

Antimony(V) chloride-promoted room temperature aromatization of 1,4-dihydropyridines in non-acidic solvent

Mirela Filipan-Litvić,^a Mladen Litvić,^{a*} Ivica Cepanec,^a and Vladimir Vinković^b

^a*BELUPO Pharmaceuticals, Inc., R&D, Danica 5, 48000 Koprivnica, Croatia*

^b*Institute Ruđer Bošković, Bijenička c. 54, 10002 Zagreb, Croatia*

E-mail: mladen.litvic@belupo.hr

Abstract

Antimony(V) chloride acts as an efficient oxidant for the aromatization of 1,4-dihydropyridines in dichloromethane at room temperature. The products of high purity were isolated after simple work-up in high-excellent yield. Plausible non-typical two-electron transfer mechanism of the reaction was postulated to explain results obtained with 4-alkyl substituted 1,4-DHPs.

Keywords: 1,4-Dihydropyridines, pyridines, aromatization, antimony(V) chloride

Introduction

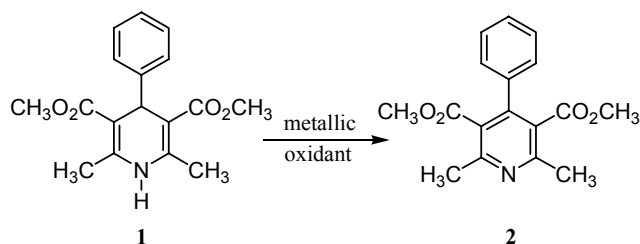
1,4-Dihydropyridines (1,4-DHPs) are one of the most important class of heterocyclic compounds due to their pharmacological activity as calcium antagonists or agonists.¹ The 1,4-DHPs cause vasorelaxation by blocking voltage-operated calcium channel in smooth muscle cells and also by increasing NO release from the intact endothelium.² Recently, some other pharmacological activities have been reported such as: antitumor,³ bronchodilating,⁴ antidiabetic,⁵ antiviral⁶ and antianginal.⁷ The 1,4-DHPs have also been extensively utilised as analogs of NAD(P)H coenzymes to study the mechanism and synthetic potential of various redox processes.⁸ The oxidation (aromatization) of 1,4-DHPs into corresponding pyridines is one of the main metabolic pathways of these drugs. This process is catalysed by the cytochrome P450 (CYP) 3A4 isoform.^{9,10} Moreover, the products of aromatization (substituted pyridines) have found use in treatment of atherosclerosis.¹¹ Consequently, this aromatization reaction continues to attract the attention of researchers for the discovery of mild and general oxidant to a wide variety of substituted 1,4-DHPs. Several oxidizing agents have been used for that purpose including metallic salts,¹² non-metallic reagents¹³ among others.¹⁴ However, most of the methods suffer from low selectivity, harsh reaction condition, use of toxic and expensive reagents, corrosive solvents, tedious work-up, etc. Therefore, development of mild, more selective and practical method for this transformation is still in demand.

In continuation of our program toward development of more facile methods for the aromatization of 1,4-DHPs,¹⁵ we wish to report our new findings that overcome above-mentioned difficulties of literature methods by using antimony(V) chloride (SbCl₅) as a mild, selective and efficient commercially available oxidant.

Results and Discussion

We began our studies with elements from 13-16 group of the periodic system. Our aim was to determine which elements from those groups are capable of reacting with 1,4-DHPs to form selectively substituted pyridines. In the literature, only Tl(III),¹⁶ Sn(IV)¹⁷ and Pb(IV)¹⁵ have been described as convenient oxidants for the aromatization of 1,4-DHPs. From the results with Bi(NO₃)₃^{12a} and BiONO₃,¹⁸ it is not clear whether Bi(III) acts as an oxidant. It is more likely to expect that reaction take place with equilibrium amount of nitric acid formed by hydrolysis of the respective salt. The preliminary results of aromatization of model 1,4-DHP **1** with In(III), Ge(IV), Sb(V), Se(IV) and Te(IV) are presented in Table 1.

Table 1. Aromatization of 1,4-DHP **1** with selected higher-valent elements from 13 – 16 group of the periodic system

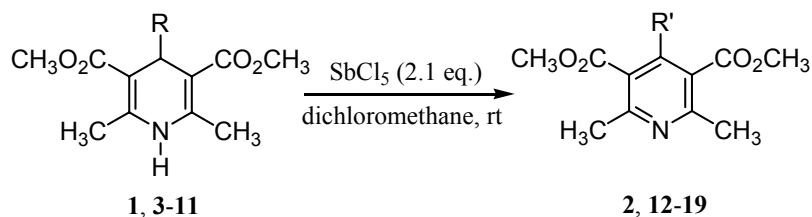


Entry	Oxidant ^a	Solvent	Reaction time [h] ^b	Conversion (Yield) [%] ^d
1	In ₂ O ₃	CH ₃ COOH	20	100 ^c (90)
2	GeCl ₄	CHCl ₃	480	100 ^c (89)
3	GeCl ₄	CH ₃ CN	84	100 ^c (80)
4	GeCl ₄	CH ₃ COOH	1080	97 ^c (85)
5	SbCl ₅	CH ₂ Cl ₂	48	100 ^c (96)
6	SbCl ₅	CH ₃ COOH	21	92 ^c
7	SeO ₂	CHCl ₃	72	98 ^c
8	SeO ₂	CH ₃ COOH	5	100 ^c (90)
9	SeCl ₄	CHCl ₃	0.25	– ^f
10	TeO ₂	CH ₃ COOH	24	0 ^e
11	TeCl ₄	CHCl ₃	24	0 ^e
12	TeCl ₄	CH ₃ COOH	24	0 ^e

^aStoichiometric amount. ^bDetermined by TLC. ^cAt room temperature. ^dIsolated yield. ^eAt reflux temperature. ^fLess polar side-products are formed.

The aromatization with stoichiometric amount of GeCl_4 (Entries 2 and 3), SbCl_5 (Entry 5) and SeO_2 (Entry 8) smoothly proceeded at room temperature and the product was isolated in good-to-excellent yield. The most reactive salt was proved to be SeCl_4 which rapidly reacted with **1** in 15 min. but with very low chemoselectivity. The reaction with In_2O_3 took place only in acetic acid at reflux temperature with good chemoselectivity. Surprisingly, the aromatization with tellurium salts (TeO_2 and TeCl_4) did not give even a trace of the product **2** even at reflux temperature of chloroform and acetic acid (Entries 10-12). From the obtained preliminary results we have decided to test in detail SbCl_5 as cheap, non-toxic and easily accessible compound. In the literature SbCl_5 has been primarily used as selective Lewis acid in many organic transformations¹⁹ but its oxidation ability was almost neglected. The optimal amount of SbCl_5 in aromatization of 1,4-DHP **2** was proved to be 2.1 equivalent and reaction was completed in 1 h. These reaction conditions were used for the aromatization of substituted 1,4-DHPs and the results are summarized in Table 2.

Table 2. Aromatization of substituted-1,4-DHPs with SbCl_5 in dichloromethane at room temperature

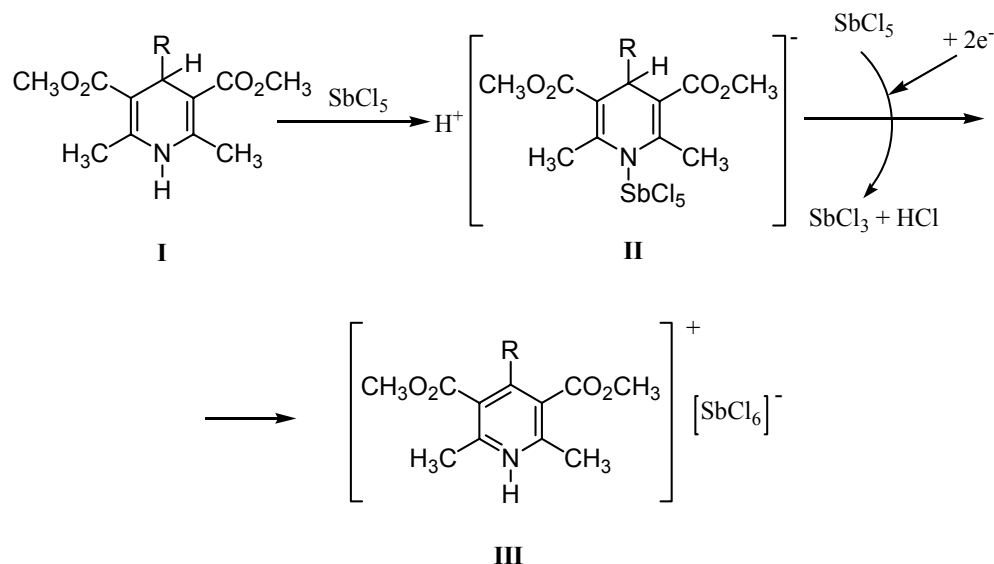


Entry	1,4-DHP	R	Product	R'	Time [min]	Yield [%]	m.p. [°C]	
							Found	Reported
1	1	Ph	2	Ph	60	96	134–136	135–136 ²⁰
2	3	H	12	H	1	91	99–100	100 ²¹
3	4	CH_2CH_3	12	H	360	90	99–100	100 ²¹
4	5	$\text{CH}(\text{CH}_3)_2$	13	$\text{CH}(\text{CH}_3)_2$	5	– ^a	Oil	–
5	6	CH_2Ph	14/12	$\text{CH}_2\text{Ph} / \text{H}$	1	– ^b	– ^c	–
6	7	<i>o</i> - ClC_6H_4	15	<i>o</i> - ClC_6H_4	60	90	70–71	70 ^{12c}
7	8	<i>m</i> - $\text{CH}_3\text{C}_6\text{H}_4$	16	<i>m</i> - $\text{CH}_3\text{C}_6\text{H}_4$	60	95	93.5–95.5	–
8	9	<i>p</i> - $\text{OCH}_3\text{C}_6\text{H}_4$	17	<i>p</i> - $\text{OCH}_3\text{C}_6\text{H}_4$	60	92	114–116	115–117 ^{12j}
9	10	2-thienyl	18	2-thienyl	2	81	79–81	–
10	11	2-furyl	19	2-furyl	1	80	60–62	Oil ²²

^aIsolated in low yield (<5 %) with decomposition products. ^bIsolated as a mixture with product of dealkylation **12** (85% : 15%, determined by HPLC). ^cMixture of viscous oil and crystals.

The main characteristics of the reactions are short reaction times (1–360 min), good-to-excellent yields (80–86%) and high purities of crude products. Substituted aryl groups (Entries

6–8) were well tolerated including highly reactive 2-thienyl and 2-furyl analogues (**10,11**), which were almost instantly oxidised. The most interesting results was obtained with ethyl analogue **4** which was slowly but selectively dealkylated to give **12**, while benzyl analogues **6** was only partially dealkylated giving a mixture of expected (non-dealkylated) and dealkylated products in a ratio 5.7 : 1.0 with small amount (15%) of benzyl-chloride as dealkylation side product. Interestingly, isopropyl derivative **5** was selectively oxidised affording pyridine **13** in low yield. This is a first example of reversed dealkylation obtained during the aromatization of 4-alkyl-1,4-DHPs. Usually, secondary and benzylic substituents are easily dealkylated while primary alkyl groups remain intact.²³ To explain this observation we have proposed a mechanism which is outlined in Scheme 1.



Scheme 1. Plausible mechanism for the aromatization of 1,4-DHPs with SbCl_5 .

As already mentioned, in the first step the complex **II** is formed by action of SbCl_5 (Lewis acid) on the nitrogen center of 1,4-DHP **I**. This process deactivates one equivalent of the oxidant and second equivalent is needed to accelerate the reaction. In the next step, it is not likely to expect one-electron transfer from 1,4-DHP yielding 1,4-DHP radical-cation and Sb(IV) similarly to the mechanism with manganese triacetate mediated aromatization.¹²¹ It is rather to expect two-electron transfer from 1,4-DHP ring forming more stable oxidation state of antimony (+3). By this process, one mole of HCl is evolved (noticed in reaction) and the product as hexachloroantimonate salt **III** is generated in a single step. This type of mechanism we have recently proposed in aromatization of 1,4-DHP with lead(IV) acetate.¹⁵ This mechanism was additionally proved in an enantioselective version of the reaction with tartarate modified Pb(IV) salts.²⁴ Sterical hindrances between SbCl_5 and bulky complex **II** are probably the main reason for non-typical behavior of alkyl substituents in the reaction. More sterically demanded isopropyl

substituent, upon hydride abstraction gave, **13**. In contrast, less sterical benzyl and ethyl groups were cleaved prior to CH bond.

The regeneration of antimony(V) after the reaction is possible by the action of 30% H₂O₂ in methanol at room temperature according to literature methods.²⁵ The investigation of catalytic version of the method employing H₂O₂ and O₂ as oxidants is in progress and the results will be published in due course.

Conclusions

Antimony(V) chloride acts as a mild, selective and efficient oxidant for the aromatization of 1,4-DHPs to substituted pyridines in dichloromethane as a solvent at room temperature. Complete dealkylation of derivative with ethyl group was observed while derivative with benzyl group was only partially dealkylated. On the contrary, isopropyl derivative was selectively oxidised without a presence of dealkylation product. To explain this non-typical behavior plausible mechanism is proposed which include two-electron transfer from 1,4-DHP ring to Sb(V) cation.

Experimental Section

General Procedures. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. ¹H NMR and ¹³C NMR were recorded on a Bruker 600 for CDCl₃ solutions, shifts are given in ppm downfield from TMS as an internal standard. HPLC analyses were performed with a Thermo Separation Products (San Jose, USA) instrument equipped with vacuum degasser SCM 1000, quaternary gradient pump P 4000, autosampler AS 3000, scanning UV/VIS detector UV 3000 HR and ChromQuest 251 software. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel 60₂₅₄. Melting points were determined using a Büchi B540 instrument. Elemental analyses were done in Central Analytical Service (CAS) at Ruder Bošković Institute. Gram-scale samples of 1,4-DHPs were prepared by literature methods.²⁶ The products of aromatization were characterized by a comparison with authentic samples (melting point) and their IR and NMR (¹H, ¹³C) spectra.^{27,28}

General Procedures for the aromatization of 1,4-DHPs with SbCl₅

To a solution of 1,4-DHP (1.0 mmol) in dichloromethane, SbCl₅ (0.27 mL, 2.1 mmol) was added at once. The resulting solution was stirred at room temperature for the time indicated in Table 2. After that, to the reaction mixture was added water (20 mL) and solid NaHCO₃ in small portions to pH>7 (foaming!). The phases were separated, and the aqueous phase was additionally extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and evaporated to dryness. The crude products were recrystallized from diisopropyl ether to give products of purity >99%.

Spectral and physical data for selected compounds

16. Yield 93 %. Yellow crystals, mp 93.5–95.5 °C; R_f (CH₂Cl₂/EtOAc, 9:1) = 0.31. IR ν = 2959, 2927, 1733, 1606, 1563, 1488, 1454, 1428, 1373, 1289, 1239, 1209, 1106, 1033 cm⁻¹; ¹H NMR (CDCl₃): δ = 2.35 (s, 3H, Me), 2.59 (s, 6H, Me), 3.55 (s, 6H, OMe), 7.02–7.05 (m, 2H), 7.16–7.18 (m, 1H), 7.23–7.28 (m, 1H); ¹³C NMR (CDCl₃): δ = 21.2 (C₆H₄CH₃), 22.8 (CH₃), 52.0 (OCH₃), 124.7, 126.6, 128.0, 128.2, 129.2, 136.2, 137.8, 146.2, 155.3, 168.4 (CO). Anal. Calcd. for C₁₈H₁₉NO₄: C 68.99, H 6.11, N 4.47; found: C 68.8, H 5.9, N 4.3.

18. Yield 81 %. Pale yellow crystals, mp 79.0 – 81.0 °C, R_f (CH₂Cl₂/EtOAc, 9:1) = 0.39. IR ν 2955, 2855, 1731, 1630, 1558, 1435, 1398, 1381, 1373, 1244, 1208, 1106, 1039 cm⁻¹; ¹H NMR (CDCl₃) δ 2.58 (s, 6H, CH₃), 3.68 (s, 6H, OCH₃), 7.04 – 7.07 (m, 2H), 7.28 – 7.43 (m, 1H), ¹³C NMR (CDCl₃) δ 22.93 (CH₃), 52.46 (OCH₃), 127.27, 127.78, 128.47, 135.84, 138.42, 145.11, 155.51, 168.30 (CO). Anal Calcd. for C₁₅H₁₅NO₄S: C 59.00, H 4.95, N 4.95, S 10.50. Found: C 59.11, H 5.01, N 4.99, S 10.41.

Acknowledgements

The authors wish to express their gratitude to the Belupo Pharmaceuticals Inc. for financial support of this research.

References and Notes

1. Grün, G.; Fleckenstein, A. *Arzneim. Forsch. (Drug Res.)* **1972**, *22*, 334.
2. Berkels, B.; Roesen, R.; Dhein, S.; Fricke, U.; Klaus, W. *Cardiovasc. Drug Rev.* **1999**, *17*, 179.
3. Tsuruo, T.; Iida, H.; Nojiri, M.; Tsukagoshi, S.; Sakurai, Y. *Cancer Research* **1983**, *43*, 2905.
4. Chapman, R. W.; Danko, G.; Siegels, M. I. *Pharmacology* **1984**, *29*, 282.
5. Malaise, W. J.; Mathias, P. C. F. *Diabetologia* **1985**, *28*, 153.
6. Krauze, A.; Germane, S.; Eberlins, O.; Sturms, I.; Klusa, V.; Duburs, G. *Eur. J. Med. Chem.* **1999**, *34*, 301.
7. Peri, R.; Padmanabhan, S.; Rutledge, A.; Singh, S.; Triggle, D. J. *J. Med. Chem.* **2000**, *43*, 2906.
8. Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223.
9. Böcker, R. H.; Guengerich, F. P. *J. Med. Chem.* **1986**, *29*, 1596.
10. Kudo, S.; Okumura, H.; Miyamoto, G.; Ishizaki, T. *Drug. Metab. Dispos.* **1999**, *27*, 303.
11. Bischoff, H.; Angerbauer, R.; Bender, J.; Bischoff, E.; Faggiotto, A.; Petzinna, D.; Pfitzner, J.; Porter, M. C.; Schmidt, D.; Thomas, G. *Atherosclerosis* **1997**, *135*, 119.

12. (a) Mashraqui, S. H.; Karnik, M. A. *Synthesis* **1998**, 713. (b) Khadilkar, B.; Borkar, S. *Synth. Commun.* **1998**, 28, 207. (c) Pfister, J. R. *Synthesis* **1990**, 689. (d) Sabitha, G.; Kiran Kumar Reddy, G. S.; Reddy, Ch. S.; Fatima, N.; Yadav, J. S. *Synthesis* **2003**, 1267. (e) Balogh, M.; Hermeicz, I.; Mészáros, Z.; Laszlo, P. *Helv. Chim. Acta* **1984**, 67, 2270. (f) Vanden Eynde, J. J.; Mayence, A.; Maquestiau, A. *Tetrahedron* **1992**, 48, 463. (g) Zolfigol, M. A.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Choghamarani, A. G.; Taqian-Nasab, A. *Asian J. Chem.* **2001**, 13, 887. (h) Zolfigol, M. A.; Salehi, P.; Ghorbani-Choghamarani, A.; Safaiee, M.; Shahamirian, M. *Synth. Commun.* **2007**, 37, 1817. (i) Vanden Eynde, J. J.; D'Ozario, R.; Van Haverbeke, Y. *Tetrahedron* **1994**, 50, 2479. (j) Bagley, M. C.; Lubinu, M. C. *Synthesis* **2006**, 1283. (k) Vanden Eynde, J. J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. *Tetrahedron* **1995**, 51, 6511. (l) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, 40, 21.
13. (a) Kröhnke, F.; Ahrenhok, G. M.; Gross, K. F. *J. Prakt. Chem.* **1960**, 11, 256. (b) Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Memarian, H. R.; Mohammadpoor-Baltork, I. *Synth. Commun.* **2000**, 30, 2945. (c) Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R. *Synth. Commun.* **2000**, 30, 3919. (d) Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R. *Synth. Commun.* **2000**, 30, 551. (e) Ortiz, M. E.; Núñez-Vergara, L. J.; Squella, J. A. *Pharm. Res.* **2003**, 20, 292. (f) Chavan, S. P.; Dantale, S. W.; Kalkote, U. R.; Jyothirmai, V. S.; Kharul, R. K. *Synth. Commun.* **1998**, 28, 2789. (g) Cai, X.-hua; Yang, H.-jun; Zhang, G.-lin *Can. J. Chem.* **2005**, 83, 273. (h) Panchgalle, S. P.; Choudhary, S. M.; Chavan, S. P.; Kalkote, U. R. *J. Chem. Res. (S)* **2004**, 550.
14. (a) Mashraqui, S. H.; Karnik, M. A. *Tetrahedron Lett.* **1998**, 39, 4896. (b) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, 4, 3955. (c) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis* **2004**, 1015. (d) Zolfigol, M. A.; Choghamarani, A. G.; Shahamirian, M.; Safaiee, M.; Mohammadpoor-Baltork, I.; Mallakpour, S.; Abdollahi-Alibeik, M. *Tetrahedron Lett.* **2005**, 5581. (e) Anniyappan, M.; Muralidharan, D.; Perumal, T. *Tetrahedron* **2002**, 58, 5069. (f) Mao, Y.-Z.; Jin, M.-Z.; Liu, Z.-L.; Wu, L.-M. *Org. Lett.* **2000**, 2, 741.
15. Litvić, M.; Cepanec, I.; Filipan, M.; Kos, K.; Bartolinčić, A.; Drušković, V.; Tibi, M. M.; Vinković, V. *Heterocycles* **2005**, 65, 23.
16. (a) Hashemi, M. M.; Zakeri, M. S.; Arianfar, S. *Iran. J. Chem. & Chem. Eng.* **2003**, 22, 9. (b) Momeni, A. R.; Massah, A. R.; Naghash, H. J.; Aliyan, H.; Solati, S.; Sameh, T. *J. Chem. Res. (S)* **2005**, 4, 227.
17. Jain, S. M.; Kant, R.; Dhar, K. L.; Singh, S.; Singh, G. B. *Ind. J. Chem.* **1990**, 29B, 277.
18. Rajanarendar, E.; Ramesh, P.; Srinivas, M.; Ramu, L.; Mohan, G. *Synth. Commun.* **2006**, 36, 665.
19. (a) Huang, A.; Liu, X.; Li, L.; Wu, X.; Liu, W.; Liang, Y. *Adv. Synth. Catal.* **2004**, 346, 599. (b) Kobayashi, S.; Tamura, M.; Mukaiyama, T. *Chem. Lett.* **1988**, 91.
20. Zeynizadeh, B.; Dilmaghani, K. A.; Roozizoy A. *J. Chem. Res.* **2005**, 657.

21. Chavan, S. P.; Kharul, R. K.; Kalkote, U. R.; Shivakumar, I. *Synth. Commun.* **2003**, *33*, 1333.
22. Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 21.
23. Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. *Tetrahedron Lett.* **2005**, *46*, 2775.
24. Litvić, M. Enantioselective and Diastereoselective Preparations of 1,4-Dihydropyridines, Doctoral thesis, University of Zagreb, 2004.
25. (a) Leuz, A. K., Hug, S. J., Wehrli, B., Johnson, C. A. *Environ. Sci. Technol.* **2006**, *40*, 2565. (b) Knör, G. *Inorg. Chem.*, **1996**, *35*, 7916.
26. Litvić, M.; Cepanec, I.; Vinković, V. *Heterocycl. Commun.* **2003**, *9*, 385.
27. Filipan-Litvić, M.; Litvić, M.; Cepanec, I.; Vinković, V. *Molecules* **2007**, *12*, 2546.
28. Filipan-Litvić, M.; Litvić, M.; Cepanec, I.; Vinković, V. *Tetrahedron* **2008**, submitted for publication.