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Lipase-initiated one-pot synthesis of spirooxazino derivatives: redesign of multicomponent reactions to expand substrates scope and application potential

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ABSTRACT

Enzymatic multicomponent reactions (MCR) are very powerful for complex organic synthesis with environmentally friendly, highly efficient and selective characters, while sometimes having some unavoidable shortages such as narrow substrate scope and so on. Herein, this work demonstrated how to redesign one previously reported lipase-catalyzed MCR to achieve more broad substrates and more efficient synthesis. Twelve new spirooxazino derivatives with different substitutions were obtained in moderate to good yield, while all of them could not be synthesized using the previous route. Reaction conditions such as enzymes, enzyme concentration, amides and ratio of substrates were screened. Furthermore, particularly interesting is that chiral spirooxazino could also be obtained through a further developed two-enzymatic MCR process in one pot. As a domino process simultaneously constructing six new C-C/N bonds and two rings in only one step, the work will remarkably expand the application scope of enzymatic MCR for simple and green synthesis of complex compounds.

1. Introduction

Hydrolases are known to be highly selective for the hydrolysis or transesterification of esters and amides, and recent progress in catalytic promiscuity of hydrolases has further expanded their application scope in organic synthesis.[1] This promiscuous property of enzymes endows one enzyme with catalytic multi-functions, allowing multi-step reactions catalyzed by one enzyme under multicomponent reactions (MCR) manner.[2] For example, the work by Yu et al. demonstrated a lipase-catalyzed three-component Mannich reaction under aqueous conditions.[2a] Our group developed a direct method to construct 3,4-dihydropyridin-2-ones through enzymatic condensation of aldehyde with cyanoacetamide and 1,3-dicarbonyl compounds in one-pot.[2d] In comparison with stepwise process, MCR are more powerful approaches for the preparation of structurally complex compounds, like spiro motifs.

However, sometimes enzymatic MCR are not fully satisfactory, in some respects, such as narrow substrate scope and low reaction efficiency due to the reaction complexity and the specific structure of enzymes. Researchers often ignored less active substrates, rather than studying the internal reason and redesigning the MCR. Actually, one MCR process usually has different reaction pathways or routes, rational redesign or recombination of one MCR usually can bring some advantages to overcome those obstacles. There are some successful examples reported in chemical MCR, while to the best of our knowledge, similar reports in enzymatic MCR are few. For examples, standard Ugi reaction employs four components, an acid, an amine, an aldehyde or ketone, and an isocyanide.[3] Fülöp[4] et al. reported a Ugi three-component reaction starting from alicyclic β-amino acids, for the synthesis of alicyclic β-lactams, which greatly expanded the substrate scope of Ugi reaction.

Spirocycles are very important structural units widely found in natural products, synthesized pharmacological agents, agricultural products, and also some new ligands or catalysts such as spirobisoxazolines, SPINOL (1,1′-spirobiindane-7,7′-diol), SPINOL-derived phosphoric acids.[5] Moreover, the unique structural feature of spirocyclic compounds endows them with special fluorescent or photochromic properties, and thus important applications in the fields of fluorescent chemosensors,[6a] information memory and storage,[6b] artificial intelligent materials.[6c] For example, spirooxazines are the most popular class of photochromic materials because of their good performances in terms of stability and response speed.[7] However, the synthesis difficulty of complicated spirocompounds usually limits their wide application in academic and industrial fields. For this reason, the development of highly efficient synthesis methodology for complicated spirocompounds, is still an enormous challenge for chemists.

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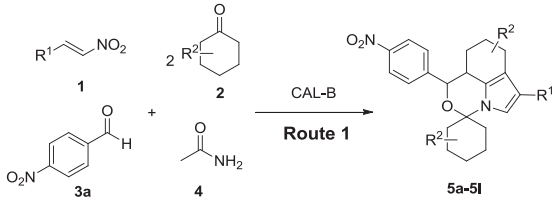
We are continuously devoting to the study of enzymatic MCR for the synthesis of complicated compounds. Recently, our group reported a novel CALB-initiated MCR for the synthesis of spirooxazino derivatives, while the substrate scope was quite narrow.[8] Herein, basing on the comparative study of several synthetic routes accessing to spirooxazino derivatives, we developed a more efficient synthesis methodology for the complicated spirooxazinos derivatives than before. Twelve new spirooxazino derivatives with different substitutions were obtained in moderate to good yield, while all of them could not be synthesized using the previous route. Particularly interesting is that chiral spirooxazino could be obtained through a two-enzymatic process in one pot.

2. Results and discussion

In our previous work, the spirocompounds were formed efficiently only for 4-nitrobenzaldehyde (**3a**) (Table 1).[8] When other aldehydes (**3b**–**f**) were used, although corresponding products could be detected, reaction yields were very low (Table 2). We found this failure was probably caused by the fact that those substituted aldehydes, as well as aliphatic aldehydes, almost could not react with cyclohexanone to form the corresponding aldol intermediate under the catalysis of *Candida antarctica* lipase B (CALB). After we were aware of this point, we designed another lipase-mediated MCR route (Route 2) for the synthesis of spirocompounds. A chemically prepared aldol intermediate was used as one starting molecule instead of aldehydes and cyclohexanones, and remarkable improvements of substrate scope and reaction efficiency were observed (Scheme 1).

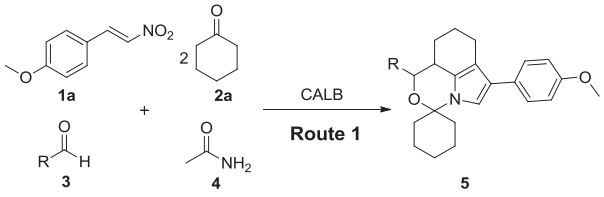
Table 1
Spirooxazinos compounds successfully obtained via Route 1 MCR[8]



Entry	R^1	R^2	Product	Yield (%)[a]
1	4-CH_3O-C_6H_4 (**1a**)	H (**2a**)	**5a**	72
2	4-HO-C_6H_4 (**1b**)	H (**2a**)	**5b**	84
3	3-HO-C_6H_4 (**1c**)	H (**2a**)	**5c**	85
4	C_6H_5 (**1d**)	H (**2a**)	**5d**	30
5	4-CH_3-C_6H_4 (**1e**)	H (**2a**)	**5e**	34
6	4-*i*Pr-C_6H_4 (**1f**)	H (**2a**)	**5f**	21
7	4-N$(CH_3)_2$-C_6H_4 (**1g**)	H (**2a**)	**5g**	41
8	4-F-C_6H_4 (**1h**)	H (**2a**)	**5h**	47
9	C_6H_5 (**1d**)	*p*-CH_3 (**2b**)	**5i**	25
10	4-F-C_6H_4 (**1h**)	*p*-CH_3 (**2b**)	**5j**	25
11	4-HO-C_6H_4 (**1b**)	*p*-CH_3 (**2b**)	**5k**	38
12	4-CH_3O-C_6H_4 (**1a**)	*p*-CH_3 (**2b**)	**5l**	36

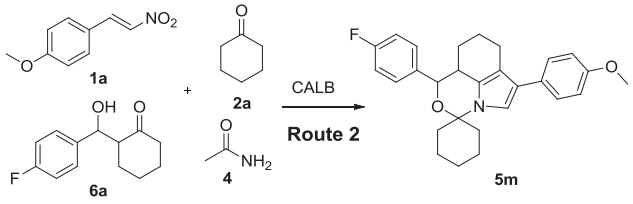
[a] Data from the previous work.[8]

Table 2
The influence of structure of aldehydes on Route 1 MCR[a]



Entry	R	Product	Yield (%)[b]
1	*p*-FC_6H_4 (**3b**)	**5m**	7
2	*p*-ClC_6H_4 (**3c**)	**5n**	<5
3	*p*-$CF_3C_6H_4$ (**3d**)	**5o**	<5
4	*p*-$CH_3OC_6H_4$ (**3e**)	**5p**	<5
5	C_6H_5 (**3f**)	**5q**	<5

[a] Experimental conditions: 0.25 mmol aldehyde, 1.5 mmol 4-methoxy-β-nitrostyrene, 1 mL cyclohexanone, 1.25 mmol acetamide, 70 mg CALB, 50 °C, 6 days.
[b] Yields were determined by HPLC.



Scheme 1. Route 2: CALB-catalyzed MCR starting from chemo-aldol intermediate (model reaction of this work).

We investigated the Route 2 for the synthesis of spirooxazino derivatives using the model reaction of 4-methoxy-β-nitrostyrene (**1a**), cyclohexanone (**2a**), aldol intermediate from 4-fluorobenzaldehyde (**6a**), and acetamide (**4**) (Scheme 1). After screening a lot of enzymes (Table S1, see Supplementary data), we found that only CALB catalyzed this reaction for the formation of spirocompound **5m**. Control reactions did not happen under the catalysis of BSA (Bull Serum Albumin) or denatured CAL-B (Table S1, entries 3 and 4), ruling out the possibility that amino acids on the surface of CAL-B or other impurities could promote the MCR. On the other hand, these results also validated that the specific active site of CAL-B was essential in the MCR. Then the reaction conditions such as enzyme concentration, structure of amide, amount of acetamide, molar ratio of substrates and reaction time were examined further. Among the tested structurally different amides, acetamide and formamide showed the best results for this transformation, while three other amides including propanamide, benzamide and thioacetamide displayed almost no effects (Table 3). From the influence of enzyme concentration on the reaction, it was found that the use of CAL-B concentration of 60 mg/ml was enough to obtain the best yield for the tested reaction (Fig. 1). It is also noteworthy that the amount of acetamide and the molar ratio of substrates have important influence on the output of the multi-component reaction (Figs. 2 and 3). The optimal dosage of acetamide (**4**) and 4-methoxy-β-nitrostyrene (**1a**) were 0.75 M and 1.25 M, respectively, in the tested model reaction containing 0.25 M aldol intermediate and 1 mL cyclohexanone. Moreover, the optimization of reaction time showed that 96 h was enough for this domino reaction (Fig. S1, see Supplementary data). Finally, under the optimized conditions, spirocompound **5m** were obtained in the highest 67% yield (Entry 1, Table 4), showing a sharp contrast with only 7% yield in Route 1 (Entry 1, Table 2).

Table 3
Amide screening for CALB-catalyzed Route 2 MCR[a]

Entry	Amide	Yield (%)
1	Formamide	27
2	Acetamide	32
3	Propanamide	6
4	Benzamide	9
5	Thioacetamide	0

[a] Experimental conditions: 0.25 M 2-((4-fluorophenyl)-(hydroxy)methyl)cyclohexanone, 0.5 M 4-methoxy-β-nitrostyrene, 1 mL cyclohexanone, 1 M amide, 60 mg CALB, 50 °C, 3 days. All yields were detected by HPLC.

Then, a series of spiro-products with different substitutions at R^1, R^2, R^3 and R^4 (Table 4) were successfully obtained in moderate to good yields under the above optimized conditions. It was noteworthy that most of the products with various substitutions at R^3 such as F, CF_3, Cl, CH_3O, H, in Table 4, could not be prepared using