



# A new synthetic approach to polysubstituted-2-pyridones from enamino esters and diethyl ethoxymethylenemalonate under catalyst- and solvent-free conditions



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## ABSTRACT

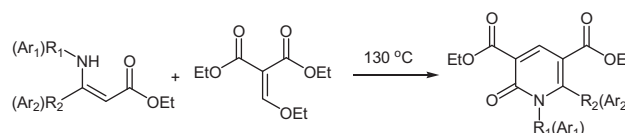
A simple and novel synthesis of polytrisubstituted-2-pyridones derivatives by the reaction of enamino esters and diethyl ethoxymethylenemalonate has been reported. The method provides a rapid synthetic route for the construction of 2-pyridones under catalyst- and solvent-free reaction conditions in moderate-to-good yields.

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## Introduction

The 2-pyridone is an important structural unit found in many natural compounds with biological and pharmaceutical activity.<sup>1</sup> Therefore, they have drawn considerable interest from synthetic chemists.<sup>2</sup> Many literature sources describe more general approaches involving Michael addition of acetonitrile derivatives to an  $\alpha,\beta$ -unsaturated carbonyl substrate and subsequent hydrolytic cyclization followed by oxidative aromatization of the resulting 3,4-dihydropyridone or by eliminative aromatization employing acetoamino and benzenetriazolyl leaving groups.<sup>3</sup> In many cases, strongly basic catalysts such as sodium hydride or alkoxides are required for this transformation.<sup>4</sup> Enamino esters are also important intermediates for the synthesis of heterocycles.<sup>5</sup> Enamino esters usually react as ambident nucleophiles at nitrogen and/or the C-3 position to form heterocycles. However, few reports have been concerned with the preparation of 2-pyridones starting from enamino esters.<sup>6</sup> Thus, the development of efficient methods using nucleophiles derived from enamino esters toward 2-pyridones is still highly desirable.

Diethyl ethoxymethylenemalonate is a useful reagent for synthesis of heterocyclic compounds.<sup>7</sup> However, most literature reported that the first step of formation of heterocyclic compounds is ethoxy group substituted by nitrogen. Recently, Poudel reported



**Scheme 1.** Synthesis of polysubstituted-2-pyridones from enamino esters and diethyl ethoxymethylenemalonate.

4-oxo-4H-chromene-3-carbaldehydes with 1,3-diketesters and anilines for the synthesis of 2-pyridone derivatives. In this reaction mechanism, firstly, amine was as ambident nucleophiles to open the cycle, then heterocycles were formed through ring closure.<sup>8</sup>

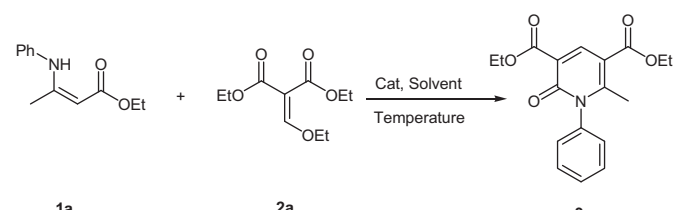
In our work, enamino esters react as nucleophiles at the C-3 position to form heterocycles. Herein, we introduce a catalyst- and solvent-free synthesis of polysubstituted 2-pyridones using the reaction of enamino esters and diethyl ethoxymethylenemalonate (Scheme 1).

## Results and discussion

The reaction of (*Z*)-ethyl-3-(phenylamino)but-2-enoate (**1a**) with diethyl ethoxymethylenemalonate (**2a**) was selected as a prototypical case to screen the experimental condition, and the results are depicted in Table 1. When the reaction was carried out using CuI (10 mol%) as the catalyst in MeCN under a nitrogen

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**Table 1**  
Optimization of the reaction conditions for the synthesis of **3a**<sup>a</sup>



Entry	Catalyst	Solvent	Temp/°C	Time/h	Yield/% <sup>b</sup>
1	CuI	CH <sub>3</sub> CN	80	24	10
2	CuI	DMSO	130	6	55
3	FeCl <sub>3</sub>	DMSO	130	12	23
4	ZnCl <sub>2</sub>	DMSO	130	12	21
5	EtONa	DMF	130	12	0
6	<i>t</i> -BuOK	DMF	130	12	0
7	NaH	DMF	130	12	0
8	—	DMSO	130	6	58
9	—	DMF	130	12	23
10	—	Toluene	130	12	12
11	—	1,4-Dioxane	130	12	8
12	—	—	130	6	63
13	—	—	130	6	43 <sup>c</sup>
14	—	—	140	6	62
15	—	—	120	8	52
16	—	—	110	14	47

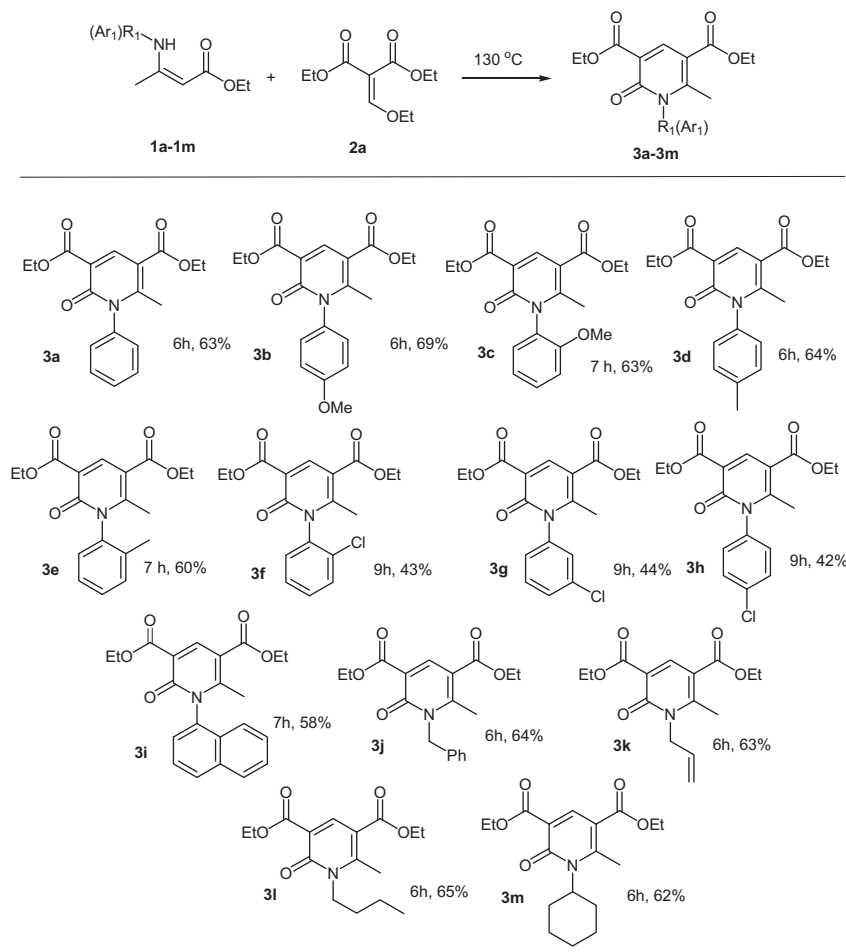
<sup>a</sup> Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), nitrogen.

<sup>b</sup> Isolated yield.

<sup>c</sup> Reaction carried out open to air.

atmosphere at 80 °C, the corresponding 2-pyridone (**3a**) was obtained in 10% isolated yield within 24 h (Table 1, entry 1). **3a** could be produced in 55% yield using DMSO as the reaction solvent at 130 °C with CuI (10 mol %) as catalyst for 6 h (entry 2). Other Lewis acid catalysts such as FeCl<sub>3</sub> and ZnCl<sub>2</sub> gave lower yields under the same reaction conditions (entries 3 and 4). The influence of a strong base, such as NaOEt, KOBu, NaH, on the reaction yield was also examined (entries 5–7). The desired product (**3a**) was not afforded in DMF at 130 °C using a strong base (30 mol %) as catalyst even after 12 h. When the reaction was performed in the absence of a catalyst in DMSO at 130 °C under a nitrogen atmosphere. The product (**3a**) was obtained in 58% yield (entry 8). Switching to other solvents such as DMF, toluene and 1,4-dioxane afforded unsatisfactory results (entries 9–11). It was noteworthy that the reaction proceeded smoothly under solvent-free conditions and the product (**3a**) was obtained in 63% yield (entry 12). In addition, the yield of product (**3a**) decreased when the reaction was conducted in open air (entry 13). Finally, the influence of temperature on the reaction was also investigated. High temperatures (130 °C) proved the best choice for promoting the reaction, as using lower temperatures increased the reaction time and reduced the reaction yield (entries 14–16). In addition, higher temperatures did not accelerate the reaction or promote the reaction yield.

A variety of enamino esters were synthesized to explore the scope of the 2-pyridone under the optimized reaction conditions.<sup>9</sup> The representative results are shown in Scheme 2. The substituents effects on the aromatic amine were studied. Enamino esters bearing electron-withdrawing aryl groups afforded the desired



**Scheme 2.** Substrate scope of the reaction between various methyl enamino esters and diethyl ethoxymethylenemalonate. Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), 130 °C, nitrogen atmosphere; isolated yield.

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