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REMOVAL OF O-AND N-BENZYL GROUPS BY FUNGAL BIOTRANSFORMATION

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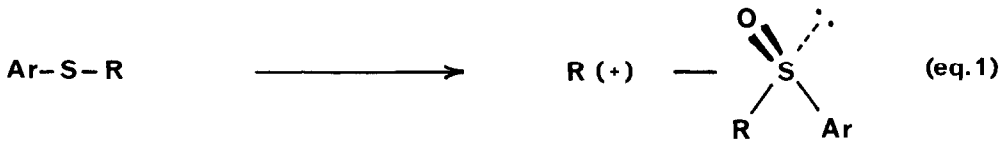
Summary: Biotransformation by resting cultures of the aerobic fungi Mortierella isabellina NRRL 1757 and Helminthosporium species NRRL 4761 can be used as method for the removal of O- and N-benzyl groups, respectively, under neutral, room temperature conditions.

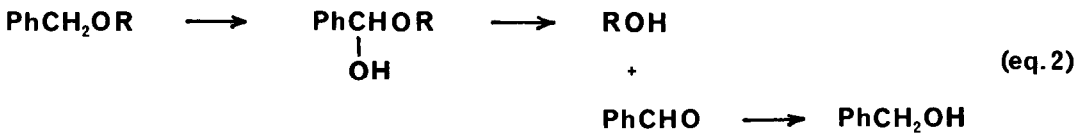
Fungal biotransformation has been developed as a useful synthetic route for asymmetric sulfur oxidation,[1] hydroxylation at unactivated carbon,[2] and ester and amide hydrolysis.[2] We have previously used the ability of resting cultures of Mortierella isabellina NRRL 1757 to oxidise sulfur in the production of a range of chiral alkyl aryl sulfoxides[3] (Equation 1), and later showed that the same fungus was able to hydroxylate a benzylic methylene group to produce chiral 1-phenylethanols.[4]



(eq.1)

We have now extended the scope of the latter reaction to include benzyl ethers, and have found that M. isabellina is capable of the cleavage of benzyl ethers, a process which by analogy with the known benzylic hydroxylating capability of this fungus is thought to proceed as outlined in Equation 2.

The isolation of benzyl alcohol rather than benzaldehyde as a reaction product is consistent with the known ability of M. isabellina to reduce the latter quantitatively under normal incubation conditions.[5]

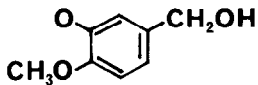
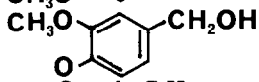
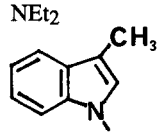


(eq.2)

Reactions were routinely carried out on a 1g scale using normal biotransformation procedures.[4] Details of substrates and conversions are presented in the Table. In all cases, percentage recoveries were high (≥ 70%) and percentage conversions are based on isolated, purified products. M. isabellina efficiently removes the benzyl group from a variety of ethers. It is specific for benzyloxy vs. methoxy cleavage (see entries 4-6), but does not react with secondary alkyl or naphthyl benzyl ethers (see entries 7-9), probably for steric reasons. Although M. isabellina does not remove benzyl groups from benzylamines (entries 10-14), this process can be carried out by another benzylic hydroxylating fungus,[4] Helminthosporium species NRRL 4671, in cases where the basicity of the amino nitrogen is low (entries 11 and 14). Neither fungus performs O-demethylation to a detectable degree, so that selective removal of benzyl protecting groups is possible. The basic secondary amine (entry 10) was acylated by both M. isabellina and H. species to give the acetyl and formyl derivatives, respectively, neither of which (or the amide 12) were metabolized, suggesting a limitation on the whole cell biotransformation process.

In a reaction thought to proceed by a route analogous to that of Equation 2, oxidative (hydroxylating) enzymes are known to be capable of ester hydrolysis[6] and demethylation of methyl ethers[7] via hemiacetal formation, and of the removal of N-methyl groups by formation of hemiaminals.[8] However, specific removal of benzyl groups from oxygen or nitrogen by biotransformation has not hitherto been reported: indeed, N-benzyl group survive intact during N-demethylation by Cunninghamella elegans.[8,9]

Table . Debenzylation by Biotransformation

Entry No.	R of BzR	% debenzylation	
		M. isabellina	H. species
1.	OC_2H_5	60	30
2.	OCH_2Ph	50	0
3.	OPh	100	0
4.	O-pC_6H_4-OCH_3	50	0
5.		33	25
6.		40	0
7.	O-cyclo-C_6H_{11}	0	-
8.	O-1-naphthyl	0	-
9.	O-2-naphthyl	0	-
10.	NH CH_3	0+	0*
11.	NH Ph	0	25
12.	NHCOPh	0	0
13.	NEt_2	0	0
14.		0	10

\+ Ph $CH_2N(CH_3)$ $COCH_3$ formed
* Ph $CH_2N(CH_3)$ CHO formed

The method reported herein therefore not only represents a new mode of biotransformation of benzyl ethers and amines, but also provides a mild, neutral, room temperature alternative to the classic strong acid or more modern reductive[10] methods for the removal of benzyl protecting groups from phenolic oxygen or indole nitrogen. It therefore has potential in organic synthesis as a preparative procedure which, moreover, may show stereoselectivity in cases where starting materials contain one or more centres of chirality. This latter aspect remains to be investigated.

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1. H.L. Holland. Chem. Rev. 88, 473 (1988).
2. H.-J. Rehm and G. Reed, eds. Biotechnology, 6A, Verlag-Chemie, Weinheim, 1984.
3. H.L. Holland, H. Popperl, R.W. Ninniss and P.C. Chenchaiah. Can. J. Chem. 63, 1118 (1985)
4. H.L. Holland, E.J. Bergen, P. C. Chenchaiah, S.H. Khan, B. Munoz, R.W. Ninniss, and D. Richards. Can. J. Chem. 65, 502 (1987).
5. H.L. Holland and M. Conn. Unpublished data.
6. F.P. Guengerich, J. Biol Chem. 262, 8459 (1987).
7. A.G. Katopodis, H.A. Smith, and S.W. May. J. Am. Chem. Soc. 110, 897 (1988).
8. C.E. Cerniglia, E.B. Hansen, K.J. Lambert, W.A. Korfmacher, and D.W. Miller. Xenobiotica 18, 301 (1988).
9. E.B. Hansen, C.E. Cerniglia, W.A. Korfmacher, D.W. Miller, and R.H. Heflich. Drug Metab. Dispos. 15, 97 (1987).
10. S. Ram and L.D. Spicer. Tet. Letters 28, 515 (1987).

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