# Synthesis of Pyridines and Pyrido[2,3-*d*]pyrimidines by the Lewis Acid Catalysed Bohlmann-Rahtz Heteroannulation Reaction

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**Abstract:** Lewis acids catalyse the Bohlmann-Rahtz heteroannulation reaction to generate highly functionalised pyridines from enamino esters and alkynones in a single synthetic step. Of the catalysts studied, ytterbium(III) trifluoromethanesulfonate and zinc(II) bromide are the two most efficient for the synthesis of pyridines and pyrido[2,3-*d*]pyrimidines, from ethyl  $\beta$ -aminocrotonate or 2,6-diaminopyrimidin-4-one respectively, in up to 94% yield.

Key words: pyridines, Bohlmann-Rahtz heteroannulations, heterocycles, Lewis acids

The synthesis, reactions and biological properties of pyridine-containing derivatives is an ever-expanding subject in heterocyclic chemistry. This structural motif may be found in a large number of pharmaceutical agents,<sup>1</sup> as a pharmacophore of considerable historical importance, and so new methods for their preparation have received a great deal of attention in the literature. The synthesis of pyridine 4 in two steps by Michael addition-cyclodehydration of ethyl  $\beta$ -aminocrotonate 1 and but-3-yn-2-one 2 was first reported by Bohlmann and Rahtz in 1957 and proceeds via aminoheptadienone intermediate 3, that is isolated and heated to high temperature to facilitate the cyclisation (Scheme 1).<sup>2</sup> Since its discovery, it is noteworthy that very few applications of this reaction have appeared in the literature. A synthesis of the modified core of promothiocin antibiotics has been reported,<sup>3</sup> using the Bohlmann-Rahtz heteroannulation reaction for the preparation of clusters of pyridine-containing heterocycles that were elaborated to the natural product.<sup>4,5</sup>



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In order to improve the utility of the Bohlmann-Rahtz pyridine synthesis, and facilitate the transfer of this technology to the solid phase, we demonstrated that this method, which traditionally requires high cyclodehydration temperatures, may be affected in a single synthetic step for the synthesis of tetrasubstituted pyridines **5** using either acetic acid or Amberlyst 15 ion exchange resin at 50 °C (Scheme 2).<sup>6</sup> These modified conditions were for the most part unsuccessful for the synthesis of pyrido[2,3-*d*]pyrimidine **7** from 2,6-diaminopyrimidin-4-one **6**, although the traditional two-step Bohlmann-Rahtz heteroannulation reaction,<sup>2</sup> that proceeds by Michael addition in DMSO and subsequent cyclodehydration at 180 °C, proved to be a highly expedient method for the preparation of these heterocycles (Scheme 3).<sup>7</sup>



Scheme 2



Scheme 3

In order to establish a new one-step general method for the synthesis of pyridines and pyrido[2,3-*d*]pyrimidines that avoids the use of high temperatures, we have investigated the use of Lewis acid catalysts in the Bohlmann-Rahtz heteroannulation reaction. To test the validity of this approach, Bohlmann-Rahtz intermediate aminodienone **3** was prepared by standard procedures<sup>2</sup> and treated with a Lewis acid to see if cyclodehydration could be conducted at a lower reaction temperature. The use of BF<sub>3</sub>·OEt<sub>2</sub> failed to generate even a trace of pyridine **4**, whereas zinc(II) bromide (15 mol%) or ferric chloride (10 mol%) in dichloromethane did promote the cyclisation. Full conversion was achieved when a solution of aminodienone **3** and zinc(II) bromide (15 mol%) in toluene was heated at

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reflux for 5 hours, to give pyridine **4** as the only product in 59% yield (Scheme 4).



### Scheme 4

The success of this reaction catalysed by zinc(II) bromide demonstrated that Lewis acids facilitate the cyclodehydration at a lower reaction temperature. To examine if these conditions were suitable for the synthesis of pyrido[2,3-*d*]pyrimidines, a solution of pyrimidine **8a** or **8b** and zinc(II) bromide (20 mol%) in DMSO was stirred overnight at 110 °C to give the heteroannulated product, **7a** or **7b** respectively, in quantitative yield (Figure).





Since it was clear that this method had the potential to generate either pyridine or pyrido[2,3-d]pyrimidine heterocycles in a single synthetic step, a range of different Lewis acids was screened in a known Bohlmann-Rahtz heteroannulation reaction.<sup>6</sup> A solution of ethyl β-aminocrotonate 1 and 4-trimethylsilylbut-3-yn-2-one 9a in either dichloromethane or toluene was heated at reflux overnight in the presence of 10-100 mol% of a Lewis acid (Scheme 5). In all of these experiments the Lewis acid promoted the formation of pyridine 5a, catalysing both the Michael addition and subsequent cyclodehydration. Aminoheptadienone intermediate **3** or its trimethylsilyl derivative was not isolated from any of these reactions, leading to the conclusion that, in the presence of a Lewis acid, cyclodehydration occurred spontaneously under the reaction conditions. Furthermore it was also apparent that the trimethylsilyl moiety was stable to these conditions as pyridine 4 could not be detected and this was in marked contrast to similar reactions catalysed by Amberlyst 15 ion exchange resin.<sup>6</sup> Although the yields were variable, for the most part, only a single identifiable product was formed. However, out of the Lewis acids that were investigated, only zinc(II) bromide or ytterbium(III) trifluoromethanesulfonate (ytterbium(III) triflate) gave consistent results, generating pyridine 5a in 90% yield in both instances (Table 1).

This study illustrated that Lewis acids promote the Bohlmann-Rahtz reaction. In order to demonstrate the utility and versatility of this new method for the synthesis of pyridines and pyrido[2,3-*d*]pyrimidines, a range of enamino



Scheme 5

**Table 1**Lewis Acid Catalysed Synthesis of Pyridine **5a** 

Lewis acid	Cat. mol%	Solvent	Yield <sup>a</sup> %
None	-	Toluene	0 <sup>b</sup>
ZnBr <sub>2</sub>	100	$CH_2Cl_2$	26 <sup>b,c</sup>
ZnBr <sub>2</sub>	20	CH <sub>2</sub> Cl <sub>2</sub>	29 <sup>b</sup>
ZnBr <sub>2</sub>	10	Toluene	53
ZnBr <sub>2</sub>	15	Toluene	90 <sup>d</sup>
$ZnCl_2$	100	Toluene	42
$ZnCl_2$	20	Toluene	44
$ZnI_2$	100	Toluene	35
$ZnI_2$	20	Toluene	66
Sc(OTf) <sub>3</sub>	20	Toluene	60
Tb(OTf) <sub>3</sub>	100	Toluene	75
Tb(OTf) <sub>3</sub>	20	Toluene	45
Yb(OTf) <sub>3</sub>	100	Toluene	70
Yb(OTf) <sub>3</sub>	20	Toluene	90

<sup>a</sup> Isolated yield after column chromatography.

<sup>b</sup> Only unreacted starting material 1 was isolated.

<sup>c</sup> Crude vield.

<sup>d</sup> Reaction was heated at reflux for only 5 h.

esters and ethynyl ketones was submitted to our Lewis acid catalysed heteroannulation conditions (Scheme 6). Enamino esters, prepared by standard procedures,<sup>8</sup> were reacted with a number of alkynones<sup>9</sup> in toluene in the presence of either zinc(II) bromide or ytterbium(III) triflate (Table 2).<sup>10</sup> In general, reactions catalysed by zinc(II) bromide were faster (complete after 5 hours as opposed to 24 hours) and more efficient than those conducted in the presence of ytterbium(III) triflate, with a few notable exceptions (such as the synthesis of pyridine **5b** and **5f**). In all cases the Lewis acid catalysed Bohlmann-Rahtz heteroannulation reaction was successful to give, following spontaneous cyclodehydration, tri- and tetrasubstituted pyridine **5a-h**.<sup>11</sup>





	R <sup>2</sup>	R <sup>3</sup>	$\mathbb{R}^4$	R <sup>6</sup>	Yb(OTf) <sub>3</sub> Yield%	ZnBr <sub>2</sub> Yield%
5a	Me	EtO <sub>2</sub> C	Me3Si	Me	90 <sup>a</sup>	90
5b	Me	EtO <sub>2</sub> C	Et	Me	83	67
5c	Me	EtO <sub>2</sub> C	Ph	CO <sub>2</sub> Et	55	85 <sup>b</sup>
5d	Me	EtO <sub>2</sub> C	Me <sub>3</sub> Si	CO <sub>2</sub> Et	33	44 <sup>c</sup>
5e	Ph	EtO <sub>2</sub> C	Et	Me	32	72
5f	Ph	EtO <sub>2</sub> C	Ph	Me	68	62
5g	Ph	EtO <sub>2</sub> C	Ph	CO <sub>2</sub> Et	44	65
5h	Ph	EtO <sub>2</sub> C	Н	Me	58	70

<sup>a</sup> 20 mol% catalyst was used.

<sup>b</sup> 10 mol% catalyst was used. <sup>c</sup> Desilylated pyridine (R<sup>4</sup> = H) was also isolated.

Following the success of the zinc(II) bromide catalyst, compared with previous results,<sup>6</sup> a solution of 2,6-diaminopyrimidin-4-one 6 and either 4-trimethylsilylbut-3-yn-2-one 9a or ethyl 2-oxo-4-(trimethylsilyl)but-3-ynoate 9b in DMSO was stirred at 110 °C in the presence of either zinc(II) bromide (20 mol%) or ytterbium(III) triflate (20 mol%). After 72 hours and standard work  $up^{12}$  the zinc(II) catalysed reactions gave pure pyrido[2,3-d]pyrimidine 7a,b in 92% and 89% yield, respectively, whereas the ytterbium(III) catalysed process gave a slightly impure product 7a,b in 94% and 91% respective yield (Scheme 7). In contrast to the behaviour of pyrimidinone 6 in the uncatalysed Bohlmann-Rahtz heteroannulation reaction,<sup>7</sup> in the presence of a Lewis acid Michael addition and cyclodehydration were facilitated in a single synthetic step in excellent yield at a lower reaction temperature. Notably, in this case, desilylation occurred in the course of the reaction in an analogous fashion to the two-step synthesis of pyrido[2,3-*d*]pyrimidine 7.



#### Scheme 7

In summary, the Lewis acid catalysed Bohlmann-Rahtz heteroannulation reaction was successful in both reducing the temperature of this transformation and, more importantly, affecting the synthesis in a single preparative step using a single experimental procedure for both the synthesis of pyridines and pyrido[2,3-*d*]pyrimidines. Work is now underway to transfer this technology to the solid phase and apply our new general procedure to the synthesis of a number of biologically active heterocycles.

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- (10) In a typical experimental procedure, a solution of ethyl  $\beta$ aminocrotonate (0.13 g, 1.0 mmol), 4-(trimethylsilyl)but-3yn-2-one (0.15 g, 1.1 mmol) and ytterbium(III) trifluoromethanesulfonate (0.12 g, 0.2 mmol) in toluene (6 mL) was heated at reflux for 5 hours. Water (6 mL) was added, the solution was heated at reflux for 20 minutes and allowed to cool. The aqueous phase was separated and extracted with ethyl acetate (2 × 10 mL) and the organic extracts were combined, washed with brine, dried (MgSO<sub>4</sub>) and evaporated in vacuo. The residue was purified by flash chromatography on silica, eluting with light petroleum-ethyl acetate (3:1), to give ethyl 2,6-dimethyl-4-(trimethylsilyl)pyridine-3-carboxylate (0.23 g, 90%) as a colourless oil.

- (11) All compounds exhibited spectroscopic properties that agreed with literature data according to reference 6.
- (12) In a typical experimental procedure, a solution of 4-(trimethylsilyl)but-3-yn-2-one **9a** (0.17 g, 1.2 mmol), 2,4diamino-6-hydroxypyrimidine **6** (0.16 g, 1.2 mmol) and zinc(II) bromide (56 mg, 0.24 mmol) in DMSO (5 mL) was

stirred at 110 °C for 72 h.  $H_2O$  (30 mL) was added and the precipitated solid was filtered, washed with water and dried to give 2-amino-7-methyl-5-trimethylsilyl-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **7a** (0.20 g, 92%) as a pale yellow solid; spectroscopic properties agreed with literature data according to reference 7.