Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2017, 9(5):164-169

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

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 arylidene derivatives (1) and (11) with DMFDMA afforded enamine derivatives (2) and (12) in good yield. The novel pyrimidine (3), pyrimidinone (4) and [1,8]naphthyridine (7) derivatives were obtained by treatment of enamine (2) with $AcNH_4$/AcOH, HCl/AcOH and malononitrile dimer. Also, the novel 1,2,5,6,8-pentaazaacenaphthylene (14) and pyrazolo[3,4-d]pyrimidine (15) derivatives obtained by treatment of enamine (12) with hydrazine hydrate and HCl/AcOH.

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

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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 and pyrazolopyrimidines 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, [3] antitumor, [4] anticancer, [5] anti-inflammatory [6] and antimicrobial [7]. 1,8-naphthyridine derivatives have promisingmedicinal properties, including anti-HIV [8], anticancer [9], anti-inflammatory [10], antibacterial [11], antiprotozoals [12], antimycobacterial [13]. pyrazolopyrimidines and related fused heterocycles have been identified as bioactive molecules [14]. They are known to function as CNS (Central Nervous System) depressants [15] and as tuberculostatic [16]. Pyrazolo[3,4-d]pyrimidines were identified as a general class of adenosine receptors [17,18].

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)formimid-amide (2):**

A mixture of 2-amino-4-(4-(dimethylamino)phenyl)buta-1,3-diene-1,1,3-tricarbonitrile 1 [19] (2.63 g, 10 mmol) and DMFDMA (1.32 ml, 10 mmol) in (20 ml) dry 1, 4-dioxane as solvent was left under reflux for 3 hours and 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°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):
A mixture of *N*,*N*-dimethyl-*N'*-(1,1,3-tricyano-4-(4-(dimethylamino)phenyl)buta-1,3-dien-2-yl)for-mimidamide **2** (3.18 g, 10 mmol) with acetic acid (10 ml) and ammonium acetate (2.3 g, 30 mmol) was left under reflux for 2 hours and 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°C. FT-IR (KBr, υ, cm^{-1}): 3394, 3250 (NH_2) and 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 (3.18 g, 10 mmol) with acetic acid and hydrochloric acid (3:1) was left under reflux for 2 hours and then cool. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with water and recrystallized from ethanol as violet crystals. Yield 72%, m.p: 280-282°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)phen-yl)-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** (3.18 g, 10 mmol) with malononitrile dimer (132 g, 10 mmol) in (20 ml) 1,4-dioxane as solvent and few drops of triethylamine as base was left under reflux for 3 hours and 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°C. FT-IR (KBr, υ, cm^{-1}): 3322, 3208 (NH_2, NH) and 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) and 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%.

N'-(4-cyano-3-(1-cyano-2-(4-(dimethylamino) phenyl) vinyl)-1H-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 11 [19] (2.78 g, 10 mmol) and DMFDMA (1.32 ml, 10 mmol) in dry (20 ml) 1, 4-dioxane as solvent was left under reflux for 3 hours and 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°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 (3.33 g, 10 mmol) and hydrazine hydrate (0.75 ml, 15 mmol) in ethanol as solvent was left under reflux for 2 hours and 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. Yield 70%; m.p >300°C. FT-IR (KBr, υ, cm^{-1}): 3405, 3356, 3260, 3199 (NH_2, NH) and 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%.

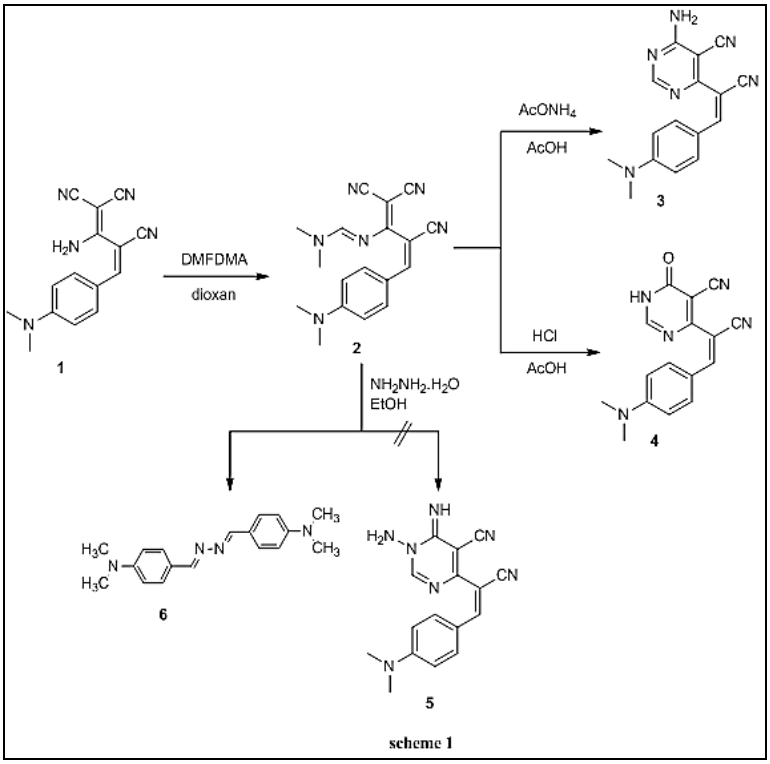
3-(4-(dimethylamino)phenyl)-2-(4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)acry-lonitrile (15):
A mixture of *N*'-(4-cyano-3-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-1*H*-pyrazol-5-yl)-*N*,*N*-dimethyl formimidamide 12 (3.33 g, 10 mmol) with acetic acid and hydrochloric acid (3:1) was left under reflux for 2

hours and then cool. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with water and recrystallized from ethanol as violet crystals. Yield 71%, m.p: 264-266°C. FT-IR (KBr, υ, cm^{-1}): 3330, 3215 (2NH), 2213 (C≡N) and 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) and 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

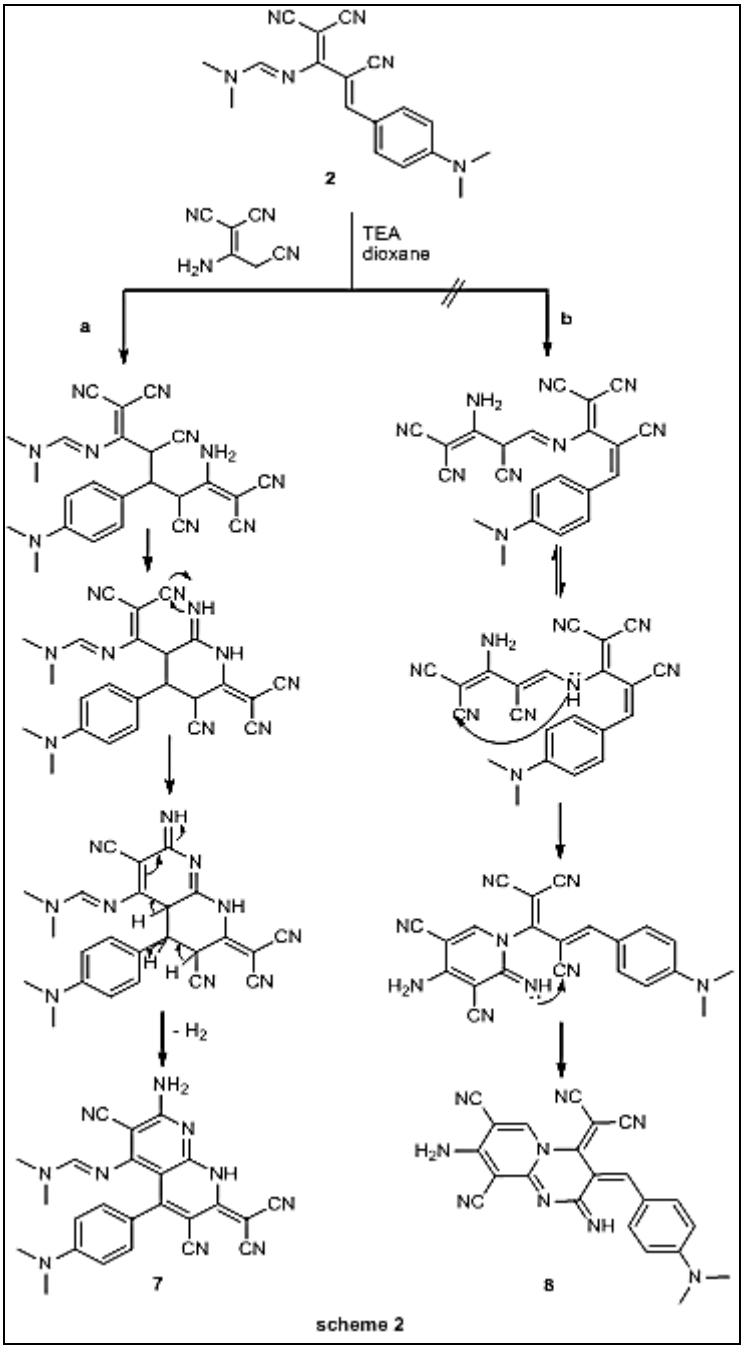
Treatment of 2-amino-4-(4-(dimethylamino)phenyl)buta-1,3-diene-1,1,3-tricarboni-trile 1 with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in dry 1,4-dioxane afforded the respective enamine derivative 2 in good yield. The structure of isolated compound 2 was confirmed by spectral data as well as 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 poly 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 amino group at υ_{max} 3394, 3250 cm^{-1} and the ^{1}H NMR spectrum shows appearance of singlet signal at δ_H 7.76 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 6 [19]. The other possible structure 5 ruled out on the basis of spectral data. IR spectrum of isolated product shows the absence of amino and cyano groups (Scheme 1).



Scheme 1: IR spectrum of isolated product shows the absence of amino and cyano groups

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 involves the Michael

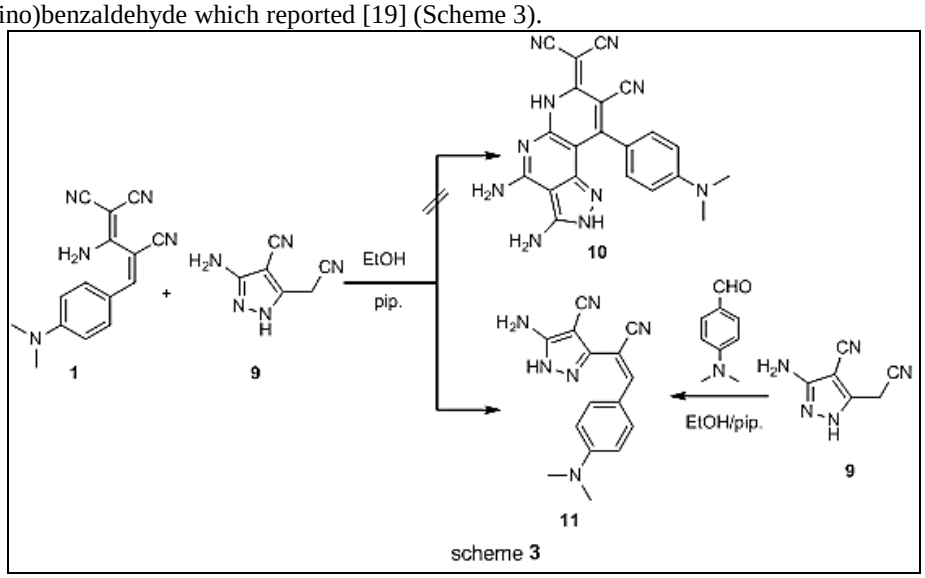
addition of the active methylene of malononitrile dimer on the double bond of arylidene followed by cyclization and aromatization to give 7. The route b involves addition of malononitrile dimer on the double bond of imino moiety followed by cyclization to give compound 8 (Scheme 2). The structure of 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.



Scheme 2: Addition of malononitrile dimer on the double bond of imino moiety

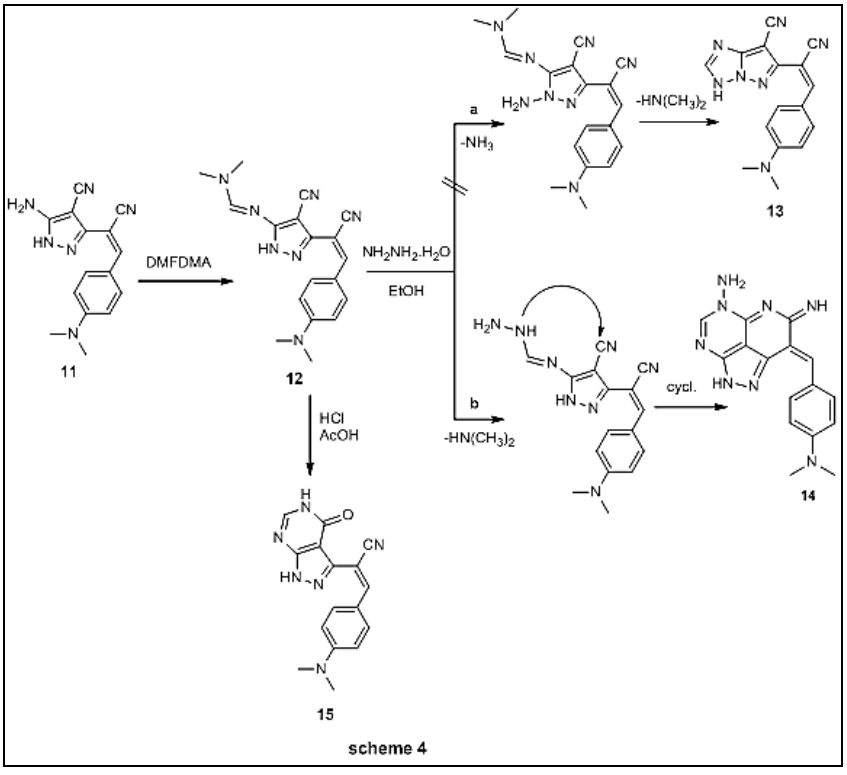
Reaction of 2-amino-4-(4-(dimethylamino)phenyl)buta-1,3-diene-1,1,3-tricarbonitr-ile 1 with 3-amino-5-(cyanomethyl)-1*H*-pyrazole-4-carbonitrile 9 expected to afford compound 10 *via* the Michael addition of the methylene group of pyrazole on the double bond of arylidene followed by cyclization and aromatization 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 arylidene derivative 11 not 10. [20]. 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 [19] (Scheme 3).



Scheme 3: Reaction of 3-amino-5-(cyanomethyl)-1H-pyrazole-4-carbonitrile 9 with 4-(dimethylamino)

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 of CH proton of enamine. The enamine compound 12 can be cyclized by hydrazine hydrate which may be proceeding by two possible routes. The route 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)a-crylonitrile 15. The structure of compound 15 was confirmed by IR spectrum which shows appearance of amide carbonyl at 1697 cm^{-1} (Scheme 4).



Scheme 4: IR spectrum which shows appearance of amide carbonyl

CONCLUSION

Cyclization of enamines 2 and 12 with ammonium acetate/acetic, hydrochloric/acet-ic, malononitrile dimer, hydrazine hydrate to give novel pyrimidines, 1,8-naphthyr-idine and pyrazolo[3,4-d]pyrimidine derivatives.

ACKNOWLEDGEMENT

The authors would like to thank the Chemistry Department, Faculty of Science, Al-Azhar University at Assist for their financial support to facilitate the publication of this study.

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