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A novel and practical synthesis of 2-benzoylbenzothiazoles and 2-benzylbenzothiazoles

Xuesen Fan *, Yan He, Yangyang Wang, Zaikun Xue, Xinying Zhang, Jianji Wang

School of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, PR China

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ABSTRACT

A novel methodology for the synthesis of 2-benzoylbenzothiazoles and 2-benzylbenzothiazoles through $FeCl_3·6H_2O$ catalyzed, air oxidized tandem process from commercially available 2-aminothiophenols and phenylacetaldehydes by using an ionic liquid as both reaction medium and co-catalyst was developed.

2-Substituted benzothiazoles have attracted much attention due to their diverse biological activities and increasing applications in material fields.[1] Among them, α-ketobenzothiazoles are of special interests and have been studied as potential inhibitors of GAR transformylase and AICAR transformylase.[2] In addition, α-ketobenzothiazole moiety has been introduced at the C-terminal end of the peptidyl prolyl endopeptidase (PEP) inhibitors to increase the oral potency and penetration in the central nervous system and to enhance the PEP inhibitory activity.[3] Moreover, they have been used as an interesting subtype of carbonyl compounds to study the regio-selectivity in the reaction of Grignard reagents.[4]

α-Ketobenzothiazoles are usually obtained from lithiated heterocycles and Weinreb amides,[2,5] or through Swern oxidation of α-hydroxyheterocycles, which are prepared from lithiated heterocycles and aldehydes under drastic conditions.[3] Another protocol involves the pre-made 2-(trimethylsilyl)-1,3-benzothiazole and benzoyl chlorides.[4] While literature methods are generally efficient,[2–7] they still suffer from harsh reaction conditions, pre-made or expensive starting materials, or generation of hazardous wastes. Therefore, there is an urgent need to develop a more practical and clean method. In this regard, we envisioned a novel route through benzylic oxidation of 2-benzylbenzothiazoles, which could be obtained through the known oxidative condensation of phenyl acetaldehyde with 2-aminothiophenols.

In recent years, iron as an abundant, economical, and environmentally friendly metal has shown increasing promise as a catalyst in many organic syntheses.[8] Among various iron compounds, $FeCl_3·6H_2O$ is not only readily available, but also is extremely cheap. It has showed versatile reactivity and has been used as either oxidant or Lewis acid catalyst in a wide variety of organic reactions.[9–18]

Based on the above facts, we began to study our envisioned route toward 2-α-ketobenzothiazoles through tandem reaction of 2-aminothiophenols and phenyl acetaldehydes by using $FeCl_3·6H_2O$ as an oxidant (Scheme 1). For this study, we chose $[bmim]BF_4$ as the reaction medium since the application of ionic liquids (ILs) as 'green' alternatives to conventional solvents has become increasingly important. Moreover, ILs' high polarity and the ability to solubilize both inorganic and organic compounds can result in enhanced rates of chemical processes and provide higher selectivity compared to conventional solvents.[19,20]

Firstly, 2-aminothiophenol (**1a**) and phenyl acetaldehyde (**2a**) were treated with $FeCl_3·6H_2O$ (0.1 equiv) in $[bmim]BF_4$. It showed that in the first several hours upon heating at 60 °C, the reaction mainly gave 2-benzylbenzothiazole **3a** (Table 1, entry 1). Over prolonged treatment, to our delight, **3a** gradually turned into 2-benzoylbenzothiazole **4a** (entry 2). Further study showed that the tandem process from **1a** and **2a** to **4a** completed in 16 h at 60 °C (entry 3). When it was run at 80 °C, the period for a complete transformation was shortened to 12 h (entry 6). It was also found that increasing the amount of $FeCl_3·6H_2O$ to 0.2 equiv did not improve the reaction (Table 1, entry 7). On the other hand, in the absence of either $FeCl_3·6H_2O$ (entry 8) or air (entry 9), only trace amount of **4a** were formed as indicated by TLC analysis, indicating that both $FeCl_3·6H_2O$ (cat.) and air are indispensable for the tandem process leading to **4a**.

Then, a variety of ferric salts were examined. With $FeCl_3$ or $Fe(NO_2)_3·9H_2O$ (entries 10 and 11), the reactions gave similar results as that of $FeCl_3·6H_2O$. With $Fe_2(SO_4)_3·xH_2O$, however, the yield of **4a** was much lower (entry 12). While the exact cause is still under study, the decreased activity of $Fe_2(SO_4)_3·xH_2O$ may be attributed to its lower solubility in $[bmim]BF_4$. Finally, the effect of different solvents was investigated. In this regard, $[bmim]PF_6$ was found to be as effective as $[bmim]BF_4$ (Table 1, entry 13). In the case of 1-*n*-butyl-2,3-dimethylimidazolium hexafluorophosphate ($[bmmim]PF_6$), with the proton of C-2 on the imidazole ring

* Corresponding author. Tel.: +86 373 332 9261; fax: +86 373 332 6336.
E-mail address: xuesen.fan@henannu.edu.cn (X. Fan).

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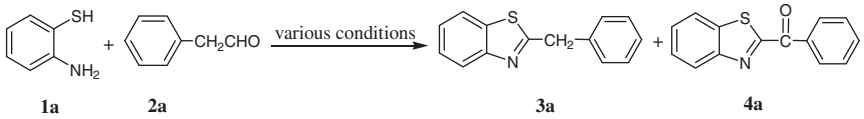
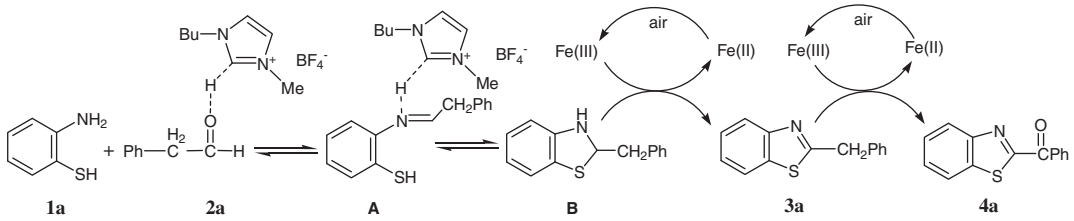


Scheme 1.

Table 1
Optimization of the tandem reaction of **1a** and **2a**[a]

Entry	Solvent	Catalyst	Amount (equiv)	Time (h)	Temp. (°C)	Yield[b] (%)	
						3a	**4a**
1	[bmim]BF_4	$FeCl_3·6H_2O$	0.1	2	60	53	Trace
2	[bmim]BF_4	$FeCl_3·6H_2O$	0.1	8	60	20	55
3	[bmim]BF_4	$FeCl_3·6H_2O$	0.1	16	60	—	80
4	[bmim]BF_4	$FeCl_3·6H_2O$	0.1	2	80	57	Trace
5	[bmim]BF_4	$FeCl_3·6H_2O$	0.1	8	80	10	70
6	[bmim]BF_4	$FeCl_3·6H_2O$	0.1	12	80	—	82
7	[bmim]BF_4	$FeCl_3·6H_2O$	0.2	12	80	—	81
8	[bmim]BF_4	—	—	12	80	Trace	Trace
9	[bmim]BF_4	$FeCl_3·6H_2O$	0.1	12	80	Trace[c]	Trace[c]
10	[bmim]BF_4	$FeCl_3$	0.1	12	80	—	84
11	[bmim]BF_4	$Fe(NO_2)_3·9H_2O$	0.1	12	80	—	78
12	[bmim]BF_4	$Fe_2(SO_4)_3·xH_2O$	0.1	12	80	25	41
13	[bmim]PF_6	$FeCl_3·6H_2O$	0.1	12	80	—	80
14	[bmmim]PF_6	$FeCl_3·6H_2O$	0.1	12	80	10	52
15	THF	$FeCl_3·6H_2O$	0.1	12	Reflux	12	43
16	CH_3CN	$FeCl_3·6H_2O$	0.1	12	Reflux	10	40
17	Toluene	$FeCl_3·6H_2O$	0.1	12	80	15	38

[a] Reaction conditions: 1 mmol of **1a** and **2a**; 1 mL of solvent for entries 1–13, 5 mL of solvent for entries 14–16.
[b] Isolated yields.
[c] Under N_2.

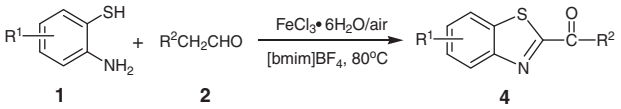


Scheme 2.

being replaced by a methyl group, the yield of **4a** dropped to 52% while other conditions remained unchanged (entry 14). When utilizing THF, CH_3CN, or Toluene, however, the reactions under similar conditions afforded a mixture of **4a** and **3a** (entries 15–17) and **4a** was obtained in low yield.

Based on the above observations, a plausible mechanism for the formation of **3a** and **4a** is depicted in Scheme 2. Firstly, the accelerating effect showed by [bmim]BF_4 compared with conventional organic solvents is most probably attributed to the acidity of the hydrogen on the 2-position of the imidazolium cation and to its ability to act as a hydrogen bond donor. The formation of the O–H hydrogen bond between $[bmim]^+$ and the carbonyl oxygen of **2a** induces electrophilic activation of aldehyde, which benefits the initial condensation of **1a** with **2a** to give an imine **A**. Moreover, it may further form an N–H hydrogen bond with the in situ formed imine **A** and this would accelerate the subsequent *intramolecular* nucleophilic cyclization to afford **B**. **B** is then oxidized by Fe(III) to give **3a**, which subsequently undergoes a benzylic oxidation promoted by Fe(III) to give **4a** as the final product. At the same time, the in situ formed Fe(II) could be oxidized by air to regenerate Fe(III) for the next catalytic cycle. It is noted that in the above process, Fe(III)'s role as a Lewis acid in promoting the condensation of **1a** and **2a** should not be eliminated.

The optimized reaction conditions were then applied to a series of substituted *o*-aminothiophenols and phenyl acetaldehydes to explore its scope and generality (Scheme 3, Table 2). It showed that all the substrates reacted smoothly and efficiently to give **4** in good yields. For aldehydes and aminobenzothiols with electron-withdrawing or electron-donating groups on the phenyl rings, the reactions proceeded with almost equal efficiency. Various functional groups, such as methyl, methoxy, nitro, fluoro, chloro, and bromo groups, were well tolerated under this condition. To our knowledge, this is the first report in which $FeCl_3·6H_2O$ (cat.) and air act as efficient oxidant for the tandem process including oxidative cyclization and subsequent benzylic oxidation to afford 2-benzoylbenzothiazole. Though it has been reported by Bolm et al.[8b] that ketones could be formed through benzylic oxidation in the presence of catalytic amount of $FeCl_3·6H_2O$, *tert*-butyl hydroperoxide (TBHP) was employed therein acting as a stoichiometric

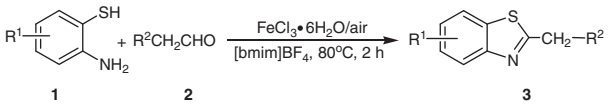


Scheme 3.

Table 2
$FeCl_3·6H_2O$ catalyzed tandem reactions of 2-aminothiophenols (**1**) with phenyl acetaldehydes (**2**)[a]

Entry	R^1 (**1**)	R^2	Product	Time (h)	Yield[b] (%)
1	H	C_6H_5	**4a**	12	82
2	H	4-$CH_3OC_6H_4$	**4b**	12	83
3	H	4-$CH_3C_6H_4$	**4c**	12	80
4	H	4-FC_6H_4	**4d**	12	79
5	H	3-$CH_3C_6H_4$	**4e**	12	75
6	4-Cl	C_6H_5	**4f**	12	87
7	4-Cl	4-$CH_3C_6H_4$	**4g**	12	85
8	4-Cl	4-FC_6H_4	**4h**	12	79
9	4-Cl	3-$CH_3C_6H_4$	**4i**	12	77
10	3-Cl	C_6H_5	**4j**	14	74
11	3-Cl	4-$CH_3C_6H_4$	**4k**	14	76
12	3-Cl	4-FC_6H_4	**4l**	14	68
13	3-Cl	3-$CH_3C_6H_4$	**4m**	14	66
14	3-Cl	4-BrC_6H_4	**4n**	14	65
15	5-CH_3	4-$CH_3OC_6H_4$	**4o**	12	74
16	5-CH_3	4-$CH_3C_6H_4$	**4p**	12	76
17	5-CH_3	4-FC_6H_4	**4q**	12	75
18	5-CH_3	4-ClC_6H_4	**4r**	12	80
19	5-CH_3	4-BrC_6H_4	**4s**	12	81
20	5-CH_3	4-$NO_2C_6H_4$	**4t**	12	82

[a] Reaction conditions: 1 mmol of **1** and **2**, 0.1 mmol of $FeCl_3·6H_2O$, 1 mL of [bmim]BF_4, 80 °C.
[b] Isolated yields.



Scheme 4.

oxidant. Therefore, the protocol presented herein results in a highly straightforward, mild, and practical method leading to α-ketobenzothiazoles from readily available starting materials.[21]

Next, the recyclability of Fe(III) together with [bmim]BF_4 was studied by using **1a** and **2a** as model substrates. Upon completion of the tandem reaction, Fe(III) and [bmim]BF_4 were easily recovered after the reaction mixture was extracted with ethyl ether (5 mL × 3) and dried under vacuum at 90 °C overnight. The recovered Fe(III)/[bmim]BF_4 was reused three times and gave **4a** in yield of 80%, 76% and 75% over each recycle. In these reactions, [bmim]BF_4 acts as not only a reaction medium, but also as a co-catalyst and an immobilizing agent for facilitating the catalyst recycling.

Last but not the least, 2-benzylbenzothiazoles (**3**) are also an important subtype of benzothiazoles and have been studied as novel class of potent, orally active aldose reductase inhibitors,[22] potential antidepressants[23], or as potential photochromic compounds.[24] Therefore, the search for practical methods to prepare this class of heterocycles certainly benefits both synthetic and medicinal chemistry.[25] Based on the results listed in Table 1, we were able to find that the preparation of **3** could be conveniently accomplished by simply reacting substrates **1** and **2** at 80 °C for 2 h in [bmim]BF_4 in the presence of 0.1 equiv of $FeCl_3·6H_2O$ (Table 1, entry 4).[26] The reaction was illustrated in Scheme 4 and the results were listed in Table 3.

Table 3
Preparation of 2-benzylbenzothiazoles (**3**)[a]

Entry	R^1 (**1**)	R^2	Product	Yield[b] (%)
1	H	C_6H_5	**3a**	57
2	4-Cl	C_6H_5	**3b**	60
3	5-CH_3	C_6H_5	**3c**	53
4	3-Cl	C_6H_5	**3d**	51
5	H	4-FC_6H_4	**3e**	52
6	4-Cl	4-FC_6H_4	**3f**	53

[a] 1 mmol of **1** and **2**, 0.1 mmol of $FeCl_3·6H_2O$, 1 mL of [bmim]BF_4, 80 °C, 2 h.
[b] Isolated yields.

In conclusion, we have developed a straightforward and novel methodology for the synthesis of 2-benzoyl benzothiazoles through $FeCl_3·6H_2O$ (cat.)/air promoted tandem process from commercially available *o*-amino thiophenol and phenyl acetaldehyde. Moreover, from the same reaction system, 2-benzylbenzothiazoles could also be obtained selectively with shorter reaction period. Compared with literature methods, advantages of this new strategy include high efficiency, simple procedure, readily available starting material and reagents, and an environmentally benign nature. Further studies to search for more applications of this novel tandem procedure are currently underway and the results will be reported in due course.

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21. *General procedure for the preparation of 2-benzoyl benzothiazoles* (**4**): To 1 mL of [bmim]BF_4 were added 2-aminothiophenol (1 mmol), phenylacetaldehyde

(1 mmol) and $FeCl_3{\cdot}6H_2O$ (0.1 mmol). The reaction mixture was stirred at 80 °C for the time period as shown in Table 2. Upon completion, the mixture was cooled to room temperature and extracted with ethyl ether (5 mL × 3). The combined organic phases were concentrated under vacuum. The crude product was purified by column chromatography eluting with ethyl acetate/hexane (1–10%) to give the desired product **4**. Details of analytical data of selected compounds are presented as follows: **4a**: yellow solid, mp 96–98 °C (lit.[4] mp 98–99 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55–7.63 (m, 4H, ArH), 7.69 (t, 1H, J = 7.2 Hz, ArH), 8.04 (d, 1H, J = 7.2 Hz, ArH), 8.27 (d, 1H, J = 7.6 Hz, ArH), 8.58 (d, 2H, J = 7.2 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 122.16, 125.72, 126.92, 127.61, 128.50, 131.26, 133.90, 134.95, 136.99, 153.87, 167.09, 185.39. MS: m/z 240 $(MH)^+$. **4b**: colorless solid, mp 120–121 °C (lit.[4] mp 122–123 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (s, 3H, OCH_3), 7.05 (d, 2H, J = 8.8 Hz, ArH), 7.52–7.61 (m, 2H, ArH), 8.02 (d, 1H, J = 7.6 Hz, ArH), 8.24 (d, 1H, J = 8.4 Hz, ArH), 8.65 (d, 2H, J = 8.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.58, 113.88, 122.14, 125.53, 126.81, 127.39, 127.71, 133.85, 136.85, 153.86, 164.37, 167.87, 183.46. MS: m/z 270 $(MH)^+$. **4h**: pink solid, mp 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23–7.26 (d, 2H, J = 8.8 Hz, ArH), 7.53 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.0 Hz, ArH), 7.94 (d, 1H, J = 8.8 Hz, ArH), 8.23 (d, 1H, J = 1.6 Hz, ArH), 8.64–8.68 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 115.73, 115.94, 122.98, 125.19, 128.32, 130.90, 133.07, 134.16, 134.26, 135.17, 154.51,165.22, 168.80, 183.13. MS: m/z 292 $(MH)^+$. HRMS (FAB) calcd for $C_{14}H_8ClFNOS$: 292.0000 [M+H], found: 291.9992. **4j**: pale brown solid, mp 110–112 °C (lit.[6] mp 106–108 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (t, 1H, J = 8.0 Hz, ArH), 7.57–7.71 (m, 4H, ArH), 7.92 (dd, 1H, $J1$ = 8.0 Hz, $J2$ = 0.8 Hz, ArH), 8.68 (dd, 2H, $J1$ = 8.4 Hz, $J2$ = 1.2 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 120.63, 127.04, 128.04, 128.55, 130.63, 131.51, 134.12, 134.56, 138.42, 151.00, 167.79, 184.49. MS: m/z 274 $(MH)^+$. **4k**: colorless solid, mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (s, 3H, CH_3), 7.38 (d, 2H, J = 8.0 Hz, ArH), 7.47 (t, 1H, J = 8.0 Hz, ArH), 7.61 (d, 1H, J = 8.0 Hz, ArH), 7.91 (d, 1H, J = 8.0 Hz, ArH), 8.59 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.87, 120.65, 126.99, 127.95, 129.36, 130.50, 131.66, 131.98, 138.37, 145.35, 151.10, 167.50, 184.08. MS: m/z 288 $(MH)^+$. HRMS (FAB) calcd for $C_{15}H_{11}ClNOS$: 288.0251 [M+H], found: 288.0249.

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26. *General procedure for the synthesis of 2-benzyl benzothiazoles* (**3**): To 1 mL of $[bmim]BF_4$ were added 2-aminothiophenol (1 mmol), phenylacetaldehyde (1 mmol) and $FeCl_3{\cdot}6H_2O$ (0.1 mmol). The reaction mixture was stirred at 80 °C for 2 h. Upon completion, the mixture was cooled to room temperature and extracted with ethyl ether (5 mL × 3). The combined organic phases were concentrated under vacuum. The crude product was purified by column chromatography eluting with ethyl acetate/hexane (1–10%) to give the desired product **3**. Details of analytical data of selected compounds are presented as follows: **3a**: syrup (lit.[25]), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.45 (s, 2H, CH_2), 7.29–7.39 (m, 6H, ArH), 7.46 (td, 1H, J_1 = 7.6 Hz, J_2 = 0.8 Hz, ArH), 7.79 (d, 1H, J = 8.0 Hz, ArH), 8.01 (d, 1H, J = 8.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.61, 121.50, 122.76, 124.80, 125.95, 127.33, 128.85, 129.15, 135.66, 137.18, 153.25, 171.18. MS: m/z 226 $(MH)^+$. **3c**: syrup, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.45 (s, 3H, CH_3), 4.41 (s, 2H, CH_2), 7.24–7.36 (m, 6H, ArH), 7.57 (s, 1H, ArH), 7.86 (d, 1H, J = 8.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.43, 40.55, 121.24, 122.21, 127.25, 127.48, 128.80, 129.12, 134.85, 135.81, 137.29, 151.31, 169.99. MS: m/z 240 $(MH)^+$. HRMS (FAB) calcd for $C_{15}H_{14}NS$: 240.0848 [M+H], found: 240.0844. **3e**: syrup, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.41 (s, 2H, CH_2), 7.04 (t, 2H, J = 8.4 Hz, ArH), 7.31–7.36 (m, 3H, ArH), 7.46 (td, 1H, J_1 = 7.2 Hz, J_2 = 0.8 Hz, ArH), 7.80 (d, 1H, J = 7.6 Hz, ArH), 7.99 (d, 1H, J = 8.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.71, 115.60, 115.82, 121.52, 122.78, 124.90, 126.03, 126.15, 130.64, 130.72, 135.55, 153.22, 170.80. MS: m/z 244 $(MH)^+$. HRMS (FAB) calcd for $C_{14}H_{11}FNS$: 244.0597 [M+H], found: 244.0596.