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MICROWAVE-ASSISTED SYNTHESIS OF SOME NEW BENZYLIDENAMINO COMPOUNDS AND POTENTIOMETRIC DETERMINATION OF THEIR pKa

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A growing body of literature has shown the effectiveness of using microwaves in chemical reactions. The aim of this study is to demonstrate a rapid and highly efficient synthesis of some new benzylidenamino compounds (4a-f) via microwave heating using a monomode microwave. Compounds 4a–f were potentiometrically titrated with tetrabutylammonium hydroxide (TBAH) in four nonaqueous solvents (isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N,N*-dimethyl formamide). Also half-neutralization potential values and the corresponding pKa values were determined in all cases.

INTRODUCTION

Microwave assisted synthesis have become an established tool in organic synthesis.[1] This synthesis technique is much quicker and provides higher yields under microwave irradiation than those of conventional heating. In many cases, reactions that usually require many hours at the reflux temperature under classical condition can be completed within a few minutes in microwave irradiation, even at similar reaction temperatures.[2-4] Microwave synthesis gives organic chemists more time to expand their scientific creativity, test new theories and develop new processes. In addition to this microwave-assisted heating under controlled conditions is an invaluable technology for medicinal chemistry and drug discovery applications because instead of spending hours or even days synthesizing a single compound, chemists can now perform that same reaction in minutes.[5] A previous study from our laboratory[6-8] demonstrated a synthesis of a number of triazoles by environmentally friendly microwave methods.

In recent years, 5-alkyl-4-alkylidenamino-2,4-dihydro-2H-1,2,4-triazol-3-ones have been found to be associated with diverse antimicrobial, anti-inflammatory, analgesic, antitumor, anticonvulsant properties.[9-12] In this study we want to report here a successful microwave assisted synthesis of some new 5-alkyl-4-alkylidenamino-2,4-dihydro -2H-1,2,4-triazol-3-one derivatives with less time and good yields. Structure of new compounds was identified by spectroscopic methods using IR, ^{1}H-NMR, ^{13}C-NMR.

Acidity measurements of organic compounds have a long history dating back to the end of the 19th century, when the first pKa was measured. Since then a vast body of data on acidities in various solvents has been collected.[13] The measurements have mostly been limited to polar solvents, however, with water being by far the most exploited medium, followed by alcohols and dipolar aprotic solvents. It is known that 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives have weak acidic properties.[14] The acidity of a compound in a given medium is influenced by both

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the electronic effects of the substituents and the solvent effects of the medium. Moreover, it is sometimes extremely difficult to assess how much each effect contributes to the acidity. Small differences in acidity between similar molecules are also extremely difficult to interpret and one must be very careful in deciding which structural effect has the main influence on acidity.

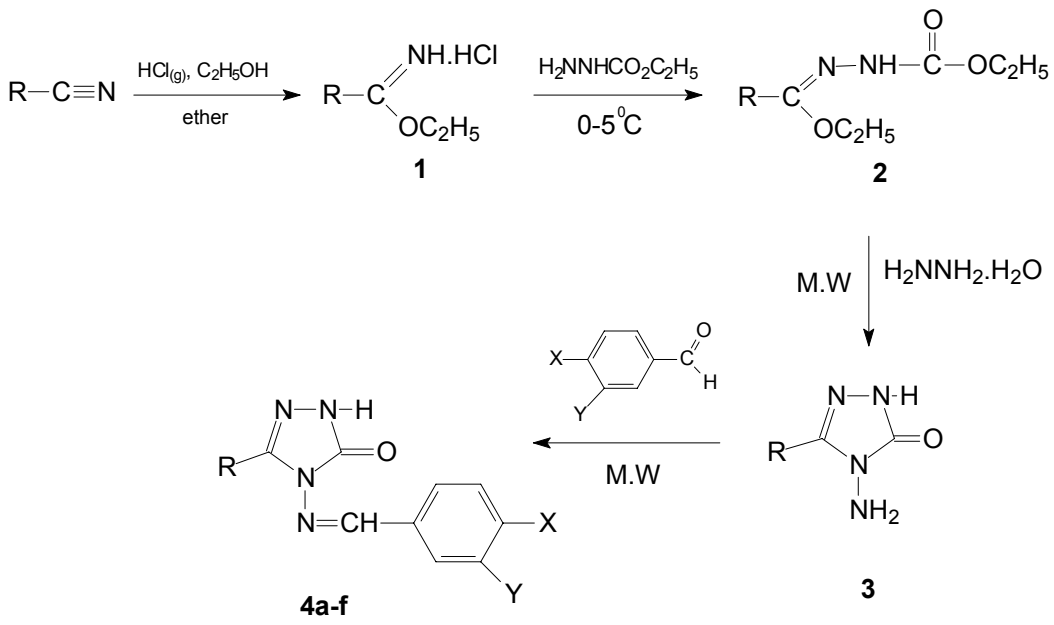
RESULTS AND DISCUSSION

Ether carbetoxy hydrazones **1** can be considered as useful intermediates leading to the formation of some heterocycles such as 5-alkyl-4-amino-1,2,4-triazole-3-ones, which are used in the synthesis of 1,2,4-triazole derivatives that showed pharmacological activities.[15,16] In order to synthesize 2,4-dihidro-4-amino-5-alkyl-3H-1,2,4-triazol-3-one, several methods have been developed.[5-6] One of these methods is the reaction of ester ethoxycarbonylhydrazne (**2**), with hydrazine in ethanol for 6 hour. In this study, the formation of compound **3** was achieved by solvent-free microwave conditions as a better solution. The absence of solvents coupled with the high yields and short reaction times for the synthesis of this compound. We now report a simple and rapid procedure for the synthesis of benzylidenamino compounds. The reaction of compounds **3** with appropriate aldehydes under microwave irradiation leading to the products **4a-f**. The reactions were performed in dry ethanol. The reaction time was as short as 4 min., and **4a-f** were isolated in up to 93% yield. This method can be a general technique for the synthesis of benzylidenamino compounds. When compared to the conventional (thermal) heating method, microwave heating offers more advantages such as reduced reaction time low cost, simplicity in processing, reduced pollution and high yield. Compare of yields and time under microwave irradiation and conventional heating are given in Table 1. The general reactions representing benzylidenamino compounds are illustrated in Scheme 1.

Table 1

Compare of yields and time under microwave irradiation and conventional heating

Product	Conventional		MWI	
	Time (min.)	Yield (%)	Time (min.)	Yield (%)
4a	120	88	4	93
4b	120	90	4	95
4c	120	89	4	94
4d	120	91	4	94
4e	120	88	4	95
4f	120	88	4	94



	4a	4b	4c	4d	4e	4f
R	o-$ClC_6H_5CH_2$	o-$ClC_6H_5CH_2$	o-$ClC_6H_5CH_2$	o-$ClC_6H_5CH_2$	m-$ClC_6H_5CH_2$	m-$ClC_6H_5CH_2$
X	F	H	F	NO_2	F	NO_2
Y	H	Cl	Br	H	H	H

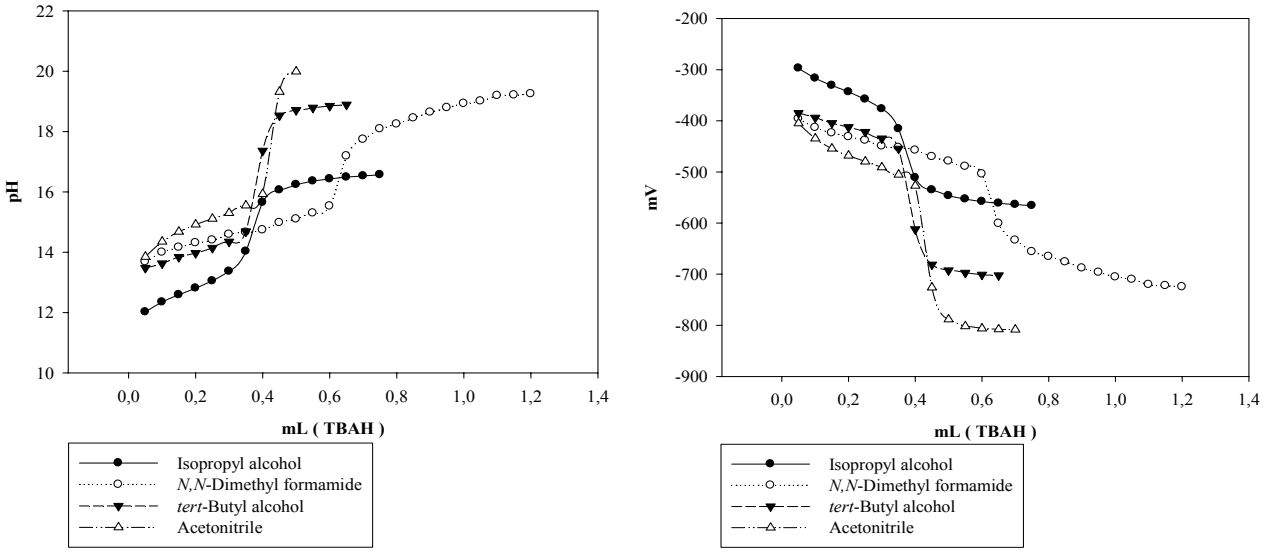
Scheme 1

In this study, compounds **4a-f** were titrated potentiometrically with TBAH in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N,N*-dimethyl formamide. The mV values read in each titration were drawn against TBAH volumes (mL) added and potentiometric titration curves were formed for all the cases. From the titration curves, the HNP values were measured and the corresponding pKa values were calculated. The half-neutralization potential (HNP) values and the corresponding pKa values of all triazole derivatives, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N,N*-dimethyl formamide, are presented in Table 2. The pH of the weak acids are given by the following equation:

$$pH = pKa + \log [A^-]/[HA]$$

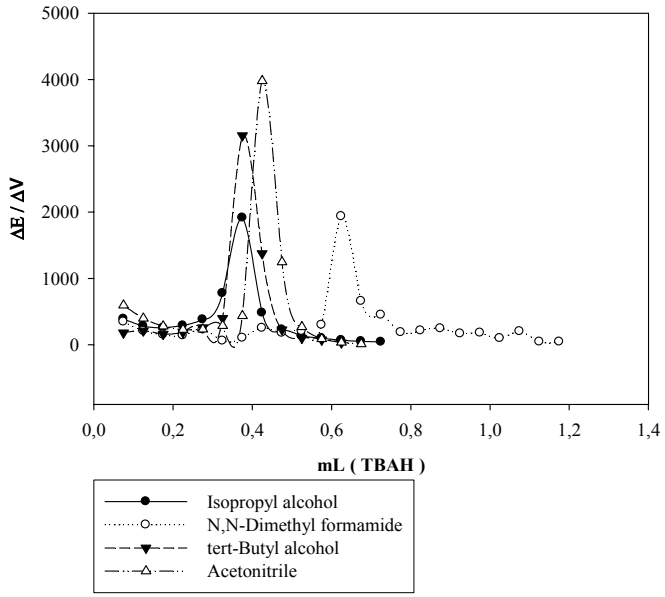
pH = pKa occurs when $[A^-]$ is equal to [HA] at the half-neutralization point. Therefore, the pH values can be regarded as pKa at the half-neutralization points. When the dielectric permittivity of solvents is taken into consideration, the acidic arrangement can be expected as follows: *N,N*-dimethyl formamide (ε=36.7)>acetonitrile (ε=36.0) > isopropyl alcohol (ε=19.4) > *tert*-butyl alcohol (ε=12.0). The acidity of a compound depends on several factors. The two most important factors are the solvent effect and molecular structure. Table 2 shows that the half-neutralization potential (HNP) values and the corresponding pKa values obtained from potentiometric titrations depend on the type of non-aqueous solvents used and molecular structure of the compound.

As seen in Table 2, the acidic order for compounds **4a-e** and **4f** is: isopropyl alcohol > *ter t*-butyl alcohol > *N,N*-dimethyl formamide > acetonitrile. In isopropyl alcohol, **4a-e** and **4f** compounds show the strongest acidic properties. **4a-e** and **4f** compounds show the weakest acidic properties in acetonitrile. This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules in the amphiprotic neutral solvents. Autoprotolysis is an acid-base reaction between identical solvent molecules is which some act as an acid and others as a base.

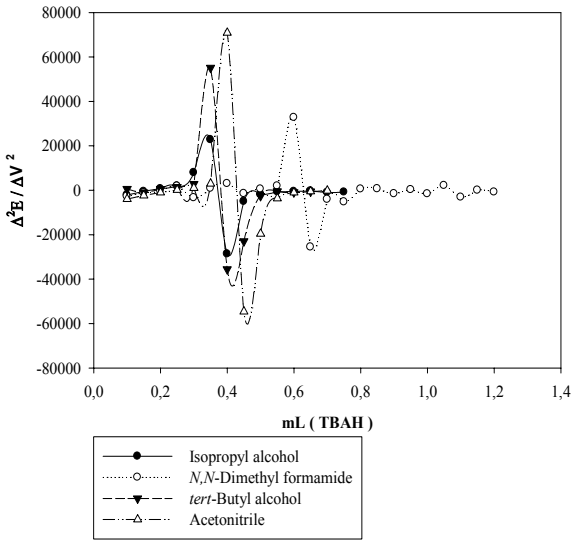


a)

b)



c)



d)

Fig. 1 – (a) pH – mL (TBAH) (b) mV – mL (TBAH) (c) $\Delta E/\Delta V$ – mL (TBAH) (d) $\Delta^2E/\Delta V^2$ – mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **4c** titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

Table 2

Half-neutralization potential (HNP) values and the corresponding pKa values
of all triazole derivatives in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile

Compd. No	Isopropyl alcohol		*N,N*-Dimethyl formamide		*tert*-Butyl alcohol		Acetonitrile	
	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)
4a	13.12±0.18	-361.4±1.8	14.86±0.13	-464.4±2.1	14.40±0.21	-437.7±1.9	15.32±0.21	-491.9±2.1
4b	12.89±0.13	-348.6±1.4	14.32±0.16	-434.8±1.8	14.07±0.17	-418.2±2.3	15.06±0.16	-477.0±1.8
4c	12.74±0.19	-339.2±1.9	14.62±0.18	-451.0±2.0	13.93±0.15	-409.8±1.4	14.99±0.14	-472.2±1.9
4d	12.23±0.20	-308.5±1.7	14.22±0.12	-425.8±1.6	13.62±0.17	-391.5±1.8	14.89±0.21	-466.9±1.6
4e	13.19±0.23	-365.0±2.0	14.66±0.20	-452.8±1.8	14.27±0.21	-430.2±2.1	15.08±0.16	-477.8±1.8
4f	12.52±0.19	-326.4±2.2	14.45±0.17	-440.4±1.5	13.62±0.19	-391.3±1.7	14.84±0.12	-464.1±2.0

EXPERIMENTAL

The 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. The ^{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. A monomode 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^{o}C via air jet cooling. The starting compounds **1** and **2** were prepared by published methods.[15,2]

General procedure for synthesis of **3**: A mixture of **2** (0.01 mol), hydrazine hydrate (0.03 mol) was heated under microwave irridation in closed vessels with pressure control at 125°C for 5 min. (hold time) at 300 W maximum power. At the end of this period, TLC monitoring (AcOEt/hexane 3:1) was conducted to determine if the reaction was over. The reaction mixture was cooled to room temperature and was crystallized from ethyl acetate.

General procedure for synthesis of **4a-f**, Conventional method

Equimolar quantities (0.01 mol) of **3** and the corresponding aldehyde were dissolved in ethanol (40 mL). The reaction mixture was refluxed for 2 h (monitored by TLC, ethylacetate:Hexane, 3:1) and cooled. The precipitate formed was filtered and dried. Recrystallization of the product from ethanol gave pure compounds **4a-f**.

Microwave method

A mixture of **3** (0.01 mol), corresponding aldehyde (0.01 mol) and glacial acetic acid (0.1 mL) was heated under microwave irridation in closed vessels with pressure control at 115°C for 4 min. (hold time) at 300 W maximum power. At the end of this period, TLC monitoring (AcOEt/hexane 3:1) was conducted to determine if the reaction was over. The reaction mixture was cooled to room temperature and was crystallized from ethanol.

5-(o-Chlorobenzyl) - 4 - o - fluorobenzyliden amino-2,4-dihydro-2H-1,2,4- triazol -3-one (**4a**)**.**

Yield 93 %. M.p: 188-189 ^{o}C. IR (KBr), ν/cm^{-1}: 3164 (NH), 1715 (C=O), 1593 (C=N), 1412, 1060, 723. ^{1}H NMR (200 MHz, DMSO-d_6): 12.02 (s, 1H, NH), 9.71(s, 1H, CH), 7.28-7.90 (m, 8H, Ar-H), 4.19 (s, 2H, CH_2). ^{13}C NMR (50 MHz, DMSO-d_6): 29.57 (CH_2), 105.00, 116.59, 117.03, 127.97, 129.54, 129.98, 130.71, 130.87, 131.98, 133.89, 133.92, 145.70, 151.84, 153.26 (2xC=N), 167.11 (C=O).

5-(o-Chlorobenzyl) - 4 - m -chloro benzylidenamino -2,4-dihydro-2H-1,2,4-triazol-3- one (**4b**).

Yield 95 %. M.p: 210-211 ^{o}C. IR (KBr), ν/cm^{-1}: 3164 (NH), 1701 (C=O), 1585 (C=N), 1417, 1047, 741. ^{1}H NMR (200 MHz, $CDCl_3$-d_6): 10.22 (s,1H, NH), 9.15 (s, 1H, CH), 7.20-7.81 (m, 8H, Ar-H), 4.22 (s, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$-d_6): 29.21 (CH_2), 126.76, 127.08, 127.21, 128.87, 129.81, 130.11, 130.88, 131.39, 132.56, 134.24, 135.04, 152.72, 153.60 (2xC=N), 166.80 (C=O).

5-(o-Chlorobenzyl) - 4 -m-bromo-4-fluoro benzylidenamino-2,4-dihydro-2H-1,2,4 - tri azol-3-one (**4c**).

Yield 94 %. M.p: 210-211 ^{o}C. IR (KBr), ν/cm^{-1}: 3165 (NH), 1710 (C=O), 1600 (C=N), 1417, 1058, 723. ^{1}H NMR (200 MHz, DMSO-d_6): 12.00 (s,1H, NH), 9.70 (s, 1H, CH), 7.20-7.88 (m, 8H, Ar-H), 4.20 (s, 2H, CH_2). ^{13}C NMR (50 MHz, DMSO-d_6): 29.50 (CH_2), 105.10, 115.89, 117.00, 127.60, 129.10, 129.90, 130.70, 130.98, 131.74, 133.80, 133.91, 145.50, 151.84, 154.02 (2xC=N), 167.10 (C=O).

5-(o-Chlorobenzyl) - 4 - p - nitrobenziliden amino-2,4-dihydro -2H-1,2,4-triazol-3- one (**4d**).

Yield 94 %. M.p: 229 ^{o}C. IR (KBr), ν/cm^{-1}: 3164 (NH), 1705 (C=O), 1598 (C=N), 1412, 1065, 723. ^{1}H NMR (200 MHz, DMSO-d_6): 12.01 (s,1H, NH), 9.69 (s, 1H, CH), 7.25-7.88 (m, 8H, Ar-H), 4.18 (s, 2H, CH_2). ^{13}C NMR (50 MHz, DMSO-d_6): 29.54(CH_2), 104.60, 115.79, 116.23, 127.90, 129.50, 129.98, 130.69, 130.86, 131.90, 133.85, 133.92, 145.70, 151.80, 153.23 (2xC=N), 167.08 (C=O).

5-(m-Chlorobenzyl) - 4 - p - fluorobenziliden amino-2,4-dihydrz-2H-1,2,4-triazol - 3 - one (**4e**).

Yield 95 %. M.p: 191-192 ^{o}C. IR (KBr), ν/cm^{-1}: 3164 (NH), 1702 (C=O), 1600 (C=N), 1413, 1060, 723. ^{1}H NMR (200 MHz, DMSO-d_6): 12.01 (s,1H, NH), 9.71(s, 1H, CH), 7.28-7.90 (m, 8H, Ar-H), 4.20 (s, 2H, CH_2). ^{13}C NMR (50 MHz, DMSO-d_6): 28.78(CH_2), 104.21, 115.82, 116.26, 127.18, 128.75, 129.19, 129.92, 130.10, 131.19, 133.10, 133.13, 144.91, 151.05, 152.50 (2xC=N), 166.32 (C=O).

5-(m-Chlorobenzyl) - 4 - p-nitrobenziliden amino-2,4-dihydro -2H-1,2,4-triazol-3-one (**4f**).

Yield 94 %. M.p: 223-224 ^{o}C. IR (KBr), ν/cm^{-1}: 3164 (NH), 1710 (C=O), 1598 (C=N), 1412, 1058, 723. ^{1}H NMR (200 MHz, DMSO-d_6): 12.02 (s,1H, NH), 9.70 (s, 1H, CH), 7.30-7.93 (m, 8H, Ar-H), 4.21 (s, 2H, CH_2). ^{13}C NMR (50 MHz, DMSO-d_6): 29.67(CH_2), 104.20, 115.89, 116.80, 127.34, 127.90, 129.98, 130.01, 130.57, 131.19, 133.12, 133.50, 141.80, 151.14, 152.55 (2xC=N), 167.30 (C=O).

HNP and pKa Value Determination with potentiometric Titrations

Potentiometric titrations an Orion 720A model pH-ionmeter equipped with a combined pH electrode (Ingold) and indicator electrode 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. 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 (TBAH) by dilution, was used. The 0.05 M solution of TBAH in isopropyl alcohol, which is widely used in the titration of acids, was used as

titrant. The mV values that were obtained in pH-meter were recorded. Finally, the half-neutralization potential (HNP) values were determined by drawing the mL (TBAH)-mV graphic.

CONCLUSION

Consequently, we have developed a practical, new and very simple green procedure for the preparation of 2,4-dihidro-4-amino-5-alkyl-3H-1,2,4-triazol-3-ones. The synthesis of benzylidenamino compounds were achieved by microwave irradiation in ethanol with less time-consuming nature and good yields. The extent of an autoprotolysis reaction depends both on the intrinsic acidity and the instrinsic basicity of the solvent. The importance of the autoprotolysis constant in titrations lies in its effect on the completeness of a titration reaction. The acidity of a compound depends on mainly two factors, *i.e.* solvent effect and molecular structure. Half-neutralization potential (HNP) values and corresponding pKa values obtained from the potentiometric titrations rely on the non-aqueous solvents used and the substituents at C-3, in triazole ring.

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