Communication

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Posted Date: 28 December 2023

doi: 10.20944/preprints202312.1232.v1

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A Simple and Efficient Multicomponent Synthesis of Novel Pyrazole, N-Aminopyridine and Pyrazolo[3,4-*b*]Pyridine Derivatives in Water

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Abstract: The three-component reaction of enaminones, benzaldehyde and hydrazine-HCl or four-component reaction of enaminones, benzaldehyde, hydrazine–HCl and ethyl cyanoacetate in water in the presence of catalytic amount of ammonium acetate has been devised as a straightforward , sustainable approach for the synthesis of 1-*H*-pyrazole, N-aminopyridine and pyrazol[3,4-*b*]pyridine derivatives . The key benefits of this approach is simple experimental procedure associated with cost effective and environmentally friendly techniques.

Keywords: multicomponent reaction; enaminones; water; pyrazoles; pyrazolo[3,4-*b*]-pyridine; 1,2-bis-arylidenehydrazine

1. Introduction

Nitrogen-containing heterocycles were recognized to possess diverse activities in fields related to biological and medicinal activities [1–4]. Among nitrogen-containing heterocycles pyrazole derivatives, play a crucial role in agrochemical and pharmacological research [5,6].

The most extensively utilized method for pyrazole synthesis was made through condensation reaction of hydrazine with α,β-unsaturated carbonyl scaffolds [7–10].

Other commonly utilized methods for pyrazole synthesis relied on 1,3-dipolar cycloaddition of toxic explosive diazo compounds onto triple bond systems [11], or the nucleophilic attack of hydrazines to isoxazoles, flavones or chromones [12], or tosyl hydrazine with substituted aldehydes [13–15]. It is worth mentioning that although hydrazine hydrate is applied as a major source of nitrogen, however a disadvantage associated with this protocol is the usual formation of 4,5-dihydro pyrazoles which needs further oxidation to the final pyrazole derivative. Examples of biologically active pyrazole-based moieties are illustrated below in Figure 1.

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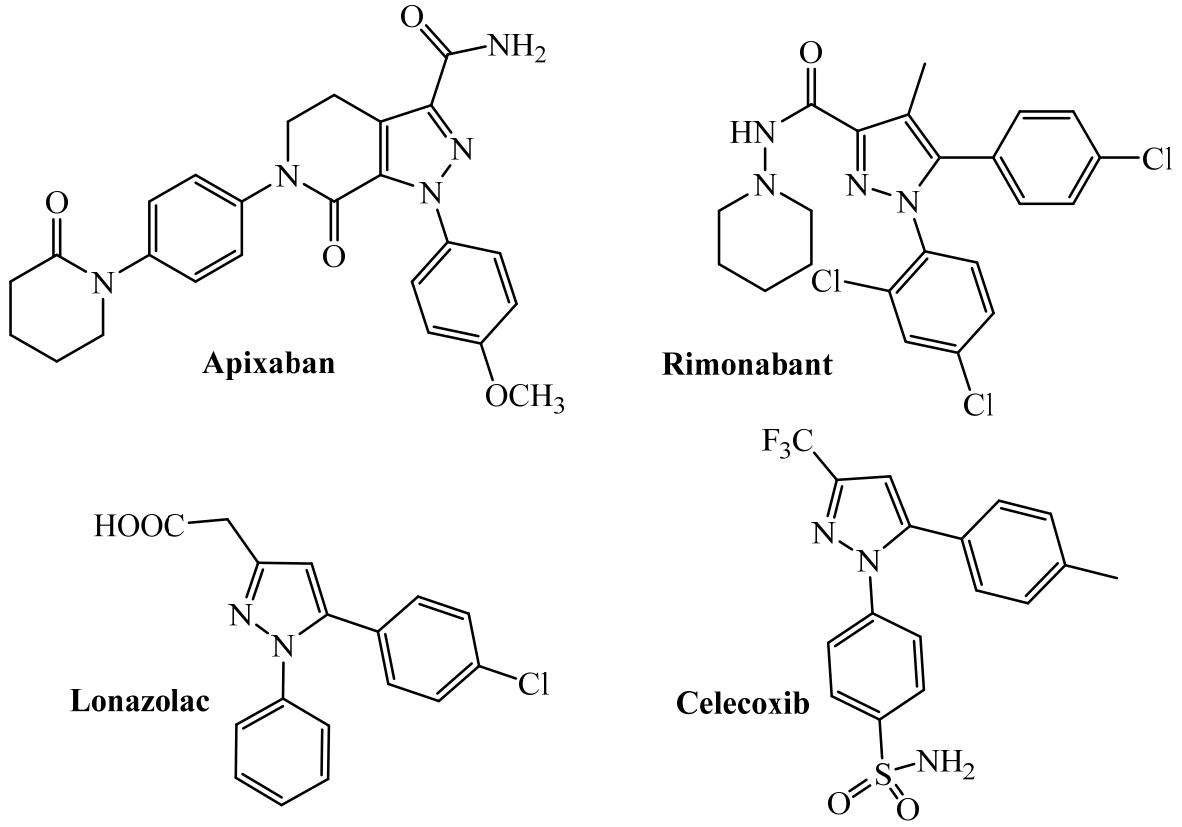

Figure 1. Pyrazole-based moieties marketed drugs.

Pyrazolo[3,4-*b*]pyridine derivatives acquired significant attention in medicinal chemistry for their potent and privileged range of biological activities [16–18]. Several approaches have been reported for their synthesis. The reaction of 5-aminopyrazoles with 1,3-bis-electrophiles or unsaturated carbonyl compounds are among the widely used protocols [19–25]. However, these approaches usually afford dihydropyrazolo[3,4-*b*]pyridine derivatives. The synthesis of pyrazolo[3,4-*b*]pyridines has received little attention and few approaches addressed their direct synthesis [26–29]. Although these protocols have their specific advantages, they are limited by several factors such as low yields, multistep synthetic approaches, long reaction times, tedious work up either in conducting the reaction or isolation of products, as well as the use of hazardous catalysts and solvents.

Currently, multi-component reactions (MCRs) are recognized as important and reliable strategies in the rapid synthesis of complex molecules from readily available starting materials in a single step [30,31]. Therefore MCRs-based syntheses provide sustainable utility of chemical resources by reducing waste as well as minimizing the number of steps required for organic transformations [32].

Large quantities of solvents are essential for chemical reactions, extraction and purification processes [33]. Moreover, many organic solvents are toxic, hazardous, or environmentally harmful which pose risks to both the environment and human health [34]. In this regard the use of water as a green solvent with its low ESH (Environmental Safety and Health) impact, has led to intriguing developments of organic synthesis due to its environmental benignity, safety and low-cost nature [35–40].

As a part of our continuing work concerning the green synthesis of biologically relevant heterocycles, we report, herein a facile synthesis of novel polyfunctionally substituted pyrazoles and pyrazolo[3,4-*b*]pyridine derivatives via one-pot multi-component reaction of enaminones **1**, benzaldehyde **2**, and hydrazine hydrochloride **3** and ethyl cyanoacetate **5** in water in the presence of catalytic amount of ammonium acetate at reflux.

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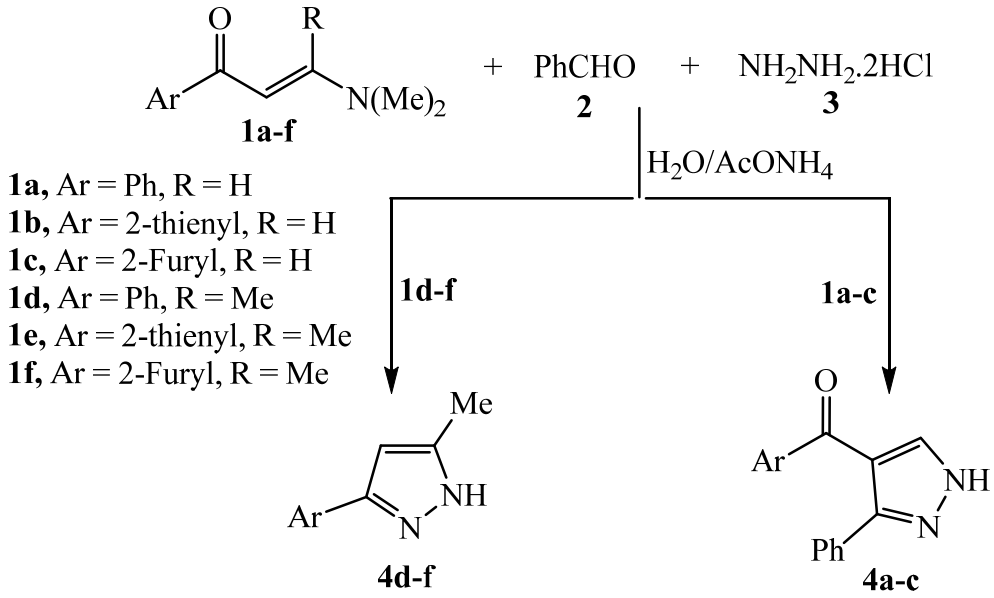
2. Results and Discussion

For optimizing the reaction conditions, the three-component reaction of equimolar amounts of enaminones **1a** with benzaldehyde **2** and hydrazine hydrochloride **3** in water/ammonium acetate was selected as the model reaction for initial studies (Table 1).We are delighted to found that pyrazole **4a** was obtained in good yield when the reaction mixture was heated under reflux for 1 hour. Several green solvents including glycerol and **PEG** [41–46] were examined and it was found that water provided the best yield.

The structure assigned for **4a** was established based on analytical and spectral data. The mass The structure assigned for **4a** was established based on analytical and spectral data. The mass spectrum of **4a** showed a molecular ion peak m/z = 249 (M^++1) (55%). The ^{1}H NMR revealed signals at δ ppm 12.78 (1H, br s, D_2O exchangeable, NH), 8.42 (1H, s, H-5), 8.10-8.01 (2H, m, phenyl-H), 7.91-7.51 (8H, m, phenyl-H).

Subsequently, the scope of such reaction with a variety of enaminones has been investigated. Thus, the reaction of **1b, c** with **2** and **3** performing the same reaction conditions afforded the corresponding pyrazole derivatives **4b,c**.

However, the reaction of **1d**, with **2** and **3** afforded product **4d** with molecular ion peak m/z = 158.06 (100%). Its ^{1}H NMR revealed absorption bands at δ = 12.58 (1H br s, NH), 7.70-7.72 (2H, m, phenyl-H), 7.34-7.23 (3H, m, phenyl-H), 6.39 (1H, s, H-4), 2.21 (3H, s, CH_3). Structure **4d** was assigned for the reaction product which confirmed the non-involvement of benzaldehyde **2** in the reaction course presented in Table 1. Similarly, enaminones **4e,f** reacted with **2** and **3** yielding the corresponding pyrazoles **4e,f** in moderate yields (Scheme 1).



Scheme 1. Multicomponent reaction of enaminones **1a-f** with benzaldehyde **2** hydrazine hydrochloride and ammonium acetate in water.

Table 1. Description of synthesized pyrazole derivatives **4a-f**.

Product	R	Ar	Yield %	m.p [°C]
4a	H	Phenyl	75	160-162
4b	H	2-Thienyl	77	156-158
4c	H	2-Furyl	73	170-172
4d	Methyl	Phenyl	60	124-126
4e	Methyl	2-Thienyl	66	173-175
4f	Methyl	2-Furyl	63	162-164

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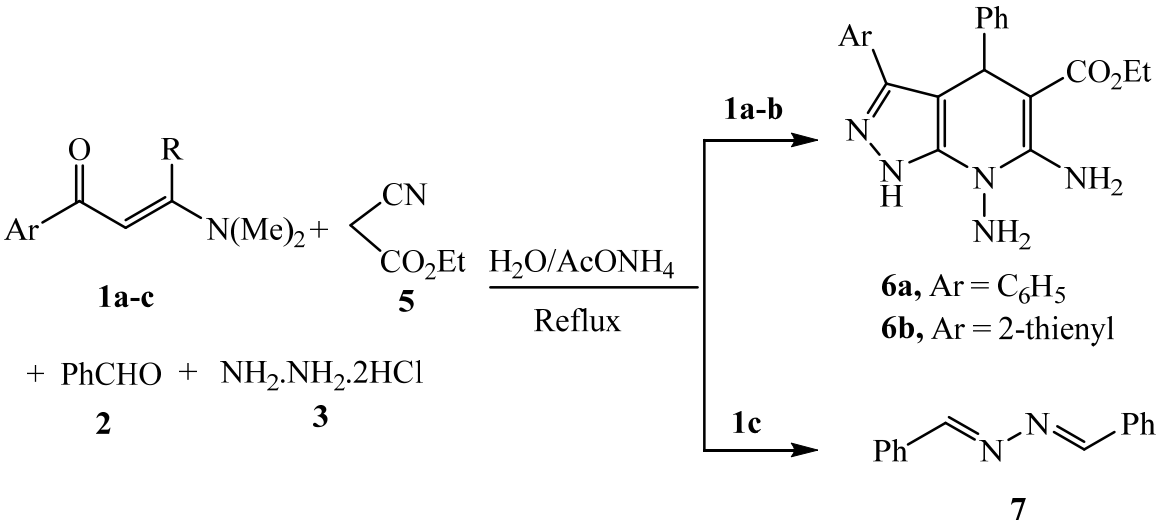
It is worth mentioning that – and to the best of our knowledge , it is the first reported synthesis of aryl/heteroaryl (3-phenyl-1*H*-pyrazol-4-yl)methanone **4a-c**, while 3-aryl/heteroaryl-5-methyl-1*H*-pyrazoles **4d-e** were synthesized via Heck reactions in a lengthy and expensive procedure [47].

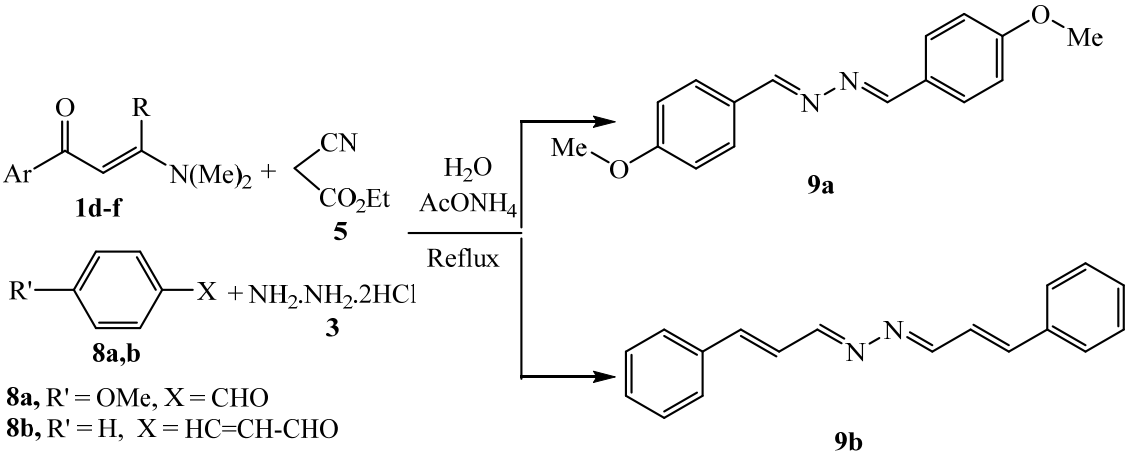
To explore the generality of our procedure, we replicated our previous protocol with a four-component reaction of enaminones **1a-c**, benzaldehyde **2**, hydrazine hydrochloride **3** and ethyl cyanoacetate **5**. Thus, equimolar amounts of **1a, 2, 3** and **5** were heated under reflux in water/ammonium acetate, a product of molecular formula $C_{21}H_{21}N_5O_2$ was obtained which was assigned the corresponding pyrazolo[3,4-*b*]pyridine **6a** based on its analytical data, which showed a molecular ion peak m/z = 374 (M^+ -1) (100%). The ^{1}H NMR spectra revealed signals at δ 8.37 (1H, s, NH), 7.67 (2H, br s, NH_2), 7.63-7.55 (5H, m, phenyl-H), 7.45-7.23 (5H, m, phenyl-H), 7.20 (2H, br s, NH_2), 5.10 (1H, s, H-4), 4.01 (2H, q, *J*=7.2 Hz, CH_2), 1.16 (3H, t, *J* = 7.2 Hz, CH_3). The ^{13}C NMR showed characteristic bands at δ= 193.86 (CO), 169.13 (C-6), 59.13 (CH_2), 39.78 (C-4), 14.98 (CH_3). Similarly, the reaction mixture of **1b, 2, 3** and **5** afforded the corresponding pyrazolo[3,4-*b*]pyridine derivatives **6b** (Scheme 2).

On the other hand, the reaction mixture of **1c, 2, 3** and **5** afforded the corresponding 1,2-di-benzylidine)-hydrazine **7** as a result of the reaction of two molecules of benzaldehyde with one molecule of hydrazine HCl (Scheme 2).



Scheme 2. Multicomponent reaction of enaminones **1a-c** with benzaldehyde **2** hydrazine hydrochloride, ethyl cyanoacetate and ammonium acetate in water.

Similar to the behavior of **1c** toward **2, 3** and **5,** the reaction mixture of **1d-f** with **3, 5** and aryl aldehyde derivatives **8a,b**, afforded the corresponding (1,2-di-arylidine)-hydrazines **9a-b** (Scheme 3).



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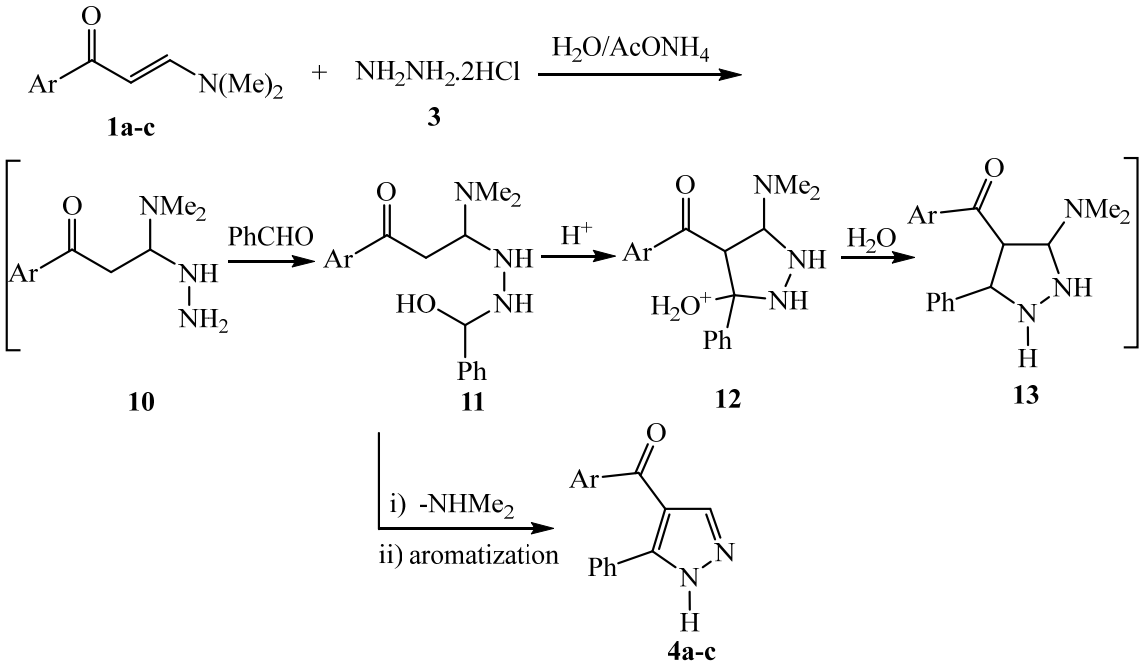
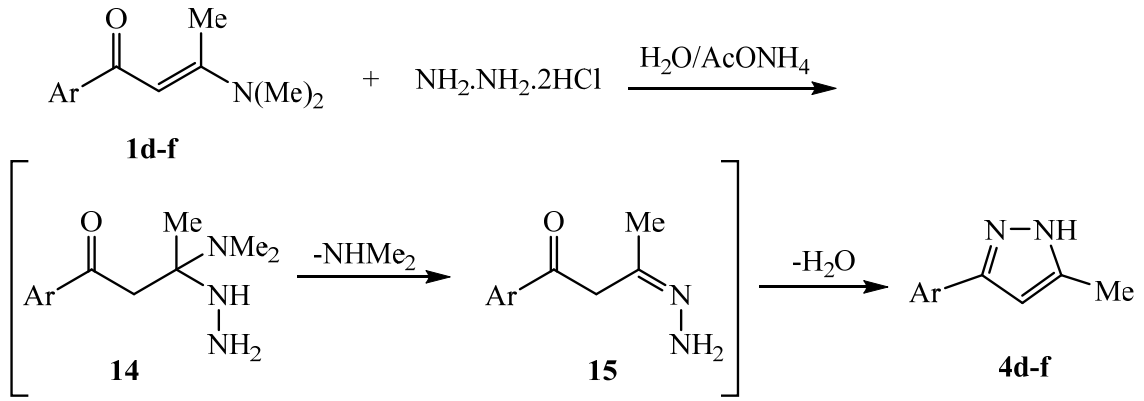
Scheme 3. Synthesis of (1,2-di-arylidine)-hydrazines **9a-b**.

A reasonable mechanism to rationalize the formation of the reaction products **4a-c** was depicted in (Schemes 4 and 5). where **1a-c** reacted with hydrazine hydrochloride in water/ammonium acetate to yield the addition adduct **10** followed by attack of the amino group to the activated carbonyl group of benzaldehyde, afforded **11** which cyclizes to the corresponding dihydropyrazole **12**, this is followed by aromatization via loss of dimethylamine in **13** to yield the final isolable products **4a-c**.



Scheme 4. Reasonable mechanism to rationalize for the synthesis of pyrazole derivatives **4a-c.**

Concerning for enaminones **1d-f**, the formed sterically hindered 1:1 adduct **14** loses the dimethylamino function, affording **15,** which will cyclizes to pyrazoles **4d-f** via water molecule loss (Scheme 5).



Scheme 5. Proposed mechanism for the synthesis of pyrazole derivatives **4d-f.**

Regarding the formation of **6a,b** it is assumed that the condensation step of benzaldehyde and ethyl cyanoacetate afforded the in situ-formed benzylidene ethyl cyanoacetate **16,** which reacted with enaminones **4a-b** and hydrazine hydrochloride yielding N-aminopyridine derivative **17**. The reaction of **17** with a second molecule of hydrazine hydrochloride yielded the final isolable products **6a-b** (Scheme 6).

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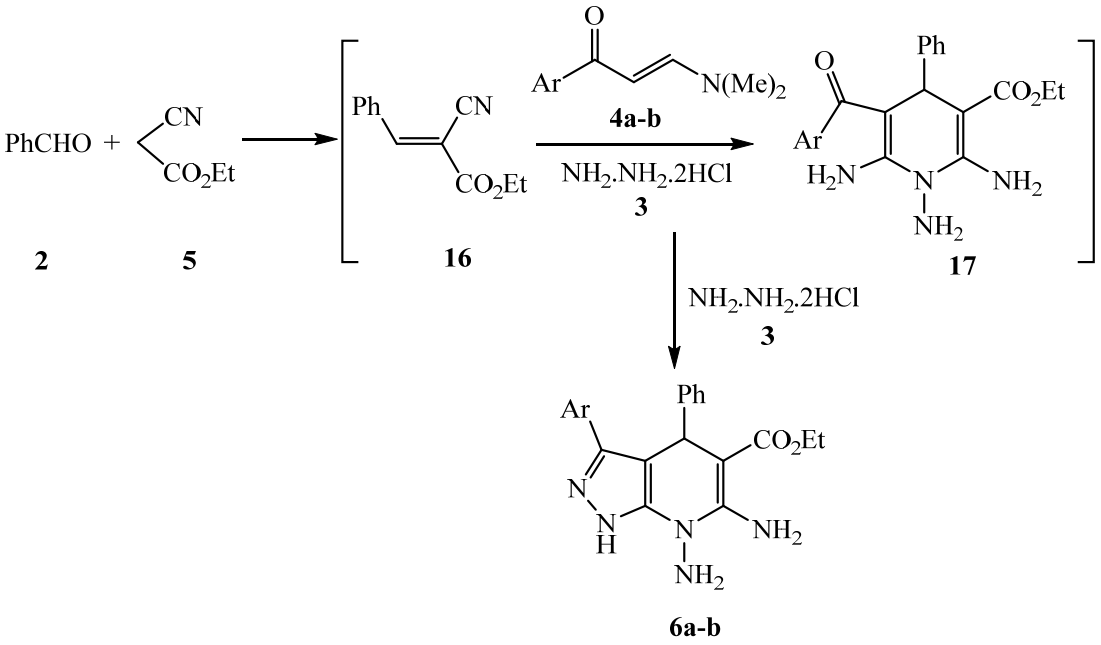

Scheme 6. Proposed mechanism for the synthesis of pyrazolo[3,4-*b*]pyridine derivatives **6a-b.**

3. Materials and methods

3.1. General Information

Aldehydes, Ethyl cyanoacetate , N,N-Dimethylformamide dimethylacetal, N,N-dimethyl acetamide dimethyl acetal and Ketones were of commercial grade and purchased from Aldrich and Merck companies. IR spectra were measured on a PerkinElmer 317 grating IR spectrophotometer using KBr pellets. ^{1}H NMR (500 MHz) and ^{13}C NMR (500 MHz) spectra were recorded using JEOL E.C.A- spectrometer (δ ppm). Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. Mass spectrometry was performed on a JEOL JMSAX 500 spectrometer. The appropriate precautions in handling moisture-sensitive compounds were considered. Solvents were dried by standard techniques. Elemental analyses were carried out at the Microanalysis Laboratory, National Research Center, Giza, Egypt; their values agreed favorably with the calculated ones.

3.2. Synthesis of Compounds

3.2.1. General procedure for compounds **1a-c** and **1d-f**

Compounds **1a-c** were prepared as described previously [48]

Compounds **1d-f** were prepared via adding dropwise N,N-dimethyl acetamide dimethyl acetal (1.33g,10 mmol) to a stirred solution of each of acetophenone, 2- acetyl thiophene, 2- acetyl furan (10 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred at ambient temperature (25^{0}C) for 24 hours. The solid product formed after removing solvent under reduced pressure was filtered and crystallized from cyclohexane.

3.2.2. 3-Hydroxy-1-phenylbut-2-en-1-one **1d**

Yellowish crystals, yield 1.21 g (75 %), mp 86-88 ^{o}C. IR (cm^{-1}): 1594cm^{-1} (CO) ; ^{1}H NMR: (500 MHz, DMSO-d_6) δ 16.30 (1H, br s, OH); 7.91-7.93 (2H, m, Ph-H); 7.49-7.93 (3H, m, Ph-H); 6.53 (1H, s, ethylene-H); 2.20 (3H, s, CH_3). EIMS (m/z): 162 (M^{+}) for $C_{10}H_{10}O_2$ (162).

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3.2.3. 3-(Dimethylamino)-1-(thiophen-2-yl)but-2-en-1-one **1e**

Brown crystals, yield 1.46 g (75 %); mp 101-103 °C; IR (cm^{-1}): 1530 cm^{-1} (CO); ^{1}H NMR: (500 MHz, DMSO-d_6) δ 7.60-7.62 (2H, m, thienyl H-3,5); 7.06 (1H, t, *J* = 5.0 Hz, thienyl H-4); 5.61 (1H, s, ethylene-H); 3.01 (6H, s , NCH_3); 2.51 (3H, s, CH_3). EIMS: (m/z): 195 (M^+) for $C_{10}H_{13}NOS$ (195).

3.2.4. 3-(Dimethylamino)-1-(furan-2-yl)but-2-en-1-one **1f**

Brown crystals, yield 1.30 g (73 %); mp 94-96 °C; IR (cm^{-1}): 1538 cm^{-1} (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 (1H, d, J = 5.0 Hz, furyl H-5); 6.94 (d, 1H, d, *J* = 5.0 Hz, furyl H-3); 6.51 (1H, t, *J* = 5.0 Hz, furyl H-4); 5.56 (1H, s, ethylene-H); 2.99 (6H, s , NCH_3); 2.52 (3H, s, CH_3). EIMS: (m/z): 180 (M^{+1}). $C_{10}H_{13}NO_2$ (179).

3.2.5. General procedure for the preparation of **4a-c** and **4d-f**

To a stirred suspension of enaminones **1a-f** (10 mmol) and hydrazine hydrochloride **2** in water (10 ml), benzaldehyde **3** and ammonium acetate was refluxed under heating for 1 hr. The solid product formed after evaporation of solvent in vacuum, and trituration with ethanol was collected and crystalized from the proper solvent. In some cases, flash chromatography on silica gel using chloroform/n-hexane (3:1) as eluent was performed to afford analytically pure samples

3.2.6. Phenyl(3-phenyl-1*H*-pyrazol-4-yl)methanone **4a**

Yellow crystals, yield 1.86 g (75 %) ; mp 160-162 °C. IR (cm^{-1}): 3197 (NH) and 1658 cm^{-1} (CO); ^{1}H-NMR (500 MHz, DMSO-d_6) δ 12.78 (1H br s, NH,); 8.42 (1H, s, H-5) ; 8.10-8.01 (2H, m, phenyl-H) ; 7.91-7.51 (8H, m, phenyl-H). ^{13}C-NMR (500 MHz, DMSO-d_6) δ 188.40, 149.89, 147.14, 144.51, 139.45, 133.98, 133.86, 128.84, 128.58, 127.32, 126.94, 111.14. EIMS: (m/z): 249 (M^{+1}) for $C_{16}H_{12}N_2O$ (248).

3.2.7. (3-phenyl-1*H*-pyrazol-4-yl)(thiophen-2-yl)methanone **4b**

Brown crystals, yield 1.95g (77 %) ; mp 156-158 °C; IR (cm^{-1}): 3432 br (NH) and 1654 cm^{-1} (CO); ^{1}H-NMR: (500 MHz, DMSO-d_6) δ 7-79-7.41 (7H, m, phenyl and thienyl-H); 8.09 (1H, *J* = 5 Hz, thienyl H-5); 8.36 (1H, s, H-5); 11.07 (1H, br s, NH). ^{13}C-NMR (500 MHz, DMSO-d6) δ: 182.64, 149.79, 147.61, 146.53, 144.61, 134.53, 133.08, 132.56, 130.46, 129.35, 128.84, 127.44. EIMS: (m/z): 255 (M^{+1}) for $C_{14}H_{10}N_2OS$ (254)

3.2.8. Furan-2-yl(3-phenyl-1*H*-pyrazol-4-yl)methanone **4c**

Yellow crystals, yield 1.74g (73 %) ; mp 170-172 °C; IR (cm^{-1}): 3428 br (NH) and 1650 cm^{-1} (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99-7.62 (7H, m, phenyl and furyl-H); 8.09 (1H, d, *J* = 5Hz, furyl H-5); 8.37 (1H, s, H-5); 12.47 (1H, br s, NH); ^{13}C-NMR (500 MHz, DMSO-d_6) δ: 176.99, 154.63, 150.00, 147.39, 146.69, 146.24, 134.51, 130.49, 129.38, 127.45, 115.16, 114.89, 112.71. EIMS m/z: 240 (M^{+2}) for $C_{14}H_{10}N_2O_2$ (238).

3.2.9. 5-methyl-3-phenyl-1*H*-pyrazole **4d**

Yellow crystals, yield 0.95 g (60 %) ; mp 124-126 °C. IR (cm^{-1}): 3179 (NH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.58 (1H, br s, NH, D_2O exchangeable). 7.70-7.72 (2H, m, Ph-H); 7.23-7.34 (3H, m, Ph-H); 6.39 (1H, s, H-4); 2.21 (3H, s, CH_3). ^{13}C-NMR (500 MHz, DMSO-d_6) δ: 129.13, 127.75, 125.49, 101.73, 100.0, 11.45. EIMS (m/z) 158 (M^+) for $C_{10}H_{10}N_2$ (158).

3.2.10. 5-methyl-3-(thiophen-2-yl)-1*H*-pyrazole **4e**

Brown crystals, yield 1.08 g (66 %); mp 173-175 °C; IR (cm^{-1}): 3120 br (NH); ^{1}H NMR (500 MHz, DMSO-$_{d6}$) δ 12.50 (1H, br s NH); 7.36 (1H, d, *J* = 5.0 Hz, thienyl H-5); 7.27 (1H, t, *J* = 5.0 Hz, thienyl H-3); 7.02 (1H, t, *J* = 5 Hz, thienyl H-4); 6.28 (1H, s, pyrazolyl-H); 2.20 (3H, s, CH_3); ^{13}C-NMR (500 MHz, DMSO-d_6) δ: 139.74, 127.50, 124.24, 123.20, 120.4, 100.94, 54.55, 10.69. EIMS m/z : 164 (M^+) for $C_8H_8N_2S$: (164).

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3.2.11. 3-(Furan-2-yl)-5-methyl-1*H*-pyrazole **4f**

Brown crystals, yield 0.93 g (63 %); mp 162-164 °C; IR (cm^{-1}): 3206 br (NH); ^{1}H NMR (500 MHz, DMSO-*d6*) δ 12.46 (1H, br s, NH); 7.26-7.34 (2H, m, furyl 3,5- H); 7.01 (1H, t, *J* = 5.0 Hz, futyl H-4); 6.27 (1H, s, pyrazolyl-H); 2.21 (3H, s, CH_3). ^{13}C-NMR (500 MHz, DMSO-d_6) δ: 11.01, 101.53, 123.73, 124.77, 128.03, 138.05, 140.03, 146.59. EIMS m/z: 148 (M^+) for $C_8H_8N_2O$: (148).

3.2.12. General procedure for the synthesis of **6a-b** and **7**

A stirred suspension of hydrazine hydrochloride **3** in water (20 ml) and ammonium acetate (1 g), was treated with each of the enaminone **1a-c** (10 mmol), benzaldehyde **2** (10 mmol) and ethyl cyanoacetate **5** (10 mmol). The reaction mixture was heated at refluxed for 1 hr., allowed to cool to room temperature, and the formed precipitate was filtered of and crystallized from ethanol to afford analytically pure samples.

3.2.13. Ethyl 6,7-diamino-3,4-diphenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate **6a**

Yellow crystals, yield 1.68g (45 %); mp 160-162 °C; IR (cm^{-1}): 3779, 3467 and 3334 (NH_2) and (NH); and 1662 cm^{-1} (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (1H, s, NH). 7.67 (br s, 2H, NH_2); 7.55-7.63 (m, 5H, phenyl-H); 7.23-7.45 (5H, m, phenyl-H); 7.20 (2H, br s, NH_2); 5.10 (1H, s, H-4); 4.01 (2H, q, *J* = 7.2 Hz, CH_2); 1.16 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR: (500 MHZ, DMSO-d_6) δ: 193.86 (CO), 169.13 (C-6), 152.29, 148.10, 146.75, 132.06, 129.33, 129.03, 128.59, 128.80, 127.70, 126.50, 120.51, 79.06, 59.13 (CH_2), 39.78 (C-4), 14.98 (CH_3). EIMS m/z: 374 (M^+-1) for $C_{21}H_{21}N_5O_2$: (375)

3.2.14. Ethyl 6,7-diamino-4-phenyl-3-(thiophen-2-yl)-4,7-dihydro-1*H*-pyrazolo[3,4-b]pyridine-5-carboxylate **6b**

Yellow crystals, yield 2.20g (58 %); mp 237-239 °C; IR (cm^{-1}): 3467, 3402 and 2973 and (NH_2 and NH) and 1662 cm^{-1} (CO); ^{1}H NMR (500 MHz-DMSO-d_6) δ 8.54 (1H, br s, NH); 7.90-8.04 (5H, m, thienyl-H and NH_2); 7.40 (2H, br s, NH_2); 7.07-7.19 (5H, m, phenyl-H); 5.03 (1H, s, H-4); 4.00 (2H, q, *J* = 7.2 Hz, CH_2); 1.13 (3H, t, *J* = 7.2 Hz, CH_3). ^{13}C NMR: (500 MHZ, DMSO-d_6) δ: 184.93, 169.08, 152.33, 147.78, 146.70, 143.81, 133.98, 133.69, 133.27, 129.23, 128.80, 128,56, 127.71, 100.0, 78.93, 59.10, 14.97 .EIMS m/z: 380 (M^+-1) $C_{19}H_{19}N_5O_2S$: (381).

3.2.15. 1,2-Dibenzylidenehydrazine **7**

Light brown crystals, yield 0.832g (40 %); mp 93-95 °C (lit. mp 92-93 °C) [49]; IR (cm^{-1}): 1669 cm^{-1} (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47-7.48 (6H, m, phenyl-H), 7.85-7.86 (4H, m, phenyl-H); 8.68 (s, 2H, Benzylidinimine-H). ^{13}C NMR (500 MHZ, DMSO-d_6) δ 162.01 (C=N); 134.35; 131.89; 129.45; 128.9 EIMS m/z: 208 (M^+) for $C_{14}H_{12}N_2$.

3.2.16. General procedure for the preparation of **9a**

To a mixture of hydrazine hydrochloride **3** and ammonium acetate (1 g), suspension in water (20 ml) was added the enaminone **1d-f** (10 mmol), ethyl cyanoacetate **5** (10 mmol) and benzaldehyde derivatives **8a-b** (10 mmol). The resulting mixture was refluxed for 1hr. and left to cool to room temperature. The precipitated product was collected by filtration and recrystallized from ethanol affording desired products **9a, b.**

3.2.17. 1,2-bis(4-methoxybenzylidene)hydrazine **9a**

Yellow crystals, yield 1.79 g (67 %) ; mp 174-176 °C. IR (cm^{-1}): 1656 cm^{-1} (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (2H, s, aldimine-H); 7.78 (4H, d, *J* = 7.5 Hz, phenyl H); 7.02 (4H, d, *J* = 7.5 Hz, phenyl H); 3.78 (6H, s, OCH_3). ^{13}C NMR (500 MHZ, DMSO-d_6) δ 162.22 (CO-Me); 160.98 (C=N); 130.53; 127.08; 114.94; 55.92. EIMS m/z: 267 (M^+-1) for $C_{16}H_{16}N_2O_2$: (268).

3.2.18. 1,2-bis-3-phenylallylidene)hydrazine **9b**

Light brown crystals, yield 1.82 g (70 %) ; mp 173-175 ^{o}C. IR (cm^{-1}): 1643 cm^{-1} (C=N); MS m/z (M^{+}-1) = 259; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (2H, d, *J* = 9.50 Hz, aldimine -H); 7.62 (2H, d, *J* = 7.15 Hz, ethylene-H); 7.39 (2H, t, *J* = 7.15 Hz, ethylene-H); 7.25-7.35 (4H, m, phenyl-H); 7.09-7.14 (6H, m, phenyl-H). EIMS m/z: 259 (M^{+}-1) for $C_{18}H_{16}N_2$: (260).

4. Conclusion

In summary a straightforward access to novel polyfunctionally substituted pyrazole and pyrazolo[3,4-*b*]pyridines were developed via three-component reaction of enaminones, benzaldehyde and hydrazine hydrochloride or four-component reaction of enaminones, benzaldehyde, hydrazine hydrochloride and ethyl cyanoacetate. The procedure reported herein is a simple, green and an efficient protocol. It is highly applicable and has the advantages of short reaction times and ease of execution either in conducting the reaction or isolation of products.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Mervat Mohammed Abdelkhalik: Conceived and designed the experiments; Analyzed the Data, Wrote original and final draft. Abdulaziz Alnajjar: Writing-review & editing. Solwan Maher Ibrahim: Performed the experiments, Analyzed the Data. Mohammed Abdelmonem Raslan: Review & editing. Kamal Usef Sadek: Visualization, Methodology.

Funding: This research was done by the financial support of Public Authority for Applied Education and Training (Transform Grant TS-15-02) of Kuwait.

Acknowledgments: This work was supported by the Public Authority for Applied Education and Training of Kuwait.

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