Convenient Synthesis of Polyaza-2-(heteroaryl)pyridine Derivatives

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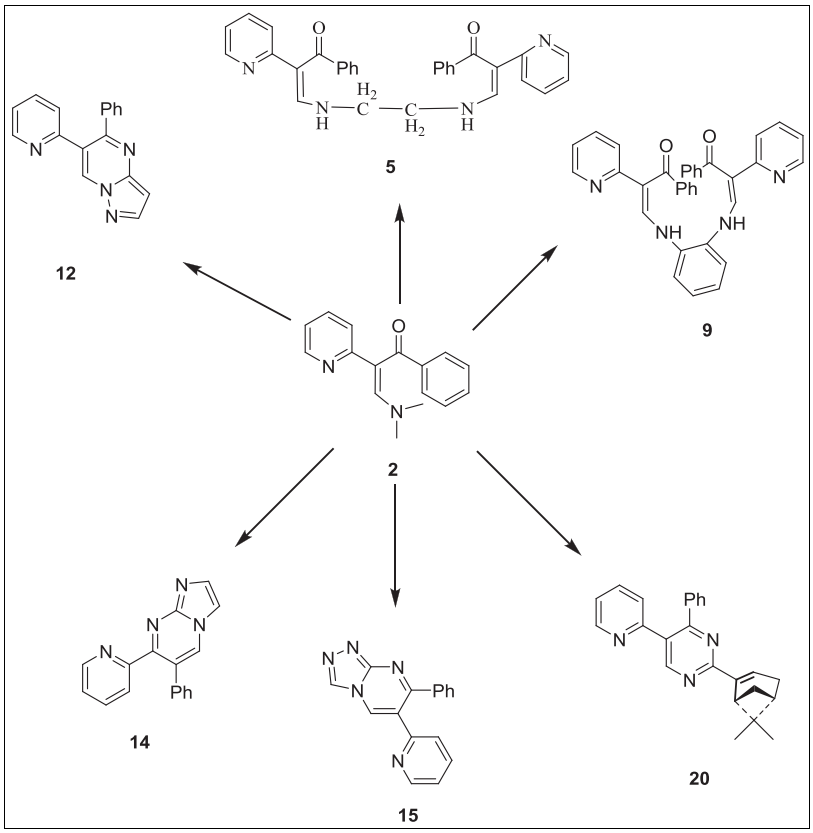
Received August 13, 2017
DOI 10.1002/jhet.3076
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



A simple and efficient method for the synthesis of new heterocyclic compounds containing pyridine and 1,3-pyrimidine units has been developed. It is based on the reaction of the appropriate enaminone with some *N*-nucleophiles.

J. Heterocyclic Chem., **00,** 00 (2018).

INTRODUCTION

Enaminones are chemical compounds consisting of an amino group linked through a C═C to a carbonyl group. They are versatile synthetic intermediate that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones.

Enaminone derivatives are highly reactive intermediates extensively used for synthesis of heterocyclic compounds. On the other hand, a great deal of interest has been focused on the synthesis of the functionalized pyridine derivatives due to their biological activity [1,2]. Some 2-pyridine derivatives are considered as cardiotonic agents such as milrinone and as potential human immunodeficiency virus 1-specific transcriptase inhibitors [3,4]. Moreover, it has been reported that there are many review articles that deal with the synthesis of pyridine derivatives from enaminones [5–9].

In view of our interest in developing efficient synthesis of 2-pyridine derivatives by utilizing the enaminones as starting material, we report here several approaches to the synthesis of pyridine derivatives using compound **2** as a precursor.

RESULTS AND DISCUSSION

Firstly, 2-pyridylacetophenone was formed by the reaction of α-picoline with benzonitrile or ethyl acetate in

the presence of *n*-butyllithium according to the reported method [10,11] (Scheme 1).

The required enaminone **2** can be easily prepared in excellent yield by the treatment of **1** with dimethylformamide/dimethyl acetal (DMF/DMA) in refluxing dry xylene (Scheme 1). The structure of **2** was deduced from ^{1}H-NMR spectroscopic data. In the ^{1}H-NMR spectrum of **2**, the two methyl and methine protons appeared as two singlets at δ 3.25 and 7.30 ppm, respectively. In compound **2**, there are three nucleophilic sites (a, c, and e) and two electrophilic sites (b and d).

Thus, the reaction of **2** with different types of nucleophiles under different reaction conditions gave 2-substituted pyridine derivatives.

The reaction of equimolar amounts of the monoenaminone **2** with ethylenediamine in refluxing ethanol gave the respective enaminone **3**. On the other hand, when this reaction was carried out in refluxing DMF catalyzed by triethylamine (TEA) afforded the corresponding pyridyldiazepine derivative **4** (Scheme 2). The structures **3** and **4** were established on the basis of both elemental and spectral data. Moreover, compound **4** was confirmed by an alternative synthesis. Thus, refluxing compound **3** in DMF in the presence of a catalytic amount of TEA gave a product that proved identical in all respects [infrared (IR), ^{1}H-NMR, and mass spectra] to **4**.

Compound **2** (2 mmol) heated with ethylenediamine (1 mmol) in refluxing ethanol afforded the bis(enaminone) **5** (Scheme 2).

^{1}H-NMR spectra of compounds **3** and **4** showed, in each case, two CH_2 groups as triplet–triplet in the region 2.77–3.67 ppm, while in compound **5**, the CH_2 protons appeared as singlet at δ 3.72 ppm. The mass spectra of **3**, **4**, and **5** showed the molecular ion peaks at *m*/*z* = 267, 249, and 474, respectively, corresponding to the molecular formula $C_{16}H_{17}N_3O$, $C_{16}H_{15}N_3$, and $C_{30}H_{26}N_4O_2$, respectively. These mass spectra showed, in addition to the molecular ion peak, a fragment ion peak at *m*/*z* corresponding to the 2-pyridyl radical cation. Moreover, assignment of compound **4** is consistent with literature report [12].

Similarly, heating of compound **2** with *o*-phenylene diamine in refluxing ethanol afforded the enaminone derivative **6** (Scheme 3). When the same reaction was carried out in refluxing, DMF solution catalyzed by TEA gave the corresponding benzodiazepine derivative **7** (Scheme 3). Compound **7** was also obtained when **6** was refluxed in DMF containing a catalytic amount of TEA.

The structures of **6** and **7** were established on the basis of their spectral and elemental analysis data. Thus, the IR spectrum of **6** showed the presence of absorption frequencies at 3430 and 3310 cm^{-1} due to NH_2 and NH functions. The IR spectrum of **7** revealed the absence of a NH_2 function at 3400 cm^{-1} region. Also, the ^{1}H-NMR spectrum of **7** showed, in addition to the expected signals, a singlet at δ 5.50 ppm corresponding to C_2–H of diazepine.

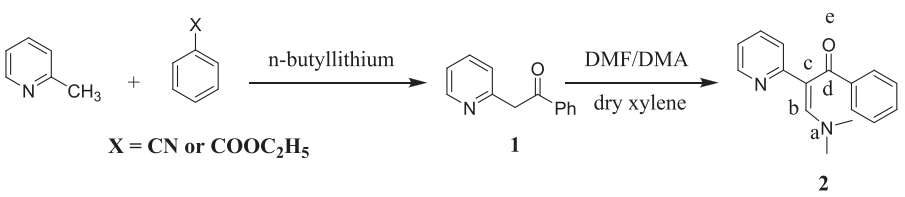
On the other hand, compound **2** refluxed with *o*-phenylenediamine in molar ratio 2:1 in boiling ethanol afforded the corresponding bis(enaminone) derivative **8** (Scheme 3). The IR spectrum showed absorption band at 3330 and 1710 cm^{-1} due to NH and CO functions.

The work was extended further to study the behavior of **2** towards the action of heterocyclic amines. Thus, compound **2** readily reacted with 5-aminopyrazole in boiling ethanol yielding the corresponding enaminone **9** (Scheme 4). The elemental analyses and spectral data were in accordance with the proposed structure.

Its IR spectrum showed a broad NH_2 band in the region 3430 cm^{-1} and the CO function group at 1700 cm^{-1}. Also, ^{1}H-NMR spectrum revealed two singlet signals at δ 6.22 ppm assignable to (D_2O exchangeable) NH_2 protons and at δ 6.82 ppm due to olefinic CH proton, two doublet signals at δ 6.62 and 7.32 ppm with the same coupling constant *J* = 7 Hz assignable to H-3 and H-4 of the pyrazole ring residue, respectively. The mass spectrum revealed the molecular ion peak at *m*/*z* = 290 corresponding to the molecular formula $C_{17}H_{14}N_4O$.

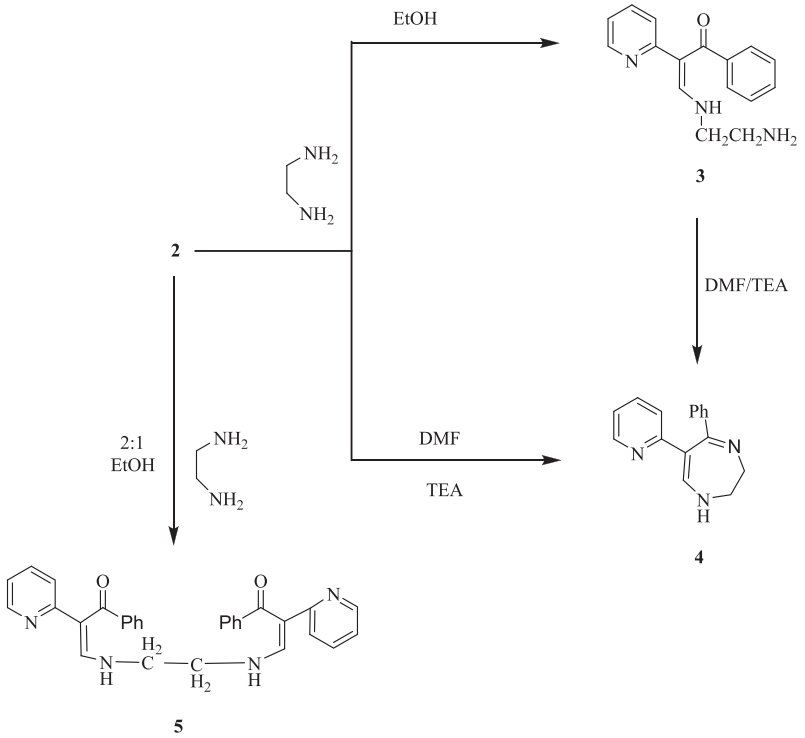
Compound **9** heated in DMF solution catalyzed with TEA or refluxed in glacial acetic acid afforded only one isolable product, which identified as 5-phenyl-6-(pyridine-2-yl)pyrazolo[1,5-*a*]pyrimidine (**10**). Structure **10** was established on the basis of spectral and elemental analysis data. The IR spectrum showed the absence of both the CO and NH_2 bands present in the spectra of the starting enaminone **9**. Also, the ^{1}H-NMR spectrum showed singlet signal at δ 9.25 ppm assignable to CH of pyrimidine ring, two doublet signals at δ 6.25 and

Scheme 1. Synthesis of 2-pyridylacetophenone (**1**) and 3-(dimethylamino)-1-phenyl-2-(pyridine-2-yl)prop-2-en-1-one (**2**). DMF/DMA, dimethylformamide/dimethyl acetal.

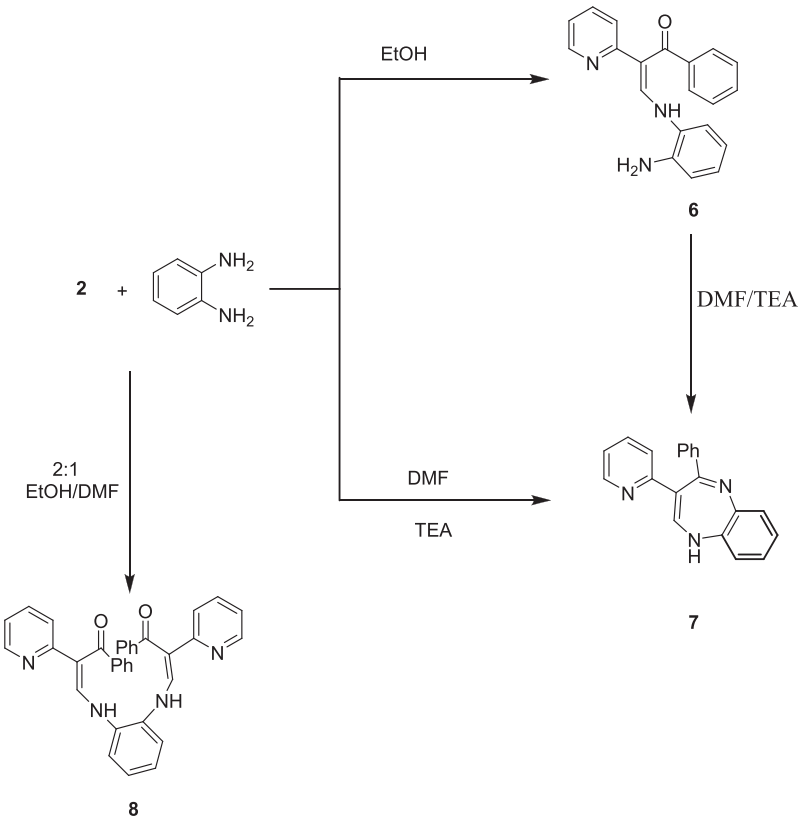


X = CN or $COOC_2H_5$ **1** **2**

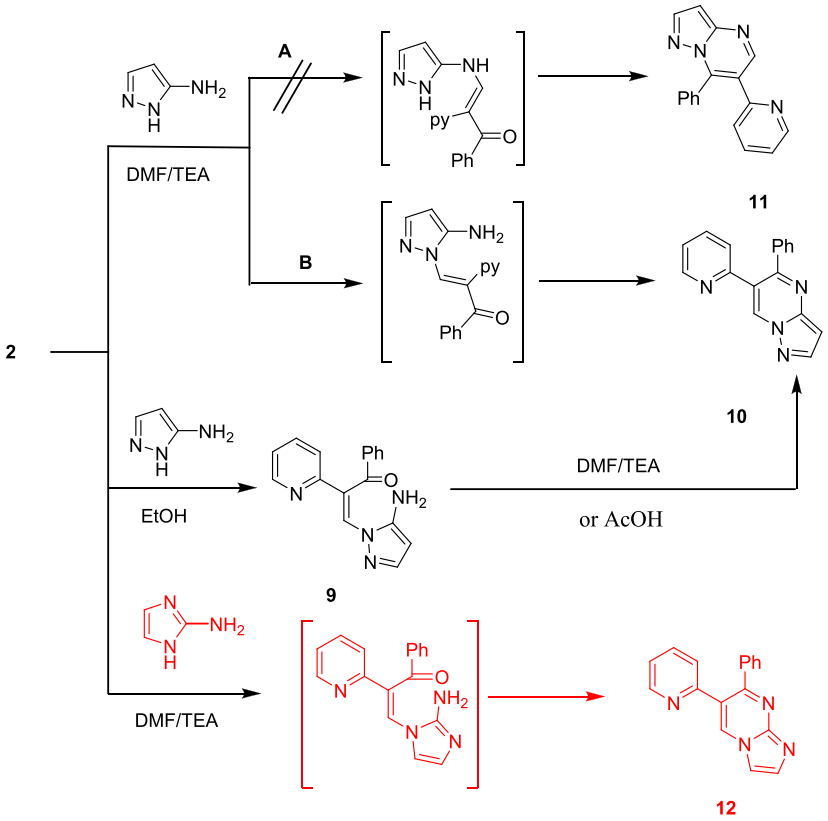
Scheme 2. Reaction of compound **2** with ethylene diamine in different solvents. DMF, dimethylformamide; TEA, triethylamine.



Scheme 3. Reaction of compound **2** with *o*-phenylene diamine in different solvents. DMF, dimethylformamide; TEA, triethylamine.



Scheme 4. Reactions of compound **2** with 5-amino pyrazole and 2-amino imidazole. DMF, dimethylformamide; TEA, triethylamine. [Color figure can be viewed at wileyonlinelibrary.com]



7.45 ppm with the same coupling constant $J = 7.2$ Hz. The assigned structure **10** was confirmed by an alternative synthesis. Thus, the reaction of **2** with 5-aminopyrazole in refluxing DMF in presence of TEA or heating in glacial acetic acid gave a product that proved identical in all respects (mp, IR, ^{1}H-NMR, and mass spectra) to **10**. This reaction can proceed through two possible routes to give **7**-substituted pyrazolo[1,5-*a*]pyrimidine (route A) and/or its 5-substituted isomer (route B) (Scheme 4). However, literature reports indicate that such a reaction is site selective as it afforded in most cases 5-substituted isomer. In our hands, the reaction proceeded by route B to give **10**.

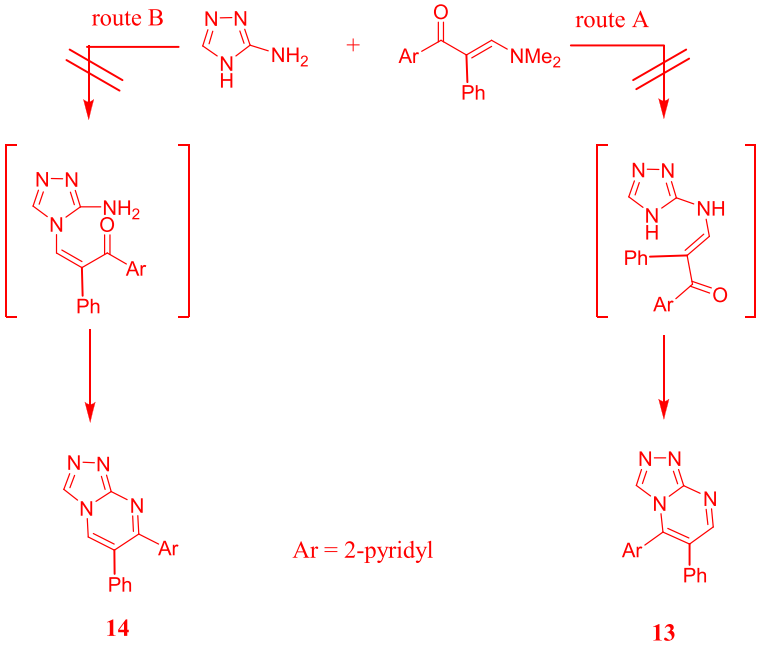
Formation of **10** is assumed to proceed via Michael-type addition of the most basic ring-N in pyrazole followed by intramolecular cyclodehydration and dimethylamine elimination under the reaction condition.

Similarly, compound **2** reacted with 2-aminoimidazol in boiling DMF containing TEA to afford imidazolopyrimidine derivative **12** (Scheme 4). The structure of **12** was established based on its elemental analysis and spectroscopic studies. Thus, the IR showed the absence of both CO and NH_2 function groups. Its ^{1}H-NMR spectrum showed the absence of $N(CH_3)_2$ signals, beside two doublets at δ 7.00 and 7.25 ppm assignable to two imidazole protons and singlet signal at δ 9.02 ppm due to CH pyrimidine ring. Formation of **12** is assumed to proceed via the proposed mechanism as shown in Scheme 4.

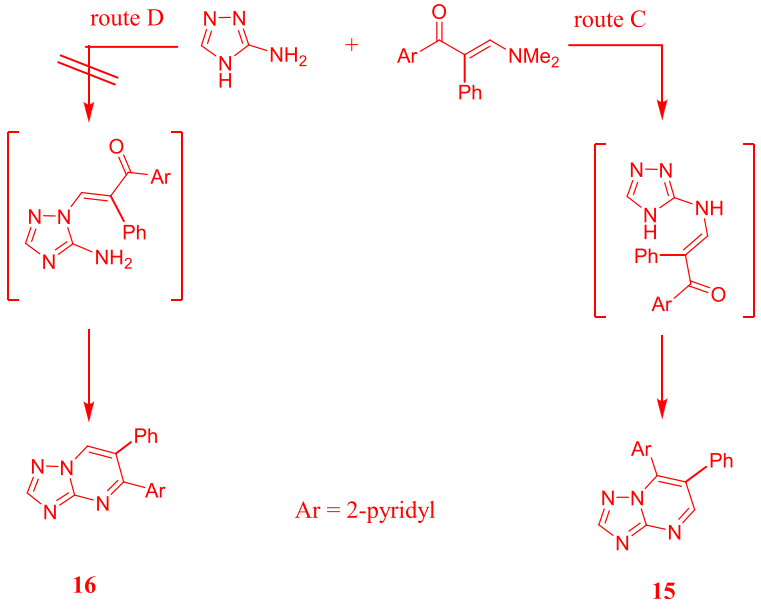
The reactivity of the enaminone **2** towards 3-amino-1,2,4-triazole was next studied to shed some light on its site selectivity, such a reaction can led to one or more of four possible condensation products **13–16**. This is because of the following: (1) 3-amino-1,2,4-triazole can exist in one of the two tautomeric forms, namely, 3-amino-4*H*-1,2,4-triazole and 3-amino-2*H*-1,2,4-triazole and (2) the reaction of each tautomer with an enaminone can proceed through two possible pathways involving initial attack by either exocyclic NH_2 group or the cyclic NH group. The expected products are thus **13–16** (5-Ar-6-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidine, 7-Ar-6-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidine, 7-Ar-6-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidine, and 5-Ar-6-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidine, respectively) as shown in Schemes 5 and 6. In our hands, the reaction of **2** with 3-amino-1,2,4-triazole in refluxing DMF containing a catalytic amount of TEA or by refluxing in glacial acetic acid yielded, in each case,

only one isolable product. The separated product was identified as 7-(pyridin-2-yl)-6-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (**15**) and not their isomers **13**, **14**, and **16**. Structure **15** was confirmed on the basis of elemental and spectral analyses. The IR spectrum showed the absence of CO and NH_2 groups present in the starting material. ^{1}H-NMR spectrum showed two singlet signals at δ 8.62 and 9.23 ppm attributable to CH triazole proton and CH pyrimidine proton, respectively. Such assignments are consistent with literature reports on ^{1}H-NMR spectra of 1,2,4-triazolo[1,5-*a*]pyrimidine and its [4,3-*a*] isomers [13]. To account for the formation of **15**, it is suggested that the reaction start with Michael-type addition of the exocyclic NH_2 group of the amine to the activated double bond of **2** followed by elimination of dimethylamine and dehydrative cyclization by

Scheme 5. Proposed mechanism for the synthesis of triazolo pyrimidines. [Color figure can be viewed at wileyonlinelibrary.com]



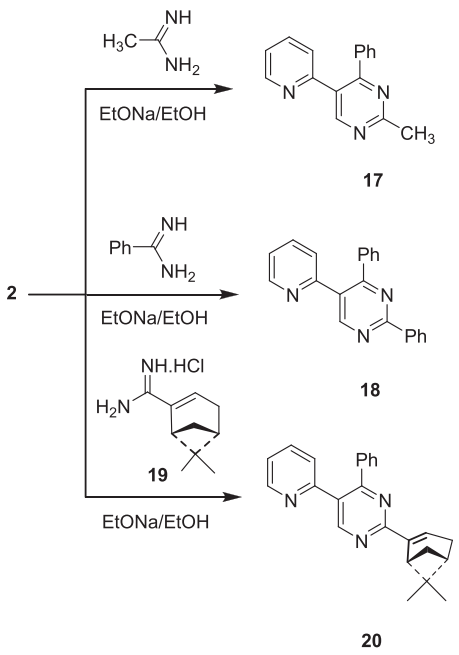
Scheme 6. Synthesis of 7-(pyridin-2-yl)-6-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (**15**). [Color figure can be viewed at wileyonlinelibrary.com]



condensation of the cyclic NH group with the enone moiety. Such result found a great agreement with the previously reported work [12,14]. However, various literature reports indicate that such a reaction is site selective and regioselective [12,14].

The work was further extended to study the behavior of **2** towards the action of some amidines. Thus, the reaction of **2** with five equivalents of each of acetamidine HCl and sodium ethoxide in boiling ethanol resulted in the formation of pyridyl pyrimidine **17** in excellent yield (Scheme 7).

Scheme 7. Reaction of compound **2** with different amidines.



Similar reaction of **2** with five equivalents of benzamidine HCl and five equivalents of sodium ethoxide in refluxing ethanol resulted in the formation of pyridyl pyrimidine derivative **18** (Scheme 7).

Enaminone **2** reacted also with pinene-2-carboxamidine HCl **19** (it was prepared according to the previously reported procedure [14]) to give pyridylpyrimidine **20** (Scheme 7).

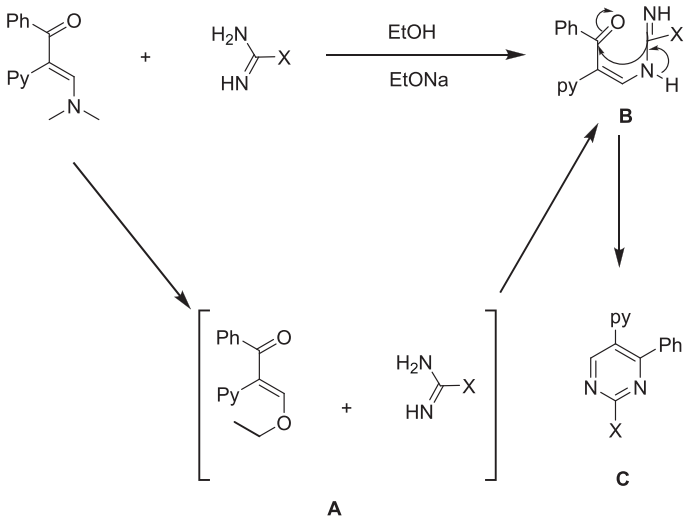
The general mechanistic pathways for the formation of the pyrimidine from the corresponding enaminone with amidines can be rationalized as shown in Scheme 8.

The structure of compounds **17**, **18**, and **20** was confirmed by elemental and spectral data. The IR spectra, in general, showed the absence of C═O function group in the region 1700 cm^{-1}. The ^{1}H-NMR spectra, in general, revealed the absence of $-N(CH_3)_2$ signals. The mass spectra showed the molecular ion peaks at *m*/*z* (%) = 247 (25), 309 (100), and 353 (45), respectively, corresponding to the molecular formula $C_{16}H_{13}N_3$, $C_{21}H_{15}N_3$, and $C_{24}H_{23}N_3$, respectively.

EXPERIMENTAL

Instruments. All melting points are incorrect in degree centigrade and determined on Gallenkamp electric melting point apparatus. The IR spectra were recorded (KBr disk) on a Mattson 5000 FTIR spectrometer at the Faculty of Science, Mansoura University, Egypt. The ^{1}H-NMR spectra were determined on a Bruker WPSY 400-MHz spectrometer with tetramethylsilane as an internal standard, and the chemical shifts are in δ ppm using dimethyl sulfoxide (DMSO-d_6) as a solvent. The mass spectra were recorded at 70 eV with Varian MAT 311 at the Microanalytical Center, Faculty of Science, Cairo

Scheme 8. Proposed mechanism for the reaction of enaminone **2** with different amidines.



University. Elemental analyses (C, H, and N) were carried out at the Faculty of Science, Cairo University. The results were found to be in a good agreement (±0.03) with the calculated values.

Synthesis of 2-pyridylacetophenone (1). It was prepared according to the reported procedure in 75%, mp 40–42°C; MS: *m*/*z* (%) = 198 (M^+, 100%), lit. [10,11] (mp 39–44°C).

Synthesis of 3-(dimethylamino)-1-phenyl-2-(pyridine-2-yl) prop-2-en-1-one (2). A mixture of 2-pyridylacetophenone (**1**) (0.01 mol) and DMF–DMA (0.01 mol) was refluxed in dry xylene for 6 h. The mixture was then left to cool at room temperature, filtered off, dried, and recrystallized from ethanol to give **2** in 68% yield.

Mp 178°C; IR (KBr): ν/cm^{-1} = 1710 (CO); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 3.25 (s, 6H, $2CH_3$), 7.30 (s, 1H, CH), 7.50–7.75 (m, 8H, Ar–H), 8.30 (d, 1H, C_6–H pyridine); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 44.5, 118.3, 120.1, 122.7, 128.5, 129.2, 134.5, 137.0, 137.9, 148.8, 155.7, 156.9, 197.5; MS (EI, 70 eV): *m*/*z* (%) = 252 (M^+, 100), 208 (15), 131 (35), 92 (95), 91 (25), 90 (10), 77 (70). *Anal.* Calcd for $C_{16}H_{16}N_2O$ (252.32): C, 76.16; H, 6.39; N, 11.10%. Found: C, 76.02; H, 6.25; N, 11.00%.

Synthesis of 3-((2-aminoethyl)amino)-1-phenyl-2-(pyridin-2-yl)prop-2-en-1-one (3). To a solution of enaminone **2** (0.01 mol) in absolute ethanol (30 mL) was added ethylene diamine (0.01 mol) dropwise. The reaction mixture was refluxed for 4 h. The mixture was cooled at room temperature. The separated solid material was filtered off, dried, and recrystallized from ethanol to give **3** in 75% yield.

Mp 210°C; IR (KBr): ν/cm^{-1} = 3410 (NH_2), 3305 (NH), 1710 (CO), 1602 (C═C); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 1.50 (s, 2H, NH_2), 2.77 (t, 2H, CH_2NH_2), 3.67 (t, 2H, CH_2NH), 7.20–7.82 (m, 9H, CH + Ar–H), 8.45 (d, 1H, C_6–H pyridine), 10.03 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 44.5 ($2CH_3$), 120.1 (C═), 120.9–137.9 (9C–Ar), 149.1 (C═N), 156.0 (C═C–N), 166.7 (N═C), 197.0 (C═O), 145 (2C), 152.5; MS (EI, 70 eV): *m*/*z* (%) = 267 (M^+, 100), 237 (20), 208 (80), 131 (30), 98 (10), 97 (10), 85 (50), 83 (45). *Anal.* Calcd for $C_{16}H_{17}N_3O$ (267.33): C, 71.89; H, 6.41; N, 15.72%. Found: C, 71.81; H, 6.38; N, 15.67%.

Synthesis of 5-phenyl-6-(pyridin-2-yl)-2,3-dihydro-1H-1,4-diazepine (4). Method A. An equimolar amount of enaminone **2** (0.01 mol) and ethylenediamine (0.01 mol) in DMF (30 mL) with few drops of TEA (four drops) was heated for 6 h. The reaction mixture was left to cool at room temperature. The precipitated solid material was filtered off, dried, and recrystallized from ethanol to give **4**.

Method B. When compound **3** was refluxed in DMF (30 mL) catalyzed with TEA (four drops) and left to cool, it gave compound **4**.

Yield 60–66%; mp 257°C; IR (KBr): ν/cm^{-1} = 3320 (NH); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 3.47 (t, 2H, CH_2–NH), 3.67 (t, 2H, CH_2–N), 5.23 (s, 1H, CH═C), 7.45–7.69 (m, 8H, Ar–H), 8.45 (d, 1H, C_6–H pyridine), 8.72 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 46.9, 57.6, 120.9, 122.7, 128.8, 129.2, 131.0, 137.0, 139.2, 144.1, 148.8, 155.7, 164.6; MS (EI, 70 eV): *m*/*z* (%) = 249 (M^+, 100), 206 (25), 103 (90), 97 (20), 77 (60), 69 (30), 57 (100). *Anal.* Calcd for $C_{16}H_{15}N_3$ (249.32): C, 77.08; H, 6.06; N, 16.85%. Found: C, 76.95; H, 5.86; N, 16.71%.

Synthesis of 3,3′-(ethane-1,2-diylbis(azanediyl))bis(1-phenyl-2-(pyridin-2-yl)prop-2-en-1-one) (5). A mixture of enaminone **2** (0.025 mol) and ethylenediamine (0.01 mol) was refluxed in boiling EtOH (30 mL) for 6 h. The reaction mixture was left to cool at room temperature. The separated solid material was filtered off, dried, and recrystallized from EtOH to give **5** in yield 78%.

Mp 281°C; IR (KBr): ν/cm^{-1} = 3310 (NH), 1705 (CO); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 3.72 (s, 4H, $2CH_2$), 7.35 (s, 1H, CH), 7.56–7.81 (m, 16 H, Ar–H), 8.50 (d, 2H, $2C_6$–H pyridine), 10.13 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 46.1, 120.1, 122.3, 122.7, 123.6, 128.5, 129.2, 134.5, 137.0, 137.9, 146.0, 148.8, 155.7, 197.5; MS (EI, 70 eV): *m*/*z* (%) = 474 (M^+, 100), 237 (70), 132 (25), 105 (30), 78 (15), 70 (25). *Anal.* Calcd for $C_{30}H_{26}N_4O_2$ (474.56): C, 75.93; H, 5.52; N, 11.81%. Found: C, 75.81; H, 5.48; N, 11.76%.

Synthesis of 3-((2-aminophenyl)amino)-1-phenyl-2-(pyridin-2-yl)prop-2-en-1-one (6). A mixture of enaminone **2** (0.01 mol) and *o*-phenylenediamine (0.01 mol) was refluxed in boiling EtOH for 6 h. The reaction mixture was left to cool at room temperature. The precipitate solid product was filtered off, dried, and recrystallized from EtOH to give **6** in 71% yield.

Mp 187°C; IR (KBr): ν/cm^{-1} = 3430 (NH_2), 3310 (NH), 1710 (C═O); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 5.31 (s, 2H, NH_2), 7.52 (s, 1H, CH), 7.62–7.80 (m, 12H, Ar–H), 8.51 (d, 2H, C_6–H pyridine). 11.12 (s, 1H, NH); MS (EI, 70 eV): *m*/*z* (%) = 315 (M^+, 100), 238 (20), 223 (25), 132 (20), 118 (15), 107 (25), 93 (25), 77 (20). *Anal.* Calcd for $C_{20}H_{17}N_3O$ (315.38): C, 76.17; H, 5.43; N, 13.32%. Found: C, 75.96; H, 5.38; N, 13.30%.

Synthesis of 4-phenyl-3-(pyridin-2-yl)-1H-benzo[b][1,4] diazepine (7). Method A. A mixture of enaminone **2** (0.01 mol) and *o*-phenylenediamine in DMF (30 mL) containing a catalytic amount of TEA (four drops) was heated for 6 h. The reaction mixture was left to cool at room temperature. The separated solid was filtered off, dried, and recrystallized from EtOH to give **7** in 75% yield.

Mp 265°C; IR (KBr): ν/cm^{-1} = 3310 (NH); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 5.50 (s, 1H, CH), 7.39–7.71 (m, 12H, Ar–H), 8.52 (d, 1H, C_6–H pyridine), 9.52 (s, 1H, NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 108.0, 113.5, 120.9, 122.7, 123.5, 124.1, 126.5, 128.8, 129.2,

131.0, 133.1, 137.0, 138.2, 141.6, 148.8, 155.7, 164.6; MS (EI, 70 eV): *m*/*z* (%) = 297 (M^+, 100), 206 (25), 103 (75), 91 (20), 78 (40), 76 (20). *Anal.* Calcd for $C_{20}H_{15}N_3$ (297.36): C, 80.78; H, 5.08; N, 14.13%. Found: C, 80.70; H, 5.00; N, 14.10%.

Method B. Refluxing compound **6** in boiling DMF containing a catalytic amount of TEA for 8 h after working up afforded compound **7**.

Synthesis of 3,3′-(1,2-phenylenebis(azanediyl))bis(1-phenyl-2-(pyridin-2-yl)prop-2-en-1-one) (8). A mixture of enaminone (0.025 mol) and *o*-phenylenediamine (0.01 mol) was refluxed in absolute EtOH (30 mL) for 8 h. The reaction mixture was then left to cool at room temperature. The separated solid material was filtered off, dried, and recrystallized from EtOH to give compound **8** in 60% yield.

Mp >300°C; IR (KBr): ν/cm^{-1} = 3330 (NH), 1710 (CO); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 7.39–7.81 (m, 20H, Ar–H), 7.95 (d, 2H, 2C_6–H pyridine), 11.08 (s, 2H, 2NH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 46.1, 116.9, 119.5, 120.2, 120.9, 122.7, 128.5, 129.2, 131.3, 134.5, 137.0, 137.9, 147.1, 148.8, 155.7, 197.5; MS (EI, 70 eV): *m*/*z* (%) = 522 (M^+, 100), 299 (25), 223 (15), 209 (10), 145 (10), 105 (50), 91 (15), 78 (20). *Anal.* Calcd for $C_{34}H_{26}N_4O_2$ (522.21): C, 78.14; H, 5.01; N, 10.72%. Found: C, 78.07; H, 5.00; N, 10.70%.

Synthesis of 3-(5-amino-1H-pyrazol-1-yl)-1-phenyl-2-(pyridin-2-yl)prop-2-en-1-one (9). A mixture of **2** (0.01 mol) and 5-aminopyrazole (0.01 mol) was refluxed in boiling EtOH (30 mL) for 6 h. The reaction product was left to cool. The separated solid product was filtered off and recrystallized from ethanol to give **9** in 80% yield.

Mp 210°C; IR (KBr): ν/cm^{-1} = 3430 (NH_2), 1700 (CO), 1590 (C═C); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 6.22 (s, 2H, NH_2), 6.62 (d, 1H, *J* = 7.00 Hz, CH–pyrazole), 6.82 (s, 1H, CH═C), 7.32 (d, 1H, *J* = 7.00 Hz, CH–N pyrazole), 7.62–7.80 (m, 8H, Ar–H), 8.51 (d, 1H, C_6–H pyridine); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 96.9, 120.5, 123.6, 127.5, 128.7, 129.2, 131.6, 137.2, 144.7, 148.2, 149.2, 154.6, 158.6, 161.2; MS (EI, 70 eV): *m*/*z* (%) = 290 (M^+, 100), 274 (20), 208 (15), 131 (35), 95 (30), 77 (35). *Anal.* Calcd for $C_{17}H_{14}N_4O$ (290.33): C, 70.33; H, 4.86; N, 19.30%. Found: C, 70.31; H, 4.82; N, 19.25%.

Synthesis of 5-phenyl-6-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine (10). *Method A.* An equimolar amount of **2** (0.01 mol) and 5-aminopyrazole (0.01 mol) was refluxed in DMF solution containing a catalytic amount of TEA or glacial acetic acid for 6 h. The reaction mixture was filtered off, dried, and recrystallized from EtOH to give **10** in 72% yield.

Mp 218°C; IR (KBr): ν/cm^{-1} = 1600 (C═N); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 6.25 (d, 1H, *J* = 7.2 Hz, CH–pyrazole), 7.45 (d, 1H, *J* = 7.20 Hz, CH═N pyrazole), 7.60–7.85 (m, 8H, Ar–H), 8.52 (d, 1H, C_6H–pyridine), 9.25 (s, 1H, CH═C pyrimidine). ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 96.9, 120.5, 123.6, 127.5, 128.7, 129.2, 131.6, 137.2, 144.7, 148.2, 149.2, 154.6, 158.6, 161.2; MS (EI, 70 eV): *m*/*z* (%) = 272 (M^+, 30), 206 (20), 103 (80), 96 (40), 91 (15), 78 (20), 66 (70). *Anal.* Calcd for $C_{17}H_{12}N_4$ (272.31): C, 74.98; H, 4.44; N, 20.58%. Found: C, 74.95; H, 4.39; N, 20.51%.

Method B. Compound **9** (0.01 mol) was refluxed in boiling DMF (30 mL) with few drops of TEA (four drops) or glacial acetic acid for 6 h. The reaction mixture was cooled at room temperature. The solid product was filtered off, dried, and recrystallized from EtOH to give compound **10** in 65% yield.

Synthesis of 7-phenyl-6-(pyridin-2-yl)imidazo[1,2-a]pyrimidine (12). An equimolar amount of enaminone **2** (0.01 mol) and 2-aminoimidazole (0.01 mol) was refluxed in boiling DMF containing TEA for 6 h. The reaction mixture was left to cool, and the separated solid material was filtered off, dried, and recrystallized from EtOH to give **12** in 75% yield.

Mp 260°C; IR (KBr): ν/cm^{-1} = 1620 (C═N); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 7.00 (d, 1H, *J* = 7.00 Hz, CH–imidazole), 7.25 (d, 1H, *J* = 7.00 Hz, CH–imidazole), 7.60–7.79 (m, 8H, Ar–H), 8.51 (d, 1H, C_6H–pyridine), 9.02 (s, 1H, CH–pyrimidine); MS (EI, 70 eV): *m*/*z* (%) = 272 (M^+, 30), 206 (30), 168 (20), 104 (15), 102 (40), 82 (10), 80 (30), 74 (10), 66 (40). *Anal.* Calcd for $C_{17}H_{12}N_4$ (272.31): C, 74.98; H, 4.44; N, 20.58%. Found: C, 74.90; H, 4.40; N, 20.52%.

Synthesis of 7-(pyridin-2-yl)-6-phenyl-[1,2,4]triazolo[1,5-a]pyrimidine (15). A mixture of equimolar quantities of enaminone **2** (0.01 mol) and 3-amino-1*H*-[1,2,4]-triazole was refluxed in DMF solution catalyzed with TEA for 8 h. The reaction mixture was left to cool at room temperature. The separated solid product was filtered off, dried, and recrystallized from ethanol to give **15** in 70% yield.

Mp 245°C; IR (KBr): ν/cm^{-1} = 1610 (C═N); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 7.70–8.01 (m, 8H, Ar–H), 8.62 (s, 1H, C_3H triazole), 8.71 (d, 1H, C_6H–pyridine), 9.01 (s, 1H, C_5H–pyrimidine); MS (EI, 70 eV): *m*/*z* (%) = 273 (M^+, 25), 196 (30), 169 (35), 102 (20), 97 (35), 83 (45), 77 (25), 67 (45), 57 (80). *Anal.* Calcd for $C_{16}H_{11}N_5$ (273.30): C, 70.32; H, 4.06; N, 25.63%. Found: C, 70.30; H, 4.00; N, 25.60%.

Reaction of enaminone 2 with amidines. General procedure. A mixture of **2** (0.01 mol) and amidine derivatives, namely, acetamidine hydrochloride, benzamidine hydrochloride, and pinene-2-carboxamidine hydrochloride (**19**) (0.052 mol) was refluxed in boiling EtOH in the presence of sodium ethoxide (prepared from 1.2 g sodium and 30 mL absolute EtOH) (0.05 mol) for 6 h. The reaction mixture was left to cool at room temperature then filtered. The filtrate was concentrated

and purified by column chromatography using *n*-hexane : AcOEt 6:1 as eluent.

2-Methyl-4-phenyl-5-(pyridin-2-yl)pyrimidine (17). Yield 85%; mp 120°C; IR (KBr): ν/cm^{-1} = 1620 (C═N); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 2.30 (s, 3H, CH_3), 7.50–7.85 (m, 8H, Ar–H), 8.51 (d, 1H, C_6H–pyridine), 9.35 (s, 1H, CH); MS (EI, 70 eV): *m*/*z* (%) = 247 (M^+, 25), 170 (25), 155 (30), 129 (30), 98 (20), 82 (35), 77 (25), 67 (30). *Anal.* Calcd for $C_{16}H_{13}N_3$ (247.30): C, 77.71; H, 5.30; N, 16.99%. Found: C, 77.68; H, 5.20; N, 16.88%.

2,4-Diphenyl-5-(pyridin-2-yl)pyrimidine (18). Yield 81%; mp 180°C; IR (KBr): ν/cm^{-1} = 1610 (C═N), 1500 (Ph); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 7.70–8.09 (m, 13H, Ar–H), 8.55 (d, 1H, C_6H–pyridine), 9.02 (s, 1H, CH); MS (EI, 70 eV): *m*/*z* (%) = 309 (M^+, 100), 231 (10), 154 (10), 103 (10), 97 (35), 83 (45), 77 (20), 69 (50). *Anal.* Calcd for $C_{21}H_{15}N_3$ (309.37): C, 81.53; H, 4.89; N, 13.58%. Found: C, 81.50; H, 4.85; N, 13.54%.

2-Pinino-4-phenyl-5-(pyridine-2-yl)pyrimidine (20). Yield 76%; mp 80°C; IR (KBr): ν/cm^{-1} = 1610 (C═N), 1600 (C═C); ^{1}H-NMR (DMSO-d_6) δ (ppm) = 1.03 (s, 6H, $2CH_3$), 1.38 (d, 1H, *J* = 8 Hz, CH), 1.72 (d, 1H, *J* = 8 Hz, CH), 2.07 (m, 1H, CH), 2.19 (m, 2H, CH_2), 2.70 (t, 2H, *J* = 6 Hz, CH_2), 6.01 (t, 1H, *J* = 6 Hz, CH), 7.32–7.81 (m, 8H, Ar–H), 8.59 (d, 1H, C_6H–pyridine), 9.57 (s, 1H, C_4H–pyrimidine); MS (EI, 70 eV): *m*/*z* (%) = 353 (M^+, 45), 232 (20), 155 (15), 123 (30), 81 (40), 77 (20), 57 (30). *Anal.* Calcd for $C_{24}H_{23}N_3$ (353.47): C, 81.55; H, 6.56; N, 11.89%. Found: C, 81.45; H, 6.55; N, 11.80%.

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