Novel biocatalytic reduction of aryl azides: chemoenzymatic synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine antibiotics[1]

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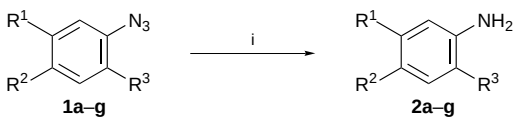
The chemoselective reduction of aryl azides to aryl amines, and the synthesis of the imine-containing pyrrolo[2,1-*c*]-[1,4]benzodiazepine DNA-binding antitumour antibiotics by selective biocatalytic reductive cyclization of azido aldehydes, has been achieved by employing baker's yeast.

In the recent years there has been a growing interest in biocatalysis and, in particular, transformations[2] mediated by baker's yeast (*Saccharomyces cerevisiae*). Reduction of carbonyl compounds by baker's yeast has become a valuable strategy in organic synthesis.[3] A variety of new and novel abilities of baker's yeast have been reported by us,[4,5] for example regeneration of carbonyl compounds and biooxidative conversion of thio to oxo functionality. In continuation of these efforts, we herein report a novel reduction of aryl azides to aryl amines in quantitative yield. This is an exceptionally mild, convenient and facile reduction employing baker's yeast. However, in the literature[6] alkyl keto azides have been reduced by baker's yeast to afford the corresponding alkyl azido alcohols. This is consistent with our finding that various alkyl azides, *e.g.* 1-azido-3-aryloxypropan-2-ols, are resistant to baker's yeast reduction. Further, this biocatalytic reductive methodology has been applied to the chemoenzymatic synthesis of the DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) system[7] *via* the reductive cyclization of aryl azido aldehydes. Interestingly, this investigation has revealed the unusual chemoselective reduction of the aryl azido group in the presence of an aldehyde group by baker's yeast.

Some representative aryl azides **1a**–**g** have been reduced by baker's yeast to afford the corresponding aryl amines **2a**–**g** (yields 83–92%), as illustrated in Scheme 1.†

This biocatalytic reduction employing baker's yeast has been extended to the chemoenzymatic synthesis of the PBD class of antitumour antibiotics. Although PBDs with either a secondary amine or amide functionalty at N(10)–C(11) are readily synthesised, the introduction of an imine or amino alcohol at this position is problematic due to the reactivity of these functional groups.[8] In the literature, various approaches to the synthesis of these antibiotics have been investigated.[9] Our interest in the design and synthesis of PBD analogues[10] has led us to develop a new chemoenzymatic methodology for the DNA-interactive PBDs. This approach is based on the formation of the seven-membered ring *via* an enzymatic azido reductive cyclization process. This enables cyclization of the diazepine ring to take place under extremely mild and ambient conditions, and involves a simple and rapid work-up procedure.



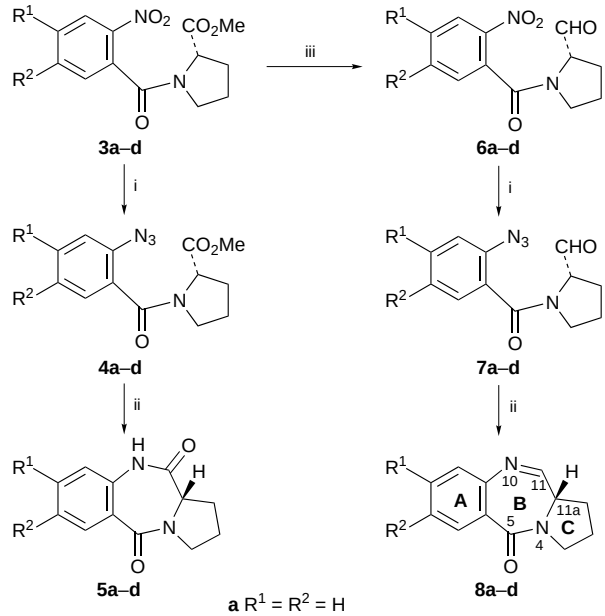
a $R^1 = R^2 = R^3 = H$
b $R^1 = R^3 = H$, $R^2 = Cl$
c $R^1 = R^3 = H$, $R^2 = F$
d $R^1 = R^3 = H$, $R^2 = Me$
e $R^1 = R^3 = H$, $R^2 = OMe$
f $R^1 = R^2 = H$, $R^3 = CO_2H$
g $R^1 = Me$, $R^2 = H$, $R^3 = OH$

Scheme 1 *Reagents and conditions*: i, baker's yeast (phosphate buffer, pH 7.2), aq. EtOH, 6–8 h

The initial studies were carried out on the preparation of PBD dilactams by the azido bioreductive cyclization process to assess the scope of this reaction. The starting materials, methyl (2*S*)-*N*-(2-nitrobenzoyl)pyrrolidine-2-carboxylate esters **3**, were prepared[8] from 2-nitrobenzoic acids *via* their acid chlorides, which were coupled with (*S*)-proline methyl ester hydrochloride. The reaction of **3** with NaN_3 in HMPA‡ gave the azido derivatives **4** which, upon reduction with baker's yeast, gave the PBD dilactams **5a**–**d** in quantitative yield (Scheme 2).

The precursor for PBD imine **8** was prepared by the reduction of **3** with DIBAL-H to give the corresponding (2*S*)-*N*-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehydes **6**. These, upon subsequent reaction with NaN_3 in HMPA followed by reduction with baker's yeast and chromatography of the crude product (silica, chloroform–methanol, 9.8 : 0.2), gave the PBD imines **8a**–**d**.§ This novel biocatalytic methodology has also been extended to the synthesis of the natural product DC-81 **8c**.

The results contained in this report demonstrate that it is not only possible to convert aryl azides to the amino arenes by employing baker's yeast, but also the usefuleness of baker's



a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = Me$
c $R^1 = OH$, $R^2 = OMe$
d $R^1 = OBn$, $R^2 = OMe$

Scheme 2 *Reagents and conditions*: i, NaN_3, HMPA, 6–8 h; ii, baker's yeast (phosphate buffer, pH 7.2), aq. EtOH, 1–2 d; iii, DIBAL-H, CH_2Cl_2, −78 °C, 45 min

yeast in the chemoenzymatic synthesis of natural and synthetic analogues of PBDs. The present approach, which is performed under extremely mild conditions, should maintain the stereochemical integrity at C(11a) and may not effect the DNA binding potential of the PBD imines, unlike other chemical methods.[10d]

Footnotes

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† *General procedure*. To a solution of 2-azidobenzoic acid **1a** (0.31 mmol) in aq. EtOH (50%, 2 cm^3) was added to a preincubated suspension of baker's yeast (2 g) in phosphate buffer solution of pH 7.2 (20 cm^3) and shaken in an orbital shaker for 6 h. The reaction was monitored by TLC (EtOAc–hexane, 1 : 1). On completion of the reaction, EtOAc (20 cm^3) was added to the reaction mixture. The organic phase was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was subjected to column chromatography (silica gel, EtOAc–hexane, 1 : 1) to afford the reduced product, 2-aminobenzoic acid **2a** in 85% yield.

‡ *General procedure*. A solution of nitro esters **3** (514 mg, 1.85 mmol) or nitro aldehydes **6** (459 mg, 1.85 mmol) and sodium azide (247 mg, 3.80 mmol) in HMPA (15 cm^3) was stirred at room temperature for 6–8 h. The reaction mixture was poured onto water and then extracted several times with diethyl ether. Evaporation of the combined diethyl ether extract gave the crude azides in 90–95%, which was further purified by column chromatography on silica gel. *Selected spectra data* for **7a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90–2.39 (m, 4 H), 3.32 (t, 2 H, *J* 7.0 Hz), 4.74 (t, 1 H, *J* 7.2 Hz), 7.50–7.98 (m, 3 H), 8.29 (d, 1 H, *J* 6.2 Hz); 9.87 (d, 1 H, *J* 4.2 Hz); *m/z* 244 (M^+, 8%).

§ *Selected spectra data* for **8a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56–2.48 (m, 4 H), 3.20–3.89 (m, 3 H), 7.10–7.59 (m, 3 H), 7.66 (d, 1 H *J* 4.2 Hz), 8.02 (d, 1 H, *J* 5.8 Hz); *m/z* 200 (M^+ 100%).

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