Heterocyclic Synthesis *via* Enaminones: Novel Synthesis of (1*H*)-Pyridin-2-one, Pyrazolo[1,5-*a*]pyrimidine and Isoxazole Derivatives Incorporating a *N*-Methylphthalimide and Their Biological Evaluation

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Received April 29, 2004

Novel synthesis of (1*H*)-pyridin-2-one, pyrazolo[1,5-*a*]pyrimidine and isoxazole derivatives incorporating *N*-methylphthalimide moiety are reported. Reaction of enaminone **2** with malononitrile affords **4**. Condensation of **2** with cyanothioacetamide or benzoylacetonitrile affords compounds **6** and **7** respectively. Reaction of **2** with hydrazine hydrate afford 2,3-dihydrophthalazine-1,4-dione (**10**). Condensation of **2** with hydroxylamine and 3-aminopyrazole derivatives affords compounds **12** and **15a,b** respectively. Antimicrobial and antifungal activity were determined for representative compounds and most of them showed moderate activity as antimicrobial agents, while compounds **2** and **7** show strong activity against *Aspergillus niger*. The structure of the newly synthesized compounds was elucidated by elemental analyses and ^{1}H nmr spectra and some cases by ^{13}C nmr investigation.

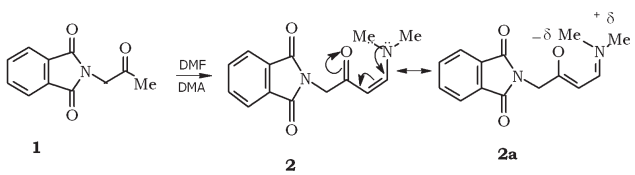
J. Heterocyclic Chem., **42**, 307 (2005).

N-alkylphthalimides attracted a great deal of interest due to their biological properties such as potent acetylcholinesterase (ACHE) inhibitors [1,2], antihypertensive, CNS depressant activities [3,4] and potent enhancing activity on TPA-induced TNF-α (tumor necrosis factor alpha) production [5]. Furthermore, several studies have also pointed out the value of imide derivatives as intermediates in synthesis [6] and in polymer chemistry [7]. In continuation of our current interest in the synthesis of functionally substituted heteroaromatic compounds as potential pharmaceuticals utilizing enaminones [8-12]. We report here on the utility of unreported enaminone (**2**) as a building block for the synthesis of (1*H*)-pyridin-2-one, (1*H*)-pyridin-2-thione, isoxazol and pyrazolo[1,5-*a*]-pyrimidine derivatives in which an *N*-alkylphthalimide ring is incorporated along with the results of their antimicrobial antifungal activities.

Thus, treatment of *N*-phthalimidoacetone **1** with dimethylformamide dimethylacetal (DMFDMA) in refluxing xylene for 6 hours was unsatisfactory. However, when the reaction was refluxed for 20 hours a yellow crystalline product was obtained that was assigned as the *Z*-isomer based on ^{1}H nmr, which revealed methylene protons as a singlet at δ_H 4.44 ppm and two doublets at δ_H 5.05 and 7.61 ppm corresponding to vinylic protons with J=10 Hz as expected for protons in a *Z* configuration. In addition, two singlets are observed at δ_H 2.80 and 3.05 ppm corresponding to the two *N*-methyl groups, thus showing that they are non-equivalent. Nonequivalence is due to resonance of the nitrogen atom lone pair of electrons with the α,β-unsaturated carbonyl group which causes partial double bond character and thus restricted rotation (conformation **2a** in Scheme 1). Moreover, the ^{13}C nmr spectrum revealed the presence of only three sp^3 carbon atoms that resonate at δ_C 46.90, 45.08 and 35.57 ppm for the methylene and two non-equivalent methyl groups, respectively (Scheme 1).

The reactivity of **2** towards active methylene nitriles was investigated. Thus, the reaction of compound **2** with malononitrile in refluxing ethanol along with a catalytic amount of piperidine gave the substituted 2,4-pentadienamide **3**. Heating of **2** with malononitrile at 150 °C gave a single product identified as *N*-[(3-Cyano(1*H*)-2-oxopyridin-4-yl)methyl]phthalimide (**4**). Heating 2,4-pentadienamide derivative **3** at 180 °C also affords **4 (**the product is identical in all respects, mp and spectra, with that obtained previously from reaction of **2** with malononitrile).

Scheme 1



Compound **4** was also obtained by an independent synthesis. Treatment of *N*-phthalimidoacetone **1** with malononitrile in refluxing ethanol in the presence of piperidine afforded 2-cyano-3-methyl-4-(phthalimido)-2-butenamide (**5**). Heating **5** with DMF DMA also afforded **4**. On the other hand, **4** also can be obtained *in situ*, *via* the one-step process of heating **1** with DMF DMA at 150 °C followed by the treatment of the reaction mixture with malononitrile or *vice versa* (Scheme 2). Formation of **4** is assumed to be formed *via* initial hydrolysis of malononitrile to cyanoacetamide followed by condensation of the active methylene group with the carbonyl function group of **2** to form **3** which readily undergoes intramolecular cyclisation into the (1*H*)-pyridin-2-one derivative **4** *via* loss of dimethylamine molecule.

In a similar manner, compound **2** reacted also with cyanothioacetamide or benzoylacetonitrile in refluxing ethanol

to afford the (1*H*)-pyridine-2-thione and (1*H*)-pyridin-2-one derivatives **6** and **7**, respectively. The structure of both compounds **6** and **7** was established on the basis of their elemental analysis and spectral data (see Section 2).

On the other hand heating *N*-phthalimidoacetone **1** with malononitrile followed by treatment of the reaction mixture with benzylidinemalononitrile *in situ* afforded compound **8** in good yield. The ir spectrum of **8** showes absorption bands at 3474 and 3338 cm^{-1} due to NH_2 group in addition to strong absorption bands at 2204, 1774, 1719 cm^{-1} which are assigned to the nitrile and two phthalimide carbonyl groups respectively. The ^1H nmr spectrum showed signlets at δ_H 2.24 and δ_H 4.58 ppm for H-6 and methylene protons, respectively. Also revealed broad signals (D_2O exchangeable) at δ_H 8.32 ppm due to NH_2 and multiplets at δ 7.23 – 7.95 ppm corresponding to aromatic protons. Finally, a signal corresponding to an acetyl group at approximately δ_H 2.50 ppm was not observed (Scheme 2).

The reactivity of enaminone **2** towards some nitrogen nucleophiles was also investigated. Thus treatment of compound **2** with hydrazine hydrate in refluxing ethanol in an attempted to prepare pyrazolo derivative **9a** was unsuccessful. The isolated product was identified as 2,3-dihydrophthalazine-1,4-dione (**10**) with mp similar to those reported in the literature [13].

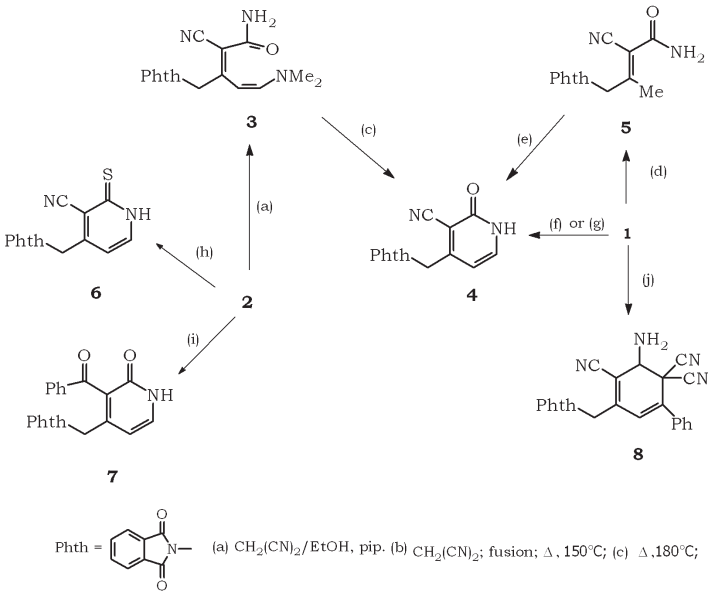
On the other hand, compound **1** reacted with phenylhydrazine in ethanol at reflux temperature to afford a yellow product that was identified as *N*-[(2-phenylhydrazono)-2-propyl]phthalimide (**11**). The latter compound fails to react with DMF DMA to yield the pyrazolo derivative **9b** under a variety conditions.

Reaction of **2** with hydroxylamine hydrochloride yielded an isoxazole derivative that was assigned structure **12** rather than **13** based on both ^1H and ^{13}C nmr. The ^1H nmr spectrum showed a resonance at δ_H = 8.39 ppm corresponding to H-3 of isoxazole [14,15]. If the reaction product is **13**, then the H-5 proton should resonate at lower field δ_H = 9.7 ppm [8]. Moreover, the ^{13}C nmr spectrum of the reaction product revealed three low field signals at δ_C 167, 157, 151 ppm. The signal at δ_C 167 ppm corresponding to the two phthalimide carbonyl groups, while the signals at δ_C 157 and 151 ppm corresponding to quaternary carbon (C-5) and to the (C-3) carbon coupled with a proton. As in the isoxazole system, the carbon resonating at δ_C 151 ppm corresponds to C-3 [14,15]. The formation of **12** is assumed to proceed *via* 1,4-addition across the α,β-unsaturated ketone moiety with loss of dimethylamine which then readily undergoes intramolecular cyclisation into the isoxazole derivative *via* loss of a water molecule (Scheme 3).

The foregoing results prompted us to investigate the behavior of **2** towards some heterocyclic amines as potential precursors for fused heterocyclic system. Thus, treatment of compound **2** with each of 3-amino-5-methyl-1*H*-pyrazole and 3-amino-5-phenyl-1*H*-pyrazole in refluxing pyridine furnished in each case a single product identified as pyrazolo[1,5-*a*]-pyrimidine derivatives with possible structures **15** or its isomer

Scheme 2

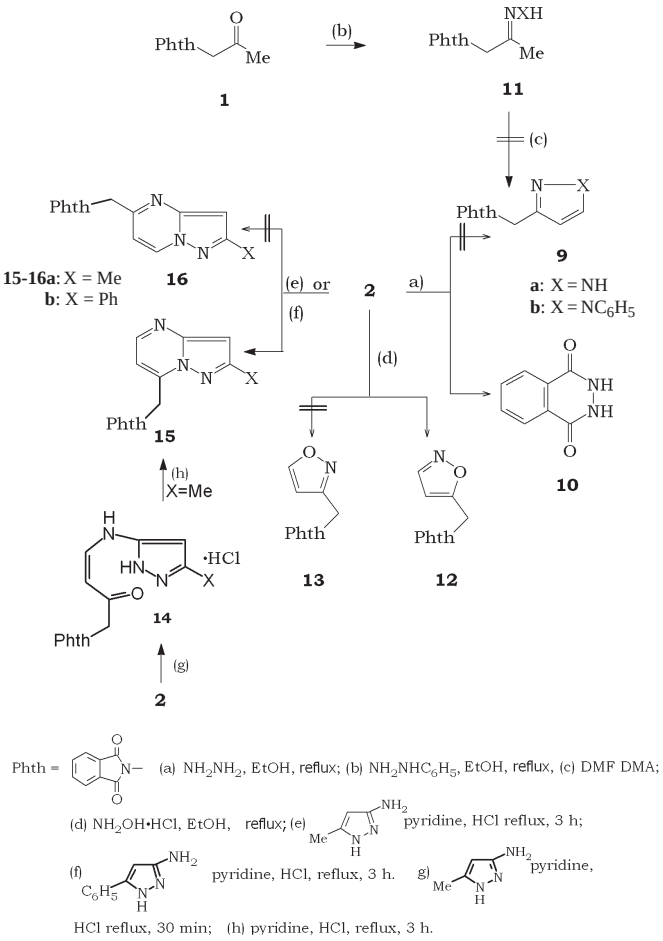
Scheme 2:



Phth =

(a) $CH_2(CN)_2$/EtOH, pip. (b) $CH_2(CN)_2$; fusion; Δ, 150°C; (c) Δ,180°C;
(d) $CH_2(CN)_2$, EtOH, pip. reflux; (e) DMF-DMA, Δ, 150°C; f) 1)DMF-DMA, 2) $CH_2(CN)_2$, Δ, 150°C;
(g) 1, $CH_2(CN)_2$, 2) DMF-DMA, Δ, 150°C; h) NH_2CSCH_2CN; i) $PhCOCH_2CN$; j) 1) $CH_2(CN)_2$; pip.;
2) $PhCH=C(CN)_2$ Δ, 180°C.

Scheme 3



16. The ir spectrum of the reaction product showed the two phthalimide carbonyl absorptions at 1773 and 1710 cm^{-1}. Also the ^1H nmr spectrum revealed three singlet at δ_H= 2.57, 5.40 and 6.57 ppm corresponding to methyl, methylene and pyrazol proton resonances respectively, in addition to the characteristic two doublets at 6.94 ppm and 8.33 ppm due to pyrimidine protons with J=4 Hz and multiplets for aromatic protons at δ 7.27 – 7.97 ppm. Structure **16** was readily ruled out on the basis of isolated intermediate **14** that was cyclized into **15a** on refluxing pyridine and in the presence of hydrochloric acid [8].

Biological Activity.

The biological activities of some newly synthesized compounds were screened for their antifungal activity against *Aspergillus niger* and *Fusarium oxysporiurn* while the antibacterial activity was tested against *Eschirichia coli*, *Bacillus subtilis* and *Staphylococcus aureus*. Bacteria and Fungi were maintained on nutrient agar slops (NA) and sabouraud agar (SA), respectively. When calculated, a loop full of bacteria was grown on tryplic Saaybroth, while fungi were subcultured on a yeast nitrogen base supplemented with glucose (YNBG). All media used were of dificagrade. Table 1 shows *in vitro* bactericidal and fungicidal activities of some newly synthesized compounds.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra (KBr) were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. ^1H, ^{13}C nmr spectra and NOE experiments were recorded on a Brucker 400 MHz spectrometer with dimethyl-d_6-sulfoxide (DMSO-d_6) or deuteriochloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as an internal standard; chemical shifts are reported as δ units (ppm). Microanalyses were performed on a LECO CHNS 932 analyzer.

N-[2-Oxo-4-(*N*,*N*-dimethylamino)-3-butenyl]phthalimide(**2**).

A solution of **1** (2.03 g, 10 mmol) in xylene (20 mL) was treated with DMF DMA (1.33 g, 10 mmol) and refluxed for 20 hours. The solvent was evaporated under reduced pressure. The solid product, so formed, was collected by filtration and recrystallized from ethanol as yellow crystals (2.11 g, 82%); m.p. 155-158 °C; ir: ν_{max}: 1769 and 1715 (phthalimide CO) and 1660 cm^{-1} (conj. CO); δ_H 2.80 (s, 3H, Me); 3.05 (s, 3H, Me); 4.44 (s, 2H, CH_2); 5.05 (d, 1H, J=10 Hz, H-3); 7.61 (d, 1H, J=10 Hz, H-4); 7.84-7.91 ppm (m, 4H, phthalimide-H);^{13}C (dimethyl-d_6-sulfoxide): δ_C 187.22 (conj.CO), 168.26 (phthalimide CO); 135.57 (vinylic C-3), 132.57, 124.29, 124.16, 121.31 (phthalimide carbons & vinylic C-4); 46.90 (CH_2); 45.08 and 35.57 ppm (NMe).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.12; H, 5.52; N, 10.84. Found: C, 65.09; H, 5.46; N, 10.80.

Table 1

In *Vitro* Bactericidal and Fungicidal Activity of Newly Synthesized Compounds

Compound	*E-coli*	*B-subtilis*	*S-aureus*	*A-niger*	*F-oxysporium*
2	—	—	++	++++	++
4	—	—	+++	++	—
7	++	++	++	++++	—
8	+	+	++	++	+
12	+	+	—	+	
14a	—	—	++	+	—
14b	—	—	—	—	++

No effect = -; slight effect = +; Moderate effect = ++; strong effect = +++, ++++

2-Cyano-5-(*N*,*N*-dimethylamino)-3-(*N*-phthalimidomethyl)-2,4-pentadienamide (**3**).

A mixture of enaminone **2** (2.58 g, 10 mmol), malononitrile (0.66 g, 10 mmol) in ethanol (20 mL) and a few drops of piperidine was refluxed for 6 hours, then left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from ethanol as brown crystals (2.78 g, 86%), m.p. 254-256 °C; ir: ν_{max}: 3442, 331 (NH_2), 2194 (CN), 1771 and 1719 (phthalimide CO) and 1668 cm^{-1} (amide CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 2.95 (s, 6H, NMe_2), 4.79 (s, 2H, CH_2), 5.45 (d, 1H, J = 10 Hz, vinylic-H), 7.00 (bs, 2H, NH_2-D_2O exchangeable); 7.87-7.90 (m, 4H, phthalimide-H), 8.24 ppm (d, 1H, J = 10 Hz, vinylic-H).

Anal. Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.90; H, 5.05; N, 17.30.

1,2-*N*-[3-Cyano-(1*H*)-2-oxopyridin-4-yl)methyl]phthalimide (**4**).

Method A.

A mixture of enaminone **2** (2.58 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and few drops of piperidine was heated in an oil bath at 150-160 °C for 10 minutes. The reaction mixture was left to cool at room temperature the solid product was dissolved in a mixture of ethanol/DMF (10/5 mL) and then refluxed for 1 hour. The solid product, so formed, was collected by filtration and recrystallized from ethanol as brown crystals (2.26 g, 75%).

Method B.

Compound **3** (3.24 g, 10 mmol) was heated at 180 °C for 10 minutes, then allowed to cool at room temperature. The reaction mixture was dissolved in a mixture of ethanol/DMF (10/5 mL) and refluxed for 1 hour. The solid product, so formed, was collected by filtration and recrystallized from ethanol as brown crystals (2.03 g, 70%).

Method C:

In a similar manner to that described in *Method B*. A mixture of compound **5** (3.24 g, 10 mmol) and DMF DMA (1.33 g, 10 mmol) was heated at 150-160°C for 10 minutes gave compound **4** (2.09 g, 71%).

Method D.

A mixture of **1** (2.03 g, 10 mmol), DMF-DMA (1.33 g, 10 mmol) (2.09 g, 71%) was heated in oil bath at 150-160 °C for 10 minutes and then allowed to cool at room temperature. The reaction mixture was treated with malononitrile (0.66 g, 10 mmol) and heated for 10 minutes in oil bath at 150-160 °C. The reaction product was dissolved in a mixture of ethanol/DMF (10/5 mL) and refluxed for 1 hour. The solid product, so formed, was collected by filtration and recrystallized from ethanol as brown crystals (2.20 g, 73%).

Method E.

In a similar manner to that described in Method D, a mixture of compound **1** (2.03 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and a few drops of piperidine was heated in an oil bath at 150-160 °C for 10 minutes. The reaction mixture was treated with DMF DMA (1.33 g, 10 mmol) and heated for 15 minutes. The solid product so formed was collected by filtration and recrystallized as brown crystal (2.09 g, 73%). Compound **4** has m.p. 170-172°C; ir: ν_{max}: 3446 (NH), 2203 (CN), 1775 and 1717 (phthalimide CO) and 1622 cm^{-1} (amide CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 4.67 (s, 2H, CH_2), 6.43 (d, 1H, J=6.8 Hz, H-5), 7.67 (d, 1H, J=6.8 Hz, H-6), 7.76-7.91 (m, 4H, phthalimide-H) and 9.74 ppm (bs, 1H, NH, D_2O exchangeable).

Anal. Calcd. for $C_{15}H_9N_3O_3$: C, 64.51; H, 3.25; N, 15.05. Found: C, 64.75; H, 3.22; N, 15.23.

2-Cyano-3-methyl-4-(*N*-phthalimido)-2-butenamide (**5**).

A mixture of **1** (2.03 g, 10 mmol) and malononitrile (0.66 g, 10 mmol) in ethanol (20 mL) and few drops of piperidine was refluxed for 15 minutes then left to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from ethanol as yellow crystals (2.28 g, 85%) m.p. 150-152 °C; ir: ν_{max}: 3440, 3370 (NH_2), 2211 (CN) 1774 and 1718 (phthalimide CO); 1646 cm^{-1} (amide CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 2.29 (s, 3H, Me); 5.42 (s, 2H, CH_2); 7.77-7.94 ppm (m, 6H, phthalimide-H and NH_2).

Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.28; H, 3.99; N, 15.71.

1,2-*N*-[3-Cyano-(1*H*)-2-thioxopyridin-4-yl)methyl]phthalimide (**6**).

A mixture of enaminone **2** (2.58 g, 10 mmol) and cyanothioacetamide (1.0 g, 10 mmol) in ethanol (20 mL) was refluxed for 2 hours, then left to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from ethanol as green crystals (1.94 g, 66%), m.p. 271-272 °C; ir: ν_{max}: 3467 (NH), 2233 (CN), 1775 and 1712 cm^{-1} (phthalimide CO); ^1H nmr (dimethyl-d_6-sulfoxde): δ_H 4.85 (s, 2H, CH_2), 6.79 (d, 1H, J = 7 Hz, H-5), 7.86-7.93 (m, 4H, phthalimide-H); 7.98 (d, 1H, J=7Hz, H-6), 14.60 ppm (bs, 1H, NH_2-D_2O exchangeable); ^{13}C nmr (dimethyl-d_6-sulfoxide); δ_C 179.16 (C-2), 168.78 (phthalimide CO); 153.64, 146.01, 135.98, 132.82, 124.81, 121.31 (aromatic carbons), 118.02 (CN) and 111.19 (C-3) and 44.97 ppm (CH_2).

Anal. Calcd. for $C_{15}H_9N_3O_2S$: C, 61.02; H, 3.07; N, 14.23. Found: C, 61.11; H, 3.22; N, 14.42.

N-[3-Benzoyl-(1*H*)-2-oxopyridin-4-yl)methyl]phthalimide (**7**).

A mixture of compound **2** (2.58 g, 10 mmol) and benzoylacetonitrile (1.45 g, 10 mmol) in ethanol (20 mL) was refluxed for 2 hours then left to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from ethanol as brown crystals (2.43 g, 68%), m.p. 120-121 °C; ir: ν_{max}: 3441 (NH), 1771 and 1714 (phthalimide CO), 1685 (keto CO) and 1617 cm^{-1} (amide CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 4.60 (s, 2H, CH_2), 6.22 (d, 1H, J=6 Hz, H-5), 7.23-7.95 ppm (m, 11H, Ar-H and NH-D_2O exchangeable).

Anal. Calcd. for $C_{21}H_{14}N_2O_4$ requires: C, 70.38; H, 3.94; N, 7.82. Found: C, 70.18; H, 4.09; N, 8.03.

N-[(6-Amino-1,5,5-tricyano-4-phenyl-1,3-cyclohexadien-2-yl)methyl]phthalimide (**8**).

A mixture of **1** (2.03 g, 10 mmol), malononitrile (0.66 g, 10 mmol), and few drops of piperidine was heated at 180 °C for 10 minutes, then allowed to cool at room temperature. To the reaction mixture benzylidenemalononitrile (1.45 g, 10 mmol) was added then heated at 160-170 °C for 10 minutes. The fused mixture was allowed to cool at room temperature and dissolved in a mixture of EtOH/DMF in ratio (2:1) then refluxed for 1 h. The solid product so formed was collected by filtration and recrystal-

lized from a mixture of EtOH/DMF in ratio (2:1) as brown crystals (3.15 g, 78%); m.p. 224-226°C, ir: ν_{max} 3474 and 3338 (NH_2), 2204 (b, 3CN), 1774 and 1719 cm^{-1} (phthalimide CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 2.24 (s, 1H, H-6), 4.58 (s, 2H, CH_2), 7.23-7.95 (m, 10H, Ar-H), 8.32 (bs, 2H, NH_2).

Anal. Calcd. for $C_{24}H_{15}N_5O_2$: C, 71.10; H, 3.73; N, 17.28. Found: 70.99; H, 3.66; N, 17.09.

2,3-Dihydrophthalazine-1,4-dione (**10**).

A mixture of compound **2** (2.58 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) in absolute ethanol (20 mL) was refluxed for 3 hours then allowed to cool at room temperature. The solid product so formed was collected by filtration and recrystallized form ethanol as brown crystals (1.16 g, 72%); m.p. >300°C, Lit [13] >300°C.

N-[(2-phenylhydrazono)propyl]phthalimide (**11**).

A solution of **1** (2.03 g, 10 mmol) in ethanol (20 mL) was treated with phenylhydrazine (1.08 g, 10 mmol). The reaction mixture was refluxed for 2 hours, and allowed to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from ethanol as yellow crystals (2.26 g, 71%), m.p. 120-122°C; ir: ν_{max}: 3471 (NH), 1776 and 1720 cm^{-1} (phthalimide CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 1.91 (s, 3H, Me), 4.38 (s, 2H, CH_2), 6.59 (t, 1H, J=6 Hz, Ar-H), 6.74 (d, 2H, J=6 Hz, Ar-H), 6.96 (t, 2H, J=6 Hz, Ar-H); 7.82-7.94 (m, 4H, phthalimide-H) and 8.90 ppm (bs, 1H, NH).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.32. Found: C, 69.52; H, 5.24; N, 14.12.

N-[(Isoxazol-5-yl)methyl]phthalimide (**12**).

A mixture of **2** (2.58 g, 10 mmol) and hydroxylamine hydrochloride (0.69 g, 10 mmol) in ethanol (30 mL) was refluxed for 1 hour and then left to cool at room temperature. The solid product so formed was collected by filtration and recrystallized from ethanol as brown crystals (1.66 g, 73%); m.p. 119-121 °C; ir: ν_{max}: 1775 and 1721 cm^{-1} (phthalimide CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 5.04 (s, 2H, CH_2); 6.29 (s, 1H, H-4); 7.77-7.97 (m, 4H, phthalimide-H) and 8.39 ppm (s, 1H, H-3); ^{13}C nmr (diemthyl-d_6-sulfoxide); δ_C 167.93 (CO), 157.88 (C-5), 151.95 (C-3), 135.74, 132.44, 124.40 (phthalimide carbons), 124.16 (C-4) and 44.97 ppm (CH_2).

Anal. Calcd. for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 62.92; H, 3.64; N, 12.02.

N-[4-(3-Methyl-(1H)-pyrazolo-5-yl)amino-2-oxo-3-butenyl]-phthalimide hydrochloride (**14**).

A solution of **2** (2.58 g, 10 mmol) in pyridine (20 mL) was treated with 3-amino-5-methyl-(1*H*)-pyrazole (0.97 g, 10 mmol). The reaction mixture was refluxed for 30 minutes, then allowed to cool at room temperature and neutralized with hydrochloric acid (10%). The solid product, so formed, was collected by filtration and recrystallized from ethanol as pale yellow crystals (2.52 g, 73%) mp. 115-117°C; ir: ν_{max}: 3454 and 3145 (2NH), 1767 and 1711 (phthalimide CO) 1659 and (conj. CO); ^1H nmr (dimethyl-d_6-sulfoxide); δ_H 2.53 (s, 3H, Me), 5.19 (s, 2H, CH_2); 5.25 (d, 1H, J=10 Hz, H-3), 6.67 (s, 1H, pyrazol-H); 6.98 (d, 1H, J=10 Hz, H-4); 7.91-7.97 (m, 4H, phthalimide-H); 8.52 (bs, 1H, NH, D_2O exchangeable); 8.93 ppm (bs, 1H, NH, D_2O exchangeable).

Anal. Calcd. For $C_{16}H_{15}N_4O_3Cl$: C, 55.42; H, 4.36; N, 16.15. Found: C, 55.34; H, 4.31; N, 16.35.

General Procedure for the Synthesis of (**15a,b**).

A solution of **2** (2.58 g, 10 mmol) in pyridine (20 mL) was treated with 3-amino-5-methylpyrazole (0.97 g, 10 mmol) or 3-amino-5-phenylpyrazole (1.59 g, 10 mmol). The reaction mixture was refluxed for 3 hours, then allowed to cool to room temperature and neutralized with hydrochloric acid (10%). The solid product so formed was collected by filtration and recrystallized from ethanol.

N-[2-Methylpyrazolo[1,5-*a*]pyrimidin-7-yl]methyl]phthalimide (**15a**).

This compound was obtained as pale yellow crystals (2.36 g, 81%), m.p. 228-230 °C, ir: ν_{max}: 1773 and 1721 cm^{-1} (phthalimido CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 2.57 (s, 3H, Me), 5.40 (s, 2H, CH_2), 6.57 (s, 1H, H-3), 6.94 (d, 1H, J=4.0 Hz, H-6), 7.27-7.97 (m, 4H, phthalimide-H), 8.33 ppm (d, 1H, J = 4.0 Hz, H-7); ^{13}C nmr (dimethyl-d_6-sulfoxide): δ_C 168.53 (2CO), 155.40 (C-7), 150.01, 143.60, 135.72, 132.86, 124.75, 124.47, 105.18, 96.82 (aromatic carbons); 45.30 (CH_2), 15.51 ppm (Me).

Anal. Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.74; H, 4.13; N, 19.16. Found: C, 65.74; H, 4.08, N, 19.01.

N-[2-phenylpyrazolo[1,5-*a*]pyrimidin-7-yl]methyl]phthalimide (**15b**).

This compound was obtained as yellow crystal (3.0 g, 85%), m.p. 236-238 °C; ir: ν_{max}: 1783 and 1721 cm^{-1} (phthalimide CO); ^1H nmr (dimethyl-d_6-sulfoxide): δ_H 5.33 (s, 2H, CH_2), 7.12 (d, 1H, J = 6 Hz, H-6), 7.32 (s, 1H, H-3), 7.41-7.53 (m, 5H, Ar-H), 7.89-7.98 (m, 4H, phthalimide-H) and 8.48 ppm (d, 1H, J=6 Hz, H-5); ^{13}C nmr (dimethyl-d_6-sulfoxide): δ_C 168.53 (2CO), 155.95, 150.64, 143.79, 135.94, 133.29, 132.79, 130.38, 129.89, 127.40, 124.80, 124.47, 107.03, 95.38 (aromatic carbons), 45.09 (CH_2) and 14.14 ppm (Me).

Anal. Calcd. for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81. Found: C, 71.07; H, 4.02; N, 15.75.

Biological Testing.

Some of the newly synthesized compounds were tested against the specified microorganism, using 400 μg/mL (w/v) solutions in sterile dimethyl disulfoxide-d_6 (DMSO). A solution of the tested compound (0.01 mol) was poured aseptically in a well of 6 mm diameter made by a Cork borer in the nutrient agar medium for bacterial test and in Sabourund agar for fungal test. After placing the same volume in wells of all tested microorganisms nutrient agar plates were incubated at 37 °C for 24 h and sabourund dextrose agar plates were incubated at 25 °C for 48 h. The activities were expressed as inhibition zones (mm, diameter, as clear areas) as antibacterial and antifungal effect. The least concentration, which showed inhibitory effect on any specific microorganism, was considered as the minimum inhibitory concentration (MIC), which was determined using *streptomycin* (50 μg/ml) as the references.

Acknowledgement.

This work was financed by University of Kuwait, Research Grant SC 08/00. We are grateful to the Faculty of Science, Chemistry Department, SAF facility for the analytical and spectral measurement (Project G01/01 & G 03/01). We are also grateful to Dr. I. H. Abbas for the biological activity tests.

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