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Iron-catalyzed arylation or aroylation of benzothiazoles with benzylic alcohols and aryl ketones

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ABSTRACT

An iron-catalyzed arylation or aroylation of benzothiazoles with alcohols and aryl ketones via an in situ cross-trapping strategy has been described. Both the use of an iron catalyst and the ratio of substrates are important for this transformation, and this reaction is sensitive to the electronic effects of the substituents.

1. Introduction

Benzothiazoles belong to one of the most important classes of heterocycles for the synthesis of pharmaceuticals, natural products, functional materials, and many other biologically active molecules.[1–5] Among them, 2-aryl benzothiazoles and 2-acylbenzo thiazoles are of special interest owing to their potent utility as antitumor agents[6,7] and inhibitors of glycinamide ribonucleotide transformylase (GAR Tfase) or aminoimidazole carboxamide ribonucleotide transformylase (AICAR Tfase).[8] Many reports have appeared in the literature describing the approaches for assembly of these important compounds, such as condensation of 2-aminothiophenols with aldehydes[9–12] or acetophenone,[13] intramolecular cyclization of thioformanilides,[14–16] transition metal-catalyzed cross couplings,[17,18] and the classical Friedel–Crafts acylation.[19] While the aforementioned methods are generally efficient and reliable, they often suffer from harsh reaction conditions, expensive catalysts, and specially made or oxidizable starting materials. Recently, Wu and co-workers reported an efficient strategy for the in situ cross-trapping between metastable α-ketoaldehyde intermediates and another in situ formed 2-aminobenzenethiol, providing a new method for direct synthesis of 2-acylbenzo thiazoles.[20,21] Two other similar in situ trapping strategies have also been developed by Li's[22] and Tan's[23] group for the synthesis of 2-aryl benzothiazoles using benzothiazoles and aromatic aldehydes. All of their studies described how ring-opening, condensation, and cyclization smoothly occurred through domino reactions of the readily available starting materials under mild conditions.

Benzylic alcohols and aryl ketones are naturally abundant, stable, cheap, commercially available, and easy to handle[24,25] and thus can potentially be used as ideal arylation or aroylation reagents. To prepare the aryl or acyl-substituted benzothiazoles, it would be highly desirable to develop a process using benzothiazoles and aromatic benzylic alcohols or aryl ketones as starting materials with inexpensive and non-toxic catalysts, such as iron. Herein, we wish to report a new convenient method of iron-catalyzed arylation or aroylation of benzothiazoles with alcohols and aryl ketones based on an in situ cross-trapping strategy.

2. Results and discussion

Our initial investigations were focused on the arylation of benzothiazole (**1a**) with benzyl alcohol (**2a**) in DMSO/H_2O by using $K_2S_2O_8$ as an oxidant at 100 °C, and the results are summarized in Table 1. When benzyl alcohol reacted with 3 equiv of benzothiazole in the absence of any catalyst, the desired product **3a** was obtained in a very low yield of 12% (Table 1, entry 1). A better yield of 31% was obtained by changing the ratio of benzothiazole to benzyl alcohol from 3:1 to 1:3 (Table 1, entry 2). With the two different ratios of reactants, the desired product was obtained in 18% and 59% yields when 20 mol % $FeSO_4 \cdot 7H_2O$ was added as catalyst (Table 1, entries 3 and 4). Other iron salts were also investigated, which demonstrated that $FeCl_3 \cdot 6H_2O$ was the best choice (Table 1, entries 6–11). Interestingly, slightly higher yields were obtained when the catalyst

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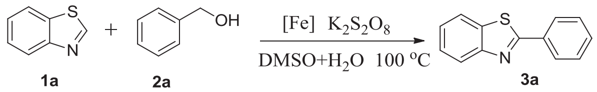
Table 1
Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	[Fe] (equiv)	Oxidant (equiv)	Solvent (ml)	Yield (%)[b]
1[c]	None	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	12
2	None	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	31
3[c]	$FeSO_4\cdot 7H_2O$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	18
4	$FeSO_4\cdot 7H_2O$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	59
5	FeS (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	30
6	$FeC_2O_4\cdot 2H_2O$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	36
7	$Fe(NO_3)_3\cdot 9H_2O$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	40
8	$FeCl_2\cdot 4H_2O$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	61
9	$Fe_2(SO_4)_3$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	65
10	$FeCl_3\cdot 6H_2O$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	68
11	$FeBr_3$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	46
12	$FeCl_3\cdot 6H_2O$ (0.1)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	**70**
13	$FeCl_3\cdot 6H_2O$ (0.05)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	56
14	$FeCl_3\cdot 6H_2O$ (0.5)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	42
15	$FeCl_3\cdot 6H_2O$ (0.1)	$K_2S_2O_8$ (1.0)	DMSO/H_2O (2+1)	54
16	$FeCl_3\cdot 6H_2O$ (0.1)	$K_2S_2O_8$ (3.0)	DMSO/H_2O (2+1)	**72**
17	$FeCl_3\cdot 6H_2O$ (0.1)	None	DMSO/H_2O (2+1)	Trace
18	$FeCl_3\cdot 6H_2O$ (0.1)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (1+1)	37
19	$FeCl_3\cdot 6H_2O$ (0.1)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (1+2)	36
20	$FeCl_3\cdot 6H_2O$ (0.1)	$K_2S_2O_8$ (2.0)	DMSO (2)	0
21	$FeCl_3\cdot 6H_2O$ (0.1)	$K_2S_2O_8$ (2.0)	H_2O (2)	Trace
22[d]	$FeCl_3\cdot 6H_2O$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	38
23[e]	$FeCl_3\cdot 6H_2O$ (0.2)	$K_2S_2O_8$ (2.0)	DMSO/H_2O (2+1)	0

Bold value signifies best reaction conditions and optimal conditions.

[a] Reaction conditions (unless otherwise stated): **1a** (0.5 mmol), **2a** (3.0 equiv), 3 mL of solvent (2:1, v/v), 100 °C, 12 h.

[b] Yields are determined by GC.

[c] **1a** (3.0 equiv), **2a** (0.5 mmol).

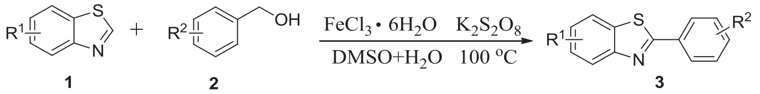
[d] 60 °C.

[e] 25 °C.

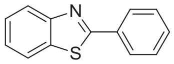
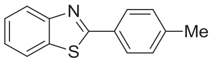
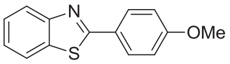
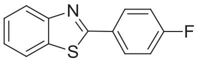
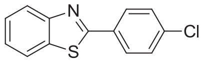
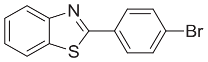
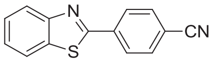
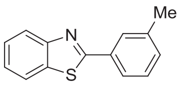
loading was decreased to 10 mol % (Table 1, entries 12–14). The amount of $K_2S_2O_8$ is another important factor for determining the yield of the product. The use of 1 equiv of $K_2S_2O_8$ significantly decreased the yield of **3a**, and the yield did not change obviously when 3 equiv of $K_2S_2O_8$ was used compared with 2 equiv (Table 1, entries 15 and 16). Further optimization of the solvents and temperature showed that DMSO/H_2O and 100 °C were necessary for the reaction to proceed smoothly (Table 1, entries 18–23). Some other oxidants and solvent systems we had tried such as *tert*-Butyl hydroperoxide (TBHP), Di-*tert*-butyl peroxide (DTBP) and Diglyme-H_2O were invalid factors in this reaction.

The substrate scope of this transformation was further investigated under optimal conditions (Table 2). The reactions with benzylic alcohols bearing electron-donating groups (4-H, 4-Me, 4-OMe) and electron-withdrawing (4-F, 4-Cl, 4-Br, 4-CN) groups at the aromatic ring proceeded to give the desired products in moderate yields (41%–70%; **3a**–**g**). The position of substituents on the phenyl ring of benzylic alcohols affected the reaction yield notably (**3h**–**k**). The closer electron-donating methyl was to the hydroxymethyl of benzylic alcohol, the higher yield of 2-tolyl benzothiazole that was obtained. However, the change trend of the yield of 2-chlorophenyl benzothiazole was inverse when the positional isomeric chlorobenzyl alcohol was employed from the 4- to 2-position. In addition to substituted benzylic alcohols, 2-pyridinemethanol and cinnamyl alcohol gave the desired products in moderate yields of 50% and 45%, respectively (**3l** and **m**). The reaction results of several benzothiazoles with benzyl alcohol (**2a**) were also investigated. Benzothiazoles bearing electron-withdrawing substituents on the phenyl ring proved to be good substrates for this transformation, affording the corresponding products **3p** and **q** in good yields. In contrast, a much lower yield of **3o** was obtained due to the effects of the electron-donating methoxy group on the phenyl ring.

Table 2
Iron-catalyzed arylation of benzothiazoles with benzylic alcohols



1 **2** **3**

Entry	Product	3	Yield (%)
1		**3a**	62
2		**3b**	47
3		**3c**	57
4		**3d**	63
5		**3e**	70
6		**3f**	41
7		**3g**	46
8		**3h**	60