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ORIGINAL ARTICLE

# An expeditious and green synthesis of new enaminones and study their chemical reactivity toward some different amines and binucleophiles under environmentally friendly conditions

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**Abstract** The condensation reaction of 3-heteroaromatic-3-oxopropanenitriles **3**, **4** and **7** with dimethylformamide–dimethylacetal (DMF–DMA) gave the corresponding enaminones **8**, **9** and **10**, respectively. Nucleophilic substitution of **8** and **9** with different amines resulted in a new derivatives of enaminones **11**–**18**. The reactivity of enaminones **8** and **9** toward some nitrogen nucleophiles was investigated with a view to synthesize new heterocyclic systems. Thus, treatment of compounds **8** and **9** with phenylhydrazine afforded the pyrazole derivatives **19** and **20**, respectively. On the other hand, reacting **8** and **9** with guanidine gave the pyrimidines **21** and **22**, respectively. Treatment of compound **9** with hydroxylamine hydrochloride afforded the aminoisoxazoles **23**. The foregoing reactions were carried out with conventional heating and under green conditions [ultrasound (US) irradiations or ionic liquids (ILs)] and a comparative study was employed. All the new structures are fully characterized.



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## 1. Introduction

Various indole derivatives have been reported to possess anti-inflammatory (Misra et al., 1996; Andreani et al., 1994), anticonvulsant (El-Gendy Adel et al., 1993), cardiovascular (Kumar et al., 1986) and antibacterial activities (Dandia et al., 1993). In addition, the indole nucleus, is an important target in organic synthesis, as this structure is found in a large

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variety of biologically active synthetic and natural products (Saracoglu, 2007; Suzen, 2007). Furthermore, some of indole derivatives, possessing a heterocyclic moiety at 3-position, have been synthesized and reported to have promising anti-inflammatory and antitumor activities (Verma et al., 1994; Farghaly, 2010). Moreover, meridianins (indole derivatives substituted in the C-3 position by a 2-aminopyrimidine ring) were successfully evaluated for their ability to inhibit various protein kinases and to display antitumor activity (Radwan and El-Sherbiny, 2007; Akue-Gedu et al., 2009). Also, it is observed from the literature that the pyrrole nucleus plays a vital role in many biological activities (El-Gaby et al., 2002; Almerico et al., 1998; Obniska et al., 1998; Reed et al., 1999). Encouraged by the above observations, we undertook the synthesis of some new 3-substituted indoles and 2-substituted pyrrole incorporating an extra heterocyclic ring: pyrazole; pyrimidine and isoxazole with the expectation that they would be of potential biological interest because of their resemblance to the above mentioned substances. Previously, we have reported several efficient routes to polyfunctionally substituted heterocycles utilizing enaminones as starting materials (Al-Zaydi et al., 2000a,b, 2007a,b, 2010; Agamy et al., 2001; Alnajjar et al., 2009). In continuation to this work and our efforts to develop efficient environmentally benign protocols for the synthesis of various heterocycles of biological interest (Al-Zaydi et al., 2004, 2007a,b, 2010; Mekheimer et al., 2008a,b), we report in this article the first synthesis of the enaminones **8**–**10**, which are considered to be very important intermediates for the synthesis of various new heterocycles of expected potential biological activity, under environmentally friendly conditions and study their chemical reactivity toward some different amines and binucleophiles under the effect of both ultrasonic (US) irradiations and in ionic liquids (ILs) as well as in the classical conditions.

## 2. Experimental

### 2.1. Measurements

Melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. The completion of the reaction was checked by thin-layer chromatography (TLC) on Merck silica gel 60 plates, 0.25 mm thick with F-254 indicator. Visualization was accomplished by UV light. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) were recorded in deuterated dimethylsulfoxide [DMSO-$d_6$] on a Bruker DPX spectrometer using tetramethyl-silane (TMS) as an internal reference; chemical shifts ($\delta$) are reported in ppm. IR spectra were recorded with a Nicolet Magna 520FT IR spectrophotometer in KBr disks. Mass spectra were measured on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Ultrasonic irradiation was carried out using a sonics and materials device, 750 W ultrasonic processor VCX 750, solid probe with non-replaceable tip, with processing capability: 10–250 ml, length: 53/8″ (136 mm), weight: 3/4 lb (340 g), titanium alloy Ti–6Al–4V, with integrated temperature control, allows sample temperature to be monitored up to 100 °C. The shape and the size of reactor dimensions (H × W × D) are 91/4″ × 71/2″ × 131/2″ and 235 × 190 × 340 mm , weight: 15 lb (6.8 kg) with sealed converter piezoelectric lead zirconate titanate crystals (PZT) of diameter: 21/2″ (63.5 mm), length: 71/4″ (183 mm), weight: 2 lb (900 g) and all reactions undergo at 300 W power (40%). Microanalyses were performed by the microanalytical data unit at Cairo University, and analytical values obtained were within ±0.4% of the calculated values. All reagents were of commercial quality or were purified before use and the organic solvents were of analytical grade or purified by standard procedures. X-ray crystallography was carried out on a Kappa CCD Enraf Nonius FR 590 diffractometer, National Research Center, Dokki, Cairo, Egypt.

### 2.2. General procedure for the synthesis of 3-heteroaromatic substituted-3-oxopropane nitriles *3*, *4* and *7*

Method I (US): to a solution of cyanoacetic acid (0.1 mol) in acetic anhydride (50 mL), compound **1** or **2** or **5** (0.1 mol) was added. The reaction mixture was exposed to US irradiation at 70 °C for 20–60 min and then left to cool to room temperature. The solid product so-formed was filtered off, dried and recrystallized from ethanol.

Method II (Δ) for compound **7**: a solution of cyanoacetic acid (0.1 mol) in acetic anhydride (20 mL) was added to a well mixed powder of compound **6** (0.1 mol) and anhyd. $AlCl_3$ (0.15 mol) dropwise. Then, the reaction mixture was refluxed under stirring for 2.5 h. After cooling to room temperature, it was poured into cold water. The resulting solid product was collected by filtration, washed well with $H_2O$, dried and recrystallized from dioxane.

#### 2.2.1. 3-Oxo-3-(1H-pyrrol-2-yl)-propionitrile *3*

Brown crystals, mp: 80–81 °C [Lit. (Walker, 1987) mp: 79–81 °C].

#### 2.2.2. 3-(1H-Indol-3-yl)-3-oxo-propionitrile *4*

Yellowish crystals, mp: 239–240 °C [Lit. (Kreher and Wagner, 1980) mp: 240 °C].

#### 2.2.3. N-(1-(2-Cyanoacetyl)-4-oxo-4H-thieno[3,4-c]chromen-3-yl)acetamide *7*

Buff crystals; mp: 220–221 °C; IR ($\nu_{max}$, cm$^{-1}$): 3250 (NH), 3091 (Ar, CH), 2229 (CN), 1685 (C═O), 1640 (amide CO). $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 2.33 (3H, s, $CH_3$), 3.97 (2H, s, $CH_2CN$), 7.30 (2H, m, Ar-H), 7.43 (1H, d, $J$ = 7.2 Hz, Ar-H), 7.99 (1H, d, $J$ = 7.2 Hz, Ar-H), 10.81 (1H, br s, NH). MS, $m/z$ = 326 ($M^+$, 3). Anal. Calcd. for $C_{16}H_{10}N_2O_4S$ (326.33): C, 58.89; H, 3.09; N, 8.58; S, 9.83%, Found: C, 58.74; H, 3.16; N, 8.69; S, 9.94%.

### 2.3. General procedure for the synthesis of enaminones *8*–*10*

Method I (Δ): to a solution of compound **3** or **4** or **7** (0.1 mol) in dry toluene (20 mL), DMF-DMA (0.1 mol) was added. The reaction mixture was heated at reflux for 8 h. The precipitated solid product was collected by filtration and dried.

Method II (US): to a solution of compound **3** or **4** or **7** (0.1 mol) in dry toluene (50 mL), DMF-DMA (0.1 mol) was added. The reaction mixture was exposed to ultrasound irradiation at 70 °C for 2.5 h and then left to cool to room temperature. The solid product so-formed was filtered off, dried and recrystallized from ethanol.

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*2.3.1. 3-Dimethylamino-2-(1H-pyrrole-2-carbonyl)acrylonitrile 8*

Buff crystals, mp: 200–201 °C; IR ($\nu_{max}$, $cm^{-1}$): 3261 (NH), 2200 (CN), 1648 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 3.27 (3H, s, $NCH_3$), 3.35 (3H, s, $NCH_3$), 6.16 (1H, m, pyrrole H-4), 7.0 (1H, m, pyrrole H-3), 7.19 (1H, m, pyrrole H-5), 8.0 (1H, s, olefinic CH), 11.63 (1H, br s, NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$), $\delta_c$ 40.4 ($NMe_2$), 76.3 (C–CN), 109.9 (pyrrole C-4), 115.6 (CN), 121.7 (pyrrole C-3), 124.3 (pyrrole C-5), 130.7 (pyrrole C-2), 159.3 (C-$NMe_2$), 176.5 (C═O). MS, $m/z$ = 189 ($M^+$, 57). Anal. Calcd. for $C_{10}H_{11}N_3O$ (189.21): C, 63.48; H, 5.86; N, 22.21%, Found: C, 63.65; H, 5.95; N, 22.16%.

*2.3.2. 3-Dimethylamino-2-(1H-indole-3-carbonyl)acrylonitrile* ***9***

Yellowish crystals, mp: 185–186 °C [Lit. (Slätt et al., 2005) mp: 187–188 °C].

*2.3.3. N-(1-(2-Cyano-3-(dimethylamino)acryloyl)-4-oxo-4H-thieno[3,4-c]chromen-3-yl)-acetamide* ***10***

Buff crystals, mp: 236–238 °C; IR ($\nu_{max}$, $cm^{-1}$): 3300 (NH), 3090 (Ar, CH), 2220 (CN) 1680 (C═O), 1644 (amide CO). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 2.34 (3H, s, $CH_3$), 3.31 (6H, br s, $NMe_2$), 7.33 (2H, m, Ar-H), 7.43 (1H, d, $J$ = 7.5 Hz, Ar-H), 7.70 (1H, s, olefinic CH), 8.04 (1H, d, $J$ = 7.5 Hz, Ar-H), 10.20 (1H, br s, NH). MS, $m/z$ = 381 ($M^+$, 22). Anal. Calcd. for $C_{19}H_{15}N_3O_4S$ (381.41): C, 59.83; H, 3.96; N,11.02; S, 8.41%, Found: C, 59.90; H, 3.79; N, 11.12; S, 8.23%.

*2.4. General procedure for the synthesis of 3-(phenylamino)-2-(1H-pyrrole-2-carbonyl)- acrylonitrile* ***11****, 2-(1H-Indole-3-carbonyl)-3-(phenylamino)acrylonitrile* ***13*** *and 3-(benzo[d]thiazol-2-ylamino)-2-(1H-pyrrole-2-carbonyl)acrylonitrile* ***14***

Method I (Δ): to a solution of **8** or **9** (0.1 mol) in ethanol (20 mL), aniline (0.1 mol) was added. The reaction mixture was heated to reflux for 4 h and was allowed to cool to room temperature. Then, the resulting solid product was collected by filtration and dried to give compounds **11** and **13**, respectively. Similarly, a solution of **8** (0.1 mol) in ethanol (20 mL) was reacted with 2-aminobenzothiazole (0.1 mol), under the same reaction conditions, to give compound **14**.

Method II (US): to a solution of **8** or **9** (0.1 mol) in ethanol (50 mL), aniline was added. The reaction mixture was exposed to ultrasound irradiation at 70 °C for 2 h and then left to cool to room temperature. The solid product so-formed was filtered off and dried to give compounds **11** and **13**, respectively. Similarly, a solution of **8** (0.1 mol) and 2-aminobenzothiazole (0.1 mol) in ethanol (50 mL) was exposed to ultrasound irradiation at 70 °C for 2 h to give compound **14**.

Method III (IL): a mixture of pyridinium chloride ([PyH]Cl) (0.4 mol), compound **8** or **9** (0.1 mol) and aniline was heated at 110 °C for 20 min. After cooling to room temperature, the reaction mixture was treated with ethanol. The resulting solid product was collected by filtration, dried and recrystallized from ethanol to give compounds **11** and **13**, respectively. In the case of **14**, a mixture of pyridinium chloride ([PyH]Cl) (0.4 mol), compound **8** (0.1 mol) and 2-aminobenzothiazole (0.1 mol) was heated at 110 °C for 20 min. and then the reaction mixture was worked up as described above.

*2.4.1. 3-(Phenylamino)-2-(1H-pyrrole-2-carbonyl)acrylonitrile* ***11***

Yellow crystals, mp: 180–181 °C; IR ($\nu_{max}$, $cm^{-1}$): 3257 (NH), 2198 (CN), 1669 (C═O).

$^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 6.25 (2H, m, pyrrole H-3, H-4), 7.38–7.45 (5H, m, Ph-H), 7.60 (1H, d, $J$ = 2.4 Hz, pyrrole H-5), 8.48 (1H, d, $J$ = 8.4 Hz, olefinic CH), 11.85 (1H, s, pyrrole NH), 12.58 (1H, d, $J$ = 7.0 Hz, NH-Ph). $^{13}C$ NMR (100 MHz, DMSO-$d_6$), $\delta_c$ 82.7 (C–CN), 110.7 (pyrrole C-4), 115.7 (CN), 118.4 (2C, Ar-C), 126.0 (Ar-C), 126.3 (pyrrole C-3), 130.1 (pyrrole C-5), 130.4 (2C, Ar-C), 130.7 (pyrrole C-2), 140.5 (NH-Ph), 153.7 (═C─NH), 178.8 (C═O). MS, $m/z$ = 237 ($M^+$, 80). Anal. Calcd. for $C_{14}H_{11}N_3O$ (237.26): C, 70.87; H, 4.67; N, 17.71%, Found: C, 70.99; H, 4.59; N, 17.90%.

*2.4.2. 2-(1H-Indole-3-carbonyl)-3-(phenylamino)acrylonitrile* ***13***

Buff crystals, mp: 174–176 °C; IR ($\nu_{max}$, $cm^{-1}$): 3253 (NH), 3046 (Ar, CH), 2200 (CN), 1667 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 6.98–7.59 (8H, m, Ar-H), 8.22 (1H, d, $J$ = 7.8 Hz, olefinic CH), 8.35 (1H, d, $J$ = 7.8 Hz, indole H-4), 8.57 (1H, s, indole H-2), 12.10 (1H, s, indole NH), 12.70 (1H, br, NH-Ph). MS, $m/z$ = 287 ($M^+$, 49). Anal. Calcd. for $C_{18}H_{13}N_3O$ (287.32): C, 75.25; H, 4.56; N, 14.63%, Found: C, 75.13; H, 4.62; N, 14.79%.

*2.4.3. 3-(benzo[d]thiazol-2-ylamino)-2-(1H-pyrrole-2-carbonyl)acrylonitrile* ***14***

Brown crystals, mp: 180–181 °C; IR ($\nu_{max}$, $cm^{-1}$): 3258 (NH), 2198 (CN), 1670 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 6.27 (1H, t, $J$ = 2.4 Hz, pyrrole H-4), 7.36 (2H, m, Ar-H), 7.49 (1H, d, $J$ = 2.3 Hz, pyrrole H-3), 7.66 (1H, d, $J$ = 2.6 Hz, pyrrole H-5), 8.0 (1H, s, olefinic CH), 8.15 (1H, d, $J$ = 7.6 Hz, Ar-H), 8.35 (1H, d, $J$ = 7.6 Hz, Ar-H), 11.75 (1H, s, pyrrole NH), 12.43 (1H, br, NH). MS, $m/z$ = 294 ($M^+$, 51). Anal. Calcd. for $C_{15}H_{10}N_4OS$ (294.33): C, 61.21; H, 3.42; N, 19.04; S, 10.89%, Found: C, 61.13; H, 3.59; N, 19.17; S, 11.04%.

*2.5. General procedure for the synthesis of enaminones* ***15–18***

Method I (Δ): to a solution of compound **8** or **9** (0.1 mol) in ethanol (20 mL), secondary amine (piperidine or morpholine) (0.1 mol) was added. The reaction mixture was heated at reflux temperature for 4 h. After cooling to room temperature, the solid product so-formed was collected by filtration and dried.

Method II (US): to a solution of compound **8** or **9** (0.1 mol) in ethanol (50 mL), secondary amine (piperidine or morpholine) (0.1 mol) was added. The reaction mixture was exposed to ultrasound irradiation at 70 °C for 2 h. After cooling to room temperature, it was poured into ice-cold water. The resulting solid product was collected by filtration and dried.

Method III (IL): a mixture of pyridinium chloride ([PyH]Cl) (0.4 mol), compound **8** or **9** (0.1 mol) and secondary amine (piperidine or morpholine) (0.1 mol) was heated at 110 °C for 20 min and was allowed to cool to room temperature. Then, it was treated with ethanol and the resulting solid

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product was collected by filtration, dried and recrystallized from ethanol.

#### 2.5.1. 3-(Piperidin-1-yl)-2-(1H-pyrrole-2-carbonyl)acrylonitrile **15**

Buff crystals, mp: 168–170 °C; IR ($\nu_{max}$, $cm^{-1}$): 3258 (NH), 2850 (aliph. CH), 2193 (CN), 1665 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 1.66 (6H, m, $3CH_2$), 3.56 (4H, br, $2NCH_2$), 6.16 (1H, t, $J$ = 2.1 Hz, pyrrole H-4), 7.07 (1H, d, $J$ = 3.6 Hz, pyrrole H-3), 7.18 (1H, d, $J$ = 2.7 Hz, pyrrole H-5), 8.01 (1H, s, olefinic CH), 11.58 (1H, s, pyrrole NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$), $\delta_c$ 23.6 ($CH_2$), 26.0 ($CH_2$), 27.0 ($CH_2$), 57.9 ($2NCH_2$), 75.4 (C═C–N), 109.8 (pyrrole C-4), 115.6 (CN), 121.7 (pyrrole C-3), 124.4 (pyrrole C-5), 130.7 (pyrrole C-2), 157.2 (olefinic carbon), 176.7 (C═O). MS, $m/z$ = 229 ($M^+$, 85). Anal. Calcd. for $C_{13}H_{15}N_3O$ (229.28): C, 68.10; H, 6.59; N, 18.33%, Found: C, 68.06; H, 6.75; N, 18.45%.

#### 2.5.2. 3-(Morpholin-4-yl)-2-(1H-pyrrole-2-carbonyl)acrylonitrile **16**

Buff crystals, mp: 216–217 °C; IR ($\nu_{max}$, $cm^{-1}$): 3290 (NH), 3090 (Ar, CH), 2920 (aliph. CH), 2220 (CN), 1665 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 3.22 (4H, m, 2 $NCH_2$), 3.60 (4H, m, 2 $OCH_2$), 6.17 (1H, t, $J$ = 2.1 Hz, pyrrole H-4), 6.98 (1H, d, $J$ = 3.6 Hz, pyrrole H-3), 7.81 (1H, d, $J$ = 2.7 Hz, pyrrole H-5), 7.99 (1H, s, olefinic CH), 11.58 (1H, br s, pyrrole NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$), $\delta_c$ 48.1 (2 $NCH_2$), 58.6 (2 $OCH_2$), 76.4 (C═C–N), 109.9 (pyrrole C-4), 115.7 (CN), 121.7 (pyrrole C-3), 124.27 (pyrrole C-5), 130.7 (pyrrole C-2), 159.43 (olefinic carbon), 176.52 (C═O). MS, $m/z$ = 231 ($M^+$, 3). Anal. Calcd. for $C_{12}H_{13}N_3O_2$ (231.25): C, 62.33; H, 5.67; N, 18.17%, Found: C, 62.25; H, 5.70; N, 18.11%.

#### 2.5.3. 2-(1H-Indole-3-carbonyl)-3-(piperidin-1-yl)acrylonitrile **17**

Yellow crystals, mp: 233–234 °C; IR ($\nu_{max}$, $cm^{-1}$): 3204 (NH), 2856 (aliph. CH), 2198 (CN), 1667 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 1.63 (6H, m, $3CH_2$), 3.57 (2H, m, $CH_2$), 3.97 (2H, m, $CH_2$), 7.19 (2H, m, Ar-H), 7.48 (1H, d, $J$ = 7.6 Hz, Ar-H), 8.01 (1H, s, olefinic CH), 8.16 (1H, d, $J$ = 7.6 Hz, Ar-H), 8.30 (1H, s, indole H-2), 11.77 (1H, s, indole NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$), $\delta_c$ 23.6 ($CH_2$), 26.0 ($CH_2$), 27.0 ($CH_2$), 57.7 (2 $NCH_2$), 77.2 (C═C–N), 112.5 (indole C-3), 115.3 (CN), 121.7 (Ar-C), 122.3 (2C, Ar-C), 123.1 (indole C-3a), 127.0 (Ar-C), 133.7 (indole C-2), 136.4 (indole C-7a), 157.2 (C═C–N), 182.5 (C═O). MS, $m/z$ = 279 ($M^+$, 100). Anal. Calcd. for $C_{17}H_{17}N_3O$ (279.34): C, 73.10; H, 6.13; N, 15.04%, Found: C, 73.18; H, 6.29; N, 15.23%.

#### 2.5.4. 2-(1H-Indole-3-carbonyl)-3-(morpholin-4-yl)acrylonitrile **18**

Yellowish crystals, mp: 187–189 °C; IR ($\nu_{max}$, $cm^{-1}$): 3254 (NH), 2928 (aliph. CH), 2189 (CN), 1667 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 3.27 (4H, m, 2 $NCH_2$), 3.75 (4H, m, 2 $OCH_2$), 7.14–7.22 (2H, m, Ar-H), 7.48 (1H, d, $J$ = 7.7 Hz, Ar-H), 8.05 (1H, s, olefinic CH), 8.15 (1H, d, $J$ = 7.7 Hz, Ar-H), 8.30 (1H, s, indole H-2), 11.80 (1H, d, $J$ = 9.5 Hz, indole NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$), $\delta_c$ 48.0 (2 $NCH_2$), 67.5 (2 $OCH_2$), 78.0 (C═C–N), 112.5 (indole C-3), 115.2 (CN), 121.7 (Ar-C), 122.3 (2C, Ar-C), 123.1 (indole C-3a), 127.1 (Ar-C), 133.7 (indole C-2), 136.4 (indole C-7a), 157.7 (C═C–N), 182.3 (C═O). MS, $m/z$ = 281 ($M^+$, 38). Anal. Calcd. for $C_{16}H_{15}N_3O_2$ (281.31): C, 68.31; H, 5.37; N, 14.94%, Found: C, 68.14; H, 5.26; N, 14.86%.

### 2.6. General procedure for the synthesis of pyrazole derivatives **19** and **20**

Method I (Δ): to a solution of compound **8** or **9** (0.1 mol) in ethanol (20 mL), phenyl hydrazine (0.1 mol) was added. The reaction mixture was refluxed for 4 h. After concentration and cooling to room temperature, the solid product so-formed was collected by filtration and dried.

Method II (US): to a solution of **8** or **9** (0.1 mol) in ethanol (50 mL), phenyl hydrazine (0.1 mol) was added. The reaction mixture was subjected to ultrasound irradiation at 70 °C for 2 h and then left to cool to room temperature. The solid product so-formed was filtered off and dried.

Method III (IL): a mixture of pyridinium chloride ([PyH]Cl) (0.4 mol), compound **8** or **9** (0.1 mol) and phenyl hydrazine (0.1 mol) was heated at 110 °C for 20 min. After cooling to room temperature, it was treated with ethanol and the resulting solid product was collected by filtration, dried and recrystallized from ethanol.

#### 2.6.1. (5-Amino-1-phenyl-1H-pyrazol-4-yl)(1H-pyrrol-2-yl)methanone **19**

Buff crystals, mp 208–210 °C; IR ($\nu_{max}$, $cm^{-1}$): 3400, 3215, 3164 (NH , $NH_2$), 1665 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 6.23 (1H, m, pyrrole H-4), 6.96 (2H, br, $NH_2$), 7.05 (1H, m, pyrrole, H-3), 7.11 (1H, d, $J$ = 2.6 Hz, pyrrole H-5), 7.45 (m, 1Ar-H), 7.60 (4H, m, Ar-H), 8.16 (1H, s, pyrazole H-3), 11.58 (1H, br, pyrrole NH). MS, $m/z$ = 252 ($M^+$, 16). Anal. Calcd. for $C_{14}H_{12}N_4O$ (252.27): C, 66.65; H, 4.79; N, 22.21%, Found: C, 66.73; H, 4.92; N, 22.02%.

#### 2.6.2. (5-Amino-1-phenyl-1H-pyrazol-4-yl)(1H-indol-3-yl)methanone **20**

Yellowish crystals, mp: 266–268 °C; IR ($\nu_{max}$, $cm^{-1}$): 3414, 3267, 3228 (NH, $NH_2$), 1667 (C═O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 6.97 (2H, br, $NH_2$), 7.19 (2H, m, Ar-H), 7.43–7.64 (6H, m, Ar-H), 8.19 (1H, s, indole H-2), 8.28 (1H, d, $J$ = 7.8 Hz, Ar-H), 8.31 (1H, s, pyrazole H-3), 11.86 (1H, s, indole NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$), $\delta_c$ 104.89 (pyrazole C-4), 112.5–130.0 (9C, Ar-C + indole C-2 and C-3), 131.8 (indole C-3a), 136.8 (indole C-7a), 138.4 (pyrazole C-3), 141.1 (N-Ph), 151.0 (pyrazole C-5), 183.6 (C═O). MS, $m/z$ = 302 ($M^+$, 48). Anal. Calcd. for $C_{18}H_{14}N_4O$ (302.33): C, 71.51; H, 4.67; N, 18.53%, Found: C, 71.66; H, 4.86; N, 18.44%.

### 2.7. General procedure for the synthesis of pyrimidine derivatives **21** and **22**

Method I (Δ): to a solution of compound **8** or **9** (0.1 mol) and guanidine (0.1 mol) in ethanol (30 mL), potassium carbonate

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(0.12 mol) was added. The reaction mixture was heated to reflux for 10 h. After cooling to room temperature, it was poured into ice-cold water. The precipitated solid product was filtered off, washed well with water and dried.

Method II (US): to a solution of **8** or **9** (0.1 mol) and guanidine (0.1 mol) in ethanol (50 mL), potassium carbonate (0.12 mol) was added. The reaction mixture was exposed to ultrasound irradiation at 70 °C for 5 h. Then, the reaction mixture was poured into ice-cold water. The solid product so-formed was filtered off, washed well with water, dried and recrystallized from ethanol.

#### *2.7.1. 2-Amino-4-(1H-pyrrol-2-yl)pyrimidin-5-carbonitrile **21***

Buff crystals, mp: 212–214 °C; IR ($\nu_{max}$, $cm^{-1}$): 3478, 3407, 3215 (NH, $NH_2$), 3064 (Ar, CH), 2207 (CN). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 6.31 (1H, br, pyrrole H-4), 7.0–7.2 (2H, m, pyrrole H-3 and H-5), 7.31 (2H, br s, $NH_2$), 8.68 (1H, s, pyrimidine H-6), 11.57 (1H, s, pyrrole NH). MS, $m/z$ = 185 ($M^+$, 100). Anal. Calcd. for $C_9H_7N_5$ (185.19): C, 58.37; H, 3.81; N, 37.82%, Found: C, 58.49; H, 3.66; N, 37.90%.

#### *2.7.2. 2-Amino-4-(1H-indol-3-yl)pyrimidin-5-carbonitrile **22***

Buff crystals; mp: 256–258 °C [Lit. (Radwan and El-Sherbiny, 2007) mp: 258–259 °C].

### *2.8. Synthesis of (5-aminoisoxazol-4-yl)(1H-indol-3-yl)methanone **23***

Method I (Δ): to a solution of **9** (0.1 mol) and hydroxylamine hydrochloride (0.1 mol) in ethanol (25 mL), potassium carbonate (0.12 mol) was added. The reaction mixture was heated to reflux for 10 h. After cooling to room temperature, it was poured into ice-cold water. The resulting solid product was collected by filtration, washed well with water and dried.

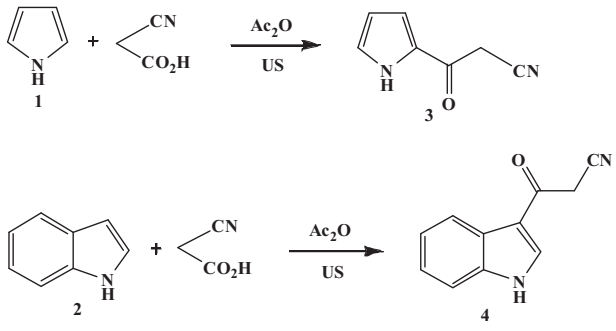
Method II (US): to a solution of compound **9** (0.1 mol) and hydroxylamine hydrochloride (0.1 mol) in ethanol (50 mL), potassium carbonate (0.12 mol) was added. The reaction mixture was exposed to ultrasound irradiation at 70 °C for 5 h. After cooling to room temperature, it was poured into ice-cold water. The solid product so-formed was filtered off, washed well with water, dried and recrystallized from ethanol to give compound **23** as buff crystals, mp: 241–243 °C; IR ($\nu_{max}$, $cm^{-1}$): 3385, 3228, 3119 (NH, $NH_2$), 1661 (C=O). $^1H$ NMR (400 MHz, DMSO-$d_6$), $\delta_H$ 6.78 (2H, s, $NH_2$), 7.0–8.10 (4H, m, Ar-H), 8.25 (1H, s, indole H-2), 8.40 (1H, s, isoxazole H-3), 11.1 (1H, s, indole NH). MS, $m/z$ = 225 ($M^+$-2, 14). Anal. Calcd. for $C_{12}H_9N_3O_2$ (227.22): C, 63.43; H, 3.99; N, 18.49%, Found: C, 63.33; H, 4.18; N, 18.62%.

## 3. Result and discussion

At the onset of the research, we investigated the synthesis of 3-heteroaromatic-3-oxo-propanenitriles **3**, **4**, and **7** and convert them to the corresponding enaminones **8**, **9** and **10**, respectively, which were selected as our primary starting materials for this series of reactions. Although, the synthesis of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**3**) and 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile (**4**) has been reported (Bergman, 1968; Slätt et al., 2004, 2005; Farag et al., 1996, 1997; Dawood et al., 1999; Gurevich and Yaroshevskya, 2000; Isobe et al., 2003; Al-Awadi et al., 2007) to the best of our knowledge, their syntheses by environmentally benign approaches have not been reported so far.

Thus, condensation of cyanoacetic acid with pyrrole or indole in acetic anhydride, under conventional heating, gave 3-heteroaromatic-3-oxopropanenitriles **3** and **4** in 70 and 77% yields, respectively (Al-Awadi et al., 2007). However, when we conducted these condensation reactions under US irradiations, compounds **3** and **4** were formed (see Scheme 1) and the yields are improved over the conventional method (see Table 1).

On the other hand, when *N*-(4-oxo-4*H*-thieno[3,4-*c*]chromen-3-yl)acetamide (**6**) prepared by acetylation of 3-amino-4*H*-thieno[3,4-c]chromen-4-one (**5**) as described in the literature (Al-Awadi et al., 2007) was subjected to react with cyanoacetic acid in acetic anhydride, under conventional heating for a long time, the expected 3-oxoalkanenitrile derivative **7** was not obtained and the starting materials were recovered. In an attempt to synthesis the desired 3-oxoalkanenitriles **7**, we repeated the reaction in the presence of Lewis acid, *viz*. $AlCl_3$.




**Scheme 1**

**Table 1** Shows yield as well as reaction times of compounds **3**–**23** by the three methodologies (thermal (Δ), ultrasound (US) and ionic liquid (IL)).

| No. | Yield (%) | | | Time (min) | | |
|---|---|---|---|---|---|---|
| | Δ | US | IL | Δ | US | IL |
| **3** | – | 88 | – | – | 20 | – |
| **4** | – | 92 | – | – | 20 | – |
| **7** | 81 | 92 | – | 150 | 60 | – |
| **8** | 68 | 86 | – | 420 | 150 | – |
| **9** | 57 | 88 | – | 420 | 150 | – |
| **10** | 75 | 92 | – | 420 | 150 | – |
| **11** | 72 | 91 | 88 | 240 | 120 | 20 |
| **13** | 70 | 90 | 86 | 240 | 120 | 20 |
| **14** | 66 | 83 | 74 | 240 | 120 | 20 |
| **15** | 69 | 85 | 80 | 240 | 120 | 20 |
| **16** | 51 | 86 | 73 | 240 | 120 | 20 |
| **17** | 73 | 88 | 83 | 240 | 120 | 20 |
| **18** | 64 | 86 | 79 | 240 | 120 | 20 |
| **19** | 66 | 82 | 77 | 240 | 120 | 20 |
| **20** | 69 | 85 | 80 | 240 | 120 | 20 |
| **21** | 44 | 85 | – | 480 | 300 | – |
| **22** | 46 | 88 | – | 480 | 300 | – |
| **23** | 42 | 71 | – | 480 | 300 | – |

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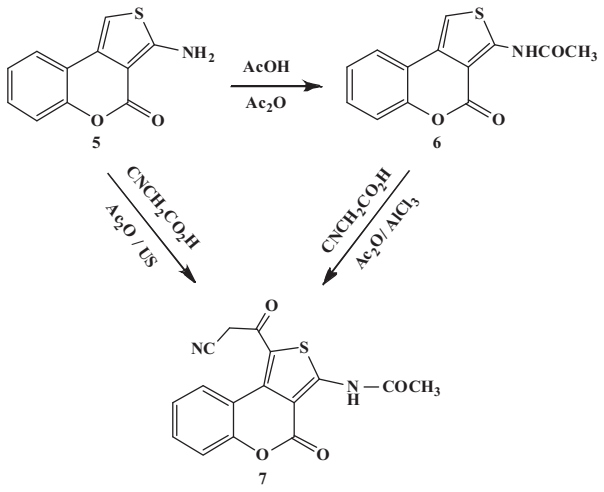



**Scheme 2**

Thus, the reaction of **6** with cyanoacetic acid in acetic anhydride and in the presence of a catalytic amount of anhydrous $AlCl_3$ afforded the requested 3-oxoalkanenitriles **7** in 81% yield. Alternatively, compound **7** could also be obtained, in one step, by reacting compound **5** with cyanoacetic acid in acetic anhydride under US irradiations (see Scheme 2).

The preparation of enaminones **8**–**10** was accomplished very easily *via* the condensation of 3-oxopropanenitriles **3**, **4** and **7** with dimethylformamide dimethylacetal (DMF-DMA) either with conventional heating for a long time or with US for 2.5 h at 70 °C. The structure of **8**, for example, was established for the reaction product on the basis of its elemental analysis and spectral data (MS, IR, NMR; see Section 2). Finally, the structure of **8** was unambiguously confirmed based on NOE difference which indicated that the proton at C-3 in pyrrole at $\delta$ = 7.0 ppm is sterically proximal to the olefinic proton at $\delta$ = 8.0 ppm.

In order to construct new derivatives of the interesting enaminones of the type **8** and **9**, we investigated the reactivity of these enaminones **8** and **9** toward some different amines. Thus, treatment of compound **8**, as example, with aniline, under different reaction conditions (conventional heating, US

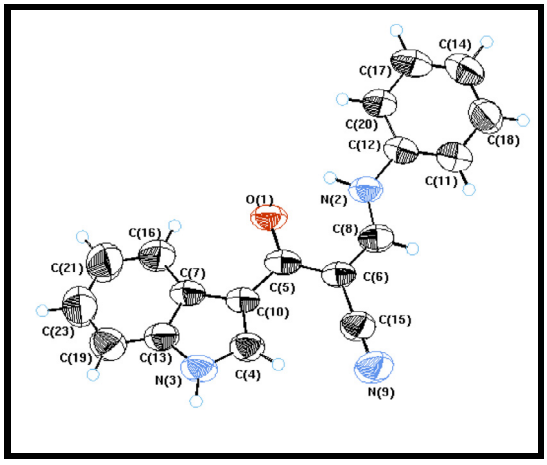
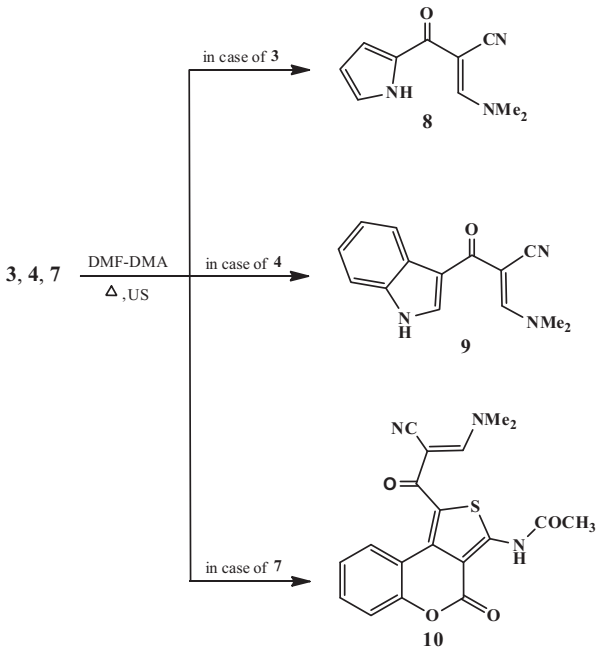



**Figure 1** X-ray crystal structure of compound **13**.

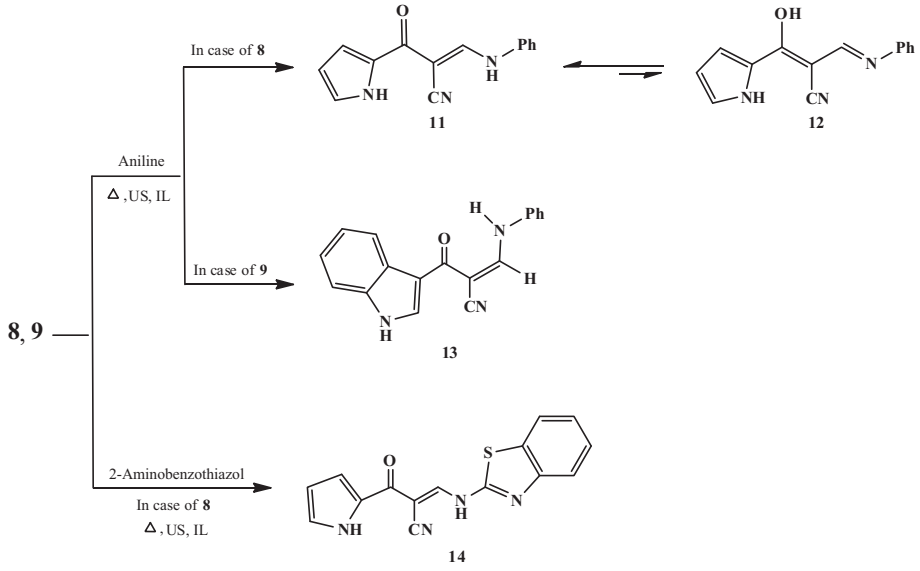



**Scheme 3**

and IL), gave a solid product whose structure was assumed to be **11** (keto form) or **12** (enol form) (Scheme 4). The $^1$H NMR revealed four signals for two protons at 12.58, 10.78, 8.48 and 7.99 ppm. The doublet signals at 12.58 and 8.48 ppm are assigned for NH and CH proton, respectively in the keto form **11** while the singlet signals at 10.78 and 7.99 ppm are assigned for OH and CH proton, respectively in the enol form **12**. From integrals, it could be calculated that the major constituent in this equilibrium mixture is the keto form **11** (80–85%), while the minor constituent is the enol form **12** (10–15%). Also, compound **9** reacted with aniline either *via* irradiation with US and/or in IL to yield 2-(1*H*-indole-3-carbonyl)-3-(phenylamino)acrylonitrile (**13**) (Scheme 4). The structure of product **13** was confirmed by X-ray crystal determination (Fig. 1) (Crystallographic data for the structure). However, reacting compound **8** with 2-aminobenzothiazol, under green conditions, afforded the new 3-(benzo[*d*]thiazol-2-ylamino)-2-(1*H*-pyrrol-2-carbonyl)acrylonitrile (**14**), in excellent yield (see Schemes 3 and 5).

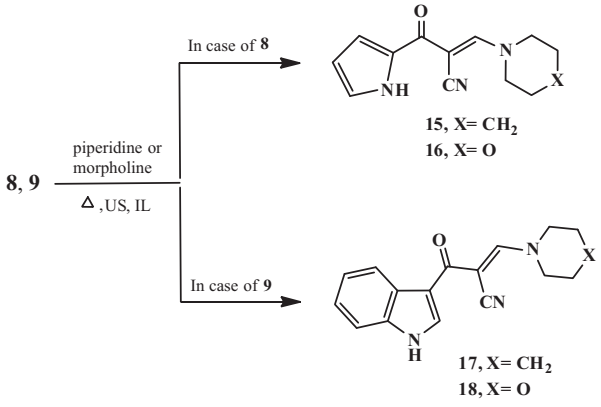
In conjunction with this study, we investigated the behavior of the reaction of enaminones **8** and **9** with secondary amines. Thus, the reaction of compounds **8** and **9** with equimolar amounts of piperidine and morpholine provided the interesting enaminone compounds **15**–**18**. As it has been reported that heterocycles with piperidine sub-structures display important biological activities, such as anti-cancer (El-Subbagh et al., 2000) and cytotoxic (Dimmock et al., 2001), besides being useful as synthons in the construction of alkaloid natural products (Lee et al., 2001). These heterocycles with piperidine sub-structures **15**–**18** could exhibit important biological properties. Compounds **15**–**18** were prepared under conventional heating or irradiating under US for 120 min at 70 °C or with heating in [PyH]Cl, as an IL, at 110 °C for 20 min and the data used to characterize them are given in the experimental section.

Attention was next turned to investigate the reactivity of enaminones **8** and **9** with some binucleophiles such as



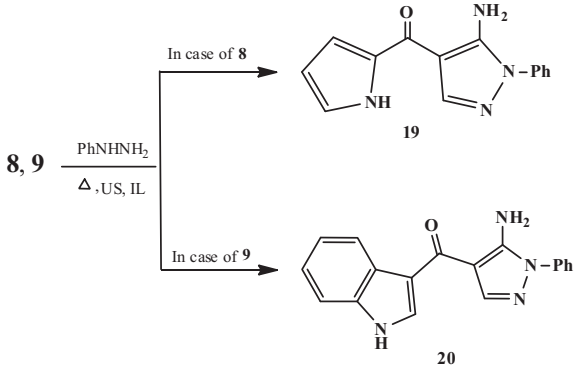

11 12 13 14

Scheme 4



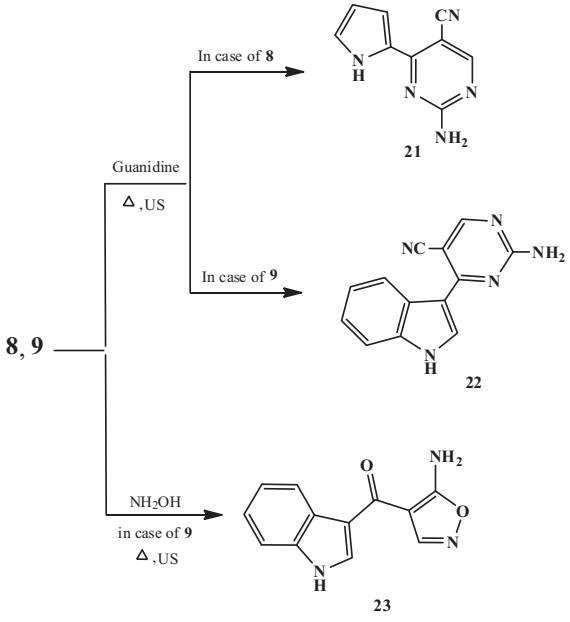

15, X= $CH_2$
16, X= O
17, X= $CH_2$
18, X= O

Scheme 5




19 20

Scheme 6




21 22 23

Scheme 7

phenylhydrazine, guanidine and hydroxylamine. Thus, treatment of compounds **8** and **9** with phenylhydrazine, under different environmentally friendly conditions (US and IL), afforded the corresponding pyrazole derivatives **19** and **20**, respectively, in high yields (77–92%) (Scheme 6). Their structures were established and confirmed for the reaction products on the basis of their elemental analyses and spectral data (MS, IR, $^1$H NMR and $^{13}$C NMR) (see Section 2).

However, treatment of enaminones **8** and **9** with equimolar amount of guanidine under either conventional heating or environmentally benign reaction conditions gave the interesting pyrimidine derivatives **21** and **22**, respectively (Scheme 7). The identity of compounds **21** and **22** was supported by correct elemental analyses and mass spectra as well as the IR and NMR spectra which were compatible with the assigned structures (see Section 2). On the other hand, compound **9** was reacted with hydroxylamine hydrochloride in the presence of anhydrous $K_2CO_3$ either at reflux temperature or under US

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activation to yield the aminoisoxazole derivative **23**. Although, the reaction completion required a long time at reflux temperature, it needed only 5 h (TLC control) for completing the reaction under US irradiation at 70 °C. The structure of **23** was confirmed as the reaction products from its IR, $^1$H NMR and correct elemental analysis as well as mass spectrum. Thus, the IR spectrum of **23** revealed the absence of the cyano group and the presence of absorption bands at $\nu$ = 3385, 3228 and 3119 cm$^{-1}$ due to amino functions (NH, $NH_2$). The $^1$H NMR spectrum of **23** displayed the absence of dimethylamino group ($NMe_2$) and olefinic CH signals at $\delta$ = 3.26, 3.36 and 8.0 ppm, respectively, present in the spectrum of **9**, and the presence of two singlet signals at $\delta$ = 6.78 and 8.40 ppm attributable to $NH_2$ and isoxazole H-3, respectively, besides signals due to the indole moiety in their expected positions. Additionally, its structure was fully supported by correct mass spectrum, which was compatible with the assigned structure (see Section 2). Analytical data was also in accordance with the proposed structure.

## 4. Conclusion

In summary, we have disclosed the green methodologies (US and IL) for the synthesis of new heterocyclic systems containing indole or pyrrole moiety starting from 3-cyanoacetyl indole and 2-cyanoacetyl pyrrole. In these methodologies, cyanoacetyl group at the 3-position of indole or 2-position of pyrrole is used as a good precursor to construct the appropriately pyrazole, pyrimidine and isoxazole derivatives. The significant advantages of these green methodologies are high yields with lesser reaction time, clean, a simple work-up procedures and no chromatographic separation is necessary to get pure compounds. In addition, the recovered IL could be directly reused after drying without any significant loss of activity. The compounds prepared are expected to be of pharmacological interest. Further application of these green approaches to the synthesis of other new heterocycles is currently ongoing in our laboratory and will be reported in due course.

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