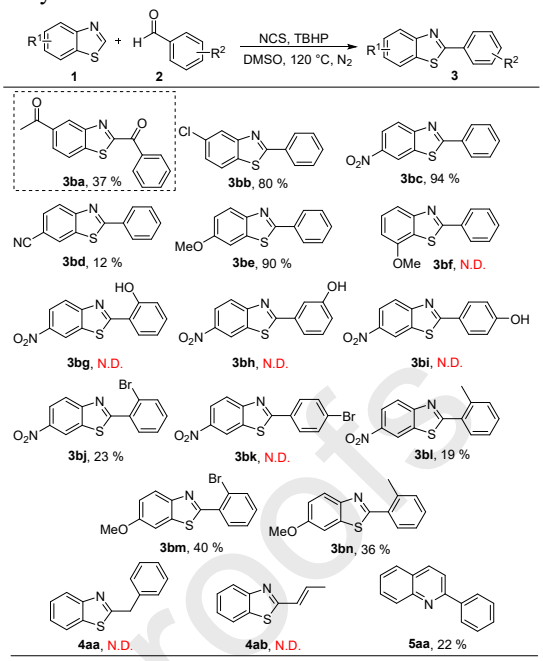
Tab …uted benzaldehydes.



[a]Reactions: **1a** (1.5 eq., 0.56 mmol), **2** (0.37 mmol), 5.5 M TBHP solution in decane (2.0 equiv, 0.74 mmol, 134 µL), NCS (30 mol%, 0.11 mmol), DMSO (0.5 mL), 120 °C, N_2, 12 h.

benzaldehydes including 2-fluorobenzaldehyde 2-chlorobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 2-bromobenzaldehyde, 3-bromobenzaldehyde, 4-bromobenzaldehyde gave the corresponding products in 34-88 % yield (**Table 2**, **3aj-3ap**). However, no desired product was detected when 2,4-dichlorobenzaldehyde reacted with benzothiazole (**Table 2**, **3aq**). Furthermore, the reaction of 2-hydroxybenzaldehyde, 4-(trifluoromethyl)benzaldehyde, 4-(*tert*-butoxyl)benzaldehyde and 2-nitrobenzaldehyde all resulted the products in good yields (**Table 2**, **3ar-3au**). However, the use of 3-nitrobenzaldehyde also did not give any product (**3av**) the same as 2,5-dimethoxybenzaldehyde (**Table 2**, **3ai**), which compared to 2-nitrobenzaldehyde (75%, **Table 2**, **3au**) and 3,4-dimethoxybenzaldehyde (44%, **Table 2**, **3ag**) respectively suggested that the position of the substituents on the benzaldehyde affected the reaction yield significantly. Surprisingly, benzaldehyde reacted with benzothiazole afforded the acylated benzothiazole as the main product in 78 % yield (**Table 2**, **3aw**), which may go through an oxidative coupling reaction between benzothiazole and aldehyde.[25]

Then, various substituted benzothiazoles and substituted benzaldehydes were explored to check the tolerance of the reaction (**Table 3**). Among them, most of the reactions gave the target arylated products, however, 5-acetalbenzothiazole afforded an acylated product under the optimized condition (**Table 3**, **3ba**). Benzothiazoles bearing a substituent (5-Cl, 6-NO_2, 6-CN, 6-OMe) afforded the expected arylated benzothiazoles in 12−94% yields (**Table 3**, **3ba-3be**). And it is known that C7 substitution on the benzothiazole has a steric hindrance.[26] Hence, it was not surprising that no product was observer with 7-methoxybenzothiazole (**Table 3**, **3bf**). Unfortunately, the target reaction also did not occur with 2-hydroxybenzaldehyde and 6-nitrobenzothiazole (**Table 3**, **3bg**), we envisioned that it might because of the steric hindrance of the 2-hydroxybenzaldehyde. Then, we tried the reactions of 3-hydroxybenzaldehyde or 4-hydroxybenzaldehyde benzaldehydes with 6-nitrobenzothiazole (**Table 3**, **3bh and 3bi**). However, neither gave the target product, which indicates that there is probably connection like hydrogen bonds between the nitro group and hydroxyl group leading to steric hindrance and hindering the reaction.[27-29] Furthermore, 2-

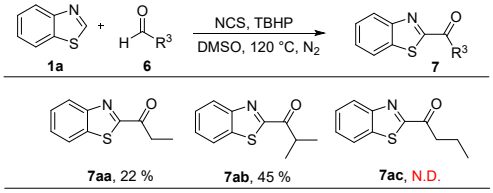


[a]Reactions: **1** (1.5 eq., 0.56 mmol), **2** (0.37 mmol), 5.5 M TBHP solution in decane (2.0 equiv, 0.74 mmol,134 µL), NCS (30 mol%, 0.11 mmol), DMSO (0.5 mL), 120 °C, N_2, 12 h.

bromobenzaldehyde and 2-methylbenzaldehyde reacted smoothly with 6-nitrobenzothiazole and 6-methoxybenzothiazole generating the corresponding products in 19%-40% yields (**Table 3**, **3bj, 3bl, 3bm, 3bn**). On the contrary, 4-bromobenzaldehyde was not tolerated with 6-nitrobenzothiazole in the reaction (**Table 3**, **3bk**). Also, phenylacetaldehyde and crotonaldehyde failed in the reaction under the current catalysts system as reported (**Table 3**, **4aa and 4ab**). In addition, quinoline underwent the *ortho*-arylation with benzaldehyde to generate the desired product in 22% yield (**Table 3**, **5aa**).

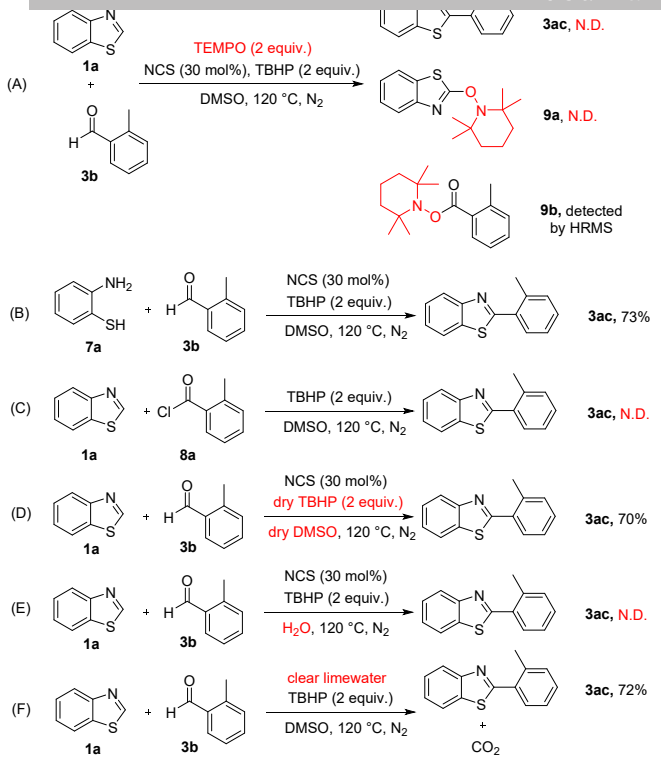
Next, the generality of this method was investigated with other substrates (**Table 4**). Notably, aliphatic aldehydes including propionaldehyde and isobutyraldehyde gave acylation products in 22% and 45% yields (**Table 4**, **7aa and 7ab**). But butyraldehyde was not a suitable substrate that did not give any product (**Table 4**, **7ac**).

Table 4. Acylation of benzothiazole with aliphatic aldehydes.

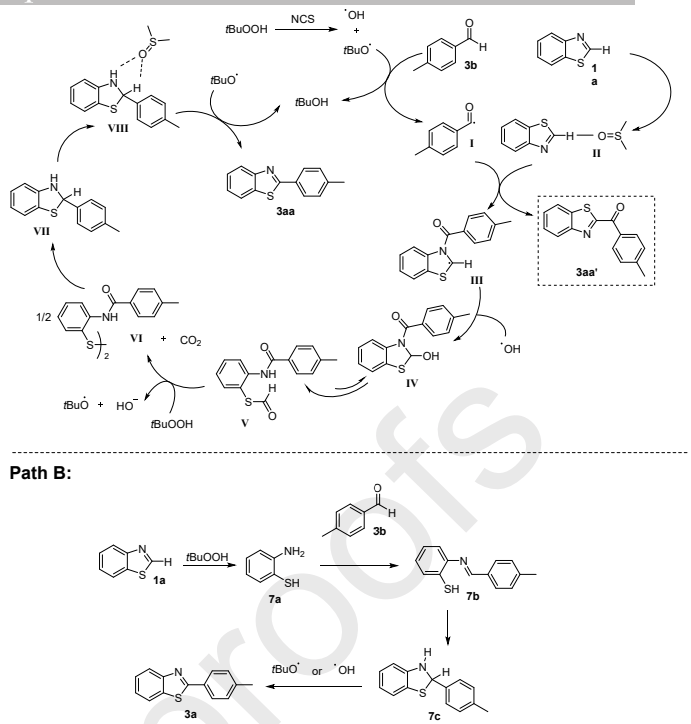


[a]Reactions: **1a** (0.37 mmol), **6** (0.5 mL), 5.5 M TBHP solution in decane (2.0 equiv, 0.74 mmol, 134 µL), NCS (30 mol%, 0.11 mmol), DMSO (0.5 mL), 120 °C, N_2, 12 h.

In addition, a series of controlled experiments were performed to explore the mechanism of this reaction as follows: (**A**) An excess of a radical trapping agent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the mixture under the optimal reaction conditions (**Scheme 2**A). The result showed that the reaction was completely inhibited by TEMPO and a TEMPO-trapped complex of a 2-methylbenzaldehyde radical (**9b**) was detected by HRMS (see the ESI†), confirming the involvement of a radical pathway. (**B**) The reaction between 2-aminothiophenol (**7a**) and 2-methylbenzaldehyde (**3b**) under optimized reaction conditions formed the target product (**3ac**) in 73% (**Scheme 2**B),



Scheme 2. Mechanistic Experiments.



Scheme 3. Plausible Mechanism

which was close to the reaction yield of benzothiazole with 2-methylbenzaldehyde (72%, **Table 2**, **3ac**). It indicated that the transformation might proceed through a ring-opening pathway.[15a,d] (**C**) 2-Methylbenzoylchloride (**8a**) was used as a substrate instead of 2-methylbenzaldehyde to react with benzothiazole in the absence of NCS (**Scheme 2**C). The possibility of intermediate 2-methyl benzoyl chloride can be ruled out since no product was observed in the reaction. (**D**) TBHP in decane and DMSO were dried over anhydrous $MgSO_4$ before adding into the mixture, and the arylated benzothiazole was obtained in 70% (**Scheme 2**D). The result demonstrated that H_2O is useless in the reaction. (**E**) The reaction using H_2O instead of DMSO as the solvent did not result in the desired product, which indicated that DMSO was very important to the reaction (**Scheme 2**E). (**F**) The reaction of benzothiazole with 2-methylbenzaldehyde was attempted connecting with clear limewater (**Scheme 2**F). The clear limewater became cloudy during the reaction, which indicated that CO_2 was generated.

Based on the mechanistic experimental results and related reports,[30] the mechanism may be proposed with the key question concerning the way of opening the benzothiazole. Two different pathways may be envisioned as shown in **Scheme 3**: A) TBHP forms a *tert*-butoxyl radical and a hydroxyl radical in the presence of NCS.[23] Then, a *tert*-butoxyl radical abstracts a H-atom from the 4-methylbenzaldehyde **2a** to form an acyl radical **I**.[31] On the other hand, DMSO coordinates C2-H of benzothiazole **1a** to form an intermediate **II**,[24] making the N atom further electron-deficient. The acyl radical **I** is nucleophilic in nature and attacks at the more electrophilic N of the intermediate **II** to form the corresponding radical intermediate **III**. At the same time, oxidative coupling reaction between acyl radical **I** and benzothiazole radical (initiated by *tert*-butoxyl radical) might produce acylated benzothiazole **3aa'** as a by-product.[25] Then radical intermediate **III-a** would react with a hydroxyl radical to form an intermediate **IV**.[32] The intermediate **IV** converted to **V** automatically through a ring-opening reaction.[15d] Subsequently, TBHP oxidized **V** to convert into disulfide intermediate **VI**[15d] *via* a thio–*ene* radical process producing CO_2 at the same time.[15d,17] Intermediate **VI** was highly reactive and would fast undergo an intramolecular condensation process to afford **VII**, which can be oxidized by H-atom transfer with a *tert*-butoxyl radical with the help of DMSO to form the desired product **3aa**;[19c] B) Direct oxidative opening of the benzothiazole ring by TBHP.[21] Then oxidative condensation of the resultant 2-amino thiophenol with the aldehyde with the help of a *tert*-butoxyl radical or a hydroxyl radical.[16]

In summary, we have disclosed a procedure for direct arylation of benzothiazoles with aryl aldehydes in DMSO, which acts as a strong Lewis base probably could promote cleavage of bonds through hydrogen bonds. The cheap organic catalyst NCS is used as a radical initiated reagent and TBHP as an oxidant. The reaction has a very broad substrate scope affording the arylated products in 12–94% yields for 28 examples. Additionally, acylated benzothiazoles are also produced from aryl aldehydes and aliphatic aldehydes with 4 examples.

Acknowledgments

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Graphical Abstract

NCS/TBHP promoted C2 Arylation of Benzothiazoles with Aldehydes in DMSO

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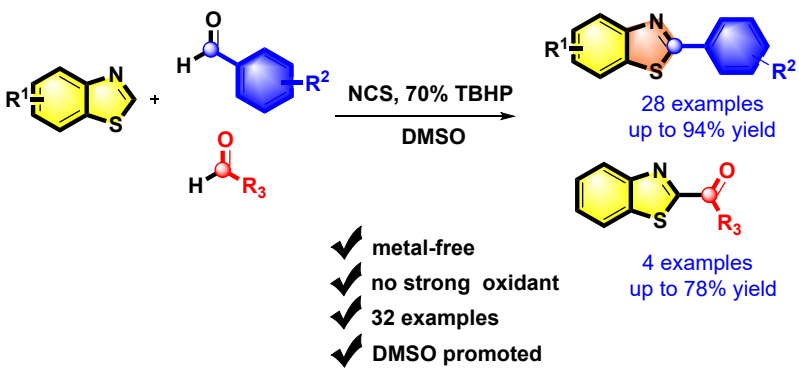

Highlights

- Arylation and acylation of benzothiazole with aldehydes.
- Metal-free oxidative system.
- Solvent as a strong Lewis base promotes the reactions.