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Communication

Visible light-induced hydroxyalkylation of 2*H*-benzothiazoles with alcohols via selectfluor oxidation

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ABSTRACT

A visible-light induced metal-free approach was described for the hydroxyalkylation of 2*H*-benzothiazoles with alcohols by using selectfluor as the oxidant. A variety of 2*H*-benzothiazoles and alcohols could be tolerated, providing a mild and simple method for the synthesis of C2-hydroxyalkylated 2*H*-benzothiazoles in moderate to good yields. Besides, ethers were also compatible in this reaction, leading to corresponding C2 ether-substituted 2*H*-benzothiazoles with high regioselectivity.

Hydroxyalkylated heterocycles are one class of important heterocyclic compounds in agricultural and pharmaceutical field [1–4]. Over the years, many hydroxyalkylated heterocycles have been synthesized as antiviral [5], antagonist [6], antifungal [7], antimalarial [8] and so on (Fig. 1).

On the other hand, cross-dehydrogenative coupling (CDC) has become a captivating strategy for bond construction, due to the "excellent step and atom economy" properties [9–14]. As one type of CDC reactions, the direct hydroxylation of heterocycles with alcohols has also received great attention because of the "readily available", "inexpensive" and "biodegradable" advantages of alcohols [15]. In 2011, Wang *et al.* [16] published the C2-alkylation of azoles with alcohols and ethers using *tert*-butyl hydroperoxide (TBHP) as the oxidant at 120 °C (Scheme 1a). And in 2017, di-*tert*-butyl peroxide (DTBP) oxidized CDC reactions of thiophenes and pyridines with alcohols and cyclic ethers at 130 °C were developed by Kianmehr and co-workers [17] (Scheme 1b). Next year, Yu group [18] reported DTBP-mediated C2-hydroxyalkylation reactions of chromones with alcohols at 140 °C (Scheme 1c). These reactions well developed heteroarenes hydroxyalkylated methods, but they still exhibit a series of disadvantages, such as relatively high reaction temperature, inflammable and explosive properties of organic peroxides oxidants. In 2019, our group [19] reported a mild and convenient direct hydroxyalkylation reaction of benzothiazoles with a variety of alcohols in the presence of $K_2S_2O_8$ in H_2O at 65 °C (Scheme 1d). Despite the fact that this methodology is milder than the reactions mentioned above, it is still carried out under heating condition.

During the past decade, photoredox catalysis, by using visible light as a renewable energy source, has facilitated a number of organic transformations that involve a single-electron transfer (SET) pathway [20–27]. There is likewise a growing trend of introducing photocatalysis into the hydroxyalkylation reaction of heterocycles. In 2016, DiRocco group [28] developed an iridium complex catalyzed hydroxymethylation of heteroaromatic bases (Scheme 1e). This reaction was carried out at room temperature, but it suffered from certain limitations such as complex handling procedure, expensive transition-metal catalyst and inevitable metal residues. Inspiringly, Lei *et al.* [29] explored a mild and metal-free photocatalytic cross-coupling of (iso)quinolines with different alcohols by using selectfluor as oxidant (Scheme 1f). In order to extend the hydroxyalkylation of various heterocycles, combining our previous researches [30–36] on photochemical reactions and green organic synthesis, we herein report a mild and convenient, visible light-induced direct hydroxyalkylation of 2*H*-benzothiazoles with alcohols by using selectfluor as oxidant at room temperature.

Initially, we chose 2*H*-benzothiazole (**1a**) and ethanol (**2b**) as the model substrates to investigate the reaction conditions. The results were outlined in Table 1. Generally, the model reaction was carried out under a nitrogen atmosphere irradiated by 30 W blue LEDs at room temperature. Firstly, a variety of oxidants were investigated in conjunction with acetonitrile (MeCN) as the solvent. It was identified that the desired hydroxyalkylated

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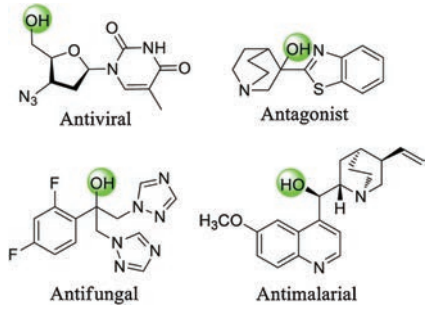
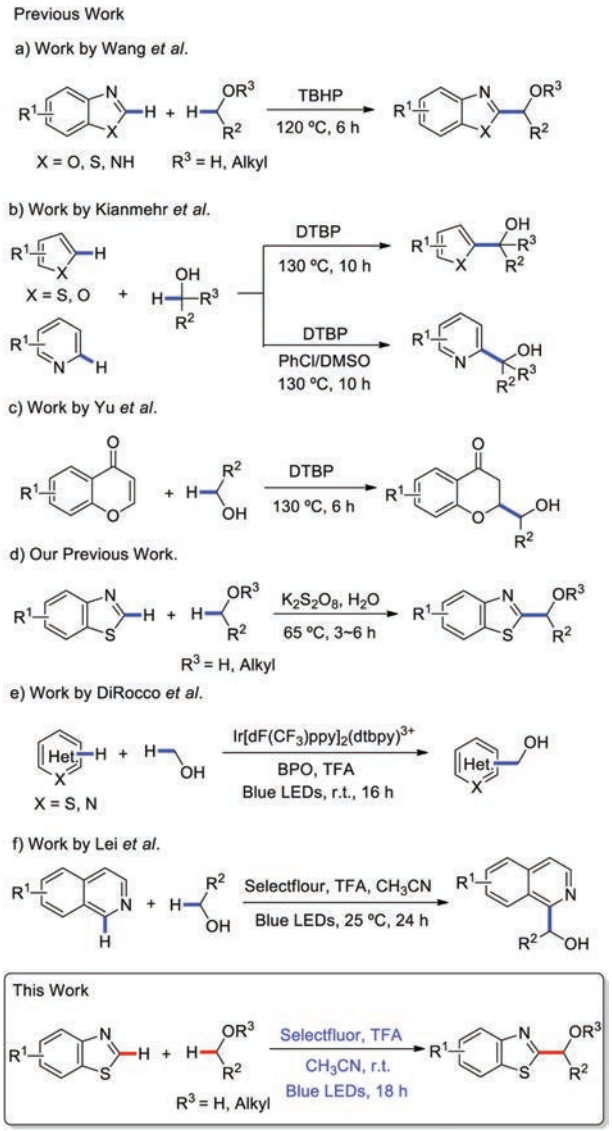


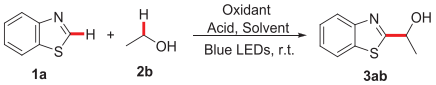
Fig. 1. Pharmaceuticals or pesticides containing hydroxyalkylated heterocycles moiety.



Scheme 1. Hydroxyalkylation reactions of heterocycles with alcohols.

product can be afforded in 34% yield using selectfluor (3 equiv.) as a visible light-activated oxidant, but the reaction could not be promoted by utilizing TBHP or $K_2S_2O_8$ (Table 1, entries 1–3). In order increase the yield of the reaction, we added trifluoroacetic acid (TFA) (1.5 equiv.) as the additive. Markedly, the yield increased to 61% (Table 1, entry 4). Subsequently, the acid was changed to *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$), acetic acid (AcOH) and hydrochloric acid (HCl), but the yields were inferior to that of

Table 1
Optimization of reaction conditions.[a]



Entry	Oxidant (equiv.)	Acid (equiv.)	Solvent (mL)	Yield (%)[b]
1	Selectfluor (3)	none	MeCN (3)	34%
2	TBHP (3)	none	MeCN (3)	N.R.
3	$K_2S_2O_8$ (3)	none	MeCN (3)	N.R.
4	Selectfluor (3)	TFA (1.5)	MeCN (3)	61%
5	Selectfluor (3)	$TsOH·H_2O$ (1.5)	MeCN (3)	Trace
6	Selectfluor (3)	AcOH (1.5)	MeCN (3)	17%
7	Selectfluor (3)	HCl (1.5)	MeCN (3)	Trace
8	Selectfluor (2)	TFA (1.5)	MeCN (3)	50%
9	Selectfluor (4)	TFA (1.5)	MeCN (3)	56%
10	Selectfluor (3)	TFA (1.0)	MeCN (3)	71%
11	Selectfluor (3)	TFA (2.0)	MeCN (3)	52%
12	Selectfluor (3)	TFA (2.5)	MeCN (3)	43%
13	Selectfluor (3)	TFA (1.0)	None	N.R.
14	Selectfluor (3)	TFA (1.0)	CH_2Cl_2 (3)	N.R.
15	Selectfluor (3)	TFA (1.0)	DMF (3)	N.R.
16	Selectfluor (3)	TFA (1.0)	DMSO (3)	N.R.
17	Selectfluor (3)	TFA (1.0)	Acetone (3)	N.R.
18	Selectfluor (3)	TFA (1.0)	MeCN (2)	33%
19	Selectfluor (3)	TFA (1.0)	MeCN (4)	49%
20[c]	Selectfluor (3)	TFA (1.0)	MeCN (3)	65%
21[d]	Selectfluor (3)	TFA (1.0)	MeCN (3)	72%

[a] Reaction conditions: 2*H*-benzothiazole (**1a**, 0.3 mmol), ethanol (**2b**, 1.5 mL), under a nitrogen atmosphere, irradiated with 30 W blue LEDs (λ = 405 nm) at room temperature for 18 h.
[b] Isolated yields.
[c] For 16 h.
[d] For 24 h.

TFA (Table 1, entries 5–7). We further tested the amount of selectfluor, but no improvement was observed with less or more than 3 equiv. of selectfluor (Table 1, entries 8 and 9). In addition, the product could be obtained in 71% yield as the amount of TFA was reduced to 1.0 equiv., but the yield decreased when the amount increased (Table 1, entries 10–12). Examination of a range of common solvents showed that the reaction could be carried out efficiently in acetonitrile while reaction without solvent or with solvents such as methylene chloride (CH_2Cl_2), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetone all did not give any product (Table 1, entries 13–17). Further studies showed that reducing or increasing the amount of acetonitrile resulted in a diminished yield of **3ab** (Table 1, entries 18 and 19). What is more, the results showed that the product yield decreased to 65% when the reaction time was shortened to 16 h, but no clear improvement in yield was observed when the reaction time increased to 24 h (Table 1, entries 20 and 21).

Subsequently, the gram-scale synthesis experiment was carried out. Notably, a comparable 67% yield was obtained under the optimized reaction conditions when the model reaction was performed in 10 mmol scale (Scheme 2). Moreover, the UV–vis spectra of selectfluor and the reaction compounds were measured, the results demonstrated that there is an overlap between the absorption spectrum of them with the emission spectrum of Blue LEDs with λ = 405 nm (see the Supporting information for further details). Then, the experiments with the light on and off were

Scheme 2. Gram-scale synthesis experiment.

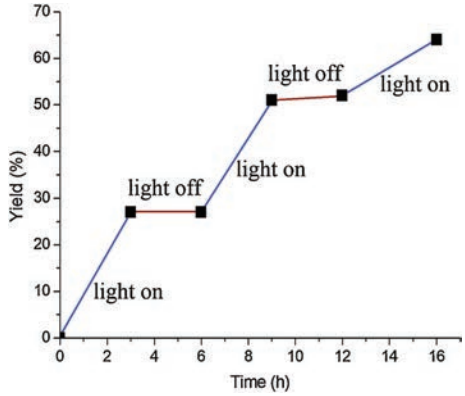
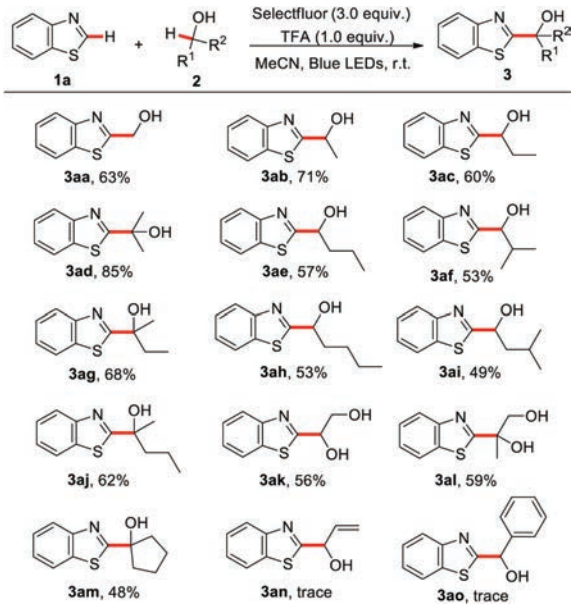


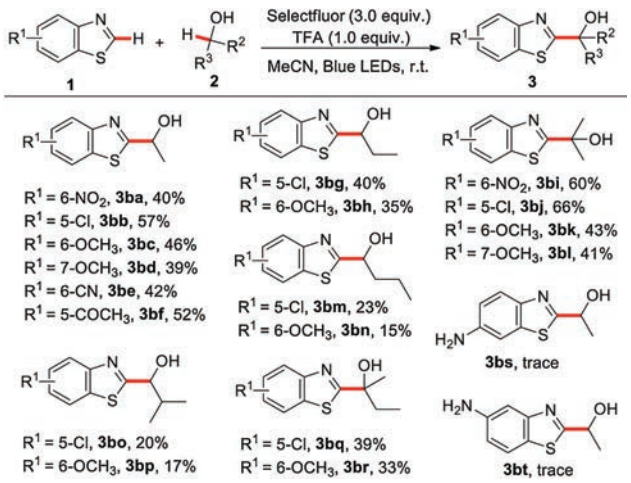
Fig. 2. Light on and off experiments.



Scheme 3. Substrate scope of alcohols. Reaction conditions: 2*H*-benzothiazole (**1a**, 0.3 mmol), alcohols (**2**, 20 equiv., 6.0 mmol), selectfluor (3.0 equiv., 0.9 mmol), TFA (1.0 equiv., 0.3 mmol), in MeCN (3.0 mL) under a nitrogen atmosphere, irradiated with 30 W blue LEDs (λ = 405 nm) at room temperature for 18 h.

conducted to prove the importance of light exposure. The reaction was inhibited in the absence of light, but was activated after light exposure, thus further confirming the crucial role of visible light in the reaction (Fig. 2).

With the optimized reaction conditions in hand, the scope of the alcohols (**2**) in the direct hydroxyalkylation with 2*H*-benzothiazole (**1a**) was investigated. As shown in Scheme 3, a broad range of structurally diverse aliphatic alcohols including methanol, ethanol, propanol, 2-propanol, butanol, 2-methyl-1-propanol, 2-butanol, pentanol, 3-methyl-1-butanol and 2-pentanol underwent direct hydroxyalkylation reactions with 2*H*-benzothiazole to afford the corresponding cross-coupling products smoothly in moderate to good yields (**3aa–3aj**). The results showed that the yields of the corresponding products obtained from the aliphatic primary alcohols gradually decreased with the increase of the carbon chain (**3ab**, **3ac**, **3ae** and **3ah**). Notably, the hydroxyalkylation of 2*H*-benzothiazoles with the secondary alcohols had higher yields than those of the primary alcohols (**3ac**, **3ae**, and **3ah** compared to **3ad**, **3ag**, and **3aj**, respectively). It was delightful that ethylene glycol and 1,3-propanediol were smoothly compatible with this system providing the desired hydroxyalkylation products in 56% and 59% yields, respectively (**3ak** and **3al**). The direct

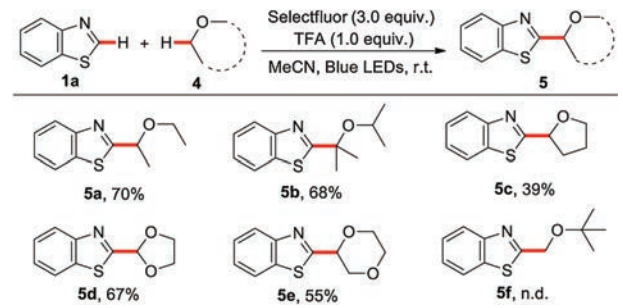


Scheme 4. Substrate scope of 2*H*-benzothiazoles. Reaction conditions: 2*H*-benzothiazole (**1**, 0.3 mmol), alcohols (**2**, 20 equiv., 6 mmol), selectfluor (3.0 equiv., 0.9 mmol), TFA (1.0 equiv., 0.3 mmol), in MeCN (3.0 mL) under a nitrogen atmosphere, irradiated with 30 W blue LEDs (λ = 405 nm) at room temperature for 18 h.

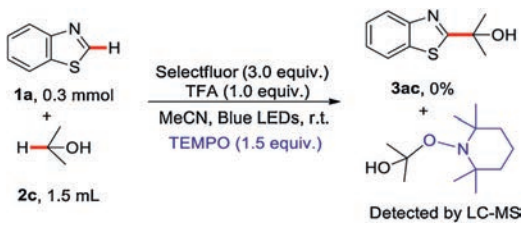
alkylation of 2*H*-benzothiazole with cyclopentanol also provided the target product in 48% yield (**3am**). Regrettably, 2*H*-benzothiazoles with allyl alcohol or benzyl alcohol only gave trace amount of the hydroxyalkylation products (**3an** and **3ao**).

Next, we turned our attention to explore the scope of substituted 2*H*-benzothiazoles. Various substituted 2*H*-benzothiazoles (**1**) and alcohols (**2**) were compatible with the catalytic system and the results are summarized in Scheme 4. In general, ethanol, propanol, 2-propanol reacted with substituted 2*H*-benzothiazoles containing an electron-withdrawing group (nitro, chloro, cyano, and acetyl) gave the desired products in 40%–66% yields (**3ba**, **3bb**, **3be**, **3bf**, **3bg**, **3bi** and **3bj**). Meanwhile, these alcohols reacted with those 2*H*-benzothiazoles containing an electron-donating group (6-methoxyl, 7-methoxyl) delivered the products in 35%–46% yields (**3bc**, **3bd**, **3bh**, **3bk**, **3bl**). The substrate scope was further extended to a series of alcohols with longer carbon chains including butanol, 2-methyl-1-propanol and 2-butanol, which were also well-tolerated (**3bm–3br**). However, 5-aminobenzothiazole and 6-aminobenzothiazole only gave trace amount of the target products (**3bs** and **3bt**), which might be due to the oxidation side reactions of the amino group.

To probe the applicability of this catalytic system, we attempted to broaden the generality of this hydroxyalkylation reaction by employing ethers as the substrates. As can be seen from Scheme 5, the C(sp^3)–H bond adjacent to the oxygen atom of ethers could also be activated under our protocol. Ethers (diethyl ether, isopropyl



Scheme 5. Further application. Reaction conditions: 2*H*-benzothiazole (**1a**, 0.3 mmol), ethers (**4**, 1.5 mL), selectfluor (3.0 equiv., 0.9 mmol), TFA (1.0 equiv., 0.3 mmol), in MeCN (3.0 mL) under a nitrogen atmosphere, irradiated with 30 W BLUE LEDs (λ = 405 nm) at room temperature for 18 h.

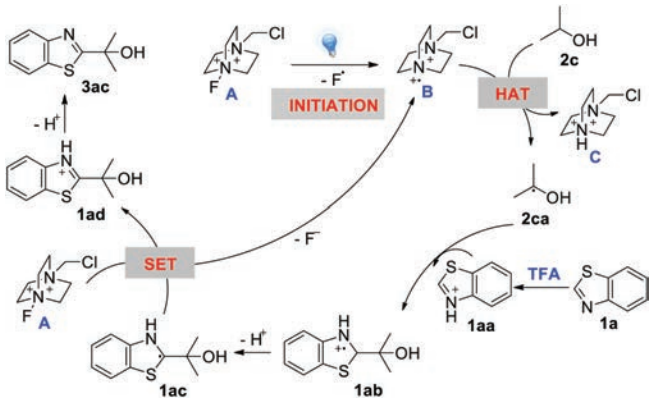


Scheme 6. Radical trapping experiment.

ether) and cyclic ethers (tetrahydrofuran, 1,3-dioxolane, 1,4-dioxane) were all compatible with the conditions providing the alkylation products in moderate to good yields (**5a–5e**). According to our previous work [19], the alkylation of 2*H*-benzothiazole and 1,3-dioxolane would give two isomers. Notably, only the 2-position of 1,3-dioxolane was alkylated in our protocol and single regioisomer (**5d**) was found. Nevertheless, methyl *tert*-butyl ether was unsuitable for this reaction (**5f**), which might be due to the unstability of the methyl *tert*-butyl ether free-radical intermediate and the steric hindrance of the bulky *tert*-butyl.

To explore the possible mechanism, a radical trapping experiment was performed by addition of a radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to the reaction system (Scheme 6). The transformation was completely inhibited and TEMPO-trapped complex was observed by LC–MS, which suggested that the reaction might proceed *via* a radical pathway.

It has been reported that selectfluor is not only a most efficient electrophilic fluorinating reagent, but also a powerful oxidant as well as a convenient mediator of several "fluorine-free" functionalizations of organic compounds [37–39]. According to the radical trapping experiment, we proposed a plausible mechanism for the hydroxyalkylation reaction of 2*H*-benzothiazole with isopropanol (Scheme 7). Under visible light irradiation, selectfluor **A** was converted to an *N* radical cation **B** and an F radical [40,41]. Afterward, the generated electrophilic *N* radical cation **B** would abstract a hydrogen atom from isopropanol **2c** to provide an ammonium ion **C** and a hydroxyalkyl radical **2ca** [29]. Subsequently, 2*H*-benzothiazole **1a** was protonated by acid to form **1aa**, the electron-deficient 2*H*-benzothiazole **1aa** would capture the relatively nucleophilic hydroxyalkyl radical **2ca** and deliver the corresponding radical cation adduct **1ab** [42]. Then, the intermediate **1ab** was deprotonated to a radical **1ac**. A single-electron transfer (SET) was followed between radical **1ac** and another selectfluor giving iminium ion **1ad** and *N* radical cation **B** [43].



Scheme 7. Proposed mechanism.

Finally, further deprotonation of **1ad** would then afford the desired hydroxyalkyl coupling product **3ac**.

In conclusion, we have developed a mild and convenient method for the C2-hydroxyalkylation of 2*H*-benzothiazoles with diverse alcohols, which was mediated by selectfluor under the blue LEDs irradiation at room temperature. This hydroxylkylation reaction tolerates a wide range of functional groups. Besides, ethers were also compatible in this reaction, leading to corresponding C2 ether-substituted 2*H*-benzothiazoles with high regioselectivity. As such, we expect that this new strategy can be applied to medicinal and agricultural chemicals studies in the future.

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.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.05.022.

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