



## Microwave-assisted novel synthesis of amino-thieno[3,2-*b*]pyridines under solvent-free conditions

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### ABSTRACT

In the presence of a catalytic amount of ytterbium(III) triflate and under microwave irradiation, mixtures of 2-amino-3-thiophenecarbonitriles, ketones, and silica gel afforded smoothly the corresponding amino-thieno[2,3-*b*]pyridine derivatives in one step. A wide variety of ketones were tested under these conditions. The reactions proceeded rapidly and afforded the desired products in good to excellent yields.

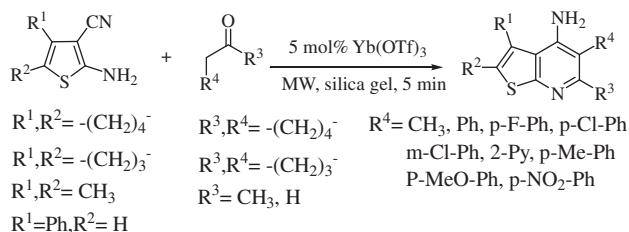
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Thieno[2,3-*b*]pyridine derivatives are of chemical and pharmacological interests due to their isosterism with quinolines and isoquinolines, two important heterocycles involved in many alkaloids. Some of them have been used as herbicides, fungicides, pesticides, medicines, and dyes.<sup>1,2</sup> Thus, the synthesis of thieno[2,3-*b*]pyridines has attracted much attention; three general routes have been developed. The most well-known and exploited route to thieno[2,3-*b*]pyridine derivatives involves the direct condensation of 2-amino-3-thiophenecarbonitriles with ketones under AlCl<sub>3</sub>, ZnCl<sub>2</sub> or SnCl<sub>4</sub> catalyzed in refluxing solution with azeotropic removal of water.<sup>3</sup>

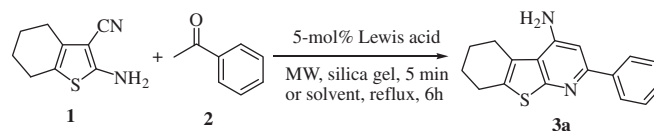
Microwave (MW) activation as a non-conventional energy source has emerged as a powerful technique to promote a variety of chemical reactions and has become a very popular and useful technology in organic chemistry.<sup>4</sup> The combination of solvent-free conditions and MW irradiation leads to large reductions in reaction times, enhancement in conversions and selectivity, and has several features of the eco-friendly approach, termed green chemistry.<sup>5</sup> Strict comparisons with conventional heating have been reported only rarely, so specific MW effects have not been particularly studied.

During the last decade, rare earth metal triflates, a new type of Lewis acid, were widely used in organic synthesis because of their low toxicity, high stability, ease of handling, water tolerance, and recoverability from water that could effectively promote several carbon-carbon and carbon-heteroatom bond-forming reactions.<sup>6</sup> We have reported Yb(OTf)<sub>3</sub>-catalyzed one-pot synthesis of 1,3-thiazolidin-

2-imines from epichlorohydrin and thioureas,<sup>7a</sup> Yb(OTf)<sub>3</sub>-catalyzed condensation reaction of β-naphthol and aldehyde in ionic liquids: a green synthesis of aryl-14*H*-dibenzo[*a,j*] xanthenes,<sup>7b</sup> synthesis of substituted 1,3-oxazolidines by ytterbium(III) triflate-catalyzed [3+2] cycloaddition of *N*-arylimines and epoxides.<sup>7c</sup> As a part of continuing program to explore the novel uses of rare earth metal triflates in organic reactions, we discovered a novel one-step synthesis



**Scheme 1.** Yb(OTf)<sub>3</sub>-catalyzed microwave-assisted synthesis of thieno[2,3-*b*]pyridine derivatives.



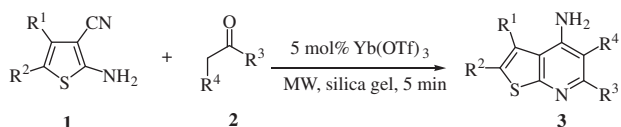
**Scheme 2.** Yb(OTf)<sub>3</sub>-catalyzed microwave-assisted synthesis of **3a**.

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**Table 1**  
Effect of catalyst, microwave, and solvent on the formation of product **3a**

Catalyst	Cat. (mol %)	Solvent	Conditions	Yield <sup>a,b</sup> (%)
ZnCl <sub>2</sub>	5	None	MW, 5 min	23
Zn(OAc) <sub>2</sub>	5	None	MW, 5 min	26
Zn(OTf) <sub>2</sub>	5	None	MW, 5 min	82
Cu(OTf) <sub>2</sub>	5	None	MW, 5 min	52
Yb(OTf) <sub>3</sub>	5	None	MW, 5 min	93
Yb(OTf) <sub>3</sub>	5	None	MW, 3 min	82
Yb(OTf) <sub>3</sub>	10	None	MW, 5 min	95
None	—	None	MW, 5 min	0
Yb(OTf) <sub>3</sub>	5	Toluene	Reflux, 6 h	63
Yb(OTf) <sub>3</sub>	5	Toluene	MW, 5 min	21
Yb(OTf) <sub>3</sub>	5	Xylene	Reflux, 6 h	71
Yb(OTf) <sub>3</sub>	5	DMF	Reflux, 6 h	73

<sup>a</sup> Compounds **1** and **2** (5 mmol) were used.<sup>b</sup> Isolated yields based on compound **3a**.**Scheme 3.** Yb(OTf)<sub>3</sub>-catalyzed microwave-assisted synthesis of **3a**.**Table 2**  
Reusability of Yb(OTf)<sub>3</sub> catalyst together with silica gel

Recycle no.	Catalyst recovered (%)	Isolated yield <sup>a,b</sup> (%)
1	98	93
2	98	92
3	97	90

<sup>a</sup> Reactions were carried out under solvent-free microwave assistance.<sup>b</sup> Yield refers to pure product after column chromatography.

of thieno[2,3-*b*]pyridine derivatives catalyzed by Yb(OTf)<sub>3</sub> under solvent-free conditions in good to excellent yields.

**Table 3**  
Microwave-assisted synthesis of thieno[2,3-*b*]pyridine derivatives catalyzed by Yb(OTf)<sub>3</sub><sup>a</sup>

Entry	Reactant 1		Reactant 2		Products	Yield <sup>b</sup> (%)
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>		
1		-(CH <sub>2</sub> ) <sub>4</sub> -	C <sub>6</sub> H <sub>5</sub> -		<b>3a</b>	93
2		-(CH <sub>2</sub> ) <sub>4</sub> -		-(CH <sub>2</sub> ) <sub>3</sub> -	<b>3b</b>	81
3		-(CH <sub>2</sub> ) <sub>4</sub> -		-(CH <sub>2</sub> ) <sub>4</sub> -	<b>3c</b>	92
4		-(CH <sub>2</sub> ) <sub>4</sub> -	CH <sub>3</sub>	CH <sub>3</sub>	<b>3d</b>	89
5		-(CH <sub>2</sub> ) <sub>4</sub> -	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> -	H	<b>3e</b>	90
6		-(CH <sub>2</sub> ) <sub>4</sub> -	<i>m</i> -Cl-C <sub>6</sub> H <sub>4</sub> -	H	<b>3f</b>	88
7		-(CH <sub>2</sub> ) <sub>4</sub> -	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> -	H	<b>3g</b>	91
8		-(CH <sub>2</sub> ) <sub>4</sub> -	<i>p</i> -CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> -	H	<b>3h</b>	93
9		-(CH <sub>2</sub> ) <sub>4</sub> -	<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -	H	<b>3i</b>	96
10		-(CH <sub>2</sub> ) <sub>4</sub> -	<i>p</i> -CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	H	<b>3j</b>	87
11		-(CH <sub>2</sub> ) <sub>4</sub> -	2-C <sub>5</sub> H <sub>4</sub> N-	H	<b>3k</b>	85
12		-(CH <sub>2</sub> ) <sub>3</sub> -		-(CH <sub>2</sub> ) <sub>4</sub> -	<b>3l</b>	81
13		-(CH <sub>2</sub> ) <sub>3</sub> -		-(CH <sub>2</sub> ) <sub>3</sub> -	<b>3m</b>	75
14		-(CH <sub>2</sub> ) <sub>3</sub> -	C <sub>6</sub> H <sub>5</sub> -	H	<b>3n</b>	85
15		-(CH <sub>2</sub> ) <sub>3</sub> -	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> -	H	<b>3o</b>	87
16		-(CH <sub>2</sub> ) <sub>3</sub> -	<i>m</i> -Cl-C <sub>6</sub> H <sub>4</sub> -	H	<b>3p</b>	86
17		-(CH <sub>2</sub> ) <sub>3</sub> -	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> -	H	<b>3q</b>	89
18		-(CH <sub>2</sub> ) <sub>3</sub> -	<i>p</i> -CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -	H	<b>3r</b>	84
19		-(CH <sub>2</sub> ) <sub>3</sub> -	<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -	H	<b>3s</b>	93
20	CH <sub>3</sub>			-(CH <sub>2</sub> ) <sub>4</sub> -	<b>3t</b>	89
21	CH <sub>3</sub>	CH <sub>3</sub>	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> -	H	<b>3u</b>	90
22	CH <sub>3</sub>	CH <sub>3</sub>	<i>p</i> -CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> -	H	<b>3v</b>	92
23	CH <sub>3</sub>	CH <sub>3</sub>	<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -	H	<b>3w</b>	96
24	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> -	H		-(CH <sub>2</sub> ) <sub>4</sub> -	<b>3x</b>	85

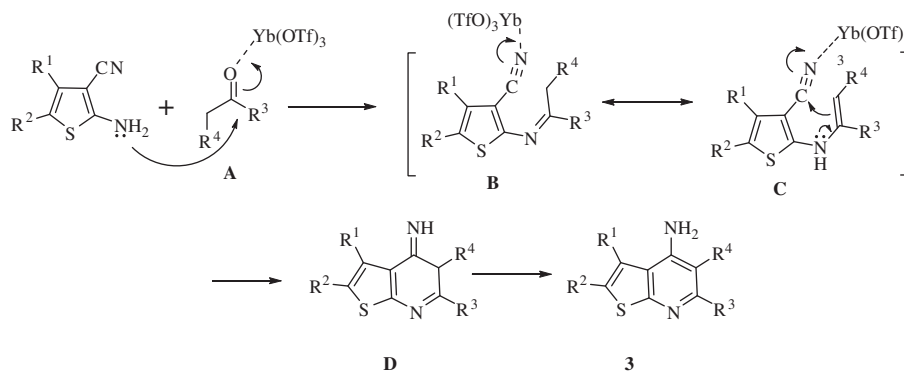
<sup>a</sup> Reactions were carried out under solvent-free microwave assistance.<sup>b</sup> Yield refers to pure product after column chromatography.

In this work, we describe the ytterbium(III) triflate-catalyzed 2-amino-3-thiophenecarbonitriles and ketones cyclization affording the corresponding amino-pyridines derivatives in a single synthetic step (Scheme 1).

The synthesis started from 2-amino-3-thiophene-carbonitriles which were prepared in one step from ketones, malononitrile, and sulfur with morpholine as a catalyst in the refluxing ethanol via the classic Gewald reaction.<sup>8</sup> In order to explore the preparation of thieno[2,3-*b*]pyridine derivatives, a model reaction was made to test the reaction condition. 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (5 mmol), acetophenone (5 mmol), and Lewis acid (0.25 mmol) were ground with silica gel (0.5 g) under microwave irradiation for 5 min (indicated by TLC) (Scheme 2).<sup>9</sup> A series of traditional Lewis acids such as ZnCl<sub>2</sub> and Zn(OAc)<sub>2</sub> were chosen to promote the cyclization reaction, and 9-amino-7-phenyl-1,2,3,4-tetrahydro-benzo-thieno[2,3-*b*]pyridine (**3a**) were obtained in low yields (23% and 26%, respectively) (Table 1, entries 1 and 2). Meanwhile, several metal triflates were also used, and the results were compared to those traditional Lewis acids with a remarkable improvement in the similar condition (Table 1, entries 3–5). In addition, the amount of catalyst, solvents, and reaction time were also tested (Table 1, entries 6–13). It was shown that of the seven catalysts used, Yb(OTf)<sub>3</sub> gave the highest yield (93%) for the desired product under solvent-free microwave assistance (Table 1, entry 5).

On the basis of the above-mentioned results, this process was then extended to other substituted 2-amino-3-thiophene-carbonitriles and ketones to investigate its scope and generality (Scheme 3). The results are listed in Table 3.

It can be seen that altering the substituent groups on the 2-amino-3-thiophenecarbonitriles showed little effect on the yields; several kinds of 2-amino-3-thiophene-carbonitriles containing cycloalkyl, alkyl, or aryl groups easily undergo with cycloalkanone, acetone, or substituted acetophenone to give the corresponding amino-thieno[2,3-*b*]pyridines in good to excellent yields (Table 2, entries 1–24). Among the substituents on arone (2), electron-withdrawing substituents improved the efficiency of the addition reaction, and **3i**, **3s**, and **3w** were obtained in excellent yields (96%, 93%, and 96%; Table 2, entries 9, 19, and 23, respectively), while



**Scheme 4.** A possible mechanism of  $\text{Yb}(\text{OTf})_3$ -catalyzed cyclization reaction of 2-amino-3-thiophenecarbonitriles and ketones.

the electron-donating substituent methoxyl improved the efficiency of the cycloaddition reaction, giving the desired product with yields (93% and 92%, Table 2, entries 8 and 22, respectively). The structure of **3** was identified by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, and MS.

Our attention was then turned to the possibility of recycling the catalyst from the reaction media since the recovery and reuse of the catalyst are highly preferable for a greener process. At completion of the reaction, the resulting mixture was dissolved by EtOAc and filtered; the filter cake was washed by EtOAc to remove the organic impurities. The catalyst together with silica gel was recovered almost quantitatively. The reusability of the catalyst was investigated by using 2-amino-4,5,6,7-tetrahydro-benzo[*b*]thiophene-3-carbonitrile and cyclo-hexanone as model substrates. After three recycles, the catalyst still had a high activity and gave the corresponding product in fairly good yield (Table 2, recycle no. 3).

A possible mechanism of  $\text{Yb}(\text{OTf})_3$ -catalyzed cyclization reaction of 2-amino-3-thiophene-carbonitriles and ketones is rationalized in Scheme 4. Referring to the literature,<sup>10</sup> we supposed that the reaction proceeded through an  $\text{S}_{\text{N}}2$ -type pathway. The ketones were first coordinated to  $\text{Yb}(\text{OTf})_3$  generating a highly reactive intermediate **A**, which reacted with 2-amino-3-thiophenecarbonitriles to give a stable intermediate **B**. Then the nitrile group of **B** coordinated to  $\text{Yb}(\text{OTf})_3$  to give a highly reactive intermediate **C**, which undergoes a ring-closing process, giving the final product amino-thieno[2,3-*b*]pyridine **3**.

In summary, we have demonstrated that the ytterbium triflates are an effective catalyst for cyclization.<sup>11</sup> By using  $\text{Yb}(\text{OTf})_3$  as a catalyst, microwave irradiation, and under solvent-free reaction conditions, the novel one-pot modified Combes reaction gave excellent yield and the reaction time was shortened from 18 h to 5 min. In addition, the catalyst can be easily recovered and reused. It not only led to economical automation but also reduces hazardous pollution to achieve environmentally friendly processes. This microwave-assisted and  $\text{Yb}(\text{OTf})_3$ -catalyzed novel one-pot synthesis of amino-thieno[2,3-*b*]pyridine therefore is a simple, high-yielding, time-saving, and environmentally friendly process.<sup>12</sup>

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.075.

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- Typical procedure for the preparation of compound 3a*: (a) Without microwave assistance in toluene: To a mixture of 2-amino-3-thiophene-carbonitrile (5 mmol), acetophenone (5 mmol) was added  $\text{Yb}(\text{OTf})_3$  (0.25 mmol) in toluene (10 mL). The mixture was heated to reflux. The progress of the reaction was monitored by TLC. The resulting mixture was washed with water ( $2 \times 10$  mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated, and the crude product was purified by column chromatography [eluent: hexane/EtOAc (95:5)] to provide 9-amino-7-phenyl-1,2,3,4-tetrahydro-benzo-thieno[2,3-*b*]pyridine (**3a**).  $\text{Yb}(\text{OTf})_3$  and silica gel were recovered and reused. Compound **3a** yield 93%; orange needles; mp 212–213 °C (Petroleum ether/EtOAc 3:1); IR(KBr): 3483 and 3329, 2937, and 2833, 1621, 1444, 845, and 773  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR(400 MHz, DMSO):  $\delta$  1.82 (d,  $J = 2.8$ , 4H, 2CH<sub>2</sub>), 2.74 (s, 2H, CH<sub>2</sub>), 3.00 (s, 2H, CH<sub>2</sub>), 6.09 (s, 2H, NH<sub>2</sub>), 7.06 (s, 1H, CH), 7.36–7.40 (m, 1H, CH), 7.44–7.48 (m, 2H, 2CH), 7.89–97 (m, 1H, CH);  $^{13}\text{C}$  NMR(100 MHz, DMSO):  $\delta$  18.6, 22.3, 25.2, 25.8, 101.6, 118.2, 126.2, 127.2, 128.4, 128.6, 130.6, 139.1, 150.9, 152.7, 161.6; MS:  $m/z$  232 (100%).