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Iron-catalyzed tandem oxidative coupling and acetal hydrolysis reaction to prepare formylated benzothiazoles and isoquinolines†

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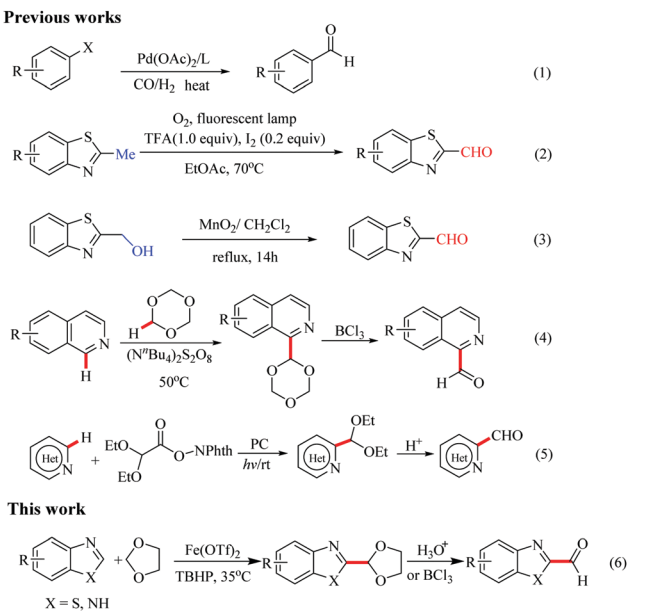
The aldehyde group is one of the most versatile intermediates in synthetic chemistry, and the introduction of an aldehyde group into heteroarenes is important for the transformation of molecular structure. Herein, we achieved the direct formylation of benzothiazoles and isoquinolines. The reaction features a novel iron-catalyzed Minisci-type oxidative coupling process using commercially available 1,3-dioxolane as a formylated reagent followed by acetal hydrolysis without a separation process. The reaction can be performed under exceedingly mild reaction conditions and exhibits broad functional group tolerance.

Nitrogen-containing heterocycles are prevalent key motifs in a myriad of biologically active compounds, agrochemicals, and organic functional materials, such as liquid crystals and fluorescent dyes.[1] Because functionalized heteroarenes are ubiquitously present in natural and pharmaceutical products, there is a continuous need for efficient synthetic methods to produce them.[2] Accordingly, introducing a formyl group into an aromatic heterocycle is important because the aldehyde group is widely used as a valuable and powerful synthon in the synthesis of drugs and industrial products.[3,4] Although aromatic aldehydes are widely applied in synthetic chemistry, their synthetic routes are rather limited. Some classical methods, such as Vilsmeier–Haack and Duff reactions, are suboptimal due to their relatively poor regioselectivity and harsh work-up.[5] Palladium-catalyzed reductive carbonylation of aryl halides is an effective route to obtain various formylated α,β-unsaturated aldehyde derivatives. However, this type of reaction always involves rigorous reaction conditions, such as high temperature and pressure, and the requirement of a pre-functionalized aryl halide (Scheme 1, eqn (1)).[6] Hence, the development of novel access to the formylation of heteroarenes under mild conditions is still of much significance.

In recent years, new reagents, such as formaldehyde,[7] alcohols,[8] formic acid,[9] glyoxylic acetal,[10] and glyoxylic acid,[11] have been developed as formylated surrogates for olefins and arenes. Benzothiazole has been used as a crucial heterocyclic skeleton, although the direct formylation has rarely been reported. In addition to classical Vilsmeier–Haack and Duff reactions, the oxidization of methyl or hydroxymethyl groups using a stoichiometric oxidant is a method currently used to obtain benzothiazole-2-carboxaldehydes (Scheme 1, eqn (2 and 3)).[12] The acetal group



Scheme 1 Strategies for the formylation.

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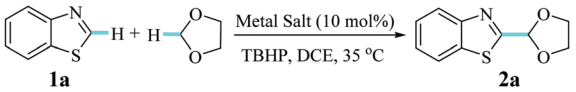
can be used as an aldehyde precursor and be introduced into a molecular skeleton by oxidative cross-coupling, and then subsequently hydrolyzed to aldehyde compounds.[13]

In 2018, Xia's group reported the formylation of heteroarenes in moderate yields using 2,2-diethoxyacetic acid (acyclic acetal form) as a formylation mask reagent under visible light irradiation.[13a] In 2018, Yeung and co-workers designed an approach that harnesses the direct activation of weak C–H bonds in acetals (trioxane) and achieved the partial formylation of N-heterocycles with a Minisci-type reaction (Scheme 1, eqn (4)).[13b,14] In 2020, Wang's group reported a protocol for a photoredox-catalyzed redox-neutral Minisci C–H formylation reaction of N-heteroarenes (Scheme 1, eqn (5)).[13c,14] In addition, 1,3-dioxolane (cyclic acetal form) as a formylation mask reagent was also applied to the introduction of the formyl group. In 2017, Doyle's group described a protocol for direct formylation of aryl halide with 1,3-dioxolane through a photoredox-catalyzed mode, where pre-functionalized aryl halide was used in this reaction.[13d]

Although some works reported Minisci-type reactions with heteroarene (arene) and cyclic ether (including cyclic acetal, such as 1,3-dioxolane), in most of them, the substrate's scope or yields were unsatisfactory, and systematic hydrolysis products (cyclic acetal) were surprisingly scarce.[15] Inspired by these reports on various acetals as formyl radical equivalents, here, we report a new iron-catalyzed cascading Minisci and hydrolysis reaction of benzothiazoles and isoquinolines with 1,3-dioxolane as a formyl equivalent under exceedingly mild reaction conditions that affords the corresponding formylated products in moderate to good yields (Scheme 1, eqn (6)). This tandem oxidative coupling-hydrolysis procedure features green and efficient C–C building from C–H/C–H and avoids the use of pre-functionalized substrates.[16]

In our initial study, benzothiazole **1a** and 1,3-dioxolane were selected as model substrates to test our designed methodology. First, we carried out the reaction in DCE/1,3-dioxolane (v/v = 1 : 1) at 35 °C in the presence of TBHP (2.5 equiv.) as oxidant, and product **2a** was not observed (Table 1, entry 1). We speculated that the catalytic nature of transition metals would have a profound impact on reactivity, and thus, the combination of transition metal catalysts (10 mol%) and TBHP was examined. It was observed that $Fe(OTf)_2$ exhibited higher catalytic activity than other metal catalysts, and afforded product **2a** in 84% yield as the main regioisomer (C2 isomer at 1,3-dioxolane; Table 1, entries 2–11), and byproduct **2a′** (C4 isomer at 1,3-dioxolane) was isolated in 7% yield (see ESI,† S2). By respectively varying the amount of $Fe(OTf)_2$ as well as TBHP, the target product was produced with inferior yield (Table 1, entries 12–15). Other oxidants, such as $Na_2S_2O_8$, DTBP, and $K_2S_2O_8$, were not satisfactory for the reaction because either lower yield or no expected product was observed (Table 1, entries 16–18). Furthermore, variations of the ratio of DCE and 1,3-dioxolane produced the product **2a** in lower yields (Table 1, entries 19–21), and incrementally decreasing amounts of 1,3-dioxolane resulted in lower yields. Instead of DCE, other solvents, such as DCM, CH_3CN, DMF, and NMP, afforded inferior yields, although these results are not shown in Table 1. Finally, increasing or lowering the reaction temperature also resulted in lower yields (Table 1, entries 22 and 23).

Table 1 Optimization of the reaction conditions[a]



1a **2a**

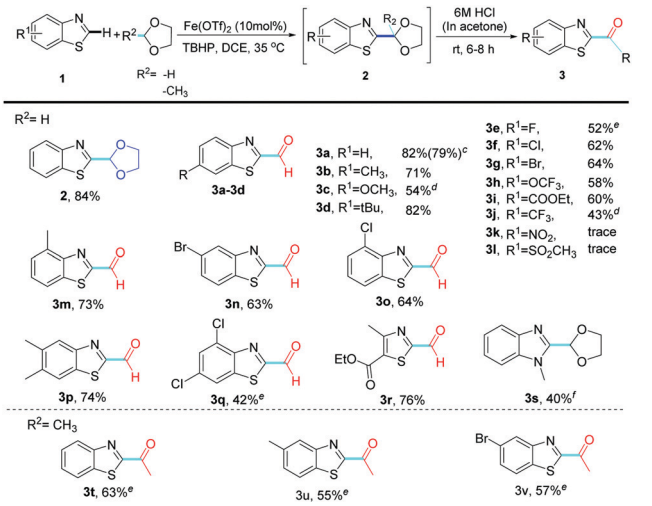
Entry	Catalyst	Oxidant	T (°C)	Yield[b] (%)
1	—	TBHP	35	NR
2	CuBr	TBHP	35	NR
3	$CuBr_2$	TBHP	35	Trace
4	$Cu(OTf)_2$	TBHP	35	Trace
5	$Cu(acac)_2$	TBHP	35	15%
6	$Cu(OAc)_2$	TBHP	35	32%
7	$CoCl_2$	TBHP	35	Trace
8	$FeCl_2$	TBHP	35	NR
9	$FeCl_3$	TBHP	35	Trace
10	$Fe(OTf)_2$	TBHP	35	Trace
11	$Fe(OTf)_2$	TBHP	35	84
12[c]	$Fe(OTf)_2$	TBHP	35	58
13[d]	$Fe(OTf)_2$	TBHP	35	74
14[e]	$Fe(OTf)_2$	TBHP	35	57
15[f]	$Fe(OTf)_2$	TBHP	35	64
16	$Fe(OTf)_2$	$Na_2S_2O_8$	35	Trace
17	$Fe(OTf)_2$	$K_2S_2O_8$	35	Trace
18	$Fe(OTf)_2$	DTBP	35	NR
19[g]	$Fe(OTf)_2$	TBHP	35	62
20[h]	$Fe(OTf)_2$	TBHP	35	67
21[i]	$Fe(OTf)_2$	TBHP	35	52
22	$Fe(OTf)_2$	TBHP	25	43
23	$Fe(OTf)_2$	TBHP	50	76

[a] Reaction conditions: **1a** (0.15 mmol), 1,3-dioxolane (1.0 mL), DCE (1.0 mL), metal salt (10 mmol%), and oxidant (2.5 equiv.) at 35 °C for 24 h under air. [b] Isolated yield. [c] $Fe(OTf)_2$ (8 mmol%). [d] $Fe(OTf)_2$ (12 mmol%). [e] TBHP (2 equiv.). [f] TBHP (3 equiv.). [g] **1,3-Dioxolane/DCE** (1.5 : 0.5, 2 mL). [h] **1,3-Dioxolane/DCE** (0.5 : 1.5, 2 mL). [i] **1,3Dioxolane** (2 mL). TBHP = *tert*-butyl hydroperoxide (5.0–6.0 M in decane).

For the synthesis of heteroarene aldehyde, 1,3-dioxolane as an aldehyde precursor is currently underutilized. The subsequent hydrolysis of **2a** was attempted to afford aldehyde derivative **3a** in the presence of 6 M HCl (in acetone) at room temperature for 6–8 h, and compound **3a** was conveniently prepared from benzothiazole **1a** and 1,3-dioxane *via* a two-step process in 79% total yields (Table 2, entry **3a**[c]). Otherwise, the byproduct **2a′** was not transferred to the hydrolysis product in the presence of protons or Lewis acids. Compared with a two-step procedure, a one-pot synthetic strategy for **3a** was also carried out, and afforded product **3a** in good yield (82% yield based on **1a**, Table 2, **3a**[b]).

Based on the above experimental results, we explored the substrate scope *via* a one-pot strategy. Various substituted benzothiazoles **1** were employed to react with 1,3-dioxolane (shown in Table 2). First, 6-substituted benzothiazoles **1** containing electron-donating groups, such as –Me, –OMe, and –^{t}Bu, reacted smoothly to generate the corresponding products (Table 2, **3b-3d**) in moderate to good yields (54–82%). Second, 6-substituted benzothiazoles **1** attached by an electron-withdrawing group, including –OCF_3, –COOEt, and –CF_3, also proceeded to deliver the corresponding products (Table 2, **3h-3j**) in moderate yields (43–60%). Additionally, 6-substituted benzothiazoles with halogen (F, Cl, Br)

Table 2 Substrate scope of benzothiazoles[ab]



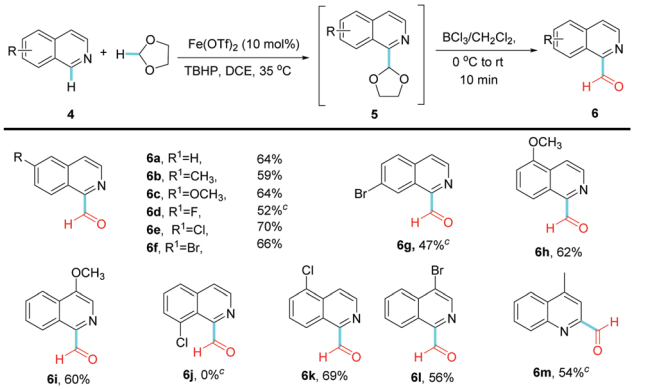
[a] Reaction conditions: **1** (0.15 mmol), 1,3-dioxolane (1.0 mL), DCE (1.0 mL), $Fe(OTf)_2$ (10 mol%), and TBHP (2.5 equiv.) at 35 °C for 24 h under air. TBHP = *tert*-butyl hydroperoxide (5.0–6.0 M in decane). [b] Isolated yield. [c] Isolated yield based on **1** *via* two-step procedure. [d] 36 h. [e] 48 h. [f] Aldehyde does not form under hydrolysis conditions.

substituents (Table 2, **3e-3g**) were also well tolerated with moderate yields (52–64%). However, 6-substituted benzothiazoles with $-NO_2$ and $-SO_2CH_3$ groups (Table 2, **3k-3l**) proved to be unsuitable for the reaction, and no desired products were detected or isolated. Third, the substituents on different positions of the benzothiazole core structure also worked well to generate the corresponding products in 42–74% yield under standard conditions (Table 2, **3m-3s**). Fourth, non-benzo-fused thiazole also afforded the desired product in 76% yield (Table 2, **3r**). Fifth, benzimidazole only afforded the oxidative crossing product under the optimized conditions.

The desired formylated product was not detected, although we also used other protons and Lewis acids ($In(OTf)_3$ and BCl_3, *etc.*) to catalyze the acetal hydrolysis reaction, but these catalysts were ineffective for the reaction (Table 2, **3s**). In addition, benzoxazole as a substrate was only transferred to the oxidative crossing product, and a hydrolysis product was not detected by GC–MS. Further investigations of benzimidazoles and benzoxazoles were not performed. Sixth, reactions with benzothiazoles and 2-methyl-1,3-dioxolane were carried out under standard conditions, hydrolysis products (ketone derivatives) were obtained in moderate yields (Table 2, entries **3t-3v**, 55–63% yields), and evident steric effects were not observed in these reactions. Finally, the model reaction on a 1 mmol scale was also carried out under the optimized conditions, and 71% isolated yield (**3a**) was obtained. However, partial substrates could not completely transfer to oxidative coupling products, even with an increase in the reaction time to 36 h or 48 h. Hydrolysis processes were always thoroughly completed in the presence of protons or Lewis acids.

To further extend the substrate scope of the above synthetic strategy, isoquinoline and quinoline substrates were explored

Table 3 Substrate scope of isoquinolines and quinolines[ab]

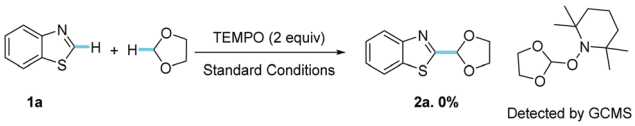


[a] Reaction conditions: **4** (0.15 mmol), 1,3-dioxolane (1.0 mL), DCE (1 mL), $Fe(OTf)_2$ (10 mol%), and TBHP (2.5 equiv.) at 35 °C for 36 h under air. TBHP = *tert*-butyl hydroperoxide (5.0–6.0 M in decane). [b] Isolated yield. [c] 48 h.

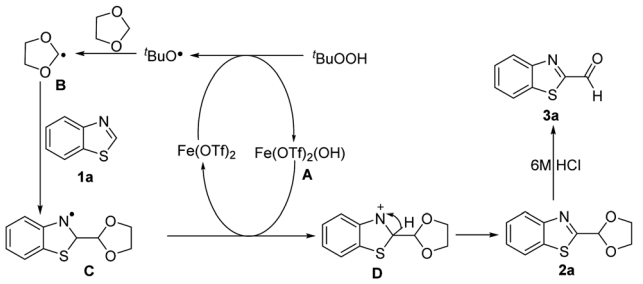
under the optimized conditions (Table 3). Fortunately, most of the available substrates smoothly completed to the desired products in moderate to good yields (Table 3, 47–70%) *via* a slightly modified hydrolysis procedure (1 M BCl_3/CH_2Cl_2 as the Lewis acid catalyst instead of 6 M HCl). The desired product was not obtained with 8-chloroisoquinoline (Table 3, **6j**), which implies that a heterocyclic skeleton may impart a steric hindrance effect.

To gain further insight to the reaction mechanism, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), as a classical radical trapping reagent, was added to the reaction under optimized conditions. The desired oxidative cross-product **2a** was not found upon addition of TEMPO, and dioxolane-TEMPO coupled species were detected by GC–MS. The reaction was entirely suppressed, which indicated that radicals may be involved in the reaction (Scheme 2). In the reaction, the homolytic cleavage of TBHP to form the hydroxide and *tert*-butoxy radical species might be accelerated in the presence of reductive ferric salt at low temperature. A significant kinetic isotopic effect (k_H/k_D = 3.18) in ref. 17*a* suggested that the $C(sp^3)$–H bond cleavage with concomitant formation of an *a*-oxyalkyl radical is likely the rate-determining step. In addition, it was proposed that benzothiazole was easily attacked by a radical.[15c]

Based on our experimental results and analyses in previous publications,[15b,15c,17] a plausible catalytic mechanism is presented in Scheme 3. Initially, single-electron transfer (SET) reduction of TBHP along with oxidation of $Fe(OTf)_2$ to $Fe(OTf)_2OH$ produced the *tert*-butyl oxygen radical (*t*-BuO•), and the radical can produce the alkyl radical **B** *via* abstracting hydrogen atoms from the



Scheme 2 Control experiment.



Scheme 3 Proposed mechanism.

1,3-dioxolane. Subsequently, radical **B** would attack benzothiazole-generated intermediate **C**, which can be oxidized to cation intermediate **D**, followed by proton release and re-aromatization to yield product **2a**. Finally, **2a** can be absolutely transformed into the desired product **3a** by an acid hydrolytic procedure. In addition, we assumed that $Fe(OTf)_2$ completed the catalytic cycle in assisting both the homolytic cleavage of TBHP and the oxidation of carbon radical **C** to cation **D**.

In conclusion, we report herein a new formylated procedure *via* iron catalytic oxidative coupling between heteroarenes and 1,3-dioxolane under mild reaction conditions, followed by the acid hydrolytic process. Under our optimized reaction conditions, benzothiazoles and isoquinolines were easily transformed to their corresponding aldehyde derivatives by a one-pot procedure. The reaction has the major characteristic advantages of a broad substrate scope and satisfactory functional group tolerance. The synthetic strategy provides a simple and efficient means of formylation of heteroarenes and their derivatives.

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Conflicts of interest

There are no conflicts to declare.

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