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Highly efficient synthesis of fused bicyclic 2,3-diaryl-pyrimidin-4(3*H*)-ones via Lewis acid assisted cyclization reaction

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Abstract

An expedient one-pot synthesis of fused bicyclic 2,3-diaryl-pyrimidin-4(3*H*)-ones from three readily available components is described. The key step is a Lewis acid assisted cyclization reaction.

Fused bicyclic pyrimidin-4(3*H*)-ones (Fig. 1), such as 1*H*-purin-6(9*H*)-one **1**[1] and 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **2**,[2] are important core structures to many biologically active small molecules. As part of an ongoing project, we were interested in developing an efficient method to construct fused bicyclic 2,3-diaryl-pyrimidin-4(3*H*)-ones **3**. As a requirement to our lead optimization program, we desired a short route from the readily accessible starting materials that was flexible enough to allow the exploration of the C2- and N3-positions as well as to the fused heteroaromatic ring. Herein, we report a new synthetic strategy for the synthesis of fused bicyclic 2,3-diaryl-pyrimidin-4(3*H*)-ones.

There are two synthetic approaches for the fused bicyclic 2,3-disubstituted-pyrimidin-4(3*H*)-ones that have been reported (Scheme 1).[3] Both started with a cyclic amino acid derivative **4**, but differed in the order of introducing the C2- and N3-substituents. Approach **A** introduced the N3-substituent first by converting **4** into amino amide **5**, which was then converted into diamide intermediate **6** by monoacylation with R^2COCl and then cyclized to give the

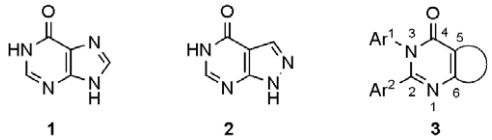
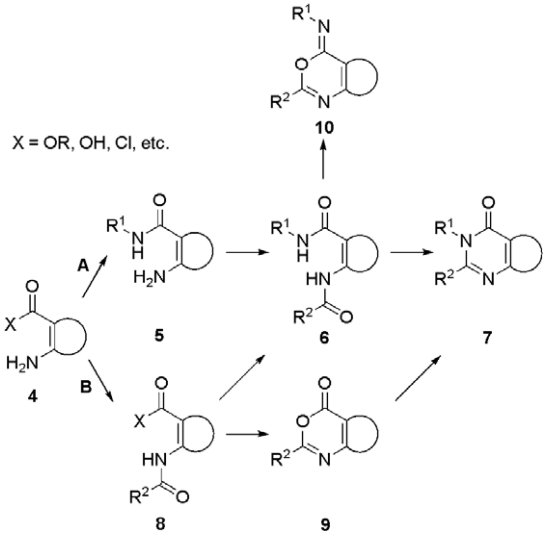


Fig. 1.



Scheme 1.

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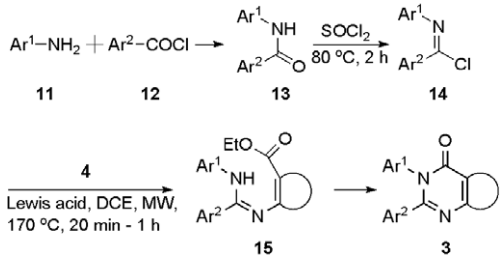
desired fused bicyclic 2,3-disubstituted pyrimidin-4(3*H*)-ones **7**.[3a,b] In some cases, the mono-acylation and cyclization steps were conducted in one pot and the diamide intermediate **6** was not isolated or characterized.[3c] Approach **B** introduced the C2-substituent first by mono-acylation of **4** to provide amide **8**, which was then converted into the same diamide intermediate **6** and then cyclized to give **7**.[3b,d] In an alternate but more common version of approach **B**, amide **8** was first converted into oxazinone **9**, which was then converted into **7** when treated with the corresponding amine R^1NH_2.[3e,f]

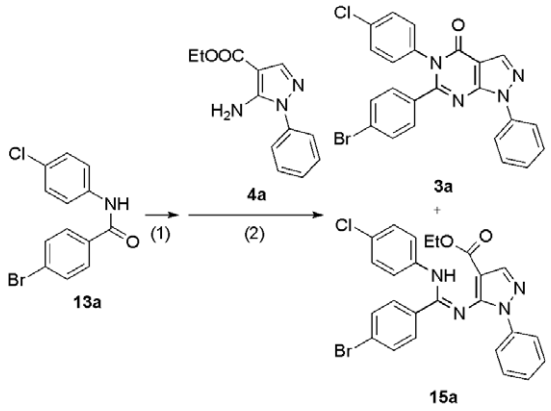
Both of the traditional routes are linear and require sequential installation of the fused ring, then the C2-, N3-substituents. One major drawback to these approaches is that they are not general in scope. Most of the reported examples are the syntheses of quinazolin-4-ones. The detailed reaction sequences, conditions, and yields varied considerably when the fused ring was heteroaromatic. Acylation of the amino group in **4** often led to a mixture of mono- and bis-acylation products. The ring opening of oxazinone **9** by an aniline was sluggish, which could be one of the reasons that the reported examples of 2,3-diaryl substitution are rare. The ring closing reaction conditions from **6** to **7** required optimization based on individual substrates and led to an undesired cyclization product **10** in some cases.[4]

Our goal was to obtain an efficient one-pot synthesis of fused bicyclic 2,3-diaryl-pyrimidin-4(3*H*)-ones **3** by employing three readily available components: aniline **11**, benzoyl chloride **12**, and a heteroaromatic amino ester **4** (Scheme 2). Amide **13** was synthesized from aniline **11** and benzoyl chloride **12** under standard conditions. After heating in $SOCl_2$ at 80 °C for 2 h, **13** was converted into imidoyl chloride **14**, which underwent the cyclocondensation reaction when treated with various heteroaromatic amino esters **4** to provide compounds of the general structure **3**. The cyclocondensation occurred in two steps, the nucleophilic attack of the imidoyl chloride by the amino group to form intermediate **15** followed by intramolecular cyclization. In some cases, intermediate **15** could be isolated. To the best of our knowledge, even though some examples of cyclocondensation between an imidoyl chloride and an amino ester have been reported, these reactions were limited to electron rich amino esters like anthranilic acid ester,[5a–g] thiophene amino ester,[5h] and amino crotonic ester.[5i] These reactions were normally conducted under basic or neat conditions. However, for electron deficient heteroaromatic amino esters, such as **4a** (Table 1), the cyclocondensation was difficult due to the poor nucleophilicity of the amino group. Fortunately, we discovered that adding an appropriate Lewis acid into the reaction system could activate the imidoyl chloride and therefore make the aforementioned cyclocondensation feasible. We were also pleased to find that microwave irradiation could be employed to accelerate the reaction.



Scheme 2.

Table 1
Lewis acid effects on the cyclization reaction[a]

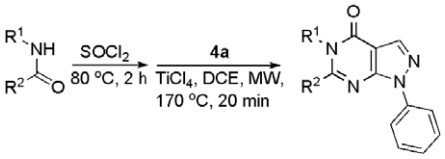


Entry	Lewis acid	**3a**[b] (%)	**15a**[b] (%)
1	TMSCl	0	7
2	$SnCl_4$	25	48
3	$TiCl_4$	66	0
4	$BF_3{\cdot}OEt_2$	44	0
5	$AlCl_3$	16	0
6[c]	$TiCl_4$	59	0
7[d]	$TiCl_4$	78	0
8[e]	$TiCl_4$	65	0

[a] Conditions: (1) $SOCl_2$, 80 °C, 2 h; (2) **4a** (1.2 equiv), $ClCH_2CH_2Cl$, Lewis acid (4.0 equiv), microwave, 170 °C, 20 min.
[b] Reported yields determined via HPLC analysis of the crude reaction mixtures.
[c] 1.0 equiv of $TiCl_4$ was used.
[d] Microwave irradiation time was extended to 1 h.
[e] Reaction was conducted in an oil bath at 150 °C overnight.

Our initial study was focused on screening a few common Lewis acids for the cyclocondensation reaction and the results are listed in Table 1. It was observed that the strength of the Lewis acid strongly affected the outcome of this reaction.[6] As illustrated in Table 1, the weak Lewis acid TMSCl (entry 1) gave only 7% of the uncyclized intermediate **15a** with no desired cyclized product **3a**. The moderately stronger Lewis acid $SnCl_4$ successfully catalyzed the nucleophilic addition; however, it was not effective enough to promote the cyclization, leading to the identification of **15a** as the major product (entry 2), which was not obtained when strong Lewis acids were used. For example, $TiCl_4$ gave 66% of the desired compound **3a** as the only product, as did $BF_3{\cdot}OEt_2$ and $AlCl_3$ (entries 3–5). However, the stronger Lewis acids $BF_3{\cdot}OEt_2$ (entry 4) and $AlCl_3$ (entry 5) gave lower yields of **3a**. Presumably, these strong Lewis

Table 2
Synthesis of 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones from various amides[a]



Entry	Product	R^1	R^2	Yield[b] (%)
1	**3a**	4-Cl–Ph	4-Br–Ph	60[c]
2	**3b**	2-Me–Ph	4-Br–Ph	74
3	**3c**	4-Me–Ph	4-Br–Ph	79
4	**3d**	4-MeO–Ph	4-Br–Ph	86
5	**3e**	4-CN–Ph	4-Br–Ph	43[d]
6	**3f**	4-NO_2–Ph	4-Br–Ph	53[e]
7	**3g**	4-Cl–Ph	4-MeO–Ph	60
8	**3h**	4-Br–Ph	4-CF_3–Ph	36
9	**3i**	4-Cl–Ph	4-Me–Ph	61
10	**3j**	4-Cl–Ph	3-Me–Ph	63
11	**3k**	4-Cl–Ph	2-Me–Ph	61
12	**16**	Me	4-Br–Ph	56
13	**16**	Me	4-Br–Ph	92[f]

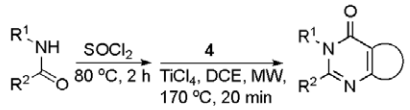
[a] General procedures refer to Ref. 7.
[b] Isolated yield with >95% purity.
[c] Reaction was conducted at 150 °C overnight.
[d] Formation of imidoyl chloride: amide was treated with $SOCl_2$ at 80 °C for 2 h with the addition of one drop of DMF.
[e] Formation of imidoyl chloride: amide was treated with $SOCl_2$ at 80 °C for 24 h.
[f] 2 equiv of amide was used.

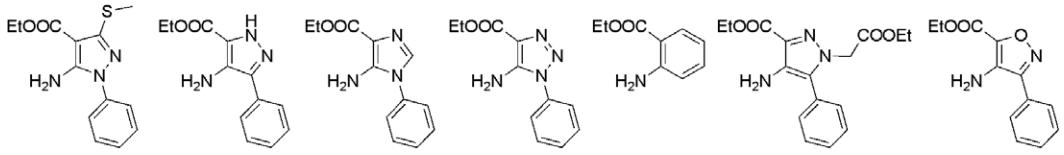
acids deactivated the nucleophile and hindered the nucleophilic addition step. Overall, $TiCl_4$ gave the highest yield of **3a** among all the Lewis acids tested and was the catalyst of choice for further optimization of the reaction conditions.

Next, we investigated the amount of $TiCl_4$, the reaction times, and the temperature to find the most optimal reaction conditions (Table 1). We found that 1 equiv of $TiCl_4$ was effective in catalyzing the reaction (59%, entry 6), but was less satisfactory than using a slight excess. Employing 8 equiv of $TiCl_4$ led to decomposition of the starting materials (not shown). Extended reaction time (1 h) slightly improved the conversion (entry 7). Extended reaction times under conventional heating gave good results (~14 h, entry 8). Finally, the optimal condition for parallel synthesis was determined to be 2 equiv of $TiCl_4$ at 170 °C under microwave irradiation for 20 min (Table 2, entry 1).

With the optimal reaction condition in hand, a variety of amides were surveyed and the results are summarized in Table 2. In general, the aromatic amides, after having first been converted into imidoyl chlorides, reacted very effectively with **4a** to give the desired products. We noted that the substitution pattern of both R^1 (**3b**,**c**) and R^2 (**3i**–**k**) had minimal impacts on the yields. There was a general trend that the aromatic amides with strong electron donating groups gave a higher overall yield (in two steps) than those with strong electron withdrawing groups. This was true for both R^1 (**3d** vs **3a**,**e**,**f**) and R^2 (**3g** vs **3h**). It

Table 3
Preparation of fused bicyclic 2,3-disubstituted-pyrimidin-4(3*H*)-ones[a]





Entry	Product	R^1	R^2	**4**	Yield[b] (%)
1	**3l**	4-Cl–Ph	4-MeO–Ph	**4b**	73
2	**3m**	4-Cl–Ph	4-NO_2–Ph	**4b**	50[c]
3	**3n**	4-Cl–Ph	4-Br–Ph	**4c**	67
4	**3o**	4-Cl–Ph	4-^{i}Pr–Ph	**4c**	74
5	**3p**	4-Cl–Ph	4-Br–Ph	**4d**	40[d]
6	**3q**	4-MeO–Ph	4-Br–Ph	**4d**	60[d]
7	**3r**	4-Cl–Ph	4-Br–Ph	**4e**	73[e]
8	**17**	Me	4-Br–Ph	**4f**	85
9	**3s**	4-Cl–Ph	4-Br–Ph	**4g**	63
10	**3t**	4-Cl–Ph	4-Br–Ph	**4h**	Trace

[a] General procedures refer to Ref. 7.
[b] Isolated yield with >95% purity.
[c] Formation of imidoyl chloride: amide was treated with $SOCl_2$ at 80 °C for 2 h with the addition of one drop of DMF.
[d] Microwave irradiation time was extended to 25 min.
[e] Reaction was heated at 170 °C in a microwave reactor for 20 min, then 130 °C in an oil bath for 14 h.

was observed that the conversion of aromatic amides into imidoyl chlorides was lower with strong electron withdrawing groups at either R^1 or R^2. In these cases, prolonged heating or addition of DMF was required to assist the conversion (**3e**,**f**). We suspect that the inefficient formation and poor stability of the imidoyl chloride contributed to the lower overall yield of the one-pot reaction. Fortunately, in the presence of excess amide, the yields were improved (entry 12 vs 13).

To further demonstrate the effectiveness of these reaction conditions, several more heterocyclic amino esters (**4b**–**h**) were investigated and the results are listed in Table 3. These amino esters were either commercially available or prepared by the known literature procedures.[8–12] Most of these heterocyclic amino esters reacted effectively with the imidoyl chloride to provide the desired bicyclic 2,3-diaryl-pyrimidin-4(3*H*)-ones in good yields. The reactivity heavily depended on the nature of the heterocyclic amino ester. For example, in the case of **4b**,[8] the additional electron donating methylthio group enhanced the nucleophilicity of the amino group relative to **4a**, leading to higher yields (**3l**,**m**). Ethyl 4-amino-3-phenyl-1*H*-pyrazole-5-carboxylate **4c**[9] also proved to be a better substrate for this reaction than **4a**. The reactions between **4c** and the imidoyl chloride normally went to completion in both steps and gave a higher isolated yield (**3n**,**o**). On the other hand, it was observed that **4d**[10] and **4e**[11] required prolonged heating to force the cyclization (**3p**–**r**). In the case of **4f**, the amino group was so nucleophilic that heating was not required for the nucleophilic attack step to occur, but the intramolecular cyclization step still needed heating to facilitate the cyclization (**17**). An example was also given to show that an ester group could survive this reaction condition (**3s**). Among all of the heterocyclic amino esters investigated, only the acid labile **4h**[12] failed to give any significant amount of the desired product (**3t**).

In summary, we have developed an efficient one-pot synthesis of fused bicyclic 2,3-diaryl-pyrimidin-4(3*H*)-ones. These molecules can be obtained in two steps from commercially or readily available starting materials in moderate to good yields. The key step is a Lewis acid assisted cyclization reaction between imidoyl chloride intermediate **14** and heteroaromatic amino ester **4**. This reaction appeared to be general, robust, and amenable for parallel synthesis.

Acknowledgments

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7. *General procedure for the synthesis of fused bicyclic 2,3-diaryl-pyrimidin-4(3H)-ones* **3**: A mixture of amide **13** (0.25 mmol) and $SOCl_2$ (0.5 mL) was heated at 80 °C till the formation of imidoyl chloride was complete (normally within 2 h). Excess $SOCl_2$ was then removed under vacuo. The residue was dissolved in anhydrous 1,2-dichloroethane (1.5 mL) and transferred into a solution of amino ester **4** (0.30 mmol) in anhydrous 1,2-dichloroethane (1.0 mL). After $TiCl_4$ (0.50 mmol) was added, the reaction mixture was heated at 170 °C by a microwave reactor for 20 min. The mixture was quenched with water (30 mL) and extracted with chloroform (3 × 15 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and purified by chromatography on silica gel (hexanes/EtOAc).
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