STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, XLV, 1-2, 2000

BIOORGANIC REDUCTION OF SOME 5-PHENYL-FURAN-2-CARBALDEHYDES MEDIATED BY BAKERS' YEAST

F. D. IRIMIE[1], CS. PAIZS, MONICA TOŞA[1], CORNELIA MAJDIK[1], PAULA MOLDOVAN[1], R. MIŞCA[1], MIHAELA CĂPRIOARĂ[1], MĂDĂLINA NEACŞU[2]

[1]Department of Biochemistry and Biochemical Engineering, "Babeş-Bolyai" University of Cluj-Napoca, ROMANIA
[2]"Bios" Center of development and production", Cluj-Napoca, ROMANIA

ABSTRACT. Eight 5-phenyl-furyl-2-carbaldehydes variously substituted with halogenes atoms at the phenyl rings, were reduced to the corresponding alcohols with Bakers' Yeast (under mild conditions), with good yields.

INTRODUCTION

Bakers' yeast (*Saccharomyces cerevisiae*) may be an easly available "reagent" in every laboratory of organic chemistry. It's biocatalytical activity has been reported in two exhaustive reports [1,2].

Bakers' yeast is 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*.

Bakers' yeast mediated reduction of some 5-phenyl-furan-2-carbaldehydes was already reported. In case of unsubstituted, 5-(4-methyl-phenyl)-furan-2-carbaldehyde and 5-(4-methoxy-phenyl)-furan-2-carbaldehyde, a large amounts of yeast was used (yeast/substrate = 50/5 (g/mmol)) and reactions were completed in six hours [3]. When 5-(2-,3- or 4-carbetoxy-phenyl)furan-2-carbaldehyde was used as substrate, bioreduction undergoes in same conditions with those presented previously, however it must be mentioned the chemioselectivity of the process, reduction undergoes without the enzymatic hydrolysis of the esteric function [4].

For investigate how the nature of substituents at the phenylic ring influence the bioreduction process, in this paper we presented the synthesis and Bakers' yeast mediated reduction of eight 5-aryl-furan-2-carbaldehydes substituted with halogen atoms.

The general procedure of synthesis and reduction of these furancarbaldehydes were presented in scheme 1.

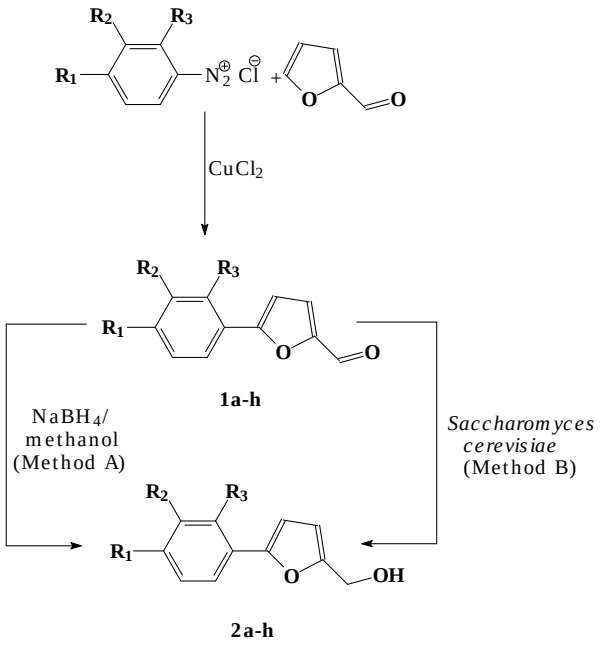
EXPERIMENTAL

The 5-phenyl-furan-2-carbaldehydes **1a-h** were prepared from the diazonium salts of the halogeneanilines and furan-2-carbaldehyde [5]. The known 5-phenyl-furan-2-carbaldehydes **1a-g** had identical physical and spectral data as described previously (Table 1).

Reagent and solvents were standard grade commercial products and used without further purification.

The elemental analysis for C, H and halogen were within ± 0,4% of the theoretical values for **1g** and **2a-h**. The reagents were products of Aldrich.

The *^{1}H-NMR* spectra were recorded on a Varian Gemini 300 spectrometer operating at 300 MHz. All spectra were taken in $CDCl_3$ solution and chemical shifts are expressed in ppm values from TMS as internal standard on δ scale. *IR* spectra were obtained in KBr pellets on a Nicolet FT 205 spectrometer and are reported in wavenumbers (cm^{-1}). The mass spectra were recorded on double focusing Varian Mat 311 spectrometer, with an electronic impact source at 70 eV and 300 mA.



Scheme 1. Synthesis and reduction of 5-aryl-furan-2-carbaldehydes **1a-h** to the corresponding alcohols **2a-h**

Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} alumina sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates.

Assymetric nitrocellulose membrane with 0.33 μm media pore diameter was produced in accord with Loeb-Sourirjean method [6].

Preparative chromatografic separations were performed using vacuumchromatography on Merck Kieselgel 60 (0.063-0.200 nm). Melting points are uncorrected. All solvents were purified and dried by standard methods as required.

General procedure for synthesis of aldehydes 1a-h

To a solution of corresponding diazonium salt (0.1 mol) in water furan-2-carbaldehyde (0.1 mol) and $CuCl_2$ solution (6 g in 40 ml water) was added. The mixture was heated at 40^0C, six hours. The organic layer was extracted with chloroform and dryed on anhydrous magnezium sulphate. The chloroform was evaporated and the crude product was distiled *in vaquo*. Yields and melting points were given in Table 1.

General procedure for reduction of carbaldehyde 1a-h with $NaBH_4$ (Method A)

$NaBH_4$ (0.1 g) was added in isopropanol (7 ml). The mixture was stirred for 1.5 hours, while adding the substrate **1a-h** (0.2 g) in small amounts. The solution was allowed to stand over night, than diluted HCl (5%) was added until no more gas evolution was observed. The organic compounds were extracted with $CHCl_3$ (five times), than the solvent was removed *in vacuo* affording the hydroxy-derivatives, which were purified by column chromaatography and finally recrystalised from ethanol:acetone (1:1, v:v). Yields and melting points were given in Table 2.

General procedure for bioreduction of carbaldehyde 1a-h (Method B)

Substrates **1a-h** (5 mmol) were dissolved in ethanol (5 ml) and added at room temperature into a suspension of fresh bakers' yeast (5 g) in water (50 ml) with glucose (5 g). After time indicated in Table 2 the products were extracted from suspension with benzene-ethylacetate (1:1, v:v) (100 ml). After extraction assymetric nitrocellulose membrane was used to removed Bakers' yeast cells. Further work up was carried out as described in Method A.

RESULTS AND DISCUSSION

Table 1. Synthesis of 5-aryl-furan-2-carbaldehydes **1a-g**

1	R_1	R_2	R_3	Yield (lit.) [%]	m.p. (lit.) [°C]
a	F	H	H	53 (48)	69 (73-74[7])
b	Cl	H	H	62 (61)	128-129 (128-129[8])
c	Br	H	H	65 (66)	153 (154[9])
d	I	H	H	64 (66)	144 (145-146[10])
e	H	Br	H	70 (67)	107(107[10])
f	H	H	Cl	55 (56)	77 (76.5-77.5[11])
g	H	H	Br	60 (56)	57 (57-58[10])

h	H	H	I	43	64

Table 2. Reduction of 5-aryl-furan-2-carbaldehydes **1a-g**

2	**Yield** [%]		**Time** [h]	**b.p. / p m.p. (lit.) [°C]**
	Method A (lit.)	**Method B**		
a	90 (80)	70	4	41 (41[7])
b	85 (80)	80	5	81-82 (82-83[8])
c	85 (80)	85	5	96-97 (97[7])
d	75	75	6	99
e	75 (70)	75	5	81 (81[13])
f	84 (70)	64	5	63 (64-5[13])
g	82	72	5	65
h	88	68	5	71

5-(2-iodophenyl)-furan-2-carbaldehyde (**1h)**

IR: 1675(CHO); *^{1}H-RMN*: 6.87 (d,1H), 7.34 (d,1H), 7.55-7.93 (m,4H), 9.65 (s,1H); *MS*: 298(100)M, 270(13), 241(32), 171(2)

(5-(4-fluorophenyl)-furan-2-yl)methanol 2a

IR: 1060, 3180 (l.b)(-CH_2-OH); *^{1}H-NMR*: 2.63 (OH), 4.69 (s,2H), 6.20 (d, 1H), 6.55 (d,1H), 7.55(d,2H), 7.96 (d,2H); *MS*: 192(100)M,193(10)M+1, 190(11)M-2, 175(95)M-17, 163(17), 146(34), 133(56)

(5-(4-chlorophenyl)-furan-2-yl)methanol 2b

IR: 1050, 3200 (l.b)(-CH_2-OH); *^{1}H-NMR*: 2.43 (OH), 4.65 (s,2H), 6.21 (d, 1H), 6.50 (d,1H), 7.39(d,2H), 7.55 (d,2H); *MS*: 208(100)M, 210(33)M, 191(80)M-17, 193(26)M-17, 178(3), 180(1), 149(37), 139(42)

(5-(4-bromoophenyl)-furan-2-yl)methanol 2c

IR: 1040, 3190 (l.b)(-CH_2-OH); *^{1}H-NMR*: 2.58 (OH), 4.67 (s,2H), 6.39 (d, 1H), 6.61 (d,1H), 7.18 (d,2H), 7.51 (d,2H); *MS*: 252, 254(100)M, 253, 255(11)M+1, 250, 252(11)M-2, 235, 237(71)M-17, 224, 226(10), 193, 195(40)

(5-(4-iodophenyl)-furan-2-yl)methanol 2d

IR: 1080, 3300 (l.b)(-CH_2-OH); *^{1}H-NMR*: 2.54 (OH), 4.51 (d,1H), 6.20 (d, 1H), 6.43 (d,1H), 7.18 (d,2H), 7.41 (d,2H); *MS*: 300(100)M, 301(9)M+1, 298(70)M-2, 283(90)M-17, 270(13), 241(32)

(5-(3-bromophenyl)-furan-2-yl)methanol 2e

IR: 1060, 3250 (l.b)(-CH_2-OH); *^{1}H-NMR*: 2.61 (OH), 4.68 (s,2H), 6.40 (d. 1H), 6.63 (d,1H),7.31-7.70 (m,3H), 7.82 (s,1H); *MS*: 252, 254(100)M, 253, 255(11)M+1, 250, 252(11)M-2, 235, 237(71)M-17, 224, 226(10), 193, 195(40)

(5-(2-chlorophenyl)-furan-2-yl)methanol 2f
IR: 1050, 3310 (l.b) (-CH_2-OH); ^{1}*H-NMR*: 2.58 (OH), 4.61 (s,2H), 6.29 (d,1H), 6.52 (d,1H), 7.30-7.87 (m,4H,); *MS*: 208(100)M, 210(33)M, 191(80)M-17, 193(26)M-17, 178(3), 180(1), 149(37), 139(42)

(5-(2-bromophenyl)-furan-2-yl)methanol 2g
IR: 1060, 3190 (l.b) (-CH_2-OH); ^{1}*H-NMR*: 2.61 (OH), 4.60 (s,2H), 6.30 (d,1H), 6.50 (d,1H), 7.30-7.80 (m,4H); *MS*: 252, 254(100)M, 253, 255(11)M+1, 250, 252(11)M-2, 235, 237(71)M-17, 224, 226(10), 193, 195(40)

(5-(2-iodophenyl)-furan-2-yl)methanol 2h
IR: 1050, 3200 (l.b)(-CH_2-OH); ^{1}*H-NMR:* 2.59 (OH), 4.60 (s,2H), 6.49 (d,1H), 6.70 (d,1H), 7.3-7.6 (m,4H); *MS*: 300(100)M, 301(9)M+1, 298(70)M-2, 283(90)M-17, 270(13), 241(32)

The elemental analysis and the spectral data of **2a-h** showed identical values with those obtained through reduction with sodium borohydride.

The *IR, MS* and ^{1}*H-NMR* spectra and the elemental analysis of the isolated products confirmed the structures of compounds **2 a-h**. In *IR* spectra the presence of bands at 1040-90 cm^{-1} and at the 3180-3350 cm^{-1} and the absence of bands at 1670-1680 cm^{-1} (which are observed in the *IR* spectra of aldehydes **1a-h**), confirmed the presence of an primary benzylic type alcohol, in the structures of compounds **2 a-h**.

Molecular peaks for **2 a-h** are clear, the characteristic fragment for benzylic type alcohols (M-17) were observed.

In case of **2 a-h**, the presence of the singlet at δ=4,6-4,8 corresponding for two protons, indicated the transformation of the aldehydic group.

The sufficient amount of yeast was ten times lower (yeast/substrate) =5/5 g/mmol) in comparison with those used in cases described in introductive section, moreover reaction times were comparable. These facts could be explained with the withdrawing character of halogen atom reducing electron density at the carbonyl group, which facilitate the hydride transfer from oxidoreductases cofactors (NADH, H^+, $FADH_2$), however reaction time probably was influenced by diffusion process too.

In case of biocatalytic reduction, secondary products were not appeared, the substrates were totally transformed. The reaction mass was simply worked up, the purification of products was simple.

CONCLUSION

Biocatalytical reduction of halogenated 5-phenyl-furyl-2-carbaldehydes is an alternative and a new synthetic procedure. The main advantages are the mild conditions, good yields and the symplicity of the method.

REFERENCES

1. C s u k, R., G l a n t z e r, B.I. *Chem.Rev*. 1991, ***91***, 49, (1991).
2. S a n t i n l e l l o, E., F e r r a b o s c h i, P., G r i s e n t e, P., M a n z o c c h i, A. *Chem.Rev*., 1992, ***92*****,** 1071.
3. I r i m i e, F.D., P a i z s, C s., S i l a g h i –D u m i t r e s c u, R., T o ş a, M., M a j d i k, C.
1. *Roum. Biotechnol. Lett.* 1999, ***4****(1),* 71.
4. I r i m i e, F.D., P a i z s, C s., S i l a g h i –D u m i t r e s c u, R., T o ş a, M., M a j d i k, C. *Progrss in catalysis* 1999**,** ***8***, 70.
5. R y o h e i, O. *Mem.Fac. Eng.Kyoto.Univ*. 1952**,** ***14***, 195; *Chem. Abstr.* ***48***, 1935f.
6. L i t e a n u, C., R ă d u l e s c u, G h. *Bazele membranologiei*, Bucureşti, 1983.
7. O l e i n i k, T. *Pharm. Chem. J. (Engl. Transl.)* 1971**,** ***5****(7)*, 401.
8. A k a s h i, O d a, *Kogyo Kagaku Zasshi* 1950, ***53***, 81; *Chem. Abstr.* 1953, 2164.
9. C h a d w i c h, R., J h o n s o n, T. *J. Chem. Soc. Perkin Trans.1* 1973, 2327.
10. O b u s h a k, N., G a n u s h c h a k, N. I., Z a v a l i i, P.Y u *J. Org. Chem. Engl. Transl.* 1986, ***22****(11)*, 2093.
11. K r u t s i k o v a, N. *Chem. Zvesti* 1971, ***25***, 142.
12. F r i m m , *Chem. Zvesti* 1972, ***26***, 55114.
13. S c h w a r z e r P h., *Handbook of Separations, Technoques for Chemical Engineers* 1988, 2-20, 2end Ed., McGraw Hill Book Co., New-York, St. Louis, San Francisco.