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Biocatalysed olefin reduction of 3-alkylidene oxindoles by baker's yeast

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3-Substituted oxindoles are very interesting molecules both for their potential biological activity and for their role as starting materials toward more complex oxindole-based structures. These molecules can be prepared by the reduction of a 3-ylidene oxindole precursor by classical metal-catalysed chemical reductions of the olefin. In this work we present a biocatalytic approach for the reduction of oxindole-based olefins using baker's yeast. All the substrates were efficiently reduced in high yields. When an α,β-unsaturated ketone was used, the corresponding saturated alcohol was obtained in high yield and ee. To further investigate the enzyme-substrate interactions a molecular docking study was also performed.
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1. Introduction

Oxindoles are present in many natural and synthetic products showing pharmaceutical and biological activities.[1,2] Oxindole derivatives have been employed as anti-cancer,[3] antimicrobial,[4,5] anti-HIV,[6] and antimalarials.[7,8] In the past we demonstrated the utility of oxindoles as peptidomimetics capable of mimicking a β-turn structure.[9,10] The most common derivatives are 3,3-disubstituted oxindoles and 3-spirooxindoles containing a quaternary carbon centre and diverse functional groups. Spirooxindoles are also related to a series of alkaloids that were first isolated from plants of the Apocynaceae[11–13] and Rubiaceae[14–17] families.

The importance of isatin derivatives and their multiple applications has stimulated the interest of the researchers. In the last few years, lots of work has been devoted to finding an easy way to produce 3-substituted oxindoles, if possible with a controlled configuration at the stereocentre. Following our research activity in the preparation of oxindole-based compounds,[18–21] we became interested in the metal-free reduction of 3-yliden-oxindole derivatives by means of biocatalysis, in order to obtain 3-alkyl-oxindoles as possible substrates for further modifications. The use of biocatalysis offers the advantage of mild reaction conditions with limited use of organic solvents. Conversions are usually very high and when prochiral substrates are employed, chiral compounds can be obtained in high enantiomeric excesses. Baker's yeast has been demonstrated to be an efficient catalyst for the reduction of activated olefins. This activity is due to the presence in this yeast of ene reductase (ER) enzymes of the OYE family. The use of baker's yeast for chemical transformations is encouraged by the fact that reactions are carried out in tap water, at room temperature and in the air in simple apparatus. The recovery of the products is easily realized by solvent extraction. An improvement of the recovery step is possible when the substrates are supported onto insoluble polystyrene resin, with the so-called Substrate Feeding Product Removal (SFPR) technique. In accordance with our experience in the use of biocatalytic systems for the reduction of activated olefins,[22–26] we decided to investigate the baker's yeast mediated reduction of olefins **1**–**13**. Very recently, a similar approach using *pseudomonas Monteilii* was reported,[27] thus confirming the urgent interest in this topic.[28] Nevertheless, *baker's yeast* is more simple to

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handle and scaling up to the preparation of grams of product is easily achievable. We selected differently substituted olefins in order to explore both the effect of different activating groups on the reactivity and the role of steric hindrance.

2. Results and discussion

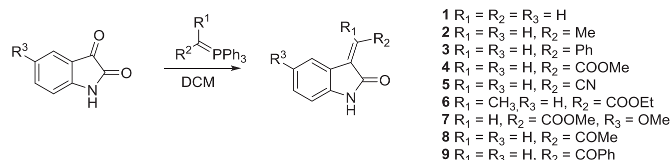
The substrates were synthesized according to Schemes 1 and 2. Compounds **1**–**9** were prepared by standard Wittig olefination on commercial isatins (see Scheme 3).

Compounds **10**–**12** were produced by the reaction of isatin with the corresponding arylmethylketone with catalytic DEA (diethylamine) followed by dehydration with thionyl chloride. The reaction of isatin with ethylcyanoacetate and catalytic DBU (1,5-diazabiciclo(5.4.0)undec-5-ene) afforded compound **13**, while grinding isatin with malononitrile and a substechiometric equivalent of water afforded derivative **14**.

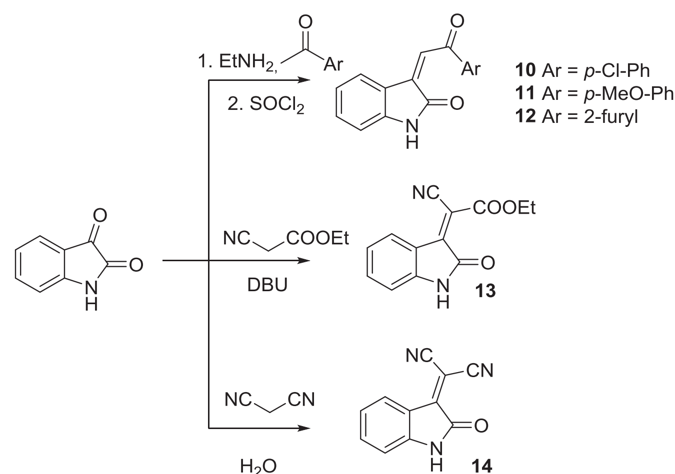
The olefins were then submitted to reaction with dried yeast (Sigma-Aldrich) in tap water (150 g/L) in the presence of D-glucose (15.0 g/L). Substrates were added at a concentration of 3 g/L. Reaction were usually carried on the 100 mg scale of olefin. If necessary, some drops of ethanol were added to facilitate the dissolution of substrates. The mixtures were incubated at 35 °C for 72 h in an orbital shaker. The same conditions were applied when using the SFPR technique. In this case the resin (Amberlite XAD 1180-N) was loaded in a 1:20 substrate/resin ratio.

Results are reported in Table 1. Products **15**–**23** were isolated from substrates **1**–**7**, **13**, **14** after chromatographic purification. As expected when unsaturated ketones **8**–**12** were employed, the corresponding saturated alcohols **24**–**28** were isolated as the major product, due to the concomitant activity of the alcohol dehydrogenase enzymes (ADH) which are present in the baker's yeast. The saturated ketones **24a-28a** were also obtained in a 2–6% yield, according to ^{1}H NMR analysis of the crude reaction mixture (products were not isolated).

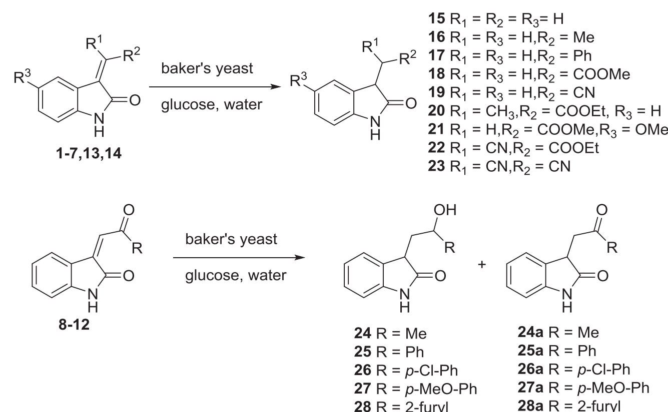
All the substrates could be efficiently transformed into products by baker's yeast. As expected, the use of the SFPR allowed isolation of the final products in significantly higher yields. The lowest yields were obtained with tetra-substituted olefins (**21**–**23**) probably due as a result of their increased steric hindrance. Despite the use of prochiral olefins, disappointingly no ee was detected after HPLC analysis of the product **18**. The preparation of enantioenriched 3-alkyl 2-oxindoles has been previously reported in the literature by means of different approaches.[29–33] In particular the reduction of 3-yliden-oxindoles catalysed by a chiral iridium complex was reported to proceed with ee up to 93%.[34] We reasoned that our results might be ascribable to an epimerisation of the newly formed stereogenic centre.[35] The chromatogram of the chiral HPLC separation of compound **18** is reported in Fig. 1. The presence of a plateau between the peaks of the two enantiomers is characteristic of a racemization process of the product during the column elution,[36] due to epimerisation at the C3 position. To further investigate this aspect, the ^{1}H NMR spectrum of **18** was first recorded in $CDCl_3$. Upon addition of few drops of CD_3OD, after 24 h at room temperature we observed the complete disappearance



Scheme 1. Synthesis of **1**–**9** by Wittig olefination.



Scheme 2. Synthesis of compounds **10**–**14** by condensation reactions on isatin.



Scheme 3. Reaction of olefins **1**–**14** with baker's yeast.

of the C3 proton as a consequence of its exchange with deuterium (see Fig. 1). These experiments proved the configurational lability of the C3 stereocenter due to the acidity of the hydrogen at C3.

Alcohols **25**–**28** were obtained as a 1:1 mixture of diastereoisomers. In this case, as expected, the reduction of the carbonyl group by ADH enzymes proved to be very enantioselective, whereas the epimerisation at C3 led to no diastereoisomeric excess. In fact, for representative compounds **24** and **25** an enantiomeric excess up to 98% could be measured by chiral HPLC. We did not determine the absolute configuration at the alcohol stereocenter of the major enantiomer, however, according to the Prelog's rule,[37] we could suggest the stereochemical outcome proposed in Scheme 4. For compound **8**, bearing the small methyl group, the *S* configuration can be safely assigned. Whereas in the presence of an aryl substituent, the opposite result should be expected.

According to the activation model for the reduction of activated olefins by baker's yeast, as observed for substrates **6, 13** and **14**, the reaction suffers from the steric hindrance around the carbon-carbon double bond. Despite the high steric demand introduced by the oxindole moiety, for trisubstituted olefins the conversions were good in all cases. Moreover, with the exception of compounds **1**–**3**, two different activating EWGs are present on the double bond, thus enabling different possible interaction modes with the ene-reductase enzymes. To better understand these aspects of the substrate-enzyme interaction, we performed a study on the

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