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Iron fluoride: the most efficient catalyst for one-pot synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles under solvent-free conditions

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ABSTRACT

A new iron fluoride assisted convenient and efficient strategy for the preparation of 4*H*-pyrimido[2,1-*b*]benzothiazoles derivatives in solvent-free media is described. The reactions can be performed at low-catalyst loadings with excellent functional group tolerance. The catalyst can be readily recovered and reused for next reaction for at least three runs without any significant impact on the yields of the products. The easy recovery of the catalyst and high yield of the products make the protocol attractive, sustainable, and economic.

1. Introduction

Rapid advances in medicinal chemistry continue to underscore the need of practical routes for the synthesis of heterocycles, as a majority of drug-like compounds and natural products contains a heterocyclic nucleus at their core.[1] In recent years, transition-metal-catalyzed reactions provided a promising algorithm to this urge, which allow the efficient conversion of simple starting materials to complex molecules in an iterative manner.[2] Among the various transition metals, iron-catalyzed tandem sequences have gained considerable attention because of their ability to activate various π-systems in mild conditions and at low-catalyst loading.[3] Iron catalysts play an important role in organic synthesis because they are relatively safe, inexpensive, stable, and less hazardous to the environment when compared to other transition-metal catalysts.[4] The combination of transition-metal catalyst and solvent-free conditions using multicomponent reactions lead to enhanced reaction rates, higher yields, easier workup, and sometimes to selective conversions, with several advantages of the eco-friendly approach in the frame work of green chemistry.

4*H*-Pyrimido[2,1-*b*]benzothiazoles derivatives are an important class of fused heterocycles due to their broad range of potential biological pharmacological activities, as well as the importance in preparation of drug molecules and natural products.[5–9] In recent years, numerous protocols for preparation of 4*H*-pyrimido[2,1-*b*]benzothiazoles have been developed in different ways by using TBAHS,[10] kaolin,[11] hydrotalcite,[12] aluminum trichloride,[13] boric acid,[14] *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea,[15] and anhydrous zinc chloride[16] as catalysts. These reported methodologies produce good results in many instances. However, some of synthetic strategies suffer with certain limitations such as expensive catalysts, low yields of products, long reaction times, tedious procedures for preparations of catalysts, and tedious workup conditions. Hence, the development of efficient, simple, easy workup, and environmentally benign protocol using recyclable catalyst and solvent-free condition for the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles derivatives is still desirable and in demand.

In recent decades, fluorine-containing catalytic applications have undergone rapid growth.[17–19] It is evident from the previous literature that iron fluoride has invoked enormous interest as a potential green and acid catalyst to construct carbon–carbon and carbon–heteroatom bonds in various organic transformations.[20–22] In continuation of our research in exploring novel and practical multicomponent reactions to synthesize useful heterocyclic compounds,[23,24] we disclosed a novel methodology for synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles by ring closure of substituted 2-aminobenzothiazole with aldehydes and 1,3-diketones in the presence of iron fluoride under solvent-free condition. To the best of our knowledge, this is the first reported synthesis of this important class of fused heterocycles from the cheap and easily available starting materials by employing cheap, recyclable, and easily available iron fluoride as an efficient catalyst in a green media (Scheme 1).

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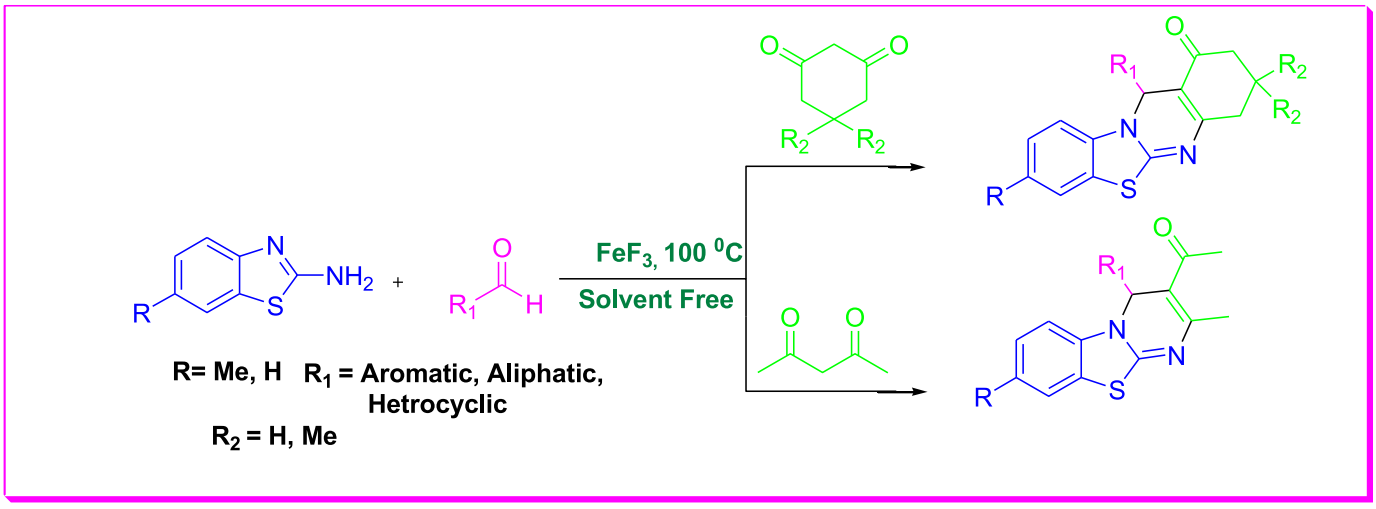


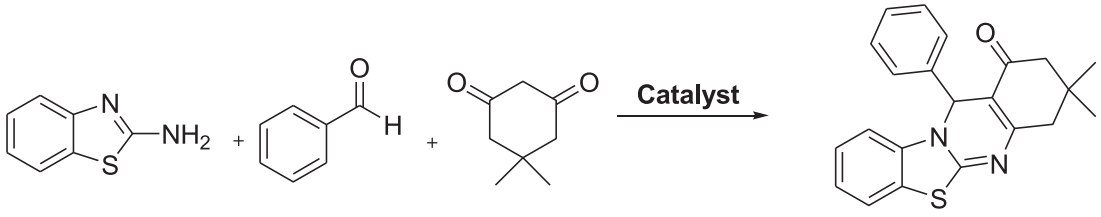
Scheme 1. One-pot synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazoles.

2. Result and discussion

To optimize the reaction condition, we began our examination of the reaction of 2-aminobenzothiazole, benzaldehyde, and dimedone in the presence of different catalysts and solvents (Table 1). In order to establish the real effectiveness of the catalyst for the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives, a test reaction was performed without catalyst using 2-aminobenzothiazole, benzaldehyde, and dimedone in neat condition at 100 °C. It was found that only a 22% amount of product was obtained in the absence of catalyst even after 8 h (Table 1, entry 1).

In search of effective, eco-friendly, and efficient reusable catalytic system for this reaction, same test reaction was performed with different supported metal Lewis acid catalysts such as Cu–Sn (200 mesh, 100 mg), $FeCl_3$, SiO_2, $CaCl_2$, $Zn(OTf)_2$, $CuCl_2$, FeF_3, Li(OTf), $SnCl_2{\cdot}2H_2O$, and CuF_2. Among all screened catalysts, FeF_3 gave the best result in view of yield and reaction time (Table 1, entry 8). In contrast Cu–Sn (200 mesh, 100 mg), $CaCl_2$, SiO_2, $Zn(OTf)_2$, $ZnCl_2$, Li(OTf), and $SnCl_2{\cdot}2H_2O$ did not afford the desired product in good yields (Table 1, entries 2–6, 11, and 12). FeF_3 was shown to be more effective than CuF_2 in terms of yield and time for completion of the reaction (Table 1, entries 8 and 14).

Table 1
Optimization of catalysts, solvents, and temperature in the synthesis of **4a**[a]



No	Catalyst (10 mol %)	Solvent	Condition	Time (h)	Yield[b] (%)
1	—	—	100 °C	8	22
2	$FeCl_3$	Ethanol	Reflux	8	35
3	SiO_2	Neat	100 °C	6	38
4	$CaCl_2$	Ethylene glycol	120 °C	3	65
5	Cu–Sn (200 mesh, 100 mg)	Methanol	80 °C	5	50
6	$Zn(OTf)_2$	Ethanol	Reflux	4	55
7	FeF_3	Ethanol	Reflux	3	90
8	FeF_3	Neat	100 °C	0.5	97
9	FeF_3	Neat	80 °C	0.5	94
10	$CuCl_2$	Neat	80 °C	3	75
11	Li(OTf)	Neat	80 °C	3	60
12	$SnCl_2{\cdot}2H_2O$	Neat	80 °C	2	65
13	$FeCl_3$	Neat	80 °C	3	85
14	CuF_2	Neat	80 °C	2	80
15	FeF_3	Water	Reflux	2	80
16	FeF_3	DMF	Reflux	3	82
17	FeF_3	Methanol	Reflux	4	85
18	FeF_3	Ethylene glycol	120 °C	3	82
19	FeF_3	ACN	100 °C	2	86
20	FeF_3	Toluene	100 °C	2.5	88
21	FeF_3	THF	Reflux	2	85
22	FeF_3 (5 mol %)	Neat	100 °C	0.5	90
23	FeF_3 (20 mol %)	Neat	100 °C	0.5	95

[a] Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), 2-aminobenzothiazole (1 mmol), catalyst (10 mol %).
[b] Isolated yield.

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