Pergamon

Tetrahedron 54 (1998) 4387–4396

TETRAHEDRON

Carboxamide Oximes as Convenient Precursors for the Synthesis of Pyrimidine *N*-Oxides

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Received 18 December 1997; revised 10 February 1998; accepted 12 February 1998

Abstract: A general method for the synthesis of pyrimidine *N*-oxides from the appropriate carboxamide oximes is described. The conversion involves a treatment of various carboxamide oximes with either 1,1,3,3-tetramethoxypropane, 2,4-pentanedione, 3-ethoxy-2-propenal, 4,4-dimethoxy-2-butanone or 4-methoxy-3-butene-2-one in the presence of trifluoroacetic acid as a catalyst. The application of an unsymmetrical dicarbonyl compound leads exclusively to one product. Our approach is a method of choice for the preparation of pyridylpyrimidine *N*-oxides.

INTRODUCTION

The chemistry and applications of *N*-oxides are well-documented.[1] *N*-Oxides were used as intermediates or auxiliary agents in the synthesis, as protecting groups, oxidants, ligands in metal complexes, as catalysts, pharmaceuticals, agrochemicals, etc.[2] Their simple and straightforward preparations remain of considerable importance to heterocyclic chemistry.

We have focused our attention to the synthesis of pyrimidine *N*-oxides. They were shown to possess hypotensive activity in man.[3] There is also a report about pyrimidine *N*-oxides as inhibitors of lysyl hydroxylase.[4] On the other hand, the introduction of *N*-oxide function into the pyrimidine molecule can result in lower inhibitory activity, which is demonstrated by the inhibition of dihydrofolate reductase with diaminopyrimidine *N*-oxides, in comparison with the diaminopyrimidines themselves.[5] Some of 2,4-diamino-5-benzylpyrimidine *N*-oxides are known to increase the activity of sulfonamides.[6] Another application deals with the use of pyrimidine *N*-oxides in preventing the loss of hair and for inducing and stimulating its growth.[7]

Most of pyrimidine *N*-oxides were prepared by the *N*-oxidation of the appropriate pyrimidines. Starting from unsymmetrically substituted pyrimidine one usually obtains the mixture of 1-oxide and 3-oxide. Recently, an improved procedure for the preparation of *N*-oxides appeared. Namely, the *N*-oxidation of pyrimidines, pyrazines, pyridines and purines was carried out by *m*-CPBA/HF/DMF-MeOH system.[8] Other methods involve

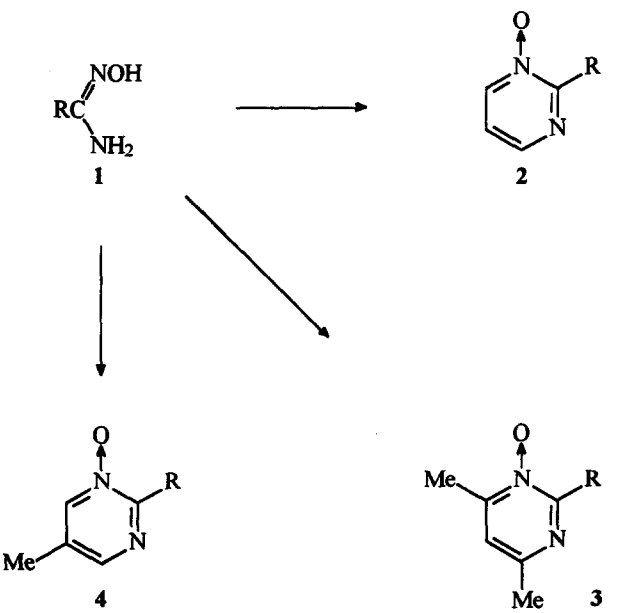
0040-4020/98/$19.00
PII: S0040-4020(98)00152-5

the formation of pyrimidine *N*-oxides by ring-closure reactions, by ring-transformation reactions, or by conversion of the substituents.[9]

In our preliminary communication we described a novel transformation of carboxamide oximes to pyrimidine *N*-oxides.[10] Carboxamide oximes have not been used before for the synthesis of pyrimidine *N*-oxides. On the contrary, they were described as convenient precursors in reactions with either acyl chlorides, carboxylic esters, orthoformates, chloroformates, aldehydes, 2,3-furanediones or nitriles to obtain 1,2,4-oxadiazoles.[11] Our approach was also the first example of the ring-closure reaction to give pyrimidine *N*-oxides in C_3-C_1N_2 fashion. Other ring-closure reactions led to pyrimidine *N*-oxides in C_3N_2-N_1 or C_4N_1-N_1 manner.[3a,12,13]

RESULTS AND DISCUSSION

We have found that carboxamide oximes reacted with 1,3-dicarbonyl compounds or their equivalents to give pyrimidine *N*-oxides. Thus, carboxamide oximes **1a-1e** were treated with 1,1,3,3-tetramethoxypropane (**A**), 2,4-pentanedione (**B**) or 3-ethoxy-2-methylpropenal (**C**), to yield 2-substituted pyrimidine 1-oxides **2a-2e**, **3a-3e** or **4a-4e** (Scheme 1, Table 1). These transformations were initially studied[10] in various solvents under acidic conditions: 2-propanol/acetyl chloride, 2-propanol-DMF/acetyl chloride, 2-butanol/acetyl chloride, acetonitrile/boron trifluoride etherate, toluene-DMF/boron trifluoride etherate and 2-propanol/trifluoroacetic acid. The last alternative gave the best results and was therefor employed throughout this paper.



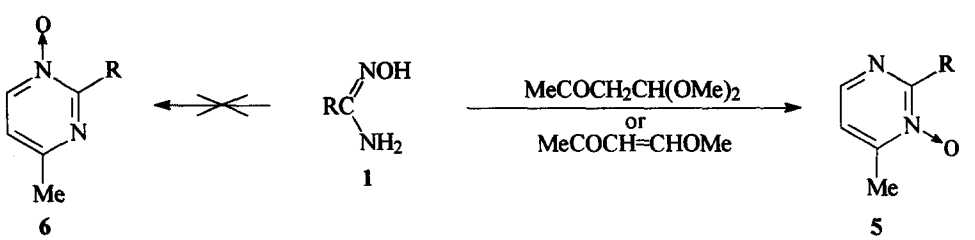
Scheme 1

Table 1. The Synthesis of Pyrimidine *N*-Oxides **2-4**.

Starting Oxime	R	Reagent[a]	Reaction Time (h)[b]	Product	Yield (%)[c]
1a	$ClCH_2$	**A**	2	**2a**	37
1a	$ClCH_2$	**B**	5	**3a**	28
1a	$ClCH_2$	**C**	0.3	**4a**	40
1b	4-$F_3CC_6H_4$	**A**	4	**2b**	19
1b	4-$F_3CC_6H_4$	**B**	17	**3b**	24
1b	4-$F_3CC_6H_4$	**C**	1	**4b**	98
1c	2-$MeOC_6H_4CH_2$	**A**	7	**2c**	28
1c	2-$MeOC_6H_4CH_2$	**B**	50	**3c**	35
1c	2-$MeOC_6H_4CH_2$	**C**	14	**4c**	58
1d	2-$O_2NC_6H_4CH_2$	**A**	5.5	**2d**	41
1d	2-$O_2NC_6H_4CH_2$	**B**	31.5	**3d**	44
1d	2-$O_2NC_6H_4CH_2$	**C**	8	**4d**	76
1e	4-$O_2NC_6H_4CH_2$	**A**	5	**2e**	45
1e	4-$O_2NC_6H_4CH_2$	**B**	45	**3e**	23
1e	4-$O_2NC_6H_4CH_2$	**C**	5.5	**4e**	65

[a] **A**: $(MeO)_2CHCH_2CH(OMe)_2$; **B**: $MeCOCH_2COMe$; **C**: EtOCH=C(Me)CHO.
[b] Reaction conditions: 2-PrOH, CF_3CO_2H, reflux.
[c] Isolated yields are given.

Carbonyl compounds **A-C** contributed a symmetrical fragment to the pyrimidine ring. It is not the case when 4,4-dimethoxy-2-butanone (**D**) was used as 1,3-dicarbonyl equivalent. One would expect the formation of 4-methylpyrimidine 1-oxides or 3-oxides. In several experiments performed during this project, we have synthesized only 3-oxides **5a-5e** (Scheme 2, Table 2); the alternative products of type **6** have never been isolated. Similar results were obtained on treatment of carboxamide oximes **1** with *trans*-4-methoxy-3-butene-2-one (**E**). The fact that products of type **5** were formed, using two different reagents, led to the conclusion that regioselective attack on carboxamide oxime took place. The formation of pyrimidine 3-oxides **5a-5e** seems to involve the reaction of the carbonyl group of the reagent **D** or **E** with the oxime nitrogen of carboxamide oximes **1a-1e**.



6 **1** **5**

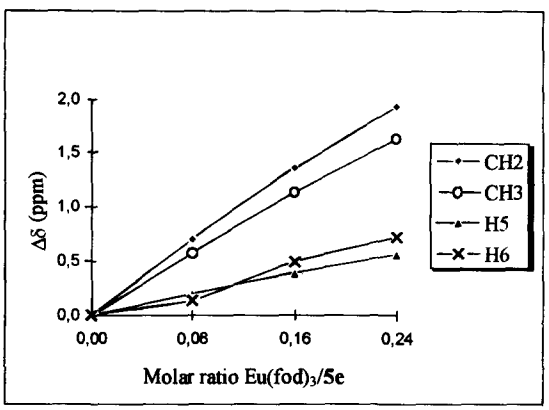
Scheme 2

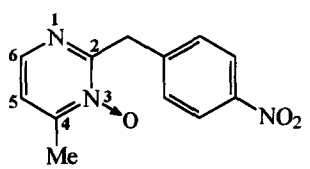
Table 2. Pyrimidine 3-Oxides **5** Prepared.

Starting Oxime	R	Reagent[a]	Reaction Time (h)[b]	Product	Yield (%)[c]
1a	$ClCH_2$	**D**	6	**5a**	24
1a	$ClCH_2$	**E**	3	**5a**	45
1b	4-$F_3CC_6H_4$	**D**	13	**5b**	83
1b	4-$F_3CC_6H_4$	**E**	1	**5b**	81
1c	2-$MeOC_6H_4CH_2$	**D**	17	**5c**	26
1c	2-$MeOC_6H_4CH_2$	**E**	5	**5c**	21
1d	2-$O_2NC_6H_4CH_2$	**D**	13	**5d**	49
1d	2-$O_2NC_6H_4CH_2$	**E**	11	**5d**	65
1e	4-$O_2NC_6H_4CH_2$	**D**	11	**5e**	49
1e	4-$O_2NC_6H_4CH_2$	**E**	6	**5e**	52

[a] **D**: $(MeO)_2CHCH_2COMe$; **E**: MeOCH=CHCOMe (*trans*).
[b] Reaction conditions: 2-PrOH, CF_3CO_2H, reflux.
[c] Isolated yields are given.

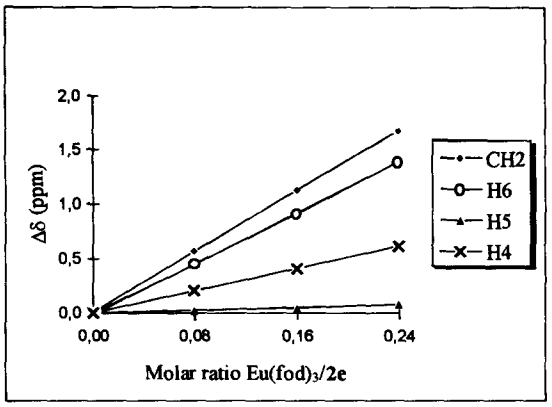
The structures of the products **5** were also supported by NMR evidence according to studies of Yamanaka and coworkers,[14] using europium(III)-tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate), $Eu(fod)_3$, as a shift reagent. *N*-Oxide group in **5** is the most appropriate site for the complexation with $Eu(fod)_3$. The largest effect of a lanthanide reagent is expected on those protons, which are closer to the *N*-oxide function. A typical example is shown below (Figure 1). Indeed, larger downfield shifts of methylene and methyl protons, comparing to the pyrimidine proton H_6, are in agreement with the proposed structure of **5e**. For the alternative *N*-oxide **6e**, larger downfield shifts should have been observed for the methylene group and the proton H_6, as it is obvious in the case of a similar *N*-oxide **2e** (Figure 2).

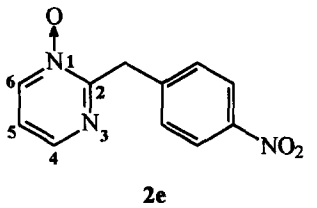




5e

Figure 1. $Eu(fod)_3$ Induced Downfield Shifts for **5e** (0.12 M $CDCl_3$ Solution, 29 °C).

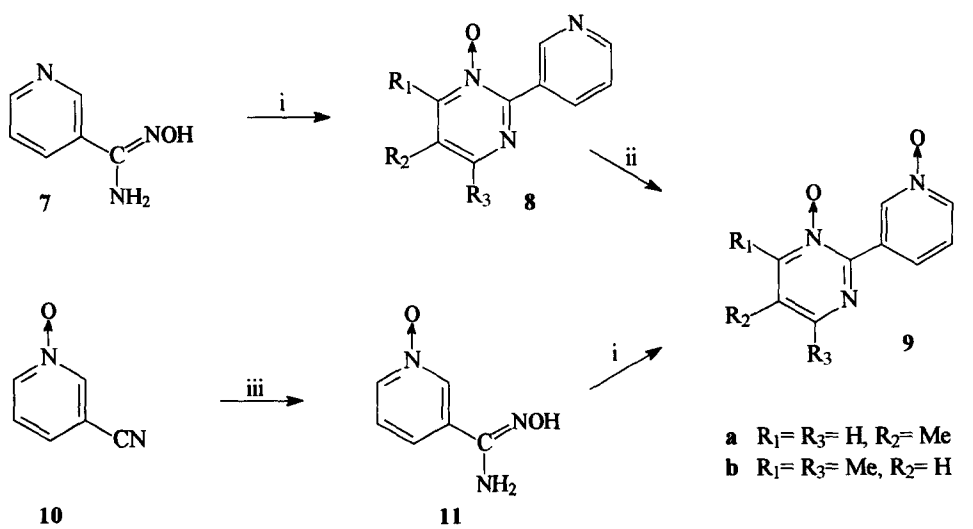




2e

Figure 2. Eu(fod)$_3$ Induced Downfield Shifts for **2e** (0.1 M $CDCl_3$ Solution, 29 °C).

Our method for the synthesis of *N*-oxides was successfully applied for the preparation of pyridylpyrimidine *N*-oxides.[10] It is known that the *N*-oxidation of pyridylpyrimidine resulted in the formation of pyrimidinylpyridine *N*-oxide due to the lower basicity of the pyrimidine nitrogens.[9,15] An introduction of the pyridine *N*-oxide function could be avoided starting from the corresponding carboxamide oxime. For example, amide oxime **7** was transformed to pyrimidine *N*-oxides **8a** and **8b** under the same reaction conditions as described for the synthesis of *N*-oxides **2-5**. Further *N*-oxidation with *m*CPBA gave di-*N*-oxides **9a** and **9b**, respectively (Scheme 3). An alternative route to the products of type **9** involved transformation of 3-cyanopyridine 1-oxide (**10**) to carboxamide oxime **11**, followed by the construction of pyrimidine *N*-oxide as mentioned above.



Scheme 3. *Reagents and Conditions:* (i) EtOCH=C(Me)CHO or $MeCOCH_2COMe$, CF_3CO_2H, 2-PrOH, reflux, 2.5-44 h, 37-77 % yield. (ii) *m*CPBA, CH_2Cl_2, r.t., 0.5-1 h, 60-65% yield. (iii) $NH_2.HCl$, $NaHCO_3$, H_2O, r.t., 1 h, 97% yield.

In conclusion, we have presented a general method for the preparation of pyrimidine *N*-oxides starting from the appropriate carboxamide oximes and the dicarbonyl equivalents in the presence of trifluoroacetic acid. Our approach enables a selective formation of pyrimidine *N*-oxide when pyridine ring is a part of carboxamide oxime molecule.

Acknowledgements. We would like to thank Dr. Bogdan Kralj and Dr. Dušan Žigon (Mass Spectrometry Center, Jožef Stefan Institute, Ljubljana, Slovenia) for mass measurements. The Ministry of Science and Technology of Slovenia and the Slovenian Science Foundation are gratefully acknowledged for the financial support.

EXPERIMENTAL

The starting materials were purchased from commercial sources (Fluka, Merck, Aldrich, Maybridge) and were used without further purification. TLC was carried out on Fluka silica gel plates (F_{254}). Chromatographic separations on chromatotron were performed with a Harrison Research instrument, model 7924 T, employing Merck silica gel 60 PF_{254}. Melting points were determined on a hot stage and were uncorrected. IR spectra, reported in cm^{-1}, were taken on a Perkin Elmer 1310 spectrometer (KBr pellets). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 29 °C in $CDCl_3$ as a solvent and TMS as an internal standard. Mass 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**,[16] **1b**,[17] **1c**,[18] **1d**,[19] **1e**[20] and **7**[17,20] were prepared as described in the literature. The carboxamide oxime **11** was obtained from the commercially available nitrile as follows: nitrile (**10**, 1 mmol), $NH_2OH.HCl$ (2 mmol), $NaHCO_3$ (2 mmol), H_2O (2.5 mL), r. t. (1 h); **11** was isolated in 97% yield, mp 229-231 °C (EtOH).

General Procedure for the Preparation of Pyrimidine *N*-Oxides. A mixture of a selected carboxamide oxime (**1**, **7** or **11**; 1 mmol), an appropriate dicarbonyl compound (**A-E**; 1.05-2 mmol) and trifluoroacetic acid (1.05-1.4 mmol) in 2-propanol (3-6 mL) was heated under reflux as indicated in Table 1, Table 2 or Scheme 3. Reaction mixture was then evaporated to dryness, treated with H_2O (1-5 mL) and neutralized with Na_2CO_3. The solid material was filtered off and rinsed with H_2O (*N*-oxides: **4b**, **4d**, **5b**, **4e**, **5d**, **5e** and **9a**). In all other cases, the neutralized mixtures were extracted with $CHCl_3$ (5 × 15 mL), the combined extracts evaporated to dryness, and *N*-oxides isolated as follows:

(a) The residue was treated with Et_2O (1 mL; **8a**) or petroleum ether (3 mL; **9b**) and the solid material was filtered off.

(b) By extraction with boiling cyclohexane (*N*-oxides: **3a**, **4a**, **5a** and **8b**).

(c) By chromatography on chromatotron using EtOAc as a solvent (*N*-oxides: **2a**, **2b**, **3b**, **2c**, **3c**, **4c**, **2d**, **3d**, **2e**, **3e** and **5c**).

2-Chloromethylpyrimidine 1-Oxide (2a): mp 113-114 °C (cyclohexane); IR 1540, 1480, 1400, 1250; ^1H NMR δ 4,93 (s, 2H), 7.35 (dd, 1H, J_1 = 6.5 Hz, J_2 = 4.6 Hz), 8.29 (dd, 1H, J_1 = 4.6 Hz, J_2 = 1.5 Hz), 8.45 (dd, 1H, J_1 = 6.5 Hz, J_2 = 1.5 Hz); ^{13}C NMR δ 40.2, 121.1, 143.3, 145.2, 157.3; MS (EI) 144 (M^+, 58), 129 (47), 127 (100). Anal. Calcd for $C_5H_5ClN_2O$: C, 41.54; H, 3.49; N, 19.38. Found: C, 41.61; H, 3.03; N, 19.18.

2-Chloromethyl-4,6-dimethylpyrimidine 1-Oxide (3a): mp 111-112 °C (hexane); lit.[12e] mp 116-118 °C; IR 1610, 1440, 1275, 1255; ^1H NMR δ 2.51 (s, 3H), 2.53 (s, 3H), 4.92 (s, 2H), 7.15 (s, 1H); ^{13}C NMR δ

17.4, 23.1, 40.7, 121.2, 153.0, 155.3, 155.7. Anal. Calcd for $C_7H_9ClN_2O$: C, 48.71; H, 5.26; N, 16.23. Found: C, 49.01; H, 5.03; N, 16.02.

2-Chloromethyl-5-methylpyrimidine 1-Oxide (4a): mp 110-111.5 °C (hexane); IR 1380, 1270, 1210; ^{1}H NMR δ 2.36 (s, 3H), 4.89 (s, 2H), 8.15 (d, 1H, J = 1.04 Hz), 8.34 (d, 1H, J = 1.04 Hz); ^{13}C NMR δ 15.1, 39.7, 132.1, 144.7, 145.0, 154.3; MS (EI) 158 (M^+, 51), 143 (48), 141 (100). Anal. Calcd for $C_6H_7ClN_2O$: C, 45.56; H, 4.46; N, 17.72. Found: C, 45.62; H, 4.23; N, 17.39.

2-(4-Trifluoromethylphenyl)pyrimidine 1-Oxide (2b): mp 124-126 °C (hexane-EtOAc); IR 3075, 1530, 1460, 1400, 1320, 1250, 1120; ^{1}H NMR δ 7.27 (dd, 1H, J_1 = 6.6 Hz, J_2 = 4.5 Hz), 7.74-7.77 (m, 2H), 8.37 (dd, 1H, J_1 = 4.5 Hz, J_2 = 1.6 Hz), 8.50 (dd, 1H, J_1 = 6.6 Hz, J_2 = 1.6 Hz), 8.65-8.67 (m, 2H); ^{13}C NMR δ 120.0, 123.8 (q, J = 272.5 Hz), 124.9 (q, J = 3.7 Hz), 125.6, 130.2, 132.7 (q, J = 32.7 Hz), 134.7, 143.6, 146.9; MS (EI) 240 (M^+, 100), 239 (73), 224 (20), 212 (33), 172 (56), 171 (53), 145 (30), 69 (50), 68 (49). Anal. Calcd for $C_{11}H_7F_3N_2O$: C, 55.01; H, 2.94; N, 11.66. Found: C, 54.95; H, 2.81; N, 11.47.

4,6-Dimethyl-2-(4-trifluoromethylphenyl)pyrimidine 1-Oxide (3b): mp 106-109 °C (cyclohexane); IR 1450, 1320, 1240, 1180, 1110; ^{1}H NMR δ 2.54 (s, 3H), 2.57 (s, 3H), 7.27 (s, 1H), 7.71-7.74 (m, 2H), 8.60-8.62 (m, 2H); ^{13}C NMR δ 17.9, 23.2, 120.5, 123.9 (q, J = 272.4 Hz), 124.7 (q, J = 3.8 Hz), 130.4, 132.1 (q, J = 32.6 Hz), 135.6, 152.9, 153.5, 156.9; MS (EI) 268 (M^+, 100), 267 (94), 82 (47). Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.05; H, 4.18; N, 10.85.

5-Methyl-2-(4-trifluoromethylphenyl)pyrimidine 1-Oxide (4b): mp 159-161 °C (CCl_4); IR 1360, 1310, 1260, 1100; ^{1}H NMR δ 2.37 (m, 3H), 7.73-7.75 (m, 2H), 8.22-8.23 (m, 1H), 8.35-8.36 (m, 1H), 8.61-8.65 (m, 2H); ^{13}C NMR δ 15.0, 123.8 (q, J = 272.4 Hz), 124.9 (q, J = 3.9 Hz), 130.1, 131.0, 132.3 (q, J = 32.5 Hz), 134.8, 145.0, 146.6, 152.7; MS (EI) 254 (M^+, 100), 253 (75), 172 (66). Anal. Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.81; H, 3.30; N, 10.85.

2-(2-Methoxybenzyl)pyrimidine 1-Oxide (2c): mp 89.5-91.5 °C (cyclohexane); IR 1500, 1410, 1270, 1250, 1230; ^{1}H NMR δ 3.75 (s, 3H), 4,44 (s, 2H), 6.90-6.97 (m, 2H), 7.14-7.32 (m, 3H), 8.12 (dd, 1H, J_1 = 4.7 Hz, J_2 = 1.7 Hz), 8.41 (dd, 1H, J_1 = 6.6 Hz, J_2 = 1.7 Hz); ^{13}C NMR δ 33.1, 55.5, 110.7, 119.0, 120.6, 124.0, 128.6, 131.1, 143.1, 144.4, 157.8, 161.9; MS (EI) 216 (M^+, 28), 199 (100), 168 (55). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.26; H, 5.45; N, 12.87.

4,6-Dimethyl-2-(2-methoxybenzyl)pyrimidine 1-Oxide (3c): mp 137-138 °C (hexane); IR 1495, 1440, 1250, 1020; ^{1}H NMR δ 2.40 (s, 3H), 2.52 (s, 3H), 3.80 (s, 3H), 4.47 (s, 2H), 6.89-6.93 (m, 2H), 7.02 (s, 1H), 7.16-7.19 (m, 1H), 7.25-7.28 (m, 1H); ^{13}C NMR δ 17.8, 23.2, 33.2, 55.5, 110.7, 119.3, 120.4, 124.7, 127.9, 130.5, 152.2, 154.7, 157.8, 159.7; MS (EI) 244 (M^+, 36), 227 (100), 196 (56). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.62; H, 6.47; N, 11.55.

2-(2-Methoxybenzyl)-5-methylpyrimidine 1-Oxide (4c): mp 86-87 °C (cyclohexane); IR 1480, 1290, 1235, 1125; ^{1}H NMR δ 2.27 (s, 3H), 3.76 (s, 3H), 4.40 (s, 2H), 6.89-6.96 (m, 2H), 7.19-7.30 (m, 2H), 7.98 (s, 1H), 8.27 (s, 1H); ^{13}C NMR δ 14.9, 32.5, 55.4, 110.6, 120.5, 124.2, 128.4, 129.5, 131.0, 144.2, 144.4, 157.7, 158.8; MS (EI) 230 (M^+, 28), 213 (100), 182 (53). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.79; H, 6.18; N, 12.14.

2-(2-Nitrobenzyl)pyrimidine 1-Oxide (2d): mp 122-124 °C (CCl_4); IR 1530, 1420, 1350, 1260; ^{1}H NMR δ 4.82 (s, 2H), 7.19 (dd, 1H, J_1 = 6.5 Hz, J_2 = 4.9 Hz), 7.42 (dd, 1H, J_1 = 7.5 Hz J_2 = 1.3 Hz), 7.51 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 7.62 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.3 Hz), 8.05 (dd, 1H, J_1 = 4.7 Hz, J_2 = 1.5 Hz), 8.15 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.3 Hz), 8.43 (dd, 1H, J_1 = 6.5 Hz, J_2 = 1.5 Hz); ^{13}C NMR δ 37.0, 119.5, 125.3, 128.6, 130.8, 133.4, 133.6, 142.4, 144.4, 149.5, 159.9; MS (EI) 232 (MH^+, 1.7), 185 (100). Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 56.78; H, 4.10; N, 17.85.

4,6-Dimethyl-2-(2-nitrobenzyl)pyrimidine 1-Oxide (3d): mp 123-125 °C (cyclohexane-EtOAc); IR 1510, 1340, 1230; ^{1}H NMR δ 2.29 (s, 3H), 2.52 (s, 3H), 4.84 (s, 2H), 7.00 (s, 1H), 7.40 (m, 1H), 8.47 (ddd, 1H, $J_1 = J_2 = 7.7$ Hz, $J_3 = 1.5$ Hz), 7.58 (ddd, 1H, $J_1 = J_2 = 7.7$ Hz, $J_3 = 1.5$ Hz), 8.07 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.5$ Hz); ^{13}C NMR δ 17.6, 23.0, 37.1, 119.7, 125.0, 128.1, 131.2, 133.1, 133.2, 150.0, 152.5, 154.9, 157.4; MS (EI) 213 (100), 149 (33), 107 (31); MS (FAB) 260 ($M^+ + 1$, 100). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.49; H, 5.18; N, 15.87.

5-Methyl-2-(2-nitrobenzyl)pyrimidine 1-Oxide (4d): mp 151-152.5 °C (CCl_4); IR 1520, 1490, 1340, 1300, 1140; ^{1}H NMR δ 2.27 (s, 3H), 4.77 (s, 2H), 7.41 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz), 7.49 (ddd, 1H, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.5$ Hz), 7.61 (ddd, 1H, $J_1 = J_2 = 7.8$ Hz $J_3 = 1.4$ Hz), 7.89 (d, 1H, $J = 1.1$ Hz), 8.12 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.4$ Hz), 8.28 (d, 1H, $J = 1.1$ Hz); ^{13}C NMR δ 14.9, 36.3, 125.1, 128.3, 130.1, 130.9, 133.1, 133.4, 143.9, 144.3, 149.4, 156.7; MS (EI) 246 (MH^+, 19), 199 (100), 183 (30). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.37; H, 4.13; N, 17.42.

2-(4-Nitrobenzyl)pyrimidine 1-Oxide (2e): mp 142-145 °C (cyclohexane-EtOAc); IR 1510, 1415, 1350, 1275; ^{1}H NMR δ 4.53 (s, 2H), 7.25 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 4.7$ Hz), 7.25-7.27 (m 2H), 8.16-8.21 (m, 2H), 8.19 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 1.5$ Hz), 8.39 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 1.5$ Hz); ^{13}C NMR δ 38.0, 120.0, 123.7, 130.6, 142.6, 143.1, 144.8, 147.1, 160.1; MS (EI) 231 (M^+, 48), 214 (61), 168 (100). Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.08; H, 3.68; N, 18.41.

4,6-Dimethyl-2-(4-nitrobenzyl)pyrimidine 1-Oxide (3e): mp 169-171 °C (EtOAc); IR 1610, 1520, 1350, 1260; ^{1}H NMR δ 2.46 (s, 3H), 2.49 (s, 3H), 4.51 (s, 2H), 7.07 (s, 1H), 7.58-7.61 (m, 2H), 8.14-8.17 (m, 2H); ^{13}C NMR δ 17.6, 23.1, 38.6, 120.2, 123.5, 130.4, 143.4, 146.9, 152.7, 155.3, 157.9; MS (EI) 259 (M^+, 43), 242 (55), 196 (100), 69 (61). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.07; H, 4.90; N, 16.39.

5-Methyl-2-(4-nitrobenzyl)pyrimidine 1-Oxide (4e): mp 138-140 °C (CCl_4-EtOAc); IR 1505, 1335, 1280; ^{1}H NMR δ 2.32 (s, 3H), 4.49 (s, 2H), 7.53-7,59 (m, 2H), 8.05 (d, 1H, $J = 1$ Hz), 8.12-8.17 (m, 2H), 8.28 (d, 1H, $J = 1$ Hz); ^{13}C NMR δ 14.8, 37.4, 123.4, 130.3, 130.7, 143.0, 144.1, 144.6, 146.8, 156.8; MS (EI) 246 (MH^+, 15), 199 (100), 182 (35). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.47; H, 4.34; N, 16.75.

2-Chloromethyl-4-methylpyrimidine 3-Oxide (5a): mp 113-115 °C (cyclohexane); 1345, 1260, 1220; ^{1}H NMR δ 2.57 (s, 3H), 4.95 (s, 2H), 7.30 (d, 1H, $J = 4.8$ Hz), 8.14 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR δ 17.4, 40.7, 121.3, 141.9, 156.3, 156.6; MS (EI) 158 (M^+, 48), 143 (36), 141 (100). Anal. Calcd for $C_6H_7ClN_2O$: C, 45.44; H, 4.45; N, 17.66. Found: C, 45.67; H, 4.23; N, 17.97.

4-Methyl-2-(4-trifluoromethylphenyl)pyrimidine 3-Oxide (5b): mp 155.5-157 °C (cyclohexane); IR 1315, 1255, 1160, 1110; ^{1}H NMR δ 2.59 (dd, 3H, $J_1 = J_2 = 0.4$ Hz), 7.27 (dq, 1H, $J_1 = 4.6$ Hz, $J_2 = 0.4$ Hz), 7.72-7.73 (m, 1H), 7.74-7.76 (m, 1H), 8.22 (dq, 1H, $J_1 = 4.6$ Hz, $J_2 = 0.4$ Hz), 8.59-8.60 (m, 2H); ^{13}C NMR δ 18.0, 120.6, 123.8 (q, $J = 272.4$ Hz), 124.7 (q, $J = 3.8$ Hz), 130.4, 132.2 (q, $J = 32.5$ Hz), 135.4, 142.2, 154.9, 157.6; MS (EI) 254 (M^+, 100), 253 (91), 82 (76). Anal. Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.52; H, 3.32; N, 10.83.

2-(2-Methoxybenzyl)-4-methylpyrimidine 3-Oxide (5c): mp 106-109 °C (cyclohexane); IR 1490, 1240, 1020, 755; ^{1}H NMR δ 2.54 (s, 3H), 3.74 (s, 3H), 4.45 (s, 2H), 6.88-6.95 (m, 2H), 7.12 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 0.6$ Hz), 7.18-7.26 (m, 2H), 7.97 (d, 1H, $J = 4.9$ Hz); ^{13}C NMR δ 17.6, 33.1, 55.2, 110.5, 119.4, 120.3, 124.2, 128.2, 130.8, 141.6, 155.0, 157.6, 160.9; MS (EI) 230 (M^+, 32), 213 (100), 182 (55), 91 (64). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.09; H, 6.13; N, 12.04.

4-Methyl-2-(2-nitrobenzyl)pyrimidine 3-Oxide (5d): mp 170-171 °C (cyclohexane-EtOAc); IR 1520, 1350, 1275, 1230; ^{1}H NMR δ 2.57 (s, 3H), 4.84 (s, 2H), 7.17 (d, 1H, $J = 4.8$ Hz), 7.41-7.53 (m, 2H), 7.59-

7.64 (m, 1H), 7.90 (d, 1H, J = 4.8 Hz), 8.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.3 Hz); ^{13}C NMR δ 17.7, 37.2, 119.9, 125.2, 128.4, 131.2, 133.3, 133.4, 141.6, 149.5, 155.5, 159.1; MS (FAB) 246 (M^+ + 1, 100), 230 (15). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 59.14; H, 4.22; N, 17.25.

4-Methyl-2-(4-nitrobenzyl)pyrimidine 3-Oxide (5e): mp 148-150 °C (EtOAc); IR 1510, 1350, 1260; ^{1}H NMR δ 2.54 (s, 3H), 4.55 (s, 2H) 7.24 (d, 1H, J = 4.8 Hz), 7.57-7.59 (m, 2H), 8.06 (d, 1H, J = 4.8 Hz), 8.17-8.19 (m, 2H); ^{13}C NMR δ 17.7, 38.5, 120.5, 123.6, 130.5, 141.8, 143.1, 147.0, 155.9, 159.4; MS (EI) 245 (M^+, 54), 228 (48), 182 (100). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.78; H, 4.31; N, 17.37.

5-Methyl-2-(3-pyridyl)pyrimidine 1-Oxide (8a): reflux, 2.5 h; 57% yield; mp 171-172.5 °C (toluene); IR 1410, 1280, 1200; ^{1}H NMR δ 2.34 (m, 3H), 7.41 (ddd, 1H, J_1 = 8.2 Hz, J_2 = 4.8 Hz, J_3 = 0.9 Hz), 8.21-8.22 (m, 1H), 8.353-8.357 (m, 1H), 8.70 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.8 Hz), 8.91 (ddd, 1H J_1 = 8.2 Hz, J_2 = 2.2 Hz, J_3 = 1.8 Hz), 9.67 (dd, 1H, J_1 = 2.2 Hz, J_2 = 0.9 Hz); ^{13}C NMR δ 14.7, 122.4, 127.4, 130.7, 136.6, 144.7, 146.1, 150.4, 150.9, 151.4; MS (EI) 187 (M^+, 100), 186 (99), 105 (52). Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.17; H, 4.63; N, 22.50.

4,6-Dimethyl-2-(3-pyridyl)pyrimidine 1-Oxide (8b): reflux, 19.5 h; 37% yield; mp 111-112 °C (cyclohexane); IR 1610, 1450, 1430, 1260; ^{1}H NMR δ 2.55 (s, 3H), 2.57 (s, 3H), 7.14 (s, 1H), 7.40 (ddd, 1H, J_1 = 8.1 Hz, J_2 = 4.9 Hz, J_3 = 0,9 Hz), 8.70 (dd, 1H, J_1 = 4.9 Hz, J_2 = 2.0 Hz), 8.94 (ddd, 1H, J_1 = 8.1 Hz, J_2 = J_3 = 2.0 Hz), 9.66 (dd, 1H, J_1 = 2.0 Hz, J_2 = 0.9 Hz); ^{13}C NMR δ 18.3, 23.6, 120.8, 122.9, 128.8, 137.7, 151.5, 151.5, 153.1, 153.5, 157.1; MS (EI) 201 (M^+, 66), 200 (100), 122 (72), 106 (78), 78 (95). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.29; H, 5.45; N, 21.16.

5-Methyl-2-(1-oxypyridine-3-yl)pyrimidine 1-Oxide (9a): reflux, 9 h; 73% yield; mp 219-222 °C (acetone); IR 1445, 1300, 1280, 1240, 910; ^{1}H NMR δ 2.40 (m, 3H), 7.40 (ddd, 1H, J_1 = 8.2 Hz, J_2 = 6.4 Hz J_3 = 0.5 Hz), 8.23-8.26 (m, 1H), 8.31 (ddd, 1H, J_1 = 6.4 Hz, J_2 =1.8 Hz, J_3 = 1.1 Hz), 8.37-8.38 (m, 1H), 8.58 (ddd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz J_3 = 1.1 Hz), 9.60 (ddd, 1H, J_1 = J_2 = 1.8 Hz, J_3 = 0.5 Hz); ^{13}C NMR δ 14.9, 125.1, 126.6, 130.9, 131.9, 140.1, 140.2, 144.9, 146.7, 148.8; MS (EI) 203 (M^+, 100), 187 (62), 160 (72), 132 (87). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.83; H, 4.09; N, 20.67. *Alternative procedure*: *N*-oxide **8a** (1 mmol) was treated with *m*CPBA (1.5 mmol) in CH_2Cl_2 (2 mL) at r. t. for 0.5 h. Reaction mixture was evaporated to dryness, neutralized with 5% $NaHCO_3$ and extracted with $CHCl_3$ (5 × 10 mL) to give **9a** in 60% yield.

4,6-Dimethyl-2-(1-oxypyridine-3-yl)pyrimidine 1-Oxide (9b): reflux, 44 h; 76% yield; mp 174-177 °C (EtOAc); IR 1260, 1220; ^{1}H NMR δ 2.55 (s, 3H), 2.56 (s, 3H), 7.12 (s, 1H), 7.40 (dd, 1H, J_1 = 8.2 Hz, J_2 = 6.5 Hz), 8.31 (ddd, 1H, J_1 = 6.5 Hz, J_2 = 1.6 Hz, J_3 = 1.1 Hz), 8.70 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.1 Hz), 9.55 (d, 1H, J = 1.6 Hz); ^{13}C NMR δ 17.7, 23.0, 121.1, 124.9, 127.3, 131.6, 140.0, 140.5, 149.5, 153.1, 157.3; MS (EI) 217 (M^+, 90), 201 (33), 146 (100). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.44; H, 5.03; N, 19.03. *Alternative procedure*: *N*-oxide **8b** (1 mmol) was treated with *m*CPBA (1.5 mmol) in CH_2Cl_2 (4 mL) at r. t. for 1 h. Reaction mixture was evaporated to dryness, neutralized with 5% $NaHCO_3$, evaporated to dryness and the solid material extracted with $CHCl_3$ (5 × 15 mL) to afford **9b** in 65% yield.

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