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A one-step, atom economical synthesis of thieno[2,3-*d*]pyrimidin-4-amine derivatives via a four-component reaction

Taoda Shi,[a] Christopher J. Zerio,[a] Jared Sivinski,[a] Andrew J. Ambrose,[a] Kohlson T. Moore,[a] Thomas Buckley,[a] Lynn Kaneko,[a] Mae Zhang,[a] Donna D. Zhang,[a] and Eli Chapman*[a]

Dedication

Abstract: A Na_2HPO_4-catalyzed four-component reaction between a ketone, malononitrile, S_8 and formamide has been realized for the first time. This reaction provides a concise approach to thieno[2,3-*d*]pyrimidin-4-amines, previously requiring 5 steps. The utility of this reaction was validated by preparing a multi-targeted kinase inhibitor and an inhibitor of the NRF2 pathway with excellent atom- and step-economy.

Introduction

Thieno[2,3-*d*]pyrimidin-4-amines (TPAs) have been discovered to possess many important bioactivities, including inhibition of hepatitis C virus (HCV) replication[1], inhibition of kinases,[2] modulation of the NRF2 anti-oxidant response pathway,[3]and inhibition of human farnesyl pyrophosphate synthase (hFPPS)[4] (Figure 1). Notably, GDC-0941 is currently being evaluated as an anticancer agent in a phase II clinical trial,[2a] while GDC-0980 and SNS-314 are both being tested as anticancer agents in phase I clinical trials[2b],[2c]. In light of the biological and pharmaceutical value of TPAs, the organic synthesis community has been interested in facile syntheses of these molecules. Currently, the reported synthesis of TPAs requires 5 steps starting with malononitrile and acetyltrimethylsilane (Scheme 1, top).[4] To develop a general, straightforward method of synthesizing TPAs, we designed a one-step synthesis using a four-component reaction between ketones, malononitrile, S_8 and formamide based on the Gewald reaction (Scheme 1, bottom).[5]

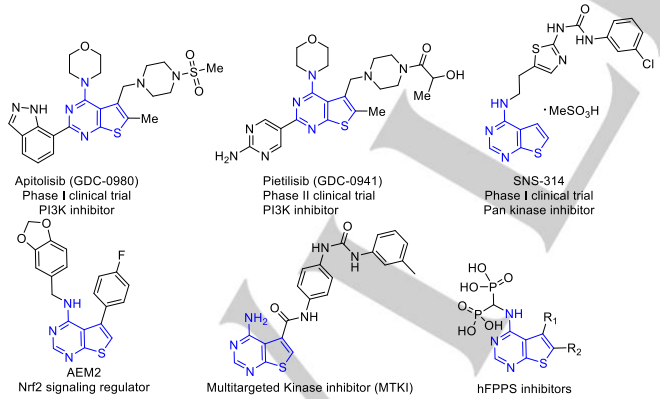
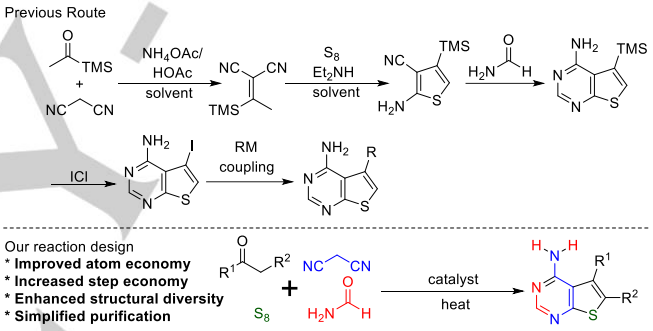


Figure 1. Bioactive molecules bearing a thieno[2,3-d]pyrimidin-4-amine core.



Scheme 1. The previously reported route of TPA synthesis and the presently reported route.

This design is expected to improve atom economy, [6] step economy,[7] structural diversity[8] and ease of purification.

Results and Discussion

To test our proposed atom-economical thieno[2,3-*d*]pyrimidin-4-amine synthesis, we started with 1 equivalent of acetophenone (**1a**), 1.5 equivalents of malononitrile (**2**), 1.1 equivalents of S_8 (**3**) and 12 equivalents of formamide (**4**). We were surprised to find that by simply heating the reaction to 170°C, even in the absence of a catalyst, we could isolate the desired product **5a** in 34% yield (Table 1, Entry 1). Next, we evaluated a panel of potential catalysts including L-proline/Et_2NH, Na_2CO_3, Na_2HPO_4, K_2CO_3, and K_3PO_4 (Table 1, Entries 2-6), and found Na_2HPO_4 as the optimal catalyst giving **5a** in 85% yield (Table 1, Entry 4). Compared to other catalysts tested, Na_2HPO_4 is the only one that could function as both a base and an acid, which is a possible reason for its superior catalytic effects. Using Na_2HPO_4 as the catalyst, we next explored solvent effects (Table 1, Entries 7-10). Water, *tert*-butanol, *sec*-butanol, and isopropanol all caused a decrease in the yield of **5a**. This result indicated that the reactant formamide, **4**, is also an excellent solvent for the reaction. Next,

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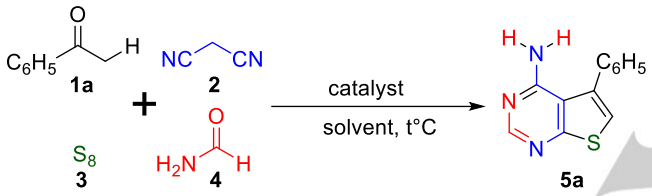
in order to optimize the efficiency of the reaction, we explored the minimum amount of **4** that could be used (Table 1, Entries 4, 11-13). With 4 eq. of **4**, the yield of **5a** was slightly lower, but when we investigated the substrate scope with 4 eq. of **4**, we found many of the substrates gave a poor yield in these conditions. When the amount of **4** dropped to 2 eq., the yield of **5a** decreased from 86% to 75%, and was further reduced to 62% if 1.5 eq. of **4** was used. Therefore, 12 eq. of **4** gives the highest yield and, importantly, the greatest substrate scope. We next explored time and temperature and found the yield increased to 91% and the reaction time could be decreased from 6 hours to 0.5 hour by increasing the temperature to 200°C (Table 1, Entry 14). Further, in the presence of 10 mol% triphenylphosphine as an additive, the yield of **5a** further increased to 96% (Table 1, Entry 15). But with Ph_3P and no Na_2HPO_4, the yield dropped to 55% (Table 1, Entry 16). The presence of Ph_3P possibly prevents the dimerization of **5a**.[9] Overall, we chose 20 mol% Na_2HPO_4 as catalyst, 10 mol% Ph_3P, and 200°C for 0.5 h, as the standard conditions for a survey of the substrate scope.

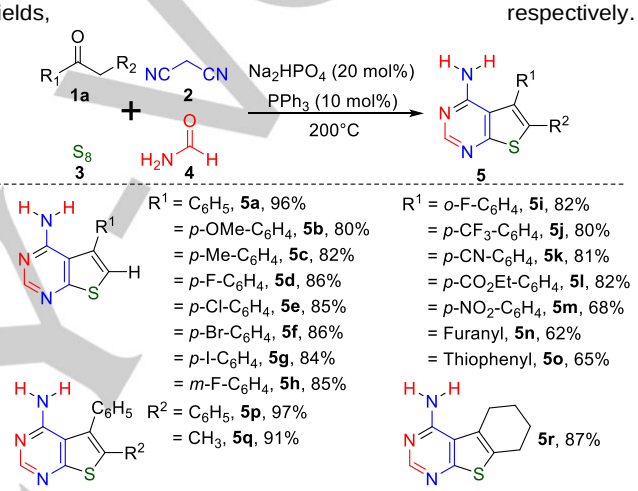
Table 1. Optimization of conditions of a four-component reaction between acetophenone **1a**, malononitrile **2**, S_8 **3**, and formamide **4**.[a]



Entry	Catalyst	Eq. of 4	Solvent	T/°C	% Yield[d]
1	None	12	-	170	34
2	L-proline/Et_2NH	12	-	170	61
3	Na_2CO_3	12	-	170	35
4	Na_2HPO_4	12	-	170	85
5	K_2CO_3	12	-	170	52
6	K_3PO_4	12	-	170	45
7	Na_2HPO_4	12	H_2O	170	10
8	Na_2HPO_4	12	*t*-BuOH	170	45
9	Na_2HPO_4	12	*s*-BuOH	170	41
10	Na_2HPO_4	12	*i*-PrOH	170	32
11	Na_2HPO_4	4	-	170	84
12	Na_2HPO_4	2	-	170	75
13	Na_2HPO_4	1.5	-	170	62
14[b]	Na_2HPO_4	12	-	200	91
15[b, c]	Na_2HPO_4	12	-	200	96
16[b]	PPh_3	12	-	200	55

[a] 1.0 eq. ketone (**1a**), 1.5 eq. malononitrile (**2**), 1.1 eq. S_8 (**3**), 12.0 eq. formamide (**4**), and 20 mol% catalyst were used for 6 hours. [b] 0.5 hour. [c] 10 mol% Ph_3P added. [d] Isolated yields.

After optimizing conditions, a set of aromatic moieties at the R^1 position were evaluated. Electron-withdrawing groups (EWG) gave an 81% average yield (Scheme 2, **5b** and **5c**). *Para*-halide substituents gave an 85% average yield (Scheme 2, **5d- 5g**). *Meta*- and *ortho*-F substituents gave 85% and 82% yields, respectively. Electron-donating groups (EDG) offered desired products in 77% average yield (Scheme 2, **5j**-**5m**). The structure of **5l** was unambiguously assigned by X-ray crystallography (Figure 2; CCDC 1904050). Heterocyclic groups including furanyl and thiophenyl generated **5n** and **5o** in 62% and 65% yields, respectively.



Scheme 2. Substrate scope of a four-component reaction of ketones **1**, malononitrile **2**, S_8 **3**, and formamide **4**.

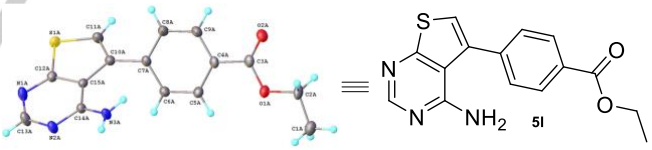


Figure 2. ORTEP diagram of **5l** with atomic labeling scheme. Thermal ellipsoids at a 50 % probability level are shown. CCDC 1904050.

Next, we set R^1 = Phenyl, and looked at the effect of changing the R^2 group. Both phenyl and methyl groups had excellent compatibility in the reaction, providing **5p** and **5q** with 97% and 91% yields, respectively. Finally, an alkyl group at both R^1 and R^2 was tested, producing **5r** in 87% yield. Generally, the reaction has broad ketone substrate scope.

Scalability of an organic reaction is one of the important features when it is used by medicinal chemists and chemical process scientists.[10] We were able to scale-up the reaction to 50 mmol, furnishing 9 grams of product **5a** in 79% yield after a simple work-up and recrystallization (Scheme 3).

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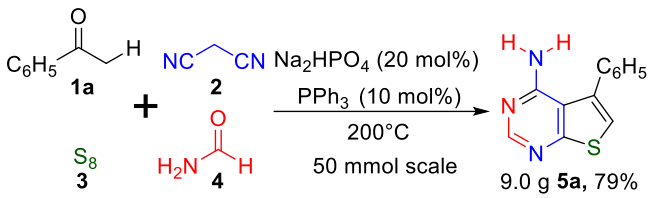
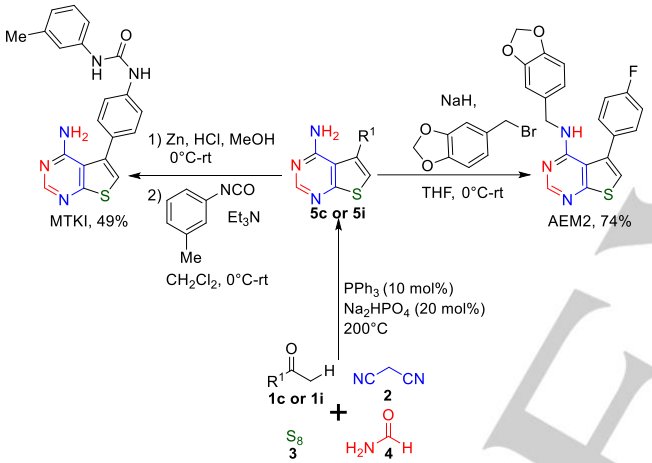


Scheme 3. Scalable four-component reaction of acetophenone **1a**, malononitrile **2**, S_8 **3** and formamide **4.**

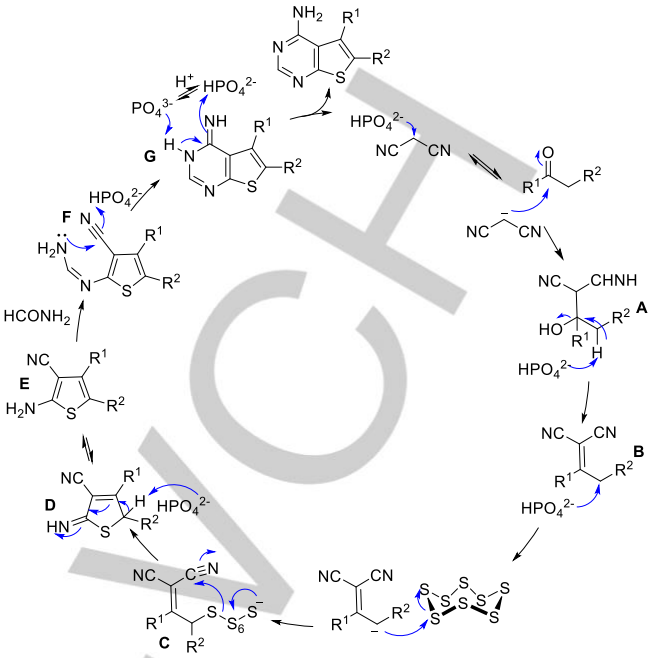
The practicality of the reaction was demonstrated by the rapid synthesis of the NRF2 regulator AEM1 and the multi-target kinase inhibitor (MTKI; Scheme 4). AEM1 could be obtained via a conventional N-alkylation of **5c** with 74% overall yield in two steps from the readily available **1c**. This is the first disclosure of the synthesis of AEM1. MTKI was synthesized with a 49% overall yield in 2 steps from the inexpensive *para*-nitro starting material, **1i**. The quick access to intermediate **5i** via the four-component reaction of **1i, 2**, **3**, and **4** makes this route an attractive alternative to the preparation the MTKI.



Scheme 4. Total synthesis of AEM2 and MTKI using a Na_2HPO_4-catalyzed four-component reaction of ketones (**1c** or **1i**), malononitrile (**2**), S_8 (**3**) and formamide (**4**).

Finally, we propose a possible mechanism of the four-component reaction of ketones, malononitrile, S_8 and formamide (Scheme 5). The reaction is initiated by Na_2HPO_4 extracting the proton of **2**. Then the ketone is subjected to nucleophilic attack of activated **2**, leading to the formation of intermediate **A**. The product of a Knoevenagel reaction[11], **B**, is generated through the elimination of **A** with the help of Na_2HPO_4. Subsequently, Na_2HPO_4 activated **B** opens the S_8 ring through nucleophilic attack to yield intermediate **C**. Intermediate **C** undergoes intramolecular addition to the cyano group to form **D**. Then Na_2HPO_4-promoted aromatization of **D** leads to the formation of Gewald reaction product **E**.[12] Condensation of **E** and **4** produces intermediate **F** which undergoes intramolecular addition to the cyano group to give **G**. Finally, the Na_2HPO_4-catalyzed tautomerization of **G** gives the product **5**.

Conclusion



Scheme 5. Proposed mechanism of the Na_2HPO_4-catalyzed four-component reaction of ketone, malononitrile, S_8 and formamide

In conclusion, we have developed a four-component reaction between ketones, malononitrile, S_8 and formamide, to prepare TPAs in 62-97% yield. This reaction provides a facile synthesis of high value intermediates with excellent atom economy, short reaction times, high structural diversity, and facile purification. In addition, the reaction could be scaled up to a multi-gram scale that did not require chromatography for purification. To demonstrate the general applicability of our four-component reaction, the reaction was applied to prepare the NRF2 regulator AEM2 and MTKI in two steps with high overall yields. In the future, the invention of this reaction is expected to accelerate the synthesis of TPA-based molecules for both drug discovery efforts and process chemistry.

Experimental Section

General procedure for the preparation of compounds 5a-r. To a 10 mL reaction vial, was added 1.0 mmol (1.0 eq.) ketone (**1a-r**), 1.5 mmol (1.5 eq.) malononitrile (**2**), 1.1 mmol (1.1 eq.) S_8 (**3**), 12 mmol (12.0 eq.) formamide (**4**), 20 mol% Na_2HPO_4, and 10 mol% PPh_3. The mixture was heated to 200°C in a sand bath for 0.5 hour. **1** was confirmed to be consumed by TLC analysis. Then 2 mL of water was poured into the reaction mixture after it cooled to 22°C. The resulting mixture was extracted with ethyl acetate (EtOAc) 3 times (5 mL EtOAc per extraction). The organic layers were combined and washed with 15 mL water. Subsequently, the organic layer was dried with anhydrous magnesium sulfate. The crude product was obtained after removing the EtOAc with vacuum rotation. Further purification was performed with flash column chromatography to afford products **5a-r** as solids.

Acknowledgements

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Keywords: atom economy• multi-component reaction• thieno[2,3-*d*]pyrimidin-4-amines • structural diversity

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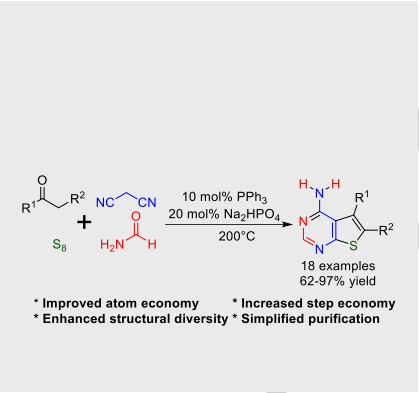

*Taoda Shi, Christopher J. Zerio, Jared Sivinski, Andrew J. Ambrose, Kohlson Taylor Moore, Thomas Buckley, Lynn Kaneko, Mae Zhang, Donna D. Zhang, and Eli Chapman**

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Improving atom economy in the synthesis of Thieno[2,3-d]pyrimidin-4-amine derivatives via a four-component reaction with ketones, malononitrile, S_8 and formamide

Concise synthesis of thieno[2,3-d]pyrimidin-4-amines with improved atom economy, increased step economy, enhanced structural diversity and simplified purification has been realized.

Layout 2:

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