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A Novel Enzymatic Synthesis of Quinoline Derivatives

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Abstract A new mild enzymatic methodology for synthesizing quinoline derivatives by Friedländer condensation was developed. A series of quinoline derivatives were synthesized and characterized by ^{1}H NMR, ^{13}C-NMR, IR and MS. The probable enzymatic mechanism was proposed. It provides a novel method to prepare quinoline derivatives.

Keywords Enzymatic catalysis · Heterocycles · Cyclization · Condensation

1 Introduction

Nitrogen-containing heterocycles have attracted much attention in the organic and medicinal chemistry fields for their diverse biological properties and pharmacophores [1–4]. Quinoline derivatives are a very important class of nitrogen-containing heterocycles, which display a broad range of biological activities such as antibacterial, antimalaria, anti-asthmatic, antitumor, antiplatelet, etc. [5–8] Traditional synthetic routes usually have poor yields, long reaction times, and harsh conditions. Therefore, new methods for constructing quinoline derivatives are constantly sought [9–17].

Owing to high efficiency and mild conditions, enzymatic synthesis has attracted much attention in organic chemistry [18–20]. As part of our continued interest in enzymatic synthesis and exploring new synthetic approaches to quinoline derivatives [21, 22], we herein report a novel, mild, and efficient preparation of quinoline derivatives using catalytic enzymes as shown in Scheme 1.

2 Experimental

Commercial reagents were used without further purification. Reactions were performed in an end-over-end rotator. TLC: Merck precoated TLC (silica gel 60 F 254) plates. The melting-point was determined using a XT-4 melting-point apparatus and were uncorrected. IR spectra were recorded on a Bruker Equinox-55 spectrophotometer using KBr discs in the 4,000–400 cm^{-1} region. ^{1}H- and ^{13}C-NMR spectra: Bruker Advance 400 spectrometer in $CDCl_3$ using TMS as internal standard. GC/MS: Agilent 5975C. All enzymes were purchased from Acros, Alfa, Aldrich and TCI, and used directly.

General procedure for the synthesis of Quinoline derivatives **3**: a mixture of 2-amino-3,5-dibromobenzaldehyde (**1**, 0.1 mmol), cyclopentanone or cyclohexanone (**2**, 0.2 mmol) and enzyme (15 mg) was introduced to a test tube (10 mL), then the mixture was subjected to a shaker under 150 rpm end-over-end rotation at 30 or 40 °C for the

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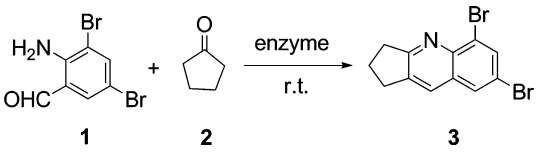


Scheme 1 Enzyme-catalyzed Friedländer reaction of 2-amino-3,5-dibromo-benzaldehyde and cyclopentanone

specified time (see Table 3). After completion of the reaction as monitored by TLC, the reaction mixture was treated with water (5 mL) and ethyl acetate (5 mL). Then the mixture was stirred for 5 min, the residue was then filtered off, the organic phase was dried over anhydrous $MgSO_4$, and evaporation of the solvent was followed by purification on silica gel to afford compounds **3**.

3 Results and Discussions

We initially chose 2-amino-3,5-dibromo-benzaldehyde and cyclopentanone in ethanol as a model reaction. The reaction was performed at room temperature (Scheme 1). In order to select the appropriate enzyme, several types of enzymes were screened (Table 1).

As illustrated in Table 1, the result with the highest conversion was achieved by using Lipase from porcine pancreas (PPL) as catalyst in 24 h (Table 1, entry 1). Pepsin from hog stomach and Albumin from bovine also showed moderate to low catalytic ability (Table 1, entry 2 and 3), and other tested enzymes exhibited very low activities for this conversion.

Table 1 Friedländer reaction between 2-amino-3,5-dibromo-benzaldehyde and cyclopentanone in the presence of different catalysts

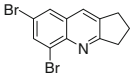
Entry	Catalyst	Time (h)	Conversion[a] (%)
1	Lipase from porcine pancreas (PPL)	24	100.0
2	Pepsin from hog stomach	24	46.3
3	Albumin from bovine	24	14.2
4	Trypsin from porcine pancreas	24	9.0
5	Amino lipase A from aspergilllus niger	24	8.4
6	Amino lipase M from mucor javanicus	24	8.0
7	Amylase	24	7.5
8	α-Amylase from *Bacillus subtilis*	24	Trace
9	Cellulase	24	Trace
10	β-Amylase from soybean Ao448	24	Trace
11	Amino lipase from *Pseudomonas fluorescens*	24	Trace
12	Lipase AY30	24	Trace
13	α-Amylase from *Aspergillus oryzae*	24	Trace
14	Lipase a cyrlic resin from *Candida antarctica*	24	Trace
15	Lipase from porcine pancreas (inactivated)[b]	24	Trace
16	No enzyme	48	0

Reaction conditions: 15 mg enzyme, 0.1 mmol 2-amino-3,5-dibromo-benzaldehyde 0.2 mmol cyclopentanone, 1 mL ethanol, 30 °C, 150 rpm end-over-end rotation for 24 h. Reaction progress was monitored by TLC (petroleum ether/dichloromethane, 1:1) and GC/MS

[a] Conversion based on GC/MS

[b] Lipase from porcine pancreas devitalized with urea at 100 °C for 10 h [23]

Table 2 Friedländer quinoline synthesis catalyzed by lipase from porcine pancreas in various solvents

Entry	Solvent	Time (h)	Conversion[a] (%)	Product
1	Dimethyl sulfoxide (DMSO)	24	100	
2	Ethanol	24	74.36	
3	Dimethyl formamide (DMF)	24	82.16	
4	Acetone	24	6.44	
5	Acetonitrile	24	3.39	
6	Tetrahydrofuran (THF)	24	3.03	
7	Ethyl acetate	24	2.67	
8	Dioxane	24	1.59	
9	Toluene	24	0.41	
10	Dichloromethane	24	8.85	
11	Cyclohexane	24	2.25	

Reaction conditions: 15 mg lipase from porcine pancreas, 0.1 mmol 2-amino-3,5-dibromo-benzaldehyde, 0.2 mmol cyclopentanone, 1 mL solvent, 30 °C, 150 rpm end-over-end rotation for 24 h

[a] Conversion based on GC/MS

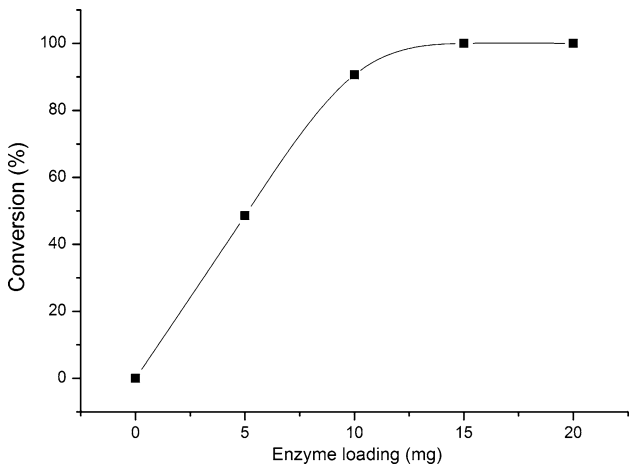
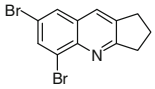
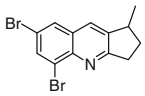
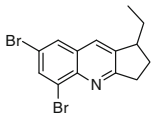
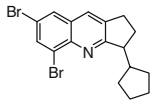
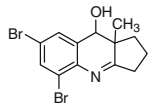
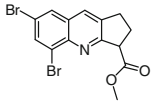
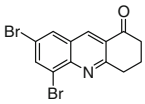
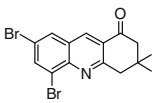
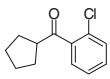


Fig. 1 Effect of PPL loading on the yield of the reaction. Conditions: 15 mg lipase from porcine pancreas, 0.1 mmol 2-amino-3,5-dibromo-benzaldehyde, 0.2 mmol cyclopentanone, 1 mL solvent, 30 °C, 150 rpm end-over-end

Table 3 PPL catalyzed synthesis of Friedländer quinolines

Entry	Substrate 2	Quinoline 3	Reaction time (h)	Yield (%)[a]	Product
1		3a	20	95	
2		3b	30	70	
3		3c	30	68	
4		3d	30	60	
5		3e	30	73	
6		3f	30	Trace	
7		3g	14	92	
8		3h	14	90	
9		3i	40	ND[b]	–
10		3g	40	ND	–
11		3k	40	ND	–

Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), 15 mg lipase from porcine pancreas, 1 mL DMSO, reactions conducted at 30 °C unless where noted, 150 rpm end-over-end rotation for certain time

[a] Isolated yield

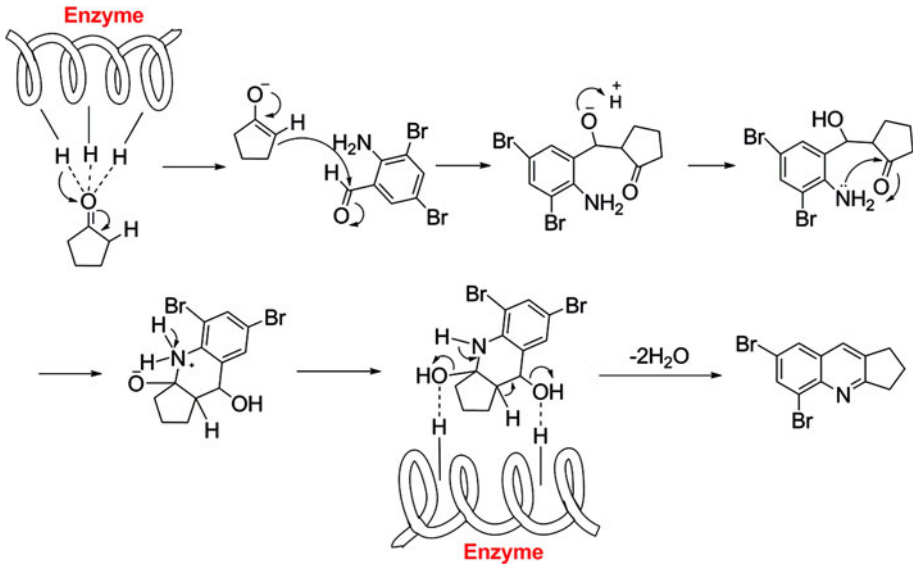
[b] No product is detected

We also performed blank control and inactivated enzyme experiments to demonstrate that this catalytic ability comes from the enzyme and not some amino acid impurities. None or a trace of quinoline product were detected (Table 1, entry 15 and 16).

The reaction solvent is one of the most important factors influencing the reaction process. Consequently, some of the common solvents were screened (Table 2). The results demonstrated that dimethyl sulfoxide was best with high conversion. Ethanol and dimethyl formamide also promoted this reaction (Table 2, entry 2 and 3). It seems likely that polar solvents are beneficial to the reaction. Based on the solvents screened, we chose dimethyl sulfoxide as the optimum solvent.

We optimized the amount of PPL on this reaction. As shown in Fig. 1, the conversion was 48.62 and 100% with 5 and 15 mg enzyme, respectively. However, amounts of PPL greater than 15 mg, did not increase the conversion to

Scheme 2 Proposed mechanism of enzymatic Friedländer condensation



product. Consequently, we selected 15 mg PPL as the optimum amount for this reaction.

We further examined the influence of reaction temperature. We carried out experiments under 25, 30, and 40°°C. Conversion was complete after 30 h at 25 °C and 20 h at 30 °C. At 40 °C, by-products were obtained. Comparing these results, we selected 30 °C as the best temperature in shorter time.

To enlarge the range of substrates, some ketones were used. The results were summarized in Table 3. Few reports of cyclopentanone derivatives [13, 24–27] have been reported. Thus we tried some cyclopentanone substrates. Cyclopentanone and cyclohexane-1,3-dione rapidly and efficiently gave quinoline products with yields above 90%.

We propose a mechanism for this process as shown in Scheme 2. The enzyme promotes formation of an enolate intermediate which then undergoes Aldol condensation reaction with 2-amino-3,5-dibromo-benzaldehyde. Subsequent intramolecular cyclization is followed by enzyme assisted dehydration producing the quinoline products. This mechanism predicts that hindered cyclopentanones would be slow to react, which was found (Table 3).

4 Conclusion

In conclusion, we have developed an efficient enzymatic method of synthesizing quinoline derivatives with good-to-excellent yields under mild conditions. It provides a new and powerful tool for preparing a wider range of quinoline derivatives.

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