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Highly Efficient Iron(II) Chloride/*N*-Bromosuccinimide-Mediated Synthesis of Imides and Acylsulfonamides

Feng Wang,[a] Hongxia Liu,[b] Hua Fu,[a,*] Yuyang Jiang,[b,*] and Yufen Zhao[a]

[a] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, People's Republic of China
Fax: (+86)-10-62781695; e-mail: fuhua@mail.tsinghua.edu.cn
[b] Key Laboratory of Chemical Biology (Guangdong Province), Graduate School of Shenzhen, Tsinghua University, Shenzhen 518057, People's Republic of China

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Abstract: We have developed a general and highly efficient iron(II) chloride/*N*-bromosuccinimide (NBS)-mediated method for the synthesis of imides and acylsulfonamides *via* couplings of thioesters with carboxamides/sulfonamides, and the method is simple, economical and shows practical advantages.

Keywords: acylsulfonamides; *N*-bromosuccinimide (NBS); homogeneous catalysis; imides; iron

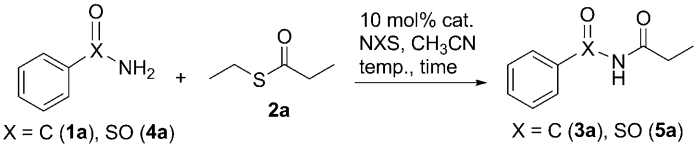
Introduction

The imide moiety represents an important substructure associated with certain natural products, such as fumaramidmycin,[1a,b] coniothyriomycin[1c] and SB-253514,[1d] and it also acts as a key component in a variety of reactions.[2] The acylsulfonamides are a class of biologically active compounds of current therapeutic interest,[3] for example they are used as HCV NS5B polymerase allosteric inhibitors,[3a] as well as anti-inflammatory[3b] and antitumor agents.[3c] Some methods for the synthesis of imides and acylsulfonamides have been reported. For example, coupling of acyl chlorides with carboxamides is a common approach to imides,[4a–c] and sometimes oxidation of *N*-alkylamides is used in the synthesis of imides.[4d,e] The usual methods for synthesis of acylsulfonamides are the coupling of sulfonamides with anhydrides, active esters or acyl chlorides[5a,b] and the direct condensation of sulfonamides with carboxylic acids in the presence of coupling agents.[5c,d] Recently, the rhodium- and ruthenium-catalyzed sulfamidation of aldehydes has been developed *via* a C–H activation strategy.[6] The copper-catalyzed three-component coupling of terminal alkynes, sulfonyl azides and water to form acylsulfonamides has been reported.[7] Every method above has it advantages and disadvantages, therefore it is still desirable to develop more convenient and efficient methods for the synthesis of imides and acylsulfonamides. Thioesters are importantly active intermediates in organic synthesis, and they can be utilized in transformations of a wide range of molecules,[8] such as the synthesis of amides.[9] The coupling reactions usually use amines (strong nucleophic reagents) as the partners of the thioesters. However, to the best of our knowledge, the coupling of various amides, such as carboxamides and sulfonamides (weak nucleophic reagents), with thioesters has not yet been reported. Iron is one of the most abundant, inexpensive and environmentally friendly metals on earth.[10] Very recently, we have developed an iron-catalyzed amidation of C–H bonds in the presence of NBS.[11] Herein, we report a novel, simple and highly efficient $FeCl_2$/NBS-mediated coupling of thioesters with carboxamides and sulfonamides to provide imides and acylsulfonamides.

Results and Discussion

Since *N*-halosuccinimides are effective N-halogenation reagents,[11,12] they can be used in our studies. At first, ethyl acetate was used as the partner of benzamide in the presence of $FeCl_2$ and NBS, and *N*-acetylbenzamide was obtained in 15% yield. *S*-Ethyl thiopropionate was chosen for its higher reactivity as model substrate to optimize the reaction conditions as shown in Table 1. The coupling provided imide **3a** in 42% yield using 0.1 equiv. of $FeCl_2$ as the catalyst, 0.4 equiv. of NBS as the N-halogenation reagent (rela-

Table 1. Metal/*N*-halosuccinimide-mediated coupling of *S*-ethyl thiopropionate with benzamide or benzenesulfonamide: optimization of conditions.[a]



X = C (**1a**), SO (**4a**) X = C (**3a**), SO (**5a**)

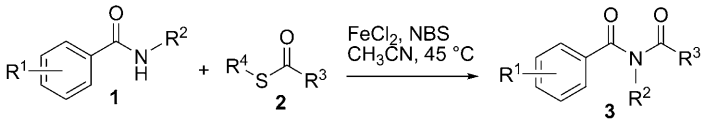
Entry	Amide	Catalyst [equiv.]	NBS [equiv.]	Temperature [°C]//time [h]	Yield [%][b]
1	**1a**	$FeCl_2$	NBS (0.4)	21/12	42
2	**1a**	$FeCl_2$	NBS (0.4)	45/12	65
3	**1a**	**$FeCl_2$**	**NBS (1)**	**45/12**	**80**
4	**1a**	$FeCl_2$	–	45/16	0
5	**1a**	–	–	45/16	0
6	**1a**	–	NBS (1)	45/12	46
7	**1a**	$FeCl_3$	NBS (1)	45/12	78
8	**1a**	$Fe(acac)_3$	NBS (1)	45/12	36
9	**1a**	CuBr	NBS (1)	45/12	76
10	**1a**	$CuCl_2$	NBS (1)	45/12	59
11	**1a**	$FeCl_2$	NCS (1)	45/12	72
12	**4a**	$FeCl_2$	NBS (1)	45/8	98
13	**4a**	**$FeCl_2$**	**NBS (0.4)**	**45/12**	**92**
14	**4a**	$FeCl_2$	–	45/12	0
15	**4a**	–	NBS (0.4)	45/12	45

[a] *Reaction conditions:* catalyst (0.1 mmol), benzamide or benzenesulfonamide (1 mmol), *S*-ethyl thiopropionate (1.2 mmol), CH_3CN (3 mL). The reaction was performed without exclusion of air.
[b] Isolated yield.

tive to amount of benzamide) and acetonitrile (CH_3CN) as the solvent at 21 °C for 12 h (entry 1), and yield of **3a** rose to 65% when temperature was increased to 45 °C (entry 2). The coupling provided an 80% yield when 1 equiv. of NBS was used (entry 3). The coupling reaction could not be performed in the absence of NBS or $FeCl_2$/NBS (entries 4 and 5), and a 46% yield of product was obtained without the addition of $FeCl_2$ (entry 6). We attempted to use other metal salts, $FeCl_3$, $Fe(acac)_3$, CuBr, and $CuCl_2$, and they showed weaker catalytic activity than $FeCl_2$ (entries 7–10). The coupling gave **3a** in 72% yield when NCS replaced NBS as the N-halogenation reagent (entry 11). We also attempted to couple of *S*-ethyl thiopropionate with benzenesulfonamide, and the reaction provided acylsulfonamide **5a** in 98% yield within 8 h (entry 12). Interestingly, 0.4 equiv. of NBS (relative to sulfonamide) was also effective for the coupling reaction (entry 13). The coupling of *S*-ethyl thiopropionate with benzenesulfonamide showed similar results to entries 4 and 6 in the absence of NBS or $FeCl_2$ (see entries 14 and 15). Investigation of the starting material stoichiometry revealed that a slight excess of *S*-ethyl thiopropionate (1.2 equiv.) was necessary to improve the yield of the products.

After the optimization process for metal salts and *N*-halosuccinimides, couplings of various thioesters with carboxamides or sulfonamides were carried out under our standard conditions: 10 mol% $FeCl_2$ and 0.4–1 equiv. of NBS (relative to carboxamide/sulfonamide) as the mediating reagents and CH_3CN as the solvent. As shown in Table 2, the coupling reactions of primary aromatic amides with aliphatic thioesters provided good to excellent yields, and aromatic amides containing electron-withdrawing groups showed higher reactivity than those containing electron-donating groups. Primary aromatic carboxamides were better substrates relative to secondary ones (entries 14 and 15), and aliphatic thioesters exhibited higher activity than *S*-ethyl thiobenzoate (entry 16). Methyl thioester **2b** (entries 6–9) displayed higher activity than ethyl thioester **2a**. Interestingly, couplings of sulfonamides with various thioesters gave good to excellent yields as shown in Table 3, and electronic variation in the sulfonamides and thioesters did not obviously affect the efficiency of the reactions. Sulfonamides and thioesters with functional groups such as ester (entry 8), amide (entry 9), nitro (entry 7), carbon-halogen bonds on aryl ring (entries 3, 10, 13, 14), and sulfur- or nitrogen-containing heterocycles (entries 10 and 14) coupled well with thioesters. Secondary sulfonamides were weaker substrates relative to primary ones (entry 11).

Table 2. $FeCl_2$/NBS-mediated couplings of carboxamides with thioesters.[a]



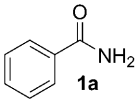
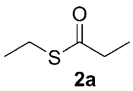
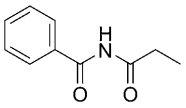
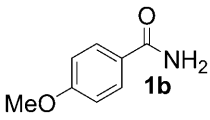
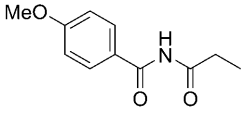
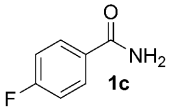
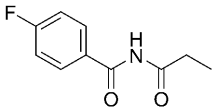
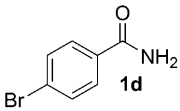
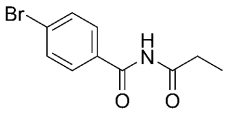
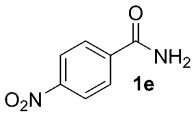
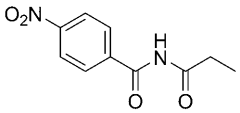
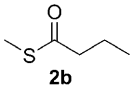
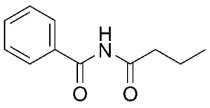
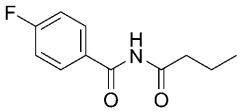
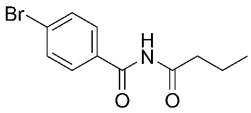
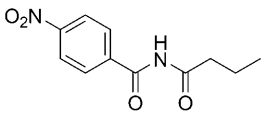
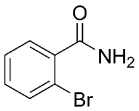
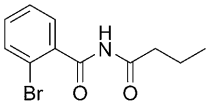
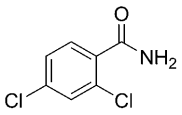
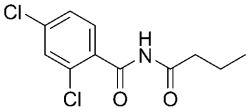
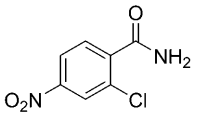
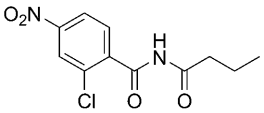
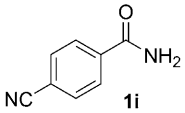
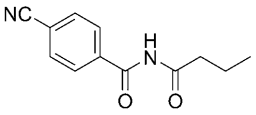
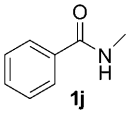
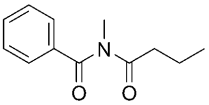
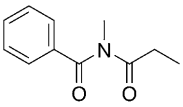
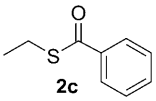
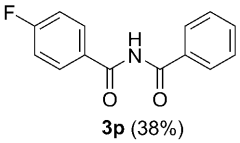
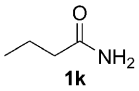
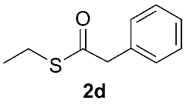
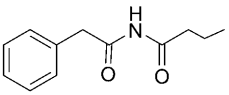
Entry	1	2	Time [h]	Product (Yield[b] [%])
1	 **1a**	 **2a**	12	 **3a** (80%)
2	 **1b**	**2a**	8	 **3b** (75%)
3	 **1c**	**2a**	12	 **3c** (86%)
4	 **1d**	**2a**	12	 **3d** (80%)
5	 **1e**	**2a**	10	 **3e** (82%)
6	**1a**	 **2b**	8	 **3f** (95%)
7	**1c**	**2b**	8	 **3g** (85%)
8	**1d**	**2b**	8	 **3h** (80%)
9	**1e**	**2b**	8	 **3i** (74%)
10	 **1f**	**2b**	16	 **3j** (58%)

Table 2. (Continued)

Entry	1	2	Time [h]	Product (Yield[b] [%])
11	 **1g**	**2b**	20	 **3k** (81%)
12	 **1h**	**2b**	20	 **3l** (90%)
13	 **1i**	**2b**	20	 **3m** (85%)
14	 **1j**	**2b**	16	 **3n** (52%)
15	**1j**	**2a**	12	 **3o** (48%)
16	**1c**	 **2c**	16	 **3p** (38%)
17	 **1k**	 **2d**	16	 **3q** 35%)

[a] *Reaction conditions:* carboxamide (1 mmol), thioester (1.2 mmol), $FeCl_2$ (0.1 mmol), NBS (1 mmol), CH_3CN (3 mL).
[b] Isolated yield.

Conclusions

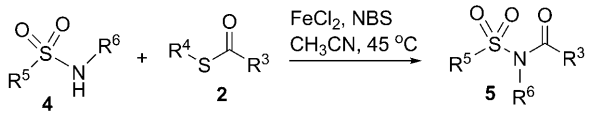
We have developed a general and highly efficient $FeCl_2$/NBS-mediated method for couplings of thioesters with carboxamides and sulfonamides in the presence of NBS, and the corresponding imides and acylsulfonamides were obtained in good to excellent yields. The protocol uses inexpensive and environmentally friendly $FeCl_2$ as the catalyst, and no additional ligand and additive were required. Therefore, our procedure may find widespread use in organic chemistry and medicinal chemistry. Further investigations in this direction are in progress.

Experimental Section

General Experimental Procedure for the Preparation of Compounds 3a–q and 5a–r

A 10-mL round-bottom flask was charged with a magnetic stirrer, carboxamide or sulfonamide (1 mmol), *N*-bromosuccinimide (NBS) (1 mmol, 178 mg for the synthesis of imides; 0.4 to 1 mmol for synthesis of acylsulfonamides), $FeCl_2$ (0.1 mmol, 13 mg) and 3 mL of acetonitrile (CH_3CN) were added to the flask at room temperature, After stirring for 1 min, thioester (1.2 mmol) was added to the solution. The mixture was stirred at 45 °C for a time as shown in Table 2 and Table 3. The resulting solution was concentrated by the rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the desired product.

Table 3. $FeCl_2$/NBS-mediated couplings of sulfonamides with thioesters.[a]



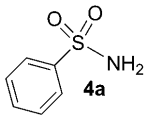
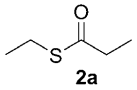
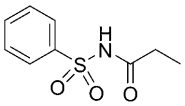
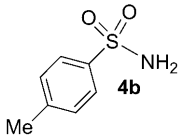
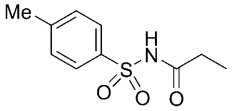
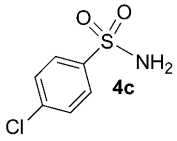
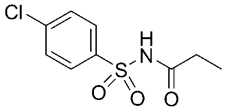
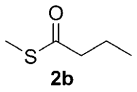
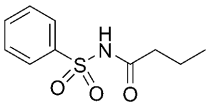
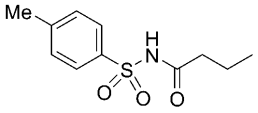
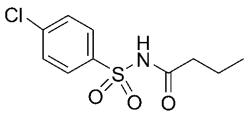
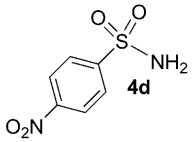
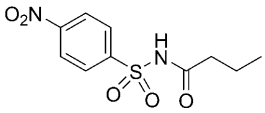
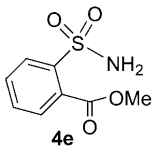
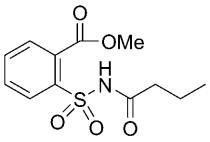
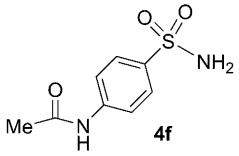
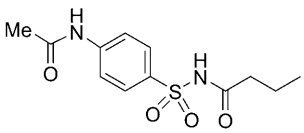
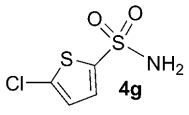
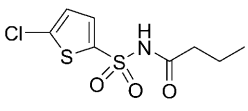
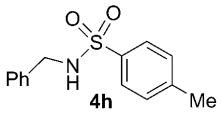
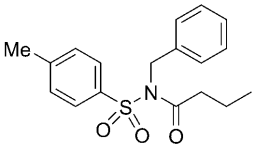
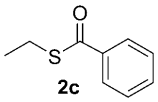
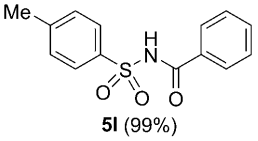
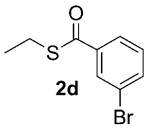
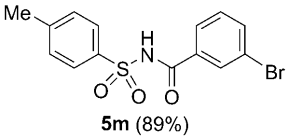
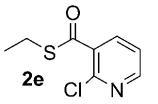
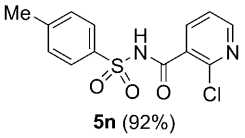
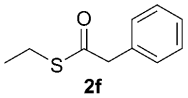
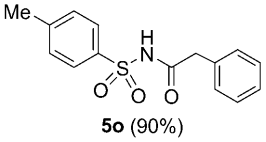
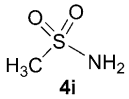
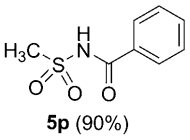
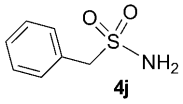
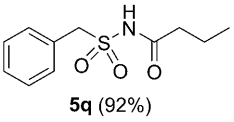
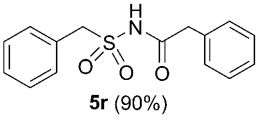
Entry	4	2	NBS [equiv]/Time [h]	Product (Yield[b] [%])
1	 **4a**	 **2a**	0.4/8	 **5a** (92%)
2	 **4b**	**2a**	0.4/8	 **5b** (94%)
3	 **4c**	**2a**	0.4/8	 **5c** (96%)
4	**4a**	 **2b**	0.8/6	 **5d** (97%)
5	**4b**	**2b**	0.4/8	 **5e** (95%)
6	**4c**	**2b**	1/8	 **5f** (98%)
7	 **4d**	**2b**	0.8/10	 **5g** (93%)
8	 **4e**	**2b**	0.8/10	 **5h** (94%)
9	 **4f**	**2b**	1/12	 **5i** (86%)
10	 **4g**	**2b**	1/8	 **5j** (98%)

Table 3. (Continued)

Entry	4	2	NBS [equiv]/Time [h]	Product (Yield[b] [%])
11	 **4h**	**2b**	1/8	 **5k** (45%)
12	**4b**	 **2c**	1/8	 **5l** (99%)
13	**4b**	 **2d**	1/10	 **5m** (89%)
14	**4b**	 **2e**	1/10	 **5n** (92%)
15	**4b**	 **2f**	0.4/10	 **5o** (90%)
16	 **4i**	**2c**	1/8	 **5p** (90%)
17	 **4j**	**2b**	1/8	 **5q** (92%)
18	**4j**	**2f**	1/8	 **5r** (90%)

[a] *Reaction conditions:* sulfonamide (1 mmol), thioester (1.2 mmol), $FeCl_2$ (0.1 mmol), NBS (0.4 to 1 mmol), CH_3CN (3 mL).
[b] Isolated yield.

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