



One-pot construction of spirooxindole backbone via biocatalytic domino reaction



Yi-Ru Liang, Yu-Jing Hu, Xue-Han Zhou, Qi Wu*, Xian-Fu Lin*

Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China

ARTICLE INFO

Article history:

Received 29 May 2017

Accepted 12 June 2017

Available online 13 June 2017

Keywords:

Spirooxindole

Enzyme

One-pot

Fluorescent properties

ABSTRACT

A simple and environmentally friendly method to synthesize spiropyrazolo[3,4-*b*]pyridines derivatives starting from isatin, cyclic-1,3-diketone and 3-methyl-5-aminopyrazole was developed. With the optimized conditions for enzymes, solvents, enzyme loading and reaction time in hand, 9 compounds were obtained in acceptable yields. Moreover, the investigation in fluorescent properties of these products showed their potential application in the field of new fluorescent material.

© 2017 Elsevier Ltd. All rights reserved.

Introduction

Spirooxindole derivatives are widely found in natural products, such as progesterone receptor modulators,¹ antimicrobial,^{2–4} anti-malarial^{5,6} and so on. Attracted by the specific structure and biological activities of spirooxindole derivatives, much attention has been paid by chemists in this field. In recent years, some spirooxindole scaffolds were constructed via organometallic and organocatalytic methods. For example, spirooxindoles containing [5.5]-fused heterocycle were obtained by Jia and co-workers through a three-component bicyclization reaction of isocyanide, substituted allenolate and isatin.⁷ Praveen has reported microwave assisted synthesis of spirooxindoles via tandem double condensation between isatins and 4-hydroxycoumarin in the presence of gold catalysis in 2016.³ Tiwari and co-workers developed an efficient synthetic method for the synthesis of new 2,3-dihydrooxazole-spirooxindoles hybrids, which showed good antibacterial activity and antifungal activity as antimicrobial agents.⁴ What is more, Tin powder-promoted one-pot synthesis of 3-spirooxindole derivatives or 3,3'-disubstituted 2-oxindoles was reported by Hu in the presence of a catalytic amount of Bronsted or Lewis acids.⁸ However, catalysts used in these methods always involve environmental problems, high cost or complicated process. Therefore, it is desirable to seek environmentally friendly and economical catalysts in this field.

Enzymatic catalysis, featured as great environmental acceptability, mild reaction conditions and high efficiency, is an attractive alternative to conventional chemical catalysis during the past

decades.^{9–13} Recently, enzymatic promiscuity (one enzyme with new catalytic characters) makes it possible to perform multicomponent reactions (MCRs) by one enzyme. Up to now, a series of elegant works of enzymatic promiscuity have been discovered, such as aldol reactions,^{14–16} Michael addition reactions,^{17,18} Henry reactions,¹⁹ Mannich reactions^{20,21} and various one-pot domino reactions.^{22–25}

Spirocyclic skeletons catalyzed by various enzymes have been reported in recent years. For example, Lipase from *porcine pancreas* (PPL) could catalyze one-pot multiple reaction to synthesize spirooxindole derivatives through the Knoevenagel condensation, Michael addition and cyclization in ethanol with the presence of water.²⁶ In 2015, α -Amylase from *hog pancreas* was discovered the same catalytic activities as PPL for this reaction and the same kind of spirooxindole pyrans were obtained.²⁷ Furthermore, Pepsin from *porcine gastric mucosa* was used as a tool in the domino Knoevenagel/Michael/Michael reaction for the synthesis of spirooxindole derivatives in methanol.²⁸ Aminoacylase displayed catalytic promiscuity in both [5+1] double Michael additions and domino Knoevenagel condensation-Michael addition-intramolecular cyclization to obtain spiro[5.5]undecane derivatives and new spirooxindole derivatives, correspondingly.^{29,30} Besides, lipase could also initiate multicomponent reaction for the one-pot synthesis of spirooxazino derivatives starting from aldehydes, activated olefins, cyclohexanone and acetamide.^{31,32} However, in order to increase the diversity of spirooxindoles, the further developments of enzymatic methods are still highly desirable.

Herein, we report a one-pot papain-catalyzed reaction to synthesize a series of spiropyrazolo[3,4-*b*]pyridines starting from isatin, cyclic-1,3-diketones and 3-methyl-5-aminopyrazoles for the

* Corresponding authors.

E-mail addresses: wuqi1000@163.com (Q. Wu), llc123@zju.edu.cn (X.-F. Lin).

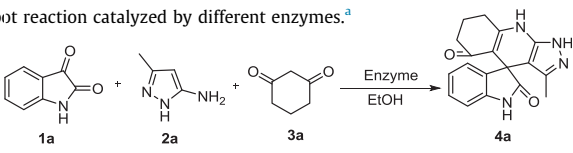
first time. It is particularly exciting to obtain most of products with strong fluorescence emission ability, providing great potential application in the field of fluorescent material.

Results and discussion

As part of our program to develop a new enzymatic and environmentally friendly method for spiro-heterocyclic compounds, isatin (**1a**), 3-methyl-5-amino-1H-pyrazol (**2a**) and 1,3-cyclohexanedione (**3a**) were chosen as model substrates to form **4a**. In order to find the suitable enzyme for the model reaction, various hydrolytic enzymes were investigated in our initial research (Table 1).

The results showed that only 11% yield of product was obtained if the reaction was carried out in the absence of catalysts (Table 1, entry 1). In contrast, the product (**4a**) was obtained in 48% yield after 48 h in EtOH when papain was added as catalyst (Table 1, entry 4). Meanwhile, some other enzymes displayed less activity

Table 1
One-pot reaction catalyzed by different enzymes.^a



Entry	Catalyst	Yield ^b (%)
1	Blank	11
2	AA	25
3	DA	24
4	Papain	48
5	PPL	22
6	CALB	36
7	MJL	37
8	Denatured papain ^c	14

^a Experimental conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), Enzyme (50 mg), EtOH (2 ml), 50 °C, 48 h.

^b All yields were determined by HPLC using Agilent 1100 series with chiralpak AD-H (250 × 4.6 mm) (*n*-hexane: Isopropyl alcohol = 65:35) and a UV detector (210 nm).

^c Denatured papain, incubated with urea at 100 °C for 24 h.

Table 2
Screen of reaction conditions for one-pot reaction.^a

Entry	Solvent	Amount/mg	Time/h	Temperature/°C	Yield ^b (%)
1	DMSO	50	48	50	Trace
2	DMF	50	48	50	Trace
3	THF	50	48	50	34
4	CH ₃ CN	50	48	50	Trace
5	Toluene	50	48	50	Trace
6	MTBE	50	48	50	Trace
7	Dioxane	50	48	50	Trace
8	MeOH	50	48	50	50
9	EtOH	50	48	50	48
10	H ₂ O	50	48	50	25
11	EG	50	48	50	19
12	EtOH	20	48	50	23
13	EtOH	80	48	50	56
14	EtOH	100	48	50	54
15	EtOH	120	48	50	57
16	EtOH	80	12	50	14
17	EtOH	80	24	50	39
18	EtOH	80	72	50	63
19	EtOH	80	96	50	61
20	EtOH	80	72	20	14
21	EtOH	80	72	30	29
22	EtOH	80	72	37	52

^a Experimental conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), papain in organic solvent (2 ml).

^b All yields were determined by HPLC using Agilent 1100 series with chiralpak AD-H (250 × 4.6 mm) (*n*-hexane: Isopropyl alcohol = 65:35) and a UV detector (210 nm).

for this reaction. For example, DA, AA and PPL exhibited low activity in yields of 24%, 25% and 22%, respectively (Table 1, entries 2, 3 and 5). However, CAL-B and MJL showed higher catalytic activity (Table 1, entries 6 and 7) compared with DA, AA and PPL. Next, urea-pretreated papain was tested to confirm the role of enzyme in overall reaction system. As a denaturation agent for enzymes, urea was employed to pretreat the papain. When the urea-pretreated papain was used in the model reaction, the desired product was obtained in a yield of 14%, which indicated that the specific three-dimensional structure of papain was crucial for its catalytic activity (Table 1, entries 8). The above investigations suggested that papain was the most suitable enzyme for this reaction.

The reaction conditions, such as reaction medium, the amount of enzyme, reaction time and reaction temperature, were screened based on the model reaction to see whether it is possible to improve the papain-catalyzed multi-component reaction (Table 2). First of all, different solvents were tested to obtain the optimum medium for this reaction. As a result, the highest yield of 50% was obtained in methanol and a similar yield of 48% was achieved in ethanol (Table 2, entries 8 and 9). However, some polar solvents, such as THF, water and ethylene glycol (EG) led to lower yields (Table 2, entries 3, 10 and 11). To our surprise, no product was obtained in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) (Table 2, entries 1 and 2). Furthermore, trace of the desired compound was achieved in acetonitrile, toluene, methyl tertiary butyl ether (MTBE) and dioxane, which could be attributed to the poor solubility of substrates in these solvents (Table 2, entries 4–7). In view of environment protection, ethanol was finally chosen as the most suitable medium for this enzymatic reaction.

Then the amount of papain was taken into account. It can be observed that the yield increased from 23% to 56%, along with the amount of papain increasing from 20 mg to 80 mg, (Table 2, entries 9, 12 and 13). Nevertheless, higher enzyme loading resulted in little increase of the product yield (Table 2, entries 14 and 15). Therefore, 80 mg papain was enough to catalyze the reaction of isatin, 3-methyl-5-amino-1H-pyrazol and cyclic-1,3-diketone. What is more, after the investigation of reaction time, 72 h was chosen as the optimal reaction time because the reaction has already reached equilibrium during this time (Table 2, entries 16–19). The results of temperature screening showed that the

Download English Version:

<https://daneshyari.com/en/article/5259134>

Download Persian Version:

<https://daneshyari.com/article/5259134>

[Daneshyari.com](https://daneshyari.com)