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Studies with enaminones and enaminonitriles: synthesis of 3-aroyl and 3-heteroaroyl-pyrazolo-[1,5-*a*]pyrimidines

Khaled D. Khalil, Hamad M. Al-Matar *, Doa'a M. Al-Dorri, Mohamed H. Elnagdi

Department of Chemistry, Faculty of Science, University of Kuwait, PO Box 5969, Safat 13060, Kuwait

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ABSTRACT

The reaction of electron rich aromatics with cyanoacetic acid and acetic anhydride afforded 3-oxoalkanenitriles. Indium trichloride was used as a Lewis acid catalyst when the aromatic ring was not sufficiently reactive. The synthesized 3-oxoalkanenitriles were subsequently condensed with dimethylformamide dimethylacetal (DMFDMA) to yield enaminones that reacted readily with hydrazine hydrate to yield 4-aroylpyrazole-3-amines. The 4-aroylpyrazole-3-amines were condensed with enaminones to yield 3-aroylpyrazolo[1,5-*a*]pyrimidines.

1. Introduction

The biological and medicinal activities of pyrazolo[1,5-*a*]pyrimidines have stimulated considerable interest in the synthesis of derivatives of this ring system.[1–4] Despite enormous number of pyrazolo[1,5-*a*]pyrimidine derivatives that have so far been synthesized,[1,2] only a few 3-aroylpyrazolo[1,5-*a*]pyrimidines have been prepared. The discovery of the biological activities of indiplon[5] has raised interest in the synthesis of 3-aroylpyrazolo[1,5-a]pyrimidines. Recently reported synthesis of **2**[6]; *R*=2-thienyl; via reacting **4**; *R*=2-thienyl; has attracted our attention as this reaction seemed an interesting entry to 3-aroylpyrazolo[1,5-*a*]pyrimidines. However it was recently reported that reacting **2**; R=Ph; with hydrazine affords also the cyanopyrazoles **3**.[7] It seemed to us that the outcome of reacting derivatives of **1** with hydrazine is very much dependent on the reactivity of the ketocarbonyl moiety in these molecules, which, in turn, is very much affected by placing an electron donating moiety at C-1. To check this assumption, we planned to synthesize a variety of substituted compounds **1** where R is an electron donating aromatic system (Scheme 1).

2. Results and discussion

The logical start for the synthesis of **1** would be the reaction of **4** and DMFDMA. Although a variety of derivatives of **4** are already known[8] and several synthetic approaches to such systems are already available a somewhat easy and efficient route to **4** (*R*=3-indolyl or 2-pyrrolyl) has been reported recently by Slatt et al.,[9] Elnagdi et al.,[10] and Ibrahim et al.[11] This attracted our attention as an efficient route to derivatives of **4**. Thus, *N*,*N*-dimethylaniline **5a** reacted readily with a mixture of acetic anhydride and cyanoacetic acid (thus producing **6** in situ) when heated at 80 °C for 10 min to yield **7a** in 80% yield. However anisole **5b** did not react under similar conditions. Despite this, adding a preheated Ac_2O/cyanoacetic acid mixture to anisole in the presence of 15% by weight indium trichloride as heterogeneous non-stoichiometric Lewis acid catalyst, **7b** was readily formed. 2-Acetylfuran **8** reacted with mixed cyanoacetic acid–acetic anhydride to yield either **9** or **10** depending on the molar ratio. Thus, when a 1:1 molar ratio of **7** and **6** were used, **9** was produced. Using 1:2 ratio afforded **10** (Scheme 2).

It is believed that under these conditions the initially formed **9** reacts further with **6** to yield **10**. In support of this view, heating **9** with **6** also afforded **10**. Under a variety of conditions, the reaction of 2-bromothiophene **11** with **6** afforded, in contrast to expectation, the acetyl derivative **12**. We thus looked for an alternative approach for the synthesis of targeted **15**. Condensing **12** with DMFDMA gave the *trans* enaminone **13** that reacted with hydroxylamine hydrochloride to yield oxime **14** that was converted to **15** when heated

* Corresponding author. Tel.: +965 24987559; fax: +965 24816482.
E-mail address: h.almatar@ku.edu.kw (H.M. Al-Matar).

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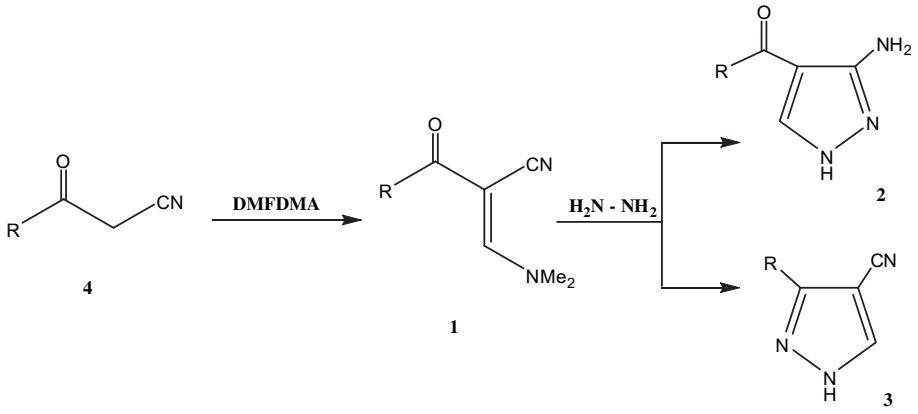
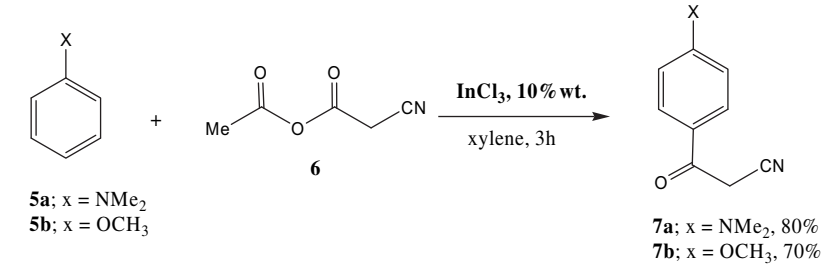
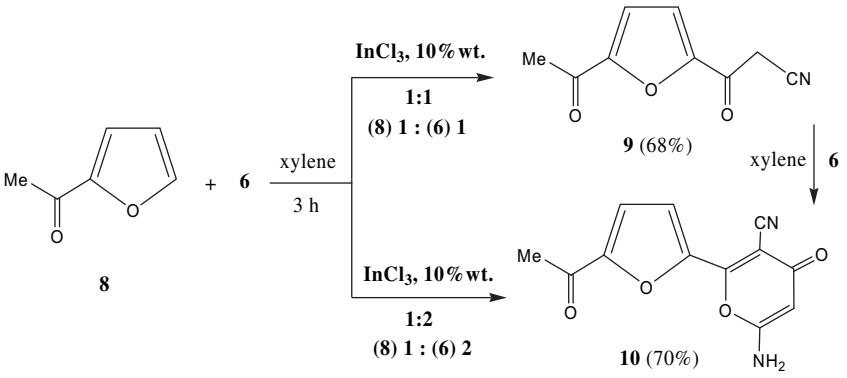


Scheme 1.





Scheme 2.

with diethyl oxalate in the presence of sodium hydride following a recently reported[12] procedure for converting oximes to nitriles (Scheme 3).

3-Acetylindole **16** reacted with **6** to yield **17** as indicated by the absence of a D_2O exchangeable indole NH (Scheme 4).

Compounds **7a**,**b**, **9**, **15**, and **17** were condensed with DMFDMA to yield enaminones **18a**,**b**–**19a**,**b**, and **20**. Data suggests one isomer but presumably it is unknown whether it is *cis* or *trans*. These reacted smoothly with hydrazine hydrate to yield aminopyrazoles **21a**,**b**, **23a**,**b**, and **25**, respectively. Although **21a**,**b**, **23a**,**b**, and **25** may exist also as **22a**,**b**, **24a**,**b**, and **25**, structures **21a**,**b**, **23a**,**b**, and **25** are established based on the ^{1}H NMR spectrum that revealed the pyrazole CH as a singlet at δ 7.84 ppm (Scheme 5).

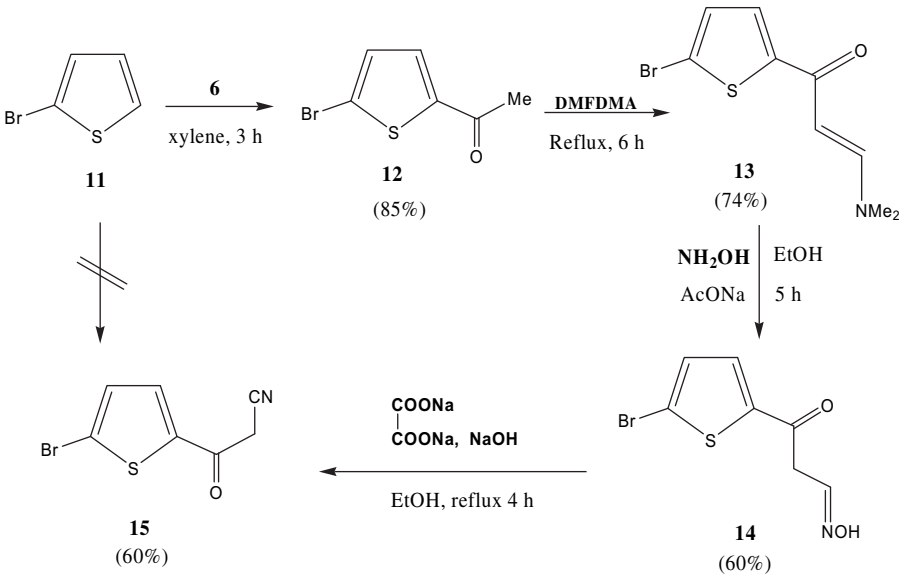
Compounds **21a**,**b** were reacted with enaminone **27** to yield the 7-substituted pyrazolo-[1,5-*a*]pyrimidines **28a**,**b** (Scheme 6).

In conclusion, 3-oxoalkanonitriles can be readily obtained by reacting cyanoacetic acid–acetic anhydride mixture with electron rich aromatics. The scope of this approach could be extended to less electron rich aromatics utilizing indium trichloride as a Lewis acid. Moreover, 2-aroyl-3-dimethylaminoacrylonitriles with electron rich donating substituent at the aroyl moiety react with hydrazines to yield aminopyrazoles as the sole products.

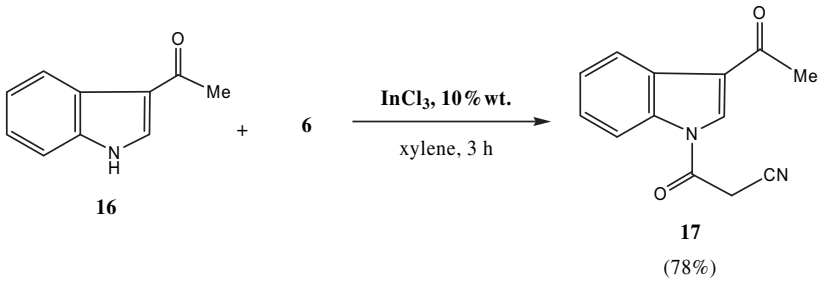
3. Experimental section

3.1. General procedures

Melting points were recorded on Gallenkamp apparatus. Infrared spectra (KBr) were determined on a Perkin–Elmer 2000 FT-IR system. NMR measurements were determined on a Bruker DPX spectrometer, at 600 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR, in DMSO-d_6 as solvent and using TMS as internal standard. Mass spectra were measured on MS 30 and MS 9 (AEI) spectrometers, with EI 70 eV. Elemental analyses were measured by means of LECO CHNS-932 Elemental Analyzer. Copies of original data can be provided upon requisite.



Scheme 3.



Scheme 4.

3.2. Synthesis of acetic 2-cyanoacetic anhydride 6

A mixture of acetic anhydride (1.02 g, 10.0 mmol) and (0.85 g, 10.0 mmol) of cyanoacetic acid was dissolved in 25 mL dry xylene and was refluxed for 15 min. The crude product, so formed, was filtered and the clear filtrate was used after cooling as cyanoacetylating agent for aromatic systems in the presence of a catalytic amount (10 wt %) of $InCl_3$ as Lewis acid.

3.3. Reaction of 6 with each of *N,N*-dimethylaniline and anisole

3.3.1. Synthesis of 3-(4-(dimethylamino)phenyl)-3-oxopropanenitrile ***7a***. A mixture of pre-prepared acetic 2-cyanoacetic anhydride **6** (1.27 g, 10.0 mmol), (1.21 g, 10.0 mmol) of *N,N*-dimethylaniline, and (0.12 g, 10 wt %) of indium trichloride in 25 mL dry xylene was refluxed for 3 h. The solid product was collected by filtration, washed with water, and recrystallized from ethanol.

This compound was obtained as dark brown solid (80%) (mp 164–165 °C); IR (KBr): ν=2180 (CN), 1705 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=3.03 (s, 6H, two CH_3), 4.54 (s, 2H, CH_2), 6.73 (d, 2H, J=8 Hz), 7.75 (d, 2H, J=8 Hz); ^{13}C NMR (DMSO-d_6): δ=28.2 (CH_2), 39.4 (two CH_3), 117.1 (CN), 119.7, 123.6, 128.9, 136.2 (aromatic carbons), 163.1 (C=O); MS, *m*/*z* (%), 188.1 (M^+, 29), 148.1 (100), 120.1 (27), 77.0 (11). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.11; H, 6.39; N, 14.80.

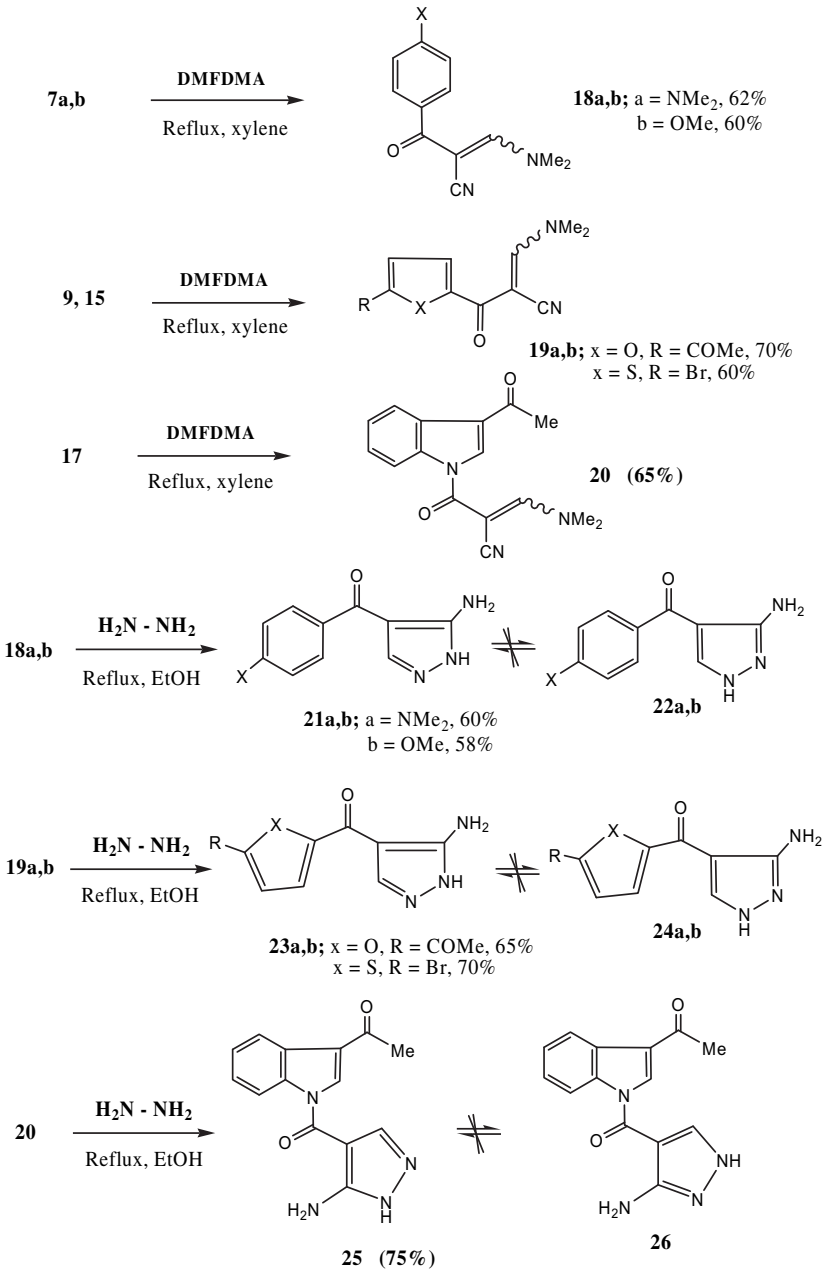
3.3.2. Synthesis of 3-(4-methoxyphenyl)-3-oxopropanenitrile ***7b***. A mixture of pre-filtered acetic 2-cyanoacetic anhydride **6** (1.27 g, 10.0 mmol), (1.08 g, 10.0 mmol) of anisole, and (0.11 g, 10 wt %) of indium trichloride in 25 mL dry xylene in 25 mL of xylene was refluxed for 3 h. The crude solid product was poured over ice-water mixture, then collected by filtration, washed with water, and recrystallized from ethanol.

This compound was obtained as brown solid (70%) (mp 135–136 °C); IR (KBr): ν=2186 (CN), 1710 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=3.71 (s, 2H, CH_2), 3.89 (s, 3H, CH_3), 7.24 (d, 2H, J=8 Hz), 7.66 (d, 2H, J=8 Hz); ^{13}C NMR (DMSO-d_6): δ=24.8 (CH_2), 53.7 (CH_3), 118.4 (CN), 118.9, 120.6, 127.1, 135.6 (aromatic carbons), 160.8 (C=O); MS, *m*/*z* (%), 175.1 (M^+, 4), 150.1 (35), 135.0 (100), 77.1 (38). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.49; H, 5.14; N, 7.94.

3.4. Reaction of 6 with 2-acetylfuran

A mixture of pre-prepared acetic 2-cyanoacetic anhydride **6** (1.27 g, 10.0 mmol), (1.10 g, 10.0 mmol) of 2-acetylfuran, and (0.11 g, 10 wt %) of indium trichloride in 25 mL dry xylene was refluxed for 3 h. The crude solid product was collected by filtration, washed with water, and was then recrystallized from ethanol to yield **9**. The experiment was then repeated with excess amount of **6** (using 1:2 ratio) and the product was triturated by the same above described way to yield **10**.

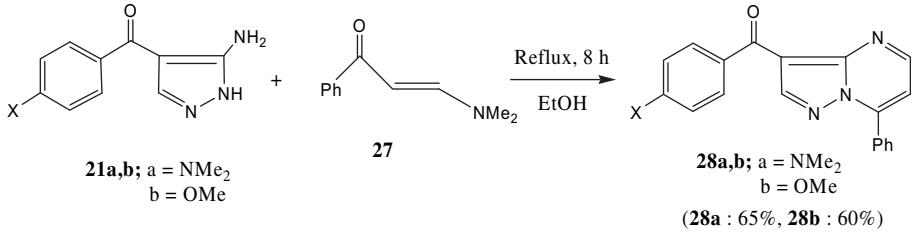
3.4.1. 3-(5-Acetylfuran-2-yl)-3-oxopropanenitrile ***9***. This compound was obtained as dark brown solid (68%) (mp 61–62 °C); IR (KBr): ν=2184 (CN), 1705 and 1708 (two C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=2.54 (s, 3H, CH_3), 3.51 (s, 2H, CH_2), 7.40 (d, 1H, J=8 Hz), 7.50 (d,



Scheme 5.

1H, J=8 Hz); ^{13}C NMR (DMSO-d_6): δ=26.7 (CH_3), 117.6 (CN), 125.1, 125.4, 150.8, 152.3 (furan carbons), 173.6176.7 (C=O); MS, m/z (%), 177.1 (M^+, 98), 162.1 (24), 137.1 (100), 134.1 (68). Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.98; H, 3.97; N, 7.80.

3.4.2. 2-(5-Acetylfuran-2-yl)-6-amino-4-oxo-4H-pyran-3-carbonitrile ***10***. This compound was obtained as brown solid (70%) (mp 83–84 °C); IR (KBr): ν=3350 (br. NH_2), 2188 (CN), 1700 and 1705 (two C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.09 (s, 3H, CH_3), 5.67 (s, 2H, NH_2), 5.96 (s, 1H, pyran H), 7.26 (d, 1H, J=8 Hz), 7.92 (d, 1H, J=8 Hz); ^{13}C NMR (DMSO-d_6): δ=24.8 (CH_3), 89.7, 90.4 (pyran C-3 and C-5), 118.2 (CN), 119.3, 121.6 (furan C-3 and C-4), 147.1, 152.4 (furan C-2 and C-5), 158.2, 160.8 (pyran C-2 and C-6), 183.5, 184.8 (two C=O); MS, m/z (%), 244.1 (M^+, 4), 229.1 (28), 201.1 (65), 109.0 (100). Anal.



Scheme 6.

Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 58.94; H, 3.27; N, 11.43.

3.5. Reaction of 6 with 2-bromothiophene

A mixture of pre-prepared acetic 2-cyanoacetic anhydride **6** (1.27 g, 10.0 mmol), (2.05 g, 10.0 mmol) of 2-bromothiophene, and (0.20 g, 10 wt %) of indium trichloride in 25 mL dry xylene was refluxed for 3 h. The crude solid product was collected by filtration, washed with water, and was then recrystallized from ethanol to yield **12**.

*3.5.1. 1-(5-Bromothiophen-2-yl)ethanone **12**.* This compound was obtained as pale green solid (85%) (mp 91–92 °C); IR (KBr): ν=1710 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=2.61 (s, 3H, CH_3), 6.78 (d, 1H, J=8 Hz), 7.71 (d, 1H, J=8 Hz); ^{13}C NMR (DMSO-d_6): δ=24.7 (CH_3), 119.7, 123.6, 128.9, 131.2 (thiophene carbons), 184.2 (C=O); MS, m/z (%), 205.9 (M^+, 76), 188.9 (100), 82 (38). Anal. Calcd for C_6H_5BrOS: C, 35.14; H, 2.46; Br, 38.96; S, 15.64. Found: C, 35.09; H, 2.40; Br, 38.91; S, 15.59.

3.6. Reaction of 12 with DMFDMA

A mixture of **12** (2.06 g, 10 mmol) and (DMFDMA) (15 mmol) was dissolved in 50 mL dry xylene and the reaction was refluxed while the reaction was followed by TLC to completion. The reaction mixture was concentrated under reduced pressure, cooled and the solid product, so formed, was then filtered and recrystallized from ethanol.

*3.6.1. 1-(5-Bromothiophen-2-yl)-3-(dimethylamino)prop-2-en-1-one **13**.* This compound was obtained as pale green crystals (74%) (mp 121–123 °C); IR (KBr): ν=1696 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=2.91 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 5.72 (d, 1H, J=14 Hz), 7.26 (d, 1H, J=8 Hz), 7.61 (d, 1H, J=8 Hz), 7.66 (d, 1H, J=14 Hz); ^{13}C NMR (DMSO-d_6): δ=42.6 (two CH_3, enamine), 96.8 (CH, enamine), 123.1, 125.7, 129.1, 133.6 (thiophene carbons), 148.4 (CH enamine), 174.2 (C=O); MS, m/z (%), 261.1 (M^+, 58), 244.1 (50), 180.1 (100), 98.0 (86). Anal. Calcd for $C_9H_{10}BrNOS$: C, 41.55; H, 3.87; Br, 30.71; N, 5.38; S, 12.33. Found: C, 41.51; H, 3.83; Br, 30.68; N, 5.32; S, 12.29.

3.7. Reaction of 13 with hydroxylamine hydrochloride

A mixture of **13** (2.61 g, 10 mmol), hydroxylamine hydrochloride (0.69 g, 10 mmol), and sodium acetate anhydrous (3 g) in ethanol (25 mL) was heated under reflux for 5 h. The reaction mixture was poured on water while a solid product was formed. The solid product, so formed, was then collected by filtration and recrystallized from ethanol to give **14**.

*3.7.1. 1-(5-Bromothiophen-2-yl)-3-(hydroxyamino)prop-2-en-1-one **14**.* This compound was obtained as pale yellow powder (60%) (170–171 °C); IR (KBr): ν=1690 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=2.71 (d, 2H, CH_2, J=6 Hz), 6.52 (d, 1H, thiophene H, J=8 Hz), 6.86 (t, 1H, J=6 Hz), 7.44 (d, 1H, thiophene H, J=8 Hz), 9.61 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ=92.1 (enamine CH), 119.7, 126.7, 132.6, 138.2 (thiophene carbons), 154.3 (enamine CH) 176.4 (C=O); MS, m/z (%), 248.0 (M^+, 3), 190.0 (100), 162.0 (43). Anal. Calcd for $C_7H_6BrNO_2S$: C, 33.89; H, 2.44; Br, 32.21; N, 5.65; S, 12.92. Found: C, 33.85; H, 2.40; Br, 32.18; N, 5.61; S, 12.89.

3.8. Reaction of 14 with diethyl oxalate and NaOH

A mixture of **14** (2.48 g, 10 mmol), diethyl oxalate (2.61 g, 15 mmol), and sodium hydroxide (1 g) in absolute ethanol (25 mL) was heated under reflux for 4 h. The reaction mixture was poured on water and neutralized with hydrochloric acid. The crude solid product, so formed, was then collected by filtration and recrystallized from ethanol to give **15**.

*3.8.1. 3-(5-Bromothiophen-2-yl)-3-oxopropanenitrile **15**.* This compound was obtained as pale brown solid (60%) (148–149 °C); IR (KBr): ν=2188 (CN), 1708 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=3.74 (s, 2H, CH_2), 7.12 (d, 1H, J=8 Hz), 7.67 (d, 1H, J=8 Hz); ^{13}C NMR (DMSO-d_6): δ=27.8 (CH_2), 116.9 (CN), 124.8, 133.2, 135.9, 143.7 (thiophene carbons), 183.1 (C=O); MS, m/z (%), 230.1 (M^+, 11), 190.1 (100), 68.1 (62). Anal. Calcd for C_7H_4BrNOS: C, 36.54; H, 1.75; Br, 34.73; N, 6.09; S, 13.94. Found: C, 36.49; H, 1.70; Br, 34.68; N, 5.96; S, 13.89.

3.9. Reaction of 6 with 3-acetylindole 16

A mixture of acetic 2-cyanoacetic anhydride **6** (1.27 g, 10.0 mmol), (1.59 g, 10.0 mmol) of 3-acetylindole, and (0.16 g, 10 wt %) of indium trichloride in 25 mL dry xylene was refluxed for 3 h. The crude solid product was collected by filtration, washed with water, and was then carefully recrystallized from absolute ethanol to yield **17**.

*3.9.1. 3-(3-Acetyl-1H-indol-1-yl)-3-oxopropanenitrile **17**.* This compound was obtained as dark brown solid (78%) (mp 160–161 °C); IR (KBr): ν=2182 (CN), 1690 and 1695 (two C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=2.74 (s, 3H, CH_3), 3.89 (s, 2H, CH_2), 7.25 (m, 4H, benzene), 7.84 (s, 1H, pyrrole CH); ^{13}C NMR (DMSO-d_6): δ=22.4 (CH_2), 31.4 (CH_3), 116.7 (CN), 116.5, 119.7, 123.6, 128.9, 133.2, 138.7, 143.1 (aromatic carbons), 193.8 (C=O); MS, m/z (%), 226.1 (M^+, 20), 159.1 (26), 144.1 (100), 116.1 (15). Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.98; H, 4.42; N, 12.32.

3.10. Reaction of DMFDMA with each of 7a,b, 9, 15 or 17

A mixture of each **7a**,**b**, **9**, **15**, and **17** (10 mmol) and DMFDMA (15 mmol) was dissolved in 50 mL dry xylene and the reaction was refluxed while the reaction was followed by TLC to completion. The reaction mixture was concentrated under reduced pressure, cooled and the solid product, so formed, was then filtered and recrystallized from ethanol.

*3.10.1. 3-(Dimethylamino)-2-(4-(dimethylamino)benzoyl)acrylonitrile **18a**.* This compound was obtained as pale brown powder (62%) (mp 205–206 °C); IR (KBr): ν=2180 (CN), 1692 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=2.76 (s, 6H, two CH_3), 2.92 (s, 6H, two CH_3), 7.18 (d, 1H, J=8 Hz), 7.84 (d, 1H, J=8 Hz), 8.28 (s, 1H, enamine H); ^{13}C NMR (DMSO-d_6): δ=38.7 (two CH_3, dimethylamino), 39.6 (two CH_3, enamine), 88.6 (C, enamine), 116.2 (2,6-CH, benzene ring), 117.6 (CN), 122.1, 127.1, 135.6 (aromatic carbons), 138.3 (CH, enamine), 172.9 (C=O); MS, m/z (%), 243.1 (M^+, 14), 148.1 (100), 120.1 (34). Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.06; H, 6.98; N, 17.21.

*3.10.2. 3-(Dimethylamino)-2-(4-methoxybenzoyl)acrylonitrile **18b**.* This compound was obtained as brown powder (60%) (mp 127–128 °C); IR (KBr): ν=1696 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ=2.53 (s, 6H, two CH_3), 3.88 (s, 3H, CH_3), 7.31 (d, 2H, J=8 Hz), 7.87 (d, 2H, J=8 Hz); 8.70 (s, 1H, enamine H); ^{13}C NMR (DMSO-d_6): δ=41.1 (two CH_3, enamine), 59.8 (CH_3, anisole), 78.6 (C, enamine), 115.8 (2,6-C, anisole), 117.7 (CN), 128.6, 134.5 (anisole carbons), 155.6 (CH, enamine), 158.6 (C-1, anisole), 180.3 (C=O); MS, m/z (%), 230.1 (M^+, 66), 135.1 (100), 107.1 (23). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.76; H, 6.09; N, 12.04.

*3.10.3. 2-(5-Acetylfuran-2-carbonyl)-3-(dimethylamino)acrylonitrile **19a**.* This compound was obtained as brown powder (70%) (mp 98–91 °C); IR (KBr): ν=2184 (CN), 1696 and 1700 (two C=O) cm^{-1}; ^1H

NMR (DMSO-d_6): δ=2.39 (s, 3H, CH_3), 2.92 (s, 3H, enamine CH_3), 3.09 (s, 3H, enamine CH_3), 7.12 (d, 1H, J=8 Hz), 7.42 (d, 1H, J=8 Hz), 7.26 (s, 1H, enamine H); ^{13}C NMR (DMSO-d_6): δ=24.9 (CH_3), 43.2 (two CH_3, enamine), 84.8 (C, enamine), 116.7 (CN), 127.1 (C-3,4, furan), 154.1, 155.2 (C-2,5, furan), 155.4 (CH, enamine), 179.8 (C=O); MS, m/z (%), 232.1 (M^+, 8), 217.1 (62), 189.1 (100). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.97; H, 5.20; N, 11.95.

3.10.4. 2-(5-Bromothiophene-2-carbonyl)-3-(dimethylamino)acrylonitrile ***19b***. This compound was obtained as pale brown powder (60%) (mp 144–146 °C); IR (KBr): ν=2185 (CN), 1700 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.91 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 7.06 (d, 1H, J=8 Hz), 7.79 (d, 1H, J=8 Hz); 8.42 (s, 1H, enamine H); ^{13}C NMR (DMSO-d_6): δ=42.7 (two CH_3, enamine), 81.4 (C, enamine), 117.6 (CN), 122.3, 125.0, 128.1, 131.2 (thiophene carbons), 156.7 (CH, enamine), 181.6 (C=O); MS, m/z (%), 286.0 (M^+, 24), 190.0 (100), 123.0 (51). Anal. Calcd for $C_{10}H_9BrN_2OS$: C, 42.12; H, 3.18; Br, 28.02; N, 9.82; S, 11.24. Found: C, 41.51; H, 3.12; Br, 27.92; N, 9.78; S, 11.21.

3.10.5. 2-(3-Acetyl-1H-indole-1-carbonyl)-3-(dimethylamino)acrylonitrile ***20***. This compound was obtained as pale yellow powder (65%) (mp 133–135 °C); IR (KBr): ν=2182 (CN), 1700 and 1693 (two C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.69 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 7.12 (m, 4H, benzene), 7.87 (s, 1H, pyrrole H H); 8.76 (s, 1H, enamine H); ^{13}C NMR (DMSO-d_6): δ=26.2 (CH_3), 40.8 (two CH_3, enamine), 92.1 (C, enamine), 113.6 (CH, benzene), 116.7 (CN), 118.9, 120.6, 124.1, 126.5, 128.3 (aromatic carbons), 162.7 (CH, enamine), 183.7 (N–C=O), 191.8 (C=O, acetyl); MS, m/z (%), 281.1 (M^+, 16), 238.1 (35), 186.1 (100). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.27; H, 5.31; N, 14.72.

3.11. Reaction of 18a,b, 19a,b, and 20 with hydrazine hydrate

A mixture of enamine **18a**,**b**, **19a**,**b**, and **20** (10 mmol) and hydrazine hydrate (10 mmol) was dissolved in 50 mL absolute ethanol and then refluxed for 6 h. The reaction mixture was cooled and the solid product, so formed, was then collected by filtration and recrystallized from ethanol.

3.11.1. (5-Amino-1H-pyrazol-4-yl)(4-(dimethylamino)phenyl)methanone ***21a***. This compound was obtained as dark brown powder (60%) (mp 241–242 °C); IR (KBr): ν=3340 (NH_2), 1688 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.89 (s, 6H, two CH_3), 3.50 (s, 2H, NH_2), 7.16 (d, 2H, J=8 Hz), 7.78 (d, 2H, J=8 Hz), 7.84 (s, 1H, pyrazole CH), 9.39 (s, 1H, pyrazole NH); ^{13}C NMR (DMSO-d_6): δ=43.1 (two CH_3), 97.5 (C-4, pyrazole), 114.4 (C-2,6, benzene), 123.9, 131.6, 156.3 (benzene carbons), 146.7 (C-3, pyrazole), 155.6 (C-5, pyrazole), 187.2 (C=O); MS, m/z (%), 230.1 (M^+, 11), 148.1 (100), 110.1 (63). Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.53; H, 6.09; N, 24.29.

3.11.2. (5-Amino-1H-pyrazol-4-yl)(4-methoxyphenyl)methanone ***21b***. This compound was obtained as dark brown powder (58%) (mp 172–173 °C); IR (KBr): ν=3350 (NH_2), 1690 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=3.74 (s, 3H, CH_3), 5.63 (s, 2H, NH_2), 7.21 (d, 2H, J=8 Hz), 7.69 (d, 2H, J=8 Hz), 7.86 (s, 1H, pyrazole CH), 11.83 (s, 1H, pyrazole NH); ^{13}C NMR (DMSO-d_6): δ=52.4 (CH_3, anisole), 89.6 (C-4, pyrazole), 115.7, 124.6, 128.4 (anisole carbons), 148.3 (C-3, pyrazole), 152.8 (C-5, pyrazole), 159.8 (C-1, anisole), 186.1 (C=O); MS, m/z (%), 135.1 (M^+, 100), 110.1 (48). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.79; H, 5.09; N, 19.26.

3.11.3. 1-(5-(5-Amino-1H-pyrazole-4-carbonyl)furan-2-yl)ethanone ***23a***. This compound was obtained as dark brown powder (65%) (mp 93–94 °C); IR (KBr): ν=3350 (NH_2), 1700 and 1686 (two C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.71 (s, 3H, CH_3), 5.31 (s, 2H, NH_2), 7.18 (d, 2H, J=8 Hz), 7.40 (d, 2H, J=8 Hz), 7.62 (s, 1H, pyrazole CH), 9.87 (s, 1H, pyrazole NH); ^{13}C NMR (DMSO-d_6): δ=25.2 (CH_3), 91.3 (C-4, pyrazole), 123.8, 124.1 (C-3,4, furan), 141.3 (C-3, pyrazole), 145.9 (C-5, pyrazole), 148.7, 148.9 (C-2,5, furan), 167.5 (C=O), 176.8 (C=O, acetyl); MS, m/z (%), 219.1 (M^+, 6), 176.1 (63), 137.1 (100). Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.72; H, 4.09; N, 18.98.

3.11.4. (5-Amino-1H-pyrazol-4-yl)(5-bromothiophen-2-yl)methanone ***23b***. This compound was obtained as pale brown powder (70%) (mp 182–183 °C); IR (KBr): ν=3330 (NH_2), 1688 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=5.70 (s, 2H, NH_2), 6.66 (d, 2H, J=8 Hz), 7.60 (d, 2H, J=8 Hz), 7.74 (s, 1H, pyrazole CH), 9.21 (s, 1H, pyrazole NH); ^{13}C NMR (DMSO-d_6): δ=87.7 (C-4, pyrazole), 120.4 (C, C–Br), 132.9, 136.7, 144.2 (thiophene carbons), 137.8 (C-3, pyrazole), 148.3 (C-5, pyrazole), 173.8 (C=O); MS, m/z (%), 272.1 (M^+, 100), 190.1 (77), 110 (35). Anal. Calcd for $C_8H_6BrN_3OS$: C, 35.31; H, 2.22; Br, 29.36; N, 15.44; S, 11.78. Found: C, 35.27; H, 2.17; Br, 29.29; N, 15.36; S, 11.71.

3.11.5. 1-(2-(5-Amino-1H-pyrazole-4-carbonyl)-1H-indol-3-yl)ethanone ***25***. This compound was obtained as pale brown powder (75%) (mp 174–176 °C); IR (KBr): ν=3340 (NH_2), 1694 and 1688 (two C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.39 (s, 3H, CH_3), 4.85 (s, 2H, NH_2), 7.31 (m, 4H, benzene), 7.89 (s, 1H, pyrazole CH), 11.87 (s, 1H, pyrazole NH); ^{13}C NMR (DMSO-d_6): δ=26.4 (CH_3), 88.6 (C-4, pyrazole), 113.1, 116.9, 120.6, 122.6, 127.1, 128.5, 135.6, 144.8, 151.6 (aromatic carbons), 177.3 (C=O), 187.4 (C=O, acetyl); MS, m/z (%), 268.1 (M^+, 8), 186.1 (100), 110.1 (39). Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.61; H, 4.47; N, 20.81.

3.12. Reaction of 21a,b with enaminone

A mixture of **21a**,**b** (10 mmol) and enaminone **23** (10 mmol) was dissolved in 50 mL absolute ethanol and then refluxed for 8 h. The reaction mixture was cooled and the solid product, so formed, was then collected by filtration and recrystallized from ethanol.

3.12.1. (4-(Dimethylamino)phenyl)(7-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methanone ***28a***. This compound was obtained as dark brown powder (65%) (mp 216–217 °C); IR (KBr): ν=1698 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.69 (s, 6H, two CH_3), 7.16 (m, 12H, aromatic); ^{13}C NMR (DMSO-d_6): δ=41.7 (two CH_3), 109.8, 113.9, 118.9, 120.6, 127.1, 128.3, 135.6, 142.7, 153.4 (aromatic carbons), 187.1 (C=O); MS, m/z (%), 344.0 (M^+, 3), 224.1 (73), 77.1 (100). Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.62; H, 5.22; N, 16.28.

3.12.2. (4-Methoxyphenyl)(7-phenylpyrazolo[1,5-a]pyrimidin-3-yl)-methanone ***28b***. This compound was obtained as dark brown powder (60%) (mp 164–165 °C); IR (KBr): ν=1695 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=3.67 (s, 3H, CH_3), 7.21 (m, 12H, aromatic); ^{13}C NMR (DMSO-d_6): δ=58.6 (CH_3), 111.6, 114.7, 116.9, 118.9, 122.1, 125.1, 135.6, 146.8 (aromatic carbons), 184.2 (C=O); MS, m/z (%), 329.1 (M^+, 18), 222.1 (78), 135.1 (100), 77 (80). Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.89; H, 4.55; N, 12.68.

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Supplementary data

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