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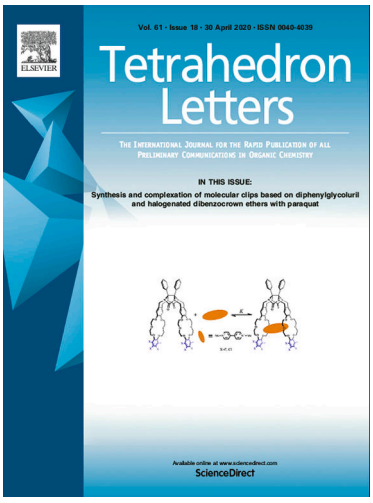

Practical synthesis of 4 *H*-pyrido[1, 2-a]pyrimidin-4-ones using ethylene glycol as a promoting solvent

Mustafa Hussain, Jianhui Liu

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Practical synthesis of 4 *H*-Pyrido[1, 2-a]pyrimidin-4-ones using ethylene glycol as a promoting solvent

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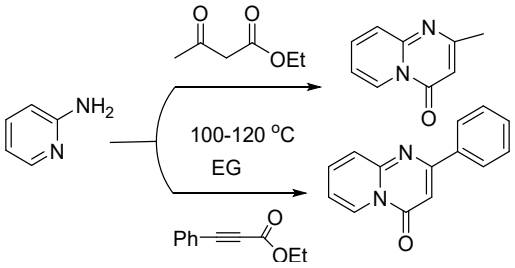
Mustafa Hussain, [a] Jianhui Liu * [a] [b]



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Practical synthesis of 4 *H*-pyrido[1, 2-a]pyrimidin-4-ones using ethylene glycol as a promoting solvent

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ABSTRACT

A simple and useful protocol leading to different 4*H*-pyrido[1, 2-a] pyrimidin-4-ones have been established by cyclization of various 2-amino pyridines with β-oxo ester or alkynoate. The use of ethylene glycol was demonstrated to facilitate this condensation. This reaction proceeds by nontoxic, cheap, environment friendliness and biodegradable solvent at the normal green atmospheric condition in the absence of catalyst.

1. Introduction

Green synthesis has a large importance in current synthetic chemistry due to the environmental, health and societal concerns. It has many diverse scope in different sectors like pharmaceutical, industry, and academia due to their facile, clean, efficient and non-polluting synthetic procedures that reduce the use of organic toxic solvents and reagents.[1] Except for a few solvents such as water, ethanol, glycerol, and ionic liquids ethylene glycol (EG) is considered to be a most important green solvent which has high boiling point, low viscosity, high specific energy and easily miscible with many other organic solvents.[2] These unique properties made it highly applicable in industry such as automobile, fine chemical, plastics, and textiles.[3] It also plays important roles in nano chemistry such as reducing agent or ligand. [4]

Of many heterocyclic compounds related to some natural products, drugs and other bio-medicinal materials[5], compounds containing pyrimidine cores have been considered to be important and attracted many attention due to their high biological activity, similarity in structure with purines bases, as well as the building block of DNA and RNA.[6] The skeletal structure of 4*H*-pyrido[1, 2-a]pyrimidin-4-ones (PPO) is the common part for many drugs such as pirenperone (tranquilizer agent), pemirolast (antiasthmatic agent), SSR69071 (human leukocytes inhastase inhibitors), risperidone and paliperidone (oral antipsychotic drugs) and lusaperidone (anti-depressant) (Fig.1).[5b, 7]

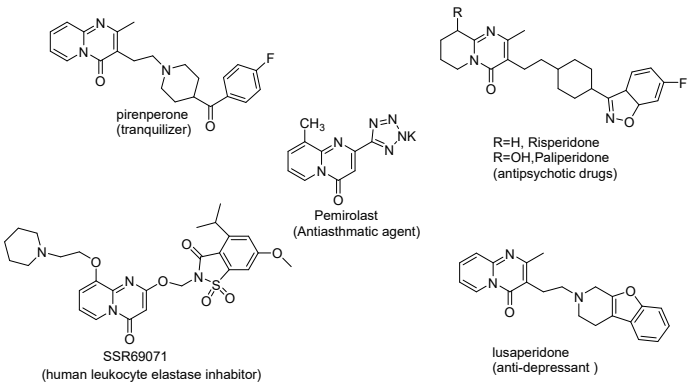


Figure 1. Selected biologically and medicinally active molecules with pyrido [1, 2-a] pyrimidin-4-ones.

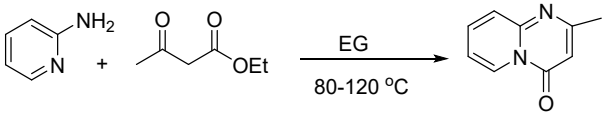
Due to their wide range of biological activities, different methods to prepare the 2-substituted 4*H*-pyrido[1,2-a]pyrimidin-4-ones were recorded in the literature. The most commonly used one remains the condensation of 2-aminopyridines and β-oxo esters. Different catalysts, such as, $AgSO_3CF_3$, $Al_3PW_{12}O_{40}$, and $BiCl_3$ are required in this process.[8, 7c] However in some cases for this transformation, the temperature needed is very high at about 150-200 °C.[9] While many new methods at lower temperature have been developed, using strong corrosive acidic reagent like H_2SO_4, $POCl_2$, and polyphosphoric acid is unavoidable.[10] Catalyst-free synthesis with low to moderate yield by refluxing in

alkynoates and alkoxyvinyl tri-chloromethyl ketones has been reported.[11] Solid-phase synthesis of different PPO derivatives have also been done at 90 °C but longer reaction time was needed in an aprotic solvent mixed with acetic acid.[12] An efficient method for the synthesis of novel PPO via $Cu(OAc)_2 \cdot H_2O$ catalyzed domino synthesis from 1,4-enediones and 2-aminoheterocycles was reported by Wu et al. to give good to moderate yields after heating at 80 °C for 6 hours.[13] Pd-catalyzed carbonylative cycloamidation of ketoimines for the construction of PPO has been disclosed by Zeng et al.[14] However, all above reported methods usually suffered from many drawbacks, such as narrow functional group compatibilities, harsh reaction conditions, a large amount of additives, complicated materials, and highly hazardous chemicals. Therefore, it is still a challenge to synthesize various substituted 4*H*-pyrido[1,2-a] pyrimidin-4-ones using readily available and inexpensive starting materials through a simple procedure. Herein we describe an efficient synthesis of EG promoted intermolecular cyclization of 2-aminopyridines with β-oxo ester or alkynoate to afford 2-substituted 4*H*-pyrido [1,2-a] pyrimidin-4-ones.

2. Result and Discussion

Initially, our investigation started with the one-pot cyclization reaction of 2-aminopyridine (**1a**) with ethyl acetoacetate (**2**), which were performed using different catalysts in toluene at 100 °C for 6 hours. When $ZnCl_2$ was used, target **3a** was formed in 15% yield (Table 1, entry 1). An improved yield (30%) was obtained when Ag_2CO_3 and AgOAc was added respectively (Table 1, entries 2-3). A better yield to 65% was observed when using CuBr (Table 1, entry 4). Next, the solvent was changed to EG with much improved yields using the same series of catalysts, affording **3a** in yields of 50%, 55%, 65% and 78% for $ZnCl_2$, Ag_2CO_3, AgOAc and CuBr (Table 1, entries 4-8). As observed, the reactivity was in the order CuBr > AgOAc ≥ Ag_2CO_3 > $ZnCl_2$ for the catalysts and EG > toluene for the solvent. CuBr was the most effective catalyst compared with other catalysts due to its unique Lewis acid property and its solubility in EG solvent making this catalyst more favorable to derive above reaction condition (Table 1, entry 8). No reactions occurred in either EtOH or DMSO with the above mentioned four catalysts (Table 1 entries 9 and 10). Then, when we performed the reaction in the absence of catalysts in MeOH and H_2O at temperature of 100 °C, the yields of desire product were 58 and 67% respectively (Table 1, entries 11 and 12). In the absence of solvent and catalyst, only 15% of desired product was obtained (Table 1 entry 13). The temperature effect was also observed. When we performed the reaction in the absence of catalysts in EG at temperature of 80 °C and 100 °C, the yields of desire product increased respectively to 80% and 85% (Table 1, entries 16 and 17). Higher temperature to 120°C afforded the same yield of 85% compared with 100°C (Table 1, entry 18). This showed that the reaction strongly depended on solvents and temperature. The best result with a yield of 85% was obtained at a temperature of 100 °C with EG as the solvent and promoting medium (Table 1, entry 17). Other factors were also considered by reducing the reaction time. The entries 12 and 14). But a further decrease to 2 h resulted in a significant drop of the yield to 55 % (Table 1 entries 14 and 15). Finally, increased concentration is a favorable effect for the yield. Decreasing the EG amount from 3.5 to 1.5 mL can increase the yield from 78% to 85% (Table 1 entries 14, 15 and 16).

Table 1. Optimization of reaction conditions [a]



1a 2 3a

S.No	Catalyst	Solvent	Temp (°C)	Time (h)	Yield %[b]
1	$ZnCl_2$	Toluene	100	6	15
2	Ag_2CO_3	Toluene	100	6	30
3	AgOAc	Toluene	100	6	30
4	CuBr	Toluene	100	6	65
5	$ZnCl_2$	EG	100	6	50
6	Ag_2CO_3	EG	100	6	55
7	AgOAc	EG	100	6	65
8	CuBr	EG	100	6	78
9	CuBr	EtOH	100	6	0
10	CuBr	DMSO	100	6	0
11	-	MeOH	100	6	58
12	-	H_2O	100	6	67
13	-	-	100	6	15
14	-	EG	100	4	78
15	-	EG	100	2	55
16	-	EG[c]	80	4	80
17	-	**EG**[c]	**100**	**4**	**85**
18	-	EG[c]	120	4	85

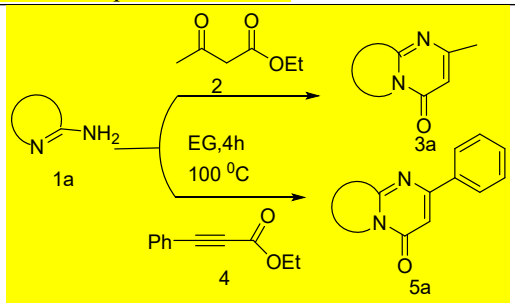
[a] Reaction conditions: **1a** (1 mmol), **2** (1 mmol), catalysts (5 mol%, 0.1mmol), and solvent (3.5 ml), [b] Isolated yield, [c] EG (1.5 ml).

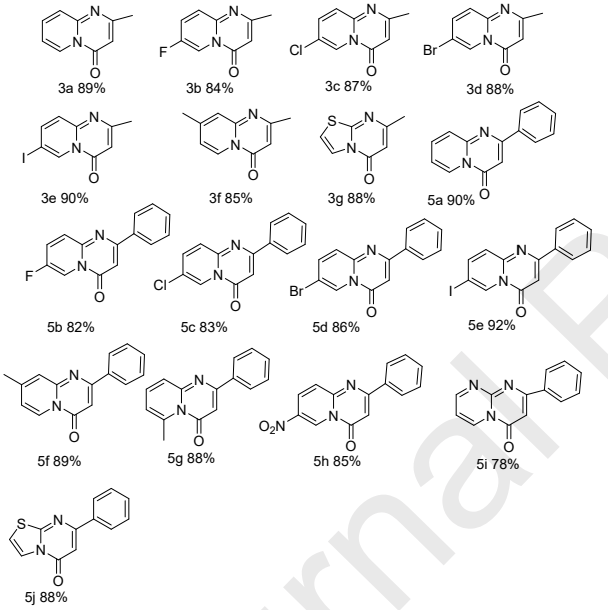
The solvent of EG promotes the reaction in the absence of any catalyst and provides a high yield as compared to other solvents due to it acidic activity, high boiling point and hygroscopic liquid with low viscosity (Table 1, entries 14-18).

According to the above results, we then investigated the scope and limitation from various substrates for the synthesis of 4*H*-pyrido[1,2-a]pyrimidin-4-ones using various 2-aminopyridines and ethyl acetoacetate (**2**) and ethyl 3-phenylpropionate (**4**), as shown in Table 2. Initially, we treated ethyl acetoacetate with 2-aminopyridine, 2-amino-5-fluoropyridine, 2-amino-5-bromopyridine, 2-amino-4-chloropyridine, 2-amino-4-methyl pyridine, and 2-aminothiazole. All products were obtained in good to excellent yield with different electronic environment of the pyridines (Table 2, 3a-3g). 2-Aminopyridines with both electron donating and electron withdrawing group tolerated the reaction and helped in cyclization (90-88%) (Table 2, 3a-3g). Unfortunately, the reaction of ethyl acetoacetate with 2-aminopyrimidine failed due to the inductive effect of the additional N-atom on the pyrimidine ring, which reduces the nucleophilicity of the NH_2 group. Since the β-oxo esters are not a strong electrophile, it would be difficult to react with pyrimidine which is not nucleophilic enough. Further work is still needed for the activation of the β-oxo esters.

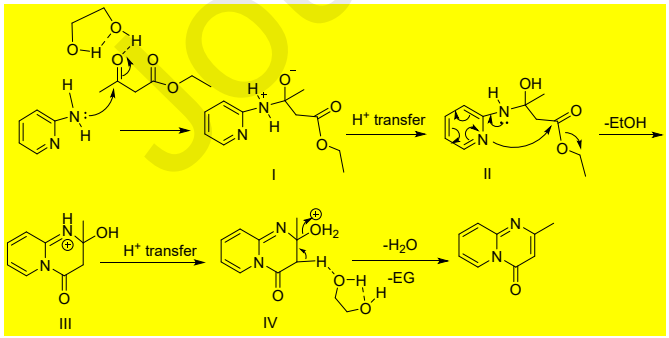
employ ethyl 3-phenylpropionate as the substrate to react with 2-amino substituted heterocycles (Table 2, 5a-5j).Indeed, the reaction was well performed, and all the products were obtained in good yields, whereas the reactions using ethyl acetoacetate took longer time for completion. It is important to mention that the 2-amino-5-nitropyridine and 2-aminopyrimidine easily cyclized with alkynoates moiety due to its higher electrophilicity compared to β-oxo esters, where we did not get the desire product (Table 2, 5h-5i).

Table 2. Scope of the reaction. [a, b]



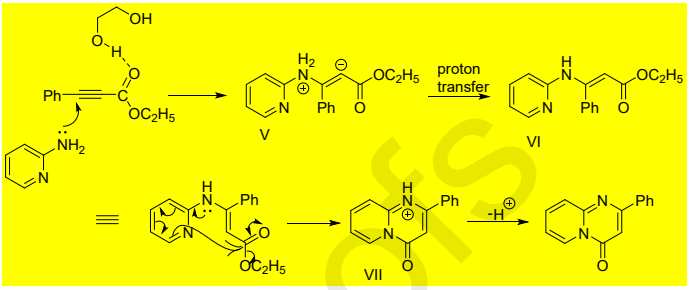


[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), **4** (1.0 mmol) and EG (1.5 ml) at 100 °C for 4 h. [b] Percentage Isolated yields.



Scheme 1. Proposed mechanism of reaction aminopyridine with β-ketoesters.

The possible reaction mechanism is proposed in scheme 1. Initially, acidic proton of EG activates the carbonyl group of ketone moiety, making the carbonyl carbon more favorable to be attacked by amine and formed intermediate **I**. Next the intermediate **II**. Then the cyclization occurs after the low laying energy π electrons attacks the carbonyl carbon of the ester group to form **III**. On further proton transfer via **IV** and elimination, the desired 4*H*-pyrido [1,2-a] pyrimidin-4-one is formed. This analysis is based on the above results and the previous reports in which, A. R. Katritzky et al. have clearly demonstrated the hemiaminal formation followed by the extrusion of ethanol, and the final water elimination gives pyrimidinone type products.[15]



Scheme 2. Proposed mechanism of reaction aminopyridine with alkynes.

The proposed mechanism for the reaction of 2-aminopyridine and ethyl 3-phenylpropionate is proposed in scheme 2 by the help of previous literatures, where W. Zhang et al have clearly demonstrated the formation of enamine intermediate followed by the cyclization.[16] Initially, EG combines the carbonyl oxygen and the β-carbon of the triple bond is activated by conjugation which become more favorable for the attack of amine to form intermediate **V**. After proton transfer to the triple bond to give **VI**, the low-lying energy π bonding electrons attacks the carbonyl groups of the ester after the lone pair nitrogen electrons delocalized to the ring to form intermediate **VII.** The desired molecule is finally formed after losing a proton.

3. Conclusion

In conclusion, we have developed an efficient methodology for the one-pot green synthesis of 4*H*-pyrido[1, 2-a]pyrimidin-4-ones from 2-aminopyridines and ethyl acetoacetate/ethyl 3-phenylpropionate. We also demonstrate the effectiveness of by EG as promoting solvent, by which no catalysts are required for this condensation. This methodology can be applied to a wide range of β-oxo esters, alkynoates, and 2-aminopyridine reagent. Different 4*H*-pyrido[1, 2-a]pyrimidin-4- ones derivatives were obtained which may have high biological activities and a broad range of application in the pharmaceutical industry. This catalyst-free protocol has several features such as environmental friendliness, easy operation, nontoxic solvents, and economical methodology.

4. Acknowledgments

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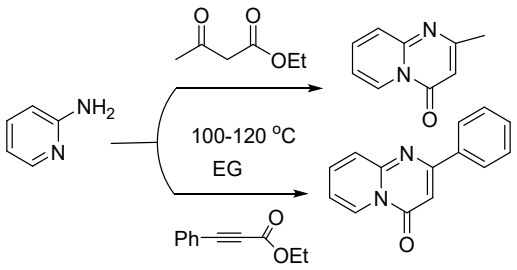

Highlights

- Green synthesis has many diverse scopes in pharmaceutical, industry and academia
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- The cyclization of various 2-amino pyridines with β-oxo ester lead to Pyrido[1,2-a] pyrimidin-4-ones
- The use of ethylene glycol was demonstrated to facilitate this condensation
- The skeletal structure of pyrido [1, 2-a] pyrimidin-4-ones is the common part for many drugs