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A NOVEL APPROACH TO THE SYNTHESIS OF 1-SUBSTITUTED-3,6-DIARYL-IMIDAZO[1,5-b]PYRIDAZINES

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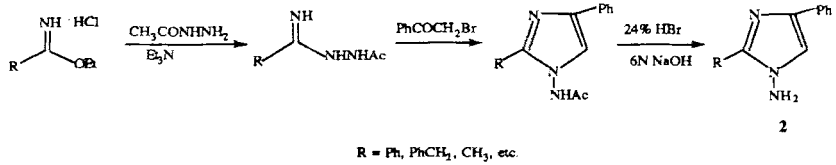
Abstract - A simple and efficient procedure for the preparation a new type of 1-substituted-3,6-diaryl-imidazo[1,5-b]pyridazines was described. This synthesis was carried out by the following three steps: Aryl methyl ketone **3** was condensed with 1-amino-2-substituted-4-arylimidazole **2** in ethanol with catalytic glacial acetic acid to afford enamines **4 a-k**. Treatment with t-butoxybis(dimethylamino)methane in DME at room temperature gave enamine (**5a-k**) which was cyclized to compound (**1a-k**) in 84 - 96% yield in trifluoroacetic acid.

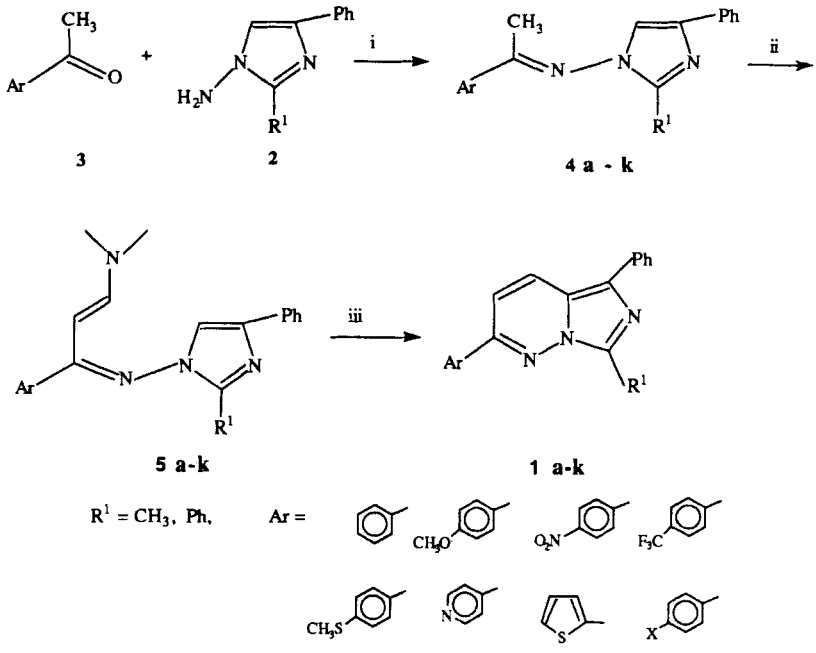
The derivatives of imidazo[1,5-b]pyridazines have been known to exhibit a variety of biological activities such as antiviral activities,[1] anti-RNA-virus,

fungicides.[2] They also have been shown to display exceptional activity against the reverse transcriptase of HIV-1, and therefore, are very promising non-nucleoside inhibitor for HIV therapy.[3] So far, only two reports exist on the synthesis of this ring system. A double acid-catalyzed cyclization of the semicarbazone produced 2-phenyl-4-acetylimidazo[1,5-b]pyridazine-5,7-(3H,6H)-dione.[4] The other synthesis begins with the preparation of pyridazine in several steps, then cyclization with polyphosphoric acid followed by treatment with $POCl_3$ produced the 3-methyl-6-chloroimidazo[1,5]pyridazines.[5] These methods, unfortunately, are too restrictive. They not only give products in unsatisfactory yield but also make the introduction of various substituents in the pyridazine ring infeasible. In connection with our synthesis program on the polyfuctional substituted imidazopyridazines with potential biological activity, we now report a general, novel, and effective synthetic approach to the previous inaccessible 3,6-diaryl imidazo[1,5-b]pyridazines **1a-k**.

In our scheme, only three steps are required to synthesize the target molecules, starting from the simple phenyl methyl ketone or substituted aryl methyl ketones (**3**) and 1-amino-2-substituted-4-arylimidazoles (**2**). The needed 1-aminoimidazoles (**2**) are synthesized according to the scheme 1.[6] We take advantage of t-butoxybis(dimethyl-amino)-methane for the enamination of the active methyl group of these imines (**4 a-k**).[7] This reaction is a key step for this synthesis, because it not only introduces the needed carbon atom for the pyridazine ring, but also provides the masked electrophilic center for the later cyclization. The use of a fuctionlized methylene group in enamines (**5a-k**) allows the direct construction of the pyridazine moiety of imidazo[1,5-b]-pyridazine of **1a-k**. Furthermore, as the aryl methyl ketone can be easily prepared by the Friedel-Crafts acylation or are commercially available, this method is suitable for synthesizing a large variety of 6-aryl-imidazo[1,5-b]pyridazines **1 a-k**.



Scheme 1



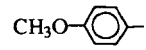
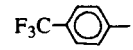
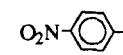
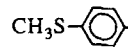
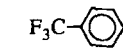
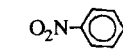
i) Ethanol, HOAc. ii) t-Butoxybis(dimethylamino)methane, DME, rt. iii) TFA, reflux

Scheme 2

The synthetic pathway to 1-substituted-3-phenyl-6-aryl-imidazo[1,5-b]-pyridazines **1a-k** is outlined in the scheme 2: various aryl methyl ketones **3** were converted to imines **4 a-k** in 82 to 97% yield by treatment with 1-amino-2-substituted-4-arylimidazoles **2** and catalytic acetic acid in ethanol at reflux. the active methyl group of imines **4 a-k** were dimethylaminomethylenated in 84 to 96% yield with t-butoxybis(dimethylamio)methane in 1,2-dimethoxylethane at room temperature to provide the enamines **5 a-k**. Enamines **5 a-k** were cyclized to 3, 6-aryl-imidazo[1,5-b]pyridazines **1a-k** in 85 to 98% yield in trifluoroacetic acid at reflux.

In conclusion, we have devised a very efficient method to prepare the compounds **1a-k** in high yield under mild conditions.

Table 1. substitution for R^1 and Ar group in compound **4 a-k** , **5 a-k** and **1 a-k**.

	R^1	Ar
a	CH_3	
b	CH_3	
c	CH_3	
d	CH_3	
e	CH_3	
f	CH_3	
g	CH_3	
h	Ph	
i	Ph	
j	Ph	
k	Ph	

EXPERIMENTAL

All melting points were determined on a Met-Temp apparatus and are uncorrected. Column chromatographies utilized Merck silica 60 (70-230 mesh or 230-400 mesh), Thin layer chromatography was performed with Merck silica gel 60 F254 0.25mm plates. ^1H and ^{13}C NMR were obtained on a Varian XL-200 MHz spectrometer. and chemical shifts are expressed in ppm(d) relative to TMS. IR spectra were recorded on Nicolet FT-5DX spectrophotometer. Microanalysis are obtained using a Perkin-Elmer 240 B element analyser. 1-Amino-2-methyl-4-

phenylimidazole and 1-amino-2,4-diphenylimidazole were prepared according to the general procedures in reference 6. and the purity was checked by NMR and melting point.

General Procedure for the Synthesis of Imines **4 a-k**:

(E)-N-[1-(4-Methoxyphenyl)ethylidene]-2-methyl-4-phenyl-1H-1,3-imidazol-1-amine (4a) as a typical procedure: A mixture of 4'-methoxyacetophenone (3.3 g, 22.0 mmol), 1-amino-2-methyl-4-phenylimidazole (3.81 g, 22.0 mmol), and a few drops of glacial acetic acid in ethanol (100 ml) was heated at reflux for 1 hr. Then the reaction mixture was cooled by ice-water. A white solid immediately precipitated, cold reaction mixture was filtered, the solid was washed with dilute hydrochloric acid followed by 40 ml of petroleum ether. The solid was recrystallized from the ethanol to afford 6.11 g (91 %) of imine **4 a** as a white needles, mp 167.5-169.5°C. IR (KBr) 3119, 1612, 1591, 1550, 1513, 1498, 1320, 1258, 1177, 1060, 940, 841, 740, 705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.92 (2H, d, J=8.9, C(2')- and C(6')-H's), 7.57 (1H, s, imidazole's 5-H), 7.47 (5H, m, phenyl), 7.01 (2H, d, J=8.9, C(3')- and C(5')-H's), 3.64 (3H, s, $-OCH_3$), 3.17 (3H, s, Het-CH_3), 2.34 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$): δ 162.02, 145.72, 143.11, 138.54, 137.42, 132.84, 131.22, 129.23, 124.88, 127.34, 126.44, 113.7, 56.03, 18.67, 16.34. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.72; H, 6.27; N, 13.76. Found: C, 74.63; H, 6.14; N, 13.56.

(E)-N-(1-Phenylethylidene)-1H-2-methyl-4-phenyl-1,3-imidazol-1-amine (4b). 96% yield, white plates (ethanol), mp 136.5-138°C. IR (KBr): 3125, 1618, 1598, 1552, 1442, 1371, 1244, 1168, 1050, 934, 768, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.94 (2H, m, C(3')- and C(5')-H's), 7.62 (5H, m, phenyl), 7.49 (3H, m, C(2') -and C(4')- and C(6')-H'S), 3.16 (3H, s, Het-CH_3), 2.34 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$) δ 145.32, 142.72, 139.24, 138.65, 137.69, 132.82, 131.22, 128.42, 127.31, 126.86, 18.58, 16.47. Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.51; H, 6.23; N, 15.26. Found: C, 78.53; H, 6.34; N, 15.55.

(E)-N-{1-(4-Trifluoromethyl)ethylidene}-1H-2-methyl-4-phenyl-1,3-imidazol-1-amine (4c). 92% yield, light yellow crysatals (ethyl acetate-hexane, 3:1), mp 121-123°C. IR (KBr) 3112, 1635, 1501, 1480, 1352, 1275, 1160,

1130, 1118, 1065, 790, 740, 713 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 8.23 (d, 2H, J=8.9, C(3')- and C(5')-H's), 8.14 (d, 2H, J=8.9, C(2')- and C(6')-H's), 7.57 (s, 1H), 7.47 (m, 5H, phenyl), 3.23 (s, 3H, Het-CH_3), 2.42 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 145.32, 142.72, 139.24, 138.65, 137.69, 132.82, 131.22, 128.42, 127.31, 126.86, 122.60, 18.58, 16.47. Anal. Calcd for $C_{19}H_{16}N_3F_3$: C, 66.46; H, 4.70; N, 12.24. Found: C, 66.37; H, 4.68; N, 12.36.

(E)-N-[1-4-Nitrophenyl)ethylidene]-1H-2-methyl-4-phenyl-1,3-imidazol-1-amine (4d) 90% yield, yellow prisms (methanol-benzene, 9:2). mp 183.5-185°C. IR (KBr) 3146, 3110, 3088, 1616, 1586, 1557, 1526, 1498, 1350, 1278, 1164, 1045, 934, 846, 764, 702 cm^{-1}; ^1H-NMR(CD_3COCD_3) δ 8.80 (d, 2H, J=9.5, C(3')- and C(5')-H's), 8.45 (d, 2H, J=9.5, C(2')- and C(6')-H's), 7.58 (s, 1H), 7.44 (m, 5H, phenyl), 3.25 (s, 3H, Het-CH_3), 2.41 (s, 3H, CH_3). ^{13}C-NMR (CD_3COCD_3): δ 147.83, 145.12, 142.32, 139.44, 138.75, 137.39, 133.12, 131.98, 128.12, 127.34, 126.56, 125.72, 123.54, 18.42, 16.37. Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49 Found: C, 67.67; H, 5.14; N, 17.66.

(E)-N-[1-(2-Thienyl)ethylidene]-1H-2-methyl-4-phenyl-1,3-imidazol-1-amine(4e) 94% yield, white needles (ethyl acetate-ethyl ether, 1:3), mp 142.5-144°C. IR (KBr): 3128, 3024, 1596, 1523, 1498, 1332, 1170, 1035,947, 757, 698, 624 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 7.65 (br d, J=4.0, 1H, C(3')-H), 7.60 (br d, J=5.0, 1H,C(5')-H), 7.17 (dd, J=4.0 and 4.9, 1H,C(4')-H), 7.69 (s, 1H), 7.35 (m, 5H, phenyl), 3.43 (s, 3H, Het-CH_3), 2.28 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ 145.67, 143.13, 139.88, 138.65, 132.82, 131.22, 128.42, 127.31, 125.70, 123.86, 18.12, 15.97. Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.21; H, 5.22; N, 14.87.

(E)-N-[1-(4-Pyridyl)ethylidene]-1H-2-methyl-4-phenyl-1,3-imidazol-1-amine (4f). 89% yield, colorless crystals (ethanol-hexane, 6:1), mp 138-140°C. IR (KBr): 3095, 2986, 2934, 1609, 1593, 1556, 1513, 1489, 1357, 1288, 1172, 1063, 955, 740, 705, 632 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 8.89 (dd, 2H, J=4.8 and 8.1,C(3')-H and C(5')-H's), 8.67 (dd, 2H, J=8.1, C(2')- and C(6')-H's). 7.67 (s, 1H), 7.38 (m, 5H, phenyl), 3.35 (s,3H, Het-CH_3), 2.28 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 151.04, 142.32, 138.78, 137.69, 132.72,

131.45, 128.62, 127.34, 125.86, 19.21, 16.43. Anal. Calcd for $C_{17}H_{16}N_4$: C, 73.88; H, 5.84; N, 20.27. Found: C, 73.67; H, 5.69; N, 20.45.

(E)-[1-[4-(methylthio)phenyl]ethylidene-1H-2-methyl-4-phenyl-1,3-imidazol-1-amine (4 g). Yield, 86%, white powder (ethy ether-hexane, 7:2) mp 97-99°C. IR (KBr) 3082, 2987, 2930, 1610, 1587, 1543, 1500, 1346, 1254, 1168, 1068, 943, 849, 738, 712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.89 (d, 2H, J=8.6, C(3')- and C(5')-H's), 7.70 (d, 2H, J=8.6, C(2')- and C(6')-H's), 7.58 (s, 1H), 7.44 (m, 5H, phenyl), 3.09 (s, 3H, Het-CH_3), 2.41 (s, 3H, CH_3), 2.12 (s, 3H, SCH_3). ^{13}C-NMR ($CDCl_3$): δ 144.92, 142.10, 138.69, 137.66, 132.72, 131.34, 128.87, 128.42, 127.45, 127.31, 126.86, 126.02, 18.02, 16.77. Anal. Calcd for $C_{19}H_{19}N_3S$: C, 70.99; H, 5.96; N, 13.07. Found: C, 71.12; H, 6.14; N; 13.26.

(E)-[1-(phenylethylidene)-1H-2,4-diphenyl-1,3-imidazol-1-amine (4h). 82% yield, white needles (2-propanol), mp 157-159°C. IR (KBr): 3096, 2982, 2944, 1613, 1587, 1557, 1516, 1479, 1323, 1251, 1167, 1059, 942, 846, 748, 712 cm^{-1}; 1H-NMR (CD_3OD). δ 7.92 (m, 2H, C(3')- and C(5')-H's), 7.48-7.65 (m, 10H, phenyl), 7.42 (3H, m, 3H, C(2') -and C(4')- and C(6')-H'S), 3.10 (s, 3H Het-CH_3), 2.31 (s, 3H, CH_3). ^{13}C-NMR (CD_3OD) δ 158.67, 142.66, 137.89, 132.98, 132.64, 132.01, 131.88, 131.43, 128.62, 128.01, 127.93, 127.21, 126.36, 123.14, 18.34, 16.27. Anal. Calcd for $C_{23}H_{19}N_3$: C, 81.87; H, 5.67; N, 12.45. Found: C, 81.66; H, 5.44; N, 12.57.

(E)-[1-(4-trifluromethylphenyl)ethylidene]-1H-2,4-diphenyl-1,3-imidazol-1-amine (4i). 92% yield, yellow needles (ethanol) . mp 162-164°C. IR(KBr) 3079, 2986, 1932, 1615, 1594, 1561,1522, 1502, 1328, 1256, 1172, 1064,952, 844,743, 701 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 8.27 (d, 2H, J=8.9,C(3')- and C(5')-H's), 8.14 (d, 2H, J=8.9, C(2')- and C(6')-H's), 7.87 (s, 1H), 7.27-7.61(m, 10H, 2,4-diphenyl), 2.18 (s, 3H, CH_3); ^{13}C-NMR (CD_3OD) δ 145.72, 142.43, 137.87, 135.88, 132.78, 131.12, 128.93, 128.42, 127.31, 127.30, 126.86, 122.61, 18.38, 16.33. Anal. Calcd for $C_{24}H_{18}N_3F_3$: C, 71.10; H, 4.47; N, 10.36. Found: C, 71.29; H, 4.50; N, 10.24.

(E)-[1-(4-nitrophenyl)ethylidene]-1H-2,4-diphenyl-1,3-imidazol-1-amine (4j). 92% yield, colorless needles (methanol-ethyl ether, 2:3), mp 202-

204°C. IR (KBr): 3087, 2976, 2933, 1602, 1594, 1557,1516, 1497, 1329, 1252, 1167, 1058, 939, 847, 760, 711cm^{-1}. ^{1}H-NMR (CD_3OD) δ 8.94 (d, 2H, J=9.5, C(3')- and C(5')-H's), 8.65 (d, 2H, J=9.5, C(2')- and C(6')-H's). 7.58 (s, 1H), 7.32-7.48 (m, 10H, phenyl), 2.31(s, 3H, CH_3); ^{13}C-NMR (CD_3OD) δ 150.73, 145.31, 142.54, 139.41, 138.65, 137.67, 133.09, 131.68, 128.42, 127.31, 126.57, 125.62, 123.64, 18.11, 16.72. Anal Calcd for $C_{23}H_{18}N_4O_2$: C, 72.24; H, 4.74; N, 14.65. Found: C, 72.14; H, 4.56; N, 14.52.

(E)-[1-(4-pyridyl)ethylidene]-1H-2,4-diphenyl-1,3-imidazol-1-amine (4k). 90% yield, light yellow prisms (acetone), mp 167-169°C. IR (KBr): 3131, 2942, 2918, 1609, 1593, 1547, 1507, 1465, 1243, 1062, 960, 780, 709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.82 (dd, 2H, J=4.8 and 8.1, C(3')-H and C(5')-H's), 8.61 (dd, 2H, J=8.1, C(2')- and C(6')-H's). 7.77 (s, 1H), 7.38-7.56 (m, 10H, phenyl), 2.18 (s, 3H, CH_3), 3.35 (s, 3H, Het-CH_3), 2.28 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ 150.64, 141.79, 139.78, 138.69, 132.79, 132.21, 131.45, 130.98, 128.62, 128.01, 127.39, 125.88, 123.65, 19.28, 16.47. Anal. Calcd for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.56. Found: C, 78.12; H, 5.43; N, 16.63.

General Procedure for The Conversion of Imines **4a-k** to Enamines **5 a-k**:

(E,E)-N-[3-(Dimethylamino)-1-(4-methoxylphenyl)-2-propenylidene] -1H-2-methyl-4-phenyl-1,3-imidazol-1-amine (5a) as a typical procedure: A suspension of imine **4a** (4.5 g, 14.7 mmol) and t-butoxybis(dimethylamino) methane (9.0 ml, 44 mmol) in dry 1,2-dimethoxyethane (150 ml) was stirred at 80 °C for 9 hr. The solvent and the volatiles were removed in vacuuo and the resulting solid was partitioned between dichloromethane (100 ml) and aqueous sodium bicarbonate (50 ml). The aqueous phase was extracted with dichloromethane (3 x 40 ml). The combined organic layers were dried with sodium sulfate and concentrated. The residue was purified by silica gel chromatography with 95: 5 dichloromethane - methanol as a eluant and gave 5.03 g (95%) of enamine **5a**. mp 184-185.5 °C. IR (KBr): 3128, 2942, 2918, 1622, 1603, 1553, 1504, 1464, 1332, 1247,1176 1065, 953, 820, 765 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 7.92 (d, 2H, J=8.9, C(2')- and C(6')-H's), 7.61 (s, 1H), 7.47 (m, 2H, phenyl), 7.01 (d, 2H, J=8.9, C(3')- and C(5')-H's), 6.81 (d, 1H, J=13.2, C(3)-H), 4.88 (d, 1H,

J=13.2, C(2)-H), 3.86 (s, 3H, OCH_3), 3.45 (s, 3H, Het-CH_3), 2.98 (broad,s, 3H, NCH_3), 2.74 (broad, s, 3H, NCH_3); ^{13}C-NMR (CD_3OD) δ 161.09, 145.32, 143.21, 138.24, 137.22, 136.14, 132.64, 131.02, 129.13, 124.58, 127.31, 126.34, 123,56, 122.89, 113.71, 32.17, 19.02, 16.74. Anal. Calcd for $C_{22}H_{24}N_4O$: C, 73.30; H, 6.71; N, 15.54. Found: C, 72.46; H, 6.82; N, 15.63.

(E,E)-N-[3-Dimethylamino)-1-phenyl-2-propenylidene]-1H-2-methyl -4-phenyl-1,3-imidazol-1-amine(5b). 93% yield, white solid (chloroform-hexane, 4 : 1), mp 135.5-137°C. IR (KBr): 3118, 2989, 2913, 1628, 1602, 1553, 1461, 1328, 1242, 1173, 1059, 958, 828, 753 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.56-7.83 (m, 10H, phenyl), 7.68 (s, 1H), 6.76 (d, 1H, J=13.2, C(3)-H), 4.82 (d, 1H, J=13.2,C(2)-H), 3.45 (s, 3H, Het-CH_3), 2.96 (s, 3H, NCH_3), 2.72 (s, 3H, NCH_3); ^{13}C-NMR ($CDCl_3$) δ 146.01, 142.31, 139.14, 138.45, 137.63, 132.78, 136.55, 131.41, 128.12, 127.33, 126.46, 124.12, 122.45, 34.12,33.32, 18.34, 16.37. Anal. Calcd for $C_{21}H_{22}N_4$: C, 76.33; H, 6.71; N, 16.96. Found: C, 76.23; H, 6.54; N, 16.87.

(E,E)-[3-(dimethylamino)-1[4-(trifluoromethyl)pheny-2-propenyli dene]-1H-2-methyl-4-phenyl-1,3-imidazol-1-amine (5c). 97% yield, white powder (dichloromethane-hexane, 7:5), mp 178-180°C. IR (KBr): 3107, 2916, 1632, 1599, 1563, 1501, 1471, 1342, 1244, 1172, 1068, 962, 818, 747 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 7.86 (d, 2H, J=8.7, C(3')- and C(5')-H's), 7.61(s,1H), 7.48 (m, 2H, phenyl), 7.55 (d, 2H, J=8.8, C(2')- and C(6')-H's), 6.69 (d, 1H, J=12.9, C(3)-H), 4.87 (d, 1H, J=12.8,C(2)-H), 3.31 (s, 3H, Het-CH_3), 3.01 (s, 3H, NCH_3), 2.75 (s, 3H, NCH_3); ^{13}C-NMR (CD_3OD) δ 145.38, 142.79, 139.42, 138.43, 137.23, 136.63, 132.72, 131.09, 128.41, 127.08, 126.36, 123.44, 122.42, 34.79, 33,13, 18.23, 16.47. Anal. Calcd for $C_{22}H_{21}N_4F_3$: C, 66.32; H, 5.31; N, 14.06. Found: C,66.53; H, 5.44; N, 14.02.

(E,E)-[3-(dimethylamino)-1-[4-nitrophenyl]-2-propenylidene]-1H-2-methyl-5-phenyl-1,3-imidazol-1-amine (5d). 88% yield, yellow powder (dichloromethane-methanol, 97:3), mp 210-212°C. IR (KBr): 3113, 3086, 1633, 1616, 1543, 1502, 1468, 1344, 1242, 1156, 1056, 963, 860, 736, 703 cm^{-1}; ^{1}H-NMR(CD_3OD) δ 8.86 (d, 2H, J=8.9, C(3')- and C(5')-H's), 8.34 (d, 2H, J=8.8, C(2')- and C(6')-H's), 7.61 (s, 1H), 7.48 (m 2H, phenyl), 6.69 (d, 1H,

J=12.9, C(3)-H), 4.87 (d, 1H, J=12.8, C(2)-H), 3.31 (s, 3H, Het-CH_3), 3.03 (s, 3H, NCH_3), 2.79 (s, 3H, NCH_3); ^{13}C-NMR (CD_3OD) δ 150.22, 145.54, 142.63, 139.51, 138.78, 137.74, 136.47, 133.11, 131.55, 128.61, 127.32, 126.44, 125.31, 123.68, 122.97, 34.6, 33.76, 18.23, 16.62. Anal. Calcd for $C_{21}H_{21}N_5O_2$: C, 67.18; H, 5.64; N, 18.66. Found: C, 67.27; H,5.74; N,18.52.

(E,E)-[3-(dimethylamino)-(2-thienyl)-2-propenylidene]-1H-2-methy-4-phenyl-1,3-imidaol-1-amine (5e). 87% yield, tan plates (dichloro methane-hexane, 5:2), mp 152-154°C. IR (KBr): 3123, 2924, 2818, 1627, 1596, 1559, 1496, 1471, 1341, 1253,1166, 1059, 951, 813, 765 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.40 (d, 1H, J=3.7, C(3')-H), 7.23 (d, J=12.7, 1H, C(3)-H), 7.15 (dd, 1H, J=3.8 and 3.9, C(4')-H), 7.14 (dd, J=0.8 and 5.3, 1H, C(5')-H, 4.73(d,J=12.9, 1H, C(2)-H),7.35 (m, 5H, phenyl), 3.45 (s, 3H, Het-CH_3), 3.01 (s, 3H, NCH_3), 2.75 (br, s, 3H, NCH_3); ^{13}C-NMR ($CDCl_3$) δ 147.37, 145.42, 142.31, 139.21, 138.46, 137.41, 136,98, 133.32, 131.78, 128.42, 127.43, 126.61, 125.42, 123.63, 34, 87, 33.62, 34.75, 33.61, 18.32, 16.47. Anal. Calcd for $C_{19}H_{20}N_4S$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.78; H, 5.82; N, 16.43.

(E,E)-[3-(dimethylamino)-1-(3-pyridyl)-2-propenylidene]-1H-2-methyl-4-phenyl-1,3-imizaol-1-amine (5f). 97% yield, white powder (dichloromethane-hexane, 7:4), mp 132-134°C. IR (KBr): 3110, 2912, 1628, 1601, 1552, 1501, 1465, 1337, 1251, 1162, 1071, 966, 759, 705 cm^{-1}; 1H-NMR (CD_3OD) δ 8.78 (dd, 2H, J=3.9 and 8.6, C(3')- and C(5')-H's), 8.58 (2H, d, J=8.9, C(2')- and C(6')-H's), 7.49 (5H, m, phenyl), 6.75 (d, 1H, J=13.1, C(3)-H), 4.91 (d, 1H, J=13.2, C(2)-H), 3.45 (s, 3H, Het-CH_3), 3.00 (s, 3H, NCH_3), 2.77 (s, 3H, NCH_3); ^{13}C-NMR(CD_3OD) δ 151.12,142.38, 138.73, 137.62, 133.45, 132.43, 131.26, 128.68, 127.39, 125.76, 35.02, 33.98, 19.01, 16.13. Anal. Calcd for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13. Found: C, 72.57; H, 6.28; N, 21.21.

(E,E)-[3-(dimethylamino)-1-[4-(methylthio)phenyl]-1H-2-propenylidene]-2-methyl-5-phenyl-1,3-imidazol-1-amine (5g). 96% yield, yellow powder (ethyl acetate-petroleum ether, 5:3), mp 92-94°C. IR (KBr): 3106, 2923, 1627, 1601, 1558, 1467, 1372, 1287, 1146, 1057, 963, 860, 712 cm^{-1}; ^{1}H-

NMR ($CDCl_3$) δ 7.49 (2H, d, J=8.9,C(3')- and C(5')-H's), 7.42 (5H, m, phenyl), 7.11 (2H, d, J=8.9, C(2')- and C(6')-H's), 6.76 (d, 1H, J=12.7, C(3)-H), 4.67 (d, 1H, J=12.8, C(2)-H), 3.32 (s, 3H, Het-CH_3), 3.00 (s, 3H, NCH_3), 2.77 (s, 3H, NCH_3); ^{13}C-NMR ($CDCl_3$) δ 145.32, 142.23, 138.79, 137.68, 135.98, 132.73, 131.44, 128.67, 128.21, 127.97, 127.61, 126.52, 126.00, 123.10, 34.65, 33.01, 18.09, 16.3 Anal. Calcd for $C_{22}H_{24}N_4S$: C, 70.55; H, 6.45; N, 14.76. Found: C, 70.43; H, 6.34; N, 14.86.

(E,E)-[3-(dimethylamino)-1-phenyl]-2-propenylidene]-2,4-diphenyl-1H-1,3-imidazol-1-amine (5h). 98% yield, white solid (dichloromethane-

(E,E)-[3-(dimethylamino)-1-(4-pyridyl)-2-propenylidene]-1H-2,4-diphenyl-1,3-imidazol-1-amine (5k). 89% yield, white powder (*dichloromethane-methanol, 18:3*), mp 156-158°C. IR (KBr): 3129, 2931, 2916, 1629, 1602, 1549, 1544, 1466, 1341, 1242, 1167, 1055, 962, 775, 723 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 7.68 (s, 1H), 7.40 (d, 1H, J=3.7,C(3')-H), 7.23 (d, J=12.7, 1H, C(3)-H), 7.15 (dd, 1H, J=3.8 and 3.9, C(4')-H), 7.14 (dd, J=0.8 and 5.3, 1H, C(5')-H, 4.73 (d, J=12.9, 1H, C(2)-H), 7.35 (m, 5H, phenyl), 3.45 (s, 3H, Het-CH_3), 3.01 (s, 3H, NCH_3), 2.75 (br s, 3H, NCH_3); ^{13}C-NMR (CD_3OD) δ 151.64, 142.69, 139.88, 138.72, 137.10, 132.64, 132.16, 131.52, 130.78, 128.56, 128.71, 127.49, 125.68, 123.68, 34.75, 33.65, 19.23, 16.67. Anal. Calcd for $C_{25}H_{23}N_5$: C, 76.31; H, 5.89; N, 17.80. Found: C, 76.56; H, 6.06; N, 17.74.

General Procedure for the Cyclization of Enamines **5a-k** to imidazo[1,5-b]pyridazine **1a-k**. **1-methyl-3-phenyl-6-(4-methoxyphenyl)-1,3-imidazo[1,5-b]pyridazine (1a)** as a typical procedure: Enamine **5a** (3.56 g, 9.87 mmol) was dissolved in hot trifluoroacetic acid (60 ml) and the solution heated at reflux for 6 hr. The cooled solution was poured into ice-water (250 ml) at which point a precipitate formed. This solid was collected by vacuum filtration. The filtrate was concentrated and purified by silica gel chromatography with 95 : 5 dichloromethane-methanol as eluant to provide a total of 2.64 g (95%) of imidazo[1,5-b]pyridazine **1a**. A sample was recrystallized from 3 : 2 of mixture of chloroform and hexane to give a white needles. (Note: all the analytical samples of

the following compounds were purified by recrystallization from the solvents indicated). mp 200-202.5 °C. IR (KBr): 3116, 3054, 1609, 1545, 1488, 1336, 1260, 1182, 1062, 832 cm^{-1}. ^{1}H-NMR (CD_3OD) δ 7.93 (d, 2H, J=8.9, C(2')- and C(6')-H's), 7.47 (5H, m, phenyl), 7.05 (d, 2H, J=8.9, C(3')- and C(5')-H's), 7.62 (1H, d, J=8Hz, imidazopyridazine 4-H), 6.36 (1H, d, J=8 Hz, imidazopyridazine 5-H), 3.68 (3H, s, -OCH_3), 3.07 (3H, s, Het-CH_3). ^{13}C-NMR (CD_3OD) δ 161.87, 152.72, 143.52, 138.99, 138.34, 137.49, 132.76, methanol, 9:1), mp 155-157°C. IR (KBr): 3102 , 2914, 1625, 1608, 1547, 1502, 1475, 1338, 1243, 1165, 1068, 946, 838, 721 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 7.56-7.83 (m, 10H, phenyl), 7.68 (s, 1H), 6.76 (d, 1H, J=13.2, C(3)-H), 4.82 (d, 1H, J=13.2, C(2)-H), 3.45 (s, 3H, Het-CH_3), 2.96 (s, 3H, NCH_3), 2.72 (s, 3H, NCH_3); ^{13}C-NMR (CD_3OD) δ 158.23, 142.64, 137.83, 136.57, 132.91, 132.63, 132.04, 131.87, 131.26, 128.52, 128.09, 127.87, 127.11, 126.26, 123.21, 34.78, 33.64, 18.54, 16.37. Anal. Calcd for $C_{26}H_{24}N_4$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.45; H, 6.14; N, 14.22.

(E,E)-[3-(dimethylamino)-1-(4-trifluromethyl)phenyl]-2-propenylidene]-1H-2,4-diphenyl-1,3-imidazol-1-amine (5i). 87% yield, white powder(dichloromethane-methanol, 25:3), mp 187-189°C. IR (KBr): 3118, 2937, 2913, 1627, 1605, 1557, 1501, 1459, 1341, 1253, 1168, 1062, 943, 832, 708 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 7.86 (d, 2H, J=8.7, C(3')- and C(5')-H's), 7.61 (s, 1H), 7.48 (m, 2H, phenyl), 7.55 (d, 2H, J=8.8, C(2')- and C(6')-H's), 6.69 (d, 1H, J=12.9, C(3)-H), 4.87(d, 1H, J=12.8, C(2)-H), 3.31 (s, 3H, Het-CH_3), 3.01 (s, 3H, NCH_3), 2.75 (s, 3H, NCH_3); ^{13}C-NMR (CD_3OD) δ 145.61, 142.38, 137.66, 135.43, 132.72, 131.19, 128.73, 128.62, 127.41, 127.40, 126.56, 122.71, 34.87, 33.64, 18.58, 16.63. Anal. Calcd for $C_{27}H_{23}N_4F_3$: C, 73.78; H, 5.27; N, 12.75. Found: C, 73.63; H, 5.24; N, 12.67.

(E,E)-[3-(dimethylamino)-1-(4-nitrophenyl)-2-propenylidene]-1H-2,4-diphenyl-1,3-imidazol-1-amine (5j). 94% yield, white powder (dichloromethane-methanol, 50:1), mp 223-225°C. IR (KBr): 3125, 2938, 2921, 1631, 1610, 1561, 1512, 1463, 1337, 1251, 1166, 1054, 957, 857, 783, 705 cm^{-1}; ^{1}H-NMR (CD_3OD) δ 8.80 (d, 2H, J=9.5,C(3')- and C(5')-H's), 8.45 (d, 2H, J=9.5, C(2')- and C(6')-H's). 7.58(s, 1H), 7.44 (m, 5H, phenyl), 3.25 (s,

3H, Het-CH_3), 3.08 (s, 3H, NCH_3), 2.79 (s, 3H, NCH_3); ^{13}C-NMR (CD_3OD) δ 150.23, 145.22, 142.36, 139.47, 138.55, 137.61, 133.32, 131.63, 128.12, 127.41, 126.47, 125.65, 123.17, 122.68, 34.87, 33.54, 18.51, 16.62. Anal. Calcd for $C_{26}H_{23}N_5O_2$: C, 71.38; H, 5.30; N, 16.00. Found: C, 71.45; H, 5.34; N, 15.97.

131.42, 129.37, 127.73, 126.34, 125.51, 117.36, 113.22, 56.38, 15.34. Anal. Calcd. for $C_{20}H_{17}N_3O$: C, 76.16; H, 5.43; N, 13.33. Found: C, 76.25; H, 5.64, N, 13.42.

1-methyl-3, 6-diphenyl-1,3-imidazo[1,5-b]pyridazine (1b). 90% yield, white needles (ethanol-ethyl acetate, 5:1), mp 192-193°C. IR (KBr): 3155, 3049, 1604, 1541, 1483, 1445, 1332, 1264, 1178, 1062, 839, 770, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.91 (dt, 2H, J=7.9, 1.5, C(2')- and C(6')-H's), 7.59 (tt, 1H, J=7.5, 1.6), 7.45 (5H, m, phenyl), 7.35 (tt, 2H, J=7.9, C(3')- and C(5')-H's), 7.67 (1H, d, J=8Hz, imidazopyridazine 4-H), 6.29 (1H, d, J=8 Hz, imidazopyridazine 5-H), 3.02 (3H, s, Het-CH_3). ^{13}C-NMR($CDCl_3$) δ 151.32, 142.72, 141.35, 139.34, 138.65, 132.69, 132.12, 131.42, 128.35, 127.21, 126.76, 125.15, 117.34, 17.47. Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.97; H, 5.30; N, 14.73. Found: C, 79.86; H, 5.38; N, 14.61.

1-methyl-3-phenyl-6-(4-trifluromethylphenyl)-1,3-imidazo[1,5-b] pyridazine (1c). 86% yield, white needles(ethyl acetate-ethyl ether, 4:1), mp 138-139°C. IR (KBr): 3115, 3064, 1602, 1544, 1473, 1338, 1278, 1168, 1124, 1065, 840, 766,708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.27 (d, 2H, J=8.8, C(3')- and C(5')-H's), 8.07 (d, 2H, J=8.9, C(2')- and C(6')-H's). 7.48 (m, 5H, phenyl), 7.66 (1H, d, J=8.3Hz, imidazopyridazine 4-H), 6.24 (1H, d, J=8.3 Hz, imidazopyridazine 5-H), 3.23 (s, 3H, Het-CH_3), ^{13}C-NMR($CDCl_3$) δ 152.19, 142.62, 141.39, 139.73, 138.35, 137.59, 132.72, 131.43, 128.31, 127.54, 126.28, 125.42, 122.21, 117.89, 17.23. Anal. Calcd for $C_{20}H_{14}N_3F_3$: C, 67.98; H, 3.99; N, 11.89. Found: C, 68.10; H, 4.22; N, 11.74.

1-methyl-3-phenyl-6-(4-nitrophenyl)-1,3-imidazo[1,5-b]pyridazine (1d). 98% yield, pale yellow needles (acetonitrile), mp 234-236°C. IR (KBr): 3145, 3078, 1597, 1548, 1483, 1453, 1392, 1334, 1267, 1180, 1069, 849, 762, 714 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.84 (d, 2H, J=9.7,C(3')- and C(5')-H's), 8.61

(d, 2H, J=9.6, C(2')- and C(6')-H's), 7.58 (s, 1H), 7.54 (m, 5H, phenyl), 7.63 (1H, d, J=8Hz, imidazopyridazine 4-H), 6.26 (1H, d, J=8 Hz, imidazopyridazine 5-H), 3.15 (s, 3H, Het-CH_3); ^{13}C-NMR($CDCl_3$) δ 153.11, 145.34, 142.42, 139.67, 138.72, 137.49, 133.52, 131.78, 128.82, 127.31, 126.30, 125.02, 123.58, 117.93, 17.74. Anal. Calcd for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 70.02; H, 4.30; N, 17.11.

1-methyl-3-phenyl- 6-(2-thienyl)-1,3-imidazo[1,5-b]pyridazine (1e). 97% yield brown plates (dichloromethane-ethyl ether, 2:1), mp 161-162.5°C. IR (KBr): 3144, 3103, 3074, 3048, 1602, 1593, 1551, 1473, 1435, 1331, 1260, 1172, 1065, 956, 839, 727, 691 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.67 (br d, J=4.3, 1H, C(3')-H), 7.60 (br d, J=5.2, 1H, C(5')-H), 7.19 (dd,J=4.2 and 5.1, 1H, C(4')-H), 7.39 (m, 5H, phenyl), 7.67 (1H, d, J=8.2Hz, imidazopyridazine 4-H), 6.27 (1H, d, J=8.3 Hz, imidazopyridazine 5-H), 3.43 (s, 3H, Het-CH_3), ^{13}C-NMR ($CDCl_3$) δ 151.67, 143.67, 139.63, 138.45, 132.52, 131.71, 128.32, 127.35, 125.63, 123.46, 117.34, 16.97. Anal. Calcd for $C_{17}H_{12}N_3S$: C, 70.32; H, 4.17; N, 14.47. Found: C, 70.44; H, 4.33; N, 14.52.

1-methyl-3-phenyl-6-(3-pyridyl)-1,3-imidazo[1,5-b]pyridazine (1f). 91% yield, orange powder (dichloromethane-methanol-hexane, 3:1:2), mp 206-208°C. IR (KBr): 3119, 3069, 3042, 1611, 1546, 1522, 1484, 1461, 1389, 1335, 1260, 1171, 1060, 820, 781, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.90 (dd, 2H, J=4.9 and 8.3, C(3')-H and C(5')-H's), 8.77 (dd, 2H, J=8.3, C(2')- and C(6')-H's), 7.38 (m, 5H, phenyl), Het-CH_3), 7.65 (1H, d, J=8.1Hz, imidazopyridazine 4-H), 6.36 (1H, d, J=8.0 Hz, imidazopyridazine 5-H), 3.12 (3H, s, Het-CH_3). ^{13}C-NMR ($CDCl_3$) δ 152.96, 151.09, 139.78, 137.54, 132.54, 131.73, 128.26, 127.84, 125.37, 118.21, 16.98. Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.56. Found: C, 75.63; H, 5.13; N, 19.76.

1-methyl-3-phenyl-6-(4-methylthiophenyl)-1,3-imidazo[1,5-b]pyridazine (1g). White needles(ethyl acetate-acetone, 7:1), 92% yield, mp 192-193°C. IR (KBr): 3145, 3069, 1609, 1587, 1546, 1529, 1484, 1462, 1382, 1334, 1259,1182, 1057, 849, 768, 707 cm^{-1}. ^{1}H-NMR (CD_3COCD_3) δ 7.87(d, 2H, J=8.7,C(3')- and C(5')-H's), 7.73 (d, 2H, J=8.7, C(2')- and C(6')-H's), 7.46 (m, 5H, phenyl), 7.59 (1H, d, J=8Hz, imidazopyridazine 4-H), 6.29 (1H, d, J=8

Hz, imidazopyridazine 5-H), 3.01 (s, 3H, Het-CH_3), 2.32 (s, 3H, SCH_3). ^{13}C-NMR(CD_3COCD_3) δ 152.09, 144.62, 141.90, 138.60, 137.56, 132.82, 131.64, 128.77, 128.32, 127.49, 127.33, 126,26, 126.22, 117.65, 16.85. Anal. Calcd for $C_{20}H_{17}N_3S$: C, 72.48; H, 5.17; N, 9.67. Found: C, 72.63; H, 5.20; N, 9.85.

1,3,6-triphenyl-1,3-imidazo[1,5-b]pyridazine (1h). 92% yield, colorless needles(methanol-ethyl ether, 8:3), mp 188-190°C. IR (KBr): 3112, 3057, 1602, 1592, 1523, 1473, 1398, 1336, 1258, 1180, 810, 791, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.90 (m, 2H, C(3')- and C(5')-H's), 7.45-7.67 (m, 10H, phenyl), 7.39 (3H, m, 3H, C(2') -and C(4')- and C(6')-H'S), 7.58 (1H, d, J=8Hz, imidazopyridazine 4-H), 6.23 (1H, d, J=8 Hz, imidazopyridazine 5-H); ^{13}C-NMR($CDCl_3$) δ 152.23, 143.74, 137.84, 136.67, 132.94, 132.66, 132.00, 131.67, 131.36, 128.42, 128.08, 127.86, 127.15, 126.36, 123.24, 117.34, 16.87. Anal. Calcd for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.09. Found: C, 83.12; H, 5.03; N, 12.32.

1,3,-diphenyl-6-(trifluromethylphenyl)-1,3-imidazo[1,5-b]pyridazine (1i). 87% yield, white needles (dichloromethane-methanol-hexane, 5:2:3), mp 223-225°C. IR (KBr): 3127, 3056, 1602, 1599, 1518, 1474, 1383, 1336, 1238, 1177, 838, 789, 711 cm^{-1}. ^{1}H-NMR (CD_3COCD_3) δ 8.27 (d, 2H, J=8.9,C(3')- and C(5')-H's), 8.15 (d, 2H, J=9.3, C(2')- and C(6')-H's), 7.37-7.64 (m, 10H, 2,4-diphenyl), 7.62 (1H, d, J=8.4 Hz, Imidazopyridazine 4-H), 6.43 (1H,d, J=8.5 Hz, imidazopyridazine 5-H); ^{13}C-NMR (CD_3COCD_3) δ 145.79, 142.73, 137.65, 135.43, 132.45, 131.10, 128.90, 128.46, 127.34, 127.20, 126.76, 122.51, 16.63. Anal. Calcd for $C_{25}H_{16}N_3F_3$: C, 72.28; H, 3.88; N, 10.11. Found: C, 72.43; H, 4.02; N, 10.23.

1,3-diphenyl- 6-(3-nitrophenyl)-1,3-imidazo[1,5-b]pyridazine (1j). 95% yield, pale yellow crystals (dichloromethane-methanol, 12:1), mp 192-193°C. IR (KBr): 3112, 3058, 1601, 1594, 1527, 1479, 1382, 1330, 1247, 1175, 838, 758, 701 cm^{-1}. ^{1}H-NMR (CD_3SOCD_3) δ 8.96 (d, 2H, J=9.4,C(3')- and C(5')-H's), 8.74 (d, 2H, J=9.4, C(2')- and C(6')-H's), 7.33-7.49 (m, 10H, diphenyl), 7.66 (1H, d, J=8.1Hz, imidazopyridazine 4-H), 6.32 (1H, d, J=8.2 Hz, imidazopyridazine 5-H). ^{13}C-NMR (CD_3SOCD_3) δ 151.73, 145.41, 142.61, 139.21, 138.25, 37.43, 133.02, 131.61, 128.32, 127.34, 126.67,

125.63, 123.84, 118.11, 17.72. Anal. Calcd for $C_{24}H_{16}N_4O_2$: C, 73.45; H, 4.11; N, 14.28. Found: C, 73.65; H, 4.21; N, 14.37.

1,3-diphenyl- 6-(4-pyridyl-1,3-imidazo[1,5-b]pyridazine (1k). 81% yield, organge needles(ethyl acetate-methanol, 8:1), mp 221-223°C. IR (KBr): 3121, 3052, 1602, 1593, 1521, 1481,1388, 1341, 1253, 1176, 859, 818, 714 cm^{-1}; ^{1}H-NMR(CD_3COCD_3) δ 8.86 (dd, 2H, J=4.9 and 8.4, C(3')-H and C(5')-H's), 8.63 (dd, 2H, J=8.3, C(2')- and C(6')-H's), 7.37-7.59 (m, 10H, phenyl), 7.68 (1H, d, J=7.9 Hz, imidazopyridazine 4-H), 6.26 (1H, d, J=8.0 Hz, imidazo pyridazine 5-H); ^{13}C-NMR (CD_3COCD_3) δ 152.42, 150.69, 141.99, 139.28, 138.37, 132.61, 132.27, 131.85, 130.76, 128.43, 128.71, 127.49, 125.66, 123.43, 117,86, 16.98. Anal. Calcd for $C_{23}H_{16}N_4$: C, 79.29; H, 4.63; N, 16.08. Found: C, 79.32; H, 4.55; N, 16.21.

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