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# Transition-metal-free highly efficient synthesis of 2-pyridones from β-keto amides and ynals

Zhengwang Chen,* Jiayang Liu,[§] Caiju Jin,[§] Qi Tan and Min Ye*
*Key Laboratory of Organo-Pharmaceutical Chemistry of Jiangxi Province, Gannan Normal University, Ganzhou, Jiangxi, 341000, PR China*

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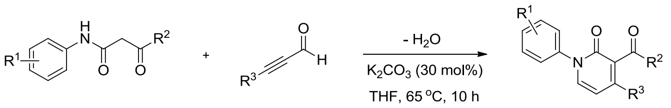
ABSTRACT

A convenient and efficient annulation reaction was developed, affording 2-pyridones in good to excellent yields. A variety of substituted β-keto amides and ynals were well tolerated, and especially the transformation produced water as only by-product under transition-metal-free conditions. Furthermore, the conjugated enyneamides were achieved from β-cyano amides and ynals in high yields.

Substituted pyridones, as attractive structural units, are commonly found in organic chemistry and natural products with interesting structural properties and remarkable bioactivity profiles.[1] They have exhibited promising biological activities, such as antibacterial, antifungal, cytotoxic and insecticidal activity.[2] As a result, many well-documented modern approaches have been developed for the construction of pyridone derivatives over the past decades. Two regular methods for the preparation of 2-pyridones involve the modification of the heterocycles[3] and the establishment of the heterocyclic skeleton from acyclic starting materials.[4] Transition-metal-catalyzed annulation reactions containing Ru,[5] Rh,[6] Pd,[7] Au,[8] and Co[9] complexes have received significant attention for the formation of 2-pyridones in recent years. Despite the significant advancement, there are still some drawbacks, such as expensive transition metal and ligand, stoichiometric excess of strong oxidant and additive, complex substrates and multi-step reactions. Considering the important application of 2-pyridone frameworks in pharmaceutical industry, continuing to explore a simple and complementary transformation involving high efficiency and practicability from readily accessible precursors is vital to the synthetic chemistry community.

Owing to the rising global environmental issue, transition-metal-free system has been attracted significant attention.[10] These transformations have several advantages, such as low price, non-toxicity, operational simplicity, good functional group tolerance and environmentally friendliness. Ynals, as readily available and valuable building blocks, have been considered as versatile substrates in organic synthesis. In particular, they have been extensively utilized in many cyclization reactions for the construction of diverse heterocyclic compounds.[11] Very recently, we have described a highly efficient catalyst-free approach for the synthesis of 3-acylated indolizines from 2-pyridylacetates and ynals.[12] As part of this continuing project accessing to nitrogen-containing heterocycles from other binucleophilic reagents and ynals, here we present a simple and efficient protocol toward 2-pyridones from β-keto amides and ynals through successive Michael addition and intermolecular dehydration process under transition-metal-catalyzed conditions (Scheme 1). It is important to note that, Constantieux's group reported an efficient synthesis of 2-pyridones from β-keto amides and ynols via cooperative organocatalysis and metal catalysis.[13]

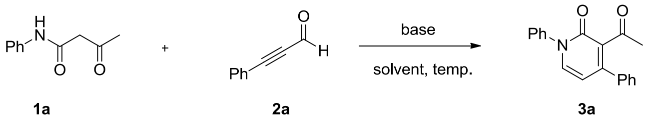


**Scheme 1.** The synthesis of 2-pyridones via intermolecular dehydration from β-keto amides and ynals

Optimization of the reaction conditions was established by varying base, solvent, and temperature (Table 1). At the beginning of our study, acetoacetanilide (**1a**) and phenylpropiolaldehyde (**2a**) were chosen as the model substrates to evaluate the reaction conditions. Various commonly used inorganic and organic bases were tested. In general, inorganic bases were more effective than organic bases, and we were pleased to find $K_2CO_3$ was the most suitable base and gave the desired product in 85% yield (Table 1, entries 1-10). The control experiment showed that the base was indispensable in the process, no product was formed without the addition of the base (Table 1, entry 11). Then a variety of solvents were screened at 100 or 65 °C. The results indicated that the solvents played an important role, and THF was found to afford the desired product with the isolated yield improved to 95% (Table 1, entries 12-18).

The reaction temperatures were also evaluated, and lower temperatures were disadvantageous to this transformation (Table 1, entries 19 and 20). Therefore, base, solvent and reaction temperature are all crucial for this transformation.

**Table 1.** Optimization of reaction conditions for the synthesis of 2-pyridonepyridone[a]



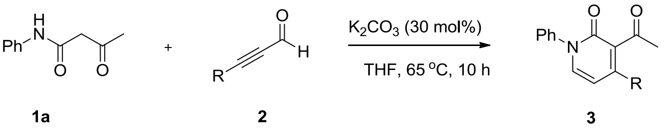
| Entry | Base | Solvent | Temp. | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | dioxane | 100 | 82 |
| 2 | $K_2CO_3$ | dioxane | 100 | 85 |
| 3 | NaOEt | dioxane | 100 | 56 |
| 4 | KOH | dioxane | 100 | 60 |
| 5 | $K_3PO_4$ | dioxane | 100 | 30 |
| 6 | NaOAc | dioxane | 100 | 21 |
| 7 | $Et_3N$ | dioxane | 100 | n.p |
| 8 | DABCO | dioxane | 100 | 18 |
| 9 | DMAP | dioxane | 100 | 47 |
| 10 | DBU | dioxane | 100 | 68 |
| 11 | - | dioxane | 100 | n.p |
| 12 | $K_2CO_3$ | DMF | 100 | 88 |
| 13 | $K_2CO_3$ | $H_2O$ | 100 | n.p |
| 14 | $K_2CO_3$ | DMSO | 100 | 54 |
| 15 | $K_2CO_3$ | toluene | 100 | n.p |
| 16 | $K_2CO_3$ | $CH_3CN$ | 65 | 62 |
| 17 | $K_2CO_3$ | THF | 65 | 98 (95) |
| 18 | $K_2CO_3$ | EtOH | 65 | 28 |
| 19 | $K_2CO_3$ | THF | 45 | 70 |
| 20 | $K_2CO_3$ | THF | 25 | 20 |

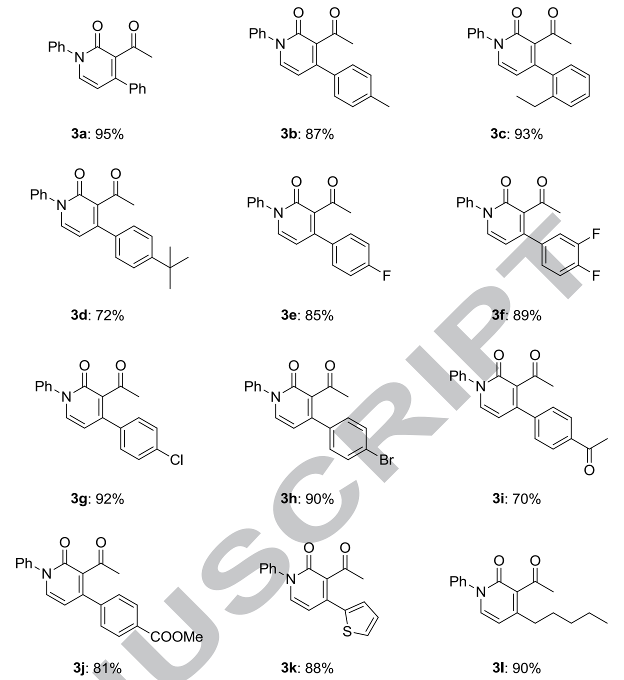
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol) with base (30 mol%) in solvent 1.0 mL for 10 h.

[b] Isolated yield. n.p=no product.

With the optimized reaction conditions, the substrate scopes were evaluated, and the results were illustrated in Scheme 2. Initially, a wide range of ynals proceeded smoothly with acetoacetanilide (**1a**) to deliver the corresponding products under the standard conditions. In general, the reaction has good functional group tolerance. Ynals with electron-donating and electron-deficient substituents were all compatible with this protocol (**3b-j**). Interestingly, the reaction gave high yield when *ortho* ethyl substituted ynal was employed (**3c**). The substrate bearing tertiary butyl group generated the product in 72% yield (**3d**). Notably, bromide-substituted ynal was suitable substrate and provided **3h** product in excellent yield (**3h**). In particular, aryl bromide was easily further functionalized under transition-metal-catalyzed conditions. The products containing acetyl and ester groups could be easily converted to other functional groups and had potential applications in organic synthesis and pharmaceutical chemistry (**3i** and **3j**). In addition, the heteroaryl substituted ynal reacted successfully to produce the product in 88% yield (**3k**). Fortunately, the aliphatic ynal also worked well in the reaction and afforded the desired product in satisfactory yield (**3l**).

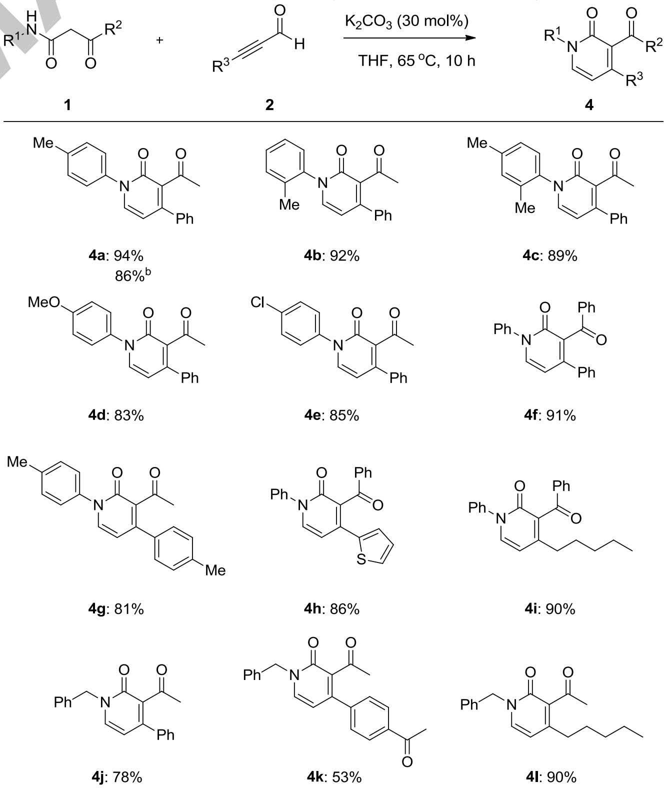
**Scheme 2.** Substrate scope of ynals[a]





[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol) with $K_2CO_3$ (30 mol%) in THF (1.0 mL) at 65 °C for 10 h; Isolated yield.

**Scheme 3.** Substrate scope of β-keto amides and ynals[a]

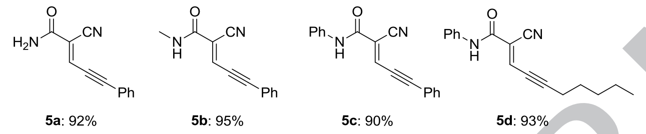


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol) with $K_2CO_3$ (30 mol%) in THF (1.0 mL) at 65 °C for 10 h; Isolated yield. [b] 10 mmol scale of the reaction.

Subsequently, we investigated the scope of β-keto amides under the standard conditions. Initially the aniline moiety was explored and the results were indicated in scheme 3. Both the electron-rich and electron-poor substituents attached to the benzene ring were favorable in the optimized conditions (**4a-e**). The steric hindrance on the benzene ring seemed to have little effect on the yields (**4b** and **4c**). When the methyl group was replaced with phenyl group, the corresponding product **4f** was obtained in 91% yield (**4f**). The aryl, heteroaryl, and aliphatic substituted ynals were also tested, and the results implied that this annulation approach can be effective for the 2-pyridone library (**4g-i**). It is noteworthy that the alkyl substituted β-keto amide was also compatible under the standard conditions (**4j-l**). The reaction yield decreased to 53% when *para* acetyl substituted ynal was applied (**4k**). To our delighted, the reaction could be performed on a gram scale, delivered the product in good yield (**4a**).

When the β-keto amide substrates were replaced with β-cyano amides, and examined the reaction with ynals under the standard conditions (Scheme 4). To our surprise, the reaction did not form any products. Interestingly, after some attempts, we found that the intermolecular dehydration products were produced as a single regioisomer without the addition of $K_2CO_3$. Following the above results, four examples of conjugated enyneamide synthesis were demonstrated. Both primary, secondary amides and aromatic, aliphatic ynals were compatible, and underwent smoothly to lead to the corresponding products in excellent yields (**5a-d**).

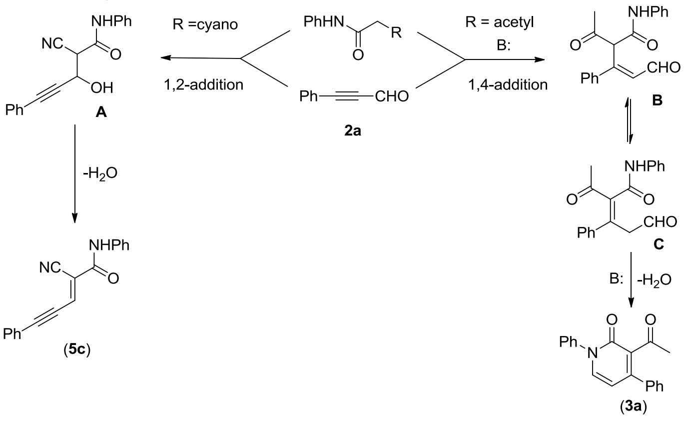
**Scheme 4.** The Intermolecular Dehydration of β-Cyano Amides and Ynals[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol) in THF (1.0 mL) at 65 °C for 10 h; Isolated yield.

On the basis of previous reports and our experimental results, a possible mechanism was depicted in Scheme 5. Phenylpropiolaldehyde **2a** underwent nucleophilic 1,2-addition with β-cyano amide to forms intermediate A, which gave the conjugated enyneamide product via a dehydration process. On the other hand, the Michael addition of **2a** with β-keto amide yielded intermediate **B**. then a proton transfer generated intermediate **C**. Finally, the desired product **3a** was formed via the nucleophilic addition and dehydration of **C** with the aid of base. It suggested that the PKa of the active methylene was essential for the 1,2-addition and 1,4-addition.

**Scheme 5.** Proposed reaction mechanism



In conclusion, we have developed a convenient and highly efficient annulation reaction of β-keto amides and ynals.[14] A series of 2-pyridones bearing various functional groups were obtained in good to excellent yields through a tandem Michael addition and dehydration process. The merits of this transformation include transition-metal-free conditions, readily available reagents, complete regioselectivity, simple operation, etc. It is noteworthy that water is the only byproduct in this transformation. Moreover, the conjugated enyneamides were formed from β-cyano amides and ynals via a nucleophilic 1,2-addition. Further studies to extend synthetic applications and detailed mechanism are currently underway in our laboratory.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/xxx

§ Contribute equally.

Corresponding author. Tel: +86 797 8393670; fax: +86 797 8393670; e-mail address:chenzwang@126.com (Z. Chen)

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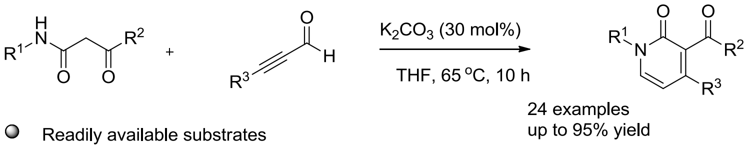
14 A mixture of β-keto amide (0.2 mmol), ynal (0.2 mmol) and $K_2CO_3$ (30 mol%) in THF (1.0 mL) was placed in a test tube (10 mL) equipped with a magnetic stirring bar. The mixture was stirred at 65 °C for 10 h. After the reaction was finished, water (5 mL) was added and the solution was extracted with ethyl acetate (3×5 mL), the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give the pure sample.

# Transition-Metal-Free Highly Efficient Synthesis of 2-Pyridones from β-Keto Amides and Ynals

Zhengwang Chen,* Jiayang Liu, Caiju Jin, Qi Tan and Min Ye*

China Key Laboratory of Organo-Pharmaceutical Chemistry of Jiangxi Province, Gannan Normal University, Ganzhou, Jiangxi, 341000, P.R.



- Readily available substrates
- Mild conditions
- Good FG tolerance and high yields

## Highlights:

·Transition-metal-free annulation reaction toward 2-pyridones.

·Convenient conditions and afford products in good to excellent yields.

·Broad substrate scope and good functional compatibility.