Article

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β-Enaminonitriles in Heterocyclic Synthesis: Synthesis of New 1,4-Dihydropyridine, Tetrahydropyridine, Nicotinonitrile and Aminopyrazole Derivatives

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A series of new pyridine, dihydropyridine, tetrahydropyridine, nicotinonitrile and pyrazole derivatives with expected biological activity were prepared through the reactions of 3-aminopent-2-enenitrile **1** with some electrophilic reagents, nucleophilic reagents, and aryl diazonium salts. The newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral studies.

Keywords: β-Enaminonitrles; 1,4-Dihydropyridine; Tetrahydropyridine; Nicotinonitrile; Aminopyrazole.

INTRODUCTION

In recent years, much synthetic heterocyclic organic chemistry involves specially designed reagents which are readily generated and used to provide molecules as functional moieties for further exploitation. Important examples of such reagents are β-enaminonitriles, which have proven to be valuable reagents in the synthesis of a wide variety of unique heterocyclic systems such as pharmaceuticals, fungicides and solavtochromatic dyes. A number of papers and patents concerning the importance of β-enaminonitriles in the synthesis of biologically active compounds such as; dihydropyridines analogous to nifedipine and amlodipine which considered as a potential calcium channel blockers in the treatment of angina and hypertension.[1-5]

Pyridine derivatives occur in numerous natural products which are of fundamental importance to living systems (e.g., nicotinamide adenine dinucleotide (NAD)). They display interesting physiological activities with attractive applications as pharmaceuticals and agro-chemicals, as well as general synthetic building blocks.[6,7] Nicotinonitrile like pyridine derivatives are of special synthetic importance,[8] the interest in further developing novel routes for the synthesis of these compounds has been revived.[9] The potent biological activity of various vitamins and drugs[10-12] is primarily contributed to the presence of pyridine ring in their molecular make-up. Also, the pyridine ring was found in the skeleton of many compounds that have potent antibacterial, antifungal and anticancer properties.[13,14] In addition, nitrogen-linked heterocyclic compounds received considerable attention in recent years because of their medicinal and pesticidal importance.[15,16] It is well known that the study of pyrazole derivatives is significant in pesticide chemistry, and some pyrazole derivatives were widely used because of their antiviral,[17] antitumor,[18] anti-inflammatory,[19] antibacterial,[20] herbi-cidal,[21] insecticidal,[22] and fungicidal activities.[23] It was also found that the o-phthalimide nucleus, which incorporates a pyrazole ring, exhibits a large number of biological activities, especially herbicidal activities.[21] In addition, it was reported that the antibiotics pyrazole C-glycoside (pyrazofurin), possess a broad spectrum of antimicrobial and antiviral activities with considerable activity against several tumor cell lines.[24]

Therefore, our interest was to develop an efficient synthesis method utilizing the readily obtainable β-enaminonitrile as a starting material for the synthesis and characterization of polyfunctionally substituted Pyridines, Nicotinonitriles and pyrazoles and some new derivatives of these compounds.

EXPERIMENTAL

Melting points were determined using a Büchi apparatus and are uncorrected. The purity of compound was confirmed by TLC using Merck silica gel 60 F254 plates using toluene, ethyl acetate and methanol as a mobile phase and spots were visualized under UV radiation. IR spectra (KBr) were recorded on a Bruker-Vector 22 instrument (Bruker) and frequencies are expressed in cm^{-1}. NMR spec-

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tra were recorded with a Varian Gemini spectrometer at 300 MHz and 200 MHz with TMS as the internal reference. Chemical shifts were reported on a δ scale (ppm) relative to TMS as a standard. EI-mass spectra were recorded with a HP D5988 A 1000MHz instrument (Hewlett-Packard). Elemental analyses were performed at the Microanalytical Centre at the Faculty of Science, Cairo University, Egypt.

Preparation of 2-((dimethylamino)methylene)-3-iminopentanenitrile (2)

A mixture of 3-aminopent-2-enenitrile **1** (0.96 g, 0.01 mol) and N,N-Dimethyl-formamide Dimethylacetal (1.19 g, 0.01 mol) was refluxed in ethanol (30 mL) for 4 h. The reaction mixture was allowed to cool and the separated solid product was collected by filtration and crystallized from ethanol (white crystals); Yield 82%; mp 145-147 °C; IR (KBr): υ cm^{-1} 3341 (NH), 2927 (CH-aliph), 2229 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 3H, CH_3), 2.01 (s, 6H, $2CH_3$); 2.71 (q, 2H, CH_2); 3.99 (br, 1H, NH); 6.09 (s, 1H, CH-olifinic); MS: *m/z* (%) 151 (M^+, 100), 136 (80), 123 (50), 109 (30), 95 (33), 68 (25), 54 (65); Anal. calcd. for $C_8H_{13}N_3$ (151.21): C, 63.54; H, 8.67; N, 27.79; Found: C, 63.48; H, 8.53; N, 27.67.

General procedure for the synthesis of 2-amino-4-(dimethylamino)-6-ethyl-1,4-dihydropyridine-3,5-dicarbonitrile (5)

Procedure (A)

A mixture of iminopentanenitrile derivatives **2** (1.51 g; 0.01 mol) and benzylidene malononitriles **3** (0.01 mol) in ethanol (80 mL) containing catalytic amount of piperidine (5 drops) was heated under reflux for 6 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give the dihydropyridine **6**.

Procedure (B)

A mixture of iminopentanenitrile derivatives **2** (1.51 g; 0.01 mol) and malononitrile (0.01 mol) in ethanol (80 mL) containing catalytic amount of piperidine (5 drops) was heated under reflux for 2 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol (brown crystals); Yield 80%; mp 152-154 °C; IR (KBr): υ cm^{-1} 3363, 3300 (NH_2), 3102 (NH), 2925 (CH-aliph), 2219 (2CN); ^{1}H-NMR ($CDCl_3$): δ 1.31 (t, 3H, CH_3), 2.53 (s, 6H, $2CH_3$), 3.20 (q, 2H, CH_2), 4.56 (s, 1H, H-4 pyridine), 5.66 (s, 2H, NH_2), 7.85 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 12.00, 21.75, 44.00, 44.00, 54.70, 56.90, 75.50, 114.60, 114.60, 152.50, 155.00; MS: *m/z* (%) 217 (M^+); Anal. calcd. for $C_{11}H_{15}N_5$ (217.27): C, 60.81; H, 6.96; N, 32.23; Found: C, 60.70; H, 6.87; N, 32.19.

2-Amino-6-ethylpyridine-3,5-dicarbonitrile (8)

A mixture of 3-aminopent-2-enenitrile 1 (0.96 g, 0.01 mol) and ethoxymethylenemalononitrile (0.01 mol) in ethanol (80 mL) containing catalytic amount of piperidine (5 drops) was heated under reflux for 7 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol (yellowcrystals).

Yield 84%; mp 182-184 °C; IR (KBr): υ cm^{-1} 3430, 3300 (NH_2), 3036 (CH-arom), 2988 (CH-aliph), 2223 (2CN); 1H-NMR ($CDCl_3$): δ 1.17 (t, 3H, CH_3), 2.60 (q, 2H, CH_2), 7.05-7.97 (m, 3H, Ar H and NH_2); MS: *m/z* (%) 172 (M^+); Anal. calcd. for $C_9H_8N_4$ (172.19): C, 62.78; H, 4.68; N, 32.54; Found: C, 62.73; H, 4.62; N, 32.49.

Preparation of 3-amino-2-(diethoxymethyl)pent-2-enenitrile (9)

A mixture of 3-aminopent-2-enenitrile **1** (0.96 g, 0.01 mol) and triethoxymethane (1.48 g, 0.01 mol) was refluxed in acetic anhydride (30 mL) for 5 h. The reaction mixture was allowed to cool and the separated solid product was collected by filtration and crystallized from ethanol (white crystals); Yield 77%; mp 243-245 °C; IR (KBr): υ cm^{-1} 3337, 3300 (NH_2), 2973 (CH-aliph), 2219 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.18 (t, 6H, $2CH_3$), 1.29 (t, 3H, CH_3); 2.64 (q, 2H, CH_2); 2.73 (q, 4H, $2CH_2$), 4.87 (s, 1H, CH); 6.11 (s, 2H, NH_2); MS: *m/z* (%) 198 (M^+); Anal. calcd. for $C_{10}H_{18}N_2O_2$ (198.26): C, 60.58; H, 9.15; N, 14.13; Found: C, 60.53; H, 9.09; N, 14.10.

General procedure for the synthesis of tetrahydropyridine derivatives (11a-c)

A mixture 3-amino-2-(diethoxymethyl)pent-2-enenitrile **9** (1.98 g; 0.01 mol) and benzylidenemalononitriles **3a-c** (0.01 mol) in ethanol (60 mL) containing catalytic amount of piperidine (5 drops) was heated under reflux for 5 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol (yellow crystals).

4,4-Diethoxy-6-ethyl-3-phenyl-1,2,3,4-tetrahydropyridine-2,5-dicarbonitrile (11a)

Yield 87%; mp 114-116 °C; IR (KBr): υ cm^{-1} 3343

(NH), 2934 (CH-aliph), 2192 (2CN); ^{1}H-NMR (DMSO-d_6):δ 1.20 (t, 6H, $2CH_3$), 1.45 (t, 3H, CH_3), 4.53 (q, 2H, CH_2), 4.55 (q, 4H, $2CH_2$), 6.77 (d, 1H, C-2), 7.15 (d, 1H, C-3), 7.20-7.70 (m, 6H, Ar H and NH); ^{13}C NMR (DMSO-d_6):δ 12.00, 15.90, 15.90, 23.10, 44.80, 51.00, 61.40, 51.40, 84.00, 111.00, 115.50, 117.60, 127.00, 128.30, 128.30, 129.50, 129.50, 137.00, 160.40; MS: *m/z* (%) 325 (M^+);Anal. calcd. for $C_{19}H_{23}N_3O_2$ (325.40): C, 70.13; H, 7.12; N, 12.91; Found: C, 70.09; H, 7.07; N, 12.86;

3-(4-Chlorophenyl)-4,4-diethoxy-6-ethyl-1,2,3,4-tetrahydropyridine-2,5 dicarbonitrile (11b)

Yield 80%; mp 121-123 °C; IR (KBr): υ cm^{-1} 3352 (NH), 3172 (CH-arom), 2954 (CH-aliph), 2210 (2CN); ^{1}H-NMR (DMSO-d_6): δ 1.29 (t, 6H, $2CH_3$), 1.35 (t, 3H, CH_3), 4.43 (q, 2H, CH_2), 4.45 (q, 4H, $2CH_2$), 6.80 (d, 1H, C-2), 7.15 (d, 1H, C-3), 7.27-7.57 (m, 5H, Ar H and NH); MS: *m/z* (%) 359 (M^+); Anal. calcd. for $C_{19}H_{22}ClN_3O_2$ (359.85): C, 63.42; H, 6.16; Cl, 9.85; N, 11.68,; Found: C, 63.20; H, 6.20; Cl, 9.80; N, 11.75.

3-(2-Chlorophenyl)-4,4-diethoxy-6-ethyl-1,2,3,4-tetrahydropyridine-2,5-dicarbonitrile (11c)

Yield 83%; mp 130-132 °C; IR (KBr): υ cm^{-1} 3465 (NH), 3050 (CH-arom), 2957 (CH-aliph), 2302 (2CN); ^{1}H-NMR (DMSO-d_6): δ 1.27 (t, 6H, $2CH_3$), 1.40 (t, 3H, CH_3), 4.45 (q, 2H, CH_2), 4.53 (q, 4H, $2CH_2$), 6.77 (d, 1H, C-2), 7.14 (d, 1H, C-3), 7.20-7.60 (m, 5H, Ar H and NH); MS: *m/z* (%) 359 (M^+); Anal. calcd. for $C_{19}H_{22}ClN_3O_2$ (359.85): C, 63.42; H, 6.16; Cl, 9.85; N, 11.68; Found: C, 63.35; H, 6.10; Cl, 9.95; N, 11.60.

General procedure for the synthesis of pyridine derivatives (14a-l)

A mixture of 3-aminopent-2-enenitrile **1** (0.96 g; 0.01 mol) and arylidenemalononitriles **3a-e** (0.01 mol) or ethyl 2-cyano-3-phenylacrylate derivatives **3f-h** (0.01 mol) or 2-cyano-3-phenylprop-2-enethioamide derivatives **3i-l** (0.01 mol) in ethanol (60 mL) containing catalytic amount of piperidine (5 drops) was refluxed for 5 h. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl, the solid product so formed was collected by filtration and crystallized from the proper solvent (Brown crystals).

2-Amino-6-ethyl-4-phenylpyridine-3,5-dicarbonitrile (14a)

Yield 64%; mp 132-134 °C; IR (KBr): υ cm^{-1} 3341, 3300 (NH_2), 3076 (CH-arom), 2929 (CH-aliph), 2173, 2200 (2CN); ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 3.43 (q, 2H, CH_2), 5.20 (s, 2H, NH_2), 7.22-8.01 (m, 5H, Ar H); ^{13}C NMR ($CDCl_3$): δ 13.00, 30.40, 85.60, 101.00, 116.50, 118.70, 125.00, 128.50, 128.50, 132.40, 132.40, 140.00, 161.30, 170.20, 172.50; MS: *m/z* (%) 248 (M^+); Anal. calcd. for $C_{15}H_{12}N_4$ (248.28): C, 72.56; H, 4.87; N, 22.57; Found: C, 72.50; H, 4.82; N, 22.50.

2-Amino-4-(4-chlorophenyl)-6-ethylpyridine-3,5-dicarbonitrile (14b)

Yield 67%; mp 136-138 °C; IR (KBr): υ cm^{-1} 3338, 3300 (NH_2), 3070 (CH-arom), 2952 (CH-aliph), 2195 (2CN); ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 3.70 (q, 2H, CH_2), 5.59 (s, 2H, NH_2), 7.20-8.00 (m, 4H, Ar H); MS: *m/z* (%) 282 (M^+); Anal. calcd. for $C_{15}H_{11}ClN_4$ (282.73): C, 63.72; H, 3.92; Cl, 12.54; N, 19.82; Found: C, 63.72; H, 3.92; Cl, 12.54; N, 19.82.

2-Amino-4-(3-chlorophenyl)-6-ethylpyridine-3,5-dicarbonitrile (14c)

Yield 62%; mp 110-112 °C; IR (KBr): υ cm^{-1} 3345, 3300 (NH_2), 3090 (CH-arom), 2928 (CH-aliph), 2198 (2CN); ^{1}H-NMR ($CDCl_3$): δ 1.42 (t, 3H, CH_3), 3.70 (q, 2H, CH_2), 5.70 (s, 2H, NH_2), 7.22-7.42 (m, 4H, Ar H); MS: *m/z* (%) 282 (M^+); Anal. calcd. for $C_{15}H_{11}ClN_4$ (282.73): C, 63.72; H, 3.92; Cl, 12.54; N, 19.82; Found: C, 63.72; H, 3.92; Cl, 12.54; N, 19.8.

2-Amino-6-ethyl-4-(4-nitrophenyl)pyridine-3,5-dicarbonitrile (14d)

Yield 83%; mp 116-118 °C; IR (KBr): υ cm^{-1} 3354, 3300 (NH_2), 2940 (CH-aliph), 2209 (2CN); ^{1}H-NMR ($CDCl_3$): δ 1.98 (t, 3H, CH_3), 3.44 (q, 2H, CH_2), 5.50 (s, 2H, NH_2), 7.26-8.40 (m, 4H, Ar H); MS: *m/z* (%) 293 (M^+); Anal. calcd. for $C_{15}H_{11}N_5O_2$ (293.28): C, 61.43; H, 3.78; N, 23.88 Found: C, 61.39; H, 3.72; N, 23.84.

2-Amino-4-(2,4-dichlorophenyl)-6-ethylpyridine-3,5-dicarbonitrile(14e)

Yield 88%; mp 124-126 °C; IR (KBr): υ_{max} = 3343, 3300 (NH_2), 3076 (CH-arom), 2931 (CH-aliph), 2195 (2CN); ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, 3H, CH_3), 3.45 (q, 2H, CH_2), 5.90 (s, 2H, NH_2), 7.24-7.66 (m, 3H, Ar H); MS: *m/z* (%) 317 (M^+); Anal. calcd. for $C_{15}H_{10}Cl_2N_4$ (317.17): C, 56.80; H, 3.18; Cl, 22.36; N,17.66; Found: C, 56.80; H, 3.18; Cl, 22.36; N, 17.66.

Ethyl 2-amino-5-cyano-6-ethyl-4-(4-nitro-phenyl)-nicotinate (14f)

Yield 87%; mp 119-121 °C; IR (KBr): υ cm^{-1} 3422, 3300 (NH_2), 3032 (CH-arom), 2992 (CH-aliph), 2225 (CN), 1720 (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.38 (t, 3H, CH_3),

1.41 (t, 3H, CH_3), 3.70 (q, 2H, CH_2), 4.40 (q, 2H, CH_2), 5.20 (s, 2H, NH_2), 7.26-8.37 (m, 4H, Ar H); ^{13}C NMR ($CDCl_3$): δ 13.30, 14.40, 30.50, 62.00, 95.10, 99.00, 132.70, 132.70, 128.30, 131.00, 131.00, 139.60, 145.10, 154.00, 167.30, 168.70, 171.20; MS: *m/z* (%) 340 (M^+); Anal. calcd. for $C_{17}H_{16}N_4O_4$ (340.33): C, 59.99; H, 4.74; N, 16.46, Found: C, 59.94; H, 4.69; N, 16.43.

Ethyl 2-amino-4-(4-chlorophenyl)-5-cyano-6-ethyl-nicotinate (14g)

Yield 92%; mp 131-33 °C; IR (KBr): υ cm^{-1} 3441, 3300 (NH_2), 3036 (CH-arom), 2990 (CH-aliph), 2223 (CN), 1724 (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.40 (t, 3H, CH_3), 1.52 (t, 3H, CH_3), 4.22 (q, 2H, CH_2), 4.40 (q, 2H, CH_2), 7.27-8.20 (m, 6H, Ar H and NH_2); MS: *m/z* (%) 329 (M^+); Anal. calcd. for $C_{17}H_{16}N_3ClO_2$ (329.78): C, 61.91; H, 4.89; N, 12.74; Cl, 10.75, Found: C, 61.85; H, 4.95; N, 12.80; Cl, 10.85.

Ethyl 2-amino-5-cyano-4-(2,4-dichlorophenyl)-6-ethylnicotinate (14h)

Yield 90%; mp 128-130 °C; IR (KBr): υ cm^{-1} 3441, 3300 (NH_2), 3076 (CH-arom), 2934 (CH-aliph), 2219 (CN), 1725 (C=O); ^{1}H-NMR ($CDCl_3$): δ 1.45 (t, 3H, CH_3), 1.60 (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 4.45 (q, 2H, CH_2), 7.27-8.20 (m, 5H, Ar H and NH_2); MS: *m/z* (%) 364 (M^+); Anal. calcd. for $C_{17}H_{15}Cl_2N_3O_2$ (364.23): C, 56.06; H, 4.15; Cl, 19.47; N, 11.54, Found: C, 56.10; H, 4.20; Cl, 19.55; N, 11.60.

2-Amino-5-cyano-6-ethyl-4-phenylpyridine-3-carbothioamide (14i)

Yield 86%; mp 260-262 °C; IR (KBr): υ cm^{-1} 3274, 3116 (NH_2), 2926 (CH-aliph), 2216 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.63 (t, 3H, CH_3), 3.00 (q, 2H, CH_2), 7.41-7.59 (m, 5H, Ar H), 8.21 (s, 2H, NH_2), 12.74 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6): δ 13.00, 29.70, 100.50, 116.00, 117.60, 126.20, 128.50, 128.50,133.40, 133.40, 139.00, 155.70, 164.70, 167.00, 194.20; MS: *m/z* (%) 282 (M^+); Anal. calcd. for $C_{15}H_{14}N_4S$ (282.36): C, 63.80; H, 5.00; N, 19.84, S, 11.36, Found: C, 63.75; H, 4.93; N, 19.79, S, 11.31.

2-Amino-4-(4-chlorophenyl)-5-cyano-6-ethyl-pyridine-3-carbothioamide (14j)

Yield 83%; mp 140-142 °C; IR (KBr): υ cm^{-1} 3415, 3400, 3194 ($2NH_2$), 3076 (CH-arom), 2934 (CH-aliph), 2195 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.60 (t, 3H, CH_3), 3.10 (q, 2H, CH_2), 7.40-7.60 (m, 4H, Ar H), 8.35 (s, 2H, NH_2), 12.70 (s, 2H, NH_2); MS: *m/z* (%) 316 (M^+); Anal. calcd. for $C_{15}H_{13}ClN_4S$ (316.81): C, 56.87; H, 4.14; Cl, 11.19; N, 17.68; S, 10.12, Found: C, 56.80; H, 4.10; Cl, 11.25; N, 17.75; S, 10.15.

2-Amino-5-cyano-6-ethyl-4-(4-methoxy-phenyl)-pyridine-3-carbothioamide (14k)

Yield 79%; mp 136-138 °C; IR (KBr): υ cm^{-1} 3377, 3277, 3166 ($2NH_2$), 2940 (CH-aliph), 2226 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.83 (t, 3H, CH_3), 3.49 (q, 2H, CH_2), 3.89 (s, 3H, OCH_3), 6.86-8.05 (m, 4H, Ar H), 8.74 (s, 2H, NH_2), 10.00 (s, 2H, NH_2); MS: *m/z* (%) 312 (M^+); Anal. calcd. for $C_{16}H_{16}N_4OS$ (312.39): C, 61.52; H, 5.16; N, 17.93, S, 10.26, Found: C, 61.46; H, 5.11; N, 17.90, S, 10.19 %.

2-Amino-5-cyano-4-(2,4-dichlorophenyl)-6-ethyl-pyridine-3-carbothioamide (14l)

Yield 76%; mp 121-123 °C; IR (KBr): υ cm^{-1} 3480, 3337, 3170 ($2NH_2$), 3090 (CH-arom), 2924 (CH-aliph), 2215 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, 3H, CH_3), 3.45 (q, 2H, CH_2), 7.30-7.66 (m, 3H, Ar H), 8.90 (s, 2H, NH_2), 10.20 (s, 2H, NH_2); MS: *m/z* (%) 351 (M^+); Anal. calcd. for $C_{15}H_{12}Cl_2N_4S$ (351.25): C, 51.29; H, 3.44; Cl, 20.19; N, 15.95; S, 9.13, Found: C, 51.35; H, 3.50; Cl, 20.15; N, 15.90; S, 9.15.

General procedure for the synthesis of diazenyl derivatives (16a-e)

A cold suspension of aryl diazonium salts **15a-e** (0.01 mol) (prepared from 0.01 mol of aromatic amine in 5 mL concentrated HCl with the appropriate quantities of sodium nitrite 0.7 g in 10 mL H_2O) was gradually added to a cold solution (0-5 °C) of **1** (0.01 mol) in ethanol (50 mL) containing anhydrous sodium acetate (5 g) with continuous stirring for 1 hr. The resulting reaction product was filtered off, washed with water and crystallized from the proper solvent (reddish brown).

3-Amino-2-(phenyldiazenyl)pent-2-enenitrile (16a)

Yield 69%; mp 113-115 °C; IR (KBr): υ cm^{-1} 3433, 3106 (NH_2), 2924 (CH-aliph), 2194 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.27 (t, 3H, CH_3), 3.33 (q, 2H, CH_2), 7.17-7.41 (m, 7H, Ar H and NH_2); MS: *m/z* (%) 200 (M^+); Anal. calcd. for $C_{11}H_{12}N_4$ (200.24): C, 65.98; H, 6.04; N, 27.98; Found: C, 65.94; H, 5.97; N, 27.91.

3-Amino-2-((4-nitrophenyl)diazenyl)pent-2-enenitrile (16b)

Yield 72%; mp 118-120 °C; IR (KBr): υ cm^{-1} 3401, 3116 (NH_2), 2908 (CH-aliph), 2204 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 2.22 (q, 2H, CH_2), 4.80 (s, 2H, NH_2), 7.26-8.43 (m, 4H, Ar H); MS: *m/z* (%) 245 (M^+); Anal.

calcd. for $C_{11}H_{11}N_5O_2$ (245.24): C, 53.87; H, 4.52; N, 28.56; Found: C, 53.81; H, 4.49; N, 28.53.

3-Amino-2-((4-bromophenyl)diazenyl)pent-2-enenitrile (16c)

Yield 67%; mp 115-117 °C; IR (KBr): υ cm^{-1} 3266, 3192 (NH_2), 2956 (CH-aliph), 2212 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 2.08 (q, 2H, CH_2), 5.00 (s, 2H, NH_2), 7.06-8.28 (m, 4H, Ar H); MS: *m/z* (%) 279 (M^+); Anal. calcd. for $C_{11}H_{11}N_4Br$ (279.14): C, 47.33; H, 3.97; Br, 28.63; N, 20.07; Found: C, 47.40; H, 4.00; Br, 28.60; N, 20.0.

3-Amino-2-(p-tolyldiazenyl)pent-2-enenitrile (16d)

Yield 79%; mp 126-128 °C; IR (KBr): υ cm^{-1} 3435, 3194 (NH_2), 2924 (CH-aliph), 2213 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.25 (s, 3H, CH_3), 1.60 (t, 3H, CH_3), 2.28 (q, 2H, CH_2), 3.90 (s, 2H, NH_2), 7.07-8.32 (m, 4H, Ar H); MS: *m/z* (%) 214 (M^+); Anal. calcd. for $C_{12}H_{14}N_4$ (214.27): C,67.27; H,6.59; N,26.15, Found: C, 67.22; H, 6.52; N, 26.11.

3-Amino-2-((4-chlorophenyl)diazenyl)pent-2-enenitrile (16e)

Yield 82%; mp 120-122 °C; IR (KBr): υ cm^{-1} 3434, 3192 (NH_2), 2964 (CH-aliph), 2201 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 3H, CH_3), 2.07 (q, 2H, CH_2), 5.20 (s, 2H, NH_2), 7.17-8.10 (m, 4H, Ar H), MS: *m/z* (%) 234 (M^+); Anal. calcd. for $C_{11}H_{11}ClN_4$ (234.68): C,56.30; H,4.72; Cl, 15.11; N,23.87, Found: C,56.35; H,4.80; Cl, 15.10; N, 23.90.

General procedure for the synthesis of pyrazole derivatives (18a-c)

A mixture of compounds **16** (0.01 mole), ammonium acetate (0.01 mole) and hydrazine hydrate (0.5 g 0.01 mole) was fused in domestic microwave oven for 3 minutes. The solid precipitate so formed was treated with ethanol and filtered out and crystallized from the proper solvent.

5-Ethyl-4-((4-nitrophenyl)diazenyl)-1H-pyrazol-3-amine (18a)

Yield 68%; mp 230-232 °C; IR (KBr): υ cm^{-1} 3485, 3377 (NH_2), 3102 (NH), 2991 (CH-aliph); ^{1}H-NMR ($CDCl_3$): δ 1.45 (t, 3H, CH_3), 2.61 (q, 2H, CH_2), 4.60 (s, 2H, NH_2), 7.21-8.38 (m, 4H, Ar H), 11.45 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ 13.10, 18.7, 123.20, 123.20, 126.00, 126.00, 130.20, 145.60, 151.20, 153.70, 170.50; MS: *m/z* (%) 260 (M^+); Anal. calcd. for $C_{11}H_{12}N_6O_2$ (260.25): C, 50.77; H, 4.65; N, 32.29, Found: C, 50.71; H, 4.61; N, 32.22.

5-Ethyl-4-(p-tolyldiazenyl)-1H-pyrazol-3-amine (18b)

Yield 65%; mp 180-182 °C; IR (KBr): υ cm^{-1} 3407, 3390 (NH_2), 3154 (NH), 2923 (CH-aliph); ^{1}H-NMR ($CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.26 (s, 3H, CH_3), 2.39 (q, 2H, CH_2), 7.06-7.26 (m, 6H, Ar H and NH_2), 11.59 (s, 1H, NH); MS: *m/z* (%) 229 (M^+); Anal. calcd. for $C_{12}H_{15}N_5$ (229.28): C, 62.86; H, 6.59; N, 30.54, Found: C, 62.84; H, 6.57; N, 30.47.

4-((4-Chlorophenyl)diazenyl)-5-ethyl-1H-pyrazol-3-amine (18c)

Yield 57%; mp 129-131 °C; IR (KBr): υ cm^{-1} 3300, 3277 (NH_2), 3110 (NH), 2992 (CH-aliph); ^{1}H-NMR ($CDCl_3$): δ 1.32 (t, 3H, CH_3), 2.13 (q, 2H, CH_2), 5.80 (s, 2H, NH_2), 7.08-8.08 (m, 4H, Ar H), 12.78 (s, 1H, NH); MS: *m/z* (%) 249 (M^+); Anal. calcd. for $C_{11}H_{12}N_5Cl$ (249.70): C, 52.91; H, 4.84; N, 28.05; Cl, 14.20, Found: C, 52.87; H, 4.80; N, 27.97, Cl, 14.16.

General procedure for the synthesis of nicotino-nitrile derivatives (21a-c)

A mixture of compounds **16** (0.01 mole), ammonium acetate (0.01 mole) and malononitrile (0.66 g, 0.01 mole) was fused in domestic microwave oven for 3 minutes. The solid precipitate so formed was treated with ethanol and filtered out and crystallized from the proper solvent (reddish brown).

2,4-Diamino-6-ethyl-5-(phenyldiazenyl)nicotino-nitrile (21a)

Yield 64%; mp 130-132 °C; IR (KBr): υ cm^{-1} 3480, 3400, 3337, 3300 ($2NH_2$), 3064 (CH-arom), 2934 (CH-aliph), 2193 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, 3H, CH_3), 3.20 (q, 2H, CH_2), 5.40 (s, 4H, 2 NH_2), 7.40-8.00 (m, 5H, ArH); MS: *m/z* (%) 266 (M^+); Anal. calcd. for $C_{14}H_{14}N_6$ (266.30): C, 63.14; H, 5.30; N, 31.56, Found: C, 63.11; H, 5.28; N, 31.51.

2,4-Diamino-6-ethyl-5-((4-nitrophenyl)diazenyl)-nicotinonitrile (21b)

Yield 61%; mp 280-282 °C; IR (KBr): υ cm^{-1} 3495, 3400, 3343, 3300 ($2NH_2$), 3090 (CH-arom), 2921 (CH-aliph), 2194 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, 3H, CH_3), 3.30 (q, 2H, CH_2), 5.60 (s, 4H, 2 NH_2), 7.80-8.40 (m, 4H, Ar H); MS: *m/z* (%) 311 (M^+); Anal. calcd. for $C_{14}H_{13}N_7O_2$ (311.30): C, 54.02; H, 4.21; N, 31.50, Found: C, 53.88; H, 4.19; N, 31.46.

2,4-Diamino-5-((4-bromophenyl)diazenyl)-6-ethylnicotinonitrile (21c)

Yield 66%; mp 125-127 °C; IR (KBr): υ cm^{-1} 3400,

3356, 3266 ($2NH_2$), 3090 (CH-arom), 2934 (CH-aliph), 2193 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, 3H, CH_3), 3.30 (q, 2H, CH_2), 5.60 (s, 4H, 2 NH_2), 7.40-7.90 (m, 4H, Ar H); MS: *m/z* (%) 345 (M^+); Anal. calcd. for $C_{14}H_{13}BrN_6$ (345.20): C, 48.71; H, 3.80; Br, 23.15; N, 24.35, Found: C, 48.68; H, 3.76; Br, 23.12 ; N, 24.31.

General procedure for the synthesis of pyridine derivatives (24a-c)

A mixture of compounds **16** (0.01 mole), ammonium acetate (0.01mole) and ethyl cyanoacetate (1.13 g, 0.01 mole) was fused in domestic microwave oven for 3 minutes. The solid precipitate so formed was treated with ethanol and filtered out and crystallized from the proper solvent (brown crystals).

4-Amino-6-ethyl-2-hydroxy-5-((4-nitrophenyl)-diazenyl)nicotinonitrile (24a)

Yield 65%; mp 140-142 °C; IR (KBr): υ cm^{-1} 3493 (OH), 3373, 3300 (NH_2), 2924 (CH-aliph), 2212 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 2.35 (q, 2H, CH_2), 4.60 (s, 2H, NH_2), 7.40-8.30 (m, 4H, Ar H), 11.33 (s, 1H, OH), MS: *m/z* (%) 312 (M^+); Anal. calcd. for $C_{14}H_{12}N_6O_3$ (312.28): C, 53.85; H, 3.87; N, 26.91, Found: C, 53.82; H, 3.84; N, 26.89.

4-Amino-6-ethyl-2-hydroxy-5-(p-tolyldiazenyl)-nicotinonitrile (24b)

Yield 69%; mp 279-281 °C; IR (KBr): υ cm^{-1} 3584 (OH), 3435, 3400 (NH_2), 2923 (CH-aliph), 2206 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, 3H, CH_3), 1.33 (s, 3H, CH_3), 2.30 (q, 2H, CH_2), 4.40 (s, 2H, NH_2), 7.20-8.39 (m, 4H, Ar H), 11.33 (s, 1H, OH); MS: *m/z* (%) 281 (M^+); Anal. calcd. for $C_{15}H_{15}N_5O$ (281.31): C, 64.04; H, 5.37; N, 24.90, Found: C, 63.98; H, 5.34; N, 24.88.

4-Amino-5-((4-chlorophenyl)diazenyl)-6-ethyl-2-hydroxynicotinonitrile (24c)

Yield 61%; mp 131-33 °C; IR (KBr): υ cm^{-1} 3500 (OH), 3423, 3300 (NH_2), 3050 (CH-arom), 2926 (CH-aliph), 2211 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.19 (t, 3H, CH_3), 2.11 (q, 2H, CH_2), 4.60 (s, 2H, NH_2), 7.00-8.20 (m, 4H, Ar H), 11.21 (s, 1H, OH); MS: *m/z* (%) 301 (M^+); Anal. calcd. for $C_{14}H_{12}ClN_5O$ (301.73): C, 55.73; H, 4.01; Cl, 11.75; N, 23.21, Found: C, 55.71; H, 3.89; Cl, 11.71 ; N, 23.18.

General procedure for the synthesis of dihydropyrimidine derivatives (28a-c)

A mixture of 3-aminopent-2-enenitrile **1** (0.96 g; 0.01 mol) in dry acetone (50 mL), aroyl or alkoyl isothiocyanate (0.01 mol) (prepared in situ from aroyl or alkoyl chloride and ammonium thiocyanate in refluxing acetone) was added. The reaction mixture was refluxed for 3 hrs, and then poured onto cold water. The solid product was collected by filtration, washed with water and crystallized from the proper solvent (white crystals).

6-Ethyl-4-methyl-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (28a)

Yield 62%; mp 130-132 °C; IR (KBr): υ cm^{-1} 3389 (NH), 2924 (CH-aliph), 2206 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.82 (q, 2H, CH_2), 10.22 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ 11.50, 20.50, 23.00, 93.70, 116.20, 166.20, 174.70, 182.90; MS: *m/z* (%) 179 (M^+); Anal. calcd. for $C_8H_9N_3S$ (179.24): C, 53.61; H, 5.06; N, 23.44, S, 17.89, Found: C, 53.58; H, 4.94; N, 23.41, S, 17.86.

6-Ethyl-4-phenyl-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (28b)

Yield 60%; mp 162-64 °C; IR (KBr): υ cm^{-1} = 3311 (NH), 3060 (CH-arom), 2908 (CH-aliph), 2224 (CN); ^{1}H-NMR (DMSO-d_6): δ 1.16 (t, 3H, CH_3), 2.39 (q, 2H, CH_2), 7.29-7.62 (m, 5H, Ar H), 10.63 (s, 1H, NH); MS: *m/z* (%) 241 (M^+); Anal. calcd. for $C_{13}H_{11}N_3S$ (241.31): C, 64.70; H, 4.59; N, 17.41, S, 13.29, Found: C, 64.68; H, 4.55; N, 17.38, S, 13.24.

4-(2-Chlorophenyl)-6-ethyl-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (28c)

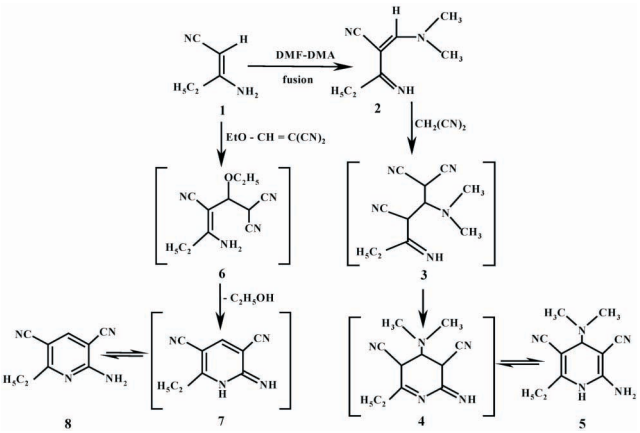
Yield 65%; mp 230-232 °C; IR (KBr): υ cm^{-1} 3433 (NH), 3071 (CH-arom), 2921 (CH-aliph), 2222 (CN); ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, 3H, CH_3), 2.60 (q, 2H, CH_2), 7.40-7.80 (m, 4H, Ar H), 10.30 (s, 1H, NH); MS: *m/z* (%) 275 (M^+); Anal. calcd. for $C_{13}H_{10}ClN_3S$ (275.76): C, 56.62; H, 3.66; Cl, 12.86; N, 15.24, S, 11.63, Found: C, 56.59; H, 3.63; Cl, 12.81; N, 15.21, S, 11.58.

RESULTS AND DISCUSSION

It was found that enaminonitrile **1** react with dimethylformamide dimethyl acetal to give a compound with molecular formula $C_8H_{13}N_3$ = 151. This was considered to be 2-((dimethylamino)methylene)-3-iminopentanenitrile **2** based on its elemental and spectral analyses. Also, the ^{1}H-NMR of compound **2** revealed the presence of a triplet signal at δ = 1.24 ppm corresponding to methyl group, a singlet signal at δ = 2.01 ppm corresponding to two methyl groups, a quartet signal at δ = 2.71 ppm corresponding to methylene group, a singlet signal at δ = 3.99 ppm corresponding to amino function and a singlet signal at δ = 6.09

ppm corresponding to olifinic proton. The mass spectrum of the same product is in accordance with the proposed structure. It shows a very intense molecular ion peak at 151. Compound **2** was allowed to reflux with malononitrile in ethanol containing a catalytic amount of piperidine to give a compound with molecular formula $C_{11}H_{15}N_5$ = 217. This was considered to be 1,4-dihydropyridine **5**. The ^{1}H-NMR spectra of compound **5** revealed the presence of a triplet signal at δ = 1.31 ppm corresponding to methyl group, a singlet signal at δ = 2.53 ppm corresponding to two methyl groups, a quartet signal at δ = 3.20 ppm corresponding to methylene group, a singlet signal at δ = 4.56 ppm corresponding to H-4 pyridine, a singlet signal at δ = 5.66 ppm corresponding to NH_2 and a singlet signal at δ = 7.85 ppm corresponding to NH. The ^{13}C NMR data of compounds **5** showed chemical shift values conform to the suggested structure, also the mass spectrum and IR spectrum of the same product agrees with the proposed structure. Formation of **5** from the reaction of malononitrile with **2** is believed to be formed via initial addition of malononitrile on the double bond system of **2** which give the acyclic intermediate **3** that cyclized in the same reaction condition to give **4** which tautomerizes into **5**. (Scheme I).

Scheme I Synthesis of compounds **2,5,8**

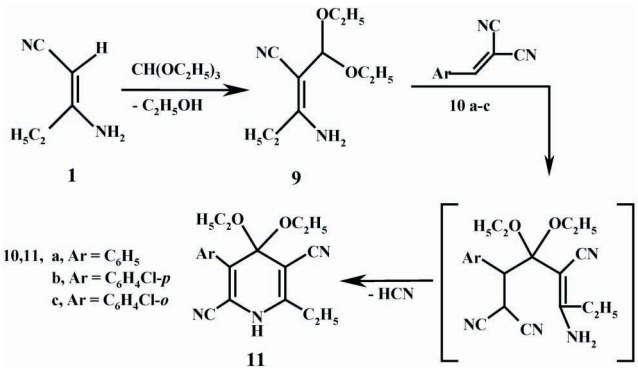


On the other hand enaminonitrile **1** reacted with ethoxymethylenemalononitrile in ethanol-reflux containing a catalytic amount of piperidine to give pyridine derivative **8** via intermediacy of non-isolable intermediates **6** and **7** (Scheme I). Confirming structures **8** was based on its elemental analysis and spectral data. The ^{1}H-NMR of compound **8** revealed the presence of a triplet signal at δ = 1.17 ppm corresponding to methyl function, a quartet signal at δ = 2.60 ppm corresponding to methylene group and a multiplet signal at δ = 7.05-7.97 ppm corresponding to aromatic proton and amino function. Formation of **8** is believed to be formed via initial addition of enaminonitrile **1** on the double bond of ethoxymethylenemalononitrile to give the non isolable intermediate **6** which gives the pyridine **8** via losing ethanol and subsequent tautomerism.

The reactivity of enaminonitrile **1** toward triethylorthoformate was also investigated. So, when **1** is allowed to react with triethylorthoformate in refluxing acetic anhydride, a product with a molecular formula $C_{10}H_{18}N_2O_2$ = 198 was obtained. This was considered to be **9** based on its elemental analysis and spectral data (Scheme II). The ^{1}H-NMR of compound **9** revealed the presence of a triplet signal at δ = 1.18 ppm corresponding to two methyl group, a triplet signal at δ = 1.29 ppm corresponding to methyl group, a quartet signal at δ = 2.64 ppm corresponding to methylene group, a quartet signal at δ = 2.73 ppm corresponding to two methylene group, a singlet signal at δ = 4.87 ppm corresponding to CH and a singlet signal at δ = 6.11 ppm characteristic for NH_2. The mass spectrum is in accordance with the proposed structure which shows a molecular ion peak at 198 (M^+).

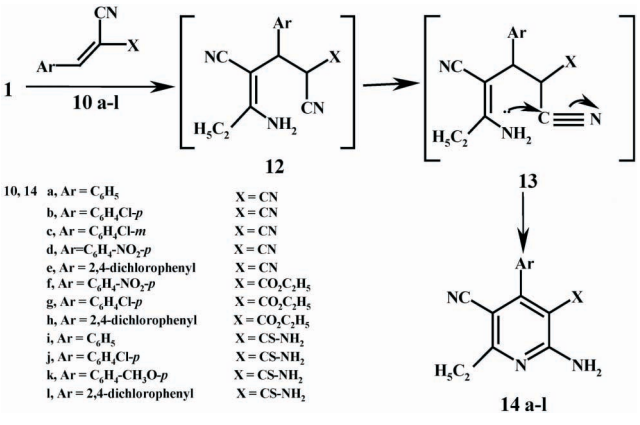
The behaviour of **9** toward benzylidenemalononitrile was also investigated. When **9** is allowed to reflux with benzylidenemalononitrile **10a** in ethanol containing a catalytic amount of piperidine, a compound with molecular formula $C_{19}H_{23}N_3O_2$ = 325 was formed. This was considered to be tetrahydropyridine **11a** based on its spectral and elemental analysis**.** Similarly **9** reacted with benzylidenemalononitrile **10b,c** in the same reaction condition to give tetrahydropyridine derivatives **11b**,**c** (Scheme II).

Scheme II Synthesis of compounds **9** and **11a-c**



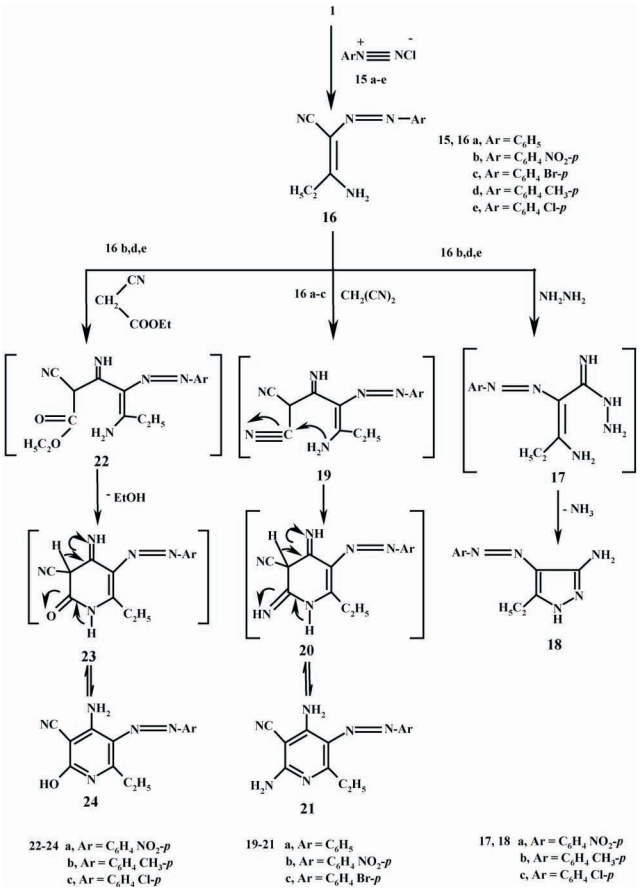
The results obtained from the reaction **9** with benzylidenemalononitrile prompted us to investigate further the behaviour of enaminonitrile **1** toward benzylidenemalononitrile derivatives. Thus, when **1** reacted with benzylidenemalononitrile **10a** under reflux in ethanol containing a catalytic amount of piperidine afforded the pyridine derivative **14a** via intermediacy of **12** and **13** (Scheme III). Establishing structure **14a** was based on its elemental and spectral analysis. Similarly, enaminonitrile **1** reacted with arylidenes **10b-h** to give pyridine derivatives **14b-h** via intermediacy of **12** and **13**. Similar to the behavior of arylidenes **10a-h**, enaminonitrile **1** reacted with arylidenecyanothioacetamide **10i-l** to give pyridine derivatives **14i-l** via intermediacy of **12** and **13**. Establishing structure **14i-l** was based on the elemental analyseis and spectral data. For example, the ^{1}H NMR of compound **14a** revealed the presence of a triplet signal at δ = 1.25 ppm corresponding to methyl function, a quartet signal at δ = 3.43 ppm corresponding to methylene function, a singlet function at δ = 5.20 ppm corresponding to amino function and a multiplet signal at δ = 7.22-8.01 ppm corresponding to aromatic protons. The mass spectrum of the same product is in accordance with the proposed structure. Thus, it showed a molecular ion peaks at 248 and a number of fragments agree with the proposed structure (Scheme III). The ^{13}C NMR data of compounds **14a** showed chemical shift values conform to the suggested structure.

Scheme III Synthesis of compounds **14a-l**



Coupling of enaminonitrile **1** with aryl diazonium salts **15a-e** was also investigated. When enaminonitrile **1** is allowed to couple with aryl diazonium salt **15a** aryl diazenyl **16a** was obtained based on its spectral data. Similarly, aryl diazonium salts **15b-e** coupled with **1** to give aryl diazenyl **16b-e**. Establishing structure **16** was based on elemental analysis and spectral data. Aryl diazenyl **16b**,**d**,**e** were allowed to react with hydrazine hydrate to give pyrazole derivatives **18a-c** via intermediacy of non-isolable acyclic intermediate **17** (Scheme IV). The structure of **18** was established on the basis of its elemental analysis and spectral data. Furthermore the behavior of aryl diazenyl **16a-c** toward active methylene reagents was also investigated. When **16a** fused with malononitrile, it affords pyridine derivatives **21a** via intermediacy of **19** that cyclizes to **20** which tautomerizes into **21**. Establishing structure **21** was based on its elemental analysis. Similarly, **16b**,**c** reacted with malononitrile to give pyridine derivatives **1b**,**c.** In contrast to this, aryl diazenyl **16b**,**d**,**e** reacted with ethyl cyanoacetate by fusion to give pyridine derivative **24** via intermediacy of **22** that cyclizes to **23** which tautomerizes into **24** (Scheme IV).

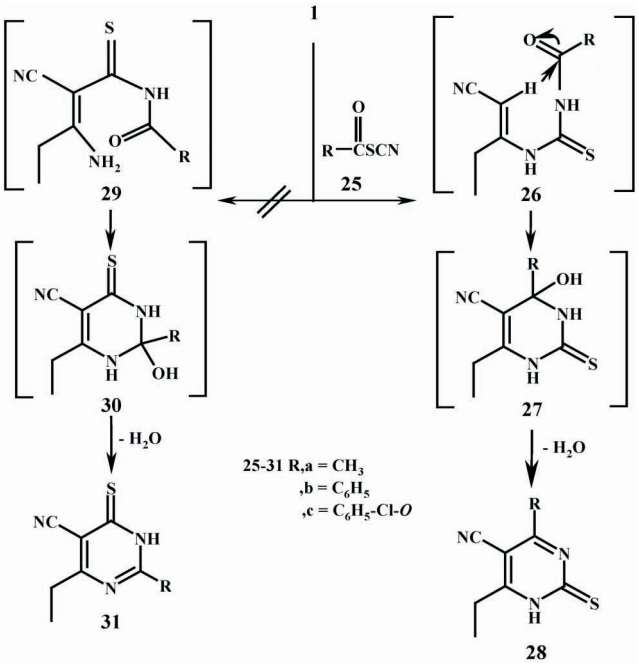
Scheme IV Synthesis of compounds **18a-c**, **21a-c**, **24a-c**



The behavior of enaminonitrile **1** toward isothiocyanate reagents was also investigated. Thus, when **1** re-

acted with acyl isothiocyanate **25a** in refluxing acetone, dihydropyrimidine **28a** was obtained rather than its tautomeric structure **31a** based on its spectral data. The ^{1}H-NMR spectrum of **28a** revealed the presence of a singlet signal for methyl function at higher field at δ = 2.07 ppm, one would expect if the reaction product was **31a** the methyl function appears at lower field. Formation of dihydropyrimidine **28** formed from the reaction of **1** with acyl isothiocyanate is believed to be formed via initial addition of enaminonitrile **1** on **25** to give the non isolable intermediate **26** that cyclizes in the same reaction condition to give **27** which readily loses a water molecule to give **28**. Similarly, enaminonitrile **1** reacted with isothiocyanate **25b**,**c** in acetone-reflux to give dihydropyrimidine derivatives **28b**,**c** (Scheme V).

Scheme V Synthesis of compounds **28a-c**



CONCLUSION

In conclusion, compounds **1** was used as efficient precursor for the synthesis of new pyridine, dihydropyridine, tetrahydropyridine, nicotinonitrile and pyrazole derivatives through the reactions with some electrophilic reagents, nucleophilic reagents, and aryl diazonium salts.

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