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Synthesis of Some Novel 4-Aminoacetophenone Diazenyl and 1,2,3-Triazole Derivatives as Potential Antibacterial Agents

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Abstract:

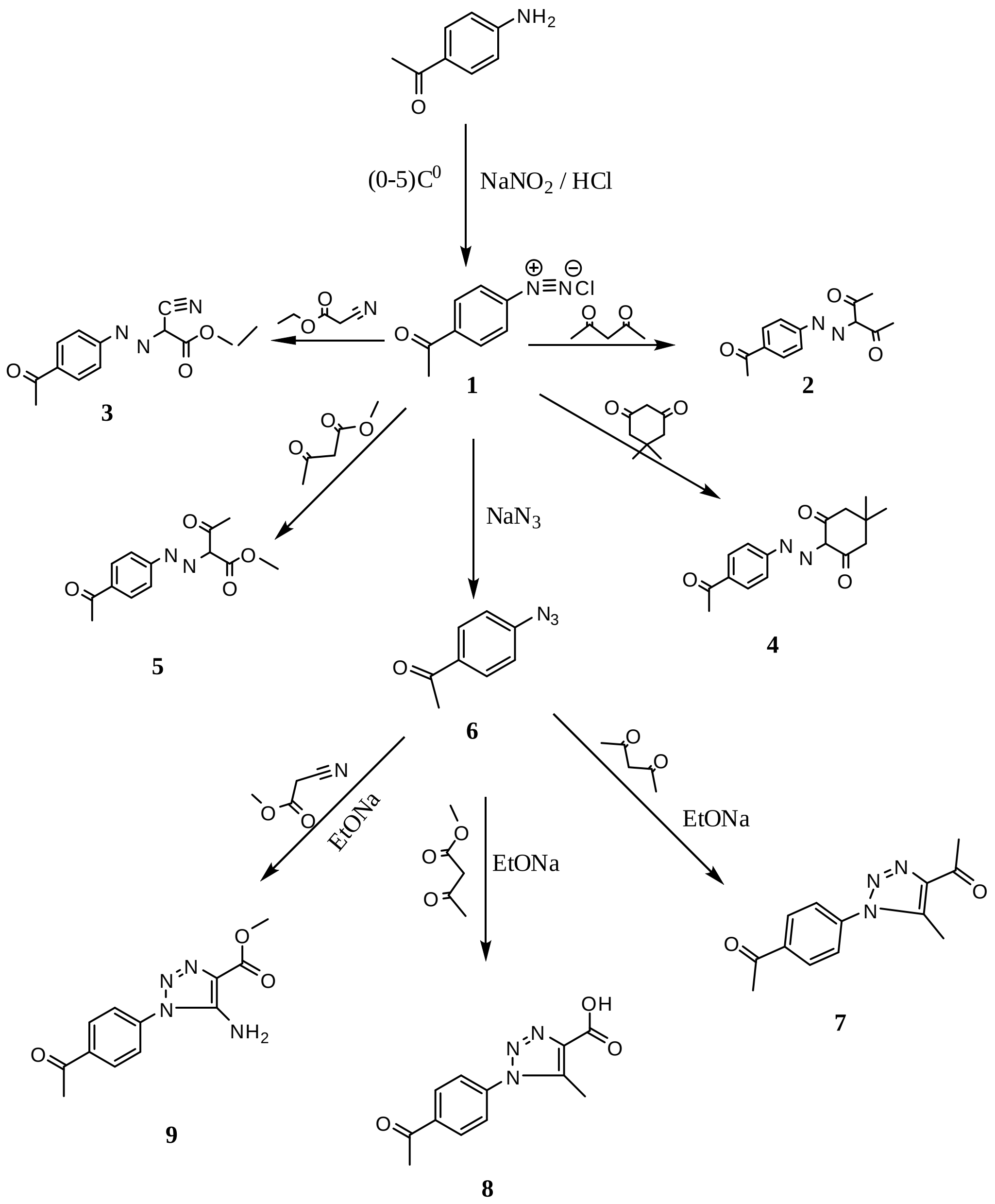
With the study of synthesizing new organic compounds and exploring biological potency. Aryldiazenyl derivatives (2-5) were carried out by coupling of diazonium salt of 4-aminoacetophenone (1) and miscellaneous active methylene compounds such as: acetylacetone, ethyl cyanoacetate, dimedone or methyl acetoacetate. Moreover substituted 1,2,3-triazole (7-9) were synthesized by the cyclization of 1-(4-azidophenyl) ethanone (6); (which was obtained by coupling of diazonium salt (1) with sodium azid); with acetylacetone, methyl acetoacetate or methyl cyanoacetate, respectively. The structures of the prepared compounds were promoted by IR, H^1NMR and UV/Visible spectra. Further, they were examined in *vetro* for antibacterial activity against five strains of bacteria *viz.*, *Staphylococcus aureus*, *Bacillus subtilis, Pseudomonas aeruginosa*, *Escherichia coli* and *Acinetobacter* uses the agar diffusion method.

Keywords: diazonium salt; cyanoacetate; strains of bacteria; triazole.

Introduction:

Azo compounds are the oldest and the largest class of industrial synthetic organic dyes due to their versatile applications. Azo compounds are characterized by the presence of the azo moiety (-N=N-) in their structure conjugated with tow, distinct or identical, mono or polycyclic aromatic systems. They have been most widely used in dyeing textile fibers, papers and coloring agents for foods and cosmetics [1, 2]. The pharmacological use

of azo compounds originates from the discovering of the antibacterial action of prontosil on *streptococcal* infections by Domagk [3]. Furthermore, azo compounds such as salicylazosulfopyridine, known drug with name azulfidine (sulfasalazine), used to treat rheumatoid arthritis [4]. These azo compounds display multiple biological and pharmaceutical applications and are known for their antimicrobial [5-9], anti-inflammatory [10, 11], antioxidant [12] and enzyme inhibitors [13]. There has been considerable attention in the development of nitrogen containing heterocyclic compounds in both medicinal and industrial chemistry. 1,2,3-triazole derivatives, which are remarkable class of heterocycles on account of their wide range of applications as pharmaceuticals due to their wide spectra of biological activities such as antimicrobial [14-16], anticancer [17-19], anticonvulsant and analgesic activity [20]. In view of these findings, we aimed to synthesize simpler substances that can have antibacterial activity.



Scheme (1)

Experimental:

Materials:

All chemicals and solvents were obtained from Fluka Company Ltd and BHD Company and were used without further purification. The compounds throughout this work were named according to the IUPAC system using Chem. Draw Ultra Computer Program.

Instruments:

All melting points are uncorrected and were determined in open capillary tubes in Gallenkamp MF-600 melting point apparatus. FT-IR spectra were

recorded on Shimadzu Spectrophotometer using KBr disc. The H^1NMR spectra were obtained on a Bruker - 500 MHz instrument using DMSO as a solvent and TMS as internal reference (ppm), measurement were made at Central lab , Tahran University (Iran). All reactions were followed by TLC ($60F_{254}$, Merck) using hexane /ethyl acetate 1:3 as a mobile phase and spots were examined by the UV lamp.

Synthesis Procedures

1-General procedure for preparation of azo compounds (1-5):

4-Aminoacetophenone (1.35gm,0.01 mol) is treated with 5 ml conc. HCl and 5ml of distilled water and stirred until the solid dissolved. The mixture was cooled to 0^oC in an ice bath with constant stirring. Solution of (0.02 mol) sodium nitrate was added dropwise. The solution was kept in an ice bath for 15 min. and then it was added dropwise to an ice cooled solution of (0.01 mol) acetyl acetone, ethyl cyanoacetate, dimedone or methyl acetoacetate dissolved in 25ml ethanol in the presence of (0.01 mol) sodium acetate with continuous stirring. After 25 min. the colored precipitates were formed and then they were filtered, washed with cold water and left to dry.

2-Preparation of 1-(4-azidophenyl)ethanone (6):

10 ml of an aqueous solution of sodium azide (0.65gm,0.01mol) was added to the diazonium salt solution from step (1) .The mixture was stirred for 25 min. and the product was filtered, washed with water and recrystallized from ethanol .

3-Preparation of 1,2,3-triazole derivatives (7-9):

To a cold solution of sodium ethoxide (7 ml) and (0.01mol) of acetylacetone, methyl acetoacetate or methyl cyanoacetate, a solution of 4-azido acetophenone in 5ml ethanol was added dropwise and the mixture was refluxed for 2hrs. The precipitate was filtered and recrystallized from ethanol .

All physical properties of the prepared compounds were reported in table (1).

Table (1)

Physical constants for compounds (1-9)

Comp. no.	Formula	Name	M.P C°	Yield %	Rf	Color
2	$C_{13}H_{14}N_2O_3$	3-(4-acetylphenyl) diazenyl) pentane-2,4-dione	141-142	81	0.60	Orange
3	$C_{12}H_{11}N_3O_3$	2-(4-acetylphenyl)diazenyl) pentane-2- cyanoacetate	155-154	71	0.53	Yellow
4	$C_{15}H_{15}N_2O$	2-(4-acetylphenyl)diazenyl)-5,5-dimethylcyclohexane-1,3-dione	170-173	54	0.44	Orange
5	$C_{13}H_{14}N_2O_4$	2-(4-acetylphenyl)diazenyl)-3-oxobutanoate	138-140	57	0.5	Greenish Yellow
6	$C_8H_7N_3O$	1-4(azidophenyl)ethanone	42-43	80	0.75	Light Biege
7	$C_{13}H_{13}N_3O_2$	1-(4-(4-acetyl-5-methyl-1H-1,2,3- triazol-1- yl) phenyl) ethanone	225-227	63	-	Yellow
8	$C_{12}H_{11}N_3O_3$	1-(4-acetylphenyl)-5-methyl-1H-1,2,3- triazole-4-carboxilic acid	255-257	58	-	Orange
9	$C_{12}H_{12}N_4O_3$	Methyl-1-(4-acetylphenyl)-5-amino-1H- 1,2,3-triazole-4-carboxylate	215-218	57	-	Orange

Table (2)Characteristic IR absorption bands

Comp. No.	Formula	υ (C-H) cm^{-1} Aroma.	υ (C-H) cm^{-1} Alpha.	υ (C=O) cm^{-1}	υ (N=N) cm^{-1}	Others cm-1
2	$C_{13}H_{14}N_2O_3$	3039	2926	1670	1498	
3	$C_{12}H_{11}N_3O_3$	3055	2991	(720-1650)	1535	2216 (C≡N)
4	$C_{15}H_{15}N_2O_3$	3066	2945	1681	1602	
5	$C_{13}H_{14}N_2O_4$	3167	2997	1720 ester	1581	1672 (C=O)
6	$C_8H_7N_3O$	3066	2926	1710		2125(N_3)
7	$C_{13}H_{13}N_3O$	3053	2956	1708	976	
8	$C_{12}H_{11}N_3O_3$	3033	2945	1664-1700	1008	2500-3300 (OH)
9	$C_{12}H_{12}N_4O_3$	3091	2924	1737	991	3304-3379 (NH_2)

Antibacterial Activity:

To study the inhibitory effect of the prepared compounds agar well diffusion method was used [21]. The plates were incubated for 24hrs at 37 ^{o} C then the inhibition zone were measured in millimeter (mm) using zone reader table (3).

Table (3)

Comp. No.	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Acinetobacter*
2	–	++	–	–	–
3	–	–	–	–	–
4	++	–	++	++	–
5	–	–	–	–	–
6	–	++	–	–	–
7	–	–	–	–	–
8	–	–	–	–	–
9	–	–	–	–	–
Control DMSO	–	–	–	–	–

Inhibition zone in (mm) - = 0 mm, + =5-10 mm, ++ = 10-15 mm, +++ = over than 15

Result and Discussion:

All compounds were synthesized according to scheme (1). The azo compounds with various substituents were synthesized by simple diazotization reaction of 4-aminoacetophenone followed by coupling reaction with active methylene compounds, namely: acetylacetone, ethyl cyanoacetate ,dimedone and methyl acetoacetate in sodium acetate solution to afford 4-acetylphenyl diazo derivatives (1-5), respectively. Structures of those derivatives were confirmed by analytical and spectral data. The FT-IR spectra of compounds (1-5) show the disappearance of the vibration absorption band at (3340-3300) cm^{-1} due to NH_2 of 4-aminoacetophenone and the appearance of high intensity bands at (1630-1498) cm^{-1} indicate the presence of azo linkage (-N=N-) and at (1730-1670) cm^{-1} assigned to carbonyl groups. While the FT-IR spectrum of compound 3 showed the absorption band at (2216) cm^{-1} corresponding to (-C≡N) group. The UV spectra of these compounds exhibit absorption bands in the region (388-360) nm according to π- π* and n - π* transitions. The ^{1}H NMR (TMS) δ ppm for compound (2): 1.12 (s, 6H, CH_3); 3.39 (s,3H, CH_3-C=O); 7.78-8.13 (d.d,4H, Ar-H). The ^{1}HNMR spectrum of compound (3) showed this signals : 1.35 (t,3H, CH_3CH_2); 2.56 (s,3H, CH_3-C=O); 3.33(s,1H, CH-CN); 4.32 (q, 2H, CH_2-O), 7.55-8.02 (d.d,4H, Ar-H). Finally, ^{1}H NMR (DMSO) δ ppm of compound (5): 7.50-8.02 (d.d, 4 H, ArH), 3.88 (s, 3 H, CH_3O-C=O), 3.33 (s, 3 H, CH_3C=O), 2.56 (s, 3H, CH_3).

Diazonium salt of 4-aminoacetophenone was converted 1-4(azidophenyl) ethanone by adding its cold solution to a solution of sodium azide in distilled water with continuous stirring. The target compound was elucidated by spectral data itsFT- IR spectrum revealed the appearance of a significant band at (2125) cm^{-1} of azid group $-(N^{-}-N^{+}\equiv N)$. 1-4(azidophenyl)ethanone was cyclized to 1,2,3-triazole (7-9) by reflexing it with several active methylene compounds such as; acetylacetone, methyl acetoacetate and ethyl cyanoacetate respectively under basic conditions using sodium ethanoate. In the IR spectra of the 1,2,3-tariazole compounds, the disappearance of azid group $-N^{-}-N^{+}\equiv N$ band at (2125) cm^{-1} and the appearance of bands around (1008-960) cm^{-1} attributed to –N–N=N– stretching vibration of triazole ring is a good evidence for the occurrence of cyclization reaction. The^{1}H NMR (TMS) δ ppm for compound (7): 2.73 (s, 3H, CH_3); 3.74 (s,3H, CH_3-C=O); 4.76 (s, 3H, CH_3CO); 7.15-8.58 (m,4H, Ar-H).The^{1}HNMR spectrum of compound (8) shows the following signals: 13.64 (s, 1H, COOH), 7.64-8.01 (d.d, 4 H, Ar-H), 3.42 (s, 3H, CH_3-CO), 2.60 (s, 3 H, CH_3-C=C). The ^{1}HNMR of compound(9), shows the following signals: 3.41 (s, 3H, CH_3), 5.00 (s, 3H, CH_3-O), 6.91-7.69 (m, 4 H, Ar-H), 9.00 (s, 2 H, NH_2).

Biological Study:

The newly compounds were evaluated *in vetro* for their antibacterial activity against five different type bacterial, *Staphylococcus aureus*, *Bacillus subtilis, Pseudomonas aeruginosa*, *Escherichia coli* and *Acinetobacter*. From table (3) we can note that compounds 2, 4 and 6 have antibacterial activity. The highest inhibitory effect was to compound 4 against *Staphylococcus aureus* and *Escherichia coli*. From these results we conclude that it is possible to use these compounds as drugs in the future after test its toxicity.

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