Regioselective Synthesis of Some Novel Pyrazoles, Isoxazoles, Pyrazolo[3,4-*d*]pyridazines and Isoxazolo[3,4-*d*]pyridazines Pendant to Benzimidazole

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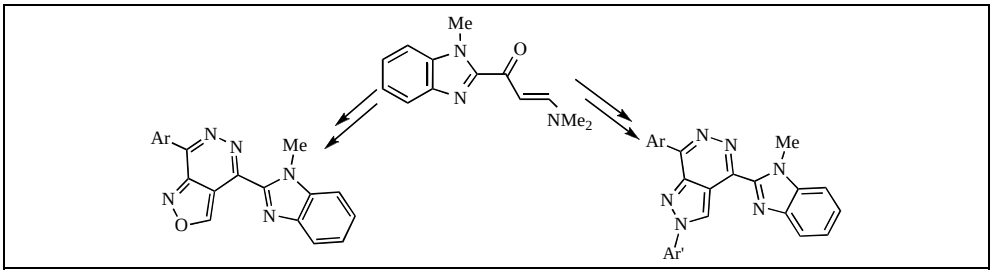

2-Acetyl-1-methyl-1*H*-benzimidazole reacts with dimethylformamide-dimethyl-acetal (DMF-DMA) to afford the corresponding *E*-1-(1-methyl-1*H*-benzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone. The latter compound reacts regioselectively with some nitrilimines and nitrile oxides to afford the corresponding pyrazole and isoxazole derivatives, respectively. These reaction products react with hydrazine hydrate to give the novel pyrazolo[3,4-*d*]pyridazine and isoxazolo[3,4-*d*]pyridazine derivatives, respectively.

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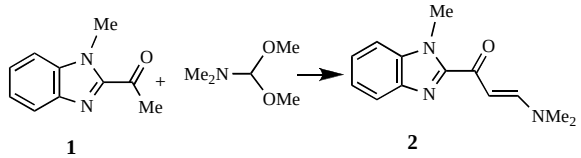
INTRODUCTION

Enaminone derivatives are highly reactive building blocks and are extensively used for the synthesis a wide variety of heterocyclic compounds [1-5]. On the other hand, a great deal of interest has been focused on the synthesis of benzimidazole derivatives because of their biological activity [6-9]. In continuation of our ongoing research program aimed at the synthesis of a variety of heterocyclic systems for biological screening [10-15], we report herein on the 1,3-dipolar cycloaddition of some nitrilimines and some nitriloxides to the versatile, *hitherto* unreported E-1-(1-methyl-*1H*-benzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone (**2**) as a convenient route for obtaining the target compounds.

RESULTS AND DISCUSSION

The key intermediate *E*-1-(1-methyl-1*H*-benzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone (**2**) was readily obtained by refluxing equimolar quantities of 2-acetyl-1-methylbenzimidazole (**1**) and dimethylformamide-dimethylacetal *(DMF-DMA)* in toluene (Scheme 1).

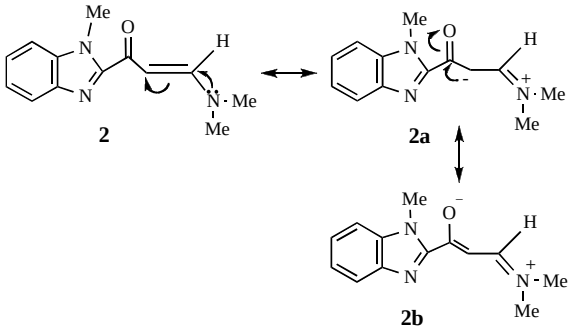
Scheme 1



1 **2**

Compound **2** can exist in two different resonance structures as shown in Scheme 2.

Scheme 2



2 **2a** **2b**

The structure of the enaminone **2** was confirmed by its elemental analysis and spectral data. Its ^{1}H nmr spectrum displayed a singlet signal at δ 3.08 due to *N*,*N*-dimethyl protons, a singlet signal at δ 4.18 due to *N*-methyl group of benzimidazole and two doublets at δ 6.37 and 7.87 (*J*=12.3 Hz) due to olefinic protons, in addition to aromatic multiplets in the region δ 7.81-7.83. The value of the coupling constant (*J*=12.3 Hz) for the ethylenic protons indicates that the enaminone **2** exists exclusively in the *E*-configuration. This conclusion was further unequivocally confirmed by X-ray crystallography (Figure 1), where single crystal X-ray diffraction of compound **2** adds sharp evidence not only for the

proposed structure but also for its stereochemical configuration.

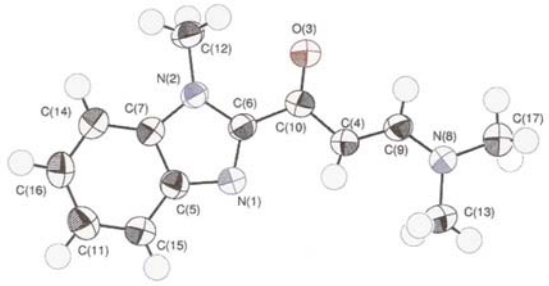


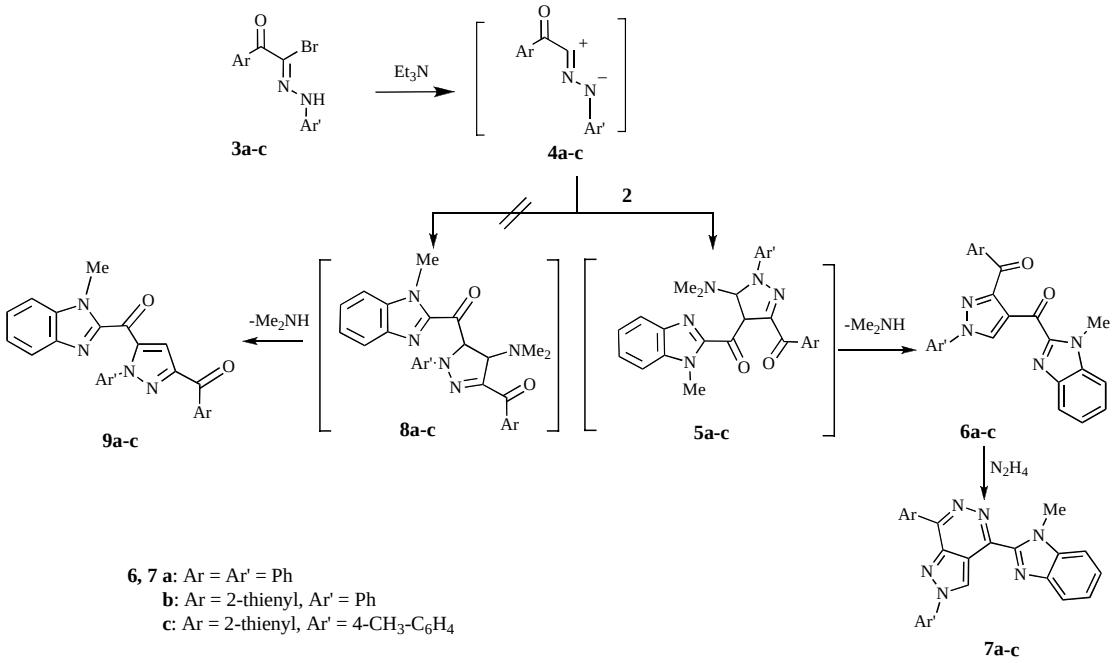
Figure 1. X- ray structure of compound **2**.

The reactivity of enaminones, in general, can be attributed to the fact that their molecules have two electron poor centers at C-1 and C-3 in addition to one electron-rich center at C-2 attributed by the delocalization of the lone pair of electrons on the nitrogen atom. When compound **2** was allowed to react with the nitrilimines **4a-c** (liberated, *in situ,* from the corresponding hydrazonyl halides **3** by the action of triethylamine in refluxing benzene), it afforded the novel pyrazole derivatives **6a-c** as shown in Scheme 3.

dipolar cycloaddition of the nitrilimines **4a-c** to the activated double bond in the enaminone **2** to afford the non-isolable dihydropyrazole intermediates **5** followed by elimination of dimethylamine yielding the pyrazole derivative **6a-c**. The other possible regioisomers **9a-c** are not observed through out the reactions and were excluded on the basis of the spectral data of the isolated products. For example, in the pyrazole ring system, C-4 is the most electron-rich carbon; thus, H-4 is expected to appear at a higher field, typically at δ 6.31. On the other hand, H-5 is linked to a carbon attached to a nitrogen atom and therefore, it is deshielded and appeared typically in the region δ 7.53-8.59. The ^{1}H nmr spectra of the isolated reaction products revealed, in each case, a singlet signal in the region of δ 8.70-9.07 which indicates the presence of the pyrazole H-5 rather than H-4 in the structure of the isolated products. This conclusion was further confirmed chemically *via* the reaction of compounds **6a-c** with hydrazine to afford the pyrazolo[3,4-*d*]pyridazine derivatives **7a-c** in almost quantitative yields (Scheme 3).

Similarly, when the enaminone **2** was allowed to react with the nitrileoxides **11a-c** [liberated, *in situ*, from the corresponding hydroximoyl chlorides **10a-c**], it led to the formation of adducts that could be converted into the isoxazole derivatives **13a-c** or their regioisomers **16a-c**

Scheme 3



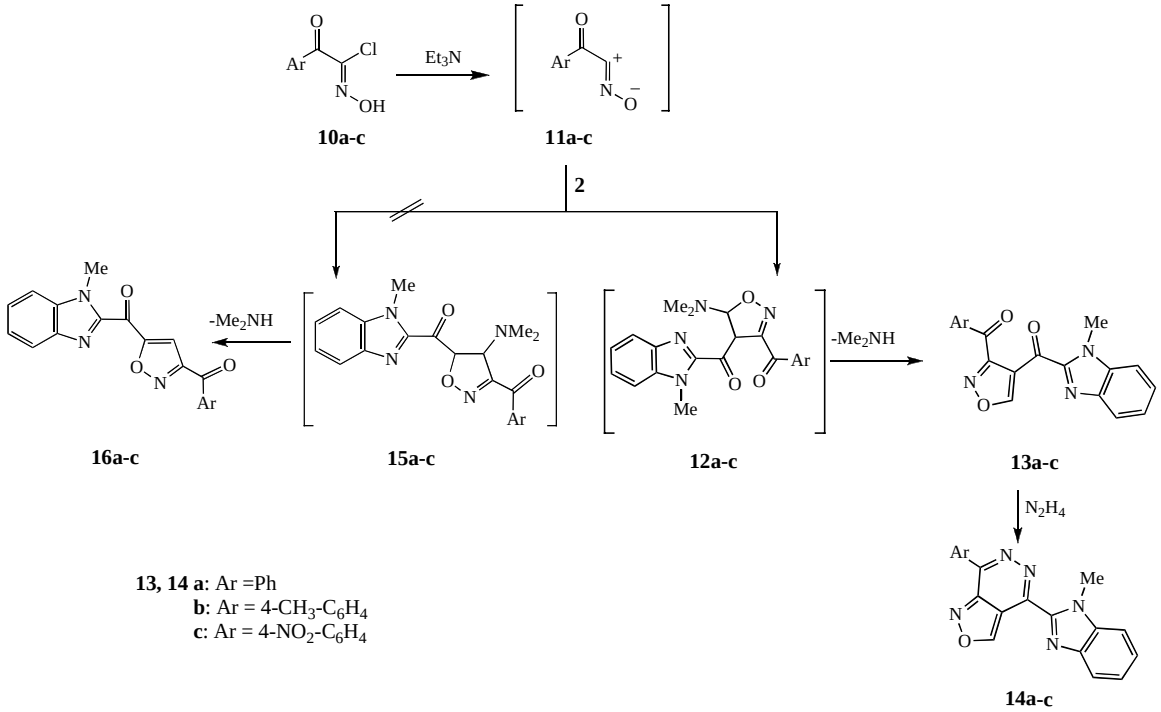
6, 7 a: Ar = Ar' = Ph
b: Ar = 2-thienyl, Ar' = Ph
c: Ar = 2-thienyl, Ar' = 4-CH_3-C_6H_4

The double bond in compound **2** can be looked on as an electron-rich one that may enter in 1,3-dipolar cycloaddition reactions. It is worthwhile to report here that, the reaction of nitrilimines **4a-c** with the enaminone **2** afforded, in each case, only one isolable product as tested by TLC analysis. The reaction products were identified as the pyrazole structure **6a-c** (Scheme 3) that are assumed to be formed *via* initial 1,3-

via elimination of dimethylamine molecule from the non-isolable intermediates **12** or **15** as depicted in Scheme 4. Structure **16** was not observed throughout the reactions and was easily ruled out on the basis of the spectral data of the reaction products. For example, the ^{1}H nmr spectra of the isolated products revealed, in each case, a singlet signal corresponding to the isoxazole H-5 proton in the

region of δ 10.01-10.02 which is in complete agreement of the proposed structure **13** (Scheme 4). A further evidence for the formation of the products **13** stems from their conversion into the corresponding isoxazolo[3,4-*d*]-pyridazine derivatives **14a-c** upon treatment with hydrazine. The structures of the products **14a-c** were confirmed on the basis of their elemental analysis and spectral data (see Experimental Part).

Scheme 4



CONCLUSION

In conclusion, we have investigated the stereochemical configuration, the applicability and synthetic potency of *E*-1-(1-methyl-1*H*-benzimidazol-2-yl)-3-*N*,*N*-dimethyl-aminoprop-2-enone (**2**) as a convenient route to synthesize, with a facile and simple reaction conditions, the novel pyrazole, isoxazole, pyrazolo[3,4-*d*]pyridazine and isoxazolo[3,4-*d*]pyridazine derivatives **6a-c, 13a-c**, **7a-c** and **14a-c**, respectively.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT ir 8101 PC infrared spectro-photometers. The nmr spectra were recorded on a Varian Mercury VX-300 nmr spectrometer. ^{1}H (300 MHz) and ^{13}C NMR (75.46 MHz) were run in deuterated chloroform ($CDCl_3$) or dimethylsulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. X-ray crystallography was carried out on a Kappa CCD Enraf Nonius FR 590 diffractometer, National Research Center, Dokki, Cairo, Egypt. 2-Acetyl-1-methyl-1*H*-benzimidazole (**1**) [16] hydrazonyl halides **3a-c** [17] hydroximoyl chlorides **10a-c** [18] were prepared according to the reported literature.

***E*-1-(1-methyl1-*H*-benzimidazol-2-yl)-3-*N*,*N*-dimethyl-aminoprop-2-enone (2).** To a solution of 2-acetyl-1-methyl-1*H*-benzimidazole (**1**) (17.4 g, 0.01 mole) in dry toluene (150 mL) was added dimethylformamide-dimethylacetal *(DMF-DMA)* (13.4 g, 0.01 mole) and the reaction mixture was refluxed for 8 h. The solvent was removed by distillation under reduced pressure. The residual reddish brown viscous liquid was taken in petroleum ether (bp 60-80°C) (20 ml) and the resulting golden yellow crystals were collected by filtration, washed thoroughly with ether, dried and finally recrystallized from dry benzene to afford the 1-(1-methyl-1*H*-benzimidazol-2-yl)-3-*N*,*N*-dimethyl-aminoprop-2-enone **2** in 70% yield, m.p 150°C; ir (KBr) ν_{max}/cm^{-1}: 1645 (C=O), 1599 (C=N); ^{1}H nmr (DMSO-d_6): δ 3.08 (s, 6H, $N(CH_3)_2$), 4.18 (s, 3H, NCH_3), 6.37 (d, 1H, J = 12.3 Hz, -CO-CH=), 7.82-7.83 (m, 4H, Ar-H), 7.87 (d, J = 12.3 Hz, 1H, =CH-N); ^{13}C nmr (DMSO-d_6): δ 31.97, 44.77, 120.23, 110.88, 123.87, 136.69, 141.26, 149.05, 179.42; MS (*m/z*): 229 (M^+). *Anal.* Calcd for $C_{13}H_{15}N_3O$ (229.28): C, 68.10; H, 6.59; N, 18.33%. Found: C, 68.20; H, 6.78; N, 18.04 %.

X-Ray crystallography. A single crystal of compound 2 was obtained by slow evaporation from a mixture of benzene and petroleum ether. The crystal structure was solved and refined using maxus (nonius, Deflt and MacScience, Japan) [19] Mo-Kα

radiation (λ = 0.71073 Å) and a graphite monochromator were used for data collection. The chemical formula and ring labeling system is shown in Figure 1.

Table 1

Crystal data of compound **2**

Chemical formula	$C_{13}H_{15}N_3O$
M	229.283
System	Monoclinic
space group	$p2_1/c$
a	9.9017 (3)Å
b	5.7614 (2)Å
c	22.2352 (12)Å
α	90.00°
β	11. (18) x 10^{1}°
V	1223.02 (9)Å^3
Z	4
Dc	1.245 Mg m^{-3}
θ	2.910—27.485 °
μ(Mo-Kα)	0.08 mm^{-1}
T	298 K
Measured reflections	4666
Independent reflections	3083
Observed reflections	1406
R_{int}	0.026
R(all)	0.115
wR(ref)	0.134
wR(all)	0.142
S(ref)	1.209
S(all)	1.118
Δ/σ_{max}	0.039
$\Delta\rho_{max}$	0.29eÅ^3
$\Delta\rho_{min}$	-0.37eÅ^3

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 297714. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union, Road, Cambridge CB2 1EZ, UK [fax: 144-(0)1223-336033 or e-mail: **deposit@ccdc.cam.ac.uk].**

General Procedure for the Reaction of Enaminone 2 with Hydrazonyl Halides 3a-c. To a mixture of *E*-1-(1-methyl-1*H*-benzimidazol-2-yl)-3-*N*,*N*-dimethylaminoprop-2-enone (**2**) (4.58 g, 0.02 mole) and the appropriate hydrazonyl bromide **3** (0.02 mole), in benzene (25 mL), an equimolar of triethylamine was added. The reaction mixture was heated under reflux for 4 h and the solvent was distilled off under reduced pressure. The residual brown viscous liquid was taken in methanol and the resulting solid was collected by filtration, washed thoroughly with methanol, dried and finally recrystallized from ethanol/DMF to afford corresponding pyrazole derivatives **6a-c** in 70-80% yield.

(3-Benzoyl-1-phenyl-1*H*-pyrazol-4-yl)-(1-methyl-1*H*-benzimidazol-2-yl)-methanone (6a). White crystals, Yield (74 %); mp. 170-171°C (ethanol/DMF); ir (KBr) ν_{max}/cm^{-1}: 1680 (C=O), 1635 (C=O), 1598 (C=N); ^{1}H nmr ($CDCl_3$): δ 4.01 (s, 3H, NCH_3), 7.36-8.02 (m, 14H, ArH's), 9.07 (s, 1H, pyrazole-5-CH); ^{13}C nmr ($CDCl_3$): δ 186.69, 136.69, 136.57, 133.29, 133.01, 129.98, 129.51, 128.24, 127.95, 125.66, 123.55, 123.37, 121.62, 120.00, 110.39, 32.05. MS (*m*/*z*, %): 406 (M$^+$, 19.1%), 329 (100%), 301 (45.8%), 105 (24.4%), 77 (78.4%). Calcd for $C_{25}H_{18}N_4O_2$ (406.44): C, 73.88; H, 4.46; N, 13.78%. Found: C, 73.76; H, 4.61; N, 13.75%.

(3-Thien-2-oyl-1-phenyl-1*H*-pyrazol-4-yl)-(1-methyl-1*H*-benzimidazol-2-yl)-methanone (6b). Buff crystals, Yield (79 %), mp.195-196°C (ethanol/DMF); ir (KBr) ν_{max}/cm^{-1}: 1690 (C=O), 1645 (C=O); ^{1}H nmr ($CDCl_3$): δ 4.09 (s, 3H, NCH_3), 7.45-8.33 (m, 12H, ArH's), 8.97 (s, 1H, pyrazole-5-CH); MS (*m*/*z*): 412 (M$^+$, 12.8%), 329 (100%), 301 (10.8%), 77 (18.4%). Calcd for $C_{23}H_{16}N_4O_2S$ (412.46): C, 66.97; H, 3.91; N, 13.58; S, 7.77%. Found: C, 67.13; H, 4.05; N, 13.38; S, 7.67 %.

(3-Thien-2-oyl-1-*p*-tolyl-1*H*-pyrazol-4-yl)-(1-methyl-1*H*-benzimidazol-2-yl)-methanone (6c). Buff crystals, Yield (70 %), mp. 204-205°C (ethanol/DMF); ir (KBr) ν_{max}/cm^{-1}: 1680 (C=O), 1639 (C=O); ^{1}H nmr ($CDCl_3$): δ 2.92 (s, 3H, CH_3), 4.04 (s, 3H, NCH_3), 7.15-8.06 (m, 11H, ArH's), 8.85 (s, 1H, pyrazole-5-CH); MS (*m*/*z*): 426 (M$^+$, 19.4%), 329 (100%), 301 (13.2%). Calcd for $C_{24}H_{18}N_4O_2S$ (426.49): C, 67.59; H, 4.25; N, 13.14; S, 7.52 %. Found: C, 67.49; H, 4.31; N, 13.12; S, 7.50 %.

General Procedure for the Synthesis of 2-Aryl-4-(1-methyl-1*H*-benzimidazol-2-yl)-7-substituted-pyrazolo[3,4-*d*]-pyridazines 7a-c. A mixture of the appropriate pyrazole derivative **6** (0.01 mole) and hydrazine hydrate (0.2 mL, 80%) in ethanol (20 mL) was refluxed for 1h. then allowed to cool. The precipitated product was collected by filtration, washed with ethanol and dried. Recrystallization from ethanol/DMF afforded the corresponding pyrazolo[3,4-*d*]pyridazine derivatives **7a-c** in 75-80% yields.

2,7-Diphenyl-4-(1-methyl-1*H*-benzimidazol-2-yl)-2*H*-pyrazolo[3,4-*d*]pyridazine (7a). Yellow crystals, Yield (77%); mp. 290-292°C (ethanol/ DMF); ir (KBr) ν_{max}/cm^{-1}: 1597 (C=N); ^{1}H nmr (DMSO-d_6): δ 4.09 (s, 3H, NCH_3), 7.45-7.75 (m, 14H, ArH's), 8.95 (s, 1H- pyrazole); MS (*m*/*z*): 402 (M$^+$, 100%), 131 (9.4%), 77 (45.2%). Calcd for $C_{25}H_{18}N_6$ (402.45): C, 74.61; H, 4.51; 20.88 %. Found: C, 74.72; H, 4.49; N, 20.79 %.

4-(1-Methyl-1*H*-benzimidazol-2-yl)-2-phenyl-7-(2-thienyl)-2*H*-pyrazolo[3,4-d]pyridazine (7b). Yellow crystals, Yield (79%); mp. > 300°C (ethanol/ DMF); ir (KBr) ν_{max}/cm^{-1}: 1597 (C=N); ^{1}H nmr (DMSO-d_6): δ 4.05 (s, 3H, NCH_3), 7.21-7.78 (m, 12H, ArH's), 9.05 (s, 1H- pyrazole); MS (*m*/*z*): 408 (M$^+$, 100%), 131 (19.2%), 77 (16.2%). Calcd for $C_{23}H_{16}N_6S$ (408.48): C, 67.63; H, 3.95; N, 20.57; S, 7.85 %. Found: C, 67.53; H, 4.05; N, 20.47; S, 7.95 %.

4-(1-Methyl-1*H*-benzimidazol-2-yl)-2-(-*p*-tolyl)-7-(2-thienyl)-2*H*-pyrazolo[3,4-d]pyridazine (7c). Pale yellow crystals, Yield (75%); mp. > 300°C (ethanol/ DMF); ir (KBr) ν_{max}/cm^{-1}: 1586 (C=N); 1H nmr (DMSO-d_6): δ 2.81 (s, 3H, CH_3), 4.05 (s, 3H, NCH_3), 7.41-7.75 (m, 11H, ArH's), 8.75 (s, 1H-pyrazole); MS (*m*/*z*): 422 (M$^+$, 100%), 131 (11.3%). Calcd for $C_{23}H_{16}N_6S$ (422.50): C, 68.23; H, 4.29; N, 19.89; S, 7.59 %. Found: C, 68.20; H, 4.35; N, 19.90; S, 7.55 %.

General Procedure for the Reaction of Enaminone 2 with Hydroximoyl Chlorides 10a-c. A mixture of the enaminone **2** (2.29 g, 0.01 mole) and the appropriate aryl hydroximoyl chloride **10** (0.01 mole), in benzene (20 mL), was heated under reflux for 2 h. The solvent was removed by distillation under reduced pressure and the residual viscous liquid was taken in methanol. The resulting solid was collected by filtration, washed thoroughly with methanol, dried and finally recrystallized from ethanol/DMF to afford the corresponding isoxazole derivatives **13a-c** in 60-65% yield.

(3-Benzoyl-oxazol-4-yl)-(1-methyl-1*H*-benzimidazol-2-yl)methanone (13a). White crystals, Yield (60%); mp. 160-161˚C (ethanol/ DMF); ir (KBr) ν_{max}/cm^{-1}: 1680 (C=O), 1645 (C=O), 1589 (C=N); ^{1}H nmr ($CDCl_3$): δ 4.11 (s, 3H, NCH_3), 7.38-8.04 (m, 9H, ArH's), 10.02 (s, 1H, isoxazole-5-CH); ^{13}C nmr (CDCl3): δ 186.61, 176.37, 164.37, 164.80, 159.84, 142.52, 141.49, 136.87, 135.61, 134.35, 129.86, 128.64, 126.34, 124.00, 121.82, 120.33, 110.51, 32.06. MS (*m/z*): 331 (M^+, 100%), 159 (11.3%), 131 (24.1%). Calcd for $C_{19}H_{13}N_3O_3$ (331.32): C, 68.88; H, 3.95; N, 12.68%. Found: C, 69.02; H, 4.01; N, 12.48%.

(1-Methyl-1*H*-benzimidazol-2-yl)-[3-(4-methylbenzoyl)-isoxazol-4-yl]-methanone (13b). White crystals, Yield (63%); mp. 147-148˚C (ethanol/ DMF); ir (KBr) ν_{max}/cm^{-1}: 1680 (C=O), 1643 (C=O); ^{1}H nmr ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 4.16 (s, 3H, NCH_3), 7.36-8.21 (m, 8H, ArH's), 10.01 (s, 1H, isoxazole-5-CH); MS (*m/z*): 345 (M^+, 100%), 159 (12.1%), 131 (21.2%). Calcd. For $C_{20}H_{15}N_3O_3$ (345.35): C, 69.56; H, 4.38; N, 12.17%. Found: C, 69.66; H, 4.40; N, 12.05%.

(1-Methyl-1*H*-benzimidazol-2-yl)-[3-(4-nitrobenzoyl)-isoxazol-4-yl]-methanone (13c). Buff crystals, Yield (65%); mp. 167-168˚C (ethanol/ DMF); ir (KBr) ν_{max}/cm^{-1}: 1685 (C=O), 1640 (C=O), 1572 (C=N); ^{1}H nmr ($CDCl_3$): δ 4.11 (s, 3H, NCH_3), 7.39-8.01 (m, 8H, ArH's), 10.01 (s, 1H, isoxazole-5-CH); MS (*m/z*): 376 (M^+, 100%), 159 (29.1%), 131 (30.2%). Calcd. For $C_{19}H_{12}N_4O_5$ (376.32): C, 60.64; H, 3.21; N, 14.89%. Found: C, 60.58; H, 3.18; N, 14.98%.

General Procedure for the Synthesis of 7-Aryl-4-(1-methyl-1*H*-benzimidazol-2-yl)isoxazolo[3,4-*d*]pyridazine derivatives 14a-c. A mixture of the appropriate isoxazole derivative **13** (0.005 mole) and hydrazine hydrate (1 mL, 80%), in ethanol (20 mL), was refluxed for 1 h then allowed to cool. The precipitated product was collected by filtration, washed with ethanol and dried. Recrystallization from ethanol/DMF afforded the corresponding isoxazolo[3,4-*d*]pyridazine derivatives (**14a-c**) in 50-55% yields.

4-(1-Methyl-1*H*-benzimidazol-2-yl)-7-phenylisoxazolo[3,4-*d*]pyridazine (14a). Yellow crystals, Yield (54%); mp. 242-243˚C (ethanol/ DMF); ir (KBr) νmax/cm^{-1}: 1590 (C=N); ^{1}H nmr (DMSO-d_6): δ 4.16 (s, 3H, NCH_3), 7.43-7.99 (m, 9H, ArH's), 10.13 (s, 1H-isoxazole); ^{13}C nmr ((DMSO-d_6): δ 154.32, 152.73, 149.39, 146.78, 141.53, 138.81, 134.02, 131.70, 129.50, 128.87, 126.08, 124.30, 121.61, 121.59, 115.32, 110.23, 32.09. MS (*m/z*): 327 (M^+, 100%), 131 (35.2%). Calcd. For $C_{19}H_{13}N_5O$ (327.34): C, 69.71; H, 4.00; N, 21.39%. Found: C, 69.81; H, 4.11; N, 21.18%.

4-(1-Methyl-1*H*-benzimidazol-2-yl)-7-*p*-tolyl-isoxazolo[3,4-*d*]pyridazine (14b). Yellow crystals, Yield (55%); mp. > 300˚C (ethanol/ DMF); ir (KBr) ν_{max}/cm^{-1}: 1591 (C=N); ^{1}H NMR (DMSO-d_6): δ 4.10 (s, 3H, NCH_3), 7.33-8.01 (m, 8H, ArH's), 10.11 (s, 1H-isoxazole); MS (*m/z*): 341 (M^+, 100%), 131 (15.2%). Calcd. For $C_{20}H_{15}N_5O$ (341.37): C, 70.37; H, 4.43; N, 20.52%. Found: C, 70.50; H, 4.45; N, 20.37%.

4-(1-Methyl-1*H*-benzimidazol-2-yl)-7-(4-nitrophenyl)-isoxazolo[3,4-*d*]pyridazine (14c). Yellow crystals, Yield (51%); mp. > 300 ˚C (ethanol/ DMF); IR (KBr) ν_{max}/cm^{-1}: 1582 (C=N); ^{1}H nmr (DMSO-d_6): δ 4.02 (s, 3H, NCH_3), 7.36-7.87 (m, 8H, ArH's), 10.06 (s, 1H-isoxazole); MS (*m/z*): 372 (M^+, 100%), 131 (22.2%). Calcd. For $C_{19}H_{12}N_6O_3$ (372.34): C, 61.29; H, 3.25; N, 22.57%. Found: C, 61.49; H, 3.15; N, 20.47%.

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