CYCLISATION REACTIONS GIVING 5,5-DIMETHYL -2-PHENYLIMIDAZOLIN-4-THIONES AND 4,4-DIMETHYL -2 -PHENYLTHIAZOLIN-5-ONES

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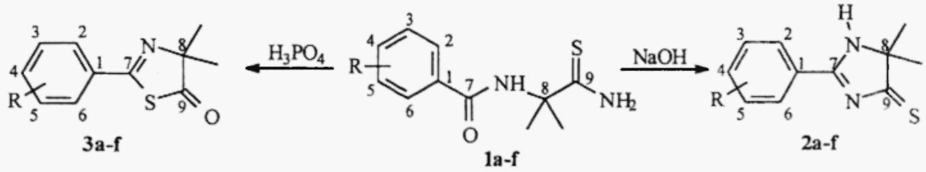
Abstract: Five substituted 2-benzoylamino-2-methyl-thiopropanamides have been prepared and their ring-closure reaction studied in basic and strongly acid media. In bases the ring closure takes place at the terminal nitrogen atom of thioamide group to give the corresponding 5,5-dimethyl-5-phenylimidazoline-4-thiones, while in strongly acid medium the reaction involves the sulphur atom to give the substituted 4,4-dimethyl-2-phenylthiazolin-5-ones. The 5,5-dimethyl-5-phenylimidazoline-4-thiones are stable in both acid and base media. The 4,4-dimethyl-2-phenylthiazolin-5-ones undergo hydrolysis to 2-methyl-2-thiobenzoylamino-propionic acids. The mechanism of ring closure in basic medium has been studied in detail: its rate-limiting step is the decomposition of tetrahedral intermediate.

Introduction: Imidazolinone derivatives belong among biologically active heterocyclic compounds that exhibit, depending on substituents, herbicidal and anticonvulsive properties (1). The most significant imidazolinones are commercially available herbicides (1). The aim of this work was to synthesise 5,5-dimethyl-2-phenylimidazoline-4-thiones **2a-f** and 4,4-dimethyl-2-phenylthiazolin-5-ones **3a-f** (Scheme 1). Attention was also given to kinetic study of base catalysed ring-closure reaction of 2-benzoylamino-2-methyl-thipropanamides **1a-f**, which forms a continuation to our previous studies (2,3) of analogous ring-closure reactions.



Scheme 1

Experimental:

2-Benzoylamino-2-methyl-thiopropanamides **1a-f**

A mixture of 2-amino-2-methyl-thiopropanamide (1.2 g; 10 mmol), dry triethylamine (1 g; 10 mmol), and acetone (60 mL) was cooled to –60 °C. A solution of the corresponding benzoyl chloride (10 mmol) in acetone (15 mL) was added thereto drop by drop within 15-20 min. The mixture was stirred at room temperature overnight. Triethylammonium chloride was collected by filtration, and the filtrate was evaporated until dry. The evaporation residue was mixed with water (20 mL), and the separated raw product was collected by suction, dried, and recrystallised from a benzene/chloroform (1:1) mixture to give white crystalline products **1a-f** (Tables 1-3).

5,5-Dimethyl-2-phenylimidazoline-4-thiones **2a-f**

A solution of the respective 2-benzoylamino-2-methyl-thiopropanamide **1a-f** (1.5 mmol) in aqueous methanol (15 mL, 50%) was treated with an aqueous solution of sodium hydroxide (1,2 mL; 2 $\mathrm{mol \cdot L^{-1}}$) added at room temperature. After 4-hour stirring, the reaction mixture was neutralised with hydrochloric acid (1:1) to pH ~ 7. The separated crystals of **2a-f** were collected by suction, washed with water, and dried (Tables 1-3).

4,4-Dimethyl-2-phenylthiazolin-5-ones **3a-f**

The corresponding 2-benzoylamino-2-methyl-thiopropanamide **1a-f** (1.65 mmol) was added to a mixture of phosphorus(V) oxide (6.7 g) and phosphoric acid (10 mL; 85%) at room temperature. After 21-day stirring at room temperature, the reaction mixture was poured onto ice (50 g) and the separated crystals were collected, washed with water, and dried. The products **3a-f** were purified by flash-chromatography (silica gel/chloroform) (Tables 1-3).

2-Methyl-2-thiobenzoylamino-propionic acids **4b** *and* **4f**

5,5-Dimethyl-2-(4-nitrophenyl)thiazolin-4-one **3b** or 5,5-dimethyl-2-(4-dimethylaminophenyl)thiazolin-4-one **3f** (150 mg; 0.6 mmol) was suspended in aqueous methanol (12 mL; 50%) and treated with an aqueous solution of sodium hydroxide (1 mL; 2 mol L^{-1}). After 24 h stirring at room temperature, the obtained clear solution was acidified with aqueous hydrochloric acid (2.1 mL; 1 mol·L^{-1}) to pH ~ 3 and cooled to –5 °C. The crystals of **4b** and **4f** formed (Tables 1-3) were collected by suction, washed with cold water, and dried.

Table 1 – Melting points and yields of compounds prepared

	R	1		2		3		4	
		M.p. (°C)	Yield (%)	M.p. (°C)	Yield (%)	M.p. (°C)	Yield (%)	M.p. (°C)	Yield (%)
a	H	167-168	45	163-165	30	oil	40	–	–
b	4-NO_2	172-174	38	204-205	55	136-139	72	165-168	75
c	4-CH_3	173-176	51	176-179	52	38-40	40	–	–
d	4-Cl	187-190	52	179-182	56	60-63	54	–	–
e	3-NO_2	173-176	44	87-90	71	86-88	63	–	–
f	4-$N(CH_3)_2$	210-213	26	236-240	64	102-105	18	159-163	62

^{1}H NMR of compounds prepared (δ; ppm) – m-multiplet, s-singlet, d-doublet, t-triplet, dd-doublet of doublet.

Compound	H-2,6 (*J*/Hz)	H-3,5 (*J*/Hz)	NH_2	NH	CH_3	R
1a	7.90m (–), 2H	7.51 m (–), 2H	9.06 + 9.69 2x bs, 2H	8.59bs, 1H	1.68s, 6H	7.56m (–), 1H, H-4
1b	8.36d (8.9), 2H	8.15d (8.9), 2H	9.10 + 9.68 2x bs, 2H	8.87bs, 1H	1.69s, 6H	–
1c	7.81d (8.1), 2H	7.31d (8.2), 2H	9.06 + 9.71 2x bs, 2H	8.54bs, 1H	1.69s, 6H	2.39s, $ArCH_3$
1d	7.94d (8.5), 2H	7.58d (8.5), 2H	9.06 + 9.66 2x bs, 2H	8.64bs, 1H	1.67s, 6H	–
1e	8.78t (2.1), 1H; 8.32d (7.8), 1H	– ; 7.81t (8.1), 1H	9.10 + 9.62 2x bs, 2H	8.64bs, 1H	1.67s, 6H	8.42dd (7.7;1.5), 1H, H-4
1f	7.76d (9.0), 2H	6.75 (9.0), 2H	9.04 + 9.69 2x bs, 2H	8.30bs, 1H	1.67s, 6H	3.00s $N(CH_3)_2$
2a	8.14d (7.5), 2H	7.59t (5.5), 2H	–	13.33bs, 1H	1.41s, 6H	7.66t (5.0), 1H, H-4
2b	8.41m (–), 2H	8.35 m (–), 2H	–	13.46bs, 1H	1.42s, 6H	–
2c	8.02d (7.9), 2H	7.39d (7.9), 2H	–	13.24bs, 1H	1.39s, 6H	2.42s $ArCH_3$
2d	8.14d (8.6), 2H	7.66d (8.6) 2H	–	13.19bs, 1H	1.40s, 6H	–
2e	8.95m (–), 1H 8.46m (–), 1H	–; 7.88t (8.1), 1H	–	13.50bs, 1H	1.42s, 6H	8.52m (–), 1H, H-4
2f	6.85d (6.3), 2H	8.01d (5.7), 2H	–	13.15bs, 1H	1.39s, 6H	3.08s $N(CH_3)_2$
3a	7.87m (–), 2H	7.60m (–), 2H	–	–	1.50s, 6H	7.66m (–), 1H, H-4
3b	8.41 m (–), 2H	8.11m (–), 2H	–	–	1.53s, 6H	–
3c	7.75d (8.5), 2H	7.40d (8.5), 2H	–	–	1.49s, 6H	2.43s $ArCH_3$
3d	7.86m (–), 2H	7.66m (–), 2H	–	–	1.49s, 6H	–

3e	8.57m (–), 1H, 8.23m (–), 1H	–; 7.90t (8.2), 1H	–	–	1.54s, 6H	8.48m (–), 1H, H-4
3f	7.64 m (–), 2H	6.82m (–), 2H	–	–	1.46s, 6H	3.05s $N(CH_3)_2$
4b	7.86m (–), 2H	8.29m (–), 2H	12.59 COOH	10.46bs, 1H	1.68s, 6H	–
4f	6.71d (8.9), 2H	7.76d (8.9), 2H	12.25 COOH	9.50bs, 1H	1.66s, 6H	3.05s $N(CH_3)_2$

^{13}C NMR of compounds prepared (δ; ppm)

Compound	C-1	C-2,6	C-3,5	C-4	C-7	C-8	C-9	CH_3	R
1a	132.9	132.4	129.3	128.0	165.2	60.8	211.1	27.3	–
1b	138.0	124.4	129.4	149.7	163.9	61.3	210.6	27.6	–
1c	130.3	128.0	129.8	142.6	165.1	60.7	211.2	27.2	21.0
1d	131.5	129.3	129.6	137.0	164.2	60.9	210.9	27.4	–
1e	131.5	131.1, 123.8	145.2, 118.7	128.2	163.5	61.3	210.6	27.7	–
1f	111.4	119.8	129.3	152.6	165.1	60.4	211.7	27.3	39.9
2a	132.1	129.0	127.6	127.6	158.1	81.8	223.0	27.4	–
2b	133.5	124.1	129.0	149.4	157.5	82.2	223.3	27.3	–
2c	142.3	124.9	127.7	129.6	158.1	81.5	223.2	27.5	21.2
2d	126.5	129.1	129.4	137.0	158.0	81.5	223.7	27.3	–
2e	133.7	130.8, 126.5	148.2, 122.4	129.3	157.2	82.0	223.4	27.3	–
2f	112.9	130.2	111.3	153.2	157.5	79.2	223.7	27.6	39.6
3a	132.9	132.4	129.3	128.0	159.8	84.0	211.3	24.53	–
3b	138.0	124.4	129.4	149.7	158.8	84.4	210.4	24.4	–
3c	130.3	128.0	129.8	142.6	159.5	83.9	211.5	24.6	21.2
3d	131.5	129.3	129.6	137.0	158.8	84.0	210.9	24.4	–
3e	131.5	131.1, 123.8	145.2, 118.7	128.2	155.6	81.2	207.3	21.4	–
3f	111.4	119.8	129.3	152.6	158.5	83.4	212.1	24.9	39.7
4b	147.5	123.2	128.6	148.1	195.2	60.2	173.2	24.1	–
4f	129.2	110.3	128.5	152.2	195.5	59.7	174.2	24.6	39.4

Table 3 - Elemental analyses of compounds prepared

		Calculated / Found			
Compound	**Formula / M_r**	**C (%)**	**H (%)**	**N (%)**	**S (%)**
1a	$C_{11}H_{14}N_2SO$ / 222.3	59.43 / 59.55	6.35 / 6.23	12.60 / 12.59	14.42 / 14.65
1b	$C_{11}H_{13}N_3SO_3$ / 267.3	49.43 / 49.66	4.90 / 4.96	15.72 / 15.85	11.99 / 12.12
1c	$C_{12}H_{16}N_2SO$ / 236.3	60.99 / 61.02	6.82 / 6.92	11.85 / 12.14	13.57 / 13.33
1d	$C_{11}H_{13}N_2SOCl$ / 256.7	51.46 / 48.78	5.10 / 4.92	10.91 / 10.43	12.49 / 11.98
1e	$C_{11}H_{13}N_3SO_3$ / 267.3	49.43 / 49.17	4.90 / 4.96	15.72 / 15.97	11.99 / 11.68
1f	$C_{13}H_{19}N_3SO$ / 265.4	58.84 / 58.84	7.22 / 7.23	15.83 / 16.05	12.08 / 11.82
2a	$C_{11}H_{12}N_2S$ / 204.3	64.67 / 64.62	5.92 / 5.90	13.71 / 13.89	15.69 / 15.79
2b	$C_{11}H_{11}N_3SO_2$ / 249.3	53.00 / 53.13	4.45 / 4.52	16.86 / 16.99	12.86 / 12.85
2c	$C_{12}H_{14}N_2S$ / 218.3	66.02 / 66.07	6.46 / 6.53	12.83 / 13.04	14.69 / 14.55
2d	$C_{11}H_{11}N_2SCl$ / 238.7	55.34 / 55.64	4.64 / 4.70	11.73 / 12.03	13.43 / 13.25

2e	$C_{11}H_{11}N_3SO_2$ / 249.3	53.00 / 53.12	4.45 / 4.68	16.86 / 16.72	12.86 / 12.89
2f	$C_{13}H_{17}N_3S$ / 247.4	63.12 / 63.25	6.93 / 6.87	16.99 / 16.89	12.96 / 12.88
3a	$C_{11}H_{11}NSO$ / 205.3	64.36 / 64.51	5.40 / 5.26	6.82 / 6.75	15.62 / 15.54
3b	$C_{11}H_{10}N_2SO_3$ / 250.3	52.79 / 52.84	4.03 / 4.01	11.19 / 11.24	12.81 / 12.60
3c	$C_{12}H_{13}NSO$ / 219.3	65.72 / 65.81	5.97 / 5.91	6.39 / 6.57	14.62 / 14.47
3d	$C_{11}H_{10}NSOCl$ / 239.7	55.12 / 55.40	4.20 / 4.38	5.84 / 5.65	13.37 / 13.36
3e	$C_{11}H_{10}N_2SO_3$ / 250.3	52.79 / 52.67	4.03 / 4.09	11.19 / 11.46	12.81 / 12.50
3f	$C_{13}H_{16}N_2SO$ / 248.3	62.87 / 62.96	6.49 / 6.35	11.28 / 11.07	12.91 / 12.84

^{1}H and ^{13}C NMR spectra were measured at 360.14 and 90.57 MHz, respectively, on a Bruker AMX 360 and Bruker Avance 500 spectrometers at 25 °C in hexadeuteriodimethyl sulfoxide, and the chemical shifts are referenced to tetramethylsilane ($\delta(^1H) = 0$) and the solvent signal ($\delta(^{13}C) = 39.6$). The CH, CH_3 and C_{quart} groups in the ^{13}C NMR spectra were distinguished by the APT method.

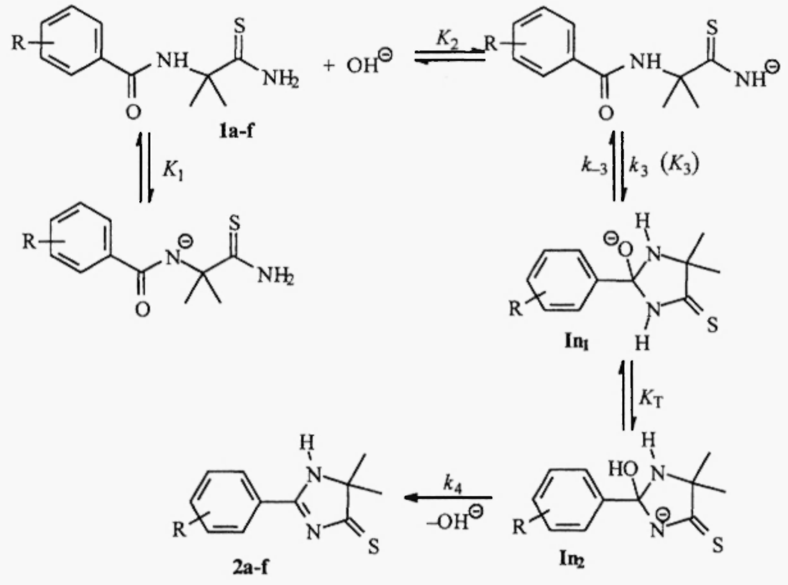
Kinetic measurements were carried out on a HP UV/VIS 8453 Diode Array apparatus. A 1 cm quartz cell was charged with 2 mL of aqueous sodium hydroxide. At 25 °C 50 μL of a methanolic solution of a substrate ($c = 5 \cdot 10^{-5}$ mol L^{-1}) was injected and the absorbance was measured at a selected wavelength.

Results and Discussion

We found out that the 2-benzoylamino-2-methyl-thiopropanamides **1a-f** undergo ring closure in aqueous methanol with base catalysis (NaOH) to give the corresponding substituted 5,5-dimethyl-2-phenylimidazolin-4-thiones **2a-f**. The reactions are finished within 4 h at room temperature.

The cyclisation reaction of 2-benzoylamino-2-methyl-thiopropanamides **1a-f** was studied in detail using aqueous solutions of sodium hydroxide in the concentration range of 0.01 – 1.0 mol·L^{-1}. The cyclisation rate has been found to depend nonlinearly on the concentration of the base used, i.e. sodium hydroxide, which applies to various substituents at the benzene ring of the starting thioamides. The following Scheme 2 can be suggested for the said ring closure. In the sodium hydroxide solutions used, a fast pre-equilibrium deprotonation takes place first: a proton is split off from both the nitrogen atom adjacent to benzene ring (the so-called blind alley, K_1) and the terminal nitrogen ($CSNH_2$ group). The nucleophilic terminal anion formed in the latter case attacks the carbonyl group of the benzoyl moiety to give a tetrahedral intermediate **In**$_1$, which undergoes a proton transfer from nitrogen to oxygen (**In**$_1$ → **In**$_2$) and then splits off hydroxyl anion to produce 5,5-dimethyl -2-phenyl-imidazolin-4-thiones **2a-f**.

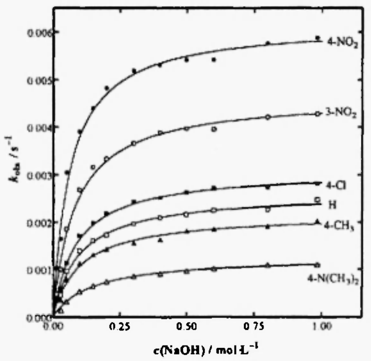
Figure 1 presents the dependence of observed rate constant k_{obs} on hydroxide concentration for the individual derivatives **1a-f**. From the course of experimentally found dependences it follows that in this case the reaction order in hydroxide is equal to one at low [OH$^-$] values and gradually drops to zero at higher [OH$^-$] values, which is characteristic of reactions with a fast pre-equilibrium followed by the rate-limiting step. For k_{obs} we can suggest Eq. 1, which contains three parameters i.e. cyclisation rate constant k_c, equilibrium constant K_1 and K_2. This three-parameter equation is not suitable for determination of the values of individual parameters. Therefore, the following simplification had to be done. In the compounds of –(C=S)–NH–R type the proton at nitrogen is much more acidic than that in the –(C=O)–NH–R type. For instance, the pK_a value of 4-nitrophenylthiourea is four orders of magnitude lower than that of 4-nitrophenylurea (4) and pK_a value of thioacetanilide is 2.5 orders lower than that of acetanilide (5). This can be expressed by $K_2 >> K_1$, and Eq. 1 can be modified to Eq. 2.



Scheme 2

$$k_{obs} = \frac{k_c \cdot K_2 \cdot [CH_3O^-]}{1 + (K_1 + K_2) \cdot [CH_3O^-]} \quad \text{Eq. 1}$$

$$k_{obs} = \frac{k_c \cdot K_2 \cdot [CH_3O^-]}{1 + K_2 \cdot [CH_3O^-]} \quad \text{Eq. 2}$$



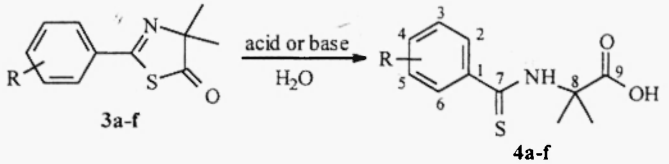
Compound	$10^3 \cdot k_c$ (s^{-1})	K_2 ($mol \cdot L^{-1}$)
1a	2.62 ± 0.06	10.2 + 0.9
1b	6.18 ± 0.11	16.0 ± 1.3
1c	2.17 ± 0.06	9.6 ± 0.9
1d	3.09± 0.06	11.3 ± 0.9
1e	4.64 ± 0.10	12.2 ± 1.1
1f	1.27 ± 0.03	6.7 ± 0.5

Fig. and Table 4. Dependence of k_{obs} (s^{-1}) of cyclisation of derivatives **1a-f** on NaOH concentration ($mol \cdot L^{-1}$).

The value of constant K_2 (Table 5) depends only little on substitution, and amounts to about 10 $L \cdot mol^{-1}$. From the K_2 values it is possible to calculate (using equation $pK_a = pK_w + pK_2$) also the pK_a of **1a-f**, which varies from 12.8 to 13.2. The used autoprotolysis constant value of water at 25 °C is $pK_w(H_2O) = 14.00$.

The values of optimised cyclisation rate constant k_c (Table 5) fulfil the Hammett correlation very well. The reaction constant $\rho = 0.45 \pm 0.03$ is substantially lower than in the case (2) of analogous 2-benzoylamino-*N*-methyl-2,3-dimethylbutanamides ($\rho = 1.4$). The literature (6,7) indicates that the ρ value for formation of tetrahedral intermediate from a nucleophile and a substituted benzoyl species is about 2. The low observed ρ value indicates that the transition state for rate-limiting step **1a-e**$^-$ → **In$_1$** is earlier than in most reactions at a benzoyl group or, most probably, that the rate-limiting step is subsequent to formation of **In$_2$** and involves a component with electron withdrawal. It is unlikely that the equilibria between **In$_1$** and **In$_2$** will have significant ρ value as the positioning of the negative charge relative to the substituent change does not alter very much, and we therefore conclude that decomposition of **In₂** is rate limiting. The proposed rate-limiting step involves expulsion of hydroxide ion, and the substituents "see" an overall low buildup of negative charge comprising electron buildup in the formation of **In₂** and electron withdrawal in its decomposition. For ρ_c we can suggest following equation: $\rho_c = \rho_3 + \rho_4 - \rho_{-3}$ (ρ_T has a negligible value) and for $k_c = K_3 \cdot K_T \cdot k_4$.

Moreover, we have found that in anhydrous strong acid medium 2-benzoylamino-2-methyl-thiopropanamides **1a-f** undergo ring closure through their sulphur atom. A similar reaction was described earlier with thioureide esters (8), selenoureide esters (9) and 2-benzoylaminothiobenzamides (10). This finding can be interpreted by the SH group being a stronger nucleophile in acid medium than the nitrogen of thioamide group, the opposite being true in basic media. Furthermore it was found out that the produced 4,4-dimethyl-2-phenylthiazolin-5-ones **3a-f** easily undergo hydrolysis both in acid and base media. This solvolysis was observed already during the isolation of the cyclisation product from strongly acid media, when in some cases a mixture of cyclisate **3a-f** and hydrolysis product (the corresponding 2-methyl-2-thiobenzoylamino-propionic acid) was obtained (Scheme 3).



Scheme 3

The base-catalysed hydrolysis of derivatives **3b** and **3f** was carried out on preparative scale in 0.2 M NaOH in 50% aqueous methanol. After the reaction was finished, the mixture was acidified to pH ~ 3-4, and yellow crystalline products **4b** and **4f** were isolated (Tables 1-3). The structure of both compounds was confirmed by ^1H and ^{13}C NMR, and the position of C=S or C=O group (signals at 195 and 173 ppm, respectively) by means of the ^1H-^{13}C correlated two-dimensional spectrum measured by *gs* HMBC technique.

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References:

1. P.J. Weplo, *Pestic.Sci.* **39**, 293 (1990).
2. M. Sedlák, A. Halama, P. Mitaš, J. Kaválek and V. Macháček, *J. Heterocycl. Chem.* **34**, 1227 (1997).
3. M. Sedlák, J. Hanusek, R. Bína, J. Kaválek and V. Macháček, *Collect. Czech. Chem. Commun.* **64**, 1629 (1999).
4. J. Kaválek, V. Štěrba and S. El Bahaie, *Collect. Czech. Chem. Commun.* **48**, 1430 (1982).
5. W. Walter and J. Voss, The Chemistry of Amides, in J. Zabicky, S. Patai (Eds.), The Chemistry of Functional Groups, Interscience Publishers, London, 1970.
6. S.L. Shames and L.D. Byers, *J. Am. Chem. Soc.* **103**, 6170 (1981).
7. J.F. Kirsch, W. Clewell and A. Simon, *J.Org. Chem* **33**, 127 (1968).
8. M. Gütschow, *J. Heterocycl. Chem.* **33**, 355 (1996).
9. J. Šibor, D. Zůrek, O. Humpa and P. Pazdera, *Molecules* **5**, 37 (2000).
10. J. Hanusek, L. Hejtmánková, L. Kubicová and M. Sedlák, *Molecules* **6**, 323 (2001).

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