Coumarin synthesis with biocatalysis

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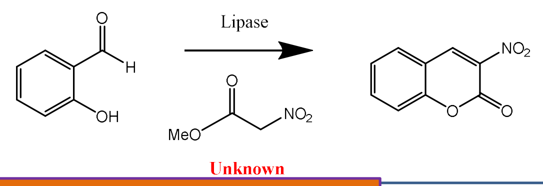
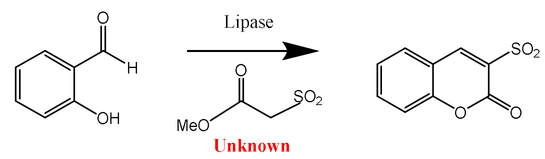
1.Introduction

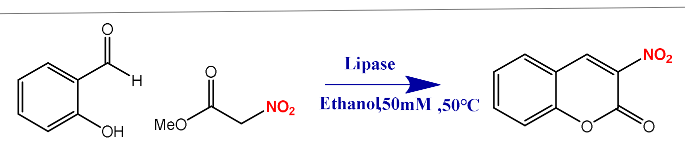
- Coumarins are well known for their potent biological activity as well as their versatility, being present in numerous natural products.
- Structure-activity relationships (SARs) of the coumarin derivatives with different substituents in various positions reveals significant information related to the development of highly specified and potent drugs.
- Usually coumarines are prepared using precious-metal catalysis, toxic reagents and high temperatures.
- In my research we will enable the transition to a more sustainable society and give access to important bioactive molecules in the process.
- The biocatalytic synthesis of coumarins from malonyl derivatives has been reported, but the substrate scope is limited. The use of nitro and sulfoacetate derivatives has not been shown previously.



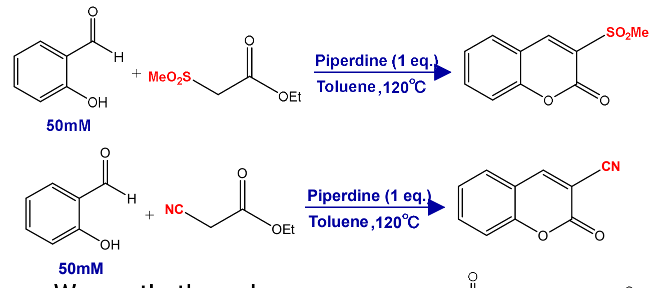


2. Optimisation of Reaction

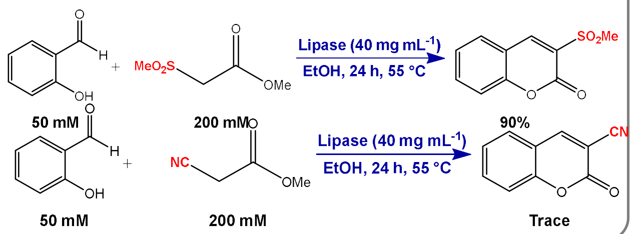
Enzyme	Amount(mg mL^{-1})	Time(h)	Nitroacetate (equivalent)	Solvent	Salycilic aldehyde %	Coumarin%
Lipase Candida rugosa	50	24	2	DMSO / H_2O	0	50
Lipase Candida rugosa	1	42	2	Ethanol	61.24	2.9
Lipase Candida rugosa	20	24	2	Isopropanol	100	0%
Lipase Candida	20	24	2	Methanol	60.31	39.68
Lipase Candida	1		2	Acetone	100	0
Lipase Candida	10	120	2	Ethanol	13.79	86.20
Amano Lipase from Pseudomous	20	24	2	Ethanol	60.15	39.84
Amano Lipase from Pseudomous	20	24	4	Ethanol	83.57	39.84
Amano Lipase from Pseudomous	40 (20 mL scale)	72	4	Ethanol	10.71	89,28



3.Proposal

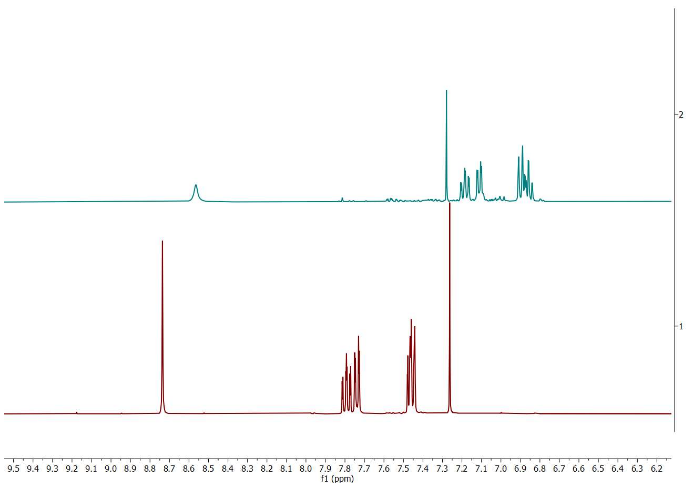


- Standards were chemically synthesized under reflux in toluene with piperidine as a base.
- We synthesed Sulfocoumarin using Amano Lipase from Pseudomous .
- After 24h of incubation the conversion was 90 % .
- All the details are shown in reaction scheme.



4.Proposed Mechanism

- Based on intermediates isolated from other reaction conditions, a proposed mechanism is shown below.
- With no enzyme present, no Knoevenagel condensation occurs so the enzyme is essential for the formation of intermediate one.
- This is followed by the ring-closing step to form the coumarin. The optimized conditions demonstrated this only occurs in the presence of EtOH as solvent.



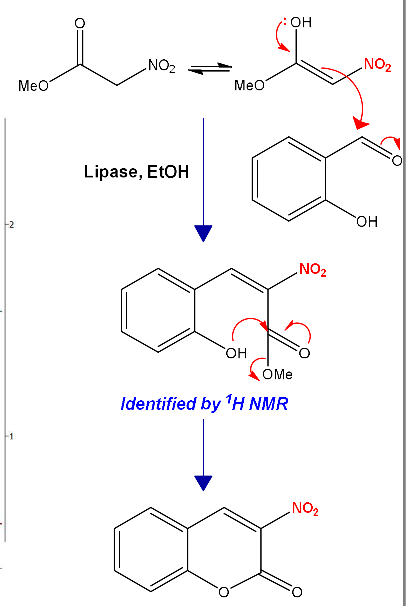


Figure 1. The top (blue) spectrum shows what we believe to be the intermediate (co-confirmation by MS analysis). The bottom spectrum (red) shows the purified 3-nitrocoumarin, confirmed by comparison with synthetic and literature standards.

5. Substrate scope

- A panel of derivatives were synthesized by varying the salicylaldehyde that was used in the reaction. This includes several halogenated compounds and mono- and di-substituted derivatives as well.

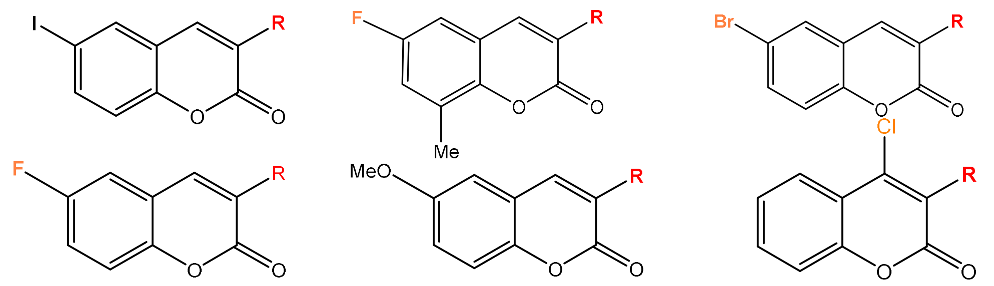
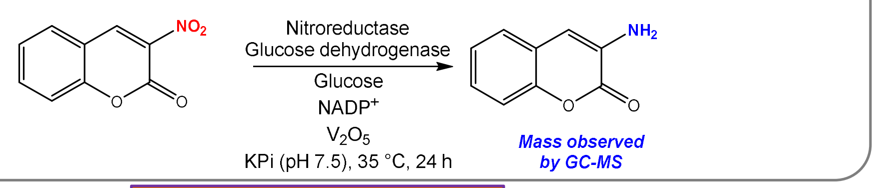


Figure 2. A panel of coumarin deriavtives synthesized under the optimal conditions R= NO_2 , SO_2

- It has also been demonstrated that the coumarin could also be a substrate for nitroreductase enzymes, which presents the opportunity to develop multi-step enzymatic cascade reactions



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Santhosh Penta, Advances in Structure and Activity Relationship of Coumarin Derivatives. December 2016.