ORIGINAL ARTICLE

A C G publications

Org. Commun. 12:3 (2019) 143-148

organic communications

A study of Minisci reaction by changing Fe^{2+} equivalency: Preparation of arylpyridinyl methanol

Bünyamin Özgeriş[1] and Ferhan Tümer[2*]

[1]*Erzurum Technical University, Faculty of Science, Department of Basic Sciences, Erzurum, Türkiye*

[2]*Faculty of Science and Arts, Department of Chemistry, Sutcu Imam University, Kahramanmaras, Türkiye*

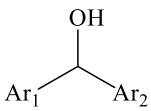
(Received June 26, 2019; Revised August 15, 2019; Accepted August 19, 2019)

Abstract: We aimed the synthesis of carboxamide **8** and **10,** however, beside the main product, one more species was detected in the reaction solution. The characterization of this side product showed that it was the other isomer of the main product. To establish reaction conditions for the synthesis of carboxamide derivatives, we have set up several experiments by changing the Fe^{2+} stoichiometry. When a molar equivalent Fe^{2+} was used, only two reaction products **8** and **10** were obtained. The increase in Fe^{2+} stoichiometry caused the formation of side product **9** and **11** even formation of reduced alcohol products (**12-15**) by Minisci reaction.

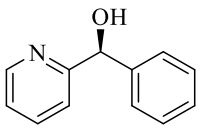
Keywords: Minisci reaction; nicotinamide; isonicotinamide; diarylmethanol.

1. Introduction

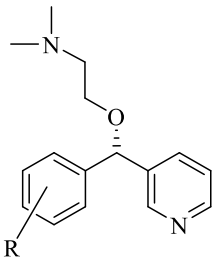
Owing to high biological activity of various derivatives, diarylmethanols (**1**) are important constituents and precursors of biologically active compounds. For example, (S)-phenyl(pyridin-2-yl) methanol, a diarylmethanol derivatives, has analgesic and anticonvulsant activities.[1] In addition, neobenodine, orphenadrine, and carbinoxamine show strong antihistaminic properties.[2-5] Enantiomerically pure diarylmethanols have been played a part as key intermediates for the synthesis of diarylalkylmethanes, which are antidepressants, antimuscarinics, and endothelin antagonists in recent years.[6,7]



1

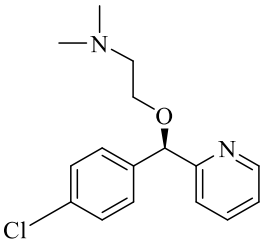


(*S*)-phenyl(pyridin-2-yl)methanol



p-Me: *(R)*-Neobenodine

o-Me: *(R)*-Orphenadrine

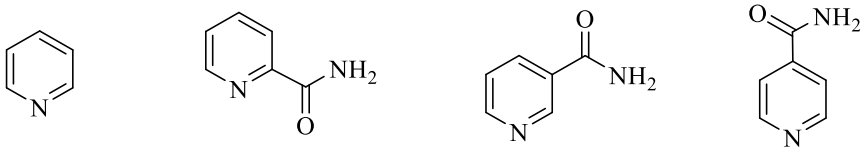


(S)-Carbinoxamine

* Corresponding author: E-mail: ftumer@ksu.edu.tr

The article was published by ACG Publications
www.acgpubs.org/organic-communications July-September 2019 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.64.19.06.1309

Pyridine is a heteroaromatic system and the compounds having this group have toxicological significance. A number of compounds having pyridine ring are used as therapeutic agents, including antihistaminic, antibacterial, anticholinergic activities.[8] Picolinamide (2-pyridinecarboxamide) **(2)**, nicotinamide (3-pyridinecarboxamide) **(3)**, and isonicotinamide (4-pyridinecarboxamide) (**4**) are a class of medicinal agents with wide range of chemical and biological applications.[9-11] Nicotinamide is a part of the pyridine nucleotides as NADC and NADPC that plays a vital role in biological oxidative chemistry and is essential for the human body system.[12-16] Isonicotinamide has strong antipyretic, antitubercular, fibrinolytic and antibacterial activities. The mixed salts of this amide have extensively uses as drugs in various biological and medicinal processes.[17]



Pyridine **2** **3** **4**

In the present work, we studied the Minisci reaction of 3-benzoylpyridine **(6)** by changing stoichiometri and obtained some further reduced products. We also aimed to synthesize new diarylmethanols, including nicotinamide and isonicotinamide derivatives **9** and **10**.

2. Experimental

2.1. Chemical Material and Apparatus

All solvents were distilled and dried according to standard procedures. Melting points were determined on a Büchi 539 capillary melting apparatus and are uncorrected. IR spectra were recorded as solutions in 0.1mm cells with a Mattson 1000 FT-IR spectrophotometer (Unicam. Ltd., York Street, Cambridge, U.K.). The ^{1}H- and ^{13}C-NMR spectra were recorded on 400 (100) MHz Varian spectrometers; δ in ppm, Me_4Si as the internal standart. All column chromatography was performed on silica gel (60-mesh, Merck). Thin layer chromatography was carried out on Merck 0.2 mm silica gel, 60 F_{254} analytical aluminum plates.

2.2. Chemistry

2.2.1. Synthesis procedures

*3-Benzoyl-pyridine (**6**):* The 3-benzoyl-pyridine (**6**) was synthesized from nicotinic acid (**5**) according to the literature procedure.[18-20]

*Pyridin-3-yl(p-tolyl)methanone (**7**):* The 3-benzoyl-pyridine (**6**) was synthesized from nicotinic acid (**5**) according to the literature procedure.[20]

*2.2.2. General procedure for synthesis of carboxamides **8-11***

To a stirred solution of 3-benzoyl-pyridine **(6)** (18.03 g, 0.1 mol) in formamide (40 mL) was added concentrated H_2SO_4 (10 mL) under N_2 at 0 °C. After the addition of $FeSO_4.7H_2O$ (56.0 g, 0.2 mol) in one portion, t-BuOOH (70%, 25 mL, 0.18 mol) was added dropwise over 1 h under N_2 at 0 °C. The reaction mixture was stirred at this temperature for 1 h then at room temperature for 7 h. The reaction mixture was cooled to 0 °C, and a solution containing H_2O (16.2 mL), KOH (22.74 g, 406 mmol), and citric acid (28.06, 146 mmol) was added to this mixture. The reaction mixture was poured into a separatory funnel containing ice (100 g), and then dilute NaOH (3M) was added (pH 12). The mixture was extracted with EtOAc (3 × 100 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. A mixture of 5-benzoyl-pyridine-2-carboxamide **(8)** and 3-benzoyl-isonicotinamide **(9)** in

a ratio of 1:1 (14 g, total yield 62%) were obtained. The resulting mixture was crystallized with CH_2Cl_2 to give 5-benzoyl-pyridine-2-carboxamide **(8)** (7.0 g, 31%) as a light yellow solid. ^{1}H-NMR and ^{13}C-NMR spectra for carboxamide **(8)** are in agreement with the literature values.[18-20]

3-Benzoyl-isonicotinamide (9): Recrystallization of the residue from MeOH gave 3-benzoyl-isonicotinamide **(9)** as a white solid (1.00 g, 10%). M.p 185-187ºC.^{1}H-NMR (400 MHz, DMSO-d_6): δ=9.65 (s, 1H, ArH), δ=8.68 (dd, *J*=4.8 Hz, 1.4 Hz, 1H, ArH), δ=7.76 (dd, *J*=7.8 Hz, 1.4 Hz, 1H, ArH), δ=7.50-7.47 (m, 2H, ArH), δ=7.37-7.28 (m, 3H, ArH).^{13}C-NMR (100 MHz, DMSO- d_6): δ=194.94, 166.15, 151.82, 145.40, 141.85, 136.93, 131.82, 129.04, 127.25, 127.06, 126.18. IR (KBr, cm^{-1}): 3734.3, 3677.4, 3648.7, 3444.6, 3244.7, 1697.6, 1587.5, 1280.5, 1197.4, 699.0.

Synthesis of 5-(4-methylbenzoyl)picolinamide (10) and 3-(4-methylbenzoyl)isonicotinamide (11) : **10** and **11** were synthesized from nicotinic acid (**5**) according to the literature procedure.[20] ^{1}H-NMR and ^{13}C-NMR spectra for carboxamides **(10** and **11)** are in agreement with the literature values.[20]

*2.2.3. General procedure for synthesis of alcohol products **12-15***

To a stirred solution of 3-benzoyl-pyridine (**6**) (18.03 g, 0.1 mol) in formamide (100 mL) was added to concentrated H_2SO_4 (10 mL) under N_2 at 0 ˚C. After the addition of $FeSO_4.7H_2O$ (86.0 g, 0.4 mol) in one portion, t-BuOOH (70%, 25 mL, 0.18 mol) was added dropwise in 1 h under N_2 at 0 ˚C. The reaction mixture was stirred at 0 ˚C for 1 h then at rt for 7 h. The reaction mixture was cooled to 0 ˚C, and a solution containing H_2O (50 mL), KOH (63.0 g, 1.12 mol), and citric acid (75.5 g 0.40 mol) was added to this mixture. This reaction mixture was poured into a separatory funnel containing ice (100 g), and then dilute NaOH (3M) was added (pH 12). The mixture was extracted with EtOAc (3 × 100 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. A mixture of 5-(hydroxy-phenyl-methyl)-pyridine-2-carboxylic acid amide (**12**) and 3-(hydroxy-phenyl-methyl)-isonicotinamide (**13**) in a ratio of 1:1 (8 g, total yield 60%) were obtained.

5-(Hydroxy-phenyl-methyl)-pyridine-2-carboxylic acid amide (12): Recrystallization of the mixture from EtOAc/hexane (30%) gave 5-(hydroxy-phenyl-methyl)-pyridine-2-carboxylic acid amide (12) as a white solid (4.0 g, 18%). M.p 235-237 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=9.44 (bs, 1H, ArH), δ=8.71 (d, *J*=4.9 Hz, 1H, ArH), 8.62 (s, 1H, NH_2), 7.69 (dd, *J*=4.9 Hz, 0.9 Hz, 1H, ArH), 7.38-7.30 (m, 5H, ArH), 5.91 (s, 1H, CH), δ=3.32 (s, 1H, OH). ^{13}C-NMR (100 MHz,DMSO- d_6): δ=168.71, 149.81, 146.43, 143.13, 139.61, 139.08, 129.59, 128.88, 127.23 117.73, 59.25. IR (KBr, cm^{-1}): 3170.3, 3065.8, 2841.7, 1699.4, 1584.9, 1428.9, 1352.8, 1027.1, 694.9.

3-(Hydroxy-phenyl-methyl)-isonicotinamide (13): Recrystallization of the residue from MeOH gave 3-(hydroxy-phenyl-methyl)-isonicotinamide (**13**) as a white solid (2,7 g, 13%). M.p 136-137 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=8.62 (s, 1H, H_6), δ=8.03 (bs, 1H, NH_2), δ=7.96 (d, *J*=8,1 Hz, A part of AB system, 1H, H_3), δ=7.88 (dd, $J_{2,3}$=8.1 Hz, $J_{2,6}$=1.83 Hz, B part of AB system, 1H, H_2), δ=7.56 (bs, 1H, NH_2), δ=7.39-7.21 (m, 5H, ArH), δ=6.18 (d, *J*=2.5 Hz, 1H, CH(OH)), δ=5.85 (d, *J*=2.5 Hz, 1H, OH(CH)). ^{13}C-NMR (100 MHz, DMSO- d_6): δ 166.57, 149.72, 147.26, 145.16, 144.31, 135.75, 129.02, 127.86, 126.93, 122.27, 72.65. IR (KBr, cm^{-1}): 3448.9, 3301.7, 3030.1, 1676.3, 1572.0, 1416.2, 1022.1, 699.9.

5-(hydroxy(p-tolyl)methyl)picolinamide (14): White solid (from EtOH), Yield 17%. M.p 140-142 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=8.58 (d, *J* = 1.8 Hz, 1H, ArH), 8.04 (bs, 1H, NH_2), 7.86 (d, *J* = 2.1 Hz, 1H, ArH), 7.84 (d, *J* = 2.1 Hz, 1H, ArH), 7.51 (bs, 1H, NH_2), 7.24 (d, *J* = 8.0 Hz, 2H, ArH), 7.11 (d, *J*= 8.0 Hz, 2H, ArH), 6.15 (d, *J*= 3.9 Hz, 1H, OH-CH), 5.80 (d, *J*= 3.9 Hz, 1H, CH-OH), 2.23 (s, 3H, CH_3). ^{13}C-NMR (100 MHz,DMSO- d_6): δ=166.8, 149.5, 147.2, 144.5, 142.1, 137.1, 135.7, 129.6, 126.9, 122.3, 72.5, 21.3. IR (KBr, cm^{-1}): 3173.1, 3041.6, 2850.3, 1694.4, 1581.5, 1430.1, 1343.6, 1022.5, 852.4, 694,3.

3-(hydroxy(p-tolyl)methyl)isonicotinamide (15): White solid (from EtOH), Yield 8%. M.p 144-146 ºC. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=8.59 (d, *J*= 1.5 Hz, 1H, ArH), 8.08 (s, 1H, NH_2), 7.87 (d, *J*= 2.1 Hz,

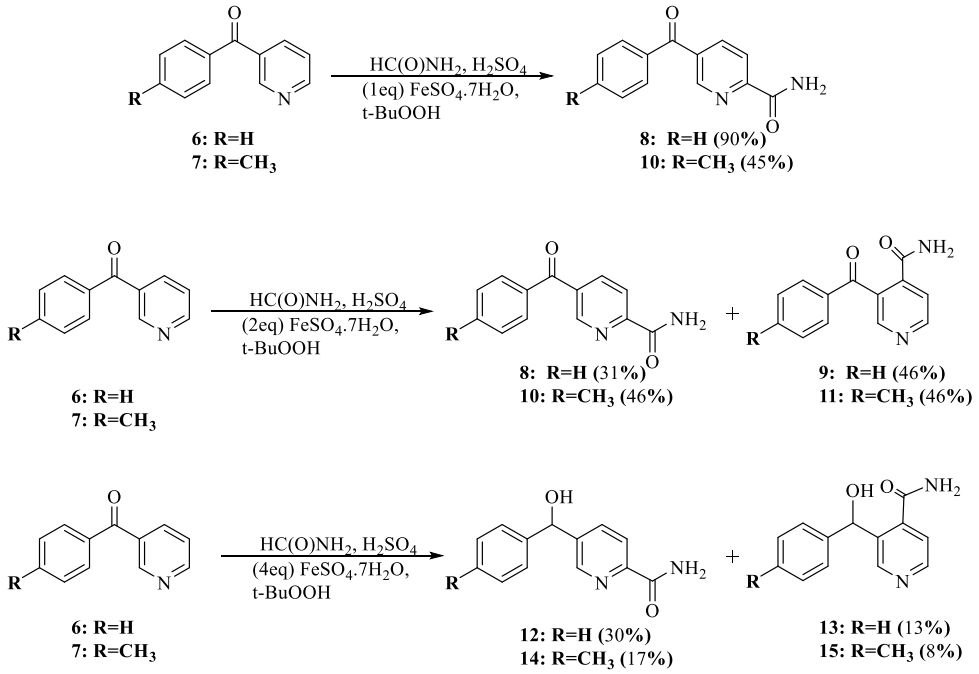
1H, ArH), 7.85 (d, *J*= 2.1 Hz, 1H, ArH), 7.53 (s, 1H, NH_2), 7.24 (d, *J*= 8.0 Hz, 2H, ArH), 7.10 (d, *J* = 8.0 Hz, 2H, ArH), 6.21 (d, *J*= 2.5 Hz, 1H, OH-CH), 5.81 (d, *J*= 2.5 Hz, 1H, CH-OH), 2.21 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO- d_6): δ=166.9, 149.4, 147.2, 144.6, 142.0, 137.1, 135.7, 129.6, 126.9, 122.3, 72.5, 21.3. IR (KBr, cm^{-1}): 3451.6, 3312.5, 3011.1, 1673.4, 1591.2, 1403.4, 1022.7, 872.8, 696.9.

3. Results and Discussion

In this study, we observed that the Fe^{2+} concentration has a dramatic effect on the distribution of reaction products. We have determined that the product distribution in the amidation of 3-benzoylpyridine **(6)** and pyridin-3-yl(p-tolyl)methanone **(7)** are dependent strongly on the Fe^{2+} concentration.

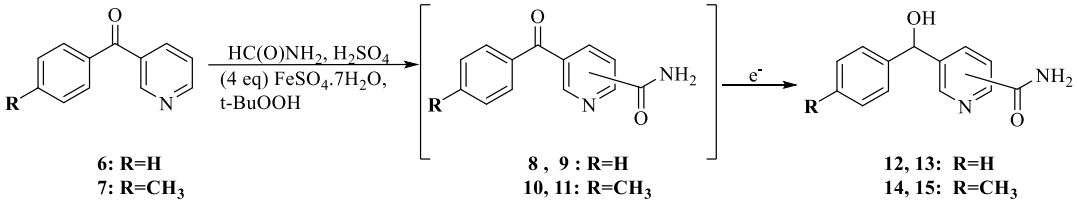
In our previous study to the given information by Langhals[18] and coworkers in 1982, from the Minisci reaction of the 3-benzoylpyridine **(6)** was only synthesized 5-benzoyl-pyridine-2-carboxamide with 45% yield **(8)**.[18] According to our study, not only 5-benzoyl-pyridine-2-carboxamide (31% yield) **(8)** but also 3-benzoyl-isonicotinamide (10% yield) **(9)** were observed. In addition to these products, we also observed 5-(hydroxy-phenyl-methyl)-pyridine-2-carboxylic acid amide **(12)** and 3-(Hydroxy-phenyl-methyl)-isonicotinamide **(13)** depending on Fe^{2+} concentration**.** Therefore we decided to study the Minisci reaction of pyridin-3-yl(p-tolyl)methanone **(7)** in detail. For this purpose we synthesized 5-(4-methylbenzoyl)picolinamide **(10)**[20], 3-(4-methylbenzoyl)isonicotinamide **(11)**[20], 5-(hydroxy(p-tolyl)methyl)picolinamide **(14)** and 3-(hydroxy(p-tolyl)methyl)isonicotinamide **(15)** depending on Fe^{2+} concentration in the same way**.**

In the presence of 1 eq Fe^{2+}, amide **8** and **10** were formed as the sole product in high yield. When the substance **(6)** and **(7)** were react with Fe^{2+} (2 eq), a mixture of two products **(8, 9 and 10, 11)** were obtained. Finally, when the 3-benzoylpyridine **(6)** and pyridin-3-yl(p-tolyl)methanone **(7)** were reacted with Fe^{2+} (4 eq), the diarylmethanols **(12, 13 and 14,15)** were obtained (Scheme 1).



Scheme 1. *In situ* generated products **(8-15)** based on the Fe^{2+} concentration

The formation of diarylmethanols can be explained with two step reactions as shown in scheme 2. The first step is amidation of benzoylpyridines **6** and **7** according to Minisci protocol. The econd step is the reduction of caroxamides **8-11** to give **12-15** via Fe^{2+} via metal reduction. alcohols by the metal electrons. The reaction mixture was separated by the crystallization technique (Scheme 2).



Scheme 2. Unexpectedly *in situ* generated alcohols based on the Fe^{2+} concentration

4. Conclusion

In this study, we synthesized carboxamide **9** and alcohols **12-15** for the first time. According to Langhals[18], although only carboxamide **(8)** was obtained from the Minisci reaction of 3-benzoylpyridine **(6)**, in our studies, carboxamides **(8, 9)** and alcohol products **(12, 13)** were also obtained. In addition to this study, we also applied the same procedure to pyridin-3-yl(p-tolyl)methanone **(7)** and obtained alcohol products **(14, 15)** together with carboxamides **(10, 11)**. Therefore, we tried a number of reactions to find how to figure it out. Finally, we found that this is based on the Fe^{2+} concentration. When the literature was searched, it was observed that there was no isomer of the carboxamide and alcohol products formed *in situ* in this way by the Minisci reaction. Therefore, this method describes directly synthesis of darylmethanol containing carboxamides via a modified Minsci protocol.

Acknowledgements

This article was produced from Msc Thesis of Bünyamin Özgeriş. The authors are thanks Prof. Dr. Süleyman Göksu for his contributions and helpful discussions on this work.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

ORCID
Bünyamin Özgeriş: 0000-0002-3783-6501
Ferhan Tümer: 0000-0003-2222-2133

References

[1] Takemoto, M.; Yamamoto, Y.; and Achiwa, K. Effect of inhibitor or immobilization on reduction of benzoylpyridines by baker's yeast. *Chem. Pharm. Bull.* **1996**, *44 (4)*, 853-855.
[2] Meguro, K.; Aizawa, M.; Sohda, T.; Kawamatsu, A.; Nagaoka, A. New 1, 4-Dihydropyridine derivatives with potent and long-lasting hypotensive effect. *Chem. Pharm. Bull*. **1985**, *33*, 3787.
[3] Toda, F.; Tanaka, K.; Koshiro, K. A new preparative method for optically active diarylcarbinols. *Tetrahedron: Asymm.* **1991**, *2*, 873-874.
[4] Stanev, S.; Rakovska, R.; Berova, N.; Snatzke, G. Synthesis, absolute configuration and circular dichroism of some diarylmethane derivatives. *Tetrahedron: Asymm.* **1995**, *6*, 183-198.
[5] Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. Synthesis of aryl 2-benzofuranyl and aryl 2-indolyl carbinols of high enantiomeric purity via palladium-catalyzed heteroannulation of chiral arylpropargylic alcohols. *Tetrahedron: Asymm.* **1996**, *7*, 1263-1266.
[6] Bolshan, K.; Chen, C.-Y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O_Shea, P. D.; Roy, A.; Tillyer, R. D. Nucleophilic displacement at benzhydryl centers: asymmetric synthesis of 1,1-diarylalkyl derivatives. *Org. Lett.* **2004**, *6 (1)*, 111-114.

[7] Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. Catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols and diarylmethylamines. *Chem. Soc. Rev*. **2006**, *35*, 454-470.
[8] Murray, M.; Sefton, R.M.; Martini, R.; Butler, A.M. Comparative induction of CYP3A and CYP2B in rat liver by 3-benzoylpyridine and metyrapone. *Chem. Biol. Interact.* **1998**, *113*, 161-173.
[9] Harms, A. F.; Nauta, W. T. The effects of alkyl substitution in drugs-I. Substituted dimethylaminoethyl benzhydryl ethers. *J. Med. Pharm. Chem*. **1960**, *2 (1)*, 57–77.
[10] Sperber, N.; Papa, D.; Schwenk, E.; Sherlock, M. Pyridyl-substituted alkamine ethers as antihistaminic agents. *J. Am. Chem. Soc*. **1949**, *71*, 887–890.
[11] Kawabata,T.; Ogino, T.; Mori, M.; Awai, M. Effect of nicotinamide and its isomers on iron-induced renal damage. *Acta Pathol. Jpn*. **1992,** *42*, 469–475.
[12] Kuca, K.; Bielavsky, J.; Cabal, J.; Bielavska, M. Synthesis of a potential reactivator of acetylcholinesterase-1-(4-hydroxyiminomethylpyridinium)-3-(carbamoylpyridinium)propane dibromide. *Tetrahedron Lett*. **2003**, *44*, 3123-3125.
[13] Jeong, H.C.; Park, N.-J.; Chae, C.H.; Musilek, K.; Kassa, J.; Kuca, K.;. Jung, Y.-S. Fluorinated pyridinium oximes as potential reactivators for acetylcholinesterases inhibited by paraoxon organophosphorus agent. *Bioorg. Med. Chem.* **2009**, *17*, 6213-6217.
[14] Sauve, A.A.; Moir, R.D.; Schramm, V.L.; Willis, I.M.; Chemical activation of Sir2-dependent silencing by relief of nicotinamide inhibition. *Mol. Cell.* **2005**, *17* (4), 595-601.
[15] Li, Y.; Bäckesjö, C.-M.; Haldosén, L.-A.; Lindgren, U.; Resveratrol inhibits proliferation and promotes apoptosis of osteosarcoma cells. *Eur. J. Pharmacol*. **2009**, *609* (1-3), 13-18.
[16] Murray, R.K.; Granner, D.K.; Mayes, P.A.; Rodwell, V.W. *Harper's Biochemistry*, Prentice Hall International Inc, London, 1990.
[17] Ahuja, I.S.; Prasad, I. Isonicotinamide complexes with some metal (II) halides and pseudohalides. *Inorg. Nucl. Chem. Lett*. **1976**, *12*, 777-784.
[18] Langhals, E.; Langhals, H.; Ruchardt, C.. Eine einfache neue synthese der fusarinsäure und anderer 5-alkyl-2-pyridincarbonsäuren. *Liebigs Ann. Chem*. **1982**, *(5)*, 930-949.
[19] Tümer F, Göksu S, Seçen H. First synthesis of (±)-vertilecanin A. *Russ. Chem. Bull*. **2005**, *54*, 2466-2467.
[20] Demirci S, Göksu S, Boztaş M, Tümer F, Seçen H. Synthesis of vertilecanin C and two new derivatives of vertilecanin A via nicotinic acid. *Turk. J. Chem*. **2008**, *32*, 287-295.