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RESEARCH ARTICLE

Reduction of substituted benzaldehydes, acetophenone and 2-acetylpyridine using bean seeds as crude reductase enzymes

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ABSTRACT

The reduction of substituted benzaldehydes, benzaldehyde, acetophenone and 2-acetylpyridine to the corresponding alcohols was conducted under mild reaction conditions using plant enzyme systems as biocatalysts. A screening of 28 edible plants, all of which have reductase activity, led to the selection of pinto, Flor de Mayo, ayocote, black and bayo beans because these enabled the quantitative biocatalytic reduction of benzaldehyde to benzyl alcohol. The biocatalyzed reduction of substituted benzaldehydes was dependent on the electronic and steric nature of the substituent. Pinto beans were the most active reductase source, reduced 2-Cl, 4-Cl, 4-Me and 4-OMe-benzaldehyde with a conversion between 70% and 100%. All the beans reduced 2- and 4-fluorobenzaldehyde at a conversion between 83% and 100%. The reduction of the ketones was low, but bayo and black beans yielded (*R*)-1-(pyridin-2-yl)ethanol in enantiopure form.

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Bean; benzyl alcohols; biocatalysis; plant reductase; enzyme

Introduction

The reduction of aldehydes and ketones constitutes an important tool in organic chemistry for the preparation of alcohols, which can be used in the synthesis of cosmetics, pharmaceuticals and agrochemicals. Even though a wide range of reduction systems are available and show high yields, most of these reaction systems use heavy metals or their hydrides and organic solvents as the reaction medium, which indicates that they are not environmentally friendly.

For organic chemists, an attractive alternative is the use of plant parts as biocatalysts because they are inexpensive and easily available (Giri et al. 2001; Cordell et al. 2007). The advantages of biocatalyzed reactions are high chemo-, regio- and stereoselectivity, diminished formation of by-products and waste, reduced energy consumption and substantially decreased negative environmental effects; therefore, these reactions can be used on a sustainable basis because they fit some of the principles of green chemistry (Clouthier and Pelletier 2012).

Reduction methodologies using enzymes avoid the formation of toxic waste, which might pollute the environment, and the use of non-sustainable heavy metals and hydride reducing agents. The biocatalytic reduction of carbonyl groups such as aldehydes and ketones can be conducted using nicotinamide-dependent dehydrogenases (E.C. 1.1.1) as the catalysts of choice (Hollmann et al. 2011). Aldo–keto reductases (AKRs) are enzymes that catalyse the biotransformation of ketones/aldehydes to the corresponding alcohols and vice versa at the expense of a nicotinamide cofactor [nicotinamide adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADPH)] (Sengupta et al. 2015). It is well established that crude preparations of parts of fresh plants, such as roots, fruits, seeds or leaves, can be used as alternative high-yield reducing agents for the synthesis of alcohols from aldehydes or ketones. Some recent examples of reductase sources include the following: fresh sugar cane (*Saccharum officinarum*) juice (Assunção et al. 2008), Damask rose (*Rosa damascena*) petals (Chen et al. 2011), mung bean (*Vigna radiata*) seeds (Colrat et al. 1999), fresh passion fruit (*Passiflora edulis*) (Machado et al. 2008), fresh vegetables, such as broccoli (*Brassica oleracea* var. italica), cauliflower (*B. oleracea* var. botrytis), spinach beet (*Beta vulgaris* var. cicla) and spinach (*Spinacia oleracea*) (Suárez-Franco

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et al. 2010), coconut (*Cocos nucifera* L.) and Asian palmyra palm (*Borassus flabellifer* L.) juices (Misra et al. 2012), Vietnamese coriander (*Persicaria odorata* Lour) leaves (Quynh et al. 2009), purple carrot (*Daucus carota*) roots (Omori et al. 2016), cassava (*Manihot esculenta*) (Machado et al. 2006), ginger (*Zingiber officinale*) (Alves et al. 2015), *Aloe vera* (Leyva et al. 2012), hemlock (*Conium maculatum*) (Salvano et al. 2011) and flax seeds (*Linum usitatissimum*) (Tavares et al. 2015).

Plants have been demonstrated to be useful catalysts for the specific reduction of aldehydes and ketones to the corresponding alcohols. Furthermore, because México is a country with high biodiversity, a screening of the natural diversity can lead to the discovery of novel biocatalysts. The reduction of benzaldehyde to benzyl alcohol was used as a model reaction to identify new sources of reductases in 28 different plants or their parts that are easily accessible in local markets. The scope of the reduction reactions with the novel biocatalysts was explored using substituted benzaldehydes with electron-withdrawing or electron-donating groups, acetophenone and 2-acetylpyridine.

Materials and methods

Materials

2-,3- and 4-Chlorobenzaldehydes, 2- and 4-fluorobenzaldehyde, 2- and 3-bromobenzaldehyde, 2- and 4-tolualdehyde, 4-methoxybenzaldehyde, benzaldehyde and $NaBH_4$ were purchased from Sigma-Aldrich. All the solvents used were purchased from J.T. Baker or Techrom and used without further purification.

Preparation of the alcohols

The corresponding alcohols were prepared by reducing the substituted benzaldehydes and ketones with $NaBH_4$ following standard methods (Tae et al. 2006) and were identified by ^{1}H-NMR, ^{13}C-NMR and IR (Supplementary material). NMR spectra were recorded on an Agilent DD2-600 at 25 °C using $CDCl_3$ as the solvent and TMS as the internal reference.

Reductase enzyme source

Fresh vegetables and seeds (Table 1) were purchased from local markets. The biological material was disinfected with 5% sodium hypochlorite solution and rinsed with sterile distilled water. The leaves, fruit pulp, roots, florets and stalks (50 g) were cut into small pieces (0.5 cm^3), blended with distilled water (50 mL), and then centrifuged at 5000 rpm. The seeds were separately pulverized in a coffee grinder, and the powder (10 g) was stirred in distilled water (30 mL) and then centrifuged at 5000 rpm. The supernatants were used as the enzyme source.

Table 1. Reduction of benzaldehyde (AH) to benzyl alcohol (BH) with aqueous extracts from plants as enzyme sources.

	Scientific name	BH (% conv.)
Seeds		
Pinto beans	*Phaseolus vulgaris* L.	100
Flor de mayo beans	*Phaseolus vulgaris* L.	100
Ayocote beans	*Phaseolus coccineus* L.	100
Black beans	*Phaseolus vulgaris* L.	100
Bayo beans	*Phaseolus vulgaris* L.	100
Canary grass	*Phalaris canariensis*	75
Barley	*Hordeum vulgare*	64
Lentil	*Lens culinaris*	53
Oat	*Avena sativa*	51
Squash	*Cucurbita maxima*	29
Wheat	*Triticum aestivum*	28
Mamey	*Pouteria sapota*	25
Pepper	*Capsicum annuum*	23
Chili pepper	*Capsicum frutescens*	17
Avocado	*Persea americana*	14
Roots		
Carrot	*Daucus carota*	63
Radish	*Raphanus sativus*	20
Turnip	*Brassica rapa*	18
Leaves		
Lettuce	*Lactuca sativa*	22
Coriander	*Coriandrum sativum*	14
Nopal	*Opuntia ssp.*	19
Fruit		
Banana	*Coriandrum sativum*	60
Zucchini	*Cucurbita pepo*	30
Cucumber	*Cucumis sativus*	18
Florets		
Cauliflower	*Brassica oleracea* var. *botrytis*	25
Cabbage	*Brassica oleracea* var. *capitata*	24
Broccoli	*Brassica oleracea* var. *italic*	19
Celery (Stalk)	*Apium graveolens*	33

Bioreduction of aldehydes and ketones

The corresponding aldehyde or ketone (1.484×10^{-5} mol) was added to the aqueous extract of the selected bean (1 mL, Table 1). The reaction mixture was incubated at 25 °C, stirred magnetically for 24 h and then extracted with diethyl ether. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The conversion to benzyl alcohol was determined by gas chromatography, and the enantiomeric excess was determined by HPLC using a Chiracel OD column. The experiments were performed in triplicate.

Analytical methods

Gas chromatographic analyses were performed using an Agilent Technologies chromatograph (model 6890) equipped with a flame ionization detector and a

Supelcowax-10 (30 m × 25 mm ×25 μm) column. The injector and detector temperature were set to 250 °C, and nitrogen was used as the carrier gas. The HPLC analysis was performed on an Agilent 1100 liquid chromatograph equipped with a diode array detector using a Chiracel OD (25.0 cm ×0.46 cm) column (Daicel Chemical Industries, Ltd., Tokyo, Japan), and the mobile phase was a mixture of hexane and isopropyl alcohol.

Results and discussion

Selection of the biological material with reductase activity

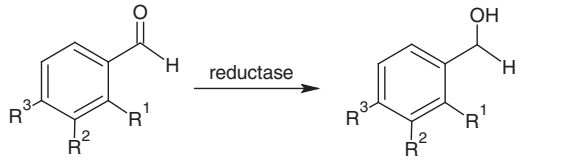
The reductase activity of 28 different parts of plants, such as seeds, roots, fruits, leaves, florets or stalks, was evaluated using benzaldehyde (AH) as the model substrate to obtain benzyl alcohol (BH). As shown in Table 1, all the tested biological materials showed reductase activity; however, the seeds of plants of the *Phaseolus* genus were identified as the source of the most active reductases. The reduction of benzaldehyde to benzyl alcohol with seeds of pinto, Flor de Mayo, ayocote, black and bayo beans was quantitative, and these beans were thus selected for the reduction of other carbonyl substrates. *Daucus carota* (carrot), one of the most studied reductase sources (Omori et al. 2016), yielded a moderate conversion to AH (63%) under our reaction conditions.

Bioreduction of substituted benzaldehydes

The catalytic specificity of the reduction using the selected beans as biocatalyst sources was examined with benzaldehydes substituted with electron-donating groups (methoxy and methyl groups) and electron-withdrawing groups (fluoride, chloride or bromide) in the *ortho*, *meta* and *para* positions (Figure 1). As shown in Table 2, both the reducing activity and the extent of conversion to the corresponding alcohol depended on the electrophilic activating/deactivating effects of the substituents, the steric hindrance, the position with respect to the carbonyl in the benzene ring and the source of the biocatalyst (Figure 1).

The extent of the bioreduction of *para*-substituted benzaldehydes was dependent on the electronic properties of the substituent and the biocatalyst source. The presence of electron-withdrawing groups decreased the electron density and subsequently increased the nucleophilicity of the carbonyl, and the electron-deficient aldehydes were reduced at a higher extent than the electron-rich aldehydes (Mayr and Nidetzky 2002; Pratihar 2014). The reduction was improved in the presence of electron-withdrawing substituents: the reduction of A4F showed between 96% and 100% conversion, and A4Cl was reduced at a conversion between 50% and 100%. In contrast, the presence of electron-donor groups diminished the conversion: the reduction of A4Me ranged from 1% to 48%, but 97% conversion was obtained with pinto beans, and A4OMe was reduced at a conversion between 42% and 77%. The extent of the biocatalysed reduction of A3Cl and A3Br was between 3% and 28% with all the tested biocatalyst sources, the substituents in the *meta* position relative to the carbonyl did not favour the enzymatic reaction with the beans selected.

The chemical reactivity of *ortho*-substituted aromatic rings is not completely explained by the electronic properties of the substituent, because proximity effects at the reaction centre like intramolecular hydrogen bond formation, steric inhibition of resonance, steric hindrance and short-range polar effects are also involved in the reactivity of the compound (Sedon and Zuman 1976; Sayyed and Suresh 2009; Santiago et al. 2016). The extent of the reduction of A2Me was very low (8%–15%, Table 2) with all the tested biocatalyst sources, and this low reduction was probably due to steric factors and the



(A) (B)

	R^1	R^2	R^3		R^1	R^2	R^3
H	H	H	H	**2Br**	Br	H	H
2F	F	H	H	**3Br**	H	Br	H
4F	H	H	F	**2Me**	CH_3	H	H
2Cl	Cl	H	H	**4Me**	H	H	CH_3
3Cl	H	Cl	H	**4OMe**	H	H	OCH_3
4Cl	H	H	Cl				

Figure 1. Reduction of benzaldehydes (A) to the corresponding alcohols (B) using reductase enzymes from plants.

Table 2. % Conversion of benzaldehydes (A) to the corresponding alcohols (B) using *Phaseolus* seeds as reductase sources.

Entry	Bean	AH	A2F	A4F	A2Cl	A3Cl	A4Cl	A2Br	A3Br	A2Me	A4Me	A4OMe
1	Pinto	100	99	96	70	16	97	55	25	13	97	77
2	Bayo	100	83	100	11	18	100	47	28	15	29	71
3	Black	100	98	100	12	20	100	10	23	14	48	54
4	Ayocote	100	88	98	11	23	77	16	17	8	4	42
5	Flor de Mayo	100	89	100	3	3	50	18	7	8	1	50

electron-donating nature of the methyl group, which deactivates the carbonyl towards nucleophilic attack. The extent of the reduction of A2F (99%), A2Cl (70%) and A2Br (55%) using pinto beans as the reductase source could be explained by the steric hindrance effect and electronegativity of the halogen atoms F, Cl and Br, because the fluorine is the smallest and the most electronegative atom that favored the reduction to a greater extent than the larger and less electronegative bromine atom. The other reductase sources only yielded a high reduction of A2F (83%–98%), whereas the conversion of A2Cl and A2Br was between 3% and 11% and 10%–47%, respectively.

Pinto beans were the most active and versatile reductase source because five (AH, A2F, A4F, A4Cl and A4Me) of the 11 aldehydes were reduced to the corresponding alcohols at a conversion higher than 90% and A2Cl, A2Br and A4OMe were reduced at a conversion between 55% and 77%. Bayo and black beans reduced AH, A2F, A4F and A4Cl at a conversion higher than 80%, whereas ayocote and Flor de Mayo beans reduced AH, A2F and A4F at a conversion higher than 80%.

There are reports on the reduction of benzaldehyde using several plants, in this work the beans pinto, Flor de Mayo, ayocote, black and bayo reduced 100% of benzaldehyde in 24 h, similar to *C. maculatum* (Salvano et al. 2011) whereas with *M. esculenta* and *M. dulcis* (Machado et al. 2006), *Ximenia Americana* (da Silva et al. 2018) and *Saccharum officinarum* (Assunção et al. 2008) the conversion was also 100% but in 72 h.

Bioreduction of acetophenone and 2-acetylpyridine

The reduction of acetophenone (PhAc) and 2-acetylpyridine (PyAc) to the corresponding alcohols, PhOH and PyOH, respectively, with the beans selected seeds was lower with respect to the reduction of the aldehydes, probably due to the steric factor, which decreases the reactivity of the ketones (Table 3).

However, the enantioselectivity of the reaction was highly influenced by the nature of the aromatic ring and the enzyme source: bayo and black beans gave enantiopure (*R*)-1-(pyridin-2-yl)ethanol (PyOH), and bayo beans provided the highest enantiomeric excess (*ee*) for (*R*)-1-phenylethanol (PhOH), which was 53%. These results are in agreement with those reported by Pal et al. (2012), who compared the reduction of PhAc and PyAc using three fungi as reductase source, the *ee* of **PyOH** was 99%, whereas PhOH was obtained with a lower enantiopurity. The researchers speculated that the nitrogen in the pyridine ring possibly promoted a better interaction between the active site of the enzyme and the substrate, which would allow enantioface-selective delivery of hydride from the bound cofactor (Pal et al. 2012).

Table 3. Reduction of ketones PhAc and PyAc to the corresponding alcohols PhOH and PyOH using bean seeds as reductase sources.

Beans	PhOH %conv	PhOH[a,b] %*ee*	PyOH %conv	PyOH[b,c] %*ee*
Pinto	25	48	10	77
Bayo	25	53	8	100
Black	17	39	10	100
Ayocote	17	38	12	62
Flor de Mayo	22	45	8	77

[a]The configuration of PhOH was assigned as (*R*) by comparison of the optical rotation in the literature (Basavaiah et al. 2004).
[b]Determined by chiral HPLC.
[c]The configuration of PyOH was assigned as (*R*) by comparison of the optical rotation in the literature (Soai et al. 1987).

With *D. carota* the reduction of PhAc was 100% and the *ee* was 99%; the same *ee* was obtained with *F. vulgare* and *C. pepo* however conversions were 37% and 10% respectively in 72 h (Bruni et al. 2002). The reduction of PhAc with the beans negro, bayo, flor de mayo, ayocote and pinto was similar to that with *Ximenia americana* (54% conv, 48% *ee*) (da Silva et al. 2018) and *Saccharum officinarum* (39% conv, 57%*ee*) (Assunção et al. 2008) in 72 h. Regarding the chiral reduction of PyAc, the conversions with *D. carota* and *V. radiata* were100% and the corresponding *ee* was 99% and 100%, respectively (Lakshmi et al. 2011, the conversion was100% and the *ee* was 83%) (Santhanam et al. 2017). In this work, the *ee* of PyOH obtained with the bayo and black beans was 100%, however the conversions were low (8% and 10%, 24 h)

Conclusions

The seeds from plants of the *Phaseolus* genus, namely, pinto, bayo, black, ayocote and Flor de Mayo beans, are reductase sources that can reduce a variety of benzaldehydes. The extent of conversion was influenced by the reductase source and by the nature and position of the substituents on the aromatic ring. Pinto beans were identified as the most versatile biocatalyst source due to their tolerance of *para*- and *ortho*-substituted benzaldehydes as substrates. With regard to ketones, the interaction of a heteroaromatic ketone with the enzyme was more efficient than that of the other ketone, and the optical purity of the resulting alcohol was higher.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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