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SHORT COMMUNICATION

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Solvent-Free Synthesis of 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones Catalyzed by $BiCl_3$: A Green Route to a Privileged Backbone

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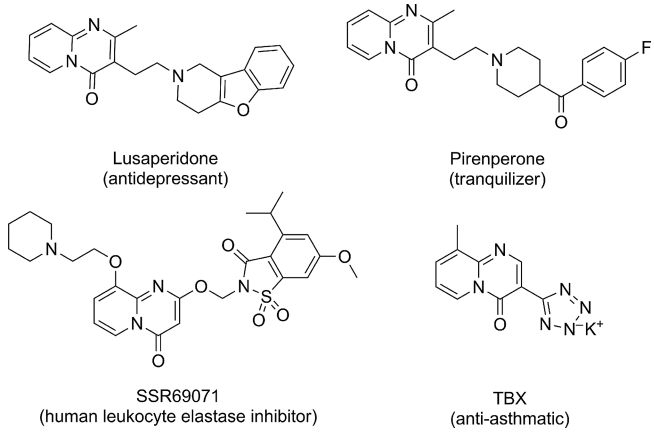
Keywords: Bismuth / Green chemistry / Solvent-free reactions / Cyclization / Heterocycles

An extensive array of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones have been synthesized from commercially available 2-aminopyridines and β-oxo esters with excellent yields under solvent-free conditions. The reaction, catalyzed by cheap and nontoxic $BiCl_3$, proceeds with short reaction times under mild conditions and normal atmosphere. Only water and alcohol are formed as co-products in this green reaction.

Introduction

4*H*-Pyrido[1,2-*a*]pyrimidin-4-one is a privileged scaffold that appears in many fused heterocyclic compounds, which fulfill Lipinski's rule of fives for orally active drugs with good bioavailability.[1] Thus, it is not surprising that several derivatives of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one possess biological activities,[2] and this skeletal structure can be found in drugs with anti-asthmatic, anti-cancer, anti-depressant, anti-hypertensive, anti-malarial, anti-microbial, anti-oxidant, anti-ulcerative, tranquillizing, and analgesic properties as well as a human leukocyte elastase inhibitor (Scheme 1).[3] 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones are also used as photographic sensitizers, curing agents for polyisocyanates, dyes for acrylic nylon and polyester fibres, organic blue-emitting compounds and as synthetic intermediates.[4]



Scheme 1. Drugs possessing the 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones skeleton.

The traditional method to construct 4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones from 2-aminopyridines and various β-oxo esters requires high reaction temperatures of 150–200 °C and corrosive acidic reagents like polyphosphoric acid, sulfuric acid or phosphoryl chloride.[5] Cassis et al. reported a noncorrosive synthesis of 2-aminopyridines with Meldrum's acid, but the reaction required a temperature of 250 °C.[6] Besides oxo esters, (2-alkoxymethylene)malonic esters, 3-alkoxyacrylic esters, succinic esters and glutaric esters are used with 2-aminopyridines.[7] More recent syntheses allow for lower reaction temperatures but still require harsh acidic conditions or activated starting materials that have to be synthesized.[8] Recently, Bonacorso et al. formed 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones using β-alkoxyvinyl trichloromethyl ketones and 2-aminopyridines under reflux in ethanol but obtained low to moderate yields of up to 81% only.[9] Solid-phase synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones could be carried out at 90 °C but still required the use of acetic acid as a cosolvent with DMF and long reaction times of 16 h.[10] Use of activated 1,4-enediones and $Cu(OAc)_2 \cdot H_2O$ as catalyst enabled the synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones at 80 °C with good to moderate yields of up to 91% after 6 h.[11] We envisioned that by replacing corrosive Brønsted acids with a mild, moisture- and air-stable Lewis acid like $Bi(OTf)_3$ or $BiCl_3$, the reaction between 2-aminopyridines and β-oxo esters could be made to proceed under more benign conditions and thereby offer an environmentally friendly alternative. Bismuth catalysis has gained attention over the past decade due to an increasing focus on green chemistry.[12] Although bismuth is a heavy metal, it is not carcinogenic.[13] Bismuth salts are nontoxic and are, in fact, rated with lower toxicity than even NaCl.[14] They are cheap, readily available and easy to handle, being moisture- and air-stable.

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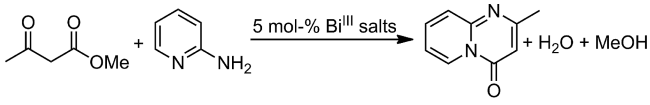
We hereby report a bismuth(III)-catalyzed solvent-free synthesis of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its analogues from readily available and inexpensive starting materials, i.e., 2-aminopyridines and β-oxo esters. The reaction can be carried out neat, requiring only short reaction times and low temperatures to access a wide scope of products. Water and alcohols are formed along with the desired product.

Results and Discussion

Initially, several solvents were tested for the reaction between methyl acetoacetate (**1**) and 2-aminopyridine (**2**) using 5 mol-% of $Bi(OTf)_3$ as the catalyst (Table 1, Entries 1–4). The best yield of 88% was obtained in toluene. Following previous literature on solvent-free bismuth-catalyzed reactions,[15] we tried a neat reaction and were delighted that the reaction proceeded with > 99% yield (Table 1, Entry 5). A blank without catalyst was also conducted, but only traces of **3aa** were formed, confirming that bismuth(III) salts are necessary to catalyze the reaction (Table 1, Entry 6). Other bismuth(III) salts were screened for the reaction, and $BiCl_3$ was found to give > 99% yield of **3aa** (Table 1, Entries 7–8). In comparison, only traces of the product were observed with $InCl_3$ or $ZnCl_2$ as catalyst (Table 1, Entries 9–10). Because of its much lower cost compared to $Bi(OTf)_3$, $BiCl_3$ was chosen as the catalyst in further optimization studies.

Table 1. Optimization parameters for Bi^{III}-catalyzed syntheses of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.[a]



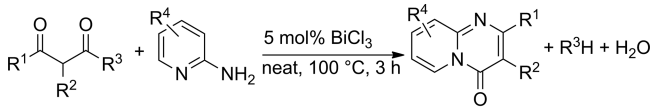
1 **2** **3aa**

Entry	Solvent	Catalyst	*T* [°C]	*t* [h]	Yield [%][b]
1	dioxane	$Bi(OTf)_3$	100	8	37 (28)
2	NO_2Me	$Bi(OTf)_3$	100	8	38 (28)
3	H_2O	$Bi(OTf)_3$	100	8	41 (35)
4	toluene	$Bi(OTf)_3$	100	8	88 (85)
5	–	$Bi(OTf)_3$	100	8	100 (100)
6	–	–	100	8	traces
7	–	$Bi(OAc)_3$	100	8	21(10)
8	–	$BiCl_3$	100	8	100 (99)
9	–	$InCl_3$	100	5	traces
10	–	$ZnCl_2$	100	5	0
11	–	$BiCl_3$	100	5	99 (98)
12	–	$BiCl_3$	100	3	97 (95)
13	–	$BiCl_3$	100	1	85 (82)
14	–	$BiCl_3$	80	3	75 (70)
15	–	$BiCl_3$	50	3	52 (46)

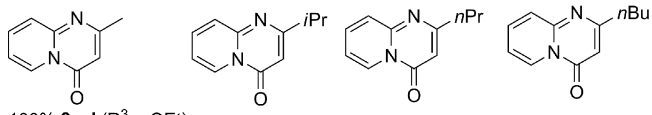
[a] Reaction conditions: **2** (0.5 mmol), **1** (2.0 equiv.) and catalyst (0.025 mmol) in 4 mL of solvent. [b] Yield determined by GC analysis; isolated yields in parentheses.

Reducing the reaction time from 8 to 3 h did not affect the reaction, but a further decrease to 1 h resulted in a significant drop of the yield of **3aa** to 85% (Table 1, Entries 8,

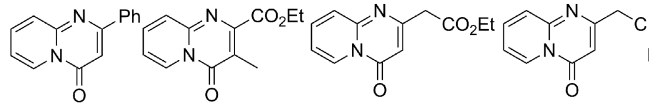
Table 2. Scope of the reaction.[a]



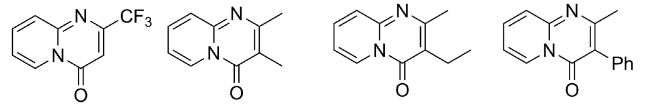
1 **2** **3**



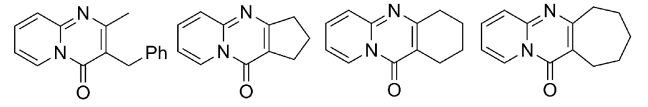
100% **3aa'** (R^3 = OEt)
99% **3aa''** (R^3 = SEt)
99% **3aa'''** (R^3 = NEt_2)
91% **3ba**[b]
96% **3ca**[b]
95% **3da**



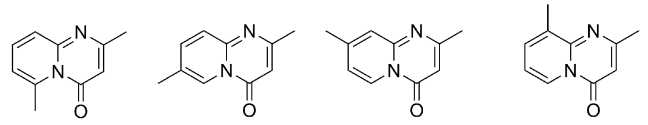
85% **3ea**[b]
96% **3fa**[b]
80% **3ga**[b]
72% **3ha**[c]



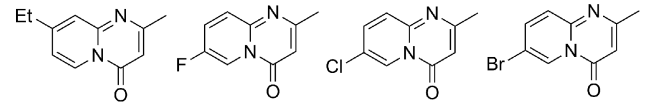
81% **3ia**[b]
99% **3ja**[b]
99% **3ka**
94% **3la**[b]



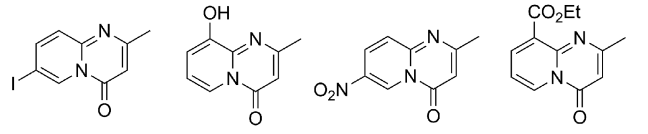
98% **3ma**[b]
95% **3na**[b]
97% **3oa**[b]
92% **3pa**[b]



97% **3ab**
95% **3ac**
98% **3ad**
98% **3ae**



99% **3af**
95% **3ag**
97% **3ah**
95% **3ai**



92% **3aj**
97% **3ak**
65% **3al**
86% **3am**

94% **3an**
traces **3ao**

[a] Reaction conditions: **2** (0.5 mmol), **1** (1.0 mmol) and $BiCl_3$ (0.025 mmol) neat at 100 °C for 3 h. Percentage isolated yields. [b] The ethyl carboxylate derivative is used instead of the methyl carboxylate. [c] Reaction was carried out in 4 mL of toluene.

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11–13). Lowering of the reaction temperature from 100 to 80 and 50 °C led to a reduction in yield to 75 and 52%, respectively (Table 1, Entries 13–15). Hence, the reaction can be carried out with high yields of **3aa** by using 0.5 mmol of **2**, 2 equiv. of **1**, and 5 mol-% $BiCl_3$ (relative to **2**) as catalyst, neat, at 100 °C for 3 h.

Next, the scope of the reaction under the optimized conditions was investigated (Table 2). Essentially quantitative yields were obtained when β-oxo thioesters and β-oxo amides were treated with **2** (Table 2, **3aa′′** and **3aa′′′**). The reaction proceeded well with ethyl carboxylates of β-oxo esters (Table 2, **3aa′**). Excellent yields were also obtained with bulkier substituents at the C-2 position of the desired product, although the yield was slightly lower when a phenyl substituent was used (Table 2, **3ba**–**3ea**). Interestingly, reactions of **2** with diethyl 2-methyl-3-oxosuccinate and diethyl 3-oxopentanedioate gave good to excellent yields (Table 2, **3fa** and **3ga**). However, when ethyl 4-chloroacetoacetate was used as the substrate, good yields of **3ha** were obtained only when the reaction mixture was diluted with toluene. Under solvent-free conditions, the chloro substituent was replaced by an ethoxy group. Pleasingly, a good yield of 81% was obtained with a trifluoromethyl substituent at the C-2 position (Table 2, **3ia**). Introduction of a CF_3 moiety frequently enhances certain biological, chemical and physical properties and increases lipophilicity and bioavailability.[16] Hence, it is found in pharmaceutical compounds such as Sorafenib and Leflunomide.[17] We were elated that even with substituents at the C-3 position, the reaction gave excellent yields (Table 2, **3ja**–**3ma**).

A comparison between the yields for **3ea** and **3la** with the substituent at C-2 and C-3 position, respectively, suggests that steric factors are more prominent for bulky R^1 than R^2 in **1**. The reaction also proceeded smoothly with various cyclic β-oxo esters to form the corresponding products in good to excellent yields (Table 2, **3na**–**3pa**).

Several substituted 2-aminopyridines were also treated with **1** under the optimized conditions. Excellent yields were obtained with substrates bearing a methyl group at C-3, C-4, C-5 or C-6 of the 2-aminopyridine structural motif and even for an ethyl group at the C-4 position (Table 2, **3ab**–**3af**). Substrates with a halogen substituent at the C-5 position of 2-aminopyridine gave high yields of 95–97% (Table 2, **3ag**–**3aj**). The reaction also proceeded well with an OH or CO_2Et group at the C-3 position to form **3ak** and **3am** with 97 and 86% yield, respectively. However, only a moderate yield of 65% of **3al** was obtained when the strongly electron-withdrawing NO_2 group was present at the C-5 position. Furthermore, while the reaction proceeded with a high yield of 94% of **3an** with 2-aminothiazole, only traces of **3ao** were formed with 2-aminopyrimidine (Table 2, **3an** and **3ao**). This could be due to the inductive effect of the additional N-atom on the pyrimidine ring, which reduces the nucleophilicity of the NH_2 group.

A plausible mechanism for the reaction (Figure 1) is proposed. In the first step, a molecule of $BiCl_3$ complexes to **1** through the carbonyl group of the ketone moiety. This enhances the electrophilicity of the carbonyl functionality and promotes the nucleophilic addition of the amino group of **2**, forming intermediate **A** with release of one HCl molecule. A ring-closing condensation reaction forms intermediate **B** with release of MeOH. Abstraction of the α-H atom as HCl and transfer of the oxygen atom to the bismuth center generate BiOCl intermediate **C** and release the product **3aa**. The $BiCl_3$ catalyst is regenerated by the reaction of **C** with the 2 equiv. of HCl formed during the reaction, and the cycle can be repeated.

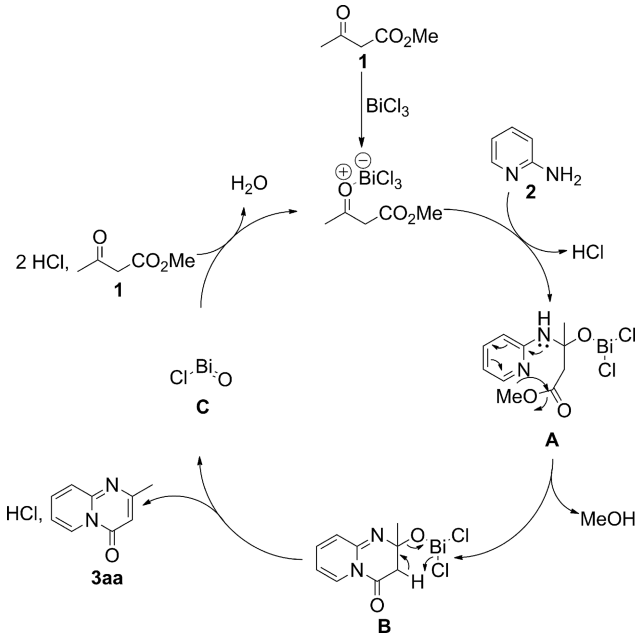
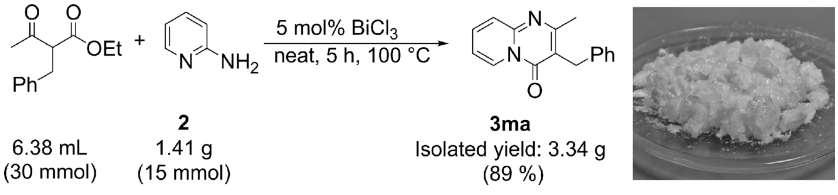


Figure 1. Proposed mechanism for the Bi^{III}-catalyzed formation of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

To further explore the usefulness of this method, the synthesis of **3ma** was scaled up by using 15 mmol of aminopyridine **2** and 2 equiv. of ethyl 2-benzyl-3-oxobutanoate (Scheme 2). An isolated yield of 89% of white needle-like crystals of **3ma** was obtained after workup and recrystallization.



Scheme 2. Scaled-up synthesis of **3ma**.

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Conclusions

We have developed an efficient new method to 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones using $BiCl_3$ as catalyst. The reaction applies to a wide spectrum of β-oxo esters as well as the 2-aminopyridine substrates. These starting compounds are cheap and commercially available. Excellent yields are obtained in a short reaction time under mild reaction conditions without needing any solvent or an inert atmosphere. This green reaction forms only water and alcohol as coproducts. A mechanism has been proposed based on a tandem nucleophilic addition and ring-closing condensation reaction.

Experimental Section

General Procedure for Formation of 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones: A 5 mL round-bottomed flask was charged with methyl acetoacetate (**1**) (107.9 μL, 1 mmol), 2-aminopyridine (**2**) (47.1 mg, 0.5 mmol) and $BiCl_3$ (7.9 mg, 0.025 mmol). The reaction mixture was stirred at 100 °C for 3 h. The mixture was taken up in a minimal amount of ethanol and filtered. The filtrate was purified by column chromatography with a short column, using ethyl acetate and hexane (9:1, v/v) as eluent to afford clear needle-like crystals of **3aa** in essentially 100% yield.

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (3aa): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.93 (d, J = 7.2 Hz, 1 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 7.03 (t, J = 6.6 Hz, 1 H), 6.24 (s, 1 H), 2.37 (s, 3 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 165.1, 157.6, 150.5, 136.1, 127.0, 125.6, 114.9, 103.1, 24.5 ppm. HRMS (ESI): calcd. for $C_9H_9N_2O$ $[M - H]^+$ 161.0709, found 161.0712.

General Procedure for the Scaled-up Synthesis of 3ma: A 50 mL round-bottomed flask was charged with ethyl 2-benzyl-3-oxobutanoate (6.38 mL, 30 mmol), 2-aminopyridine (**2**) (1.41 g, 15 mmol) and $BiCl_3$ (237 mg, 0.75 mmol). The reaction mixture was stirred at 100 °C for 5 h. The mixture was diluted with a minimal amount of ethanol and filtered. The filtrate was purified by column chromatography using ethyl acetate/hexane (2:3, v/v) as eluent and further recrystallization with ethanol, providing **3ma** as white needle-like crystals in 89% yield.

3-Benzyl-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (3ma): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, J = 4.5 Hz, 1 H), 7.35 (s, 2 H), 7.24–6.96 (m, 5 H), 6.82 (s, 1 H), 3.97 (s, 2 H), 2.36, (s, 3 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 161.6, 157.5, 148.0, 139.3, 134.5, 127.8, 127.8, 126.6, 125.6, 125.1, 114.3, 114.1, 31.7, 22.4 ppm. HRMS (ESI) calcd. for $C_{16}H_{15}N_2O$ $[M - H]^+$: 251.1179, found 251.1174.

Acknowledgments

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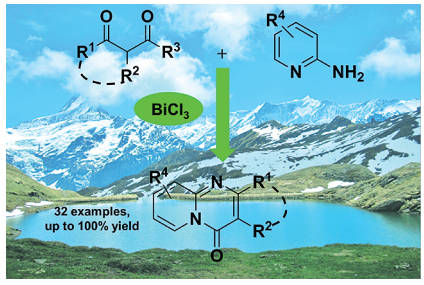
4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones, a privileged backbone for developing drugs with good oral bioavailability, are easily synthesized by a solvent-free $BiCl_3$-catalyzed tandem reaction with an expanded scope and excellent yields.



Keywords: Bismuth / Green chemistry / Solvent-free reactions / Cyclization / Heterocycles

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