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Microwave-assisted reactions of substituted furo[3,2-*b*]pyrrole-5-carboxhydrazides and their biological activity

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Abstract: The microwave-assisted reactions of substituted furo[3,2-*b*]pyrrole-5-carboxhydrazides **1** with 5-substituted furan-2-carboxaldehydes **2**, thiophene-2-carboxaldehyde **3** and 2-formyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate **4** have been studied under microwave irradiation. Reactions of **1** with 4-substituted 1,3-oxazol-5(4*H*)-ones **8** led to imidazole derivatives **9.** The effects of hydrazones **5-7** on inhibition of photosynthetic electron transport in spinach chloroplasts were investigated.

Keywords: furo[3,2-*b*]pyrrole-5-carboxhydrazide, furan-2-carboxaldehyde, thiophene-2-carboxaldehyde, 2-formyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate, microwave irradiation

Introduction

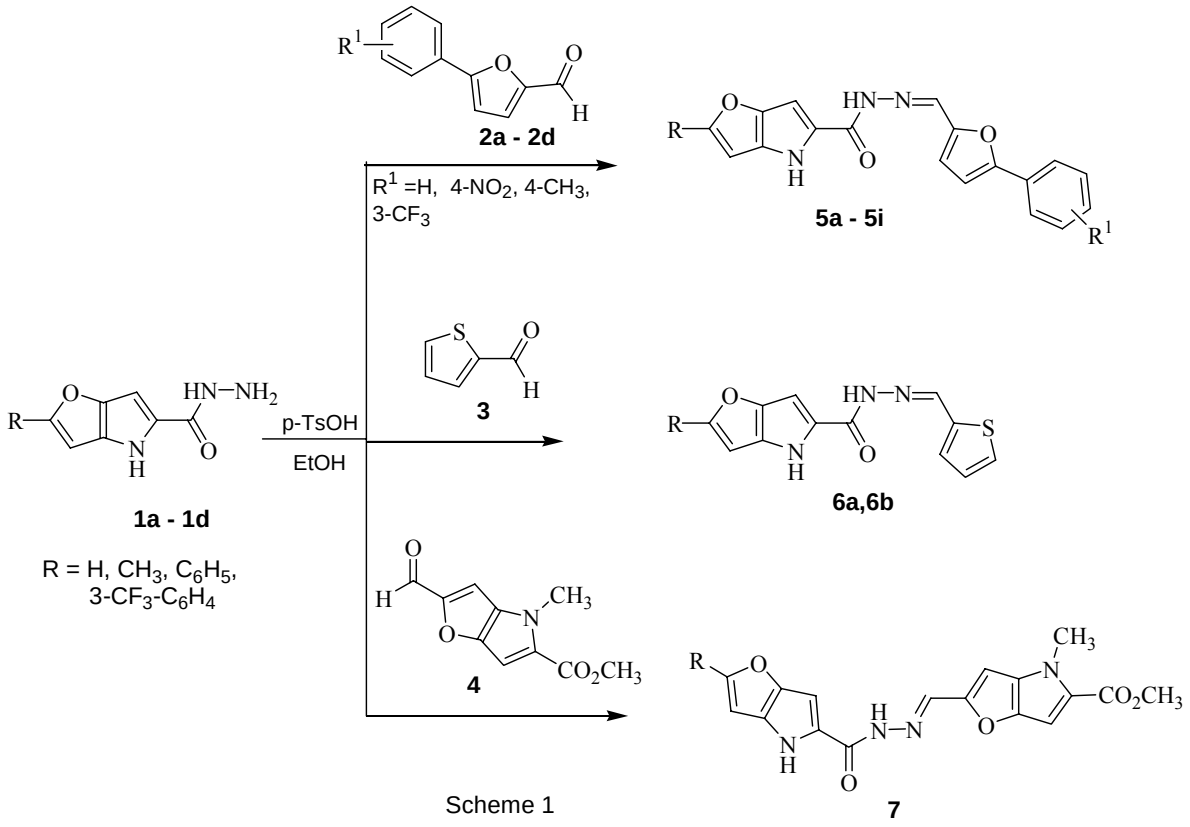
Carboxhydrazides and their derivatives have been described as useful building blocks for various heterocyclic rings [1-4]. A large number of carboxhydrazides exhibit wide variety of biological activities, e.g. antimicrobial [5,6], antifungal [7], antimycobacterial [8], analgesic and anti-inflammatory [9]. 5-Substituted furan-2-carboxaldehydes and some of their derivatives show antibacterial [10] or antiviral [11] activities.

The aim of this study was to synthesize some new hydrazones **5-7** derived from furo[3,2-*b*]pyrrole-5-carboxhydrazides **1** by their reactions with substituted furan-2-carboxaldehydes **2,** thiophene-2-carboxaldehyde **3,** or methyl 2-formyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate **4** and investigate some reactions of furo[3,2-*b*]pyrrole-5-carboxhydrazides **1** 1,3-oxazol-5(4*H*)-ones **8** as a convenient way to the new heterocycles **9.** The use of microwave technology has had

a remarkable influence on rate enhancement of reactions as well as in increasing the purity and yields of products.

Results and discussion

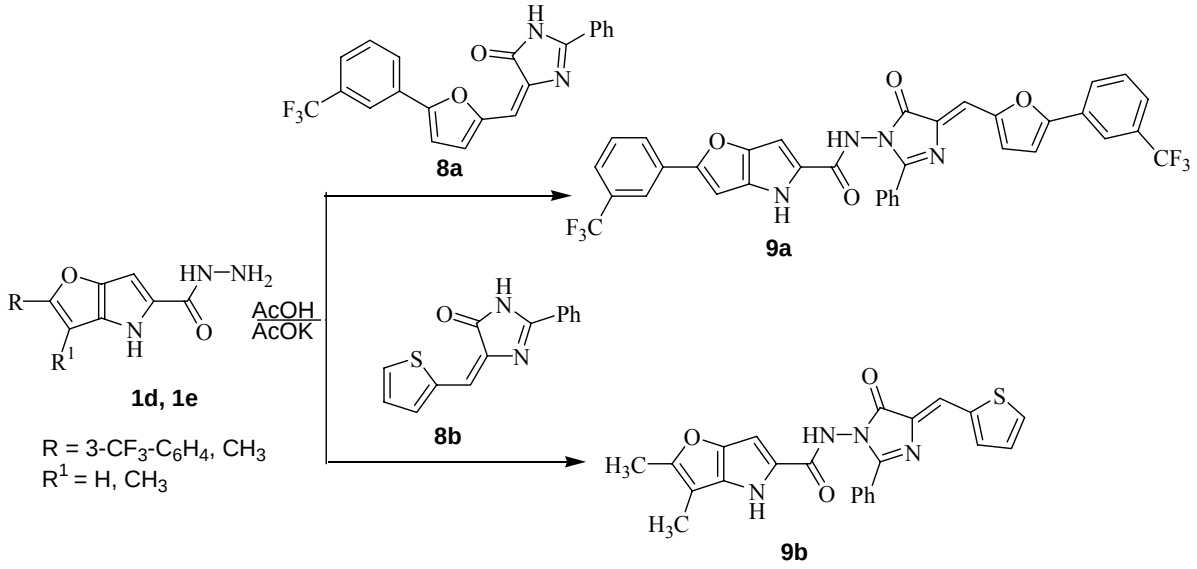
N′-[5-(R[1]-Phenyl)furan-2-yl)methylene]-2-R-4-*H*-furo[3,2-*b*]pyrrole-5-carboxhydrazides **5a – 5i** *N*′-[(thiophen-2-yl)methylene]-2-R-4-*H*-furo[3,2-*b*]pyrrole-5-carboxhydrazides **6a, 6b** and *N*′-{[(5-methoxycarbonyl-4-methyl)furo[3,2-*b*]pyrrol-2-yl]methylidene}-2-(3-trifluoromethylphenyl)-4-*H*-furo[3,2-*b*]pyrrole-5-carbohydrazide **7** were synthesized in 40 – 87 % yields by microwave-assisted reaction of **1** with **2 - 4** in ethanol in the presence of *p*-toluenesulfonic acid using a power output of 90 W over the period given in Table 1.



Scheme 1

The [1]H NMR spectra of compounds **5a – 7** displayed signals of H-6 pyrrole protons in the 6.99 – 7.31 ppm range and signals due to CH=N bonded protons in 8.12 – 8.60 ppm range. The chemical shifts and the multiplicity confirmed the proposed structures (Table 2). We also investigated the reaction of 5-substituted furan or thiophene derived 1,3-oxazol-5(4*H*)-ones, **8a, 8b** with substituted furo[3,2-b]pyrrole-5-carboxhydrazides **1d**, **1e**. When 2-phenyl-4-[(5-(3-trifluormethylphenyl)furan-2-yl)methylene]-1,3-oxazol-5(4*H*)-one **8a,** or 2-phenyl-4-[(thiophen-

2-yl)methylene]-1,3-oxazol-5(4*H*)-one **8b** were treated with furo[3,2-*b*]pyrrole-5-carboxhydrazides **1d**, **1e** in acetic acid in the presence of a catalytic amount of fused potassium acetate under microwave irradiation for 8 - 11 min, imidazoles **9a** or **9b** were obtained in 73 and 76 % yields, respectively. (Scheme 2).



Scheme 2

^{1}H NMR spectra of compounds **9a**, **9b** displayed the signals of H-6 pyrrole protons at 6.92 and 6.95 ppm while the signal of CH=C bonded protons at 7.10 and 7.72 ppm, respectively. The presence of two signals of NH protons in 11.10 - 11.89 ppm range gives evidence of the 1,3-imidazole ring formation.

Experimental Part

All experiments were performed inWhirpool M401 type microwave oven. The apparatus was adapted for laboratory applications – n-hexane was used as coolant for the condenser. ^{1}H NMR spectra were obtained on a 300 MHz spectrometer VARIAN GEMINI 200 in DMSO-d_6 with tetramethylsilane as an internal standard. Melting points of products were determined on a Kofler hot plate apparatus and are uncorrected. All solvents were predistilled and dried appropriately prior to use. The course of reactions was monitored by TLC chromatography in ethyl acetate – n−hexane. The protocols in [12] and [13] were followed for the synthesis of furo[3,2-*b*]pyrrole-5-carboxhydrazides and 5-arylfuran-2-carboxaldehydes, respectively.

Table 1 Characteristic data of compounds **5-9**

Compound	R R^1	Formula Mw	Mp (°C)	Yield (%)	React. time (min.)
5a	H 4-NO_2	$C_{18}H_{12}N_4O_5$ 364.3	279-282	73	3
5b	H 3-CF_3	$C_{19}H_{12}F_3N_3O_3$ 387.3	188-191	55	5
5c	H 4-CH_3	$C_{19}H_{15}N_3O_3$ 333.1	208-210	65	4.5
5d	CH_3 3-CF_3	$C_{20}H_{14}F_3N_3O_3$ 401.3	207-210	55	5
5e	C_6H_5 3-CF_3	$C_{25}H_{16}F_3N_3O_3$ 463.4	236-240	40	10
5f	C_6H_5 4-CH_3	$C_{25}H_{19}N_3O_3$ 409.4	290-292	65	10
5g	3-CF_3-C_6H_4 4-NO_2	$C_{25}H_{15}F_3N_4O_5$ 508.3	245-248	51	0.5
5h	3-CF_3-C_6H_4 4-CH_3	$C_{26}H_{18}F_3N_3O_3$ 477.4	256-258	69	1
5i	3-CF_3-C_6H_4 3-CF_3	$C_{26}H_{15}F_6N_3O_3$ 531.1	243-244	52	1
6a	H -	$C_{12}H_9N_3O_2S$ 259.3	235-238	67	5
6b	3-CF_3-C_6H_4 -	$C_{19}H_{12}F_3N_3O_2S$ 403.4	241-243	87	2
7	3-CF_3-C_6H_4 -	$C_{25}H_{19}F_3N_4O_6$ 528.4	236-238	63	2
9a	-	$C_{35}H_{20}F_6N_4O_4$ 674.5	172-175	76	8
9b	-	$C_{23}H_{18}N_4O_3S$ 430.5	325-328	73	11

General procedure

Synthesis of 5a-7

A mixture of 2-R-furo[3,2-*b*]pyrrole-5-carboxhydrazides **1a – 1d** (1.21 mmol), 5-R[1]-phenylfuran-2-carboxaldehydes **2** (or thiophene-2-carboxaldehyde **3,** 2-formyl-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate **4**) (1.21 mmol) and catalytic amount of *p*-toluenesulfonic acid in ethanol (5 ml) was irradiated in microwave oven at 90 W over a time period as stated in Table 1. After cooling, the solid products were filtered off, dried and crystallized from ethanol.

Synthesis of 9a, 9b

A mixture of 2-(trifluormethylphenyl)furo[3,2-*b*]pyrrole-5-carboxhydrazide **1d** (or 2,3-dimethylfuro[3,2-*b*]pyrrole-5-carboxhydrazide **1e**) (1.4 mmol), 2-phenyl-4-[(5-(trifluormethyl-phenyl)furan-2-yl)methylene]-1,3-oxazol-5(4*H*)-one **8a** (or 2-phenyl-4-[(thiophen-2-yl) methylene]-1,3-oxazol-5(4*H*)-one **8b**) (1.5 mmol) and catalytic amount of potassium acetate in conc. acetic acid (10 ml) was irradiated in microwave oven for 8-11 min (see Table 1). After cooling the solid products **9a, 9b** were filtered off and crystallized from ethanol.

Table 2. ^{1}H NMR spectra (DMSO-d_6)

5a	11.59 (s, 2H, NH); 8.31 (s, 1H, CH); 7.76-7.85 (m, 4H, H_{arom}); 7.58, 7.54 (d, 1H, *J* = 12 Hz, H-3'); 7.55, 7.51 (d, 1H, *J* = 12 Hz, H-4'); 7.21, 7.23 (d, 1H, *J* = 6 Hz, H-2); 7.11 (s, 1H, H-6); 6.59, 6.57 (d, 1H, *J* = 6 Hz, H-3).
5b	11.60 (s, 2H, NH); 8.37 (s, 1H, CH); 7.95-7.78 (m, 4H, H_{arom}); 7.63, 7.61 (d, 1H, *J* = 12 Hz, H-3'); 7.59, 7. 55 (d, 1H, *J* = 12 Hz, H-4'); 7.28, 7.26 (d, 1H, *J* = 6 Hz, H-2); 7.11 (s, 1H, H-6); 6.71, 6.68 (d, 1H, *J* = 6 Hz, H-3).
5c	11.49 (s, 2H, NH); 8.28 (s, 1H, CH); 7.77, 7.75 (d, 1H, *J* = 3.9 Hz, H-2); 7.71-7.30 (m, 4H, H_{arom}); 7.08, 7.06 (d, 1H, *J* = 3.6 Hz, H-4'); 7.02, 7.01 (d, 1H, *J* = 3.6 Hz, H-3'); 6.99 (s, 1H, H-6); 6.61, 6.59 (d, 1H, *J*= 3.9 Hz, H-3); 2.36 (s, 3H, CH_3).
5d	11.51 (s, 1H, NH); 11.39 (s, 1H, NH); 8.27 (s, 1H, CH); 8.09-7.71 (m, 4H, H_{arom}); 7.39, 7.38 (d, 1H, *J* = 3.6 Hz, H-4'); 7.08, 7.07 (d, 1H, *J* = 3.6 Hz, H-3'); 6.99 (s, 1H, H-6); 6.26 (s, 1H, H-3); 2.39 (s, 3H, CH_3).
5e	11.69 (s, 1H, NH); 11.62 (s, 1H, NH); 8.12 (s, 1H, CH); 7.84 –7.72 (m, 5H, H-4', H_{arom}); 7.47-7.28 (m, 6H, H-3', H_{arom}); 7.16 (s, 1H, H-6); 7.11, 7.10 (d, 1H, *J* = 3.6 Hz, H-3).
5f	11.69 (s, 1H, NH); 11.55 (s, 1H, NH); 8.29 (s, 1H, CH); 7.84 – 7.73 (m, 4H, H_{arom}); 7.47-7.29 (m, 6H, H-4', H_{arom}); 7.16 (s, 1H, H-6); 7.08, 7.07 (d, 1H, *J* = 3.3 Hz, H-3'); 7.04 (s, 1H, H-3); 2.35 (s, 3H, CH_3).
5g	11.82 (s, 1H, NH); 11.71 (s, 1H, NH); 8.37-8.32 (m, 3H, CH, H_{arom}); 8.15-8.12 (m, 2H, H-arom.); 8.07, 8.04 (d, 2H, *J* = 9 Hz, H_{arom}); 7.73-7.59 (m, 3H, H-6, H_{arom}); 7.51, 7.49 (d, 1H, *J* = 3,6 Hz, H-4'); 7.44 (s, 1H, H-3); 7.17, 7.16 (d, 1H, *J* = 3,3 Hz, H-3').

5h	11.77 (s, 1H, NH); 11.58 (s, 1H, NH); 8.31 (s, 1H, CH); 8.13- 8.12 (m, 2H, H_{arom}); 7.78-7.64 (m, 5H, H-6, H_{arom}); 7.43 (s, 1H, H-3); 7,32, 7,29 (d, 2H, *J* = 8,1 Hz, H_{arom}); 7.09, 7.08 (d, 1H, *J* = 3,6 Hz, H-4‘); 7.04, 7.03 (d, 1H, *J* = 3,6 Hz, H-3‘); 2.35 (s, 3H, CH_3).
5i	11.78 (s, 1H, NH); 11.61 (s, 1H, NH); 8.31 (s, 1H, CH); 8.13-8.11 (m, 2H, H_{arom}); 7.91-7.83 (m, 3H, H-6, H_{arom}); 7.68-7.59 (m, 4H, H_{arom}); 7,43 (s, 1H, H-3); 7.22, 7.21 (d, 1H, *J* = 3,6 Hz, H-4‘); 7.07, 7.06 (d, 1H, *J* = 3,6 Hz, H-3‘).
6a	11.49 (s, 1H, NH); 11.54 (s, 1H, NH); 8.13 (s, 1H, CH); 7.77 (d, 1H, *J* = 2.4 Hz, H-2); 7.67 (d, 1H, *J* = 5.4 Hz, H-5’); 7.46 (d, 1H, *J* = 3.6, H-3’); 7.16 (dd, 1H, *J* = 3.6 Hz, H-4’); 7.01 (s, 1H, H-6); 6.61 (d, 1H, *J* = 2.1 Hz, H-3).
6b	11.72 (s, 1H, NH); 11.54 (s, 1H, NH); 8.60 (s, 1H, CH); 8.12- 8.10 (m, 2H, H_{arom}); 7.68-7.62 (m, 3H, H_{arom}, H-3’); 7.46, 7.45 (d, 1H, *J* = 3,9 Hz, H-5’); 7.41 (s, 1H, H-6); 7.17, 7.14 (dd, 1H, *J* = 3,6 Hz, *J* = 1,5 Hz, H-4’); 7.05 (s, 1H, H-3).
7	11.81 (s, 1H, NH); 11.69 (s, 1H, NH); 8.27 (s, 1H, CH); 8.11- 8.12 (m, 2H, H_{arom}); 7.63-7.70 (m, 2H, H_{arom}); 7.43 (s, 1H, H-6’); 7.31 (s, 1H, H-6); 7.03 (s, 1H, H-3’); 7.02 (s,1H, H-3); 5.76 (s, 2H, CH_2); 3.81 (s, 3H, CH_3); 3.23 (s, 1H, CH_3).
9a	11.89 (s, 1H, NH); 11.45 (s, 1H, NH); 8.42 8.37 (m, 4H, H-arom.); 8.23- 8.11 (m, 6H, H_{arom}); 7.75- 7.72 (m, 3H, H_{arom}); 7.53, 7.52 (d, 1H, *J* = 3.2 Hz, H-4‘); 7.49, 7.48 (d, 1H, *J* = 3.1 Hz, H-3‘); 7.25 (s, 1H, H-3), 7.10 (s, 1H, CH); 6.95 (s, 1H, H-6).
9b	11.50 (s, 1H, NH); 11.10 (s, 1H, NH); 8.08 - 8.02 (m, 3H, H_{arom}); 7.85, 7.83 (d, 1H, *J* = 4.5 Hz, H-3’); 7.72 (s, 1H, CH); 7.52-7.60 (m, 3H, H_{arom}); 7.27 (d,d, 1H, *J* = 5.1 Hz, H-4’); 6.92 (s, 1H, H-6); 2.30 (s, 3H, CH_3); 2.03 (s, 3H, CH_3).

Study of inhibition of photosynthetic electron transport in spinach chloroplasts:

Spinach chloroplasts were prepared according to Walker [14]. The effect of the compounds **5-7** on the inhibition of photosynthetic electron transport (PET) in spinach chloroplasts was investigated spectrophotometrically in the presence of electron acceptor 2,6-dichlorophenol indophenol (DCPIP) (30 µmol.l-1). Before measurements, the chloroplasts were resuspended in phosphate buffer (20 mmol.l^{-1}; pH = 7.2) containing 5 mmol. l^{-1} $MgCl_2$ and 15.mmol. l^{-1} NaCl. The chlorophyll content in the suspension was adjusted to 30 mg.l^{-1}. Samples were irradiated at 25°C with a halogen lamp (250 W) at a distance of 1 dm. A 4 cm water filter was used to prevent overheating of the samples. The PET-inhibitory activity of the compounds studied was expressed in term of IC_{50} values as their negative logarithms thus, corresponding to molar concentrations of inhibitors causing a 50% decrease of oxygen evolution rate (OER) with respect to the untreated control sample. Due to lower aqueous solubility of the compounds studied, these were dissolved in dimethyl sulfoxide. The effect of DMSO on OER in the suspensions of spinach chloroplasts was in the range of experimental error and could be neglected.

Table 3 Inhibitory effect of compounds **5-7** on photosynthetic electron transport in spinach chloroplasts.

	log (1/IC_{50})	IC_{50}		log (1/IC_{50})	IC_{50}
5a	3.5505	0.285	**5h**	2.8936	1.278
5b	3.2948	0.507	**5i**	**4.1513**	**0.099**
5c	3.5680	0.270	**6a**	3.4470	0.764
5f	3.3871	0.410	**6b**	3.2194	0.604
5g	**4.0244**	**0.139**	**7**	2.2948	1.468

Compounds **5-7** showed relatively low inhibitory effect on photosynthetic electron transport (PET) in spinach chloroplasts (Table 3). The most effective inhibitors were compounds **5g** and **5i**, indicating that the CF_3 substituent at position 3 on the benzene ring contributed to the enhanced inhibition of PET by the compounds. PET-inhibitory activity is exhibited by many compounds possessing X = C-NH group with an sp^2 hybridized carbon atom (i.e. ureas, triazines, anilides [15,16], etc). Due to formation of hydrogen bonds between this group and the target proteins in photosynthetic centers of thylakoid membranes, changes in protein conformation may occur resulting in inhibition of photosynthetic electron transport [17].

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References

[1] Jedlovská E., Gavláková E.: *Collect. Czech. Chem. Commun*. **59**, 1892, (1994).

[2] Jedlovská E., Leško J.: *Synth. Commun*. **24**, 1879, (1994).

[3] Cao L.H., Cui P.Y.: *J. Chinese Chem. Soc*. **50**, 903, (2003).

[4] Obreza A., Urleb U.: *Acta Chim. Slov*.**49**, 605, (2002).

[5] El-Shaaer H.M., Foltínová P., Lácová M., Chovancová J., Stankovičová H.: *Il Farmaco* **53**, 224, (1998).

[6] Foltínová P., Lácová M., Loos D.: *Il Farmaco* **55**, 21, (2000).

[7] Dutta M.M., Goswami B.N., Kataky J.C.S.: *J. Heterocycl. Chem*. **23**, 793, (1986).

[8] El-Shaaer H.M., Lácová M., Odlerová Ž., Furdík M.: *Chem. Papers* **48**, 344 , (1994).

[9] Santos M.R.L., Barreiro E.J., Braz-Filho R., Miranda A.L.P.: *J. Braz. Chem. Soc.* **8**, 471, (1997).

[10] Shindhar D.R., Sastry C.V.R., Vaidya N.K.: *J. Indian. Chem. Soc*. **57**, 1118, (1980); *Chem. Abstr*. **94**, 174765j, (1981).

[11] Shigetaka Y., Akira T., Gang-Nan Y., Hsing-Chien H.: *Yakugaku Zasshi* **90**, 1150, (1970); *Chem. Abstr*. **73**, 120433x, (1970).

[12] Krutošíková A., Dandárová M., Bobošík V.: *Collect. Czech. Chem. Commun.* **59**, 473, (1994).

[13] Frimm R., Kováč J., Krutošíková A.: *Chem. Zvesti*, **27**, 101, (1973).

[14] Walker D.A.: In: San Pietro (Ed.): *Methods in Enzymology*, Vol. 69, Part C, Academic Press, New York, 1980, pp. 94–104.

[15] Král'ová K., Šeršeň F., Kubicová L., Waisser K.: *Chem. Papers* **53**, 328, (1999).

[16] Miletin M., Doležal M., Opletalová V., Hartl J., Král'ová K., Macháček M.: *Molecules* **6**, 603, (2001).

[17] Draber W., Tietjen K., Kluth J.F., Trebst A.: *Angew. Chem. Int. Ed. Engl*. **30,** 1621, (1991).