Environmentally Friendly Iron-Catalyzed Cascade Synthesis of 1,2,4-Benzothiadiazine 1,1-Dioxide and Quinazolinone Derivatives

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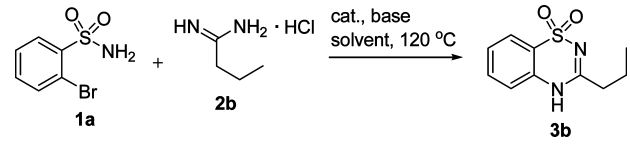
We have developed an efficient iron-catalyzed method for the cascade synthesis of 1,2,4-benzothiadiazine 1,1-dioxide and quinazolinone derivatives. The protocol uses inexpensive and environmentally friendly $FeCl_3$ as the catalyst, and no ligand or additive was required. This is the first example of construction of nitrogen-containing heterocycles via iron-catalyzed *N*-arylation in the absence of ligand. Therefore, this method is of practical application for the synthesis of the two different nitrogen-containing heterocycles.

Introduction

Benzothiadiazine-1,1-dioxide and quinazolinone derivatives are known to show various useful biological and medicinal activity. Benzothiadiazine-1,1-dioxide derivatives have been used as ATP-sensitive potassium channel openers (such as diazoxide in Figure 1),[1] and they have been shown to reduce the AMPA receptor desensitization[2] and improve the impaired synaptic transmission of functions, which are useful in the treatment of early stages of Alzheimer disease.[3] Some of them (**M**, Figure 1) have also been shown to possess antiviral activity,[4] particularly against human herpes virus 6 (HHV-6), human cytomegalovirus (H-CMV), and Varicella-Zostervirus (VZV), and are used as inhibitors of PDE7 with concurrent inhibitory activity at PDE4 and PDE3.[5] The quinazolinone motif widely occurs in natural products, such as luotonin **A** from *Peganum nigellastrum*,[6a] 2-methyl-4(3*H*)-quinazolinone from *Bacillus cereus*,[6b] 2-(4-hydroxybutyl)quinazolin-4-one from *Dichroa febrifuga*,[6c] and bouchardatine from *Bouchardatia neurococca* (Figure 1).[6d] The quinazolinone derivatives have also been shown to exhibit various biological activity, such as hypnotic, sedative, analgesic, anticonvulsant, antitussive, antibacterial, antidiabetic, anti-inflammatory, and antitumor.[7,8] Moreover, several therapeutic agents containing the quinazolinone structure are currently on the market or are in clinical trials for the treatment of cancer.[9]

Although several methods have previously been developed for the synthesis of benzothiadiazines-1,1-dioxides derivatives[1b−e,4e,6] and quinazolinone derivatives,[7,10,11] their routes are often troublesome and some of starting materials are not readily available. Recently, the transition metal-catalyzed formation of C−N bonds has attracted much attention.[12] So far, this field has been largely dominated by palladium[13] and copper-based methods.[12a−d] However, despite the efficiency of these protocols, the development of less expensive and environmentally more benign catalysts is still desirable for organic synthesis. Recently, iron-catalyzed N-arylations have been developed.[14] The efficiency of the iron-catalyzed coupling reactions highly depended on involvement of the suitable ligands. However, to the best of our knowledge, there are no examples from the literature demonstrating N-arylation or constructing N-heterocycles with iron-catalysis without the presence of an external ligand. We have previously reported the synthesis of N-heterocycles via Ullmann coupling strategies.[15] Herein, we report a simple, practical, and

Table 1. Iron-Catalyzed Coupling of 2-Bromobenzenesulfonamide with Butyramidine Hydrochloride: Optimization of Conditions[a]



entry	catalyst	base	solvent	yield (%)[b]
1	$FeCl_3$	Cs_2CO_3	DMF	80
2	$FeCl_2$	Cs_2CO_3	DMF	77
3	$Fe(acac)_3$	Cs_2CO_3	DMF	40
4	Fe_2O_3	Cs_2CO_3	DMF	75
5	Fe-powder	Cs_2CO_3	DMF	70
6	$FeCl_3$	K_2CO_3	DMF	65
7	$FeCl_3$	K_3PO_4	DMF	75
8	$FeCl_3$	Cs_2CO_3	1,4-dioxane	40
9	$FeCl_3$	Cs_2CO_3	toluene	trace
10	$FeCl_3$	Cs_2CO_3	DMF	65[c]
11	-	Cs_2CO_3	DMF	trace

[a] Reaction conditions: nitrogen atmosphere, 2-bromobenzenesulfonamide (1 mmol), butyramidine hydrochloride (1.2 mmol), iron catalyst (0.1 mmol), base (2 mmol), solvent (2 mL), and reaction time (12 h). [b] Isolated yield. [c] In the absence of nitrogen atmosphere.

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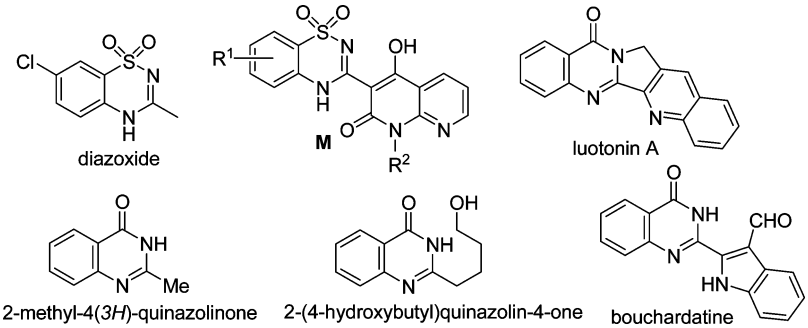
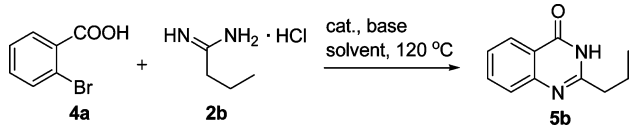


Figure 1. Examples of benzothiadiazine-1,1-dioxide and quinazolinone derivatives.

Table 2. Iron-Catalyzed Coupling of 2-Bromobenzoic Acid with Butyramidine Hydrochloride: Optimization of Conditions[a]



entry	catalyst	base	solvent	yield (%)[b]
1	$FeCl_3$	Cs_2CO_3	DMF	82
2	$FeCl_2$	Cs_2CO_3	DMF	70
3	$Fe(acac)_3$	Cs_2CO_3	DMF	50
4	Fe_2O_3	Cs_2CO_3	DMF	78
5	Fe-powder	Cs_2CO_3	DMF	55
6	$FeCl_3$	K_2CO_3	DMF	72
7	$FeCl_3$	K_3PO_4	DMF	76
8	$FeCl_3$	Cs_2CO_3	1,4-dioxane	50
9	$FeCl_3$	Cs_2CO_3	toluene	trace
10	$FeCl_3$	Cs_2CO_3	DMF	70[c]
11	-	Cs_2CO_3	DMF	trace

[a] Reaction conditions: nitrogen atmosphere, 2-bromobenzoic acid (1 mmol), butyramidine hydrochloride (1.2 mmol), iron catalyst (0.1 mmol), base (2 mmol), solvent (2 mL), reaction time (12 h). [b] Isolated yield. [c] In the absence of nitrogen atmosphere.

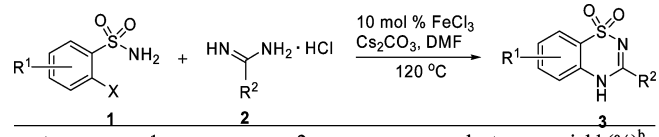
efficient method for the iron-catalyzed synthesis of benzothiadiazine-1,1-dioxide and quinazolinone derivatives without any additional ligand or additive.

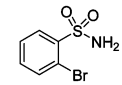
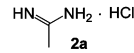
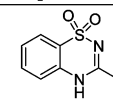
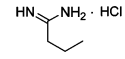
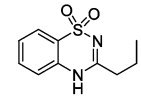
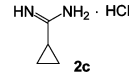
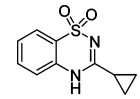
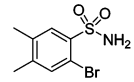
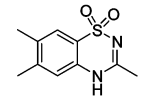
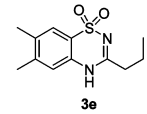
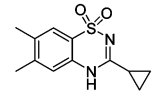
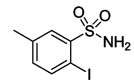
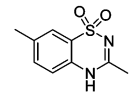
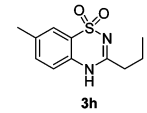
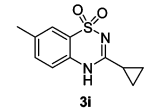
Results and Discussion

Optimization of Conditions. We first chose 2-bromobenzenesulfonamide and butyramidine hydrochloride as the model substrates to optimize the catalysis conditions, including iron catalysts, bases and solvents under nitrogen atmosphere. As shown in Table 1, several iron catalysts, $FeCl_3$, $FeCl_2$, $Fe(acac)_3$, Fe_2O_3, and Fe-powder (10 mol % relative to 2-bromobenzenesulfonamide) were tested in DMF (entries 1−5), and $FeCl_3$ was demonstrated to be the most effective. Several bases were attempted, and Cs_2CO_3 was shown to be a suitable base (compare entries 1, 6, and 7). The effect of solvents (DMF, 1,4-dioxane, toluene) was also investigated (compare entries 1, 8, and 9), and DMF afforded the highest yield. Lower yields were observed in the absence of nitrogen atmosphere (entry 10). Trace amount of the expected product were observed in the absence of catalyst (entry 11). The optimal reaction temperature was also investigated, and the yield of the target product reached a maximum at 120 °C.

As shown in Table 2, the optimization process was also performed for the synthesis of quinazolinone using 2-bromobenzoic acid and butyramidine hydrochloride as the model substrates, following procedures similar to Table 1. From these results, the optimum conditions for the preparations of benzothiadiazine-1,1-dioxide and quinazolinone deriva-

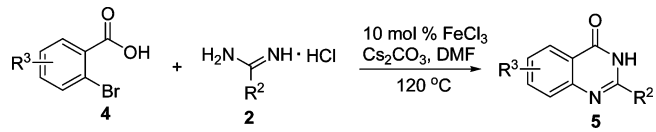
Table 3. Iron-Catalyzed Synthesis of 1,2,4-Benzothiadiazine 1,1-Dioxide Derivatives[a]



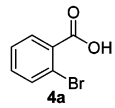
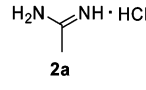
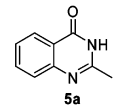
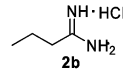
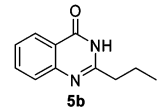
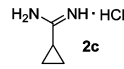
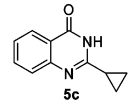
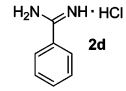
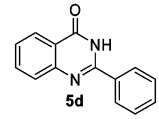
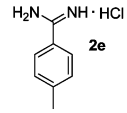
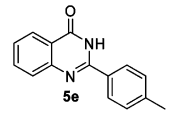
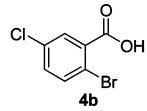
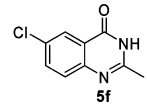
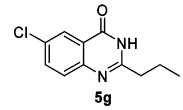
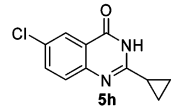
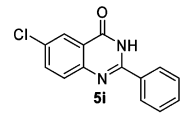
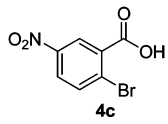
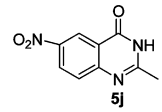
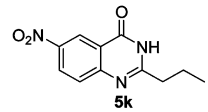
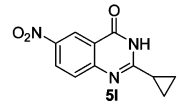
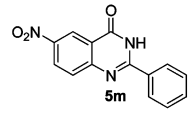
entry	1	2	product	yield (%)[b]
1	 1a	 2a	 3a	73
2	**1a**	 2b	 3b	80
3	**1a**	 2c	 3c	72
4	 1b	**2a**	 3d	72
5	**1b**	**2b**	 3e	70
6	**1b**	**2c**	 3f	73
7	 1c	**2a**	 3g	81
8	**1c**	**2b**	 3h	80
9	**1c**	**2c**	 3i	78

[a] Reaction conditions: nitrogen atmosphere, substituted 2-halobenzenesulfonamide (1 mmol), amidine hydrochloride (1.2 mmol), $FeCl_3$ (0.1 mmol), Cs_2CO_3 (2 mmol), DMF (2 mL), reaction time (12 h). [b] Isolated yield.

Table 4. Iron-Catalyzed Synthesis of Quinazolinone Derivatives via Cascade Reactions of Substituted 2-Halobenzoic Acid with Amidine Hydrochlorides[a]



4 2 5

entry	1	2	product/time	yield (%)[b]
1	 4a	 2a	 5a	80
2	**4a**	 2b	 5b	82
3	**4a**	 2c	 5c	74
4	**4a**	 2d	 5d	79
5	**4a**	 2e	 5e	83
6	 4b	**2a**	 5f	60
7	**4b**	**2b**	 5g	62
8	**4b**	**2c**	 5h	65
9	**4b**	**2d**	 5i	71
10	 4c	**2a**	 5j	70
11	**4c**	**2b**	 5k	82
12	**4c**	**2c**	 5l	75
13	**4c**	**2d**	 5m	82

[a] Reaction conditions: nitrogen atmosphere, substituted 2-halobenzoic acid (1 mmol), amidine hydrochloride (1.2 mmol), $FeCl_3$ (0.1 mmol), Cs_2CO_3 (2 mmol), DMF (2 mL), reaction time (12 h). [b] Isolated yield.

tives were shown to be: 10 mol % $FeCl_3$ as the catalyst, 2 equiv of Cs_2CO_3 as the base (relative to amount of 2-bromobenzenesulfonamide or 2-bromobenzoic acid), and DMF as the solvent at 120 °C under nitrogen atmosphere.

Iron-Catalyzed Synthesis of 1,2,4-Benzothiadiazine 1,1-Dioxide and Quinazolinone Derivatives. As shown in Table 3, the optimal coupling reactions gave the desired 1,2,4-benzothiadiazine 1,1-dioxide derivatives in good to excellent isolated yields for all of the substrates examined. For substituted 2-halobenzenesulfonamides, the aryl iodide showed better conversion to the desired product than the aryl bromides. Of the amidines examined in this coupling reaction, no significant reactivity differences were observed.

The scope of coupling reaction of substituted 2-bromobenzoic acids with amidines was also investigated. As shown in Table 4, the coupling reactions provided good yields. The electronic effect of the substituted groups in the 2-bromobenzoic acids including electron-rich, -neutral, and -deficient substituents did not display evident difference in reactivity. Both aliphatic and aromatic amidines provided high yields.

Conclusion

We have developed a simple and efficient iron-catalyzed synthesis of benzothiadiazine-1,1-dioxide and quinazolinone derivatives. These cascade coupling reactions were performed using inexpensive and environmentally friendly $FeCl_3$ as the catalyst and readily available 2-halobenzenesulfonamides, 2-bromobenzoic acids and amidine hydrochlorides as the starting materials, and no additional ligand or additive was required. The environmentally friendly protocol provides opportunity for the construction of diverse bioactive molecules in medicinal and combinatorial chemistry.

Experimental Section

General Procedure for Synthesis of Compounds 3a−i and 5a−m. A 25 mL round-bottom flask was charged with a magnetic stirrer and 2 mL of DMF. Substituted 2-halobenzenesulfonamide (**1**) or 2-bromobenzoic acid (**4**) (1 mmol) and amidine hydrochloride (**2**) (1.2 mmol) were added to the flask. After the mixture was stirred for 10 min under nitrogen atmosphere, $FeCl_3$ (0.1 mmol, 162 mg) was added to the solution. The mixture was stirred at 120 °C for 12 h. After completion of the reaction, the resulting solution was filtered, and the solvent of the filtrate was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel to give the desired product. Two selected examples are shown as follows:

3-Propyl-2*H*-1,2,4-benzothiadiazine-1,1-dioxide (3b). Eluent: petroleum ether/ethyl acetate (2:1). Yield: 180 mg (80%) as a white solid. mp: 187−189 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.97 (s, br, 1H), 7.79 (d, 1H, J = 7.89 Hz), 7.67 (t, 1H, J = 7.89 Hz), 7.43 (t, 1H, J = 7.20 Hz), 7.33 (d, 1H, J = 8.25 Hz), 2.54 (t, 2H), 1.72 (m, 2H), 0.95 (t, 3H, J = 7.20 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 160.7, 135.7, 133.6, 126.7, 124.0, 121.7, 117.8, 37.8, 20.1, 13.7. ESI-MS: $[M + H]^+$ *m/z* 224.7, $[M+Na]^+$ *m/z* 246.8.

6-Chloro-2-phenylquinazolin-4(3*H*)-one (5i).[16] Eluent: petroleum ether/ethyl acetate (3:1). Yield: 182 mg (71%) as a white solid. mp: 250−251 °C (lit.[16] 210 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.73 (s, br, 1H), 8.18 (d, 2H, J = 7.60 Hz), 8.10 (s, 1H), 7.88 (d, 1H, J = 6.00 Hz), 7.77 (d, 1H, J = 6.00 Hz), 7.59 (m, 3H).^{13}C NMR (DMSO-d_6, 75 MHz): δ 161.9, 153.4, 148.0, 135.3, 133.0, 132.2, 131.3, 131.1, 129.2, 128.4,125.4, 122.2. ESI-MS: $[M + H]^+$ *m/z* 257.3.

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Supporting Information Available. Synthetic procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of these synthesized compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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