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Mild chemo-enzymatic synthesis of polymer-supported cinchona alkaloids and their application in asymmetric Michael addition

Vilas Athawale* and Narendra Manjrekar

Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai 400 098, India

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Abstract—Cinchona alkaloid (CA) monomers were synthesised enzymatically in high yield (90%) by selectively acrylating the primary -OH group of the CA, and the co-polymers obtained with acrylonitrile were tested for their efficiency for asymmetric induction in Michael addition reactions.

Asymmetric synthesis of optically active compounds from prochiral substrates using chiral catalysts is a very attractive methodology in organic chemistry. However, removal of the expensive chiral catalyst from the crude reaction product after the completion of reaction is a tedious job. Polymer-supported catalysts are advantageous, as they can be recovered from the reaction product by simple filtration and can be reused, thus, making the process economically viable.

A systematic study of the addition of thiols to α,β-unsaturated ketones in the presence of cinchona alkaloids as chiral catalyst has been reported.[1] Polymer-supported cinchona alkaloids have been synthesised chemically,[2–4] however, no reports are available on a biocatalytic approach for the synthesis of derivatives of the alkaloids.

Enzyme mediated processes are becoming standard synthetic technologies for selective transformations in organic synthesis. Among biocatalysts of synthetic interest, lipases (triglycerol hydrolases, EC 3.1.1.3) have been used most frequently because they are cheap, available from many sources, easy to handle, and compatible with a broad range of substrates.[5,6] Lipase catalysed reactions show high chemo-, regio- and enantioselectivities and, unlike chemical reactions, no undesirable side-products are formed.

In the present study, porcine pancreatic lipase (PPL) was used for acrylating selectively the primary -OH group of the CA, in the presence of the secondary -OH group, to obtain the acrylate derivative of CA (Scheme 1).

In the cinchona alkaloid catalysed Michael addition of thiols, the -OH group at C(9) in the cinchona alkaloid should be free to form a hydrogen bond with thiophenoxide ion, thereby enhancing the rate of reaction and enantiomeric excess. It has been reported that in transesterification reactions catalysed by PPL, the primary -OH group of a diol was selectively acylated in the presence of a secondary -OH group.[7]

A primary -OH group was introduced into the CAs quinine **1** and quinidine **2** by reacting them with 2-mercaptoethanol using AIBN to obtain the corresponding diols, 11-[2-thioethanol]-10,11-dihydroquinine **3** and 11-[2-thioethanol]-10,11-dihydroquinidine **4**.[3] The transesterification of **3** or **4** with 2,3-butanedione mono-oxime acrylate **7** in the presence of PPL selectively leads to the formation of 11-[2-(acryloyloxy)ethylthio]-10,11-dihydroquinine **5** and 11-[2-(acryloyloxy)ethylthio]-10,11-dihydroquinidine **6**, respectively[8] (Scheme 1), in which the -OH group at C(9) is free, which was confirmed by NMR data.[9] The reactivity of the enzyme towards **3** and **4** is similar as expected since the primary hydroxyl groups in both substrates are away from the bulkier part of the molecule, making it easily available for attack by the enzyme–acylating agent complex. The type of organic solvent used has a profound effect on the reaction kinetics and stability of enzymes. Reactions were carried out in chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) with

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* Corresponding author. Tel.: 91:22:652 7957-61, ext. 567; fax: 91:22:652 85 47; e-mail: polymer2000@rediffmail.com

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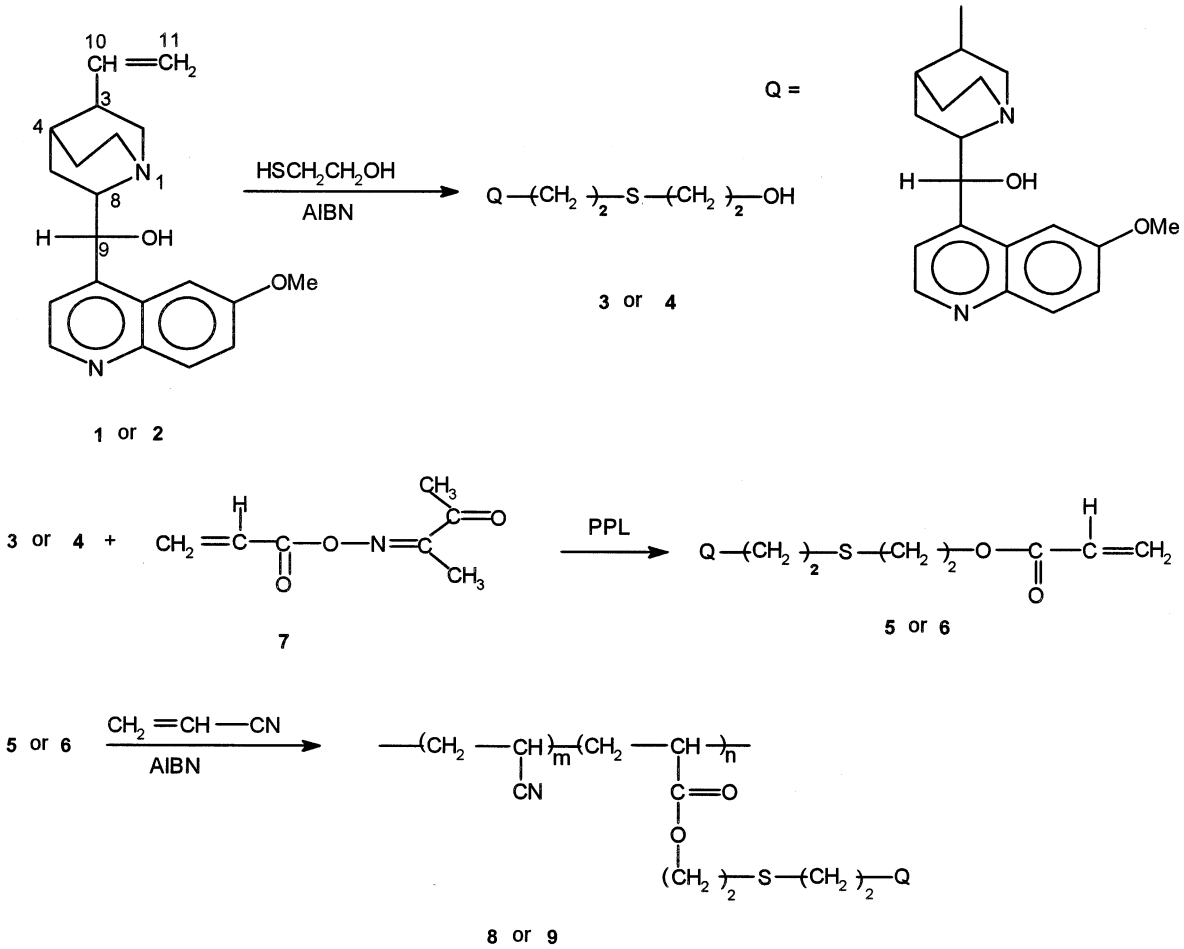
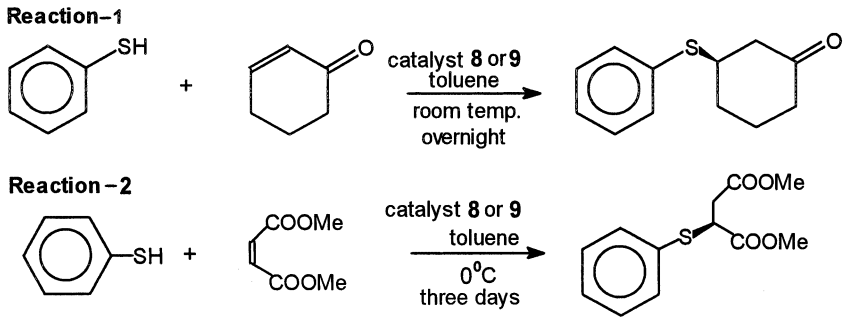


Scheme 1.

stirring at 30°C for 6 h. Among the solvents tried, $CHCl_3$ proved to be a better solvent (92% yield) compared to CH_2Cl_2 (84% yield). The lowest conversion in the case of THF (56% yield) as solvent can be attributed to the fact that THF must absorb water from the enzyme, which is essential for its catalytic activity. The effect of variation in temperature on the rate of transesterification was studied at 10, 20, 30 and 40°C in $CHCl_3$ for 6 h. It was found that at lower temperatures (10 and 20°C) the yields were very low (36 and 75%, respectively), indicating a slow rate of reaction. When the reaction was carried out at 30°C there was a gradual increase in the yield (92%). With further increase in the temperature (at 40°C) there was no change in the yield (90%). The copolymers of monomers **5** and **6** were obtained by reacting 1 mol of **5** or **6** with 9 mol of acrylonitrile, using AIBN as an initiator under an argon atmosphere (Table 1). Molecular weights (M_w) of the polymer catalysts **8** and **9** were determined using GPC and their values were 15,682 and 16,894, respectively. Incorporation of the alkaloid derivatives **5** and **6** was confirmed by hydrolysing the polymers **8** and **9** followed by Soxhlet extraction. The alkaloid contents in polymers **8** and **9** were 9.12 and 8.94%, respectively. The polymers **8** and **9** obtained were tested for their efficiency in catalysing the Michael addition of thiophenol (Scheme 2) to 2-cyclohexen-1-one (reaction 1, Table 2)[1] and dimethyl maleate (reaction 2, Table 3).[10] In the case of reaction 1, the Michael adducts showed higher ee's (50%) as compared to the products obtained by using non-polymeric catalyst (41%),[11] whereas the Michael adducts in reaction 2 showed lower optical rotations compared to those obtained by using non-polymeric catalysts.[12]

Table 1. Preparation of alkaloid–acrylonitrile copolymers

Copolymer	Yield (%)	$[\alpha]_D^{25}$ in DMF	Elemental analysis (%)		
			C	H	N
Polymer **8**	65	−31 (*c* 1.003)	66.21	6.19	18.12
Polymer **9**	66.2	+33 (*c* 1.01)	66.83	6.22	18.47



Scheme 2.

Table 2. Asymmetric addition of the thiophenol catalysed on 2-cyclohexen-1-one

Catalyst	Yield (%)	%ee
Polymer **8**	86	51
Polymer **9**	85	50

Table 3. Asymmetric addition of the thiophenol catalysed on dimethyl maleate

Catalyst	Yield (%)	$[\alpha]_D^{25}$ in CH_2Cl_2
Polymer **8**	87	+17.6 (*c* 5.00)
Polymer **9**	85	−17.1 (*c* 5.02)

In conclusion, the above-mentioned chemo-enzymatic method is a mild and selective route. This method may be of importance in the synthesis of the compounds, where selectivity as well as mild reaction conditions are required by simultaneously replacing conventional catalysts with environment-friendly 'green catalysts'.

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8. Preparation of 11-[2-(acryloyloxy)ethylthio]-10,11-dihydroquinine **5** and 11-[2-(acryloyloxy)ethylthio]-10,11-dihydroquinidine **6**: A mixture of the alkaloid **3** or **4** (3 g, 7.45 mmol), 2,3-butanedione mono-oxime acrylate **7** (0.577 g, 3.73 mmol) and enzyme (500 mg) was dissolved in $CHCl_3$ and the reaction mixture was stirred at 35°C for 6 h. The reaction mixture was filtered to separate the enzyme and the filtrate was concentrated. The residue was treated with 2 M HCl and extracted with ether (2×25 mL). The aqueous layer was made alkaline with Na_2CO_3 and extracted with dichloromethane. The extracts were washed with brine and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel column {eluent $CHCl_3$ (50): MeOH (2): Et_3N (1)} to give monomer **5**, yield = 3.14 g (92%) $[\alpha]_D^{25} = -108$ (*c* 1.032 in EtOH) and monomer **6**, yield = 3.04 g (89%) $[\alpha]_D^{25} = +110$ (*c* 1.04 in EtOH), respectively.
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11. The ee for the Michael adduct from reaction 1 using non-polymeric catalyst was 41% (Reference 1).
12. The optical rotations for the Michael adduct from reaction 2 using non-polymeric catalysts were $[\alpha]_D^{23} = +18.1$ (*c* 5.00, CH_2Cl_2) and $[\alpha]_D^{23} = -29.2$ (*c* 5.00, CH_2Cl_2), respectively, (Reference 7).