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Research Article

Utility of arylidenes in heterocyclic synthesis: synthesis of pyrimidines, 1,8-naphthyridine and pyrazolo [3,4-d] pyrimidine

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ABSTRACT

Treatment of 2-amino-4-(4- (dimethylamino)phenyl) buta-1,3-diene-1,1,3-tricarbonitrile (**1**) and 5-amino-3-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-1*H*-pyrazole-4-carbonitrile (**11**) with DMFDMA afforded *N,N*-dimethyl-*N'*-(1,1,3-tricyano-4-(4-(dimethylamino)phenyl)buta-1,3-dien-2-yl)formimidamide (**2**) and *N'*-(4-cyano-3-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-1*H*-pyrazol-5-yl)-*N,N*-dimethyl formimidamide (**12**) respectively in good yield. The novel 4-amino-6-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)pyrimidine-5-carbonitrile (**3**), 4-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4**) and *N'* -(2-amino-3,6-dicyano-7- (dicyanomethylene) -5- (4-(dimethylamino)phenyl) -7,8- dihydro -1,8-naphthyridin-4-yl) -*N,N* - dimethylformimidamide (**7**) were obtained by treatment of *N,N* – dimethyl -*N'*- (1,1,3-tricyano -4- (4-(dimethylamino)phenyl)buta-1,3-dien-2-yl) formimidamide (**2**) with $AcNH_4$/AcOH, HCl/AcOH and malononitrile dimer respctively. Also, the novel 3-(4-(dimethylamino)benzylidene)-4-imino-3,4-dihydro-1,2,5,6,8-pentaazaacenaphthylen-6(1*H*)-amine (**14**) and 3-(4-(dimethylamino)phenyl)-2-(4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)acrylonitrile (**15**) derivatives obtained by treatment of *N'*-(4-cyano-3-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-1*H*-pyrazol-5-yl)-*N,N*-dimethyl formimidamide (**12**) with hydrazine hydrate and HCl/AcOH respectively.

Keywords: DMFDMA, pyrimidines, 1,8-naphthyridine, pyrazolo [3,4-d]pyrimidine, 3-amino-5-cyanomethyl-1*H*-pyrazole-4-carbonitrile

INTRODUCTION

N,N-dimethylformamide dimethyl acetal (DMFDMA) acts as formulating agent, so that it has been used in the synthesis of enamines from active methylenes and active methyl groups, and amidines from amines and amides or thioamide groups[1]. DMFDMA is potentially valuable as a building block for heterocyclic synthesis[2] such as pyrimidine 1,8-Naphthyridine[3] and pyrazolopyrimidine derivatives. Pyrimidine and their derivatives are considered to be important for drugs and agricultural chemicals. A large number of pyrimidine derivatives are reported to exhibit antimycobacterial[4], antitumor[5], anticancer[6], anti-inflammatory[7] and antimicrobial[8]. 1,8-naphthyridine derivatives have promising medicinal properties, including anti-HIV[9], anticancer[10], anti-inflammatory[11], antibacterial[12], antiprotozoals[13], antimycobacterial[14]. Pyrazolo [3,4-*d*] pyrimidines and related fused heterocycles are a class of compounds with a good activity against several cancer cell lines[15,16], have been identified as bioactive molecules[17]. They are known to function as CNS (Central Nervous System) depressants[18] and as tuberculostatic[19]. Pyrazolo [3,4-d] pyrimidines were identified as a general class of adenosine receptors[20,21]. In this work we can synthesize a novel pyrimidine, pyyrazolo [3,4-d] pyrimidine and 1,8-naphthyridine derivatives from *N,N* – dimethyl -*N'*-(1,1,3-tricyano-4-(4-(dimethylamino)phenyl) buta-1,3-dien-2-yl)formimidamide (**2**) and *N'*-(4-cyano-3-

(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-1*H*-pyrazol-5-yl)-*N*,*N*-dimethyl formimidamide (**12**).

MATERIALS AND METHODS

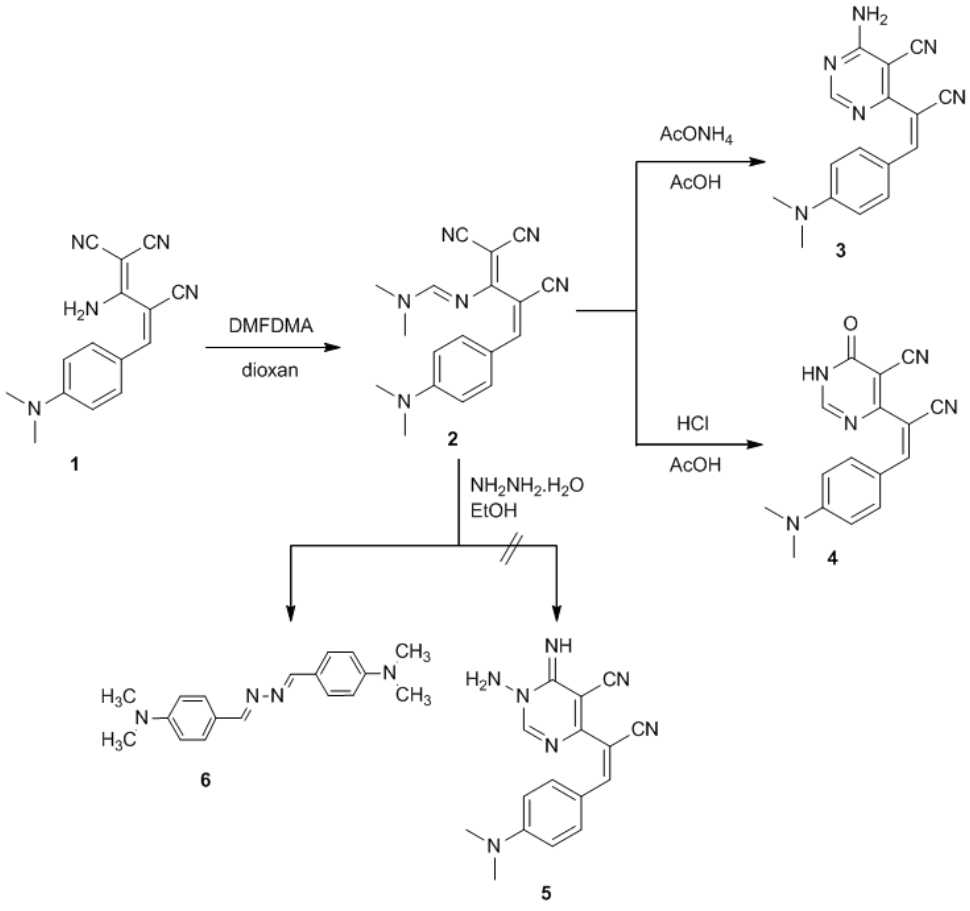
All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 17,100 FTIR spectrometer as KBr disks. NMR spectra were recorded on a Varian Gemini (400 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard unless otherwise. Mass spectra were obtained on Finnigan 4500 (low resolution) spectrometers using electron impact (EI). Elemental analyses were carried out in the Micro-analytical Center Cairo University, Giza, Egypt.

Chemistry

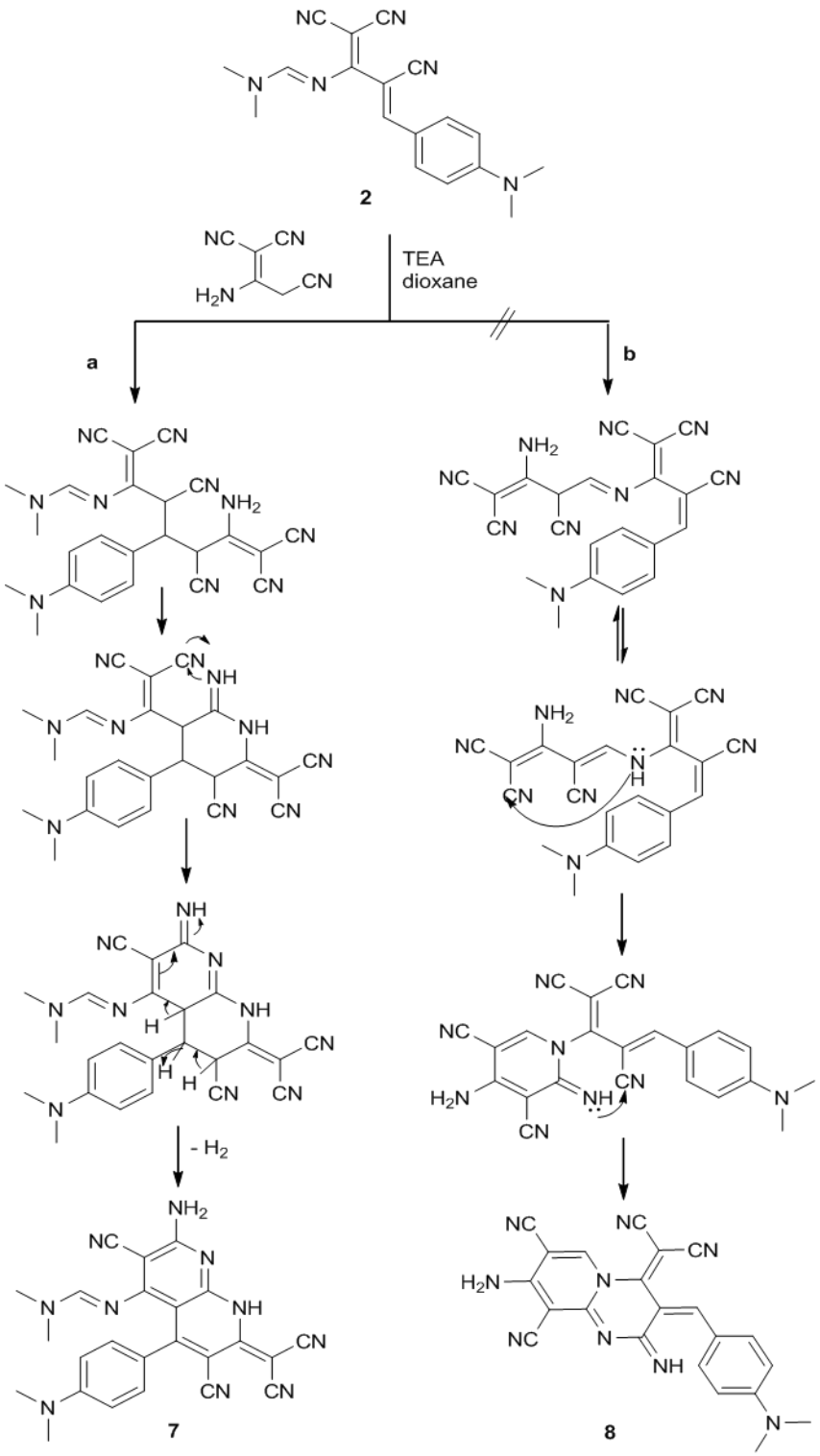
_N,N_-Dimethyl-_N'_-(1,1,3-tricyano-4-(4-(dimethylamino)phenyl)buta-1,3-dien-2-yl)formimidamide (2):

A mixture of 2-amino -4- (4-(dimethylamino)phenyl) buta-1,3-diene-1,1,3-tricarbonitrile[22] **1** (2.63g, 10 mmol) and DMFDMA (1.32mL, 10 mmol) in (20mL) dry 1,4-dioxane as solvent was left under reflux for 3 hours then left to cool. The resulting solid was collected by filtration, washed with ethanol, and recrystallized from ethanol to afford the respective enamine derivative as orange crystals. Yield 81%; m.p: 200-202 ^{o}C. FT-IR (KBr, υ, cm^{-1}): 2919 (CH aliph.), 2214, 2197 (2 C≡N); ^{1}H NMR (DMSO–d_6, δ, ppm): 3.02, 3.09 (2s,12H, 4CH_3), 6.86, 6.88 (d, 2H, Ar-H), 7.62 (s, 1H, CH), 7.89, 7.91 (d, 2H, Ar-H), 8.29 (s, 1H, CH); Anal. Calcd. for ($C_{18}H_{18}N_6$), requires C 67.9, H 5.7, N 26.4 %; found C 67.96, H 5.78, N 26.51 %.

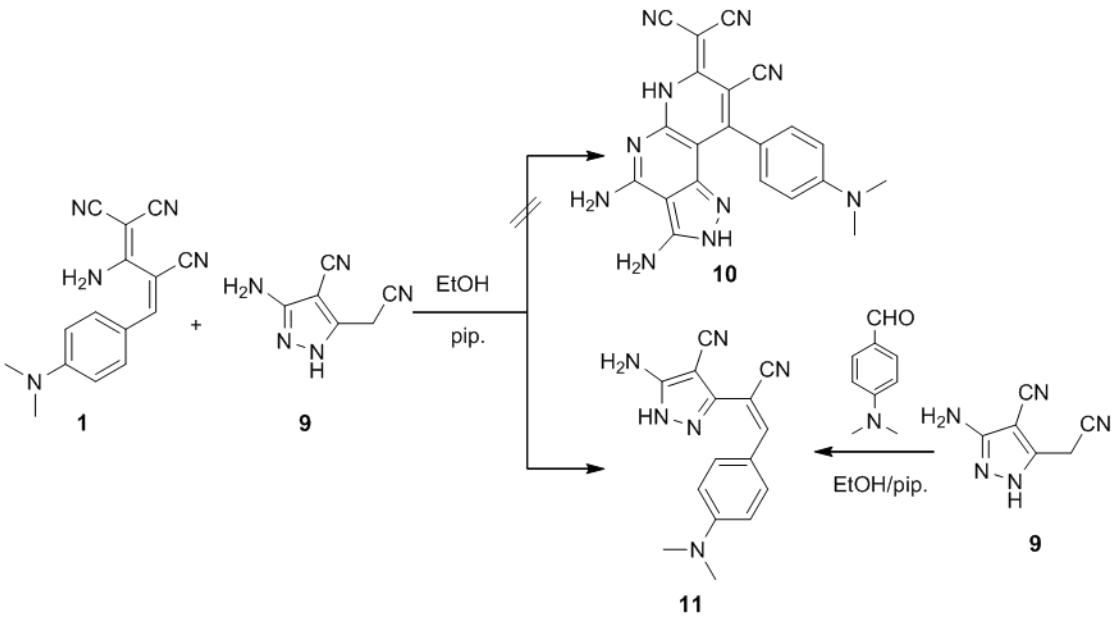
4-Amino-6-(1-cyano-2-(4-(dimethylamino) phenyl)vinyl)pyrimidine-5-carbonitrile (3):



Scheme 1



Scheme 2



Scheme 3

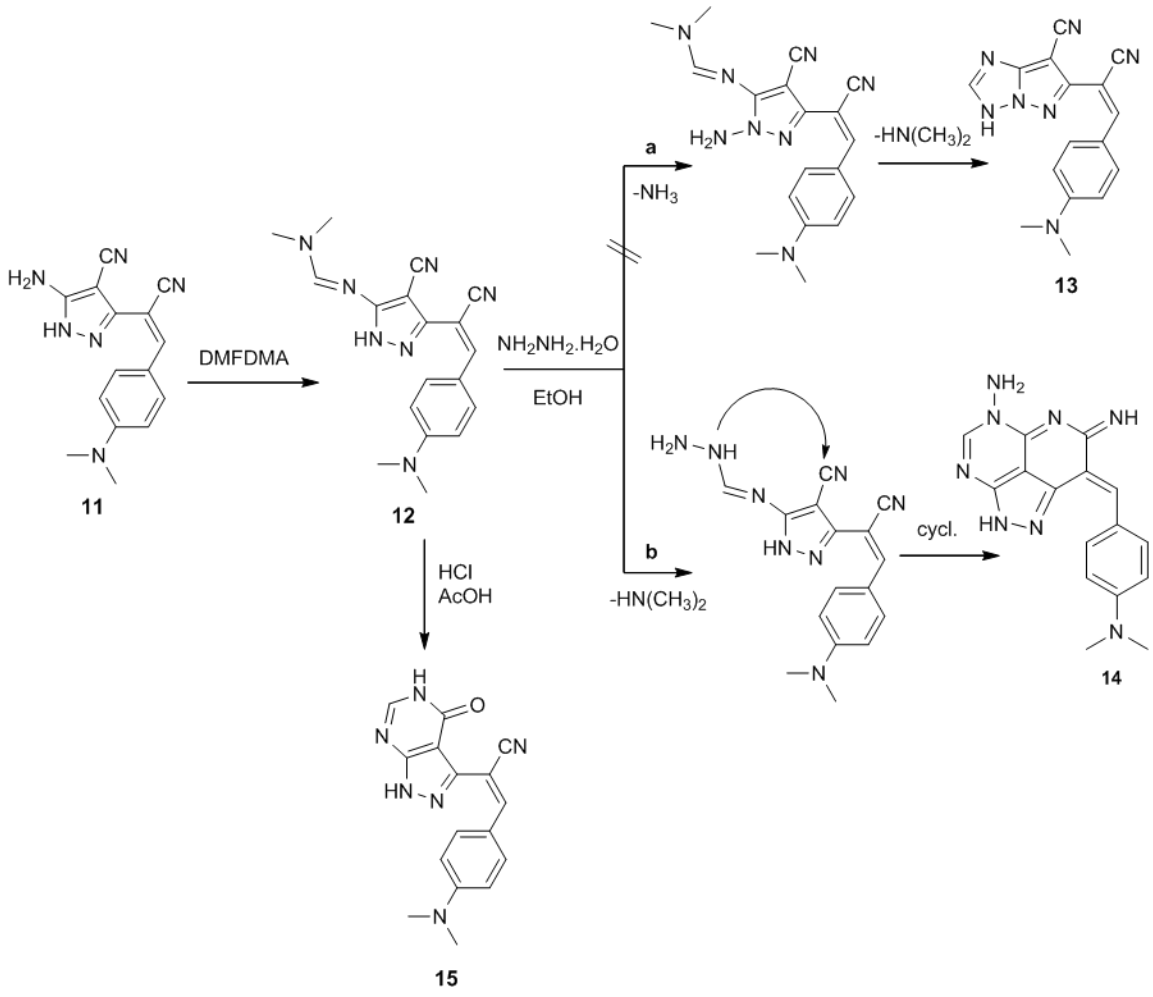
A mixture of *N,N* - dimethyl -*N'*- (1,1,3-tricyano-4-(4- (dimethylamino) phenyl) buta-1,3-dien-2-yl) formimidamide**2** (3.18g, 10 mmol) with acetic acid (10 ml) and ammonium acetate (2.3g, 30mmol) was left under reflux for 2 hours then left to cool. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with water, and recrystallized from ethanol as brown crystals. Yield 74.7%, m.p: 236-238^{o}C. FT-IR (KBr, υ, cm^{-1}): 3394, 3250 (NH_2), 2212 (C≡N). ^{1}H NMR (DMSO–d_6,δ, ppm): 3.05 (s, 6H, $2CH_3$), 6.85, 6.87 (d, 2H, Ar-H), 7.76 (s, 2H, NH_2, D_2O exchangeable), 7.89, 7.91 (d, 2H, Ar-H), 8.16 (s, 1H, CH), 8.52 (s, 1H, CH). Anal.Calcd. for($C_{16}H_{14}N_6$), requires, C 66.19, H 4.86, N 28.95 %, found C 66.26, H 4.92, N 28.99 %.

4-(1-Cyano-2-(4-(dimethylamino)phenyl)vinyl)-6-oxo-1,6-dihydropyrimidine-5- carbonitrile(4):

A mixture of *N, N* – dimethyl -*N'*- (1,1,3-tricyano-4-(4- (dimethylamino)phenyl) buta-1,3-dien -2-yl) formimidamide **2** (3.18g, 10 mmol) with acetic acid and hydrochloric acid (9mL, 3:1) was left under reflux for 2 hours then cool. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with water, recrystallized from ethanol as violet crystals. Yield 72%, m.p: 280-282^{o}C. FT-IR (KBr, υ, cm^{-1}): 3350 (NH), 2220 (C≡N) and 1686 (C=O amide).^{1}H NMR (DMSO–d_6, δ, ppm): 3.12 (s, 6H, $2CH_3$), 6.88, 6.9 (d, 2H, Ar-H), 7.26(s, 1H, CH), 7.36 (s, 1H, CH),7.97, 7.99 (d, 2H, Ar-H), 8.44 (s, 1H, NH, D_2O exchangeable).^{13}C NMR (DMSO–d_6,δ, ppm): 40.7, 97.4, 112.42, 115.8, 128.89, 130.93, 134.2, 152, 153.17, 160.18, 164.69. Anal.Calcd. for($C_{16}H_{13}N_5O$), requires C, 65.97; H, 4.50; N, 24.04 %; found C, 66.05; H, 4.57; N, 24.12%**.**

***N'*-(2-Amino-3,6-dicyano-7-(dicyanomethylene)-5-(4-(dimethylamino)phenyl)-7,8-dihydro-1,8-naphthyridin-4-yl)-*N,N*-dimethylformimidamide(7):**

A mixture of *N,N* – dimethyl -*N'*- (1,1,3-tricyano-4-(4-(dimethylamino)phenyl)buta-1,3-dien-2-yl)formimidamide **2** (3.18g, 10 mmol) with malononitrile dimer (132g, 10 mmol) in (20mL) 1,4-dioxane as solvent and few drops of triethylamine as base was left under reflux for 3 hours then cool. The reaction mixture was poured onto ice water and acidified using dilute HCl until the solid formed. The solid so formed was filtered off, washed with water and recrystallized from ethanol as deep brown crystals. Yield 74.5%, m.p: 190-192 ^{o}C.FT-IR (KBr, υ, cm^{-1}):3322, 3208 (NH_2, NH), 2207 (C≡N).^{1}H NMR(DMSO–d_6,δ, ppm):3.03,3.08 (2s, 12H, $4CH_3$), 4.19 (br., 2H, NH_2, D_2O exchangeable), 6.85, 6.87 (d, 2H, Ar-H), 7.76, 7.78 (d, 2H, Ar-H), 7.89 (s, 1H, CH), 8.73 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO– d_6, δ, ppm):42.87, 44.2, 86.66, 92.47, 112.21, 115.39, 115.95, 116.49, 117.11, 119, 130.69, 134, 151.65, 153.29, 153.98, 154.63, 159.33, 161.77, 167.36.Anal.Calcd. for ($C_{24}H_{20}N_{10}$), requires C 64.27, H 4.49, N 31.23 %; found C 64.34, H 4.45, N 31.31 %.



Scheme 4

***N'*-(4-Cyano-3-(1-cyano-2-(4-(dimethylamino) phenyl)vinyl)-1*H*-pyrazol-5-yl)-*N,N*-dimethylformimidamide(12):**

A mixture of 5-amino-3-(1-cyano-2-(4-(dimethylamino) phenyl) vinyl) -1*H*- pyrazole -4-carbonitrile[22] **11** (2.78g, 10 mmol) and DMFDMA (1.32mL, 10 mmol) in dry (20 mL) 1, 4-dioxane as solvent was left under reflux for 3 hours then cool. The resulting solid was collected by filtration, washed with ethanol, and recrystallized from DMF/ethanol as brown crystals to afford the respective enamine derivative. Yield 80%; m.p: 246-248^{o}C. FT-IR (KBr, υ, cm^{-1}): 3222 (NH), 2915 (CH aliph.), 2212 (C≡N); ^{1}H NMR (DMSO–d_6,δ, ppm): 3.06, 3.1 (2s, 12H, 4CH_3), 6.74, 6.88 (d, 2H, Ar-H), 7.6 (s, 1H, CH), 7.62, 7.76 (d, 2H, Ar-H), 8.18 (s, 1H, CH), 12.4 (s, 1H, NH, D_2O exchangeable); Anal. Calcd. for($C_{18}H_{19}N_7$), requires C, 64.85; H, 5.74; N, 29.41%; found C 64.92, H 5.65, N 29.48 %.

3-(4-(Dimethylamino)benzylidene)-4-imino-3,4-dihydro-1,2,5,6,8-pentaazaacenaphthylen-6(1*H*)-amine (14):

A mixture of *N*'-(4-cyano-3-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-1*H*-pyrazol-5-yl)-*N,N*-dimethyl formimidamide **12** (3.33g, 10 mmol) and hydrazine hydrate (0.75mL, 15mmol) in ethanol as solvent was left under reflux for 2 hours then cool. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with ethanol and recrystallized from DMF/ethanol as deep brown crystals.Yield70%; m.p> 300^{o}C. FT-IR (KBr, υ, cm^{-1}): 3405, 3356, 3260, 3199 (NH_2, NH), 2895 (CH aliph.); ^{1}H NMR (DMSO–d_6, δ, ppm): 3.05 (s, 6H,

$2CH_3$), 5.1 (br., 2H, NH_2, D_2O exchangeable), 5.8 (br., 1H, NH, D_2O exchangeable), 6.72, 6.79 (d, 2H, Ar-H), 6.9 (s, 1H, CH), 7.74, 7.81 (d, 2H, Ar-H), 8.1 (s, 1H, CH), 12.4 (s, 1H, NH, D_2O exchangeable); Anal. Calcd. for ($C_{16}H_{16}N_8$), requires C, 59.99; H, 5.03; N, 34.98%; found C, 60.04; H, 5.1; N, 35.06%.

3-(4-(Dimethylamino)phenyl)-2-(4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)acrylonitrile (15):

A mixture of *N*'-(4-cyano-3-(1-cyano-2-(4-(dimethylamino) phenyl)vinyl) -1*H*- pyrazol-5-yl)-*N*,*N*-dimethyl formimidamide **12** (3.33g, 10 mmol) with acetic acid and hydrochloric acid (9 mL, 3:1) was left under reflux for 2 hours then cool. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with waterand recrystallized from ethanol as violet crystals. Yield71%, m.p: 264-266^{o}C. FT-IR (KBr, υ, cm^{-1}): 3330, 3215 (2NH), 2213 (C≡N), 1697(C=O amide). ^{1}H NMR (DMSO–d_6, δ, ppm): 3.08 (s, 6H, $2CH_3$), 6.5 (s, 1H, CH), 6.7, 6.82 (d, 2H, Ar-H), 7.62, 7.74 (d, 2H, Ar-H), 7.8 (s, 1H, CH), 7.9, 12.6(2s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for ($C_{16}H_{14}N_6O$), requires C, 62.74; H, 4.61; N, 27.44%; found C, 62.82; H, 4.76; N, 27.51%**.**

RESULTS AND DISCUSSION

Chemistry

Treatment of 2-amino-4-(4-(dimethylamino)phenyl) buta-1,3-diene-1,1,3-tricarbonitrile **1** with *N*, *N* - dimethylformamide dimethyl acetal (DMFDMA) in dry 1,4-dioxane afforded the respective enamine derivative **2** in good yield. The structure of isolated compound **2** was confirmed by spectral data as well as elemental analysis. Where, IR spectrum shows disappearance of amino group and ^{1}H NMR spectrum shows absence of amino protons and appearance of singlet signal at δ_H 7.62 ppm corresponding to CH proton of enamine. The enamine **2** is very important in organic synthesis because it has polyfunctionally groups which can be cyclized by different reagents to give pyrimidines[23,24], fused heterocyclic compounds. So that compound **2** treated with ammonium acetate in acetic acid to afford 4-amino -6- (1-cyano-2-(4-(dimethylamino) phenyl) vinyl) pyrimidine-5-carbonitrile **3**. The formation **3** assumed to proceeds *via* addition of ammonia on one of cyano group followed by cyclization to give the target compound **3**. The structure of isolated compound **3** was confirmed by spectral data. Where, IR spectrum shows appearance of aminogroup at υ_{max} 3394, 3250cm^{-1} and the ^{1}H NMR spectrum shows appearance of singlet signal at δ_H7.76 ppm corresponding to amino protons and appearance of singlet signal at δ_H 8.52 ppm corresponding to one proton of pyrimidine ring. Also, treatment of enamine **2** with acetic acid and hydrochloric acid afforded 4-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **4**.The formation **4** also, assumed to proceeds *via* the hydrolysis of one of cyano group followed cyclization. The structure of the isolated product **4** was established by IR spectrum which shows appearance of bands characterizes for NH group at υ_{max} 3350 $cm^{-1}$and carbonyl group of amide at 1686 cm^{-1}. Also, the ^{1}H NMR spectrum shows appearance of singlet signal at δ_H 7.36 ppm corresponding to proton of pyrimidinone ring and appearance of singlet signal at δ_H 8.44 ppm corresponding to NH proton. Boiling of enamine **2** with hydrazine hydrate in ethanol afforded bishydrazone[22] **6**. The other possible The other possible structure **5** ruled out on the basis of spectral data. IR spectrumof isolated product shows the absence of amino and cyano groups (Scheme 1**)**.

Reaction of enamine **2** with malononitrile dimer in 1,4-dioxane containing of triethylamine to give product is formulated **7** or **8**. The reaction may be proceeding by two possible routes, the route **a** involves the Michael addition of the active methylene of malononitrile dimer on the double bond of arylidene followed by cyclization and aromatization to give **7**. The route **b** involves addition of malononitrile dimer on the double bond of imino moiety followed by cyclization to give compound **8** (Scheme 2**)**.The structure of the isolated product was established by spectral data as well as elemental analysis. Where, the ^{1}H NMR spectrum shows presence of two singlet signals at δ_H 3.03, 3.08 ppm corresponding to two $-N(CH_3)_2$ moieties and singlet signal at δ_H 7.89 ppm corresponding to one CH proton of enamine and there is no protons of pyridine ring and CH of arylidene as in structure **8**. This indicate the isolated compound is**7** not **8**. So, that the reaction proceed by route **a** not **b**.

Reaction of 2-amino -4- (4-(dimethylamino) phenyl) buta-1,3-diene -1,1,3- tricarbonitrile **1** with 3-amino-5 - (cyanomethyl) -1*H*- pyrazole -4- carbonitrile **9** expected to afford compound **10** *via* the Michael addition of the methylene group of pyrazole on the double bond of arylidene followed by cyclization and aromatization to give **10** but the spectral data not compatible with structure **10**. Where, IR spectrum shows 3333, 3247, 3195 cm^{-1}corresponding to NH_2, NH groups and 2213 cm^{-1} corresponding to cyano group. Also,^{1}H NMR spectrum shows δ_H 3.1, 6.5, 6.75, 6.82, 7.64, 7.9, 8.3 and 12.3 corresponding to protons of CH_3, NH_2, AB-system of Ar-H, CH and NH. But these data compatible with structure of

arylidenederivative[25]**11** not **10**. . Good evidence, we can be obtain the product **11** *via* direct reaction of 3-amino-5-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile **9** with 4-(dimethylamino) benzaldehyde which reported[22] (Scheme 3).

Treatment of 5-amino -3- (1-cyano-2-(4-(dimethylamino) phenyl) vinyl) -1*H*- pyrazole-4-carbonitrile **11** with DMFDMA in dry 1,4-dioxane afforded enamine **12**. IR and ^{1}H NMR spectra show disappearance of amino group and appearance of singlet signal at δ_H 7.6 ppm in ^{1}H NMR spectrum corresponding to CH proton of enamine. The enamine compound **12** can be cyclized by hydrazine hydrate which may be proceeding by two possible routes. Theroute **a** involves elimination of ammonia and dimethyl amine molecules to give compound **13**. The route **b** involves elimination of dimethyl amine followed by cyclized to give **14**.The structure of the isolated product was established by spectral data as well as elemental analysis, where, the IR spectrum shows disappearance of cyano groups and appearance of NH_2, NH groups at 3405, 3356, 3260, 3199 cm^{-1}. This indicates the isolated compound is **14** not **13** and the reaction proceeds *via* route **b** not **a**. Also, we can be cyclized enamine **12** by boiling it in hydrochloric and acetic acids to afford 3-(4-(dimethylamino) phenyl) -2- (4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl) acrylonitrile **15**. The structure of compound **15** was confirmed by IR spectrum which shows appearance of amide carbonyl at 1697 cm^{-1} (Scheme 4).

CONCLUSION

Cyclization of enamines **2** and **12** with $AcONH_4$/AcOH, HCl/AcOH, malononitrile dimer, hydrazine hydrate to give novel pyrimidines, 1,8-naphthyridine and pyrazolo [3,4-d] pyrimidine derivatives.

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