BazıYeniPotansiyelBiyolojik 4-(Arylidenamino)-2, 4-dihidro-3*H*-1,2,4-Triazol-3-one BileşiklerininMikrodalga-destekliSentezivepKaDeğerlerininBelirlenmesi

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Özet

Buçalışmada,sekiz yeni bazı potansiyel biyolojik aktif 4-(arilidenamino)-2,4-dihidro-1*H*-1,2,4-triazol-3-on bileşikleri mikrodalga yöntemi kullanılarak sentezlendi. Bu bileşiklerin yapıları farklı spektroskopik yöntemle (IR, ^{1}H NMR, ^{13}C NMR and elemental analiz) kullanılarak karakterize edildi. Bu bileşiklerin asit ayrışma sabitleri teorik olarak 25^{o}C'de yirmi beş farklı çözücü içerisinde SPARC bilgisayar programı vasıtasıyla belirlendi. Çözücülerin asit ayrışma sabitleri üzerindeki etkileri tartışıldı.

Anahtar Kelimeler — Asit ayrışma sabiti, 4-Amino-1,2,4-triazol, İmin, Mikrodalga Sentez, NMR.

Microwave-assisted Synthesis of Some New Potential Biological 4-(Arylidenamino)-2, 4-dihydro-3*H*-1,2,4-Triazol-3-ones and Determination of pKa Values

Abstract

In the present study, eight new 4-(arylideneamino)-2,4-dihydro-1*H*-1,2,4-triazol-3-ones that may show some potential biological properties were synthesized using microwave method. These compounds were characterized by different spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR and elemental analysis). Acid dissociation constants (pKa) were determined theoretically with SPARC computer program in different twenty five solvents at 25^{o}C. The effects of solvents composition on the acid dissociation constants are discussed.

Keywords — Acid dissociation constant, 4-Amino-1,2,4-triazol, Imines, Microwave synthesis, NMR.

1 Introduction

Medicinal chemistry has tremendously benefited from the technological advances. This situation has created a need for an innovative machine for the development of methods which will accelerate the design, synthesis and purification of compound libraries. Therefore, microwave chemistry has become a central tool. The short reaction times provided by microwave synthesis make it ideal for rapid reaction. It is also known reduce side reactions, increase yields, and improve reproducibility [1-6]. In recent years, 1,2,4-triazol-3-ones have found to be associated with diverse antibacterial,

antifungal, anticonvulsant and antitumor properties [7-11].Acid dissociation constants are very important parameters, which can provide critical information about chemical properties such as acidity [12-15]. Hence, the relationship between the acid dissociation constants and structure in molecules is important [13, 14, 16,17]. Acid dissociation constants are also important parameters for the selection of the optimum conditions in the development of analytical methods [16, 18] and provide information about the stereo chemical and conformational structures of active centers of enzymes [19]. Acid dissociation constants are determined by several methods such as potentiometric [16], spectroscopic [17], electrophoretic methods [13, 20] and theoretical [19]. Thus, the acid dissociation constants of these compounds is still of great interest.

2 Results and Discussion

Iminoester hydrochlorides **1** were prepared according to the reported literature procedure [21]. Ester ethoxycarbonylhydrazones**2** and 4-amino-1,2,4-triazoles **3** were synthesized according to the reported literature [22].

In this report, a practical method has been proposed for the synthesis of 4-(arylidenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **4a-h**. This reaction was carried out by using microwave irradiation Scheme 1.

All pKa values are presented in Table 1. Theoretical calculated all pKa values were comparison in all worked solvents at 25°C in Figure 1.

3Experimental

All the chemicals were supplied from Merck, Aldrich and Fluka. Melting points were determined on capillary tubes on Buchi oil heating melting point apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were performed on Varian-Mercury 400 MHz spectrometer in DMSO-d_6 using TMS as internal. The elemental compositions were determined on a Carlo Erba 1106 CHN analyser; the experimental values were in agreement (±0.4 %) with calculated ones.All reactions were monitored by TLC using precoated aluminum sheets (silica gel 60 F 2.54 0.2 mm thickness). A mono mode CEM-Discover Microwave 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 at a constant value by a discrete modulation of delivered microwave power. After completion of the reaction, the vial was cooled to 60 °C via air jet cooling.

3.1 Microwave method for the synthesis of type (4a-h):

A mixture of 3 (0.01 mol), corresponding aldehyde (0.01 mol) and 1-2 drops acetic acid was heated under microwave irridation in closed vessels with pressure control at 115 ^{0}C for 2 min. at 300 W maximum power. TLC Monitoring (AcO-Et/hexane 4:1) was conducted to determine if the reaction was over. The reaction mixture was cooled to room temperature and was crystallized from ethanol.

5-(2-Chlorobenzyl)-4-{[(4-fluorophenyl)methylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4a):

Yield: 94%; M.p. 188-190 °C;^{1}H NMR (400 MHz, DMSO-d6) (δ/ppm): 12.04 (s, 1H, NH), 9.86 (s, 1H, CH), 7.87-7.18 (m, 8H, Ar-H), 4.16 (s, 2H, CH2); ^{13}C NMR (100 MHz, DMSO-d6) (δ/ppm): 28.12 (CH_2), 106.21, 114.80, 115.16, 126.18, 127.60, 128.18, 129.02, 130.12, 132.00, 144.60 (2C), 146.50 (2C), 152.30 (C=N), 155.22 (C=O); IR (ν/cm^{-1}): 3172(NH), 1704 (C=O), 1579 (C=N), 1124 (C-F), 676 (C-Cl); Analysis (% Calculated/found) for $C_{16}H_{12}ClFN_4O$ (Mw 330.74) C: 58.10/58.03, H: 3.66/3.61, N: 16.94/16.82.

5-(2-Chlorobenzyl)-4-{[(2-hydroxy-5-chlorophenyl)methylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4b):

Yield: 92%; M.p. 240-241°C; ^{1}H NMR (400 MHz, DMSO-d6) (δ/ppm): 12.04 (s, 1H, NH), 9.86 (s, 1H, CH), 7.87-7.18 (m, 8H, Ar-H), 4.16 (s, 2H, CH2); ^{13}C NMR (100 MHz, DMSO-d6) (δ/ppm): 28.12 (CH_2), 106.21, 114.80, 115.16, 126.18, 127.60, 128.18, 129.02, 130.12, 132.00, 144.60 (2C), 146.50 (2C), 152.30 (C=N), 155.22 (C=O); IR (ν/cm^{-1}): 3172(NH), 1704 (C=O), 1579 (C=N), 1124 (C-F), 676 (C-Cl); Analysis

(% Calculated/found) for $C_{16}H_{12}Cl_2N_4O_2$ (Mw 363.20) C: 52.91/52.80, H: 3.33/3.22, N: 15.45/15.36.

5-(2-Chlorobenzyl)-4-{[(2-hydroxy-5-bromophenyl)methylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4c):

Yield: 86%; M.p. 245-246°C; ^{1}H NMR (400 MHz, DMSO-d6) (δ/ppm): 12.10 (s, 1H, NH), 10.60 (s, 1H, OH), 9.93 (s, 1H, CH), 7.68-7.28 (m, 7H, Ar-H), 4.20 (s, 2 H, CH_2); ^{13}C NMR (100 MHz, DMSO-d6) (δ/ppm): 28.85 (CH_2), 118.14, 121.24, 123.18, 124.61, 127.20, 128.69, 129.22, 131.01, 132.14, 133.01, 133.22, 144.97, 147.95, 151.09 (C=N), 156.22 (C=O); IR (ν/cm^{-1}): 3195 (NH), 1708 (C=O), 1583 (C=N), 1263 (C-O), 682 (C-Cl); Analysis (% Calculated/found) for $C_{16}H_{12}BrClN_4O_2$ (Mw 407.64) C: 47.14/47.05, H: 2.97/2.86, N: 13.74/13.65.

5-(2-Chlorobenzyl)-4-{[(3,4-dihydroxyphenyl)methylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4d):

Yield: 93%; M.p. 278-279°C; ^{1}H NMR (400 MHz, DMSO-d6) (δ/ppm): 11.78 (s, 1H, NH), 9.60 (s,1H, OH), 9.32 (s, 1H, CH), 9.20 (s, 1H, OH), 7.48-7.14 (m,7H, Ar-H), 4.21 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d6) (δ/ppm): 28.79 (CH_2), 94.12, 113.26, 115.83, 121.28, 124.93, 126.22, 127.83, 128.96, 130.12, 132.27, 143.18, 145.60, 148.18, 150.13 (C=N), 155.22 (C=O); IR (ν/cm^{-1}): 3418 (OH), 3178 (NH), 1704 (C=O), 1602 (C=N), 1243 (C-O), 677 (C-Cl); Analysis (% Calculated/found) for $C_{16}H_{13}ClN_4O_3$ (Mw 344.75) C: 55.74/55.68, H: 3.80/3.71, N: 16.25/16.18.

5-(3-Chlorobenzyl)-4-{[(2-hydroxy-5-bromophenyl)methylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4e):

Yield: 96%; M.p. 236-238°C; ^{1}H NMR (400 MHz, DMSO-d6) (δ/ppm): 11.78 (s, 1H, NH), 9.60 (s,1H, OH), 9.32 (s, 1H, CH), 9.20 (s,1H, OH), 7.14-7.48 (m,7H, Ar-H), 4.21 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d6) (δ/ppm): 28.79 (CH_2), 94.12, 113.26, 115.83, 121.28, 124.93, 126.22, 127.83, 128.96, 130.12, 132.27, 143.18, 145.60, 148.18, 150.13 (C=N), 155.22 (C=O); IR (ν/cm^{-1}): 3418 (OH), 3178 (NH), 1704 (C=O), 1602 (C=N), 1243 (C-O), 677 (C-Cl); Analysis (% Calculated/found) for $C_{16}H_{12}BrClN_4O_2$ (Mw 407.64) C: 47.14/47.08, H: 2.97/2.84, N: 13.74/13.68.

5-(3-Chlorobenzyl)-4-{[(2-hydroxy-5-chlorophenyl)methylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4f):

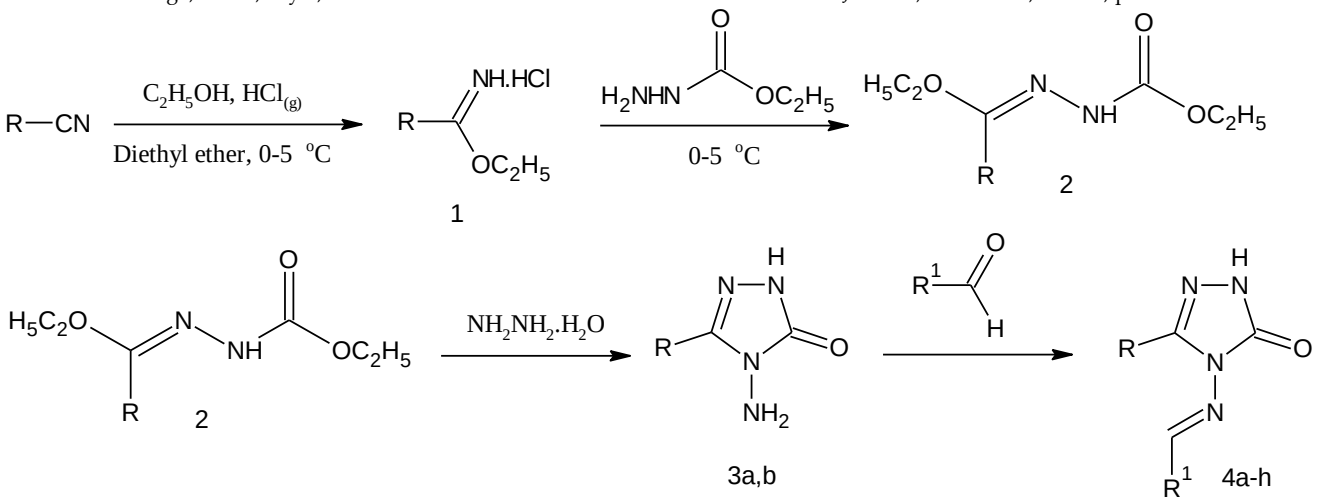
Yield: 91%; M.p. 238-240°C; ^{1}H NMR (400 MHz, DMSO-d6) (δ/ppm): 11.91 (s, 1H, NH), 10.46 (s,1H, OH), 9.88 (s, 1H, CH), 6.84-7.78 (m,7H, Ar-H), 4.17 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d6) (δ/ppm): 28.86 (CH_2), 95.42, 110.71, 118.46, 121.81, 127.03, 127.64, 128.71, 129.71, 130.90, 133.10, 134.72, 144.79, 147.99, 151.05 (C=N), 156.59 (C=O); IR (ν/cm^{-1}): 3400 (OH), 3186 (NH), 1712 (C=O), 1585 (C=N), 1261 (C-O), 682 (C-Cl); Analysis (% Calculated/found) for $C_{16}H_{12}Cl_2N_4O_2$ (Mw 363.20) C: 52.91/52.78, H: 3.33/3.21, N: 15.45/15.33.

5-(3-Chlorobenzyl)-4-{[(3-bromo-4-florophenyl)methylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4g):

Yield: 94%; M.p. 213-214°C; ^{1}H NMR (400 MHz, DMSO-d6) (δ/ppm): 11.98 (s, 1H, NH), 9.70 (s, 1H, CH), 6.64-7.48 (m,7H, Ar-H), 4.08 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d6) (δ/ppm): 28.81 (CH_2), 95.40, 116.95, 127.09, 128.65, 129.18, 129.40, 129.56, 129.22, 131.03, 131.64, 131.71, 131.97, 133.04, 133.16, 144.81 (C=N), 152.00 (C=O); IR (ν/cm^{-1}): 3169 (NH), 1706 (C=O), 1582 (C=N), 1045 (C-F), 712 (C-Cl); Analysis (% Calculated/found) for $C_{16}H_{11}BrCl_2N_4O$ (Mw 426.09) C: 45.10/45.01, H: 2.60/2.53, N: 13.15/13.09.

5-(3-Chlorobenzyl)-4-{[(3,4-dihydroxyphenyl)methylidene]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (4h):

Yield: 92%; M.p. 280-281°C; ^{1}H NMR (400 MHz, DMSO-d6) (δ/ppm): 11.82 (s, 1H, NH), 9.58 (s, 1H, OH), 9.42 (s,1H,CH), 9.21 (s,1H,OH), 676-7.45 (m, 7H, Ar-H), 4.23 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d6) (δ/ppm): 30.56 (CH_2), 95.41, 113.10, 115.41, 121.49, 124.55, 126.99, 128.56, 129.10, 131.15, 133.24, 144.63, 145.65, 149.19, 149.19, 151.21 (C=N), 154.57 (C=O); IR (ν/cm^{-1}): 3422 (OH), 3296 (NH), 1700 (C=O), 1594 (C=N),1250 (C-O), 651(C-Cl); Analysis (% Calculated/found) for $C_{16}H_{13}ClN_4O_3$(Mw 344.75) C: 55.74/55.67, H: 3.80/3.73, N: 16.25/16.17.



Scheme 1. Synthetic pathway for the preparation of compounds **4a-h**

	R	R^1		R	R^1
4a	$CH_2C_6H_4Cl_{(o)}$	$C_6H_4F_{(p)}$	**4e**	$CH_2C_6H_4Cl_{(m)}$	$C_6H_3OH_{(2)}Br_{(5)}$
4b	$CH_2C_6H_4Cl_{(o)}$	$C_6H_3OH_{(2)}Cl_{(5)}$	**4f**	$CH_2C_6H_4Cl_{(m)}$	$C_6H_3OH_{(2)}Cl_{(5)}$
4c	$CH_2C_6H_4Cl_{(o)}$	$C_6H_3OH_{(2)}Br_{(5)}$	**4g**	$CH_2C_6H_4Cl_{(m)}$	$C_6H_3F_{(p)}Br_{(m)}$
4d	$CH_2C_6H_4Cl_{(o)}$	$C_6H_3OHOH_{(3,4)}$	**4h**	$CH_2C_6H_4Cl_{(m)}$	$C_6H_3OHOH_{(3,4)}$

Table 1. Calculated pKa values for all molecules in worked solvents at 25°C.

Solvent	pKa							
	Molecule							
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
Water	10,3252	10,4351	10,4278	10,5744	10,4718	10,4791	10,3251	10,6184
n-Butanol	11,6671	11,7257	11,7037	11,9164	11,7844	11,8064	11,6011	11,9971
n-Propanol	11,9091	11,9677	11,9457	12,1584	12,0264	12,0484	11,8431	12,2391
2-Propanol	15,6123	15,6710	15,6490	15,8617	15,7297	15,7517	15,5390	15,9423
N,N-Dimethylformamide	23,7668	23,8328	23,8035	24,0235	23,8841	23,9061	23,7008	24,0968
Acetone	27,4481	27,5141	27,4847	27,7047	27,5654	27,5874	27,3821	27,7781
Acetonitrile	21,9995	22,0582	22,0362	22,2562	22,1168	22,1388	21,9262	22,3295
Benzene	21,8969	21,9482	21,9335	22,1388	22,0069	22,0289	21,8235	22,2195
Carbontetrachloride	25,1381	25,1968	25,1748	25,3874	25,2554	25,2774	25,0721	25,4681
Chloroform	23,8841	23,9428	23,9208	24,1335	24,0015	24,0235	23,8181	24,2068
Dimethylsulfoxide	12,8331	12,8917	12,8697	13,0824	12,9504	12,9724	12,7671	13,1630
Dioxane	16,5290	16,5876	16,5656	16,7783	16,6463	16,6683	16,4630	16,8590
Ethanol	11,6304	11,6891	11,6671	11,8797	11,7477	11,7697	11,5571	11,9604
Ethyl acetate	29,1714	29,2300	29,2080	29,4207	29,2814	29,3034	29,0980	29,4940
Diethyl ether	30,5133	30,5720	30,5500	30,7627	30,6307	30,6527	30,4473	30,8433
Hexane	31,1220	31,1807	31,1587	31,3713	31,2320	31,2613	31,0487	31,4446
Methanol	12,2097	12,2684	12,2464	12,4591	12,3271	12,3491	12,1364	12,5397
Nitrobenzene	14,2630	14,3217	14,2997	14,5123	14,3804	14,4024	14,1970	14,5857
Pyridine	18,4283	18,4869	18,4649	18,6703	18,5456	18,5603	18,3623	18,7509
Tert-Butanol	18,7363	18,7949	18,7729	18,9856	18,8536	18,8756	18,6629	19,0662
Tetrahydrofuran	21,7722	21,8309	21,8089	22,0215	21,8895	21,9115	21,7062	22,0949
Toluene	22,3662	22,4248	22,4028	22,6155	22,4835	22,5055	22,3002	22,6962
Benzaldehyde	16,7050	16,7636	16,7416	16,9543	16,8223	16,8443	16,6390	17,0276
Ethylbenzoate	21,2369	21,2955	21,2735	21,4862	21,3542	21,3762	21,1709	21,5669
Phenol	10,1638	10,2224	10,2004	10,4131	10,2811	10,3031	10,1051	10,4938

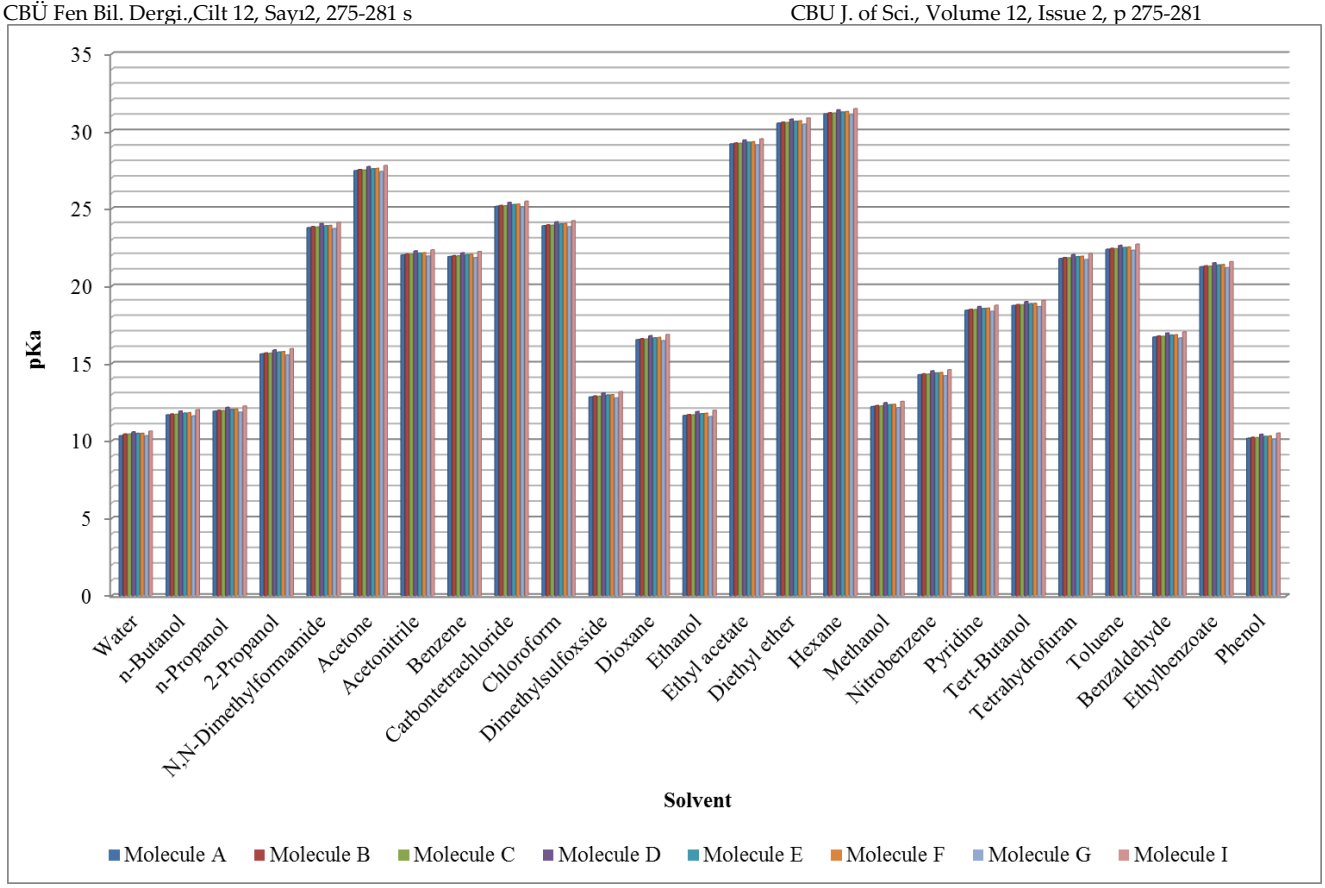
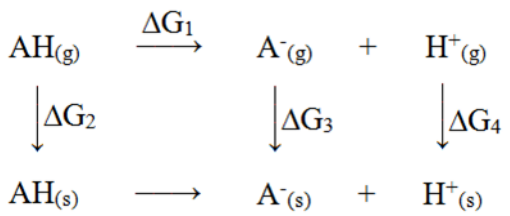


Figure 1. All pKa values were comparison in all worked solvents at 25 ^{0}C.

When the dielectric constant of solvents is taken into consideration, the acidic arrangement can be expected as follows: water (ε = 80.1) > dimethylsulfoxide (ε = 46.7) > acetonitrile (ε = 37.5) > N,N-dimethylformamide (ε = 36.7) > nitrobenzene (ε = 34.8) > methanol (ε = 32.7) > ethanol (ε = 24.6) > acetone (ε = 20.7) > n-propanol (ε = 20.3) > 2-propanol (ε = 17.9) > n-butanol (ε = 17.5) > benzaldehyde (ε = 17.0) > pyridine (ε = 12.4) >*tert*-butanol (ε = 12.0) > tetrahydrofuran (ε = 7.6) > ethyl acetate (ε = 6.0) = ethylbenzoate (ε = 6.0) > chloroform (ε = 4.8) > diethyl ether (ε = 4.3) = phenol (ε = 4.3) > toluene (ε = 2.4) > dioxane (ε = 2.3) = benzene (ε = 2.3) > carbontetrachloride (ε = 2.2) > hexane (ε = 1.9). But, in this studied that it is observed; all molecules are showed high acidic properties in phenol, but these molecules are showed low acidic properties in hexane. High acidity is showed change as pKa = 10.1051 (molecule G) >pKa = 10.1638 (molecule A) >pKa = 10.2004 (molecule C) >pKa = 10.2224 (molecule B) >pKa = 10.2811 (molecule E) >pKa = 10.3031 (molecule F) >pKa = 10.4131 (molecule D) >pKa = 10.4938 (molecule I) in phenol. Low acidity is showed change as pKa = 31.0487 (molecule G) >pKa = 31.1220 (molecule A) >pKa = 31.1587 (molecule C) >pKa = 31.1807 (molecule B) >pKa = 31.2320 (molecule E) >pKa = 31.2613 (molecule F) >pKa = 31.3713 (molecule D) >pKa = 31.4446 (molecule I) in hexane. G compound was observed to stronger acidic properties (water (pKa : 10.3251), n-butanol (pKa : 11.6011), n-propanol (pKa : 11.8431), 2-propanol (pKa : 15.5390), N,N-dimethylformamide (pKa : 23.7008), acetone (pKa : 27.3821), acetonitrile (pKa : 21.9262), benzene (pKa : 21.8235), carbontetrachloride (pKa : 25.0721), chloroform (pKa : 23.8181), dimethylsulfoxide (pKa : 12.7671), dioxane (pKa : 16.4630), ethanol (pKa : 11.5571), ethyl acetate (pKa : 29.0980), diethyl ether (pKa : 30.4473), hexane (pKa : 31.0487), methanol (pKa : 12.1364), nitrobenzene (pKa : 14.1970), pyridine (pKa : 18.3623), *tert*-butanol (pKa : 18.6629), tetrahydrofuran (pKa : 21.7062), toluene (pKa : 22.3002), benzaldehyde (pKa : 16.6390), ethylbenzoate (pKa : 21.1790), phenol (pKa : 10.1051) than the other compounds in all solvents

3.2 Acidity:

The computer program SPARC (SPARC Performs Automated Reasoning in Chemistry) was developed to predict numerous physical properties such as vapor pressure, distribution coefficient, and GC retention time as well as chemical reactivity parameters such as pKa and electron affinity. SPARC predicts both macroscopic and microscopic pKa values strictly from molecular structure using relatively simple reactivity models [23]. The operating mechanism of this program is shown in Scheme 2.



Scheme 2. The operating mechanism of SPARC computer program for pKa

$$\Sigma\Delta G = [((\Delta G3 + \Delta G4) - \Delta G2) + \Delta G1]$$

$$\Sigma\Delta G = -2.303 \, . \, R. \, T. \log Ka$$

The ionization of weak acid (HA) is given for the gas and liquid phase in Scheme 1. Calculations of pKa were made using the free energy changes in the thermodynamic cycle. Respectively ΔG1, ΔG2, ΔG3 and ΔG4 are calculated for find the ΣΔG. ΣΔG values is given for all molecules in Table 2. Then, pKa is calculated using the equation with calculated ΣΔG. We calculated of all pKa values in different twenty five solvents (water, n-butanol, n-propanol, 2-propanol, *N,N*-dimethylformamide, acetone, acetonitrile, benzene, carbontetrachloride, chloroform, dimethylsulfoxide, dioxane, ethanol, ethyl acetate, diethyl ether, hexane, methanol, nitrobenzene, pyridine, *tert*-butanol, tetrahydrofuran, toluene, benzaldehyde, ethylbenzoate, phenol) at 25^{0}C.

4 Conclusion

A good and effective method as an alternative to conventional method [9, 24] has been proposed for the synthesis of 4-(arylidenamino)-2,4-dihydro-3*H*-1,2,4-Triazol-3-ones **4a-h**, using microwave heating. Kahveci and İkizler [24] were completed synthesis of these compounds by conventional techniques in 1 hour, with high yields. In this study, we complete synthesis with high yield in a short period of 2 minutes using MW. Eight new 1*H*-1,2,4-triazol-5-one derivatives obtained in the study are expected to show some biologically active properties. And these molecules have showed various pKa values in different twenty five solvents at 25^{0}C. When examined leveling and differential effect of solvents, all of the compounds was differentiated in the studied solvents.

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