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Efficient one pot synthesis of triazolotriazine, pyrazolotriazine, triazole, isoxazole and pyrazole derivatives

Abstract: 3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (**1**) was used as a starting material for synthesis of functionalized heterocyclic derivatives mentioned in the title.

Keywords: 4-arylhydrazono-2,3-dihydroisoxazolone; 3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile; pyrazolotriazine; 1,2,3-triazole; triazolopyrimidine; triazolotriazine.

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Introduction

Cyanoacetyl derivatives are versatile and highly reactive reagents in the synthesis of various heterocyclic compounds (Zayed et al., 1985; Ahmed et al., 1996; Elgemeie et al., 2004; Said et al., 2006; Samir et al., 2011), such as pyrazoles (Badawy et al., 1990; Daidone et al., 1998; Finn et al., 2003; Ma et al., 2010), triazoles (Wamhoff, 1984; Kadaba, 1988; Katritzky et al., 1994; El Sayed and Khodairy, 1998a,b; Zhu et al., 2000; Khodairy, 2001) and triazines (Bork et al., 2003; Khersonsky and Chang, 2004). In continuation of our efforts directed towards the application of simple and efficient procedures for the synthesis of heterocyclic compounds (Abd El Latif et al., 2002; El Rady et al., 2004, 2006, 2008), we wish to report the results of our investigation on the chemistry of 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (**1**).

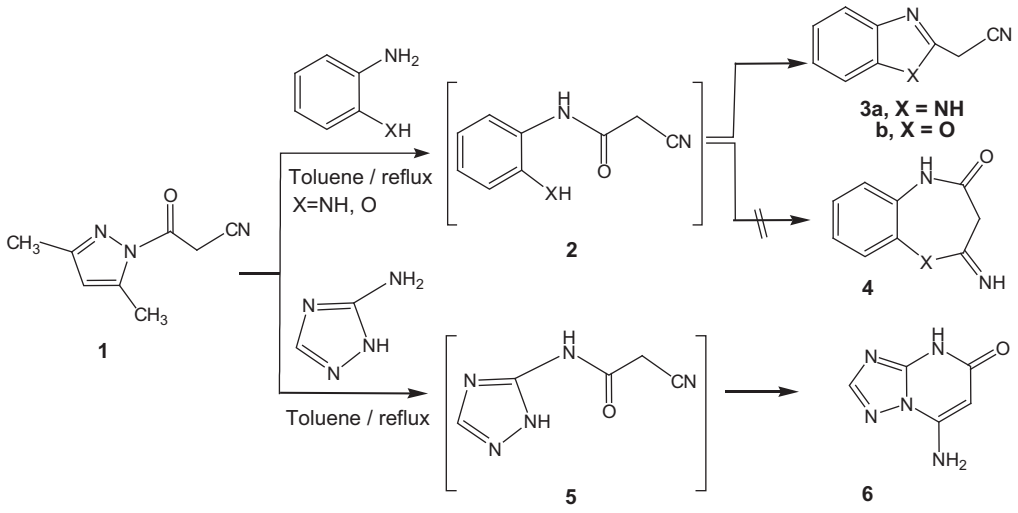
Results and discussion

The reaction of 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (**1**) with 2-phenylenediamine, 2-aminophenol and 5-amino-1,2,4-triazole in refluxing toluene results in the displacement of the 3,5-dimethylpyrazole moiety from substrate 1 to give known benzimidazol-2-yl-acetonitrile (**3a**), benzoxazol-2-yl-acetonitrile (**3b**) (Khalafalh et al., 1995) and 7-amino-[1,2,4]triazolo[1,5-*a*]pyrimidine-5(4*H*)-one (**6**) (Levin et al., 1964; Tenor and Kroeger, 1964), respectively, as shown in Scheme 1. The structure of the reaction products were confirmed based on spectral and analytical data and comparison with the authentic samples (**3a,b** and **6**). It can be suggested that compounds **3a,b** are formed via aminolysis reaction of compound **1** followed by cyclization of the resultant intermediate product **2**. Compound **4** would be expected to form via cycloaddition of **2**, which was not the case. Product **6** is formed through the intermediary of **5** which undergoes cyclization in the last step. The IR spectrum of compound **6** shows intense bands at 1710, 3210 and 3440 cm^{-1} due to carbonyl, imino and amino groups, respectively. The ^1H NMR spectrum of **6** shows singlets at δ 2.59, 7.31, 7.53 and 8.39 ppm due to amino, pyrimidine, triazole and imino protons, respectively. The mass spectrum of **6** shows a molecular ion peak at m/z 151.

By contrast, reactions of **1** with 5-amino-[1,2,4]triazole and 5-amino-3-phenylpyrazole in the presence of sodium nitrite and hydrochloric acid afforded the respective products **8a** and **8b** (Scheme 2). The IR spectra of these compounds show intense bands at 1695–1698 and 3445–3448 cm^{-1} due to carbonyl and amino groups, respectively. The ^1H NMR of **8a** shows a singlet at δ 2.31 for the two methyl groups, a singlet at δ 5.32 for NH_2 and two singlets at δ 7.12 and δ 7.14 ppm due to the two protons of pyrazole and triazole. The mass spectrum of **8a** shows a molecular ion peak at m/z 257.

Direct coupling of the substrate **1** with aryldiazonium chlorides gives the corresponding 2(arylhydrazono)-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile derivatives **9a–f** in good yields. Treatment of **9a–f** with hydrazine hydrate in boiling ethanol containing few drops of piperidine afforded the corresponding products **11a–f** through the intermediary of **10** (Scheme 3). The spectral data for **11** are in full agreement with the proposed structure.

By contrast, the reaction of **9a–f** with hydroxylamine hydrochloride in boiling ethanol/piperidine gave product **13a–f** that crystallized directly from the mixture.



Scheme 1

Related reactions are known (Hafez et al., 1980; Kandeel et al., 1980). The intermediary of **12** can be suggested (Scheme 4).

Interestingly, the reaction of **9a–f** with hydroxylamine hydrochloride in the presence of anhydrous sodium acetate, when conducted under more drastic conditions using boiling DMF, afforded the previously identified compounds **11a–f** (Scheme 5).

The hydrazone **9a** was also allowed to react with hydroxylamine hydrochloride in ethanol in the presence of sodium acetate to give 2-arylhydrazono-3-oxo-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-hydroxypropanamidine (**14**), which was isolated and fully characterized. The treatment of **14** in the presence of anhydrous sodium in DMF under reflux conditions caused cyclization to give **11a**.

Finally, the reaction of **9a** with malononitrile in acetic acid under reflux conditions yielded the unexpected new compound **17** (Scheme 6). It can be suggested that addition of the active methylene moiety of malononitrile to the cyano function of **9a** generates the intermediate product **15** which undergoes intramolecular cyclization to generate another intermediate product **16** which is the final precursor to **17**.

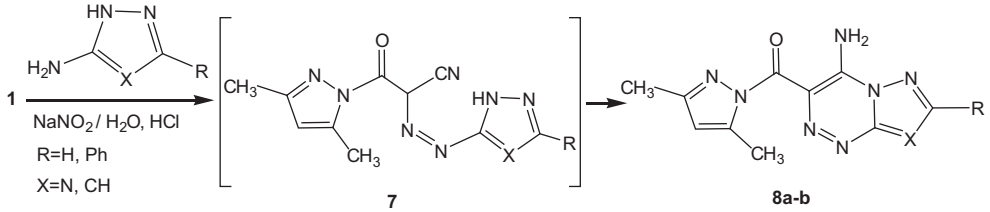
Experimental

General

Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded using potassium bromide pellets on a FTIR unit Bruker-vector 22 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained at 300 MHz and 75 MHz, respectively, on a Varian Gemini NMR spectrometer. Electron-impact mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer at 70 eV. Elemental analysis was carried out at the Micro Analytical Center of Cairo University, Egypt. Microbial assay using bacteria and fungi was performed in the Environment Studies Microbiology Laboratory, South Valley University, Faculty of Science, Aswan, Egypt.

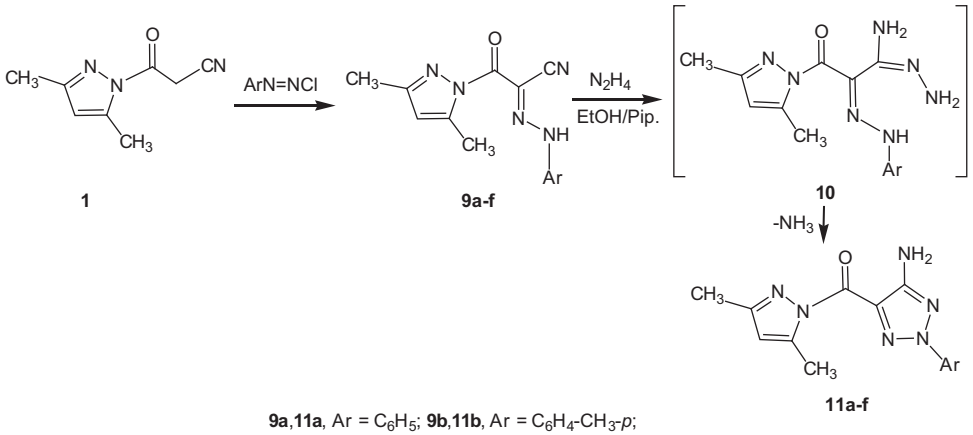
General procedure for compounds 3a and 3b

A mixture of **1** (0.16 g, 1 mmol), 2-phenylenediamine (0.10 g, 1 mmol) or 2-aminophenol (0.10 g, 1 mmol) in 20 mL of dry toluene was heated under reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol. The resulting solid product was collected by filtration and crystallized from ethanol.



8a, X = N, R = H; **8b**, X = CH, R = Ph

Scheme 2



9a,**11a**, Ar = C_6H_5; **9b**,**11b**, Ar = C_6H_4-CH_3-*p*;
9c,**11c**, Ar = C_6H_4-OCH_3-*p*; **9d**,**11d**, Ar = C_6H_4-NO_2-*p*;
9e,**11e**, Ar = C_6H_4-Cl-*p*; **9f**,**11f**, Ar = C_6H_4-Br-*p*

Scheme 3

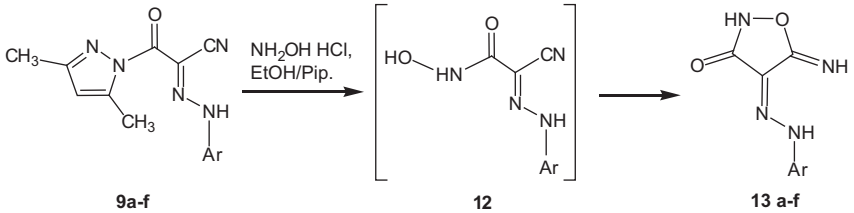
Benzimidazol-2-yl-acetonitrile (3a) Mp 200–205°C (lit. mp 212–216°C, Khalafalh et al., 1995); MS: m/z 157 (M^+). Anal. Calcd for $C_9H_7N_3$ (157.17): C, 68.78; H, 4.49; N, 26.74. Found: C, 68.78; H, 4.56; N, 26.86.

Benzoxazol-2-yl-acetonitrile (3b) Mp >300°C (lit. mp 310°C, Khalafalh et al., 1995); MS: m/z 158 (M^+). Anal. Calcd for $C_9H_6N_2O$ (158.16): C, 68.35; H, 3.82; N, 17.71. Found: 68.44; H, 3.95; N, 17.91.

7-Amino-[1,2,4]triazolo[1, 5-*a*]pyrimidine-5(4*H*)-one (6) A mixture of **1** (0.16 g, 1 mmol), 5-amino-1,2,4-triazole (0.09 g, 1 mmol) in 20 mL of dry toluene was heated under reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol. The resulting solid product was collected by filtration and crystallized from DMF/H_2O; pale yellow powder; yield 0.10 g (65%); mp >300°C (lit. mp 330°C, Tenor and Kroeger, 1964); IR: ν_{max} 1710 (CO), 3210 (NH), 3440 cm^{-1} (NH_2); ^{1}H NMR ($CDCl_3$): δ 2.59 (s, 2H, NH_2), 7.31 (s, H, CH-pyrimidine), 7.53 (s, 1H, CH-triazole), 8.39 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 85.2 (C-6), 130.1 (C-3a), 135.3 (C-2), 145.2 (C-7), 165.3 (C-5); MS: m/z 151 (M^+, 20). Anal. Calcd for $C_5H_5N_5O$ (151.13): C, 39.74; H, 3.33; N, 46.34. Found: C, 39.85; H, 3.45; N, 46.46.

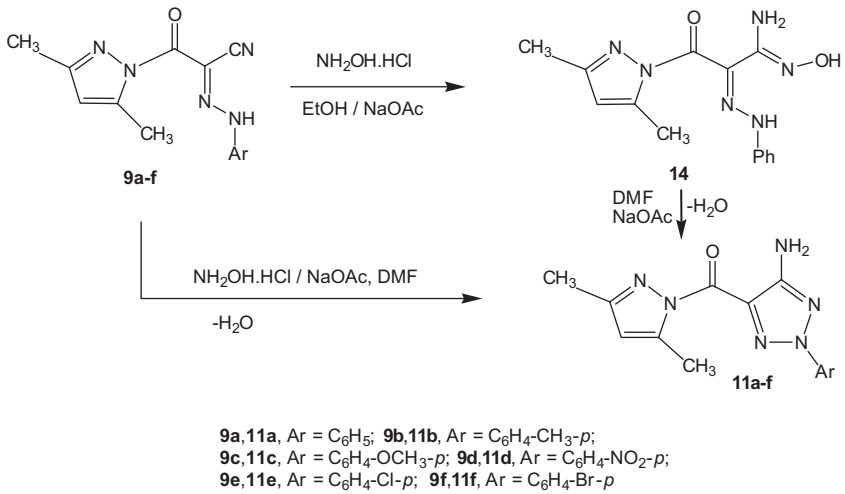
(4-Amino-[1,2,4]triazolo[5,1-c][1,2,4]triazin-3-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (8a) A solution of sodium nitrite (0.69 g, 1 mmol) in cold water (15 mL) was added dropwise during a period of 15 min to a mixture of 5-amino-[1,2,4]triazole (0.88 g, 1 mmol), ethanol (10 mL) and concentrated hydrochloric acid (3 mL). Then this mixture was added to 10 mL of a well-stirred cold ethanol solution of compound **1** (1.6 g, 1 mmol) and 2 g of anhydrous sodium acetate. The mixture was left overnight at room temperature. The precipitated solid product was collected by filtration, washed with water and crystallized from methanol; pale yellow powder, yield 0.09 g (60%); mp 195–199°C; IR (ν_{max}, cm^{-1}): 1695 (CO), 3445 (NH_2); ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 6H, 2 CH_3), 5.22 (s, 2H, NH_2), 7.12 (s, 1H, CH-4 pyrazole), 7.14 (s, 1H, CH-6 triazole); ^{13}C NMR ($CDCl_3$): δ 13.2 (CH_3), 110.2 (C-4 pyrazole), 122.4 (C-5 pyrazole), 122.5 (C-3 pyrazole), 129.1 (C-6-triazine), 133.1 (C-8a), 175.2 (CO); MS: m/z 257 (M-1, 16). Anal. Calcd for $C_{10}H_{10}N_8O$ (258.24): C, 46.51; H, 3.90; N, 43.39. Found: C, 46.62; H, 3.99; N, 43.48.

(4-Amino-7-phenylpyrazolo[5,1-c][1,2,4]triazin-3-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl) methanone (8b) The reaction of 5-amino-3-phenyl-pyrazole (1.5 g, 1 mmol) was conducted using the procedure described above; solid buff, yield 0.09 g (58%); mp 180–184°C; IR (ν_{max}, cm^{-1}): 1698 (CO), 3448 (NH_2); ^{1}H NMR ($CDCl_3$): δ ppm 2.52 (s, 6H, 2 CH_3), 5.91 (s, 2H, NH_2), 6.52 (s, 1H, CH-4 pyrazole), 7.72 (s, 1H, CH-8 pyrazole); ^{13}C NMR ($CDCl_3$): δ 13.2 (CH_3), 95.5 (C-8), 103.2 (C-4 pyrazole), 122.4 (C-3 pyrazole), 122.5 (C-5 pyrazole), 127.3, 128.3, 129.3, 133.6 (Ph), 143.1 (C-3-triazine), 144.1 (C-4-triazine), 147.1 (C-7), 150.2 (C-8a),



9a,**13a**, Ar = C_6H_5; **9b**,**13b**, Ar = C_6H_4-CH_3-*p*;
9c,**13c**, Ar = C_6H_4-OCH_3-*p*; **9d**,**13d**, Ar = C_6H_4-NO_2-*p*;
9e,**13e**, Ar = C_6H_4-Cl-*p*; **9f**,**13f**, Ar = C_6H_4-Br-*p*

Scheme 4



9a,**11a**, Ar = C_6H_5; **9b**,**11b**, Ar = C_6H_4-CH_3-*p*;
9c,**11c**, Ar = C_6H_4-OCH_3-*p*; **9d**,**11d**, Ar = C_6H_4-NO_2-*p*;
9e,**11e**, Ar = C_6H_4-Cl-*p*; **9f**,**11f**, Ar = C_6H_4-Br-*p*

Scheme 5

175.4 (CO); MS: m/z 333 (M^+, 30). Anal. Calcd for $C_{17}H_{15}N_7O$ (333.36): C, 61.25; H, 4.54; N, 29.41. Found: C, 61.32; H, 4.65; N, 29.54.

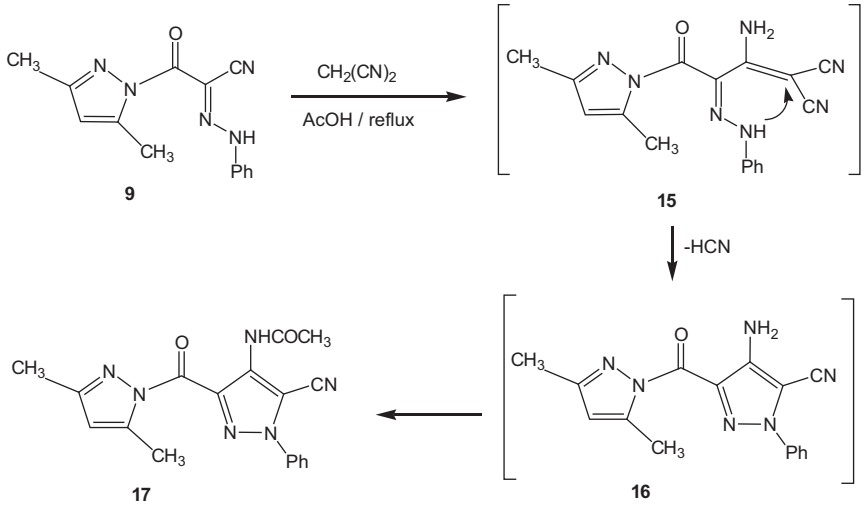
General procedure for synthesis of compounds 9a–f

To a solution of aromatic amine (1 mmol) in a mixture of 10 mL of ethanol and 3 mL of concentrated hydrochloric acid, sodium nitrite (0.69 g, 1 mmol) in 15 mL of ice water was added dropwise during a period of 15 min. The resulting solution was added to 10 mL of a well-stirred cold ethanol solution of compound **1** (1.6 g, 1 mmol) and anhydrous sodium acetate (2 g). The mixture was left overnight at room temperature. The solid product **9a–f** was collected by filtration, washed with water and crystallized from ethanol.

2-Phenylhydrazono-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (9a) Deep yellow powder; yield 0.11 g (73%); mp 120–124°C; IR (ν_{max}, cm^{-1}): 1698 (CO), 2215 (CN), 3120 (NH); ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 6H, 2 CH_3), 7.18 (s, 1H, pyrazole), 7.20–7.69 (m, 5H, Ar-H), 7.70 (s, 1H, NH); MS: m/z 267 (M^+, 30). Anal. Calcd for $C_{14}H_{13}N_5O$ (267.29): C, 62.91; H, 4.90; N, 26.20. Found: C, 62.99; H, 5.12; N, 26.33.

2-(*p*-Methylphenylhydrazono)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (9b) Yellow powder; yield 0.11 g (70%); mp 125–129°C; IR (ν_{max}, cm^{-1}): 1700 (CO), 2210 (CN), 3122 (NH); ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 6H, 2 CH_3), 3.11 (s, 3H, CH_3), 6.44 (d, 2H, *J*=6 Hz), 7.19 (s, 1H, pyrazole), 7.32 (d, 2H, *J*=6 Hz), 7.68 (s, 1H, NH); MS: m/z 281 (M^+, 30). Anal. Calcd for $C_{15}H_{15}N_5O$ (281.32): C, 64.04; H, 5.37; N, 24.90. Found: C, 64.22; H, 5.55; N, 24.99.

2-(*p*-Methoxyphenylhydrazono)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (9c) Yellow powder; yield 0.11 g (66%); mp 130–137°C; IR (ν_{max}, cm^{-1}): 1701 (CO), 2210 (CN), 3125 (NH); ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 2.30 (s, 6H, 2 CH_3), 3.31 (s, 3H, OCH_3), 6.42 (d, 2H, *J*=6 Hz), 7.10 (s, 1H, pyrazole), 7.22 (d, 2H, *J*=6 Hz), 7.71 (s, 1H,



Scheme 6

NH); MS: m/z 297 (M^+, 25). Anal. Calcd for $C_{15}H_{15}N_5O_2$ (297.32): C, 60.60; H, 5.09; N, 23.56. Found: C, 60.75; H, 5.23; N, 23.73.

2-(*p*-Nitrophenylhydrazono)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (9d) Orange powder; yield 0.10 g (60%); mp 180–184°C; IR (ν_{max}, cm^{-1}): 1698 (CO), 2205 (CN), 3127 (NH); ^1H NMR ($CDCl_3$): δ ppm 2.61 (s, 6H, 2 CH_3), 6.54 (d, 2H, *J*=6 Hz), 7.20 (s, 1H, pyrazole), 7.22 (d, 2H, *J*=6 Hz), 7.72 (s, 1H, NH); MS: m/z 313 (M+1, 15). Anal. Calcd for $C_{14}H_{12}N_6O_3$ (312.28): C, 53.85; H, 3.87; N, 26.91. Found: C, 53.99; H, 3.99; N, 26.04.

2-(*p*-Chlorophenylhydrazono)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (9e) Brown powder; yield 0.09 g (55%), 0.09 g; mp 150–154°C; IR (ν_{max}, cm^{-1}): 1698 (CO), 2205 (CN), 3128 (NH); ^1H NMR ($CDCl_3$): δ ppm 2.60 (s, 6H, 2 CH_3), 6.21 (d, 2H, *J*=6), 7.18 (s, 1H, pyrazole), 6.98 (d, 2H, *J*=6 Hz), 7.70 (s, 1H, NH); MS: m/z 301 (M^+, 15). Anal. Calcd for $C_{14}H_{12}ClN_5O$ (301.73): C, 55.73; H, 4.01; N, 23.21. Found: C, 55.87; H, 4.32; N, 23.37.

2-(*p*-Bromophenylhydrazono)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile (9f) Yellow powder; yield 0.10 g (60%); mp 190–194°C; IR (ν_{max}, cm^{-1}): 1700 (CO), 2210 (CN), 3128 (NH); ^1H NMR ($CDCl_3$): δ 2.61 (s, 6H, 2 CH_3), 6.54 (d, 2H, *J*=6 Hz), 7.19 (s, 1H, pyrazole), 7.22 (d, 2H, *J*=6 Hz), 7.64 (s, 1H, NH); MS: m/z 347 (M+1, 15). Anal. Calcd for $C_{14}H_{12}BrN_5O$ (346.18): C, 48.57; H, 3.49; N, 20.23. Found: C, 48.65; H, 3.65; N, 20.31.

General procedures for synthesis of (5-amino-2-aryl-2*H*-1,2,3-triazol-4-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanones 11a–f

Method A A mixture of **9a–f** (1 mmol) and hydrazine hydrate (excess) in 20 mL of ethanol containing 0.3 mL of piperidine was heated under reflux for 3 h. The precipitated product was collected by filtration and crystallized from DMF/H_2O.

Method B A mixture of **9a–f** (1 mmol) and hydroxylamine hydrochloride (0.67 g, 1 mmol) in 20 mL of DMF containing 0.3 g of anhydrous sodium acetate was heated under reflux for 8 h. After cooling, the mixture was poured onto ice. The product was collected by filtration, washed several times with cold water and crystallized from DMF/H_2O.

Method C A mixture of **14a** (1 mmol) in 20 mL of DMF containing 0.3 g of anhydrous sodium acetate was heated under reflux for 9 h. After cooling, the mixture was poured onto ice. The product **11a** was collected by filtration, washed several times with cold water and crystallized from DMF/H_2O.

(5-Amino-2-phenyl-2*H*-1,2,3-triazol-4-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (11a) Red crystals; yield 73%; mp 260–264°C; IR (ν_{max}, cm^{-1}): 1669 (CO), 3419 (NH_2); ^1H NMR (DMSO-d_6): δ 2.51 (s, 6H, 2 CH_3), 2.40 (s, 2H, NH_2), 7.15–7.65 (m, 6H, Ar-H + CH-pyrazole); ^{13}C NMR ($CDCl_3$): δ 13.12 (CH_3), 101.23 (C-4 pyrazole), 122.23 (C-5 pyrazole), 122.25 (C-3 pyrazole), 128.2, 129.2, 132.1 (Ph), 140.3 (C-4 triazole), 140.4 (C-5 triazole), 170.1 (CO); MS: m/z 282 (M^+, 30). Anal. Calcd for $C_{14}H_{14}N_6O$ (282.30): C, 59.56; H, 5.00; N, 29.77. Found: C, 59.68; H, 5.12; N, 29.98.

(5-Amino-2-*p*-tolyl-2*H*-1,2,3-triazol-4-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (11b) Red crystals; yield 66%; mp 265–269°C; IR (ν_{max}, cm^{-1}): 1694 (CO), 3420 (NH_2); ^1H NMR (DMSO-d_6): δ 2.55 (s, 6H, 2 CH_3), 2.56 (s, 3H, CH_3), 2.34 (s, 2H, NH_2), 6.44 (d, 2H, *J*=6 Hz), 7.15 (s, 1H, CH-pyrazole), 7.22 (d, 2H, *J*=6 Hz); MS: m/z 296 (M^+, 30). Anal. Calcd for $C_{15}H_{16}N_6O$ (296.33): C, 60.80; H, 5.44; N, 28.36. Found: C, 60.99; H, 5.56; N, 28.47.

(5-Amino-2-(4-methoxyphenyl)-2*H*-1,2,3-triazol-4-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (11c) Yellow powder; yield 0.18 g (60%); mp 250–254°C; IR (ν_{max}, cm^{-1}): 1690 (CO), 3430 (NH_2). ^1H NMR (DMSO-d6): δ 2.66 (s, 6H, 2 CH_3), 2.71 (s, 3H, CH_3), 2.38 (s, 2H, NH_2), 6.12 (d, 2H, *J*=6 Hz), 7.18 (s, 1H, CH-pyrazole), 7.34 (d, 2H, *J*=6 Hz); MS, m/z (%)=312 (M^+, 30). Anal. Calcd for $C_{15}H_{16}N_6O_2$ (312.33): C, 57.68; H, 5.16; N, 26.91. Found: C, 57.77; H, 5.29; N, 26.99.

(5-Amino-2-(4-nitrophenyl)-2*H*-1,2,3-triazol-4-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (11d) Brown powder; yield 0.18 g (60%); mp 230–234°C; IR (ν_{max}, cm^{-1}): 1692 (CO), 3430 (NH_2); ^1H NMR (DMSO-d_6): δ ppm 2.61 (s, 6H, 2 CH_3), 2.48 (s, 2H, NH_2), 6.12 (d, 2H, *J*=6 Hz), 7.22 (s, 1H, CH-pyrazole), 7.44 (d, 2H, *J*=6 Hz); MS: m/z 327 (M^+, 20). Anal. Calcd for $C_{14}H_{13}N_7O_3$ (327.30): C, 51.38; H, 4.00; N, 29.96. Found: C, 51.47; H, 4.12; N, 30.11.

(5-Amino-2-(4-chlorophenyl)-2*H*-1,2,3-triazol-4-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (11e) Brown powder; yield 0.21 g (55%); mp 310–314°C; IR (ν_{max}, cm^{-1}): 1698 (CO), 3435 (NH_2); ^1H NMR (DMSO-d_6): δ 2.62 (s, 6H, 2 CH_3), 2.42 (s, 2H, NH_2), 6.34 (d, 2H, *J*=6 Hz), 7.12 (s, 1H, CH-pyrazole), 7.33 (d, 2H, *J*=6 Hz); MS: m/z 316 (M^+, 40). Anal. Calcd for $C_{14}H_{13}ClN_6O$ (316.75): C, 53.09; H, 4.14; N, 26.53. Found: C, 53.32; H, 4.25; N, 26.76.

(5-Amino-2-(4-bromophenyl)-2*H*-1,2,3-triazol-4-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (11f) Red powder; yield 0.18 g (50%); mp 280–284°C; IR (ν_{max}, cm^{-1}): 1693 (CO), 3440 (NH_2); ^1H NMR (DMSO-d_6): δ 2.71 (s, 6H, 2 CH_3), 2.53 (s, 2H, NH_2), 6.12 (d, 2H, *J*=6 Hz), 7.23 (s, 1H, CH-pyrazole), 7.44 (d, 2H, *J*=6 Hz); MS: m/z 361 (M^+, 25). Anal. Calcd for $C_{14}H_{13}BrN_6O$ (361.20): C, 46.55; H, 3.63; N, 23.27. Found: C, 46.63; H, 3.74; N, 23.35.

General procedure for synthesis of 4-arylhydrazono-5-imino-2,3-dihydroisoxazol-3(2*H*)-ones 13a–f A mixture of **9a–f** (1 mmol), hydroxylamine hydrochloride (1 mmol) and piperidine (0.3 mL) in 20 mL of ethanol was heated under reflux for 3 h. The solid product **13a–f** was collected by filtration and crystallized from DMF/H_2O.

5-Imino-4-phenylhydrazono-2,3-dihydroisoxazol-3(2*H*)-one (13a) Yellow powder; yield 0.18 g (70%); mp 255–259°C (lit. mp 245°C; Hafez et al., 1980; lit. mp 238°C; Kandeel et al., 1980); IR (ν_{max}, cm^{-1}): 1711 (CO), 3293 (NH); ^1H NMR ($CDCl_3$): δ 7.22–7.92 (m, 7H, Ar-H + 2 NH); ^{13}C NMR ($CDCl_3$): δ 77.2 (C-4), (128.1, 128.8, 128.9) (Ph), 145.2 (C-5), 176.2 (CO); MS: m/z 204 (M^+, 25). Anal. Calcd for $C_9H_8N_4O_2$ (204.19): C, 52.94; H, 3.95; N, 27.44. Found: C, 52.99; H, 4.12; N, 27.57.

5-Imino-4-*p*-tolylhydrazono-2,3-dihydroisoxazol-3(2*H*)-one (13b) Orange powder; yield 0.16 g (55%); mp 290–292°C; IR (ν_{max}, cm^{-1}): 1715 (CO), 3294 (NH); ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, CH_3), 6.21 (d, 2H, *J*=6 Hz), 7.33 (s, 2H, 2 NH), 7.44 (d, 2H, *J*=6 Hz); MS: m/z 218 (M^+, 30). Anal. Calcd for $C_{10}H_{10}N_4O_2$ (218.22): C, 55.04; H, 4.62; N, 25.68. Found: C, 55.13; H, 4.71; N, 25.73.

5-Imino-4-*p*-methoxyphenylhydrazono-2,3-dihydroisoxazol-3(2*H*)-one (13c) Red powder; yield 0.15 g (50%); mp 270–274°C; IR (ν_{max}, cm^{-1}): 1712 (CO), 3293 (NH); ^1H NMR ($CDCl_3$): δ 3.20 (s, 3H, OCH_3), 6.11 (d, 2H, *J*=6 Hz), 7.32 (s, 2H, 2 NH), 7.47 (d, 2H, *J*=6 Hz); MS: m/z 234 (M^+, 25). Anal. Calcd for $C_{10}H_{10}N_4O_3$ (234.21): C, 51.28; H, 4.30; N, 23.92. Found: C, 51.36; H, 4.42; N, 23.99.

5-Imino-4-*p*-nitrophenylhydrazono-2,3-dihydroisoxazol-3(2*H*)-one (13d) Golden crystals; yield 60%, 0.18 g; mp 220–224°C; IR (ν_{max}, cm^{-1}): 1711(CO), 3295 (NH); ^1H NMR ($CDCl_3$): δ 6.19 (d, 2H, *J*=6 Hz), 7.24 (s, 2H, 2 NH), 7.38 (d, 2H, *J*=6 Hz); MS, m/z (%)=249 (M^+, 30). Anal. Calcd for $C_9H_7N_5O_4$ (249.19): C, 43.38; H, 2.83; N, 28.11. Found: C, 43.43; H, 2.90; N, 28.23.

5-Imino-4-*p*-chlorophenylhydrazono-2,3-dihydroisoxazol-3(2*H*)-one (13e) Brown powder; yield 52%, 0.15 g; mp 240–244°C; IR (ν_{max}, cm^{-1}): 1710 (CO), 3290 (NH); ^1H NMR ($CDCl_3$): δ 6.24 (d, 2H, *J*=6. Hz), 7.36 (s, 2H, 2 NH), 7.41 (d, 2H, *J*=6 Hz); MS: m/z 238 (M^+, 20). Anal. Calcd for $C_9H_7CLN_4O_2$ (238.63): C, 45.30; H, 2.96; N, 23.48. Found: C, 45.39; H, 2.99; N, 23.56.

5-Imino-4-*p*-bromophenylhydrazono-2,3-dihydroisoxazol-3(2*H*)-one (13f) Red powder; yield 0.18 g (50%); mp 235–239°C; IR (ν_{max}, cm^{-1}): 1711 (CO), 3298 (NH), 3448 (NH_2); ^1H NMR ($CDCl_3$): δ 2.42 (s, 2H, NH_2), 6.27 (d, 2H, *J*=6 Hz), 7.36 (s, 2H, 2 NH), 7.40 (d, 2H, *J*=6 Hz); MS: m/z 283 (M^+, 15). Anal. Calcd for $C_9H_7BrN_4O_2$ (283.08): C, 38.19; H, 2.49; N, 19.79. Found: C, 38.22; H, 2.54; N, 19.84.

2-Phenylhydrazono-3-oxo-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-hydroxy-propanamidine (14) A solution of **9a** (1 mmol), hydroxylamine (0.67 g, 1 mmol) and 0.3 g of anhydrous sodium acetate in 20 mL of ethanol was heated under reflux for 5 h. After cooling, the mixture was poured onto ice. The product **14** was collected by filtration, washed several times with cold water and crystallized from DMF/H_2O; deep yellow powder; yield 0.12 g (45%); mp 160–164°C; IR (ν_{max}, cm^{-1}): 1700 (CO), 3110 (NH), 3450 (NH_2), 3480 (OH); ^1H NMR ($CDCl_3$): δ 2.71 (s, 6H, 2 CH_3), 3.51 (s, 2H, NH_2), 7.31 (s, 1H, pyrazole), 7.33–7.98 (m, 5H, Ar-H + NH), 10.21 (s, 1H, OH); MS: m/z 300 (M^+, 30). Anal. Calcd for $C_{14}H_{16}N_6O_2$ (300.32): C, 55.99; H, 5.37; N, 27.98. Found: C, 56.09; H, 5.45; N, 28.12.

4-Acetamido-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl-1-phenyl-1*H*-pyrazole-5-carbonitrile (17) A mixture of **1** (0.16 g, 1 mmol), malononitrile (0.07 g, 1 mmol) in 20 mL of acetic acid was heated under reflux for 6 h. The solvent was evaporated under reduced pressure and the residue was triturated with methanol. The solid product **17** was collected by filtration and crystallized from the methanol; yellow crystals; yield 0.06 g (35%); mp 210–214°C; IR (ν_{max}, cm^{-1}): 1669, 1700 (CO), 2220 (CN), 3245 (NH); ^1H NMR ($CDCl_3$): δ 2.34 (s, 1H, NH), 2.56 (s, 3H, CH_3), 7.25–7.99 (m, 6H, Ar-H + CH pyrazole); MS: m/z 347 (M-1, 26). Anal. Calcd for $C_{18}H_{16}N_6O_2$ (348.36): C, 62.06; H, 4.63; N, 24.12. Found: C, 62.22; H, 4.76; N, 24.32.

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