Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(1):91-98

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Microwave-assisted synthesis of some 1,2,4-triazol-3-ones and potentiometric determination of their pKa in Amfiprotic and dipolar aprotic-water mixtures

Fatih İslamoğlu[1]*, Emre Menteşe[1], Musa Özil[1], Emine Akyüz Turumtay[1] and Bahittin Kahveci[2]

[1]Department of Chemistry, Faculty of Art and Science, Recep Tayyip Erdoğan University, 53100 Rize, Turkey.
[2]Department of Nutrition and Dietetics, Faculty of Health Sciences, Karadeniz Technical University, Trabzon, Turkey

---

ABSTRACT

*The novel 5-alkyl(aryl)-4-(aryl)-2,4-dihydro-3H-1,2,4-triazol-3-ones (**1-12**) were synthesized by reaction of (N′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester with primary amines by microwave irradiation. Stoichiometric protonation constants of **1-12** were determined potentiometrically in 50% (v/v) amfiprotic (ethanol and methanol) and dipolar aprotic (dioxan)-water mixtures at 25°C with an ionic strength of 0.10 M. The calculation of the stoichiometric protonation constants was carried out using a PKAS computer program. The effects of solvents composition on the stoichiometric protonation constants are discussed.*

Key words: Microwave-assisted synthesis, triazole, potentiometric titration, protonation constants.

INTRODUCTION

Microwave heating has been used for the rapid synthesis of a variety of compounds [1]. Conventional heating, synthesizing a single compound, chemists can now perform that same reaction in minutes [2]. Many reviews have been published recently that detail its utility [3-5]. The increase of interest in this method stems from the realization that microwave-assisted synthesis, apart from many other enabling technologies, actually provides significant practical and economic advantages [6,7].

Triazol compounds also have been found to be associated with diverse pharmacological activities such as antibacterial, antifungal, anticancer and anticonvulsant [8-13]. In recent years, the synthesis of some 1,2,4-triazol-3-one derivatives from ester (*N′*-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester has been reported [14].

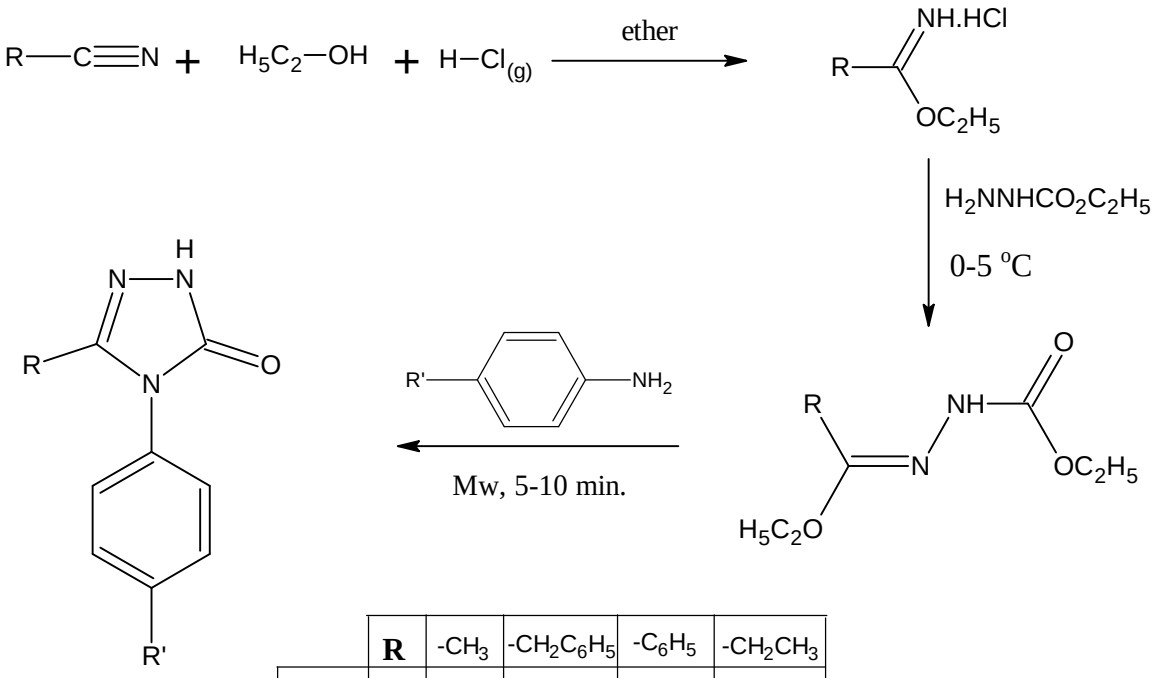
These are usually prepared by conductive heating. These reactions are time consuming. In this study, we synthesized some new 1,2,4-triazol-3-one derivatives by reaction of (*N′*-ethoxycarbonyl)-4-alkyl(aryl) hydrazonic acid ethyl ester with some primary amines under microwave irradiation in 5-10 min. **5, 6, 8, 9** and **11** compounds were synthesized by using conventional heating technique in literature [15-17]. However we synthesized and development of simple, convenient, safety and efficient methods for all compounds which was the microwave irradiation. We have already previously synthesized triazole compounds by using the microwave-irradiation method [18-20].

There have been a number of systematic studies of the acidity in different media using different techniques [21-26], but unfortunately very few have dealt with triazole. It is well known that two major factors influence the acidity of a molecule [27-29], namely, structural and solvent effects. In most molecules there are two or more structural effects

and it is usually very difficult to assess how much each effect contributes to the acidity of a molecule. Moreover, it is sometimes extremely difficult to differentiate between structural and solvent effects.

An acceptable representation of the structure of triazole must take into consideration its amphoteric nature; the mobility of the imino hydrogen atom; the great stability, aromatic character, and substitution pattern of the nucleus; and the physical evidence that suggests its considerably polar nature. Triazoles are 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 an attempt to obtain further information, we have determined potentiometrically the stoichiometric protonation constants of some 5-alkyl(aryl)-4-(substitutedphenyl)-2,4-dihydro-3*H*-1,2,4-triazol - 3 - one derivatives in various amfiprotic and dipolar aprotic-water mixtures. Furthermore, the effects of solvents composition on these constants are discussed.

Scheme 1: Synthesis of some 1,2,4-triazol-3-ones (1-12).



1-12

	R	-CH_3	-$CH_2C_6H_5$	-C_6H_5	-CH_2CH_3
R'					
-CN		**1**	**2**	**3**	**4**
-CH_3		**5**	**6**	**7**	**8**
-COOH		**9**	**10**	**11**	**12**

EXPERIMENTAL SECTION

Melting points were determined in open capillaries on an oil-heated Büchi melting point apparatus and are uncorrected. The IR spectra were recorded in KBr pellets on a Perkin –Elmer 100 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian 200 spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. The elemental analyses were determined on a Carlo Erba 1106 CHN analyzer; the measured percentages were in agreement (± 0.4%) with the calculated ones.

A monomode CEM-Discover Microwave apparatus was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in microwave process vials (30 mL) with control of the temperature by infrared detection temperature sensor. It was monitored by a computer and maintained constant by a discrete modulation of delivered microwave power. After completion of the reaction, the vial was cooled to 60^{o}C via air jet cooling.

The chemicals were purchased from Aldrich and Merck Chemical Corporation. Stock solutions of them were prepared in double-distilled conductivity water. Amfiprotic solvents (ethanol and methanol) and dipolar aprotic

solvent (dioxan) purified were used for preparation of ethanol-water, methanol-water and dioxan-water mixtures. All other chemicals used in this study were of reagent grade purity. Stock solutions of strong acid and strong base were prepared using analytical reagent-grade hydrochloric acid and sodium hydroxide, respectively. Acid solutions prepared in water were standardized by titration against primary standard sodium carbonate (Merck). Solutions of standard bases containing 0.10 M NaCl were prepared as 50% aqueous ethanol-water, methanol-water and dioxan-water solutions (v/v) an were potentiometrically standardized against hydrochloric acid solutions by use of Gran's plot techniques, allowing determination of dissolved carbonate impurity[30]. Primary standard sodium chloride (Merck) was used to keep the ionic strength constant.

The general procedure for the synthesis of 5-alkyl(aryl)-4-(p-cyanophenyl)-2,4- dihydro-3*H*-1,2,4-triazol-3-ones (1-4):
A mixture of (*N*′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester (0.01 mol) (alkyl(aryl); acetat, benzoat, phenylacetat, propionat respectively) and p-cyanoaniline (0.01 mol) in ethanol (25 mL) was irradiated in closed vessels with pressure control at 130^{o}C for 10 min (hold time) at 300 W maximum power. After the completion of the reaction (monitored by TLC, ethylacetate:Hexane, 3:1) the crude product was recrystallized from ethanol to give pure **1-4** (see Scheme 1).

5-methyl-4-(p-cyanophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1): (1.62 g, 81%, yield) as a light brown solid, mp 219-220 °C. IR (KBr)/cm^{-1}, ν= 3307 (NH), 2233 (CN), 1698 (CO), 1594 (C=N). ^{1}H-NMR (DMSO-d_6) δ=2.13 (s, 3H, -CH_3), 7.72 (quasi d, AA' part of AA'XX' system, *J*=8.2 Hz, 2H, Ar-H), 8.08 (quasi d, XX' part of AA'XX' system, *J*=8.2 Hz, 2H, Ar-H), 11.79 (s, 1H, -NH). ^{13}C-NMR (DMSO-d_6) δ=19.27, 108.22, 112.23, 123.77, 132.55, 137.32, 153.12, 155.58. Anal. Calc. for $C_{10}H_8N_4O$: C 59.99, H 4.03, N 27.99. Found: C 60.05, H 3.97, N 27.92%.

5-phenyl-4-(p-cyanophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (2): (2.28 g, 87%, yield) as a brown solid, mp 245-246°C. IR (KBr)/cm^{-1}, ν= 3171 (NH), 2225 (CN), 1706 (CO), 1603 (C=N). ^{1}H-NMR (DMSO-d_6) δ=7.63 (quasi d, AA' part of AA'XX' system, *J*=8.4 Hz, 2H, Ar-H), 8.04 (quasi d, XX' part of AA'XX' system, *J*=8.4 Hz, 2H, Ar-H), 7.20-7.48 (m, 5H, Ar-H) 12.36 (s, 1H, -NH). ^{13}C-NMR (DMSO-d_6) δ= 103.48, 118.78, 119.24, 127.35, 128.54, 129.92, 130.42, 132.99, 143.84, 152.11. Anal. Calc. for $C_{15}H_{10}N_4O$: C 68.69, H 3.84, N 21.36. Found: C 68.65, H 3.87, N 21.33%.

5-benzyl-4-(p-cyanophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (3): (2.37 g, 86%, yield) as a light brown solid, mp 244-245 °C. IR (KBr)/cm^{-1}, ν= 3186 (NH), 2230 (CN), 1691 (CO), 1581 (C=N). ^{1}H-NMR (DMSO-d_6) δ=3.91 (s, 2H, -CH_2), 7.61 (quasi d, AA' part of AA'XX' system, *J*=8.0 Hz, 2H, Ar-H), 8.06 (quasi d, XX' part of AA'XX' system, *J*=8.0 Hz, 2H, Ar-H), 6.91-7.31 (m, 5H, Ar-H) 11.98 (s, 1H, -NH). ^{13}C-NMR (DMSO-d_6) δ=31.95, 110.88, 118.12, 126.55, 128.00, 128.22, 128.51, 133.25, 134.59, 136.92, 145.38, 153.84. Anal. Calc. for $C_{16}H_{12}N_4O$: C 69.55, H 4.38, N 20.28. Found: C 69.65, H 4.35, N 20.22%.

5-ethyl-4-(p-cyanophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4): (1.78 g, 83%, yield) as a light brown solid, mp 184-187 °C. IR (KBr)/cm^{-1}, ν= 3180, (NH), 2230, (CN), 1701, (CO), 1590, (C=N). ^{1}H-NMR (DMSO-d_6) δ=1.03 (t, 3H, *J*=7.4Hz, CH_3) 2.47 (q, 2H, *J*=7.4 Hz -CH_2), 7.69 (quasi d, AA' part of AA'XX' system, *J*=8.6 Hz, 2H, Ar-H), 8.04 (quasi d, XX' part of AA'XX' system, *J*=8.6 Hz, 2H, Ar-H), 11.81 (s, 1H, -NH): ^{13}C-NMR (DMSO-d_6) δ=11.61, 26.41, 107.20, 113.19, 123.71, 131.57, 136.04, 152.21, 155.22. Anal. Calc. for $C_{11}H_{10}N_4O$: C 61.67, H 4.71, N 26.15. Found: C 61.65, H 4.68, N 26.22%.

3.2. The general procedure for the synthesis of 5-alkyl(aryl)-4-(p-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (5-8):
A mixture of (*N*′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester (0.01 mol) (alkyl(aryl); acetat, benzoat, phenylacetat, propionat respectively) and p-methylaniline (0.01 mol) in ethanol was irradiated in closed vessels with pressure control at 130^{o}C for 5 min (hold time) at 300 W maximum power. After the completion of the reaction (monitored by TLC, ethylacetate: Hexane, 3:1) the crude product was recrystallized from ethanol to give pure **5-8** (see Scheme 1).

5-methyl-4-(p-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5): (1.63 g, 86%, yield) as a white solid, mp 154-155°C. (lit. [15] mp: 155-156°C).

5-phenyl-4-(p-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (6): (2.15 g, 81%, yield) as a white solid, mp 153-154°C. (lit. [15] mp:153-154°C).

5-benzyl-4-(p-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (7): (2.12 g, 80%, yield) as a light white solid, mp 154-155°C. IR (KBr)/cm^{-1}, ν= 3216 (NH), 1693 (CO), 1544 (C=N). ^{1}H-NMR (DMSO-d_6) δ=2.31 (s, 3H, -CH_3),

3.72 (s, 2H, -CH_2), 6.68-7.27 (m, 9H, Ar-H) 11.90 (s, 1H, -NH). ^{13}C-NMR (DMSO-d_6) δ=20.67, 35.15, 124.22, 125.02, 127.14, 128.41, 128.97, 133.81, 135.39, 136.28, 146.13, 154.91. Anal. Calc. for $C_{16}H_{15}N_3O$: C 72.43, H 5.70, N 15.84. Found: C 72.37, H 5.66, N 15.88%.

5-ethyl-4-(p-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8): (1.70 g, 84%, yield) as a white solid, mp 143-145°C. (lit. [15] mp: 145-146°C).

3.3. The general procedure for the synthesis of 5-alkyl(aryl)-4-(p-carboxylphenyl)-2,4-di hydro-3*H*-1,2,4-triazol-3-one (9-12):

A mixture of (*N*′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester (0.01 mol) (alkyl(aryl); acetat, benzoat, phenylacetat, propionat respectively) and p-aminobenzoic acid (0.01 mol) in ethanol was irradiated in closed vessels with pressure control at 130^{o}C for 7 min (hold time) at 300 W maximum power. After the completion of the reaction (monitored by TLC, ethylacetate:hexane, 3:1) the crude product was recrystallized from ethanol to give pure **9-12** (see Scheme 1).

5-methyl-4-(p-carboxylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (9): (1.78 g, 81%, yield) as a light yellow, mp 225-227°C. (lit. [17] mp: 225-226°C).

5-phenyl-4-(p-carboxylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (10): (2.39 g, 85%, yield) as a yellow solid, mp 219-221°C. IR (KBr)/cm^{-1}, ν= 3260 (OH), 3179 (NH), 1703 (CO), 1677 (CO), 1600 (C=N). ^{1}H-NMR (DMSO-d_6) δ=6.92-8.05 (m, 9H, Ar-H) 11.47 (s, 1H, -NH), 12.76 (s, 1H, OH). ^{13}C-NMR (DMSO-d_6) δ=123.47, 124.72, 128.10, 129.27, 129.93, 131.79, 134.02, 140.63, 145.28, 155.13, 168.22. Anal. Calc. for $C_{15}H_{11}N_3O_3$: C 64.05, H 3.94, N 14.94. Found: C 63.95, H 3.89, N 14.95%.

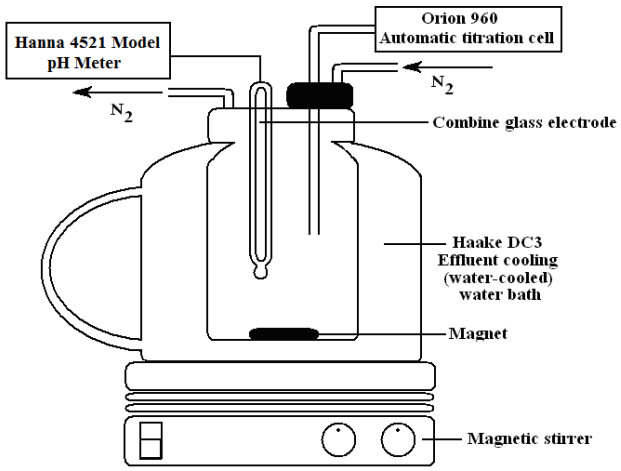
5-benzyl-4-(p-carboxylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (11): (2.20 g, 78%, yield) as a yellow, mp: 212-214°C. (lit. [17] mp: 213-214°C).

5-ethyl-4-(p-carboxylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (12): (2.03 g, 87%, yield) as a light yellow solid, mp: 232-233°C. IR (KBr)/cm^{-1}, ν= 3316 (OH), 3142 (NH), 1676 (CO), 1656 (CO), 1594 (C=N). ^{1}H-NMR (DMSO-d_6) δ=1.14 (t, 3H, J=7.0 Hz, -CH_3) 2.42 (q, 2H, J=7.0 Hz -CH_2), 7.32-8.05 (m, 4H, Ar-H) 11.49 (s, 1H, -NH), 12.52 (s, 1H, OH). ^{13}C-NMR (DMSO-d_6) δ=11.64, 27.39, 124.41, 131.20, 133.72, 142.23, 153.19, 155.67, 169.79. Anal. Calc. for $C_{11}H_{11}N_3O_3$: C 56.65, H 4.75, N 18.02. Found: C 56.66, H 4.71, N 18.08%.

Potentiometric Procedure:

All potentiometric measurements were performed in an 80-mL jacketed titration cell thermostated at 25.0±0.1°C and under nitrogen atmosphere. The potentiometric titration cell is given Fig. 1. An Hanna 4521 Model pH meter, fitted with a combined pH electrode (in gold) containing a filling solution of 0.01 M NaCl, was used for measuring the cell emf values. The potentiometric cell was calibrated before each experiment so that the hydrogen ion concentration rather than the activity was measured [31, 32]. For all the solvent mixtures examined, reproducible values of autoprotolysis constants Kw were calculated from several series of [H] and [OH] measurements at 0.10 M NaCl [33, 34].

Figure 1: Potentiometric titration cell.



The following solutions prepared in water and each of the solvent mixtures studied (total volume = 50 mL) were titrated potentiometrically with CO_2-free standard 0.1 M sodium hydroxide dissolved in the corresponding solvents:

(a) 2.5 x 10^{-3} M HCl (for cell calibration); (b) (2.5 x 10^{-3} - 7.5x10^{-3} M) HCl + 1.5x10^{-3} M triazoles. During each titration the ionic strength was maintained at 0.1 M NaCl and a potential reading was taken after a suitable time (normally 2-3 min) for equilibration. The protonation constants of the triazoles were calculated by analyzing the titration data using the computer program developed by Motekaitis and Martell [35]. Potentiometric titration curves were performed for all the cases. These curves are given Figures 2-4.

Figure 2: J–log [H] curves of compound 1, 2, 3 and 4 titrated in 50% ethanol-50% water mixtures at 25°C with an ionic strength of 0.10 M.

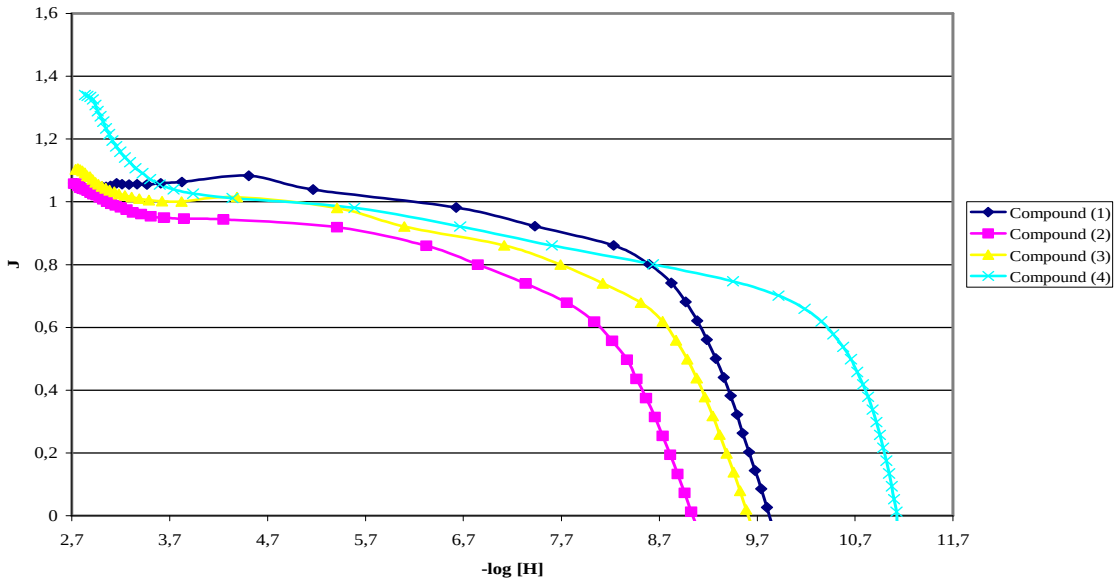
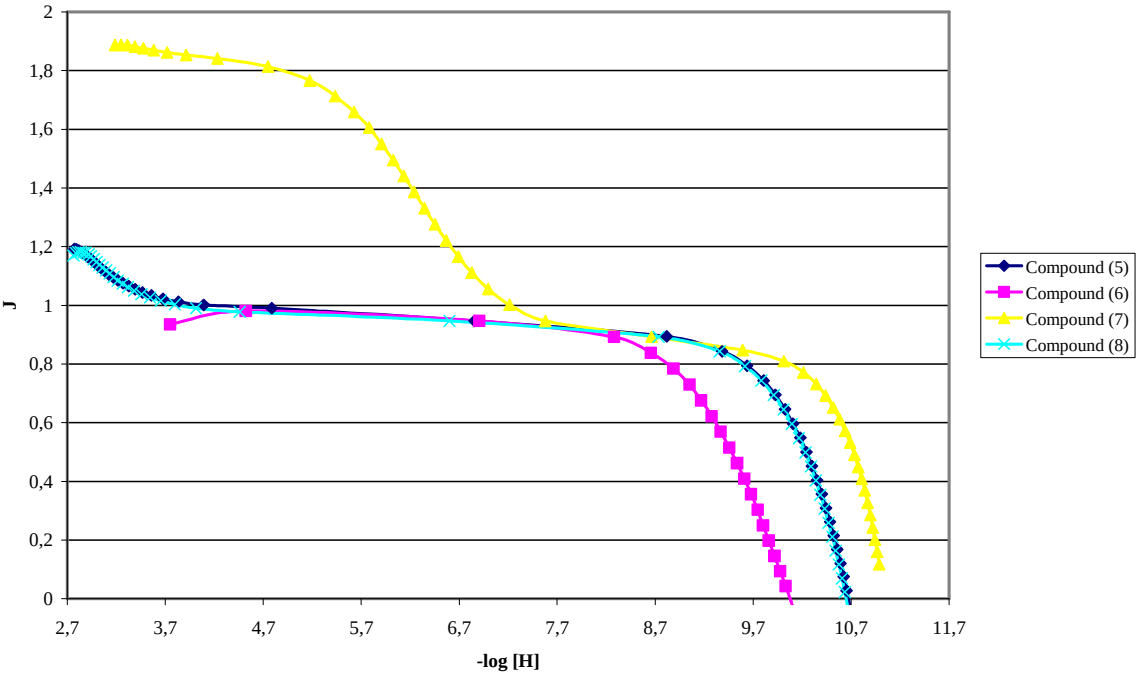
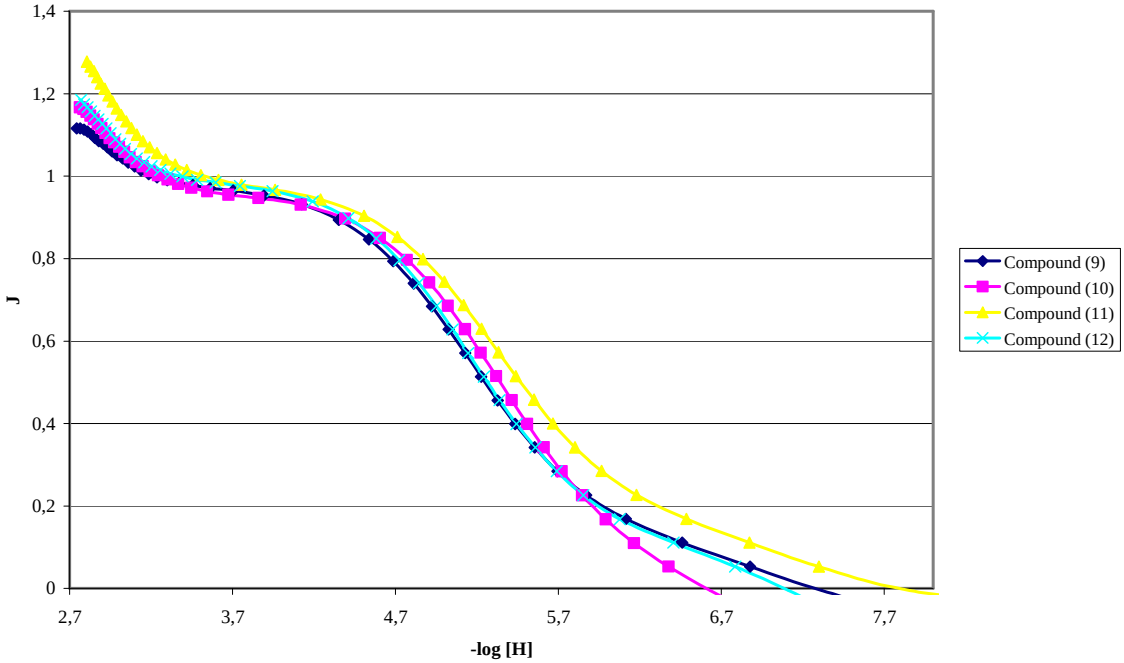


Figure 3: J–log [H] curves of compound 5, 6, 7 and 8 titrated in 50% methanol-50% water mixtures at 25°C with an ionic strength of 0.10 M.



The numerical log K_a values of these triazole derivatives determined in 50% ethanol-50% water, 50% methanol-50% water and 50% dioxan-50% water mixtures are given in Table 1. This study is also concerned with the effect of solvent composition on the stoichiometric protonation constants. The literature data indicate that the equilibrium constants are directly related to the solvent composition [36-38]. The data we obtained in our study also verify this.

Figure 4: J–log [H] curves of compound 9, 10, 11 and 12 titrated in 50% dioxan-50% water mixtures at 25°C with an ionic strength of 0.10 M.



RESULTS AND DISCUSSION

N′-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester can be considered as useful intermediates leading to the formation of heterocycles such as 1,2,4-triazole-3-ones. We synthesized some (*N′*-ethoxycarbonyl)-4-alkyl(aryl) hydrazonic acid ethyl ester according to literature [14]. Treatment of (*N′*-ethoxycarbonyl)-4-alkyl(aryl)hydrazonic acid ethyl ester (alkyl(aryl); acetat, benzoat, phenylacetat, propionat respectively) with p-cyanoaniline under microwave heating in ethanol for 10 min resulted in the formation of 5-alkyl(aryl)-4-(p-cyanophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**1-4**), treatment with p-methylaniline under microwave heating in ethanol for 5 min resulted in the formation of 5-alkyl(aryl)-4-(p-methylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**5-8**) and treatment with p-aminobenzoic acid under microwave heating in ethanol for 7 min resulted in the formation of 5-alkyl(aryl)-4-(p-carboxylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**9-12**) (Scheme 1).

The reaction temperature was constant at 130^{o}C. However reaction time changeable about nucleophilic character of aniline compounds. In this reason, reaction time for **5-8** compounds was rapidest than **1-4** and **9-12** compounds. Also reaction time for **1-4** compounds was slowest than **5-8** and **9-12** compounds. The yield was more satisfied up to 85%. The product structure was confirmed by the IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analyses.

The IR spectra of **1-4** are characterized by absorption bands around at 3180, 2225, 1700 and 1594 cm^{-1}, attributable N-H, C≡N, C=O and C=N functions, respectively and its ^{1}H NMR spectrum revealed two signals quasi dublet around at 7.63 and 8.04 ppm assigned to AA'XX' system aromatic protons. Also it revealed to signal around at 11.98 ppm assigned to NH protons. It was obvious ^{13}C NMR spectra; triazol C=O signal at about δ 155.11 ppm, C=N signal at about δ 145.38 ppm as well as the C≡N signal in average of δ 107.20 ppm, all support this conclusion. In the IR spectrum of **7** is characterized absorption bands around at 3216, 1693 and 1544 cm^{-1}, attributable N-H, C=O and C=N functions, respectively and its ^{1}H NMR spectra confirmed the presence of -CH_3, -CH_2 and -NH at 2.31, 3.72, and 11.90 ppm, respectively. Also it revealed to signal between at 6.68-7.27 ppm assigned to aromatic protons. The ^{13}C NMR spectra of triazole C=O signal at about δ 154.91 ppm, C=N signal at about δ 146.13 ppm and Ar-C signal at between δ 124.22-136.28 ppm, all support this conclusion. The IR spectra of **10** and **12** are characterized by absorption bands around at 3260 (O-H), 3142 (N-H), 1703 (C=O (triazol)), 1656 (C=O (carboxyl)), and 1594 (C=N) cm^{-1}. The ^{1}H NMR spectra revealed signals around at 6.92-8.05, 11.47 and 12.52 ppm assigned aromatic protons, –NH and –OH respectively. It was obvious ^{13}C NMR spectra; carboxyl C=O peak at near δ 168.22 ppm triazole C=O signal at about δ 155.13 ppm, C=N signal at about δ 145.28 ppm and Ar-C signal at between δ 123.47-140.63 ppm, all support this conclusion. Morover, the elemental analyses of the all compounds showed good agreement with the calculated values.

There have been studies about the potentiometric titrations of different 12 triazole derivatives in 50% ethanol-50% water, 50% methanol-50% water and 50% dioxan-50% water mixtures and the pK_a values were found between 5.873 ± 0,042- 9.965 ± 0.029 in 50% ethanol-50% water, 5.887 ± 0.041 - 10.725 ± 0.055 in 50% methanol-50% water and 5.249 ± 0.044 - 10.321 ± 0.052 in 50% dioxan-50% water. The mV values, which were read from pH meter, were plotted versus sodium hydroxide volumes (mL) added and thus potentiometric titration curves were recorded for all 3*H*-1,2,4-triazol-3-ones (**1-12**). From these curves, potential values were determined and the corresponding pK_a values were calculated using a PKAS computer program at 25^{o}C with an ionic strength of 0.10 M. All the values presented are the average of at least 5 measurements and the standard deviations of each are listed. The corresponding pK_a values for all compounds, obtained from the potentiometric titrations with sodium hydroxide in 50% ethanol-50% water, 50% methanol-50% water and 50% dioxan-50% water mixtures, are given in Table 1.

Table 1: Stoichiometric protonation constants of 1-12 at 25°C for different media-water mixtures (μ=0.1 M NaCl)

Compound	50% Ethanol - 50% Water	50% Methanol - 50% Water	50% Dioxan - 50% Water
	pKa	pKa	pKa
1	9.277 ± 0.082	10.112 ± 0.043	9.923 ± 0.058
2	8.364 ± 0.008	9.841 ± 0.058	10.142 ± 0.042
3	8.983 ± 0.161	10.019 ± 0.035	9.871 ± 0.067
4	9.277 ± 0.082	9.952 ± 0.028	9.767 ± 0.039
5	9.857 ± 0.060	10.245 ± 0.057	10.321 ± 0.052
6	9.243 ± 0.045	9.500 ± 0.072	10.157 ± 0.058
7	9.965 ± 0.029	10.725 ± 0.055	9.922 ± 0.046
8	9.821 ± 0.051	10.233 ± 0.025	9.994 ± 0.063
9	6.124 ± 0.038	5.887 ± 0.041	5.249 ± 0.044
10	5.957 ± 0.053	6.134 ± 0.058	5.342 ± 0.042
11	6.212 ± 0.067	5.962 ± 0.033	5.467 ± 0.028
12	5.873 ± 0.042	5.986 ± 0.064	5.265 ± 0.054

It is well known that the acidity of a compound depends on several factors. The two most important ones are solvent effect and molecular structure. The Table 1 shows that the corresponding pK_a values obtained from potentiometric titrations depend on the solvents used and molecular structure of the compound. As seen in the Table 1, the acidic sequence for compounds **1–12** in 50% ethanol-50% water: 12>10>9>11>2>3>6>1=4>8>5>7, in 50% methanol-50% water: 9>11>12>10>6>2>4>3>1>8>5>7, in 50% dioxan- 50% water: 9>12>10>11>4>3>7>1>8>2> 6>5. In another words, in 50% ethanol-50% water; compound **12**, in 50% methanol-50% water; compound **9**, in 50% dioxan-50% water; compound **9** show the strongest acidic properties. On the other hand, the order of the weakest acidic properties as follows: compound **7** in 50% ethanol-50% water; compound **7** in 50% methanol-50% water; compound **5** in 50% dioxan-50% water. For all compounds; compound **9** show the strongest acidic properties in 50% dioxan-50% water and compound **7** show the weakest acidic properties in 50% methanol-50% water. This situation may be attributed to H-bonding between the formed anions and the solvent molecules in amfiprotic and dipolar aprotic–water mixtures.

CONCLUSION

We have developed simple, convenient, safety and efficient approach for the synthesis of some 3*H*-1,2,4-triazol-3-ones by using microwave irradiation. The presently reported methodology for the synthesis of triazole compounds can be applied for the generation of several molecules that closely resemble biologically active products. Also, the effect of solvents composition on the stoichiometric protonation constants are discussed in this report.

Acknowledgements
This work was supported by the research fund of the Rize University (No: 2008.102.02.03)

REFERENCES

[1] S Caddick. *Tetrahedron*, **1995**, 51, 10403-10432.
[2] RS Varma. *Green Chem.*, **1999**, 1, 43-55.
[3]CO Kappe; D Dallinger. *Nature Rev. Drug Disc.*, **2006**, 5, 51-63.
[4] L Perreux; A Loupy. *Tetrahedron*, **2001**, 57, 9199-9223.
[5] P Lidstrom; J Tierney; B Wathey; J Westman. *Tetrahedron*, **2001**, 57, 9225-9283.
[6] RS Varma; KP Naicker; D Kumar; R Dahiya; PJJ Liesen. *Micro. Pow. Electromagn. Energy.*, **1999**, 34, 113-123.
[7] RS Varma. *Tetrahedron*, **2002**, 58, 1235-1255.
[8] OG Todoulou; AE Papadaki-Valiraki; S Ikeda; ED Clercq. *Eur. J. Med. Chem.*, **1994**, 29, 611-620.

[9] S Rollas; N Kalyoncuoglu; D Sur-Altiner; Y Yegenoglu. *Pharmazie*, **1993**, 48, 308-309.
[10] F Malbec; R Milcent; PJ Vicart. *J. Heterocycl. Chem.*, **1984**, 21, 1769-1774.
[11] B Kahveci; AA Ikizler. *Acta Polon. Pharm.-Drug.Res.*, **2000**, 57, 119-122.
[12] B Kahveci; O Bekircan; M Serdar; AA Ikizler. *Indian J. Chem.*, **2003**, 42, 1527-1530.
[13] O Bekircan; B Kahveci; M Küçük. *Turk. J. Chem.*, **2006**, 30, 29-40.
[14] R Ün; A İkizler. *Chim. Acta Turc.*, **1975**, 3, 113-132.
[15] B Kahveci. *Molecules*, **2005**, 10, 376-382.
[16] DA Benson; I Karsch-Mizrachi; DJ Lipman; J Ostell; BA Rapp; DL Wheeler. *Nucl. Acids Res.*, **2000**, 28, 15-18.
[17] AA Ikizler; A Ikizler; M Serdar; N Yıldırım. *Acta Pol. Pharm. Drug Res.*, **1997**, 54, 363-370.
[18] B Kahveci; M Özil, M Serdar. *Heteroatom Chem.*, **2008**, 19, 38-42.
[19] B Kahveci; M Özil; E Menteşe; O Bekircan; K Buruk. *Russ. J. Org. Chem.*, **2008**, 44, 1816-1821.
[20] B Kahveci; F Yılmaz; E Menteşe; FŞ Beriş. *J. Chem. Res.*, **2012,** 36(8), 484-488.
[21] T Gündüz; N Gündüz; E Kılıç; A Kenar. *Analyst*, **1986**, 111, 1103-1105.
[22] T Gündüz; N Gündüz; E Kılıç; A Kenar. *Analyst*, **1986**, 111, 1345-1347.
[23] MSB Munson. *J. Am. Chem. Soc.*, **1965**, 87, 2332-2336.
[24] JS Fritz. *Anal. Chem.*, **1953**, 25, 407-411.
[25] A Mucci; R Domain; RL Benoit. *Can. J. Chem.*, **1980**, 58, 953-958.
[26] S Serin; Y Gök; S Karaböcek; N Gültekin. *Analyst*, **1994**, 119, 1629-1631.
[27] JS Fritz. Acid-Base Titrations in Non-aqueous Solvents; Allynn Bacon, Boston, **1973**; pp. 53.
[28] RW Taft. *Prog. Phys. Org. Chem.*, **1983**, 14, 247-350.
[29] J Hine. Structural Effects on Equilibria in Organic Chemistry; Wiley, New York, **1975**; pp. 64.
[30] G Gran. *Analyst*, **1952**, 77, 661-671.
[31] AE Martell; RJ Motekaitis. The Determination and Use of Stability Constants; VCH, Weinheim, **1988**; pp. 102.
[32] M Meloun; J Havel. Computation of solution equilibria; Wiley, New York, **1988**; pp. 28.
[33] EP Serjeant; Potentiometry and Potentiometric Titrations; Wiley, New York, **1984**; pp. 45.
[34] S Rondinini; T Mussini; PR Mussini; P Longhi. *Pure & Appl. Chem.*, **1987**, 59, 1693-1702.
[35] RJ Motekaitis; EA Martell. *Can. J. Chem.*, **1982**, 60, 168-173.
[36] CC Panichajakul; EM Woolley. *Anal. Chem.*, **1975**, 47, 1860-1863.
[37] H Rving; HS Rossotti; *Analyst*, **1955**, 80, 245-260.
[38] RA Robinson; RH Stokes. *Electrolyte Solutions*; Academic Press, New York, **1959**; pp. 51.