Bioorganic & Medicinal Chemistry Letters, Vol.1, No.3, pp. 159-160, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

ENZYMATIC REGIOSPECIFIC OXIDATIVE CONVERSION OF 5-THIO TO 5-OXO BY BAKER'S YEAST IN 5,11-DITHIOPYRROLO[1,4]BENZODIAZEPINE ANTIBIOTICS

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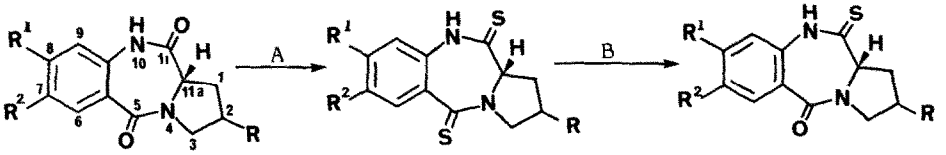
(*Received* 27 *February* 1991)

Abstract *Bio-oxidative conversion of 5-thio to 5-oxo by baker's yeast in 5,11-dithiopyrrolo[2,1-c][1,4]benzodiazepines with regiospecificity is described.*

It is well known that baker's yeast (Saccharomyces cerevisiae) reduces the carbonyl compounds regio- and stereoselectively.[1] It also reduces the aromatic nitro compounds to anilines,[2] while the reduction or oxidation of other functional groups has not been much attended. In continuation of our studies on the application of enzymes as biocatalysts in organic synthesis,[3] we herein report a regiospecific bio-oxidative conversion of (11aS)-2-acetoxy-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepine (PBD) 5,11-dithiones (2) by baker's yeast to PBD 5-one-11-thiones (3) as useful synthons in the synthesis of DNA binding PBD antibiotics.[4]

The precursors PBD-5,11-dithiones[5] (2) were obtained by the reaction of the corresponding dilactams[6] (1) with Lawesson's reagent. Compounds (2) upon incubation with baker's yeast gave PBD 5-one-11-thiones (3). This novel method of bioxidative conversion exhibited generality with various substituted PBD's having 2α or 2β acetoxy groups in 72 to 87% yields.



1a-f 2a-f 3a-f

R = OCOMe

a, $R^1 = R^2 = H$, 2α; b, $R^1 = R^2 = H$, 2β; c, $R^1 = OH$, $R^2 = OMe$, 2α;
d, $R^1 = OH$, OMe, 2β; e, $R^1 = OCH_2Ph$, $R^2 = OMe$, 2α; f, $R^1 = OCH_2Ph$, OMe, 2β

A. Lawesson's Reagent, toluene, 110°C, 3 h (83-88%)
B. Baker's yeast, EtOH, buffer (pH 11.2), 37°C, 2 days

In a typical reaction: to 2a (150 mg) dissolved in ethanol (10 ml) and 0.1 M phosphate buffer (50 ml; pH 11.2) was added baker's yeast (Sigma, Type I; 1.5 g). Incubation was carried out under aerobic condition at 37°C for 2 days with gentle shaking. The incubation mixture was extracted twice with ethyl acetate (100 ml). The extract was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The

residue was subjected to column chromatography, chloroform-methanol (96:4) to give PBD 5-one-11-thione (3a)[7] in 78% yield: m.p. 96-98°C. A control incubation using a boiled yeast preparation afforded 98% recovery of the starting compound.

During our attempts for the non-enzymatic hydrolytic desulfurization[8] of PBD 5,11-dithiones (2) the desired monothio compounds (3) or even PBD 5,11-diones (1) were not found. Whereas, in these reactions the decomposed material was isolated.

It has been observed in our earlier studies[5] that in the preparation of PBD 5-one-11-thione (a key intermediate in one of the routes for the synthesis of carbinolamine PBD antibiotics) by well established procedures[4c] usually produced 20-25% of the 5,11-dithio compounds. As such this enzymatic procedure is also of value in the selective bio-oxidative conversion of these dithio side-products to (3).

Hence, the present study demonstrates a mild and convenient method for the regiospecific bio-oxidative conversion of PBD 5,11-dithiones to PBD 5-one-11-thiones employing baker's yeast for the first time and in general has a wide potential utility in the selective bio-oxidative conversion of positionally different dithio to monothio compounds.

Acknowledgements: We thank Dr A V Rama Rao, Director for his interest and encouragement. One of us (BSPR) is grateful to CSIR, New Delhi for the award of research fellowship.

References and Notes

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7. Analytical and spectroscopic data were satisfactory. Selected data for 2a : m.p. 122-124°C; IR (KBr) 3420,1775,1590 cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$+d_6-DMSO), δ 2.09 (s,3H), 2.57 (ddd,1H,J=14.0,9.3,9.4 Hz), 3.75 (br d,1H,J=14.3 Hz with fine coupling), 4.15 (br d,1H,J=4.4 Hz), 4.36 (dd,1H,J=9.3,5.5 Hz), 4.45 (br d,1H,J=8.3 Hz), 5.35 (m,1H), 7.19-7.47 (m,3H), 8.28 (d,1H,J=8.1 Hz), 11.3 (br s,1H), ^{13}H-NMR 21.6,35.0,60.1,64.7,70.9,121.4,121.5,125.6,125.9,132.1,133.3,133.9,134.6,170.7, 192.6,199.8; MS 306 ($M^{+\cdot}$,100), 3a: IR (KBr) 3415,1770,1740,1610 cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$+d_6-DMSO), δ 2.06 (s,3H), 2.49 (ddd,1H,J=14.6,9.4,5.5 Hz), 3.65 (br d,1H,J=13.2 Hz with fine coupling), 3.84 (br d,1H,J=13.2 Hz), 4.01 (dd,1H, J=8.1,5.5 Hz), 4.29 (d,1H,J=9.4 Hz), 5.30 (m,1H), 7.12 (d,1H,J=8.1 Hz), 7.32-7.57 (m,2H), 8.07 (d,1H,J=8.1 Hz), 10.15 (br s,1H), ^{13}C NMR 21.5,35.0,52.8,60.0,71.3, 120.9,125.4,126.6,131.6,133.0,133.9,136.0,165.8,170.8,202.4; MS 290 ($M^{+\cdot}$,51).
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