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Michael Addition of 2, 4 Thiazolindione on Chalcone Mediated by Lipase in Nonaqueous Solvent

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ABSTRACT

Biocatalysts are highly enantioselctive catalysts that enforce reactive conformations of nature substrate. We report here a novel type of Michael additions on chalcone catalysed by lipase in nonaqueos solvent in efficient conditions. We first time report 2, 4 thiazolindione as Michael donor for Michael additions on chalcone, isolated product with excellent yield.

Keywords : Chalcone, Thiazolindione, Michael Addition, Organic Solvent

I. INTRODUCTION

Biocatalysis is an efficient and green tool for modern organic synthesis due to its high selectivity and mild condition, biocatalytic promiscuity provide new tool for organic synthesis and expand largely application of lipase.[1-6]

Among the catalytically promiscuous lipase, one of the mostly used as hydrolase, because of its good stability and high catalytic activity. Lipase are usually catalyses hydrolysis of ester bond in triglyceride, some lipase-catalysed unconventional reactions such as aldol,[7] nitroaldol,[8] mannish condensation,[9] michael reaction,[10] markovnikov additions[11] and acylation's, [12] have been reported in past decade.

Lipase enzyme used in aqueous medium is not useful for most of the organic reactions because substrates are not soluble in aqueous medium therefore the use of lipase enzyme in organic solvent is gaining much importance. The advantages of lipase enzyme in organic solvent such as (1) most of organic compound are soluble in organic solvent (2) product recover easier than aqoueos media (3) insolubility of bicatalyst in organic solvent which permit their easy recovery and reuse. [13-14.]

Michael addition on chalcone with different nucleophile is important C-C bond forming reaction in organic chemistry. The conjugate addition of carbanion nucleophile to unsaturated carbonyl compound represents one of the best established construction strategies for this purpose. Thus development of asymmetric catalytic version of this type of transformations has been developing intensive over past several years.[15-19.]

Here employed first time thiazolindione as nucleophile, in thiazolindione methylene hydrogen atom are highly acidic due to presence of two carbonyl. Our important of thiazolindione and chalcone, we develop efficient michael addition involved thiazolindione is still highly desirable.

Generally, michael addition are conducted in a suitable solvent in presence of strong base at room temperatures or at elevated temperatures, due to presence of strong base , side reaction such as multiple condensation, polymerisation, rearrangements.[20-23.] This type of drawback can overcome by biocatalyst, therefore selected biocatalytic protocol for michael addition.

Chalcone and their derivatives demonstrate wide range of biological activities such as anti-diabetic, anti-neoplastic, anti-hypertensive, anti-retroviral, anti-inflammatory, anti-parasital, anti-histaminic, anti-malarial, anti-oxidant, anti-fungal, anti-obesity, anti-platelet, anti-tubercular, immunosuppressant, anti-arrhythmic, hypnotic, anti-gout, anxiolytic, anti-spasmodic, anti-nociceptive, hypolipidemic, anti-filarial, anti-angiogenic, anti-protozoal, anti-bacterial, anti-steroidal.[24-27]

The thiazolidinedione also known as glitazones are a class of medications used in the treatment of diabetics. Then addition of two moieties like chalcone and thiazolindione to give resulting product shows highly biological activity. [28-30]

Catalytic power of lipase and uses of resulting product, Therefore we report develop green develop, Michael addition on chalcone with thiazolindione in acetonitrile solvent under mild condition. Resulting product is novel because, resulting product are not previously reported with any catalyst.

II. RESULTS AND DISCUSSION

Herein, first time we report a michael addition on chalcone with 2, 4 thiazolindione under mild condition catalysed Candida antatica lipase-B as biocatalyst.

In order get best experimental condition, we have considered the reaction of chalcone (1a) and 2, 4 thiazolindione (2) in presence of lipase (CAL-B)) as model reaction. **(Scheme-1)**

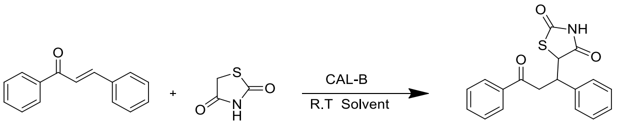
In order to best experimental result, lipase used in different organic solvent which included ethanol (C_2H_5OH), methanol (CH_3OH), acetonitrile (ACN), dimethyl sulphoxide (DMSO), dimethylformamide (DMF), and dichloromethane (DCM). Reaction proceeds in all organic solvent (**Table-1 entry 1-6)**. We analysed the all solvent, acetonitrile is best solvent for this reaction because of reaction required less time and high yield of product (**Table-1 entry 3)** compare to other solvent. Then acetonitrile was selected for model reaction.

Model reaction was proceeding without catalyst in acetonitrile solvent but no conversion even after 32 hrs. Model reaction in presence of different lipase & their amount analysed the reaction. First taken porcine pancreases lipase (50 mg) and (100 mg) reaction was successfully formation of product in 32 hrs. (**Table-2, entry-1-2**), then lipase from CAL-B (50 mg) and (100mg) reaction was successfully formation of product in 30 hrs.(**Table-2,entry 3-4**) finally lipase from Candida rugosa (50 mg) and (100 mg) reaction continue stirring with 32 hrs but no conversion of product. After analysed better result in lipase from CAL-B in 100mg. Finally model reaction was selected with lipase from CAL-B (100 mg) and acetonitrile solvent.

To generalise of chalcone, variety of chalcones react with thiazolindione by using lipase (CAL-B) in acetonitrile (**Table-2 entry 1-12**). we are prepared chalcone by using acetophenone and benzaldehyde in presence of sodium hydroxide in mixture of ethanol and water solvent. Thiazolindione are also prepared by reporting literature using Chloroacetic acid and thiourea in water.

Variety of chalcone containing electron donating and electron withdrawing group attaches to either acetophenone ring or benzaldehyde ring were successfully employed to prepared corresponding product. We conclude that Chloro substitution chalcone to give higher yield or better result. Firstly simple acetophenone containing ring and chloro, nitro substitution on benzaldehyde ring containing chalcone give desire product (**Table 2, entry 1-4**), then 2-hydroxy substituted acetophenone with chloro,nitro,metoxy,furyl substituted benzaldehyde containing chalcone give desire product (**Table 2, entry 5-8),** then 4-hydroxy substituted acetophenone ring with methoxy substituted ring benzaldehyde containing chalcone to give desire product (**Table 2, entry 9-10**), finally 3,4 Methoxy acetophenone containing ring with Chloro substituted benzaldehyde ring containing chalcone give desire product(**Table 2,entry 11-12)**

Lipase is an enzyme, Enzyme contains acidic, basic and neutral amino acid. Michael addition reaction required base but here histidine as base is because of imidazole is basic unit present. Thus histidine accepts highly acidic hydrogen of nitrogen of thiazolindione and formation of nitrine and this nitrine ions attached to β carbon of α,β unsaturated carbonyl compound, thus formation of C-N bond and enolate ions, Finally enolate ion converted into keto form to give product.



1a 2 3a

Scheme-1

Table-1 Effect of solvent on Michael addition on chalcone with thiazolindione catalysed by Lipase (CAL-B)

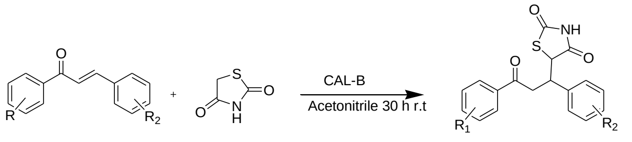
Entry	Solvent	Time(hrs)	Yield[b] (%)
1	C_2H_5OH	32	N.R[c]
2	CH_3OH	32	N.R[c]
3	DMSO	32	63
4	ACN	32	90
5	DCM	32	77
6	DMF	32	60

[a]Reaction condition-Chalcone (5mmol), thiazolindione (5mmol), Lipase CAL-B (100 mg) and 20 ml solvent at room temp. [b]Isolated yield. [c]No reaction

Table-2 Effect of catalyst & amount on Michael addition on chalcone with thiazolindione in acetonitrile solvent.

S. N	Lipase	Amount(mg)	Time(hrs)	Yield[b] (%)
1	PPL	50	32	45
2	PPL	100	32	55
3	CAL-B	50	32	54
4	CAL-B	100	32	90
5	C. rugosa	50	32	N.R[c]
6	C. rugosa	100	32	N.R[c]

[a]Reaction condition [chalcone(5mmol), thiazolindione(5 mmol), Acetonitrile(20 ml) and catalyst at room temp. [b]Isolated yield. [c]No reaction



1(a-l) 2 3(a-l)

Scheme-2

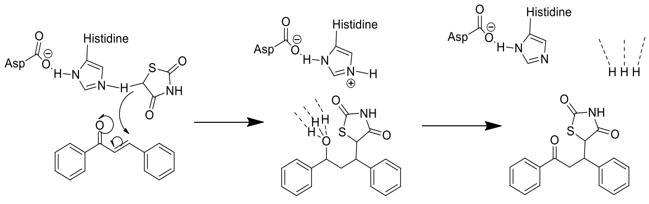


Fig 1; Plausible mechanism of michael addition reaction

Table-3 Lipase catalysed Michael addition on chalcone derivatives with thiazolindione in organic solvent.[a]

Entry	R1	R2	Product[c]	Yield[b]
1	H	H	3a	90
2	H	4-Cl	3b	85
3	H	3-NO$_2$	3c	82
4	H	2-Cl	3d	80
5	2-OH	3-NO$_2$	3e	85
6	2-OH	2-Cl	3f	82
7	2-OH	4-OCH$_3$	3g	88
8	2-OH	4-Cl	3h	78
9	4-OH	H	3i	82
10	4-OH	4-Cl	3j	82
11	3,4-OCH$_3$	H	3k	76
12	3,4-OCH$_3$	4-Cl	3l	78

[a]Reaction condition-chalcone (5 mmol), thiazolindione (5 mmol), lipase CAL-B (100 mg) and acetonitrile(20ml) at room temperature stirring for 32 hrs. [b] Isolated yield [c] Product characterised by ^{1}HNMR,^{13}C NMR and MS

III.CONCLUSION

In summary, first time successfully novel efficient michael addition on chalcone with thiazolindione catalysed by lipase. Prominent among the advantages of this new method are novelty, good yield, eco-friendly, and easy workup. Thus further studies on asymmetric reaction catalysed by lipase in our laboratory

IV.EXPERIMENTAL

General- All Chemicals purchase from commercial supplier & used without further purification. Lipase purchase from Sigma Aldrich, ^{1}H NMR and ^{13}NMR Spectra were recorded on Bucker Advanced II 400MHz spectrometer at ambient temperature in DMSO solvent at SAIF. Punjab University Chandigarh. Mass spectra were recorded using JMS-T100LC, Accu TOF in acetonitrile solvent at SAIF,CDRI Lucknow.Thin Layer chromatography was carried out aluminium backed plates pre-coated with silica gel 60.were visualised by quenching of UV florescence.

General experimental procedure for Michael addition on chalcone

A mixture of Chalcone (5 mmol), and thiazolindione (5 mmol) was dissolved in acetonitrile (15 mL) containing RB flask (50 mL), then adding lipase CAL-B (100 mg).Then reaction was continues stirring at room temperature on magnetic stirrer. The progress of the reaction was monitored by thin layer chromatography, after completion of reaction (30 h), reaction mixture was filtered to remove the catalyst and washed with acetonitrile. The filtrate was in rotary evaporator to obtain crude product. Purification is done by crystallisation from ethanol.

Spectral data of synthesize compounds

4.2.1 2-Methylene -3(3-oxo -1,3 diphenyl propyl) thiazolindione **(3a):** Yellow solid

^{1}H NMR-(400 MHz, DMSO) δ ppm 12.00 (s, 1H), 7.96 (t,2H,*J= 8.8 Hz*), 7.58(t, 1H, *J=7.6 Mz*),7.49(t,2H, *J= 7.0 Hz*), 7.35(t, *2H, J=8.4 Hz*), 7.22 (d, 2H, *J=7.4 Hz*), 4.6 (t,1H, *J=7.0 Hz*), 3.4(s,2H), 3.2(dd, 2H ,*J= 7.0,7.4 Hz*).

^{13}C NMR (100 MHz, DMSO) δ ppm 197.06, 173.40, 172.76, 141.17, 136.42, 132.99, 132.94, 129.27, 128.40, 127.45, 126.95, 78.63, 42.82, 35.4

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