Asian Journal of Chemistry Vol. 21, No. 2 (2009), 1453-1459

Determination of the Protonation Constants of Triazole Derivatives in Non-Aqueous Solvents

FATIH ISLAMOGLU*, BAHITTIN KAHVECI, MUSA ÖZIL, EMINE AKYÜZ, EMRE MENTESE and ARIFE PINAR EKINCI
Department of Chemistry, Faculty of Sciences and Arts, Rize University, 53100 Rize, Turkey
Fax: (90)(464)2235376; Tel: (90)(464)2235375-1253
E-mail: fatihislamoglu53@hotmail.com

Different 17 triazole derivatives were titrated with tetrabutylammonium hydroxide in four non-aqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, N,N-dimethylformamide and acetonitrile), using potentiometric method. The half neutralization potential values and the corresponding pKa values were determined for all cases.

Key Words: Triazoles, Non-aqueous solvents, Potentiometric method, Half-neutralization potential.

INTRODUCTION

The pKa of compound is an important property in both the life sciences and chemistry, since the propensity of a compound to donate or accept a proton is fundamental to understanding many chemical and biochemical processes[1-3]. The pKa value of a molecule also determines the amount of protonated and non-protonated forms at a specific pH and shows the equilibrium state of the chemical system[4]. Depending on the extent of solvent interactions with the associated and dissociated forms, the equilibrium can be shifted toward the acid or the conjugate base side[5]. In biochemistry, the information about the pKa values of ionizable groups in a protein is essential for understanding its functional mechanism at moleculer level[6]. Many biological systems use proton-transfer reactions to perform communication between the extra cellular and intracellular media and the rate of the proton-transfer reaction depend, among many other factors, on the pKa value of the species involved[7].

There have been a number of systematic studies of the basicity and acididity in different media using different techniques[8-20], but unfortunately very few have dealt with triazoles. It is well known that two major factors influence the basicity or acidity of a molecule[21-24], namely, structural and solvent effects. In most molecules there are two or more structural effects and it is usually difficult to assess how much each effect contributes to the basicity or acidity of a molecule. Moreover, it is sometimes extremely difficult to differentiate between structural and solvent effects. The considerable biological importance of triazoles has stimulated much work on these derivatives[25-29]. Some naturally occurring substances of pharmacological interest have been found to possess a triazole ring in their structure[30-32]. The exact role of

these derivatives in the mode of action as antibiotic or antitumor drugs remains obscure[33]. In addition, these derivatives are reported to show a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, antiinflammatory, antioxidant and anti-HIV properties[34-39].

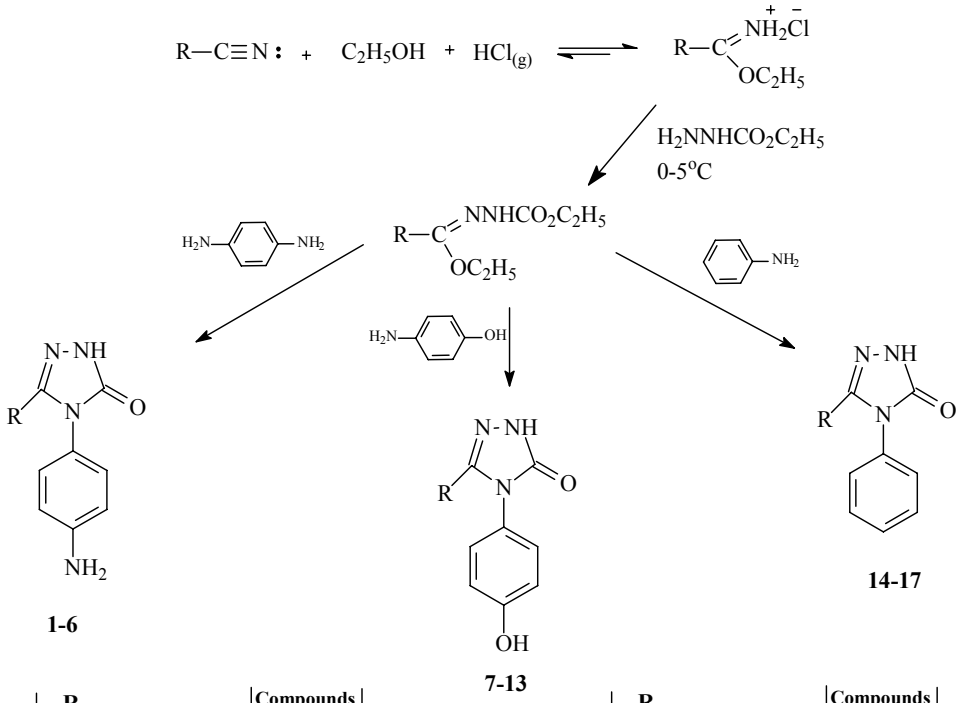
An acceptable representation of the structure of a 1,2,4-triazole must take into consideration its amphoteric nature; the mobility of the imino hydrogen atom; more stability, aromatic character and substitution pattern of the nucleus and the physical evidence that suggests its considerably polar nature. 1,2,4-Triazole is readily soluble in polar solvents and only slightly soluble in nonpolar solvents, the solubility in the latter being increased by substitution on the nitrogen atom.

In this paper, we tried to investigate structural and solvent effects of several substituents on the basicity or acidity. The 1,2,4-triazol derivatives was titrated potentiometrically as acids with tetrabutyl ammonium hydroxide in 4 non-aqueous solvents (isopropyl alcohol, *t*-butyl alcohol, N,N-dimethylformamide and acetonitrile).

EXPERIMENTAL

In this study, 17 (3 series) different triazoles [(**1-series**), 3-methyl-4-(*p*-aminophenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**1**), 3-ethyl-4-(*p*-aminophenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**2**), 3-phenyl-4-(*p*-aminophenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**3**), 3-benzyl-4-(*p*-aminophenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**4**), 3-(*p*-chlorobenzyl)-4-(*p*-aminophenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**5**), 3-(*p*-methylbenzyl)-4-(*p*-aminophenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**6**), (**2-series**), 3-methyl-4-(*p*-hydroxyphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**7**), 3-ethyl-4-(*p*-hydroxyphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**8**), 3-phenyl-4-(*p*-hydroxyphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**9**), 3-benzyl -4-(*p*-hydroxyphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**10**), 3-(*p*-chlorobenzyl)-4-(*p*-hydroxyphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**11**), 3-(*p*-methylbenzyl)-4-(*p*-hydroxyphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**12**), 3-(*p*-methoxybenzyl)-4-(*p*-hydroxyphenyl)- 4,5-dihydro-1*H*-1,2,4-triazol-5-one (**13**), (**3-series**), 3-(3'-chloro)benzyl-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**14**), 3-(2'-chloro) benzyl-4-phenyl-4,5-dihydro-1*H*-1,2, 4-triazol-5-one (**15**), 3-(2'-methyl)benzyl-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**16**), 3-(3'-methyl)benzyl-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**17**)] were synthesized. All product were synthesized according to the reported procedures[40,41] (**Scheme-I**).

Potentiometric titrations, an Orion 720A model pH-ionmeter equipped with a combined pH electrode (Ingold) and indicator elektrode were used. A magnetic stirrer, a semi micro burette and a 25 mL beaker were also used in titrations. Before potentiometric titrations, the pH meter was calibrated according to the instructions supplied by the manufactures of the pH meter. During the titrations, the titrant was added in increments of 0.05 mL after each stable reading and mV values were recorded.



R	Compounds	
$-CH_3$	1	7
$-CH_2CH_3$	2	8
$-C_6H_5$	3	9
$-CH_2C_6H_5$	4	10
$-CH_2C_6H_4$(-Cl,*p*)	5	11
$-CH_2C_6H_4$ (-CH_3, *p*)	6	12
$-CH_2C_6H_4$ (-OCH_3, *p*)		13

R	Compounds
$-CH_2C_6H_4$ (-Cl, *m*)	14
$-CH_2C_6H_4$ (-Cl, *o*)	15
$-CH_2C_6H_4$ (-CH_3, *o*)	16
$-CH_2C_6H_4$ (-CH_3, *m*)	17

Scheme-I

The necessary chemicals were supplied from Fluka and Merck. After purifications, isopropyl alcohol was used to prepare 0.05 N tetrabutylammonium hydroxide. For all potentiometric titrations, 0.05 N tetrabutylammonium hydroxide in isopropyl alcohol, which was prepared from 0.1 N tetrabutylammonium hydroxide by dilution, was used.

RESULTS AND DISCUSSION

There have been studies about the potentiometric titrations of different 17 triazol derivatives with tetrabutyl ammonium hydroxide in the non-aqueous solvents such as isopropyl alcohol, methyl alcohol, *t*-butyl alcohol and acetone and the pKa values were found between 9.79-16.05[42-44]. In this study, six compounds (**1-6**) some 3-alkyl (aryl)-4-(*p*-aminophenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones, seven compounds

(**6-13**) some 3-alkyl(aryl)-4-(*p*-hydroxyphenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones and four compounds (**14-17**) some 3-(aryl)-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ones synthesized and all compounds were titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents such as isopropyl alcohol (ε = 19.4), *t*-butyl alcohol (ε = 12), N,N-dimethylformamide (ε = 37) and acetonitrile (ε = 36).

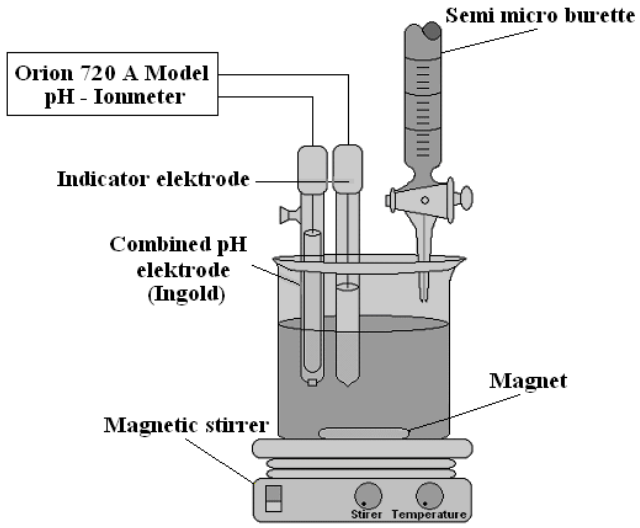


Fig. 1. Potentiometric titration cell

The mV values, which were read from pH meter, were plotted *versus* tetrabutyl ammonium hydroxide volumes (mL) added andthus potentiometric titration curves were formed for all the cases. From these curves, the half-neutralization potential values were measured and the corresponding pKa values were calculated. All the values presented are the average of at least 5 measurements and the standard deviations of each are listed. The half-neutralization potentials and the corresponding pKa values for all compounds, obtained from the potentiometric titrations with 0.05 M tetrabutylammonium hydroxide in isopropyl alcohol, *t*-butyl alcohol, N,N-dimethylformamide and acetonitrile, are given in (Table-1).

It is well known that the acidity of a compound depends on several factors. The two most important factors are the solvent effect and molecular structure[45-49]. Table-1 shows that the half-neutralization potentials values and the corresponding pKa values obtained from potentiometric titrations depend on the non-aqueous solvents used. The results obtained illustrate that *t*-butyl alcohol is the best solvent. As can be observed in (Fig. 2), for example, the potential jump of compound **3** in the end-point is very large for *t*-butyl alcohol. In addition, Table-1 shows that the molecular structure of titrated compounds effects the half-neutralization potentials and corresponding pKa values depending on the substituents in the same solvent.

TABLE-1
HALF-NEUTRALIZATION POTENTIALS (HNP) AND THE CORRESPONDING pKa VALUES OF ALL COMPOUNDS IN ISOPROPYL ALCOHOL, *t*-BUTYL ALCOHOL, N,N-DIMETHYLFORMAMIDE AND ACETONITRILE

Compd. No.	Isopropyl alcohol		*t*-Butyl alcohol		N,N-Dimethyl formamide		Acetonitrile	
	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)	pKa
1	-483.2 ± 2.5	13.48 ± 0.02	-450.5 ± 2.7	13.52 ± 0.03	-463.1 ± 2.8	13.37 ± 0.04	-441.7 ± 3.5	13.53 ± 0.03
2	-397.3 ± 2.1	12.73 ± 0.05	-384.2 ± 3.1	12.95 ± 0.07	-357.4 ± 2.5	12.94 ± 0.07	-369.8 ± 3.1	13.24 ± 0.05
3	-374.0 ± 2.9	11.69 ± 0.07	-368.7 ± 3.6	12.55 ± 0.04	-384.6 ± 3.6	13.05 ± 0.05	-376.5 ± 3.4	13.11 ± 0.06
4	-397.8 ± 3.4	11.83 ± 0.04	-372.5 ± 3.4	12.33 ± 0.05	-387.9 ± 2.8	12.93 ± 0.09	-412.2 ± 3.7	13.32 ± 0.05
5	-376.2 ± 2.8	11.52 ± 0.08	-382.3 ± 4.2	11.92 ± 0.07	-388.2 ± 3.7	13.12 ± 0.06	-385.6 ± 2.4	13.15 ± 0.07
6	-369.5 ± 4.1	11.68 ± 0.03	-362.1 ± 3.5	11.79 ± 0.08	-374.5 ± 3.5	13.18 ± 0.07	-359.1 ± 2.6	12.82 ± 0.04
7	-398.4 ± 3.9	11.82 ± 0.06	-348.7 ± 2.4	11.88 ± 0.03	-357.1 ± 2.7	12.74 ± 0.04	-379.4 ± 2.2	12.94 ± 0.09
8	-382.7 ± 4.2	11.79 ± 0.09	-369.5 ± 3.9	11.73 ± 0.04	-365.6 ± 3.4	12.86 ± 0.06	-383.6 ± 2.7	12.88 ± 0.06
9	-359.1 ± 3.0	11.66 ± 0.04	-377.2 ± 2.8	12.18 ± 0.03	-382.1 ± 2.7	12.98 ± 0.03	-371.0 ± 3.4	13.04 ± 0.05
10	-381.2 ± 3.8	12.12 ± 0.05	-341.5 ± 2.6	11.54 ± 0.04	-373.4 ± 3.7	12.81 ± 0.05	-389.4 ± 3.3	12.94 ± 0.07
11	-295.7 ± 3.2	10.35 ± 0.07	-271.8 ± 3.7	10.47 ± 0.07	-265.8 ± 3.5	11.37 ± 0.07	-252.8 ± 2.5	12.19 ± 0.03
12	-378.2 ± 3.4	11.70 ± 0.06	-381.5 ± 2.4	12.74 ± 0.05	-362.1 ± 3.4	12.78 ± 0.05	-355.3 ± 3.3	12.78 ± 0.06
13	-328.2 ± 2.8	11.27 ± 0.03	-289.9 ± 3.5	11.87 ± 0.06	-357.8 ± 3.0	12.85 ± 0.08	-379.6 ± 2.4	12.82 ± 0.05
14	-385.6 ± 3.6	11.46 ± 0.07	-376.4 ± 3.2	12.25 ± 0.05	-383.4 ± 2.9	13.10 ± 0.06	-398.1 ± 3.7	13.21 ± 0.07
15	-298.5 ± 3.2	10.65 ± 0.05	-354.1 ± 2.1	11.78 ± 0.08	-357.6 ± 3.7	12.88 ± 0.09	-367.5 ± 2.7	12.74 ± 0.04
16	-369.2 ± 2.7	11.53 ± 0.08	-352.0 ± 2.9	11.93 ± 0.04	-349.9 ± 2.9	12.61 ± 0.05	-349.7 ± 3.5	12.67 ± 0.09
17	-348.2 ± 2.9	11.47 ± 0.09	-382.2 ± 3.4	11.68 ± 0.06	-364.5 ± 4.1	12.69 ± 0.04	-383.6 ± 2.5	13.13 ± 0.08

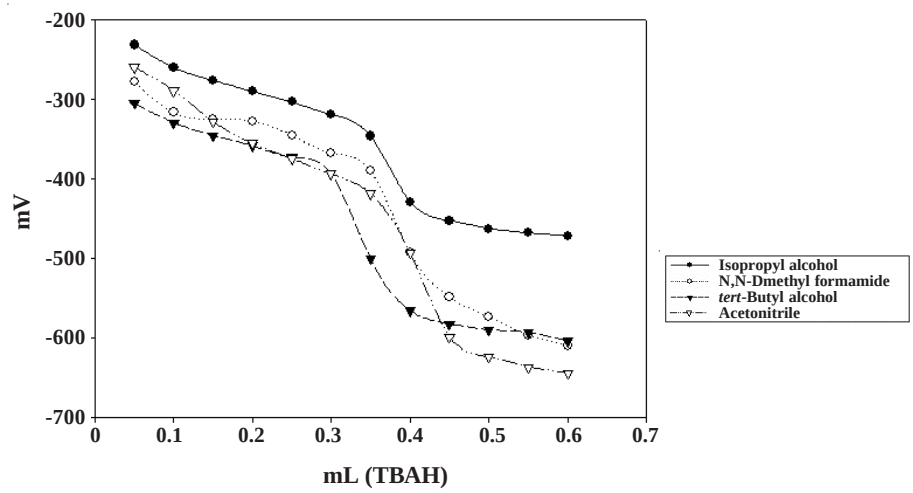


Fig. 2. Potentiometric titration curves of 10^{-3} M 3-methyl-4-(*p*-aminophenyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one (compound **1**) solutions titrated with 0.05 M tetrabutylammonium hydroxide (TBAH) in isopropyl alcohol, *tert*-butyl alcohol, N,N-dimethylformamide and acetonitrile at 25 ºC

REFERENCES

1. A.M. Magill and B.F. Yates, *Aust. J. Chem.*, **57**, 1205 (2004).
2. A.M. Magill, K.J. Cavell and B.F. Yates, *J. Am. Chem. Soc.*, **126**, 8717 (2004).
3. Y. Fu, L. Liu, H.-Z. Yu, Y. Wang and Q.-X. Guo, *J. Am. Chem. Soc.*, **127**, 7227 (2005).
4. A. Marie Toth, M.D. Liptak, D.L. Philips and G.C. Shields, *J. Chem. Phys.*, **114**, 4595 (2001).
5. C.O. Silva, E.C. Da Silva and M.A.C. Nascimento, *J. Phys. Chem. A*, **104**, 2402 (2000).
6. K. Ohno, N. Kamiya, N. Asakawa, Y. Inoune and M. Sakurai, *Chem. Phys. Lett.*, **341**, 387 (2001).
7. B.J. Smith and L. Radom, *J. Phys. Chem.*, **95**, 10549 (1991).
8. T. Gündüz, N. Gündüz, E. Kiliç and A. Kenar, *Analyst*, **111**, 1103 (1986).
9. T. Gündüz, N. Gündüz, E. Kiliç and A. Kenar, *Analyst*, **111**, 1345 (1986).
10. M.S.B. Munson, *J. Am. Chem. Soc.*, **87**, 2332 (1965).
11. J.S. Fritz, *Anal. Chem.*, **25**, 407 (1953).
12. J.S. Fritz and C.A. Burgett, *Anal. Chem.*, **44**, 1673 (1972).
13. N.V. Meurs and E.A.M.F. Dahmen, *Anal. Chim. Acta*, **21**, 193 (1959).
14. A. Mucci, R. Domain and R.L. Benoit, *Can. J. Chem.*, **58**, 953 (1980).
15. R.L. Benoit, M.J. Mackinon and L. Bergeron, *Can. J. Chem.*, **59**, 1501 (1981).
16. T. Gündüz, N. Gündüz, E. Kiliç and P. Gürkan, *Analyst*, **112**, 1057 (1987).
17. T. Gündüz, N. Gündüz, E. Kiliç, A. Kenar and G. Çetinel, *Analyst*, **111**, 1099 (1986).
18. C.W. Pifer, E.G. Wollish and M. Schmall, *Anal. Chem.*, **25**, 310 (1953).
19. S. Serin, Y. Gök, S. Karaböcek and N. Gültekin, *Analyst*, **119**, 1629 (1994).
20. A. Kenar, T. Gündüz and E. Kiliç, *Anal. Chim. Acta*, **324**, 57 (1996).
21. J.S. Fritz, Acid-Base Titrations in Non-Aqueous Solvents, Allynn Bacon, Boston, p. 47 (1973).
22. R.W. Taft, *Prog. Phys. Org. Chem.*, **14**, 247 (1983).
23. J. Hine, Structural Effects on Equilibria in Organic Chemistry, Wiley, New York, p. 69 (1975).
24. J.W. Bayles and A.F. Taylor, *J. Chem. Soc.*, 417 (1961).
25. A.A. Ikizler and K. Sancak, *Collect. Czech. Chem. Commun.*, **60**, 903 (1995).

26. J. Heeres, R. Hendrickx and J. Van Custem, *J. Med. Chem.*, **26**, 611 (1983).
27. J. Heeres, L.J.J. Backx and J. Van Custem, *J. Med. Chem.*, **27**, 894 (1984).
28. K. Richardson and P.J. Whittle, Eur. Pat. Appl. EP, 126,581 (1984).
29. P. Nusbaumer, G. Petranyi and A. Stutz, *J. Med. Chem.*, **34**, 65 (1991).
30. T. Al-Nakib, M.J. Meegan, A.M. Looney and M.L. Burke, *Eur. J. Med. Chem.*, **27**, 971 (1992).
31. E. Drouhet and B. Dupont, *Arzneim.-Forsch./Drug Res.*, **42**, 705 (1992).
32. J.M. Kane, B.M. Baron, M.W. Dudley, S.M. Sorensen, M.A. Staeger and F.P. Miller, *J. Med. Chem.*, **33**, 2772 (1990).
33. H. Yüksek, A. Demirbas, A. Ikizler, C.B. Johansson, C. Çelik and A.A. Ikizler, *Arzneim.-Forsch./Drug Res.*, **47**, 405 (1997).
34. N. Demirbas and R. Ugurluoglu, *Turk. J. Chem.*, **28**, 679 (2004).
35. A.A. Ikizler, F. Uçar, H. Yüksek, A. Aytin, I. Yasa and T. Gezer, *Acta Pol. Pharm.-Drug Res.*, **54**, 135 (1997).
36. A.R. Bhat, G.V. Bhat and G.G. Shenoy, *J. Pharm. Pharmacol.*, **53**, 267 (2001).
37. H. Yüksek, M. Küçük, M. Alkan, S. Bahçeci, S. Kolayli, Z. Ocak, Ü. Ocak, E. Sahinbas and M. Ocak, *Asian J. Chem.*, **18**, 539 (2006).
38. H. Yüksek, S. Kolayli, M. Küçük, M.O. Yüksek, Ü. Ocak, E. Sahinbas, E. Sivrikaya and M. Ocak, *Indian J. Chem.*, **45B**, 715 (2006).
39. B. Kahveci and A.A. Ikizler, *Turk. J. Chem.*, **24**, 342 (2000).
40. B. Kahveci, M. Özil and M. Serdar, *Heteroatom Chem.*, **19**, 38 (2008).
41. B. Kahveci, *Molecules*, **10**, 376 (2005).
42. A.A. Ikizler, Y. Erdogan, *Doga-Turk. J. Chem.*, **15**, 337 (1991).
43. A.A. Ikizler, H.B. Sentürk, A. Ikizler, *Doga-Turk. J. Chem.*, **15**, 345 (1991).
44. Y. Erdogan, A. Aslan, A. Demirbas and N. Yayli, *Model. Measur. Control C*, **46**, 49 (1994).
45. S. Bahçeci, H. Yüksek, Z. Ocak, A. Azakli, M. Alkan and M. Özdemir, *Coll. Czech. Chem. Commun.*, **67**, 1215 (2002).
46. S. Bahçeci, H. Yüksek, Z. Ocak, C. Köksal and M. Özdemir, *Acta Chim. Slov.*, **49**, 783 (2002).
47. A. Aslan, Y. Erdogan, A. Demirbas and S. Karslioglu, *Pharmazie*, **52**, 309 (1997).
48. A.H. Aktas, G. Yasar and G.Ö. Alsancak, *Turk. J. Chem.*, **25**, 501 (2001).
49. T. Gündüz, Susuz Ortam Reaksiyonlari, Gazi Büro Kitabevi Tic. Ltd. Sti., Ankara, p. 162 (1998).

(*Received*: 22 February 2008; *Accepted*: 8 October 2008) AJC-6930