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C2-arylacylation of 2*H*-benzothiazoles with methyl arenes *via* Selectfluor oxidation

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ABSTRACT

An efficient Selectfluor-oxidative protocol was developed for the direct C2-arylacylation of 2*H*-benzothiazoles *via* the radical reaction of 2*H*-benzothiazoles with methyl arenes. Selectfluor can effectively promote the oxidative cross-coupling without an external catalyst. This arylacylation reaction tolerates a wide range of functional groups affording 28 examples of the arylacylated products in 39–81% yield.

Introduction

Aryl ketones, including arylacylated heterocycles, are important structural motifs found in various bioactive compounds, pharmaceuticals and natural products [1–4] (Fig. 1). Amongst them, C2-arylacylated 2*H*-benzothiazoles exhibit various pharmacological effects, such as antiviral [5], antitumor [6–8] and antidiabetic activities [9,10].

Therefore, the development of efficient strategies for the synthesis of C2-arylacylated 2*H*-benzothiazoles has received much attention. The reported methods mostly depend on the tandem reactions of 2-aminothiophenols, 2-halonitroarenes, 2-haloanilines or anilines with diverse substrates including phenyl-acetaldehydes [11], 1,1-dibromoethenes [12], acetophenones [13–16], arylacetylenes [17–19], α-hydroxyacetophenones [19,20], enaminones [21] and α,α-dihaloketones [22]. However, these methodologies generally require prefunctionalized reactants and complicated handling procedures, which limits their applications. In 2013, Wu and co-workers [23] reported the I_2/KOH-catalyzed direct ring-opening arylacylation of 2*H*-benzothiazoles with aryl ketones at 100 °C (Scheme 1a). Chen and co-workers [24] also reported the C2-arylacylation of 2*H*-benzothiazoles using $K_2S_2O_8$ as the oxidant and $FeCl_3{\cdot}6H_2O$ as the catalyst at 100 °C (Scheme 1b). In 2014, a CuI-catalyzed reaction under a nitrogen atmosphere was developed by Song and co-workers [25] (Scheme 1c). In 2019, Yin and co-workers [26] reported the C2-arylacylation of 2*H*-benzothiazoles under the synergistic catalysis of *i*-PrMgCl·LiCl and CDI (Scheme 1d). In 2020, Ablajan and co-workers [27] reported a I_2/TBHP synergistically catalyzed method for the synthesis of 2-arylacylated 2*H*-benzothiazoles (Scheme 1e).

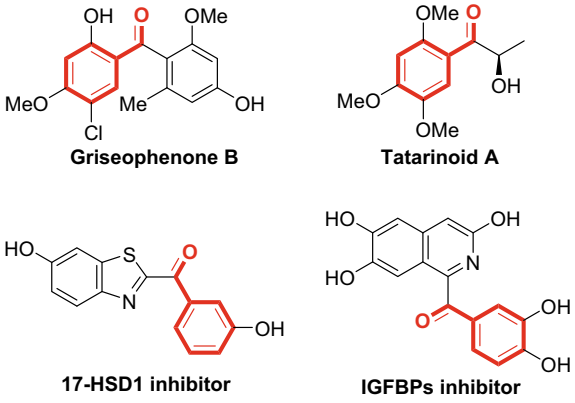

Fig. 1. Selected pharmaceuticals and natural products containing the aryl ketone moiety.

It should be noted that these methods typically use aryl ketones as the carbonyl sources, which are sensitive to oxidants and reductants. Selectfluor is known as a powerful oxidant (SCE = 0.33 V), possessing notable properties such as high thermal stability, low

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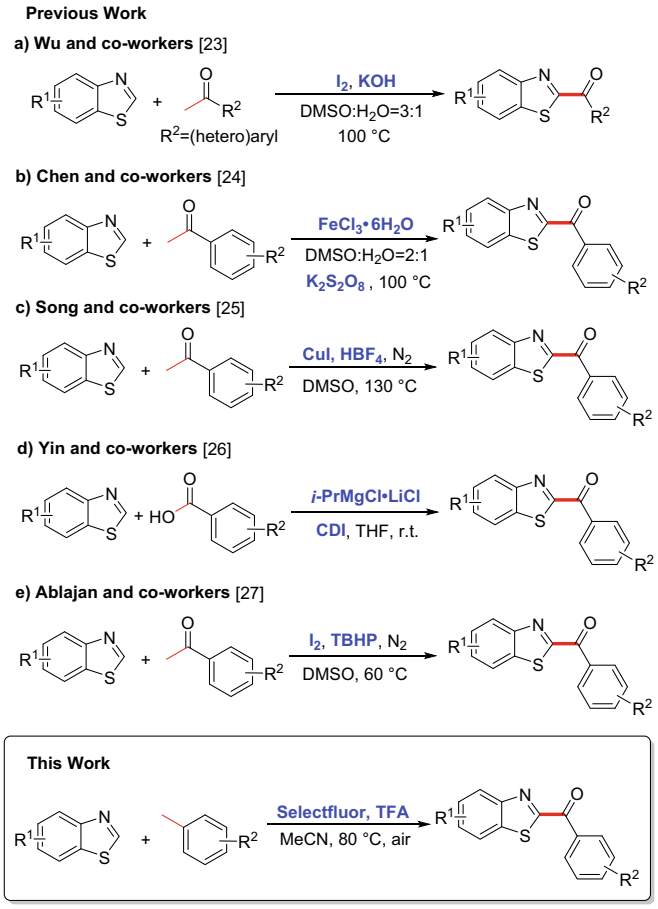


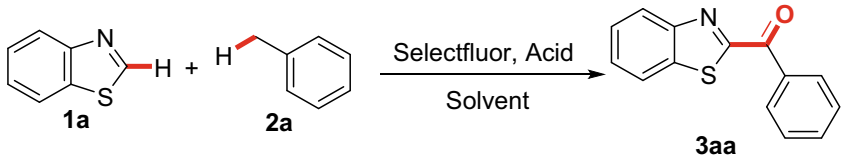
Scheme 1. Selected arylacylation reactions of 2*H*-benzothiazoles.

toxicity, good solubility and stability in polar solvents, and significant attention has been paid to its applications in organic chemistry [28–30]. Based on our previous work [31], herein we report a convenient and efficient approach for the direct C2-arylacylation of 2*H*-benzothiazoles with methyl arenes *via* Selectfluor oxidation. Compared with aryl ketones, methyl arenes are more readily available, more chemically stable and less expensive. Our process also has the advantages of mild reaction conditions and being transition metal-free.

Results and discussion

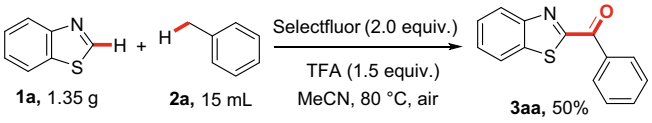
Initially, we chose 2*H*-benzothiazole (**1a**) and toluene (**2a**) as model substrates to optimize the reaction conditions (Table 1). When Selectfluor (2 eq.) was used as the oxidant, trifluoroacetic acid (TFA) (1.5 eq.) as the acid and acetonitrile (MeCN) as the solvent at 80 °C for 8 h, the desired product (**3aa**) was obtained in 47% yield (Entry 1). Next, various solvents were screened. However, the reactions without solvent or with solvents such as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and H_2O did not give any product (Entries 2–5). The mixed solvents CH_3CN/H_2O with different ratios gave lower yields compared to that of CH_3CN (Entries 6–7). Other acid such as *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$), hydrochloric acid (HCl) and acetic acid (AcOH) were less effective (Entries 8–10). In addition, the amounts of the oxidant, acid and solvent were examined; however, lower yields were found in all cases (Entries 11–18). Furthermore, lower yields were obtained when the reaction temperature was decreased to 70 °C or increased to 90 °C (Entries 19–20). Gratifyingly, the yield increased to 58% when the reaction time was extended from 8 h to 10 h, but no significant improvement was observed when the reaction time was increased to 12 h (Entries 21–22). The reaction conducted under a N_2 atmosphere resulted in a lower yield of the desired product, which showed that air was necessary for the pro-

Table 1
Optimization of the reaction conditions.[a]



Entry	Oxidant (eq.)	Acid (eq.)	Solvent (mL)	Yield **3aa**[b] (%)
1	Selectfluor (2)	TFA (1.5)	MeCN (2)	47%
2	Selectfluor (2)	TFA (1.5)	None	n.r.
3	Selectfluor (2)	TFA (1.5)	DMF (2)	n.r.
4	Selectfluor (2)	TFA (1.5)	DMSO (2)	n.r.
5	Selectfluor (2)	TFA (1.5)	H_2O (2)	n.r.
6	Selectfluor (2)	TFA (1.5)	MeCN:H_2O = 1:1 (2)	17%
7	Selectfluor (2)	TFA (1.5)	MeCN:H_2O = 100:1 (2)	45%
8	Selectfluor (2)	$TsOH{\cdot}H_2O$ (1.5)	MeCN (2)	5%
9	Selectfluor (2)	HCl (1.5)	MeCN (2)	n.r.
10	Selectfluor (2)	AcOH (1.5)	MeCN (2)	n.r.
11	Selectfluor (1.5)	TFA (1.5)	MeCN (2)	17%
12	Selectfluor (2.5)	TFA (1.5)	MeCN (2)	25%
13	Selectfluor (3)	TFA (1.5)	MeCN (2)	19%
14	Selectfluor (2)	TFA (0.5)	MeCN (2)	22%
15	Selectfluor (2)	TFA (1.0)	MeCN (2)	35%
16	Selectfluor (2)	TFA (2.0)	MeCN (2)	33%
17	Selectfluor (2)	TFA (1.5)	MeCN (1)	25%
18	Selectfluor (2)	TFA (1.5)	MeCN (3)	32%
19[c]	Selectfluor (2)	TFA (1.5)	MeCN (2)	43%
20[d]	Selectfluor (2)	TFA (1.5)	MeCN (2)	45%
21[e]	Selectfluor (2)	TFA (1.5)	MeCN (2)	58%
22[f]	Selectfluor (2)	TFA (1.5)	MeCN (2)	55%
23[e,g]	Selectfluor (2)	TFA (1.5)	MeCN (2)	28%
24[e,h]	Selectfluor (2)	TFA (1.5)	MeCN (2)	n.r.

[a] Reagents and conditions: 2*H*-benzothiazole (**1a**, 0.3 mmol), toluene (**2a**, 1.5 mL), Selectfluor, acid, solvent, 80 °C, 8 h.
[b] Isolated yield based on *2H*-benzothiazole.
[c] 70 °C.
[d] 90 °C.
[e] 10 h.
[f] 12 h.
[g] N_2 atmosphere.
[h] Irradiated with 30 W Blue LEDs (λ = 405 nm) at room temperature.

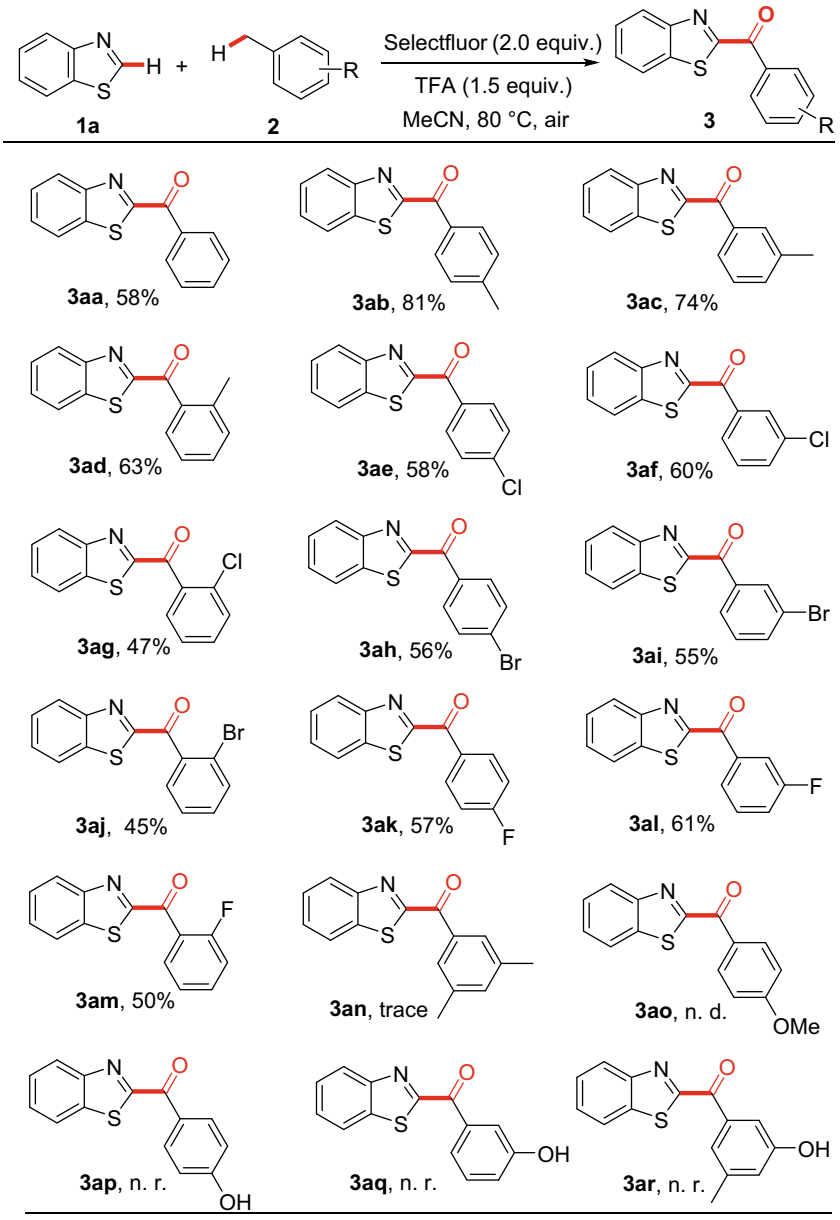


Scheme 2. Gram-scale synthesis.

tocol (Entry 23). Further investigation demonstrated that the oxidative coupling irradiated with visible light at room temperature was ineffective (Entry 24).

Moreover, a gram-scale synthesis was carried out. Gratifyingly, the reaction efficiency was not significantly affected, and the target product **3aa** was obtained in 50% yield when the model reaction was performed on a 10 mmol scale (Scheme 2).

Table 2
Substrate scope of the methyl arenes.



[a]Reagents and conditions: 2*H*-benzothiazole (**1a**, 0.3 mmol), methyl arenes (**2**, 1.5 mL), Selectfluor (2.0 eq., 0.6 mmol), TFA (1.5 eq., 0.45 mmol), MeCN (2 mL), 80 °C, 10 h.

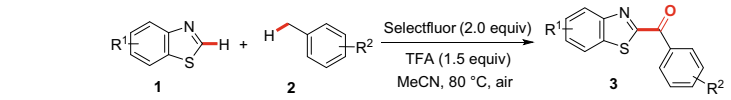
With the optimized reaction conditions in hand, the scope of substituted methyl arenes (**2**) was first explored for the arylacylation of 2*H*-benzothiazole (**1a**). As shown in Table 2, monosubstituted toluene derivatives bearing a methyl group or halogens were compatible with this oxidative coupling system (**3ab-am**). The arylacylation of 2*H*-benzothiazole with toluene derivatives containing the electron-donating methyl group gave higher yields than those containing electron-withdrawing halogens (**3ab-ad** *vs* **3ae-am**). Notably, substituents at the *meta*- and *para*-positions have no significant effect on the yields (**3ab, 3ac, 3ae, 3af, 3ah, 3ai, 3ak** and **3al**). However, substitution at the *ortho*-position generally gave the corresponding arylacylated products in lower yields (**3ad**, **3ag**, **3aj** and **3am**). Unfortunately, the reaction of 2*H*-benzothiazole with mesitylene only gave trace amounts of the target product (**3an**) and none of the desired product was detected using 1-methoxy-4-methylbenzene (**3ao**). Also, *p*-cresol, *m*-cresol and 3,5-dimethylphenol were unreactive under the current reaction conditions (**3ap**, **3aq**, **3ar**).

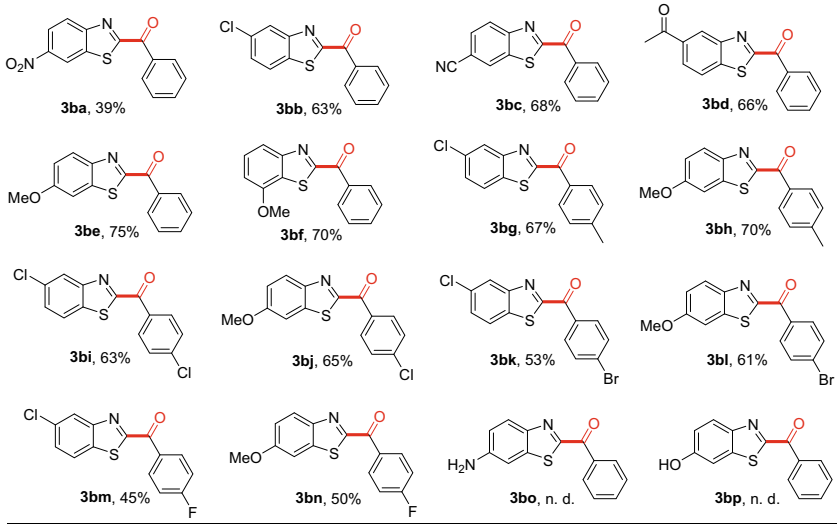
We further investigated the substrate scope of various substituted 2*H*-benzothiazoles (**1**) and substituted methyl arenes (**2**) (Table 3). Gratifyingly, toluene reacted with substituted 2*H*-benzothiazoles containing electron-withdrawing substituents (nitro, chloro, cyano and acetyl), affording the desired products in 39–68% yield (**3ba-bd**). Meanwhile, 2*H*-benzothiazoles bearing electron-donating groups (6-methoxy, 7-methoxy) gave the desired products in 70–75% yield (**3be**, **3bf**). The reactions of substituted 2*H*-benzothiazoles with various methyl arenes were also investigated and the desired products were obtained in moderate to good yields (**3bg-bm**). These results showed that the yields of 2*H*-benzothiazoles with electron-donating groups were generally higher than those of 2*H*-benzothiazoles with electron-withdrawing groups. Unfortunately, the desired reaction did not occur between 6-aminobenzothiazole and toluene (**3bo**), presumably because the amino group is readily oxidizable. In addition, the desired reaction also did not occur between 6-hydroxybenzothiazole and toluene (**3bp**).

To gain further insights into the reaction mechanism, a series of control experiments were carried out. A radical trapping experiment was performed by the addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under the optimized reaction conditions (Scheme 3A). This result showed that when 2 equivalents of TEMPO were added to the arylacylation reaction, the coupling process was completely inhibited. At the same time, a TEMPO-trapped complex from benzyl radical (**4c**) was detected by LC-MS, which indicated that a radical process may be involved in the coupling. Notably, the TEMPO-trapped complexes of 2*H*-benzothiazole radical (**4a**) and benzaldehyde radical (**4b**) were not observed. Next, TEMPO was added to the catalytic system, and the fluorine radical adduct TEMPO-F was detected by LC-MS. This result demonstrated that the N–F activation of Selectfluor could be achieved under heating (Scheme 3B) [32]. The reaction of 2*H*-benzothiazole with toluene gave 2-benzylbenzo[*d*]thiazole (**1ac**) in 70% yield under a N_2 atmosphere (Scheme 3C). 2-Benzylbenzo[*d*]thiazole (**1ac**) underwent oxidation in air to give the target product **3aa** in 72% yield (Scheme 3D). This result indicated that air is required in this reaction (see the ESI for further details).

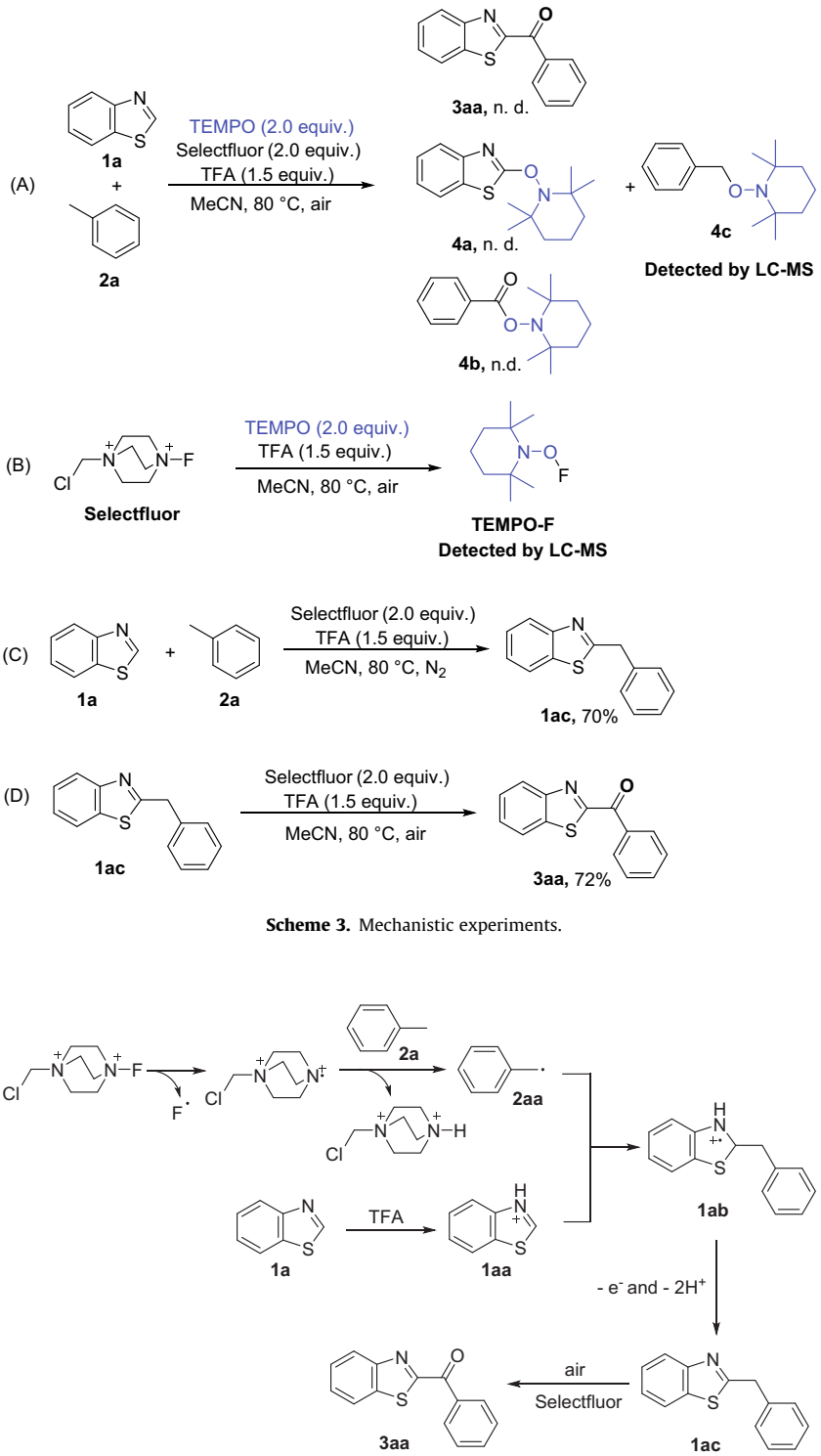
Based on the above experimental results, a plausible mechanism for this arylacylation reaction was proposed (Scheme 4). It was previously reported that Selectfluor could serve as an efficient Lewis acid catalyst and powerful oxidant [33–35]. Thus, the *N*-F bonds of Selectfluor cleaved homolytically upon heating producing an *N* radical cation and an *F* radical [36,37]. The electrophilic *N*-radical cation then abstracts a hydrogen atom from toluene **2a** to provide methyl radical **2aa** [38,39]. Meanwhile, 2*H*-benzothiazole **1a** is protonated by acid to form **1aa**, which can capture the relatively nucleophilic methyl radical **2aa** and provides the corresponding radical adduct **1ab** [40]. Oxidation and deprotonation of **1ab** by another molecule of Selectfluor then affords the coupling

Table 3
Substrate scope of the 2*H*-benzothiazoles.





[a]Reagents and conditions: 2*H*-benzothiazole (**1a**, 0.3 mmol), methyl arenes (**2**, 1.5 mL), Selectfluor (2.0 eq., 0.6 mmol), TFA (1.5 eq., 0.45 mmol), MeCN (2 mL), 80 °C, 10 h.



Scheme 3. Mechanistic experiments.

Scheme 4. Plausible reaction mechanism.

product **1ac**. Finally, oxidation of **1ac** in air affords the desired arylacylated product **3aa** [41].

In conclusion, we have developed a convenient and efficient approach for the direct C2-arylacylation of 2*H*-benzothiazoles with various methyl arenes *via* Selectfluor oxidation. This arylacylation reaction tolerates a wide range of functional groups affording 28 examples of the arylacylated products in 39–81% yield. Moreover, the direct coupling of the 2*H*-benzothiazoles without prefunctionalized substrates and without transition-metal catalysts make this protocol practical for the synthesis of C2-arylacylated 2*H*-benzothiazoles.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153184.

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