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Promiscuous enzyme-catalyzed regioselective Michael addition of purine derivatives to α,β-unsaturated carbonyl compounds in organic solvent

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ABSTRACT

Regioselective Michael addition of purine derivatives to α,β-unsaturated carbonyl compounds could be catalyzed by D-aminoacylase amano (DA) in DMSO. The influence of reaction conditions on the Michael addition, including solvent, temperature, and enzyme concentration was systematically investigated. Then we extended this methodology to six structurally diverse purine derivatives and a variety of α,β-unsaturated carbonyl compounds. 21 Michael adducts were selectively synthesized in moderate to high yields. It is the first report on enzyme-catalyzed Michael addition for the preparation of purine derivatives.

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1. Introduction

Synthesis of nucleoside derivatives has gained more attention in the past decades because of their antiviral and antitumor ability.[1] However, rare study has been focused on purine derivatives due to their low reactivity and low solubility. Moreover, regioselective reaction is difficult to undergo when purine derivatives are used as the substrates since the alkylation of 2-aminopurines usually gives rise to mixtures of N-9 and N-7 materials.[2] Hence, control of the regioselectivity is crucial during the synthetic procedure. Geen[3] reported Michael addition with 2-aminopurines catalyzed by potassium carbonate in *N*,*N*-dimethylformamide at room temperature, by extending the reaction time and increasing the quantity of Michael acceptors to obtain the exclusive N-9 alkylated products. In another way, Stephane Guillarme[4] adopted protected or deaza natural bases as the Michael donor for the synthesis of several acyclic nucleosides. Recently, Microwave irradiation technique was introduced to the Michael addition of purine derivatives, exclusive N-9 alkylated products could be obtained in a short time.[5] However, these methods always need special equipment or unrecycling catalysts. Recently, the emphasis of science and technology has diverted into environmentally friendly and sustainable resources and processes. Therefore, direct utilization of natural materials for catalytic application is a very charming strategy.

Enzymes are efficient catalysts in organic and bioorganic synthesis. Besides the natural catalytic ability to catalyze a primary reaction, many enzymes can also catalyze secondary reaction at an active site, which is termed 'catalytic promiscuity'.[6] For example, lipase can catalyze the formation of C–C,[7a] C–N,[7b] C–O,[7c] and C–S[7d] through Michael addition, arylmalonate decarboxylase can catalyze aldol additions,[7e] racemase can catalyze PLP-dependent aldol additions.[7f] Recently, enzyme promiscuity was also discovered at alternate-site besides the known natural catalytically active site.[8]

In our former works, we have demonstrated the promiscuous enzyme-catalyzed Michael addition of imidazole and pyrimidine.[9a–e] Taking the low reactivity of purine derivatives and their antiviral and antitumor ability, and the highly regioselectivity of enzyme as catalyst into account, it is very interesting and meaningful for us to exploit the catalytic capability of enzyme on the synthesis of purine derivatives .In this paper, we reported the enzyme-catalyzed Michael addition of purine derivatives (Fig. 1) to α,β-unsaturated carbonyl compound catalyzed by D-aminoacylase. Then the reaction was optimized by investigating the influence of reaction conditions on the Michael addition, including solvent, temperature, and enzyme concentration. This methodology was extended to a variety of structurally diverse purine derivatives and α,β-unsaturated carbonyl compound. 21 products were obtained in moderate to high yield under the catalysis of D-aminoacylase in DMSO at 50 °C successfully.

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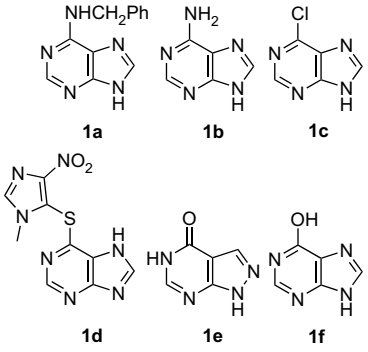


Figure 1. The structure of purine derivatives.

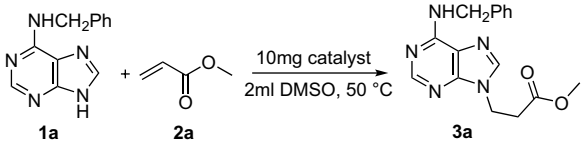
2. Results and discussion

In order to demonstrate the specific catalytic effect of catalysts, we performed some control experiments. The reaction of 6-benzylaminopurine **1a** with methyl acrylate **2a** in the absence of enzyme led to low yield adduct (8%) in 72 h. In contrast, the reaction in the presence of DA and AA is up to 50.7-fold and 28-fold faster (entries 2 and 6, Table 1). Besides, the initial reaction rate is practically proportional to the enzyme amount, also suggesting the catalytic effect of the enzyme (entries 2 and 3, Table 1). When the reactants were incubated with denatured D-aminoacylase (pre-treated with urea at 100 °C for 24 h) the rate is practically equal to the bovine serum albumin (BSA), ruling out the possibility that the polymeric support or the similar amino acid distribution on the protein surface has promoted the process. All these results suggest that the specific active sites and the tertiary structure of D-aminoacylase are responsible for the Michael addition reaction. Three widely used hydrolases, Candida antarctica lipase B (CAL-B), Lipase from *porcine pancreas* (PPL), and alkaline protease from Bacillus subtilis (PA), can only accelerate the reaction by 2.1, 7.3, and 10.7-fold, respectively. Among all the selected catalysts, D-aminoacylase (DA) was the best catalyst for this Michael addition. Thus, DA was selected for the further study.

Then the reaction conditions were optimized by using the Michael addition of 6-benzylaminopurine **1a** to methyl acrylate **2**a as model reaction. As indicated in Table 2, the enzyme-catalyzed Michael addition reaction could only be performed in some polar solvents such as DMSO and DMF (entries 1 and 2, Table 2). In other solvents including dioxane, pyridine, chloroform, and cyclohexane, only trace product was detected, which may be ascribed to the low solubility of 6-benzylaminopurine in those solvents (entries 3–6, Table 2). Then the influence of enzyme concentration on the reaction was examined. As shown in Table 2, when the enzyme concentration increased from 5 mg/ml to 20 mg/ml (entries 1 and 7–9, Table 2), the yield decreased lightly. The optimal enzyme concentration was 5 mg/ml. Next, the influence of reaction temperature on the enzymatic Michael addition reaction was also considered. It was found that the yield decreased with the decrease of temperature (entries 1, 10, and 11, Table 2). The yield was only 8% at 25 °C. The highest yield was obtained at 50 °C. All these studies promoted us to use DMSO as the solvent in the presence of 5 mg/ml enzyme concentration at 50 °C to probe the generality of the conjugated addition processes.

Having the optimal conditions in hand, we applied this method to other Michael acceptors and the results were shown in Table 3. Examination of the results of the different acrylate reveals that the chain length of the ester plays a minimal role in governing the reactivity of the conjugate addition. As the carbon chain of alcohol moiety increased, slight decrease in yield was observed (entries 1–3, Table 3). The reactions of 6-benzylaminopurine (**1a**) with methyl vinyl ketone or acrylonitrile could also provide good yields (entries 4 and 5, Table 3). Compared with acrylate and acrylonitrile, methyl vinyl ketone presented the highest activity. Then a series of sterically hindered Michael acceptors with either α-methyl or β-methyl group were studied under the same conditions (entries

Table 1
Initial rates (V_o) of the Michael addition of 6-benzylaminopurine **1a** to methyl acrylate **2a** in the presence of different catalysts



Entry	Catalyst	Amount (mg)	Yield[a] (%)	V_0 (mM h^{-1})	V_r[b]
1	—	—	8	0.15	1.0
2	D-Aminoacylase	10	92	7.6	50.7
3	D-Aminoacylase	5	88	3.9	26.0
4	DA denatured[c]	10	10	0.22	1.5
5	BSA	10	11	0.25	1.7
6	Acylase 'amano'	10	81	4.2	28.0
7	CAL-B	10	15	0.31	2.1
8	PPL	10	37	1.1	7.3
9	PA	10	58	1.6	10.7

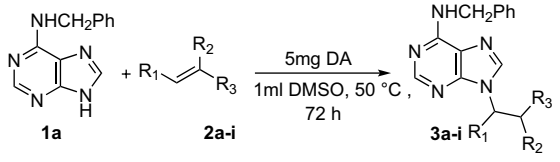
[a] Experimental conditions: 0.2 M 6-benzylaminopurine, 0.4 M methyl acrylate, 10 mg enzyme, 2 ml DMSO, 50 °C, 72 h. All yields were detected by HPLC.
[b] Relative initial rate to the reaction in absence of enzyme.
[c] Enzyme predenatured with urea at 100 °C for 24 h.

Table 2
Screen of reaction conditions of DA-catalyzed Michael addition of 6-benzylaminopurine **1a** to methyl acrylate **2a**[a]

Entry	Amount of catalyst (mg)	Solvent	Temperature (°C)	Yield[b] (%)
1	5	DMSO	50	48
2	5	DMF	50	14
3	5	Dioxane	50	<1
4	5	Pyridine	50	4
5	5	Chloroform	50	<1
6	5	Cyclohexane	50	<1
7	10	DMSO	50	44
8	15	DMSO	50	44
9	20	DMSO	50	42
10	5	DMSO	40	23
11	5	DMSO	25	8

[a] Experimental conditions: 0.5 M 6-benzylaminopurine, 2.5 M methyl acrylate, 5 mg enzyme, 1 ml solvent, 50 °C, 24 h.
[b] All yields were detected by HPLC.

Table 3
Michael addition of 6-benzylaminopurine to various Michael acceptors



Entry	Time (h)	R_1	R_2	R_3	Yield[a] (%)
1	72	H	H	$COOCH_3$	(**3a**) 92
2	72	H	H	$COOCH_2CH_3$	(**3b**) 81
3	72	H	H	$COO(CH_2)_3CH_3$	(**3c**) 78
4	48	H	H	$COCH_3$	(**3d**) 90
5	72	H	H	CN	(**3e**) 84
6	72	H	CH_3	$COOCH_3$	(**3f**) 42
7	72	CH_3	H	$COOCH_3$	(**3g**) 39
8	48	CH_3	H	$COOCH{=}CH_2$	(**3h**) 67
9	48	H	CH_3	$COOCH{=}CH_2$	(**3i**) 62

[a] All yields were detected by HPLC.

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