

AN APPROACH TO PYRIMIDINE *N*-OXIDES: CARBOXAMIDE OXIMES AS PRECURSORS

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Abstract - A method for the synthesis of pyrimidines *N*-oxides is described. Various carboxamide oximes were treated with the appropriate 1,3-dicarbonyl compounds or their equivalents in the presence of trifluoroacetic acid as a catalyst to give the corresponding pyrimidine *N*-oxides.

N-Oxides are known as intermediates for the synthesis of interesting target compounds such as acromelic acid A,¹ revenine,² pyridoxine³ etc. Some of them belong to pharmaceuticals, agrochemicals, but they can also serve as protecting groups, oxidants, ligands, catalysts or as auxiliary agents.⁴ The above reasons make each simple approach to *N*-oxides an attractive one.

We would like to report on a new method for the preparation of pyrimidine *N*-oxides.⁵ Our preliminary results have shown that carboxamide oximes represent convenient building blocks for the construction of pyrimidine *N*-oxides.⁶ Thus, a treatment of carboxamide oximes with 1,3-dicarbonyl compounds or their equivalents under acidic conditions led to the formation of the corresponding *N*-oxides. Our observation is in contrast to widely used method for the synthesis of 1,2,4-oxadiazoles, i.e. cyclization of *O*-acyl-carboxamide oximes, which starts by the acylation of carboxamide oximes with various carbonyl compounds such as acyl chlorides, carboxylic anhydrides, carboxylic esters, carboxamides, *N,N*-dialkylcarboxamide dialkylacetals etc.⁷ In addition, 1,2,4-oxadiazoles were also isolated on the treatment of carboxamide oximes with either 2,3-furandiones,⁸ β -keto esters⁹ or diketene.¹⁰

Reactions of various carboxamide oximes (Chart 1) with 1,3-dicarbonyl reagents, we were interested in, took a different course than those mentioned above. Namely, an application of 3-ethoxy-2-methylpropeanal (EMP) on carboxamide oximes (**1**) gave the corresponding 2-substituted 5-methylpyrimidine 1-oxides (**2**) (Scheme 1, Table 1). EMP contributed a symmetrical C₃ fragment of the pyrimidine ring. On the other

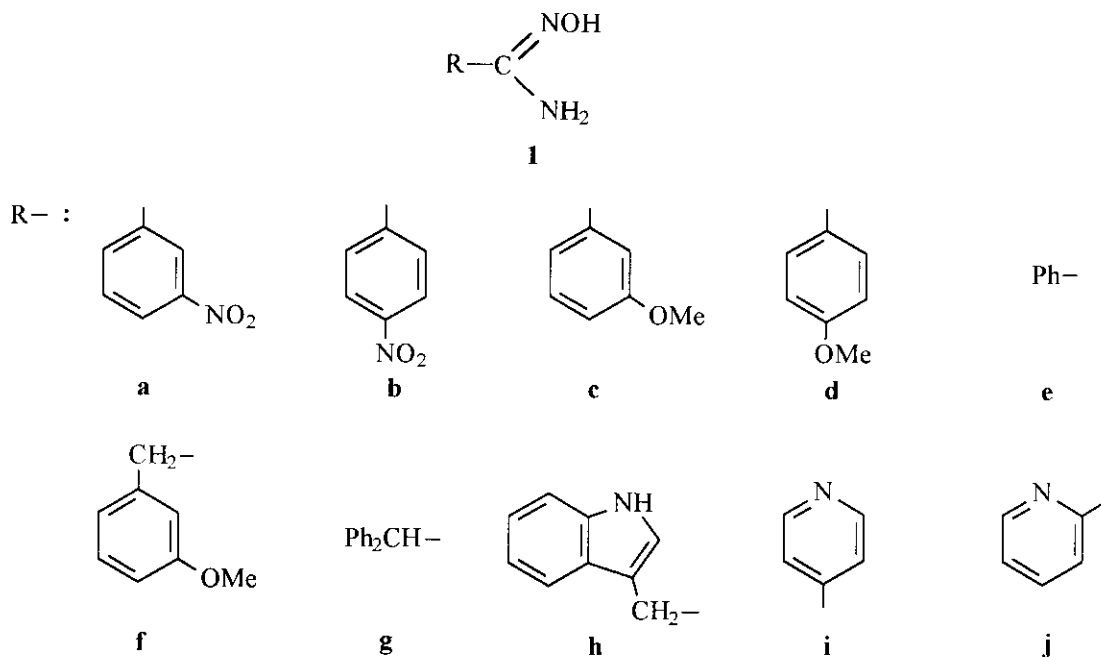
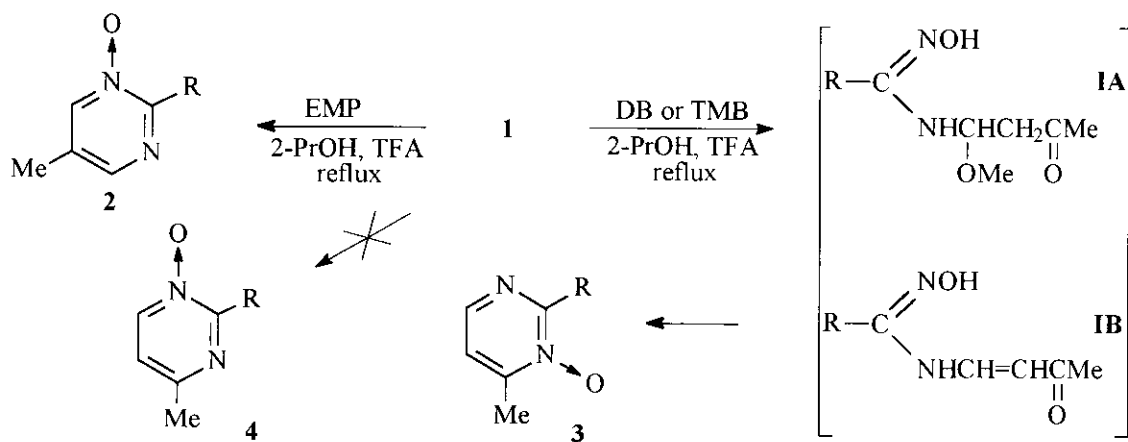


Chart 1

hand, 4,4-dimethoxy-2-butanone (DB) or *trans*-4-methoxy-3-buten-2-one (TMB) reacted with carboxamide oximes to afford 4-methylpyrimidine 3-oxides (**3**). The alternative 4-methylpyrimidine 1-oxides of type (**4**) have never been isolated. This fact might be explained by the regioselective reaction *via* the intermediate (**IA**) and/or (**IB**) (from DB) or the intermediate (**IB**) (from TMB), followed by the cyclization to *N*-oxides (**3**).



Scheme 1

Table 1. The Formation of 5-Methylpyrimidine 1-Oxides (**2**) and 4-Methylpyrimidine 3-Oxides (**3**).

Entry	Starting Oxime	Reagent	Reaction Time (h) ^a	Product	Yield (%)
1	1a	EMP	2.5	2a	92
2	1b	EMP	2	2b	66
3	1c	EMP	3.5	2c	81
4	1d	EMP	6.5 ^b	2d	73
5	1e	EMP	4	2e	52
6	1f	EMP	5	2f	43
7	1g	EMP	3	2g	33
8	1h	EMP	7.5	2h	46
9	1i	EMP	1	2i	65
10	1j	EMP	1.5	2j	83
11	1a	TMB	4	3a	68
12	1a	DB	6	3a	38
13	1b	TMB	3	3b	58
14	1c	DB	7.5	3c	52
15	1c	TMB	1.5 ^b	3c	36
16	1d	DB	15	3d	62
17	1d	TMB	11	3d	52
18	1e	TMB	3.5	3e	52
19	1f	TMB	8	3f	59
20	1f	DB	6.5	3f	29
21	1g	TMB	4.5	3g	37
22	1g	DB	3.5	3g	18
23	1i	TMB	0.5	3i	40

^a Reactions were carried out under reflux in 2-PrOH in the presence of trifluoroacetic acid (TFA).

^b 2-BuOH was used as a solvent.

The structures of 3-oxides (**3**) were supported by NMR experiments as already described for similar compounds by Yamanaka and co-workers.¹¹ For example, europium(III)-tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate), Eu(fod)₃, was employed as a shift reagent to study its effect on downfield shifts of methylene and methyl protons *versus* pyrimidine proton H-6 in 3-oxide (**3f**) (Figure 1). Larger downfield shifts of methylene and methyl protons in comparison with H-6 are in accordance with the structure (**3f**) and not with an alternative 1-oxide (**4f**).

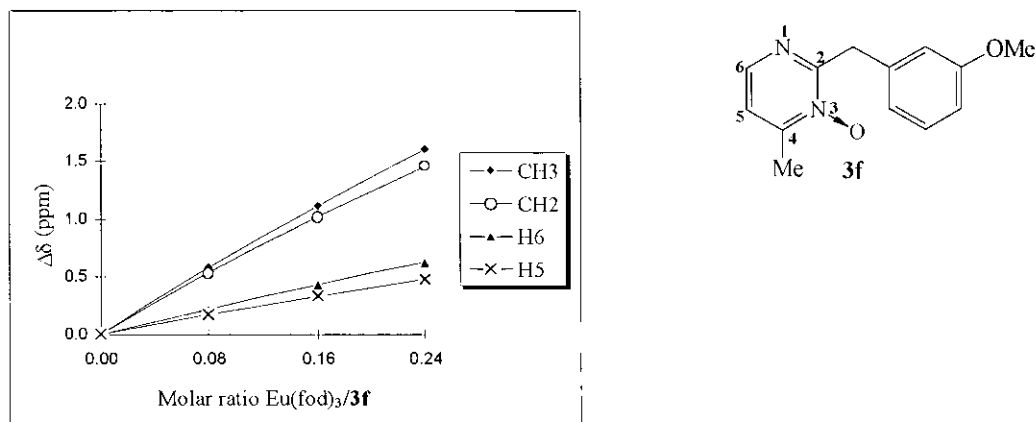
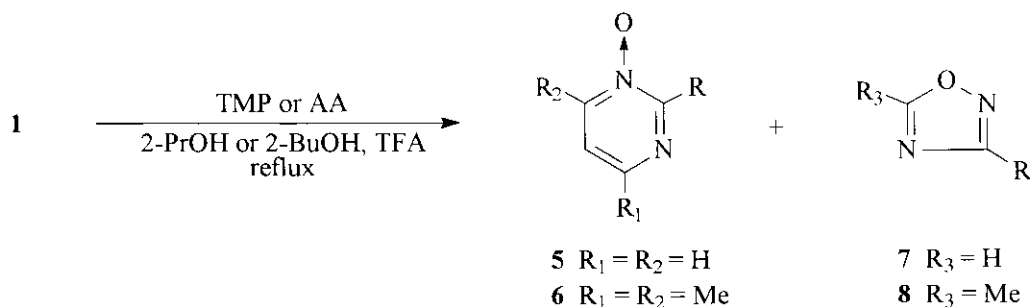


Figure 1. $\text{Eu}(\text{fod})_3$ Induced Downfield Shifts for **3f** (0.1 M CDCl_3 Solution, 29 °C).

We also investigated reactions of carboxamide oximes (**1**) with 1,1,3,3-tetramethoxypropane (TMP) or acetylacetone (AA). Transformations of **1** with TMP led to 2-substituted pyrimidine 1-oxides (**5**), while an employment of AA gave 2-substituted 4,6-dimethylpyrimidine 1-oxides (**6**). The synthesis of **5** or **6** was in some cases accompanied by the formation of 1,2,4-oxadiazoles (**7**) or (**8**) (Scheme 2, Table 2). The mechanism of this transformation is not well understood. The participation of the carboxamide oxime OH group in the first step of the reaction is unlikely process, as it would lead either to 4,5-dihydro-1,2,4-oxadiazoles (one carbon of the reagent incorporated in the ring) or to 1,2,4-oxadiazepines (three carbons of the reagent incorporated in the ring). The fragment CR_3 of the 1,2,4-oxadiazole ring probably originates from the dicarbonyl reagent. The latter transformation seems to involve the cleavage of a C-C bond in TMP or AA, since only CH moiety (from TMP) or CMe fragment (from AA) appeared in 1,2,4-oxadiazoles (**7**) or (**8**). We think the initial step of the reaction is the attack of the reagent to the amino group of the carboxamide oxime functionality. Then, it seems two competing transformations might take place: (i) a cyclization to the corresponding *N*-oxide as the favorite one; (ii) a ring-closure to the 1,2,4-oxadiazole, which required the cleavage of the C-C bond, and is observed only occasionally.



Scheme 2

Table 2. Reactions of Carboxamide Oximes (**1**) with TMP or AA.

Entry	Starting Oxime	Reagent	Reaction Time (h) ^a	Products (Yield, %)	
				<i>N</i> -Oxide	1,2,4-Oxadiazole
1	1a	TMP	8.5	5a (62)	7a (32)
2	1b	TMP	5	5b (35)	7b (27)
3	1d	TMP	12	5d (22)	7d (19)
4	1e	TMP	4	5e (77)	-
5	1f	TMP	4	5f (39)	-
6	1g	TMP	7.5	5g (35)	-
7	1a	AA	40 ^b	6a (41)	8a (18)
8	1b	AA	9	6b (65)	-
9	1c	AA	40	6c (30)	-
10	1d	AA	18	6d (61)	-
11	1e	AA	37	6e (42)	-
12	1f	AA	9	6f (28)	-
13	1g	AA	53	6g (23)	-
14	1j	AA	16.5	6j (48)	-

^a Reactions were carried out under reflux in 2-PrOH or 2-BuOH (see Experimental) in the presence of TFA.

^b About 10% of carboxamide oximes (**1a**) remained unchanged.

As it is evident from Table 1 and Table 2, the yields of the *N*-oxides are moderate in most cases. Those results can be explained taking into account the fact that carboxamide oximes are thermally unstable. Several products were identified upon their thermal decomposition: nitrogen, nitrous oxide, ammonia, water, as well as a nitrile, an amide etc.^{9a} Furthermore, water is known to hydrolyze carboxamide oxime in the presence of a strong acid to the corresponding amide or carboxylic acid.^{9a} In our cases, water is eliminated during the ring closure to the *N*-oxide (or MeOH if TMP is applied as the reagent). Several of the above mentioned by-products have been indeed identified in low yields by TLC or NMR. The reasons for their appearance seem to be quite acceptable, so no special attention was paid to their formation as soon as they were characterized.

In conclusion, we have demonstrated a simple and a general approach to pyrimidine *N*-oxides starting from carboxamide oximes and dicarbonyl equivalents under acidic conditions. Trifluoroacetic acid (TFA) was found to be the best catalyst in most cases, although HCl (obtained *in situ* from acetyl chloride and a selected alcohol) or boron trifluoride etherate could also be applied.⁶ It should be mentioned that pyridinecarboxamide oximes (**1i**) or (**1j**) were easily converted to the corresponding pyridylpyrimidine *N*-

oxides (**2i**, **2j**, **3i** and **6j**). To the best of our knowledge, the present method is the only way to such *N*-oxides. It is well-known that *N*-oxidation of pyridylpyrimidines leads to pyrimidinylpyridine *N*-oxides owing to the lower basicity of pyrimidine nitrogens.^{5,12}

EXPERIMENTAL

The starting materials and the solvents were purchased from commercial sources (Fluka, Merck, Aldrich) and were used without further purification. TLC was carried out on Fluka silica gel plates (F₂₅₄). Chromatographic separations on chromatotron were performed with a Harrison Research instrument, model 7924 T, employing Merck silica gel 60 PF₂₅₄. Melting points were determined on a hot stage and were uncorrected. IR spectra, reported in cm⁻¹, were taken on a Perkin Elmer 1310 spectrophotometer (KBr pellets). ¹H NMR spectra (at 300 MHz) and ¹³C NMR spectra (at 75 MHz) were recorded on a Bruker Avance DPX 300 spectrometer at 29 °C in CDCl₃ as a solvent, using TMS as an internal standard. MS spectra, reported in units *m/z*, were obtained with a VG-Analytical AutospecQ instrument. Elemental analysis (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Carboxamide oximes (**1a**,^{9a} **1b**,^{9a} **1d**,^{9a} **1e**,^{9a} **1f**,¹³ **1g**,¹⁴ **1h**,¹⁵ **1i**¹⁶ and **1j**¹⁶) were prepared as described in the literature. The carboxamide oxime (**1c**) was obtained from the commercially available nitrile as follows: 3-methoxybenzotrile (133 mg, 1 mmol), NH₂OH.HCl (139 mg, 2 mmol), NaHCO₃ (168 mg, 2 mmol), H₂O (1 mL), EtOH (1 mL), reflux (105 min); **1c** was isolated in 87% yield, mp 105-107 °C (benzene).

General Procedure for the Preparation of Pyrimidine *N*-Oxides. A mixture of carboxamide oxime (**1**; 1 mmol), a selected dicarbonyl compound (EMP, TMB, DB, TMP or AA; 1.5-2.5 mmol) and TFA (1.1-1.3 mmol) in 2-propanol (3-5 mL) or 2-butanol (5 mL; Table 1: Entries 4 and 15; Table 2: Entries 1, 4, 7, 8, 10-12 and 14) was heated under reflux as indicated in Table 1 and Table 2. Reaction mixture was then evaporated to dryness, treated with H₂O (3-7 mL) and neutralized with Na₂CO₃. The solid material was filtered off and rinsed with H₂O (*N*-oxides: **2a**, **2b**, **3a**, **3b** and **6b**). In all other cases, the neutralized mixtures were extracted with CHCl₃ (8 × 10 mL), the combined extracts evaporated to dryness, and *N*-oxides isolated as follows:

(a) By chromatography on chromatotron using ethyl acetate (*N*-oxides: **2d**, **2f**, **2h**, **3d**, **3e**, **3f**, **5e**, **5f**, **5g**, **6c**, **6d**, **6e**, **6f** and **6g**), petroleum ether : ethyl acetate (5 : 3, *N*-oxides: **2e**, **3c** and **3g**) or chloroform : methanol (5 : 1, *N*-oxide **6j**) as a solvent. Separations of *N*-oxides and the corresponding 1,2,4-oxadiazoles (Table 2: Entries 1, 2, 3 and 7) were carried out on chromatotron employing petroleum ether : ethyl acetate (5 : 1) to eluate **7a** and **7d**, petroleum ether : ethyl acetate (5 : 3) for **7b** and **8a**, and ethyl acetate to isolate *N*-oxides: **5a**, **5b**, **5d** and **6a**.

(b) The residue was treated with Et₂O (1 mL; *N*-oxides: **2c**, **2g** and **2j**) or petroleum ether (1 mL; *N*-oxides: **2i** and **3i**) and the solid material was filtered off.

5-Methyl-2-(3-nitrophenyl)pyrimidine 1-Oxide (2a): mp 227-228 °C (MeOH); IR 1530, 1500, 1380, 1360, 1275; ¹H NMR δ 2.61 (s, 3H), 7.67 (dd, 1H, *J*₁ = *J*₂ = 8.1 Hz), 8.24-8.25 (m, 1H), 8.34 (dd, 1H, *J*₁ = 2.1 Hz, *J*₂ = 1.1 Hz), 8.36-8.38 (m, 1H), 8.98 (ddd, 1H, *J*₁ = 8.1 Hz, *J*₂ = 1.6 Hz, *J*₃ = 1.1 Hz), 9.42 (dd, 1H, *J*₁ = *J*₂ = 2.1 Hz); ¹³C NMR δ 15.1, 125.0, 125.4, 129.0, 131.4, 133.1, 135.4, 145.0, 146.7, 148.1, 151.6; MS (EI) 231 (M⁺, 100), 215 (15), 169 (15), 157 (15). *Anal.* Calcd for C₁₁H₉N₃O₃: C, 57.14; H, 3.92; N, 18.17. Found: C, 56.92; H, 3.56; N, 17.89.

5-Methyl-2-(4-nitrophenyl)pyrimidine 1-Oxide (2b):⁶ mp 223-235 °C (acetone); IR 1510, 1345, 1270, 850; ¹H NMR δ 2.39 (s, 3H), 8.25-8.37 (m, 4H), 8.73-8.77 (m, 2H); ¹³C NMR δ 15.1, 123.1, 130.8, 131.6, 137.3, 145.0, 146.8, 148.8, 151.9; MS (EI) 231 (M⁺, 100), 230 (79), 157 (54). *Anal.* Calcd for C₁₁H₉N₃O₃: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.59; H, 3.87; N, 18.28.

2-(3-Methoxyphenyl)-5-methylpyrimidine 1-Oxide (2c): mp 89-91 °C (cyclohexane); IR 1590, 1450, 1375, 1225, 1205; ¹H NMR δ 2.26 (s, 3H), 3.85 (s, 3H), 7.03 (ddd, 1H, *J*₁ = 8.2 Hz, *J*₂ = 2.6 Hz, *J*₃ = 1 Hz), 7.37 (dd, 1H, *J*₁ = *J*₂ = 8.2 Hz), 8.06-8.13 (m, 3H), 8.29-8.30 (m, 1H); ¹³C NMR δ 14.8, 55.4, 114.6, 117.2, 122.2, 128.9, 130.2, 132.8, 144.7, 146.5, 153.5, 159.1; MS (EI) 216 (M⁺, 68), 201 (100), 173 (77), 145 (55), 133 (31). *Anal.* Calcd for C₁₂H₁₂N₂O₂: C, 66.65; H, 5.59; N, 12.95. Found: C, 67.04, H, 5.46; N, 12.66.

2-(4-Methoxyphenyl)-5-methylpyrimidine 1-Oxide (2d):⁶ mp 122-125 °C (petroleum ether : ethyl acetate, 5 : 3); IR 1600, 1460, 1255, 1175; ¹H NMR δ 2.21 (s, 3H), 3.82 (s, 3H), 6.93-6.98 (m, 2H), 8.07-8.08 (m, 1H), 8.25-8.28 (m, 1H), 8.56-8.61 (m, 2H); ¹³C NMR δ 14.7, 55.3, 113.2, 124.1, 129.1, 131.6, 144.8, 146.4, 153.3, 161.6; MS (EI) 216 (M⁺, 25), 200 (27), 137 (100). *Anal.* Calcd for C₁₂H₁₂N₂O₂: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.66; H, 5.46; N, 12.96.

5-Methyl-2-phenylpyrimidine 1-Oxide (2e): mp 101-104 °C (cyclohexane); IR 1440, 1370, 1270, 1195; ¹H NMR δ 2.29 (s, 3H), 7.46-7.49 (m, 3H), 8.16-8.17 (m, 1H), 8.31-8.32 (m, 1H), 8.44-8.48 (m, 2H); ¹³C NMR δ 14.9, 128.0, 129.7, 130.1, 130.9, 131.6, 144.8, 146.4, 154.0; MS (EI) 186 (M⁺, 100), 170 (31), 148 (50), 104 (60), 103 (57), 77 (34). *Anal.* Calcd for C₁₁H₁₀N₂O: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.16; H, 5.35; N, 15.24.

2-(3-Methoxybenzyl)-5-methylpyrimidine 1-Oxide (2f): mp 68-69 °C (cyclohexane); IR 1590, 1485, 1365, 1265, 1255, 1225, 1155; ¹H NMR δ 2.24 (s, 3H), 3.76 (s, 3H), 4.37 (s, 2H), 6.75-6.78 (m, 1H), 6.94-6.97 (m, 2H), 7.20 (dd, 1H, *J*₁ = *J*₂ = 7.7 Hz), 8.00 (s, 1H), 8.23 (s, 1H); ¹³C NMR δ 14.9, 37.6, 55.1, 112.4, 115.2, 121.9, 129.4, 130.1, 137.1, 144.1, 144.6, 158.4, 159.6; MS (EI) 230 (M⁺, 41), 213

(100), 198 (55), 170 (32). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.67; H, 5.98; N, 12.16.

2-Diphenylmethyl-5-methylpyrimidine 1-Oxide (2g): mp 143-145.5 °C (AcOEt); IR 1500, 1460, 1375, 1275, 1140, 760, 710; 1H NMR δ 2.24 (s, 3H), 6.52 (s, 1H), 7.22-7.32 (m, 10H), 8.04 (s, 1H), 8.23 (s, 1H); ^{13}C NMR δ 14.9, 49.9, 126.9, 128.3, 129.2, 129.9, 139.6, 143.7, 144.6, 160.4; MS (EI) 276 (M^+ , 6), 259 (100), 183 (24), 165 (31). *Anal.* Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.41; H, 5.59; N, 10.09.

2-(3-Indolylmethyl)-5-methylpyrimidine 1-Oxide (2h): mp 162.5-165 °C (AcOEt); IR 1480, 1360, 1265, 1225, 1125, 735; 1H NMR δ 2.23 (m, 3H), 4.55 (s, 2H), 7.08-7.14 (m, 2H), 7.24-7.29 (m, 2H), 7.69-7.70 (m, 1H), 7.98 (dd, 1H, $J_1 = 1.9$ Hz, $J_2 = 0.8$ Hz), 8.21 (dd, 1H, $J_1 = 1.9$ Hz, $J_2 = 0.7$ Hz), 8.44 (br s, 1H); ^{13}C NMR δ 14.9, 28.0, 109.0, 111.2, 119.2, 119.4, 121.9, 124.0, 127.5, 129.8, 136.1, 144.4, 144.7, 158.6; MS (FAB) 240 ($M^+ + 1$, 93), 222 (100). *Anal.* Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.08; H, 5.27; N, 17.66.

5-Methyl-2-(4-pyridyl)pyrimidine 1-Oxide (2i):⁶ mp 150-152 °C (cyclohexane); IR 1560, 1350, 1245, 1165; 1H NMR δ 2.36 (s, 3H), 8.22-8.23 (m, 1H), 8.35-8.36 (m, 1H), 8.40-8.42 (m, 2H), 8.76-8.78 (m, 2H); ^{13}C NMR δ 15.0, 123.1, 131.8, 138.6, 145.0, 146.7, 150.0, 151.6; MS (EI) 187 (M^+ , 100), 171 (33), 159 (92), 132 (35). HRMS Calcd 187.0746; Found 187.0746. *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.19; H, 5.10; N, 22.56.

5-Methyl-2-(2-pyridyl)pyrimidine 1-Oxide (2j):⁶ mp 120-123 °C (AcOEt); IR 1430, 1365, 1275, 1195, 1140; 1H NMR δ 2.32 (s, 3H), 7.39 (ddd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz, $J_3 = 1$ Hz), 7.83 (ddd, 1H, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.8$ Hz), 8.29-8.30 (m, 1H), 8.37-8.39 (m, 1H), 8.67 (d, 1H, $J = 7.8$ Hz), 8.82-8.84 (m, 1H); ^{13}C NMR δ 15.0, 124.9, 125.7, 131.6, 136.1, 145.2, 146.3, 149.1, 150.0, 152.6; MS (EI) 187 (M^+ , 91), 159 (100), 105 (73), 78 (84). *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.63; H, 4.77; N, 22.08.

4-Methyl-2-(3-nitrophenyl)pyrimidine 3-Oxide (3a): mp 191-192 °C (MeOH); IR 1520, 1350, 1260, 1240; 1H NMR δ 2.62 (s, 3H), 7.33 (d, 1H, $J = 4.6$ Hz), 7.67 (dd, 1H, $J_1 = J_2 = 8.1$ Hz), 8.26 (d, 1H, $J = 4.6$ Hz), 8.36 (ddd, 1H, $J_1 = 8.1$ Hz, $J_2 = 2.1$ Hz, $J_3 = 1.1$ Hz), 8.93 (ddd, 1H, $J_1 = 8.1$ Hz, $J_2 = J_3 = 1.1$ Hz), 9.44 (dd, 1H, $J_1 = J_2 = 2.1$ Hz); ^{13}C NMR δ 18.1, 121.0, 125.3, 125.4, 128.9, 133.6, 135.8, 142.3, 147.9, 153.8, 157.9; MS (EI) 231 (M^+ , 100), 230 (73), 82 (69). *Anal.* Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 56.92; H, 3.85; N, 18.40.

4-Methyl-2-(4-nitrophenyl)pyrimidine 3-Oxide (3b): mp 233-235 °C (acetone); IR 1585, 1505, 1340, 1250, 1230; 1H NMR δ 2.62 (s, 3H), 7.32-7.34 (m, 1H), 8.26 (d, 1H, $J = 4.7$ Hz), 8.30-8.34 (m, 2H),

8.70-8.74 (m, 2H); ^{13}C NMR δ 18.1, 121.1, 123.0, 131.2, 137.9, 142.3, 148.6, 148.8, 158.0; MS (EI) 231 (M^+ , 100), 230 (85), 157 (43), 82 (80). *Anal.* Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.59; H, 3.87; N, 18.28.

2-(3-Methoxyphenyl)-4-methylpyrimidine 3-Oxide (3c): mp 67-69 °C (hexane); IR 1590, 1455, 1420, 1325, 1255, 1225, 1035; ^1H NMR δ 2.56 (s, 3H), 3.86 (s, 3H), 7.05 (ddd, 1H, $J_1 = 8.0$ Hz, $J_2 = 2.6$ Hz, $J_3 = 1$ Hz), 7.19 (dq, 1H, $J_1 = 4.7$ Hz, $J_2 = 0.5$ Hz), 7.39 (dd, 1H, $J_1 = J_2 = 8.0$ Hz), 8.05 (ddd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz, $J_3 = 1$ Hz), 8.10 (dd, 1H, $J_1 = 2.6$ Hz, $J_2 = 1.5$ Hz), 8.16 (d, 1H, $J = 4.7$ Hz); ^{13}C NMR δ 18.1, 55.4, 114.8, 117.5, 120.0, 122.6, 128.9, 133.3, 142.1, 156.0, 157.4, 159.1; MS (EI) 216 (M^+ , 66), 201 (100), 173 (78), 145 (50). *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.76; H, 5.51; N, 12.56.

2-(4-Methoxyphenyl)-4-methylpyrimidine 3-Oxide (3d): mp 72-75 °C (cyclohexane); IR 1610, 1470, 1450, 1270, 1240, 1175; ^1H NMR δ 2.86 (s, 3H), 3.86 (s, 3H), 6.96-6.99 (m, 2H), 7.13 (d, 1H, $J = 4.5$ Hz), 8.14 (d, 1H, $J = 4.5$ Hz), 8.57-8.60 (m, 2H); ^{13}C NMR δ 18.1, 55.3, 113.1, 119.1, 124.4, 132.0, 142.1, 155.8, 157.1, 161.6; MS (EI) 216 (M^+ , 100), 187 (28), 173 (29), 133 (97). *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.43; H, 5.38; N, 13.04.

4-Methyl-2-phenylpyrimidine 3-Oxide (3e): mp 101-104 °C (cyclohexane; lit.,¹⁷ mp not reported); IR 1440, 1415, 1315, 1230, 1210; ^1H NMR δ 2.59 (s, 3H), 7.22 (dq, 1H, $J_1 = 4.7$ Hz, $J_2 = 0.5$ Hz), 7.43-7.52 (m, 3H), 8.20 (d, 1H, $J = 4.7$ Hz), 8.42-8.48 (m, 2H); ^{13}C NMR δ 18.2, 120.0, 127.9, 128.6, 130.0, 130.9, 132.1, 142.1, 157.3; MS (EI) 186 (M^+ , 100), 185 (45), 170 (44), 100 (59). HRMS Calcd 186.0793; Found 186.0795. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.16; H, 5.35; N, 15.24.

2-(3-Methoxybenzyl)-4-methylpyrimidine 3-Oxide (3f): mp 73-76 °C (cyclohexane); IR 1610, 1580, 1490, 1325, 1270; ^1H NMR δ 2.51 (s, 3H), 3.77 (s, 3H), 4.43 (s, 2H), 6.77-6.80 (m, 1H), 6.94-6.99 (m, 2H), 7.15 (d, 1H, $J = 4.8$ Hz), 7.20-7.25 (m, 1H), 8.02 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR δ 17.7, 38.4, 55.0, 112.3, 115.2, 119.9, 121.9, 129.3, 136.9, 141.6, 155.5, 159.5, 160.7; MS (EI) 230 (M^+ , 48), 213 (100), 198 (60), 170 (32). *Anal.* Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.04; H, 6.13; N, 12.38.

2-Diphenylmethyl-4-methylpyrimidine 3-Oxide (3g): mp 145-146 °C (cyclohexane); IR 1540, 1500, 1330, 1270, 710; ^1H NMR δ 2.49 (s, 3H), 6.59 (s, 1H), 7.12 (d, 1H, $J = 4.5$ Hz), 7.20-7.33 (m, 10 H), 8.05 (d, 1H, $J = 4.5$ Hz); ^{13}C NMR δ 17.8, 50.7, 119.8, 126.8, 128.3, 129.2, 139.7, 141.2, 155.6, 162.7; MS (EI) 276 (M^+ , 7), 259 (100), 183 (22), 165 (25). *Anal.* Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$: C, 78.24; H, 5.84; N, 10.14. Found: C, 77.96; H, 5.55; N, 10.29.

4-Methyl-2-(4-pyridyl)pyrimidine 3-Oxide (3i): mp 114-116 °C (cyclohexane); IR 1405, 1335, 1300, 1255, 820; ^1H NMR δ 2.61 (s, 3H), 7.31 (d, 1H, $J = 4.5$ Hz), 8.23 (d, 1H, $J = 4.5$ Hz), 8.38-8.40 (m, 2H), 8.77-8.79 (m, 2H); ^{13}C NMR δ 18.0, 121.2, 123.4, 139.3, 142.2, 150.0, 153.9, 157.8; MS (EI) 187 (M^+ , 100), 171 (31), 159 (45), 147 (33), 132 (34). HRMS Calcd 187.0746; Found 187.075. *Anal.* Calcd for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.10; H, 4.97; N, 22.53.

2-(3-Nitrophenyl)pyrimidine 1-Oxide (5a) and 3-(3-Nitrophenyl)-1,2,4-oxadiazole (7a). **5a:** mp 171.5-173 °C (MeOH : H_2O , 1 : 1); IR 1525, 1410, 1355, 1255; ^1H NMR δ 7.35 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 4.5$ Hz), 7.69 (dd, 1H, $J_1 = J_2 = 8.1$ Hz), 8.37 (ddd, 1H, $J_1 = 8.1$ Hz, $J_2 = 2.1$ Hz, $J_3 = 1.1$ Hz), 8.42 (dd, 1H, $J_1 = 4.5$ Hz, $J_2 = 1.5$ Hz), 8.54 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 1.5$ Hz), 9.00 (ddd, 1H, $J_1 = 8.1$ Hz, $J_2 = J_3 = 1.1$ Hz), 9.45 (dd, 1H, $J_1 = J_2 = 2.1$ Hz); ^{13}C NMR δ 120.4, 125.2, 125.7, 129.1, 133.0, 135.6, 143.8, 147.1, 148.0, 154.1; MS (EI) 217 (M^+ , 100), 216 (77), 102 (43), 69 (46). *Anal.* Calcd for $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.35; H, 2.97; N, 19.29. **7a:** mp 114-115.5 °C (lit.,¹⁸ mp 115-116 °C).

2-(4-Nitrophenyl)pyrimidine 1-Oxide (5b) and 3-(4-Nitrophenyl)-1,2,4-oxadiazole (7b). **5b:** mp 211-213 °C (acetone); IR 1595, 1500, 1340, 1250, 845, 725; ^1H NMR δ 7.33 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 4.5$ Hz), 8.31-8.36 (m, 2H), 8.41 (dd, 1H, $J_1 = 4.5$ Hz, $J_2 = 1.6$ Hz), 8.51 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 1.6$ Hz), 8.76-8.80 (m, 2H); ^{13}C NMR δ 120.5, 123.1, 131.0, 137.1, 143.7, 147.2, 149.0, 154.5; MS (EI) 217 (M^+ , 100), 216 (59), 143 (35), 102 (34), 69 (47). *Anal.* $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 54.98; H, 2.92; N, 29.33. **7b:** mp 166-168 °C (lit.,¹⁹ mp 164 °C).

2-(4-Methoxyphenyl)pyrimidine 1-Oxide (5d) and 3-(4-Methoxyphenyl)-1,2,4-oxadiazole (7d). **5d:** mp 111-112 °C (cyclohexane); IR 1595, 1445, 1415, 1245, 1230, 1160; ^1H NMR δ 3.88 (s, 3H), 6.98-7.01 (m, 2H), 7.13 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 4.5$ Hz), 8.30 (dd, 1H, $J_1 = 4.5$ Hz, $J_2 = 1.5$ Hz), 8.44 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 1.5$ Hz), 8.62-8.65 (m, 2H); ^{13}C NMR δ 55.3, 113.3, 118.3, 123.3, 131.9, 143.6, 146.7, 156.1, 162.0; MS (EI) 202 (M^+ , 100), 133 (97), 103 (34). *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 64.98; H, 4.97; N, 13.54. **7d:** mp 48-50 °C (lit.,¹⁹ bp 145 °C (8 Torr)).

2-Phenylpyrimidine 1-Oxide (5e):⁶ mp 84-86 °C (petroleum ether : AcOEt, 5 : 1; lit.,¹⁷ mp not reported); IR 1465, 1445, 1415, 1255, 735; ^1H NMR δ 7.14 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 4.5$ Hz), 7.45-7.50 (m, 3H), 8.27 (dd, 1H, $J_1 = 4.5$ Hz, $J_2 = 1.6$ Hz), 8.42 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 1.6$ Hz), 8.46-8.49 (m, 2H); ^{13}C NMR δ 119.4, 128.0, 129.8, 131.2, 131.5, 143.6, 146.7, 156.5; MS (EI) 172 (M^+ , 64), 104 (29), 103 (100). HRMS Calcd 172.0637; Found 172.0640. The structure of **5e** was also supported by X-Ray analysis.²⁰

2-(3-Methoxybenzyl)pyrimidine 1-Oxide (5f): mp 56-59 °C (cyclohexane); IR 1590, 1470, 1400, 1250;

$^1\text{H NMR}$ δ 3.78 (s, 3H), 4.42 (s, 2H), 6.80 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 1.9$ Hz), 6.78-6.81 (m, 1H), 7.16 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 4.6$ Hz), 7.20-7.25 (m, 2H), 8.15 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.2$ Hz), 8.36 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 1.2$ Hz); $^{13}\text{C NMR}$ δ 37.9, 55.1, 112.4, 115.2, 119.3, 121.9, 129.3, 136.6, 142.9, 144.6, 159.6, 161.3; MS (EI) 216 (M^+ , 47), 199 (100), 184 (54), 156 (37). *Anal.* Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.83; H, 5.75; N, 12.99.

2-Diphenylmethylpyrimidine 1-Oxide (5g): mp 153-154.5 °C (AcOEt); IR 1525, 1485, 1410, 1280, 1240, 730, 695; $^1\text{H NMR}$ δ 6.55 (s, 1H), 7.17 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 4.5$ Hz), 7.22-7.34 (m, 10H), 8.22 (dd, 1H, $J_1 = 4.5$ Hz, $J_2 = 1.5$ Hz), 8.38 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 1.5$ Hz); $^{13}\text{C NMR}$ δ 50.4, 119.3, 127.1, 128.5, 129.3, 139.4, 142.7, 144.8, 163.5; MS (EI) 262 (M^+ , 5), 245 (100), 165 (30); MS (FAB) 263 ($M^+ + 1$, 100). *Anal.* Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.58; H, 5.07; N, 10.76.

4,6-Dimethyl-2-(3-nitrophenyl)pyrimidine 1-Oxide (6a) and 5-Methyl-3-(3-nitrophenyl)-1,2,4-oxadiazole (8a). **6a:** mp 155-156 °C (MeOH); IR 1615, 1520, 1350, 1260; $^1\text{H NMR}$ δ 2.55 (s, 3H), 2.56 (s, 3H), 7.18 (s, 1H), 7.63 (dd, 1H, $J_1 = J_2 = 8.1$ Hz), 8.31 (ddd, 1H, $J_1 = 8.1$ Hz, $J_2 = 2.3$ Hz, $J_3 = 1.1$ Hz), 8.92-8.96 (m, 1H), 9.41-9.43 (m, 1H); $^{13}\text{C NMR}$ δ 17.8, 23.2, 120.7, 125.1, 125.3, 128.7, 133.7, 135.8, 147.8, 152.2, 153.1, 157.0; MS (EI) 245 (M^+ , 100), 183 (16), 82 (15). *Anal.* Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.76; H, 4.20; N, 16.99. **8a:** mp 106-108 °C (lit.,²¹ mp 107-110°C).

4,6-Dimethyl-2-(4-nitrophenyl)pyrimidine 1-Oxide (6b):⁶ mp 215-217 °C (AcOEt); IR 1515, 1355, 1265; $^1\text{H NMR}$ δ 2.56 (s, 3H), 2.58 (s, 3H), 7.19 (s, 1H), 8.27-8.31 (m, 2H), 8.71-8.75 (m, 2H); $^{13}\text{C NMR}$ δ 17.9, 23.3, 120.9, 122.9, 131.2, 138.1, 148.7, 152.7, 153.1, 157.2; MS (EI) 245 (M^+ , 100), 244 (57), 82 (31). *Anal.* Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.82; H, 4.74; N, 17.04.

4,6-Dimethyl-2-(3-methoxyphenyl)pyrimidine 1-Oxide (6c): mp 93-94.5 °C (cyclohexane); IR 1580, 1450, 1325, 1240, 1040, 790; $^1\text{H NMR}$ δ 2.52 (s, 3H), 2.55 (s, 3H), 3.87 (s, 3H), 7.04 (ddd, 1H, $J_1 = 8.1$ Hz, $J_2 = 2.6$ Hz, $J_3 = 1.0$ Hz), 7.08 (s, 1H), 7.38 (dd, 1H, $J_1 = J_2 = 8.1$ Hz), 8.04 (ddd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.5$ Hz, $J_3 = 1.0$ Hz), 8.11 (dd, 1H, $J_1 = 2.6$ Hz, $J_2 = 1.5$ Hz); $^{13}\text{C NMR}$ δ 18.1, 23.3, 55.4, 114.9, 117.3, 119.9, 122.8, 128.9, 133.5, 152.7, 154.7, 156.7, 159.1; MS (EI) 230 (M^+ , 58), 215 (100), 187 (76), 159 (46). *Anal.* Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.98; H, 6.13; N, 11.93.

4,6-Dimethyl-2-(4-methoxyphenyl)pyrimidine 1-Oxide (6d):⁶ mp 140-143 °C (AcOEt); IR 1605, 1455, 1265, 1180, 1045; $^1\text{H NMR}$ δ 2.49 (s, 3H), 2.53 (s, 3H), 3.86 (s, 3H), 6.95-6.98 (m, 2H), 7.00 (s,

1H), 8.58-8.63 (m, 2H); ^{13}C NMR δ 18.1, 23.3, 55.4, 113.2, 119.0, 124.7, 132.2, 152.6, 154.4, 156.5, 161.5; MS (EI) 230 (M^+ , 100), 201 (36), 133 (56). *Anal.* Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.90; H, 6.00; N, 12.22.

4,6-Dimethyl-2-phenylpyrimidine 1-Oxide (6e): mp 91-93 °C (petroleum ether : ethyl acetate, 5 : 1; lit.,^{11b} mp 91-92 °C); IR 1605, 1455, 1355, 1235, 1170, 690; ^1H NMR δ 2.41 (s, 3H), 2.46 (s, 3H), 6.96 (s, 1H), 7.41-7.44 (m, 3H), 8.45-8.50 (m, 2H); ^{13}C NMR δ 17.2, 22.5, 119.3, 127.1, 129.4, 129.9, 131.7, 152.0, 153.8, 155.8; MS (EI) 200 (M^+ ,), 199 (92), 172 (43).

4,6-Dimethyl-2-(3-methoxybenzyl)pyrimidine 1-Oxide (6f): mp 92-94 °C (AcOEt); IR 1610, 1585, 1485, 1440, 1250, 1150, 1045; ^1H NMR δ 2.43 (s, 3H), 2.47 (s, 3H), 3.77 (s, 3H), 4.41 (s, 2H), 6.77 (ddd, 1H, $J_1 = 8.1$ Hz, $J_2 = 2.6$ Hz, $J_3 = 1.0$ Hz), 6.98-7.04 (m, 3H), 7.20 (dd, 1H, $J_1 = J_2 = 8.1$ Hz); ^{13}C NMR δ 17.7, 23.2, 38.5, 55.2, 112.3, 115.2, 119.8, 122.0, 129.3, 137.4, 152.3, 155.1, 159.3, 159.6; MS (EI) 244 (M^+ , 46), 228 (32), 227 (100), 212 (43), 184 (27). *Anal.* Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: C, 68.83, H, 6.60; N, 11.47. Found: C, 68.71; H, 6.67; N, 11.22.

4,6-Dimethyl-2-diphenylmethylpyrimidine 1-Oxide (6g): mp 162-164 °C (AcOEt); IR 1605, 1490, 1440, 1235, 700; ^1H NMR δ 2.43 (s, 3H), 2.50 (s, 3H), 6.45 (s, 1H), 6.67 (s, 1H), 7.23-7.37 (m, 10H); ^{13}C NMR δ 17.9, 23.3, 50.3, 119.5, 126.7, 128.2, 129.4, 140.2, 151.9, 154.8, 161.0; MS (EI) 290 (M^+ , 14), 274 (38), 273 (100), 197 (35), 165 (27). *Anal.* Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.71; H, 6.09; N, 9.70.

4,6-Dimethyl-2-(2-pyridyl)pyrimidine 1-Oxide (6j):⁶ mp 115-117 °C (AcOEt); IR 1605, 1450, 1365, 1250; ^1H NMR δ 2.56 (s, 3H), 2.58 (s, 3H), 7.20 (s, 1H), 7.39 (ddd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz, $J_3 = 1.0$ Hz), 7.83 (ddd, 1H, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.7$ Hz), 8.47 (d, 1H, $J = 7.8$ Hz), 8.83-8.84 (m, 1H); ^{13}C NMR δ 17.8, 23.4, 121.1, 124.7, 125.8, 136.0, 150.0, 150.2, 153.4, 153.9, 156.6; MS (EI) 201 (M^+ , 36), 185 (100), 105 (55), 69 (56). *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.57; H, 5.49; N, 20.95.

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