BIOORGANIC SYNTHESIS OF SOME (5-BENZOTHIAZOL-2-YL –FURAN-2-YL)-METHANOLS IN CELL CATALYSIS USING SACCHAROMYCES CEREVISIAE

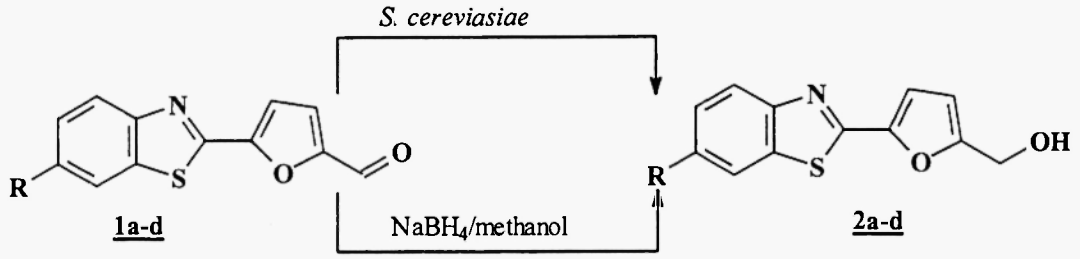
Florin-Dan Irimie*, Csaba Paizs, Cornelia Majdik, Monica Toşa,
Radu Mişca, Radu Silaghi-Dumitrescu
"Babeş-Bolyai" University, Department of Biochemistry and Biochemical Engineering,
Arany Janos 11, 3400 Cluj-Napoca, ROMANIA

Abstract: Four 6 substituted (5-benzothiazol-2-yl-furan-2-yl)-methanols were obtained from the corresponding formyl derivatives using baker's yeast as reducing agent. The structures have been confirmed by mass, infrared and ^{1}H-NMR spectrometry as well as elemental analysis.

Baker's yeast (*Saccharomyces cerevisiae*) may be an easily available "reagent" in every laboratory of organic chemistry. Its biocatalytical activity has been reported in two exhaustive reports [1,2], it's able to reduce variously substituted carbonyl groups, activated carbon-carbon double bonds and nitrocompounds. Unlike ketones, little attention has been paid to the reduction of heterocyclic aldehydes with *Saccharomyces cerevisiae*.

The use of *Saccharomyces cerevisiae* present the advantage to be cheaper than the purified oxidoreductases, which needs expensive cofactors like NADH , H^+ or NADPH , H^+. As a part of our researches in the furan series, we succeeded to obtaining four (5-benzothiazol-2yl-furan-2-yl)-methanols substituted in position 6 with -H, -CH_3 ,-OCH_3, -Br using baker's yeast as reducing agent (Scheme 1). The corresponding aldehydes were obtained by the Vilsmeier-Haack method starting from the corresponding 2-benzothiazol-2-yl-furans [3,4]. For comparison reductions were performed with sodium tetrahydroborate in methanol [4].

* To whom correspondence should be addressed: irimie@chem.ubbcluj.ro



a: R=H ; b: R=CH_3 ; c: R=OCH_3 ; d: R=Br

Scheme 1. Synthesis of (5-benzothiazol-2-yl-furan-2-yl)-methanols **2a-d** by bioreduction in cell catalysis mediated by *Saccharomyces cerevisiae*

Experimental

Reagents and solvents were products of Aldrich or Fluka. The ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 spectrometer operating at 300 MHz. Chemical shifts are expressed in ppm values from TMS as internal standard and $CDCl_3$ as solvent. IR spectra were recorded in KBr pellets with a FT-IR Nicolet 205 spectrophotometer. Mass spectra were taken on a VARIAN MAT 311 spectrometer with double focusing, using an electronic impact source at 70 eV and 300 μA. Preparative chromatographic separations were performed using vacuum chromatography [5] on Merck Kieselgel 60 (0.063-0.200 μm). Melting points were determined by hot plate method and are uncorrected. All solvents were purified and dried by standard methods as required. Asymmetric nitrocellulose membrane with 0.33 μm media pore diameter was produced in accord with Loeb-Sourirjean method [6].

General procedure for reduction

a) Biocatalytic reduction:

To a stirred (250 rpm) suspension of 80 g fresh baker's yeast in 500 ml water, 5 g glucose was added. After 30 min. stirring a solution of aldehyde (**1a-d**, 2 mmol) in hot ethanol (20 mL) was added dropwise at room temperature and the resulting mixture was stirred further at room temperature for 24 hours. After the reaction completed 200 mL benzene-ethylacetate (1:1, v:v) was added for extraction and the stirring was continued for five minutes. After extraction asymmetric nitrocellulose membrane was used to remove baker's yeast cells. The organic layer was dried over anhydrous magnesium sulfate, concentrated in vacuum and the residue was recrystallized from ethanol:carbontetrachloride (1:1, v:v) in presence of active carbon.

b) Chemical reduction:

To a stirred solution of the formyl derivative (**1a-d**, 1 mmol) in dry methanol (5 mL) $NaBH_4$ (1 mmol) was added in portions at room temperature and the resulting mixture was stirred further at room temperature for the

time given in Table 1. After the reduction was completed, the mixture was quenched by dropwise addition of 2N HCl solution (1 mL) and evaporated to a final volume of about 1 mL. To this residue water (3 mL) and dichloromethane (6 mL) was added. After separating the two layers, the aqueous layer was extracted with dichloromethane (6 mL). The organic layer was dried over anhydrous magnesium sulfate, concentrated in vacuum and the residue was recrystallized from ethanol:carbontetrachloride (1:1, v:v) in presence of active carbon.

The spectroscopic data of the products **2 a-d** showed identical values with those obtained by baker's yeast mediated reduction.

(5-benzothiazol-2-yl-furan-2-yl)-methanol (2 a)

Anal. calc. for $C_{12}H_9NO_2S$: 62.32%C, 3.92%H, 6.06%N, 13.86%S; *Found*: 62.13%C, 3.89%H, 6.11%N, 14.88%S; *IR* : 1050, 3200 (OH); *MS*: m/z (rel.intensity, %): 231 (100 M^+), 232 (11) M^++1, 233 (6) M^++2, 230 (8) M^+-1, 214 (56) M^+-17, 202 (53), 168 (32); *^{1}H-NMR*: 4.72 (2H, s), 6.69 (1H, d), 7.50 (1H, d), 7.9-8.1 (4H,

(5-(6-methyl-benzothiazol-2-yl)-furan-2-yl)-methanol (2 b)

Anal. calc. for $C_{13}H_{11}NO_2S$: 63.65%C, 4.52%H, 5.71%N, 13.07%S; Found: 63.59%C, 4.51%H, 5.74%N, 13.08%S; *IR*: 1050, 3220 (OH); *MS*: m/Z (rel.intensity, %): 245 (100)M^+, 246 (10) M^++1, 247 (8)M^++2, 244 (9)M^+-1, 228 (54)M^+-17, 216 (32), 200 (19); *^{1}H-NMR*: 2.69 (3H, s), 4.73 (2H, s), 6.60 (1H, d), 7.18 (1H, d), 7.49 (1H, d), 7.80 (1H, s), 8.03 (1H, d).

(5-(6-methoxy-benzothiazol-2-yl)-furan-2-yl)-methanol (2 c)

Anal. calc. for $C_{13}H_{11}NO_3S$: 59.76%C, 4.24%H, 5.36%N, 12.27%S; *Found* : 59.69%C, 4.28%H, 5.41%N, 12.25%S; *IR* : 1050, 3200 (OH); *MS*: m/z (rel.intensity, %): 261 (100) M^+, 262 (26) M^++1, 263 (11) M^++2, 260 (11) M^+-1, 246 (20), 245 (9), 244 (46) M^+-17, 232 (15); *^{1}H-NMR*: 3.86 (3H, s), 4.73 (2H, s), 6.67 (1H, d), 7.18 (1H, d), 7.50 (1H, d), 7.80 (1H, s), 7.99 (1H, d).

(5-(6-bromo-benzothiazol-2-yl)-furan-2-yl)-methanol (2 d)

Anal. calc. for $C_{12}H_8BrNO_2S$: 46.61%C, 2.61%H, 25.50%Br, 4.53%N, 10.35%S; *Found*: 46.60%C, 2.63%H, 25.47%Br, 4.56%N, 10.33%S; *IR*: 1050, 3250 (OH); *MS*: m/z (rel.intensity, %): 311(100) M^+, 309(20)M^+, 313(4) M^++2, 308(93)M^+-1, 294(23)M^+-17, 293(8)M^+-17, 292(30), 214(17), 212(16), 185(10), 184(2); *^{1}H-NMR*: 4.75 (2H, s), 6.73 (1H, d), 7.52 (1H,d), 7.9-8.2 (3H, m).

Results and discussion

Biocatalytic reduction of the aldehyde group in the series of 2-benzothiazol-2-yl-furan is a convenient method for the preparation of the corresponding alcohols.

Table 1. Yields and melting points for (5-benzothiazol-2-yl-furan-2-yl)-methanol **2a-d**

Compound	Time [h]		Yield [%]		M.p. [°C]
	Method A	Method B	Method A	Method B	obt.
2a	24	1	89	78	178
2b	18	1.5	82	68	211
2c	24	1.5	79	76	181
2d	24	1	82	78	184

The (5-benzothiazol-2-yl-furan-2-yl)-methanols **2a-d** were obtained by two alternative methods. The baker's yeast catalyzed reaction proved to be superior over the $NaBH_4$ reduction and yielded the products **2a-d** almost quantitatively. Surprisingly, the $NaBH_4$ reduction proved to be always accompanied by formation of several unidentified by-products. This method resulted the desired alcohols after purification by preparative chromatography in moderate yields. In case of biocatalytic reduction, secondary products were not appeared, the substrates **1a-d** were totally transformed. The reaction mass was simply worked up, the purification of products **2a-d** was simple.

The IR, MS and ^{1}H-NMR spectra as well as the elemental analysis of the isolated products from the biological reductions confirmed the structures of compounds **2 a-d**. The absence of the bands at 1670 - 1680 cm^{-1} (which are present in the IR spectra of the aldehydes) and the presence of the bands at 1050 cm^{-1} and 3200-3250 cm^{-1} confirmed the presence of a primary hydroxyl group in the structures of compounds **2a-d** . Molecular peaks for **2 a-d** are clear with a relative abundance of 100%. The characteristic peaks for fragmentations of the benzylic type alcohol group (M-17) were observed [7].

For the structures **2 a-d** the presence of the singlet at δ = 4.6 - 4.8 corresponding to two protons indicated the existence of the methylenic group, while signals of the aldehyde protons in compounds **2 a-d**, are not observed.

Conclusion

The biocatalytic reduction of 5-benzothiazol-2-yl-furan-2-carbaldehydes **1a-d** is an alternative and new synthetic procedure. The main advantages are the mild conditions, good yields and the simplicity of the method.

References

1. Csuk, R., Glantzer, B.I. *Chem.Rev.* **1991**, ***91***, 49
2. Santiniello, E., Ferraboschi, P., Grisente, P., Manzocchi, A. *Chem.Rev.* **1992**, ***92***, 1071
3. Fărcăşan, V., Paiu, F., Iuşan, C. *Studia Univ.Babeş-Bolyai, Ser.Chem.* **1977**, *1*, 15
4. Irimie, F.D., Paizs, Cs., Toşa, M.,Silaghi-Dumitrescu, R., Majdik, C. *Studia Univ.Babeş-Bolyai, Ser.Chem.* **1998**, *43*, 109
5. Poppe, L.; Novák, L. *Magy. Kem. Lapja*, **1985**, *40*, 366.
6. Schwarzer, Ph., *Handbook of Separations, Techniques for Chemical Engineers* **1988**, 2-20, 2^{end} Ed., McGraw Hill Book Co., New-York, St. Louis, San Francisco
7. Irimie, F.D., Paizs, Cs., Miclăuş, V., Toşa, M., Afloroaiei, C., Damian, G. *Balkan Phys. Lett.* **1998**, *5*, 273

Received on March 11, 2002