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One-Step Synthesis of Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones via a Catalytic Four-Component Reaction of Ketones, Ethyl Cyanoacetate, S₈ and Formamide

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Abstract

Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones are important pharmacophores that previously required a three step synthesis with two chromatography steps. We herein report a green approach to the synthesis of this pharmacologically important class of compounds via a catalytic four-component reaction using a ketone, ethyl cyanoacetate, S₈ and formamide. The reported reaction is characterized by step economy, reduced catalyst loading and easy purification.

Graphical Abstract

Green synthesis of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones via a one-step and catalytic four-component reaction.

Keywords

thieno[2,3-*d*]pyrimidin-4(3*H*)-ones; catalytic; multi-component reaction; green chemistry

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ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website.

Characterization data of **5a-5r** and **6**

The authors declare no competing financial interest.

INTRODUCTION

Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones or thieno[2,3-*d*]pyrimidin-4(3*H*)-one-derived molecules have been reported to possess multiple biological activities including inhibitory activity against the interaction between DNA repair proteins Rev7 and Rev3L,¹ HCV replication,² the transcription factor Nrf2,³ and kinases (Figure 1).⁴ Therefore, the construction of the thieno[2,3-*d*]pyrimidin-4(3*H*)-one backbone has drawn attention in the organic synthesis community.

Currently, the best reported synthesis of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones requires stoichiometric catalysts and multiple steps including a Knoevenagel condensation, followed by a Gewald reaction, and heat-promoted cyclization.^{5, 6, 7, 8, 9} To improve the synthetic efficiency of this reaction, we envisioned coupling the three steps into one-pot (Scheme 1). This four-component reaction of a ketone, ethyl cyanoacetate, S₈ and formamide is predicted to have the advantage of a multi-component reaction (MCR), including no intermediate isolation and a single purification step, which would be a greener synthetic strategy than currently available.^{10, 11, 12, 13, 14, 15, 16, 17, 18}

RESULT AND DISCUSSION

As an initial proof of concept and reaction development, we used acetophenone **1a**, ethyl cyanoacetate **2**, S₈ **3** and formamide **4** as the starting materials to perform the reaction with the reported conditions from the optimized stepwise reaction where 1.0 eq of NH₄OAc, 0.5 eq of HOAc, and 1.0 eq of Et₂NH were used as catalysts. From this, we could isolate the product **5a** in 65% yield after reaction at 200°C for 2 h (Table 1, entry 1). When instead we used a 20 mol% catalyst loading, we still obtained a 62% yield of **5a** (Table 1, entry 2). This observation could indicate the catalytic efficiency increases in the one-pot reaction MCR, perhaps this is because the formation of thermo-stable product **5a** drives the progression of the Gewald reaction and the Knoevenagel condensation.

We next set out to test the effects of different acids including benzoic acid (PhCO₂H), acetic acid (HOAc), *p*-toluenesulfonic acid (*p*-TSA), trifluoroacetic acid (TFA), glycine and L-proline in combination with the catalytic base, Et₂NH. The results showed L-proline was the best catalyst in combination with Et₂NH, affording **5a** in 78% yield (Table 1, entry 8). Whereas, the acids with lower pK_as such as *p*-TSA and TFA decreased the yields (Table 1, entries 5 and 6). This latter observation was probably due to the stronger acids inhibiting the base-promoted Gewald reaction. The removal of Et₂NH from the reaction also decreased the yields (Table 1, entries 9 and 10). Increasing the reaction time to 6 hours increased the yield by 4% (Table 1, entry 11). The temperature was lowered to 170°C without loss of yield (Table 1, entry 12). However, further lowering the temperature to 140°C was insufficient to carry out the final cyclization step, resulting in the formation of the aminoester intermediate as the major product.

Next, we worked to optimize the stoichiometry of the reaction. We lowered the amount of S₈ to 1 equivalent. Pleasingly, this improved the yield to 88% without producing the black polymer side product observed with 2 equivalents (Table 1, entry 13). Less impurities caused

the product to precipitate after water was added, allowing for facile purification. If we further cut down the amount of **4** to 2 equivalents, the yield dropped to 75% with an increase in the formation of the unknown polymer (Table 1, entry 14). However, increasing to 6 equivalents of **4** had no significant influence on the yield (Table 1, entry 16). Hence, we established the standard conditions: 20 mol% L-proline, 20 mol% Et₂NH as the catalysts; **1:2:3:4** = 1:1.5:1:4, 170°C for 6 h.

With the optimized conditions in hand, we investigated the substrate scope of the reaction. An electron-donating group (EDG) on the aromatic ring of **1** barely changed the yield (Table 2, **5b** and **5c**). Halogens on the *para* position of the aromatic ring of **1** further increased the yields, giving the products in 92%-98% yields (Table 2, **5d**, **5e**, and **5f**). Heterocycles, including furanyl, pyridinyl and thiophenyl were all compatible with the specified reaction conditions, but with slightly lower yields, producing **5g**, **5h**, and **5i** in 87%, 82% and 83% yields, respectively. An alkyl ketone, such as cyclohexanone, was also reactive, giving product **5j** with 100% yield. *Ortho*-, and *meta*-fluoro substituted phenylpropan-2-one were both active in the reaction, with only a slight decrease in the yield compared to *para*-fluoro substituted substrate (Table 2, **5k** and **5l**). 1-methyl and phenyl substituted phenylpropan-2-one were tested and gave 99% yield for **5m** and 93% yield for **5n**, respectively. Additional electron-withdrawing groups were also investigated, furnishing the products in 84%-89% yields (Table 2, **5o**, **5p**, and **5q**). Finally, an aldehyde substrate, phenylacetaldehyde, was evaluated in the reaction, giving the desired product with 98% yield (Table 2, **5r**). Overall, the reaction demonstrated broad substrate scope of substituted phenylpropan-2-ones.

To demonstrate the practicality of the reaction, the four-component reaction of **1a**, **2**, **3** and **4** was scaled up to 100 mmol, yielding 22 g of **5a** in 96% yield and requiring no chromatography (Scheme 2). We also used readily available and inexpensive materials to synthesize thieno[2,3-*d*]pyrimidin-4(3*H*)-one **5a** which is 172-fold more valuable than the total cost of the material of the reaction (Table 3).

To further explore the value of this reaction, we explored derivitization of the thieno[2,3-*d*]pyrimidin-4(3*H*)-ones. We could readily transform product **5a** into cyclic amidine **6** in 71% yield using the reported DIPEA-promoted direct amination of a cyclic amide (Scheme 3).¹⁹ Compared to traditional two-step amination of **5a** (chlorination and S_NAr substitution), this method is more straightforward. This also illustrates the versatile, rapid synthesis of high value products starting with our procedure.

Mechanistically, we propose the four-component reaction goes through L-proline and diethyl amine catalysed Knoevenagel condensation, base promoted Gewald reaction, and cyclization to yield **5** (Scheme 4). First, **1** and **2** react with the salt of L-proline and diethyl amine to form electrophilic iminium **A** and nucleophilic ion pair **B** which then form the Knoevenagel condensation product **D** through intermediate **C**. Then the methylene group of **D** is deprotonated to afford ion pair **E** which attacks S₈ to generate **F**. Intermediate **F** undergoes an intramolecular nucleophilic addition at the nitrile group to produce **G**, which can be protonated by the salt of diethyl amine to form **H**. Intermediate **H** can be aromatized with the help of diethyl amine resulting in **I**. Formamide can be activated by L-proline to form iminium **J**, which undergoes a nucleophilic attack of **I** providing **K**. Intermediate **L**

derived from the deprotonation of **K** by diethyl amine then goes through intramolecular nucleophilic addition to the ester by deprotonated amine group, following by the elimination of **M** to furnish the final product **5** and close the catalytic cycle.

CONCLUSION

In conclusion, we have developed an environmentally friendly method to synthesize thieno[2,3-*d*]pyrimidin-4(3*H*)-ones via a catalytic four-component reaction between ketones, ethyl cyanoacetate, **S₈** and formamide. This method is an appealing chemical process because it is catalytic, inexpensive, easy, and scalable. The environmental (E) factor is one of the general metrics used to define a green chemical reaction.^{20, 21} The E factor is defined by the ratio of the mass of waste generated per mass of product generated. The lower the E factor for a given reaction, the more environmentally friendly the reaction is. The E-factor of the reaction we reported here, using acetophenone as the ketone, is calculated to be 1.5 which is >49-fold lower than the calculated E factor for the previously reported synthetic method (Table 4 and Supporting Information, page S7).⁹ Notably, the E-factor of 2.0 is comparable to a previously reported green Heck reaction and green syntheses of 1,2-azido alcohols and 1,2-aminoalcohols.^{22, 23}

EXPERIMENTAL SECTION

General procedure for the synthesis of **5a-5r**.

1 mmol **1**, 1.5 mmol **2**, 1 mmol **3** and 4 mmol **4**, 20 mol% L-proline, and 20 mol% diethylamine were mixed in a vial equipped with a magnetic stir bar. The reactions were performed at 170°C for 6 h. After the vial cooled to 22°C, 1 mL of water was added to the reaction mixture, resulting in the precipitation of the product. These crystals were collected through simple filtration.

Procedure for the synthesis of **6**.

To a flame-dried 10 mL 3-neck flask, was added 0.25 mmol of **5a**, 0.75 mmol of hexachlorocyclopentadiene (HCCP), 0.75 mmol of Hünig's base (DIPEA) and 5 mL acetonitrile at 0°C, the reaction mixture was warmed to 22°C and allowed to stir for 2 h. Then 0.75 mmol of aniline was added. The resulting mixture was heated up to 120°C until the disappearance of **5a** as detected by TLC. Product **6** was purified via silica gel chromatography with a mixture of hexane and ethyl acetate as the eluting solvent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Biologically interesting molecules containing a thieno[2,3-*d*]pyrimidin moiety.

Scheme 1.

Previous work on the synthesis of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones and our proposed green synthesis.

Scheme 2.

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

Scheme 3.

The transformation of **5a** into **6** with DIPEA-promoted direct amination of cyclic amide.

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Table 1.

Optimization of conditions of a four-component reaction between acetophenone **1a**, ethyl cyanoacetate **2**, **3** and formamide **4**.^a

Entry	Catalyst 1 (loading)	Catalyst 2 (loading)	Temp (°C)	Time (h)	Yield (%) ^b
1	NH ₄ OAc/HOAc(1.0 eq/0.5 eq)	Et ₂ NH (1.0 eq)	200	2	65
2	NH ₄ OAc/HOAc(0.2 eq/0.1 eq)	Et ₂ NH (0.2 eq)	200	2	62
3	PhCO ₂ H (0.2 eq)	Et ₂ NH (0.2 eq)	200	2	68
4	HOAc (0.2 eq)	Et ₂ NH (0.2 eq)	200	2	60
5	p-TSA (0.2 eq)	Et ₂ NH (0.2 eq)	200	2	20
6	TFA (0.2 eq)	Et ₂ NH (0.2 eq)	200	2	30
7	Glycine (0.2 eq)	Et ₂ NH (0.2 eq)	200	2	74
8	L-proline (0.2 eq)	Et ₂ NH (0.2 eq)	200	2	78
9	Glycine (0.2 eq)	-	200	2	68
10	L-proline (0.2 eq)	-	200	2	65
11	L-proline (0.2 eq)	Et ₂ NH (0.2 eq)	200	2	82
12	L-proline (0.2 eq)	Et ₂ NH (0.2 eq)	170	6	82
13 ^c	L-proline (0.2 eq)	Et ₂ NH (0.2 eq)	170	6	88
14 ^{c,d}	L-proline (0.2 eq)	Et ₂ NH (0.2 eq)	170	6	75
15 ^{c,e}	L-proline (0.2 eq)	Et ₂ NH (0.2 eq)	170	6	89

^aThe reactions were performed with 1 mmol of **1**, 1.5 mmol of **2**, 2 mmol of **3** and 4 mmol of **4**. The product **5a** was purified with silica gel column chromatography or crystallization;

^bisolated yield;

^c1 eq of **3** was used;

^d2 eq of **4** was used;

^e6 eq of **4** was used.

Table 2.

Substrate scope of four-component reaction of ketones **1**, ethyl cyanoacetate **2**, S₈ **3** and formamide **4**.^a

^aThe reactions were performed with 1 mmol **1**, 1.5 mmol **2**, 1 mmol **3** and 4 mmol **4**. The products were purified with crystallization.

Table 3

The cost of the starting material of the reaction and the price of the product **5a**.

Material	1a	2	3	4	C1	C2	Total ^a	5a
Price ^b (\$/g)	0.07	0.09	0.12	0.47	0.76	0.10	0.59	102

^aMaterial cost for producing 1 g of **5a**;

^bthe price references the US market price.

Table 4.

Comparison of E-factors of our method with other reported green reactions

Methods	Currently reported conditions	Ref. 9	Heck Reaction	1,2-azido alcohols and 1,2-amino alcohols
E-factors	1.5	74.4	2.3-5.0	2.1