Phenylation of pyrimidinones using diphenyliodonium salts

Stig André Jacobsen, Synne Rødbotten and Tore Benneche *

Department of Chemistry, University of Oslo, PO Box 1033, Blindern, N-0315 Oslo, Norway

Received (in Lund, Sweden) 8th July 1999, Accepted and transferred from Acta Chem. Scand. 20th September 1999

Pyrimidinones **1** have been phenylated under basic conditions using diphenyliodonium salts, and the effect of substituents on the yield and regiochemistry has been studied.

Introduction

In recent years the synthetic utility of hypervalent iodine compounds has been greatly developed[1] and diaryliodonium salts have been used to arylate a wide variety of substrates,[2] including heterocyclic amides.[3] To our knowledge direct *O*/*N*-arylation of pyrimidinones has not been reported by use of hypervalent iodine compounds or by any other method.[4]

N-Arylpyrimidinones have earlier been prepared by condensation reactions where one of the reaction partners contains the *N*-aryl bond.[5] 2-, 4- or 6-Aryloxypyrimidines have been made from the corresponding halopyrimidine by substitution reactions.[6]

Results and discussion

In this paper we report our results from phenylation of a number of pyrimidinones using diphenyliodonium salts (Scheme 1).

In an initial study the reactivity of different counterions in the diphenyliodonium salt were tested (Table 1). As seen from the Table the more electron withdrawing the anion, the better the yield in the reaction. This is in accordance with the literature.[7] The product ratio did not vary with the counterion.

From Table 2 we see that the product ratios and the yields are dependent on the substitution pattern of the pyrimidine ring. Pyrimidin-2(1*H*)-one **1a**, 5-chloropyrimidin-2(1*H*)-one **1b** and 5-bromopyrimidin-2(1*H*)-one **1c** all give a mixture of *N*- and *O*-phenylation, with the former as the main product (entries 1–3, Table 2). 5-Methoxypyrimidin-2(1*H*)-one **1d**, on the other hand, gives only the *O*-phenylated isomer (entry 4). The yields in these reactions are low (21–35%) and in all cases a substantial amount of starting material is recovered. Prolonged reaction times, an increase in reaction temperature or amount of iodonium salt, did not improve the yields to any great extent. All reactions have been run several times.

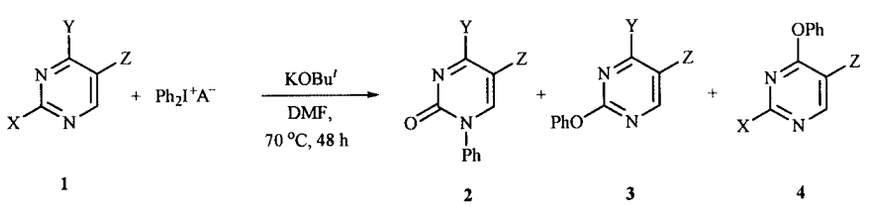
Table 1 Phenylation of pyrimidinones with different diphenyliodonium salts

Entry	Compound	Counter ion	X	Y	Z	Yield
1	**1b**	Cl^-	OH	H	Cl	16
2	**1b**	BF_4^-	OH	H	Cl	22
3	**1b**	OTf^-	OH	H	Cl	25
4	**1c**	BF_4^-	OH	H	Br	22
5	**1c**	OTf^-	OH	H	Cl	33
6	**1l**	Cl^-	OH	NH_2	H	40
7	**1l**	BF_4^-	OH	NH_2	H	53
8	**1l**	OTf^-	OH	NH_2	H	75

All pyrimidin-2-ones with an electron-donating group in the 4-position give only the N^1-phenylated pyrimidinone (entries 5–13). The yields are usually better than the pyrimidinones with a substituent only in the 5-position. The low yields in the case of **1e** and **1k** (entries 5 and 11) are probably not representative for the pyrimidinones with electron-donating substituents in the 4-position, because the reaction mixtures in these cases turned brown fairly rapidly, indicating some decomposition. In all other cases the reaction mixtures were slightly yellow during the reaction.

There is probably also a steric demand in the phenylation reaction since no phenylation was observed on N^3 in any of the 4-substituted pyrimidinones. In 2-methylthio-5-methoxypyrimidin-4(3*H*)-one **1n** both an electronic and a steric requirement might be operating in the same direction, giving only *O*-phenylation (entry 14, Table 2).

One might expect that the acidity of the pyrimidinone is important for the phenylation reaction since relatively acidic pyrimidinones are less reactive than more basic pyrimidinones in nucleophilic substitution reactions. Potassium *tert*-butoxide in DMF was expected to ionize even very weakly acidic pyrimidinones. In Table 3 the pK_a values of some of the pyrimidinones (in water) are listed together with the yields from the reaction. Comparing the acidity with the yields shows that an increase in the pK_a value of the parent pyrimidinone, generally gives an increased yield of the phenylated product. The



1 2 3 4

$A^- = Cl^-, BF_4^-, OTf^-$

X = OH, MeS

Y = H, OH, OMe, OCH_2CH_2TMS, NH_2, NMe_2

Z = H, F, Cl, Br, Me, OMe

Scheme 1

Table 2 Phenylation of pyrimidinones **1** with diphenyliodonium triflate

Entry	Compound	X	Y	Z	Product ratio **2**	**3**	**4**	Yield (%)
1	**a**	OH	H	H	67	33	0	35
2	**b**	OH	H	Cl	67	33	0	25
3	**c**	OH	H	Br	67	33	0	33
4	**d**	OH	H	OMe	0	100	0	21
5	**e**	OH	Me	H	100	0	0	22
6	**f**	OH	OH	H	100	0	0	50
7	**g**	OH	OH	Me	100	0	0	51
8	**h**	OH	OH	F	100	0	0	33
9	**i**	OH	OH	OMe	100	0	0	53
10	**j**	OH	OMe	H	100	0	0	83
11	**k**	OH	OCH_2CH_2TMS	H	100	0	0	12
12	**l**	OH	NH_2	H	100	0	0	75
13	**m**	OH	NMe_2	H	100	0	0	73
14	**n**	MeS	OH	OMe	0	0	100	52

Table 3 Yields of phenylated pyrimidinones compared with increasing pK_a-values of the pyrimidinones

Entry	Compound	X	Y	Z	pK_a[a]	Yield
1	**1c**	OH	H	Br	7.4[10]	33
2	**1g**	OH	OH	F	8.0[10]	33
3	**1a**	OH	H	H	9.2[11]	35
4	**1f**	OH	OH	H	9.5[11]	50
5	**1e**	OH	Me	H	9.8[11]	22
6	**1g**	OH	OH	Me	9.9[11]	51
7	**1j**	OH	OMe	H	(10.7)[b]	83
8	**1l**	OH	NH_2	H	12.2[11]	75
9	**1m**	OH	NMe_2	H	12.3[11]	73

[a] In water. [b] The pK_a value for 4-ethoxypyrimidin-2(1*H*)-one.[11]

unexpected low yield in the case of 4-methylpyrimidin-2(1*H*)-one **1e** (entry 5, Table 3) has been commented upon earlier. The yield in the phenylation of 5-methoxypyrimidin-2(1*H*)-one **1d** (entry 4, Table 2) is only 21%. This is unexpected since the pK_a value of 5-methoxypyrimidin-2(1*H*)-one **1d** is most likely higher than, for instance, that of 5-bromopyrimidin-2(1*H*)-one **1c**, which gives a 33% yield.†

Attempted phenylation of 1-benzyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione, and 1-benzylpyrimidine-2,4(1*H*,3*H*)-dione failed. Only starting material was recovered in both reactions.

In summary pyrimidinones with relatively high pK_a values (11–12) seem to give better yields than pyrimidinones with relatively low pK_a values (7–8). In pyrimidin-2-ones with a substituent only in the 5-position, a 5-methoxy group gives only *O*-phenylated pyrimidinone, while pyrimidin-2-ones with a hydrogen, a chlorine or a bromine in the 5-position, give a mixture of the *O*- and *N*-phenylated pyrimidinones. In pyrimidin-2-ones with a substituent only in the 4-position only N^1-phenylation is observed whether the 4-substituent is a methoxy group or a methyl group. In pyrimidine-2,4-diones only N^1 phenylation is observed (and not N^3) regardless of the nature of the substituent in the 5-position.

Experimental

All reactions were conducted under an inert atmosphere of either Ar or N_2. Dioxane was distilled from sodium and benzophenone. *N*,*N*-Dimethylformamide (DMF) was dried with CaH_2 before distillation. NMR spectra were recorded at 300 MHz (^{1}H) and at 75 MHz (^{13}C) on a Bruker Avance DPX 300 instrument. Mass spectra, under electron impact conditions, were recorded at 70 eV ionizing energy on a Fision ProSpec instrument. The spectra are presented on *m*/*z* (% relative intensity). IR spectra were recorded on a Nicolet Magna FT-IR 550 instrument using attenuated total reflection. The melting points are uncorrected.

Compounds available from the literature

Diphenyliodonium chloride,[12] diphenyliodonium trifluoromethanesulfonate,[13] 5-chloropyrimidin-2(1*H*)-one **1b**,[14] 5-bromopyrimidin-2(1*H*)-one **1c**,[14] 4-methylpyrimidin-2(1*H*)-one **1e**,[15] 2,4-dimethoxypyrimidine,[16] 4-methoxypyrimidin-2(1*H*)-one **1j**,[17] 2-methylthio-4-(2-trimethylsilylethoxy)pyrimidine,[18] 2-methylsulfonyl-4-(2-trimethylsilylethoxy)pyrimidine,[18] 4-(*N*,*N*-dimethylamino)pyrimidin-2(1*H*)-one **1m**,[19] 5-methoxy-2-methylthiopyrimidin-4(3*H*)-one **1n**.[20]

Compounds made by modified literature procedures

4-Chloro-5-methoxy-2-methylthiopyrimidine.[20] 5-Methoxy-2-methylthiopyrimidin-4(3*H*)-one[20] (23.90 g, 0.14 mol) and *N*,*N*-dimethylaniline (21.97 g, 0.14 mol) were suspended in $POCl_3$ (200 cm^3). The mixture was heated under reflux for 2 h, before excess $POCl_3$ was distilled off. The residue was poured into ice–water and the product extracted into diethyl ether (4 × 50 cm^3), dried ($MgSO_4$) and evaporated. The crude product was recrystallized from EtOH to give the title compound (23.14 g, 87%); mp 78–80 °C (from EtOH) (lit.,[20] 81–82 °C); δ_H(300 MHz, $CDCl_3$) 2.53 (3H, s, SCH_3), 3.93 (3H, s, OCH_3), 8.13 (1H, s, H-6); δ_C(75 MHz, $CDCl_3$) 14.5 (SCH_3), 56.9 (OCH_3), 140.9 (C-6), 146.6 (C-5), 150.4 (C-4), 163.2 (C-2); *m*/*z* (EI) 190/192 (M^+, 100/39%), 175/177 (71/25), 159/157 (11/4), 155 (5), 144 (23), 120 (9), 86 (7), 79 (15), 70 (15).

5-Methoxy-2-methylthiopyrimidine.[20] 4-Chloro-5-methoxy-2-methylthiopyrimidine[20] (24.56 g, 0.12 mol) and Zn-powder (28.40 g, 0.43 mol) were suspended in a mixture of benzene (60 cm^3) and 3 M NH_4Cl (150 cm^3). The mixture was heated under reflux for 8 h before it was cooled and filtered. The filtrate was washed with diethyl ether and the combined organic fractions dried ($MgSO_4$) and evaporated. The crude product was recrystallized from 60% EtOH to give the title compound (19.80 g, 98%); mp 68–70 °C (from 60% EtOH) (lit.,[20] 69 °C); δ_H(300 MHz, $CDCl_3$), 2.51 (3H, s, SCH_3), 3.83 (3H, s, OCH_3), 8.22 (2H, s, H-4/H-6); δ_C(75 MHz, $CDCl_3$), 14.4 (SCH_3), 56.0 (OCH_3), 144.0 (C-4/C-6), 150.5 (C-5), 163.4 (C-2); *m*/*z* (EI) 156 (M^+, 100%), 141 (42), 123 (16), 110 (26), 86 (20).

† Rough pK_a values of pyrimidinones can be estimated by adapting the method used for pyridin-2-ones.[8] The estimated pK_a value for 5-methoxypyrimidin-2(1*H*)-one **1d** is thus 9.17 −4.28(0.11) = 8.70. (The pK_a value of 5-methoxypyrimidin-4(3*H*)-one = 8.60).[9] The estimated pK_a value for 5-bromopyrimidin-2(1*H*)-one **1c** is 9.17 − 4.28(0.39) = 7.50. The measured value for **1c** is 7.4.[10] (σ-Meta OMe = 0.11 and σ-meta Br = 0.39 ref. 8, appendix A1, pp. 109; the σ-meta value is the best value to use since the ionization occurs from the nitrogen atom: see ref. 8, p. 54).

5-Methoxy-2-methylsulfonylpyrimidine.[21] 5-Methoxy-2-methylthiopyrimidine[20] (8.44 g, 4.69 mmol) in CH_2Cl_2 (40 cm^3) was added to 55% MCPBA (5.50 g, 17.50 mmol) in CH_2Cl_2 (40 cm^3) at 0 °C. The mixture was stirred overnight at ambient temperature, before it was washed with 3 M Na_2SO_3 (30 cm^3), 3 M $NaHCO_3$ (30 cm^3) and water (2 × 30 cm^3). The organic phase was dried ($MgSO_4$) and evaporated. The crude product was recrystallized from 96% EtOH to give title compound (8.42 g, 87%); mp 109–111 °C (from 60% EtOH) (lit.,[21] from H_2O 118–119 °C); δ_H(300 MHz, $CDCl_3$) 3.16 (3H, s, CH_3SO_2), 3.91 (3H, s, OCH_3), 8.40 (2H, s, H-4/H-6); δ_C(75 MHz, $CDCl_3$) 36.5 (CH_3SO_2), 56.4 (OCH_3), 143.8 (C-4/C-6), 154.6 (C-5), 157.3 (C-2); *m/z* (EI) 188 (M^+, 51%), 173 (8), 126 (98), 109 (100), 96 (19), 82 (59), 67 (31).

5-Methoxypyrimidin-2(1*H*)-one 1d.[22] 5-Methoxy-2-methylsulfonylpyrimidine[21] (4.09 g, 21.7 mmol) was suspended in 5 M NaOH (10 cm^3) under Ar and heated at 50 °C overnight. The reaction mixture was cooled, neutralized with HCl (pH 6) and evaporated. The crude product was recrystallized from H_2O to give the title compound **1d** (2.03 g, 74%); mp 184–185 °C (from H_2O) (lit.,[22] 187–189 °C); δ_H (300 MHz, DMSO-d_6) 3.71 (3H, s, OCH_3), 8.10 (2H, s, H-4/H-6), 11.55 (1H, s, N-H); δ_C (75 MHz, DMSO-d_6) 56.6 (OCH_3), 90.5 (C-5), 143.2 (C-4/C-6), 156.8 (C-2); *m/z* (EI) 126 (M^+, 100%), 96 (26), 84 (85), 69 (51), 66 (92), 56 (37).

5-Methoxypyrimidine-2,4(1*H*,3*H*)-dione 1i.[23] 5-Methoxy-2-methylsulfonylpyrimidine[21] (7.61 g, 40.4 mmol) was suspended in 5 M NaOH (20 cm^3) and heated at 60 °C for 1 h. The reaction mixture was cooled and neutralized with HCl (pH 6). The precipitate was recrystallized from H_2O to give the title compound **1i** (3.98 g, 70%); mp 337 °C (from H_2O) (lit.,[23] 342–344 °C); δ_H (300 MHz, DMSO-d_6) 3.57 (3H, s, OCH_3), 6.99 (1H, d, H-6, *J* 5.9), 10.38 (1H, s, N-H), 11.15 (1H, s, N-H); δ_C (75 MHz, DMSO-d_6) 57.1 (OCH_3), 121.7 (C-6), 135.2 (C-5), 150.0 (C-2), 160.0 (C-4); *m/z* (EI) 142 (M^+, 85%), 124 (26), 113 (32), 69 (21), 56 (21), 28 (100).

4-(2-Trimethylsilylethoxy)pyrimidin-2(1*H*)-one 1k. To a solution of 2-methylsulfonyl-4-(2-trimethylsilylethoxy)pyrimidine[18] (660 mg, 2.40 mmol) in dry dioxane (20 cm^3) was added 1 M NaOH (15 cm^3). The mixture was stirred for 45 min before 3 M NH_4Cl (10 cm^3) was added. The product was extracted into CH_2Cl_2, dried ($MgSO_4$) and evaporated to give the title compound **1k** (472 mg, 92%), mp 179–181 °C; ν_{max}/cm^{-1} 1640 (CO); δ_H (300 MHz, DMSO-d_6) 0.03 (9H, s, $Si(CH_3)_3$), 1.01–1.06 (2H, m, CH_2Si), 4.27–4.33 (2H, m, OCH_2), 5.78 (1H, d, H-5, *J* 7.0), 7.65 (1H, d, H-6, *J* 7.0), 11.21 (1H, s, N-H); δ_C (75 MHz, DMSO-d_6) −1.4 ($Si(CH_3)_3$), 16.6 (CH_2Si), 63.8 (OCH_2), 93.7 (C-5), 145.5 (C-6), 156.3 (C-2), 171.5 (C-4); *m/z* (electrospray): 235.0860 ([$(C_9H_{16}N_2O_2Si)Na^+$], 61%), 213.1047 ([$(C_9H_{16}N_2O_2Si)H^+$], 7).

General procedure for phenylation of pyrimidinones

The pyrimidinone (1.00 mmol) and freshly sublimed $KOBu^t$ (123 mg, 1.10 mol) was suspended in dry DMF (4 cm^3) under Ar. After stirring for 15 min, Ph_2IOTf (774 mg, 1.79 mmol) in dry DMF (2 cm^3) was added and the mixture heated at 70 °C for 48 h. Then 3 M NH_4Cl (10 cm^3) was added and the product extracted into dichloromethane (4 × 10 cm^3), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using silica gel.

1-Phenylpyrimidin-2(1*H*)-one 2a.[24] Eluent CH_2Cl_2–MeOH 40:1; ν_{max}/cm^{-1} 1660 (CO); δ_C (75 MHz, DMSO-d_6) 103.9 (C-5), 126.4 (Ph *ortho*), 128.5 (Ph *para*), 129.1 (Ph *meta*), 140.4 (Ph *ipso*), 149.6 (C-6), 154.9 (C-2), 167.2 (C-4); *m/z* (EI) 172 (M^+, 100%), 144 (53), 117 (18), 77 (75), 51 (35).

5-Chloro-1-phenylpyrimidin-2(1*H*)-one 2b. Eluent $CHCl_3$; δ_H (300 MHz, $CDCl_3$) 7.43 (5H, m, Ph), 7.76 (1H, d, H-6, *J* 3.6), 8.63 (1H, d, H-4, *J* 3.6); δ_C (75 MHz, $CDCl_3$) 111.3 (C-5), 125.8 (Ph *ortho*), 129.5 (Ph *para*), 129.7 (Ph *meta*), 139.5 (Ph *ipso*), 144.9 (C-6), 153.9 (C-2), 165.9 (C-4); *m/z* (EI) 206 (M^+, 100%), 205 (22), 180 (6), 178 (31), 171 (47), 164 (31), 143 (32), 104 (52), 77 (80).

5-Bromo-1-phenylpyrimidin-2(1*H*)-one 2c. Eluent $CHCl_3$ (Found: M^+, 251.9716. $C_{10}H_7BrN_2O$ requires 251.9721); δ_H (300 MHz, $CDCl_3$) 7.36–7.51 (5H, m), 7.82 (1H, d, H-6, *J* 3.4), 8.65 (1H, d, H-4, *J* 3.4); δ_C (75 MHz, $CDCl_3$) 96.4 (C-5), 125.8 (Ph *ortho*), 129.5 (Ph *para*), 129.7 (Ph *meta*), 139.5 (Ph *ipso*), 147.1 (C-6), 153.5 (C-2), 167.4 (C-4); *m/z* (EI) 252/250 (M^+, 72/75%), 210/208 (7/8), 172 (13), 171 (100), 143 (19), 116 (19), 104 (33).

4-Methyl-1-phenylpyrimidin-2(1*H*)-one 2e. Eluent CH_2Cl_2–EtOAc 30:1; mp 79–81 °C (Found: M^+, 186.0779. $C_{11}H_{10}N_2O$ requires 186.0793); ν_{max}/cm^{-1} 1692 (CO); δ_H (300 MHz, acetone-d_6) 2.39 (3H, s, CH_3), 7.06 (1H, d, H-5, *J* 5.0), 7.05–7.24 (3H, m, Ph), 7.38–7.44 (2H, m, Ph), 8.37 (1H, d, H-6, *J* 5.0); δ_C (75 MHz, acetone-d_6) 23.8 (CH_3), 116.7 (C-5), 122.4 (Ph *ortho*), 125.6 (Ph *para*), 130.2 (Ph *meta*), 154.4 (Ph *ipso*), 159.8 (C-6), 166.0 (C-2), 171.3 (C-4); *m/z* (EI) 186 (M^+, 100%), 171 (52), 158 (17), 77 (38).

1-Phenylpyrimidine-2,4(1*H*,3*H*)-dione 2f.[25] Eluent CH_2Cl_2–MeOH 60:1; mp 243–244 °C; δ_H (300 MHz, DMSO-d_6) 3.32 (3H, s, OCH_3), 5.65 (1H, d, H-5, *J* 7.8), 7.47 (5H, m, Ph), 7.69 (1H, d, H-6, *J* 7.8), 11.41 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 101.5 (C-5), 126.8 (Ph *ortho*), 128.2 (Ph *para*), 129.0 (Ph *meta*), 138.8 (Ph *ipso*), 145.5 (C-6), 150.3 (C-2), 163.6 (C-4); *m/z* (EI) 188 (M^+, 100%), 145 (89), 117 (90), 104 (40), 77 (76).

5-Methyl-1-phenylpyrimidine-2,4(1*H*,3*H*)-dione 2g.[26] Eluent CH_2Cl_2–MeOH 60:1; mp 201–203 °C; δ_H (300 MHz, DMSO-d_6) 1.79 (3H, s, CH_3), 7.4–7.5 (5H, m, Ph), 7.60 (1H, d, H-6, *J* 1.0), 11.40 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 11.7 (CH_3), 109.2 (C-2), 126.8 (Ph *ortho*), 128.0 (Ph *para*), 129.0 (Ph *meta*), 139.0 (Ph *ipso*), 141.2 (C-6), 150.3 (C-2), 164.3 (C-4); *m/z* (EI) 202 (M^+, 84%), 159 (26), 130 (100), 77 (48).

5-Fluoro-1-phenylpyrimidine-2,4(1*H*,3*H*)-dione 2h. Eluent CH_2Cl_2–MeOH 60:1; mp 278–279 °C (decomp.) (Found: M^+, 206.0500. $C_{10}H_7FN_2O_2$ requires 206.0491); δ_H (300 MHz, DMSO-d_6) 7.38–7.51 (5H, m, Ph), 8.19 (1H, d, H-6, *J* 6.8), 11.92 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 126.9 (Ph *ortho*), 128.2 (Ph *para*), 129.0 (Ph *meta*), 130.3 (C-6, d, $J_{C,F}$ 33.6), 138.5 (Ph *ipso*), 140.1 (C-5, d, $J_{C,F}$ 230.4), 149.1 (C-2), 157.6 (C-4, d, $J_{C,F}$ 26.0); *m/z* (EI) 206 (M^+, 100%), 163 (78), 135 (14), 108 (31), 77 (33).

5-Methoxy-1-phenylpyrimidine-2,4(1*H*,3*H*)-dione 2i. Eluent CH_2Cl_2–EtOAc 2:1; mp 219–221 °C (Found: M^+, 218.0698. $C_{11}H_{10}N_2O_3$ requires 218.0691); δ_H (300 MHz, DMSO-d_6) 3.62 (3H, s, OCH_3), 7.31 (1H, s, H-6), 7.40–7.51 (5H, m, Ph), 11.58 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 57.4 (OCH_3), 125.4 (C-6), 127.2 (Ph *para*), 128.1 (Ph *meta*), 129.3 (Ph *ortho*), 136.2 (C-5), 139.6 (Ph *ipso*), 149.1 (C-2), 159.8 (C-4); *m/z* (EI) 218 (M^+, 100%), 177 (43), 160 (25), 132 (27), 104 (38), 77 (45), 61 (77).

4-Methoxy-1-phenylpyrimidin-2(1*H*)-one 2j. Eluent CH_2Cl_2–EtOAc 9:1; mp 149–151 °C (Found: C, 65.47; H, 5.08; M^+, 202.0738. $C_{11}H_{10}N_2O_2$ requires C, 65.34; H, 4.98%; *M*, 202.0742); ν_{max}/cm^{-1} 1668 (CO); δ_H (300 MHz, acetone-d_6) 3.90 (3H, s, OCH_3), 6.01 (1H, d, H-5, *J* 7.2 Hz), 7.41–7.51 (m, 5H, Ph), 7.86 (d, 2H, H-6, *J* 7.2); δ_C (75 MHz, acetone-d_6) 54.2 (OCH_3), 95.4 (C-5), 127.4 (Ph *ortho*), 128.8 (Ph *para*), 129.8 (Ph

meta), 141.92 (Ph *ipso*), 149.1 (C-6), 155.5 (C-2), 171 (C-4); *m*/*z* (EI) 202 (M^+, 100%), 144 (36), 116 (18), 110 (45), 77 (58).

1-Phenyl-4-(2-trimethylsilylethoxy)pyrimidin-2(1*H*)-one 2k. Eluent hexane–EtOAc 6:1; oil (Found: M^+, 288.1296. $C_{15}H_{20}N_2O_2Si$ requires 288.1294); δ_H (300 MHz, acetone-d_6) 0.02 (9H, s, $Si(CH_3)_3$), 1.03–1.12 (2H, m, CH_2Si), 4.32–4.40 (2H, m, OCH_2), 6.49 (1H, d, H-5, *J* 5.7), 7.16–7.26 (3H, m, Ph), 7.39–7.43 (2H, m, Ph), 8.20 (1H, d, H-6, *J* 5.7); δ_C (75 MHz, acetone-d_6) −1.4 ($SiCH_3$), 17.7 (CH_2Si), 65.4 (OCH_2), 103.9 (C-5), 122.5 (Ph *ortho*), 125.7 (Ph *meta*), 130.1 (Ph *para*), 154.2 (Ph *ipso*), 159.8 (C-6), 165.9 (C-2), 172.1 (C-4); *m*/*z* (EI) 288 (M^+, 4%), 259 (36), 245 (100), 218 (10), 188 (41), 151 (34), 145 (57), 77 (13), 73 (95).

4-Amino-1-phenylpyrimidin-2(1*H*)-one 21. The crude product was purified by spinning first in $CHCl_3$ and then in 0.1 M NaOH; δ_H (300 MHz, DMSO-d_6) 5.77 (1H, d, H-5, *J* 7.3), 7.21 (2H, s, NH_2), 7.29–7.48 (5H, m, Ph),7.61 (1H, d, H-6, *J* 7.3); δ_C (75 MHz, DMSO-d_6) 93.8 (C-5), 126.2 (Ph *ortho*), 127.00 (Ph *para*), 128.5 (Ph *meta*), 141.2 (Ph *ipso*), 145.4 (C-6), 154.6 (C-2), 165.9 (C-4); *m*/*z* (EI) 187 (M^+, 100%), 185 (63), 145 (26), 144 (24), 143 (14), 117 (16), 114 (12), 104 (7).

4-(*N*,*N*-Dimethylamino)-1-phenylpyrimidin-2(1*H*)-one 2m. Eluent CH_2Cl_2–MeOH 40:1; mp 153–155 °C (Found: M^+, 215.1051. $C_{12}H_{13}N_3O$ requires 215.1059); ν_{max}/cm^{-1} 1653 (CO); δ_H (300 MHz, DMSO-d_6) 3.07 (6H, s, $N(CH_3)_2$), 6.11 (1H, d, H-5, *J* 7.6), 7.32–7.47 (5H, m, H-Ph), 7.72 (1H, d, H-6, *J* 7.6); δ_C (75 MHz, DMSO-d_6) 36.6 (CH_3), 37.6 (CH_3), 91.5 (C-5), 126.5 (Ph *para*), 127.3 (Ph *meta*), 128.8 (Ph *ortho*), 141.0 (Ph *ipso*), 145.7 (C-6), 154.0 (C-2), 163.5 (C-4); *m*/*z* (EI) 215 (M^+, 72%), 200 (9), 144 (11), 123 (100), 77 (26).

2-Phenoxypyrimidine 3a.[27] Eluent CH_2Cl_2–MeOH 40:1; δ_H (300 MHz, acetone-d_6) 7.16–7.26 (4H, m, Ph), 7.41–7.46 (2H, m, Ph/H-5), 8.58 (2H, d, H-4/H-6, *J* 4.7); δ_C (75 MHz, acetone-d_6) 117.4 (C-5), 122.5 (Ph *ortho*), 125.8 (Ph *meta*), 130.3 (Ph *para*), 154.3 (Ph *ipso*), 160.6 (C-4/C-6), 166.3 (C-2); *m*/*z* (EI) 172 (M^+, 100%), 171 (60), 144 (46), 117 (11), 77 (36), 51 (19).

5-Chloro-2-phenoxypyrimidine 3b. Eluent hexane–EtOAc 2:1; δ_H (300 MHz, $CDCl_3$) 7.22 (3H, m, Ph), 7.43 (1H, m, Ph), 8.47 (2H, s, H-4/H-6); δ_C (75 MHz, $CDCl_3$), 121.4 (Ph *ortho*), 125.3 (C-5), 125.8 (Ph *para*), 129.73 (Ph *meta*), 152.6 (Ph *ipso*), 157.8 (C-4, C-6), 163.5 (C-2); *m*/*z* (EI) 206 (M^+, 100%), 205 (37), 178 (27), 171 (37), 164 (27), 143 (19), 104 (31).

5-Bromo-2-phenoxypyrimidine 3c. Eluent hexane–EtOAc 2:1 (Found: M^+, 251.9737. $C_{10}H_7BrN_2O$ requires 251.9721); δ_H (300 MHz, $CDCl_3$) 7.18 (3H, m, Ph), 7.24 (1H, m, Ph), 8.54 (2H, s, H-4/H-6); δ_C (75 MHz, $CDCl_3$) 113.1 (C-5), 121.4 (Ph *ortho*), 125.1 (Ph *para*), 129.7 (Ph *meta*), 152.6 (Ph *ipso*), 160.0 (C-4, C-6), 163.9 (C-2); *m*/*z* (EI) 252/250 (M^+, 56/61%), 224/222 (5/4), 210/208 (7/7), 172 (12), 171 (100), 143 (11), 116 (14), 104 (20).

5-Methoxy-2-phenoxypyrimidine 3d. Eluent hexane–EtOAc 2:1; oil (Found: M^+, 202.0757. $C_{11}H_{10}N_2O_2$ requires 202.0742); δ_H (300 MHz, acetone-d_6) 3.92 (3H, s, OCH_3), 7.11–7.22 (3H, m, Ph), 7.37–7.43 (2H, m, Ph), 8.29 (2H, s, H-4/H-6); δ_C (75 MHz, acetone-d_6) 57.0 (OCH_3), 122.0 (Ph *ortho*), 125.3 (Ph *para*), 130.2 (Ph *meta*), 146.3 (C-4/C-6), 151.5 (C-5), 155.1 (Ph *ipso*), 160.5 (C-2); *m*/*z* (EI) 202 (M^+, 100%), 171 (21), 145 (42), 130 (32), 104 (18), 77 (43), 51 (18).

5-Methoxy-2-methylthio-4-phenoxypyrimidine 4n. Eluent CH_2Cl_2–MeOH 40:1; mp 58–60 °C (Found: M^+, 248.0611. $C_{12}H_{12}N_2O_2S$ requires 248.0619); δ_H (300 MHz, acetone-d_6) 2.27 (3H, s, SCH_3), 3.97 (3H, s, OCH_3), 7.20–7.29 (3H, m, Ph), 7.42–7.47 (2H, m, Ph), 8.23 (1H, s, H-6); δ_C (75 MHz, acetone-d_6) 14.1 (SCH_3), 57.1 (OCH_3), 122.5 (Ph *ortho*), 126.2 (Ph *meta*), 130.2 (Ph *para*), 140.4 (C-5), 141.6 (C-6), 153.3 (Ph *ipso*), 160.0 (C-2), 161.8 (C-4); *m*/*z* (EI) 248 (M^+, 100%), 233 (17), 215 (14), 202 (11), 140 (11), 86 (11), 77 (22).

References

1 A. Varvoglis, *The Organic Chemistry of Polycoordinated Iodine*, VCH Publishers, Inc., New York, 1992.
2 (*a*) Ref. 1, pp. 207; (*b*) R. M. Moriarty and R. K. Vaid, *Synthesis*, 1990, 431; (*c*) A. Varvoglis, *Synthesis*, 1984, 709.
3 (*a*) A. McKillop and R. J. Kobylecki, *J. Org. Chem.*, 1974, **39**, 2710; (*b*) W.-Y. Chen and N. W. Gilman, *J. Heterocycl. Chem.*, 1983, **20**, 663; (*c*) S. Bátori and A. Messmer, *J. Heterocycl. Chem.*, 1988, **25**, 437.
4 Direct *O*/*N*-arylation of amides has been achieved with aryl halides catalyzed by copper salts: B. Renger, *Synthesis*, 1985, 856; A. Greiner, *Synthesis*, 1989, 312; with tetraphenylbismuth trifluoroacetate: D. H. R. Barton, J.-P. Finet, W. B. Motherwell and C. Pichon, *J. Chem. Soc., Perkin Trans. 1*, 1987, 251 and with *p*-tolyllead triacetate: P. López-Alavardo, C. Avendaño and J. C. Menéndez, *Tetrahedron Lett.*, 1992, **33**, 6875.
5 (*a*) D. J. Brown and T.-C. Lee, *Aust. J. Chem.*, 1968, **21**, 243; (*b*) C. Kashima, A. Katoh, Y. Yokota and Y. Omote, *Synthesis*, 1983, 151; (*c*) J. Solberg, *PhD Thesis*, University of Oslo, 1988.
6 D. J. Brown, *The Pyrimidines*, *Supplement II*, Wiley & Sons, New York, 1985, p. 205 and references therein.
7 A. N. Nesmeyanov, L. G. Makarova and T. P. Tolstaya, *Tetrahedron*, 1957, 145.
8 D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK_a Prediction of Organic Acids and Bases*, Chapman and Hall, London, 1981.
9 A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294.
10 D. J. Brown, *The Pyrimidines*, Wiley & Sons, New York, 1962, Table XVI, pp. 472.
11 D. J. Brown, *The Pyrimidines*, *Supplement I*, Wiley & Sons, New York, 1970, Table XVI, pp. 369.
12 M. F. Beringer, A. Brierley, M. Drexler, E. M. Grindler and C. C. Lumpkin, *J. Am. Chem. Soc.*, 1953, **75**, 2705.
13 J. L. Dektar and N. P. Hacker, *J. Org. Chem.*, 1990, **55**, 639.
14 D. G. Crosby and R. V. Berthold, *J. Org. Chem.*, 1960, **25**, 1916.
15 W. Franke and R. Kraft, *Chem. Ber.*, 1953, **86**, 797.
16 G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, 1930, **52**, 2001.
17 M. Prystas, *Collect. Czech. Chem. Commun.*, 1975, **40**, 1786.
18 M. L. Falck-Pedersen, T. Benneche and K. Undheim, *Acta Chem. Scand.*, 1993, **47**, 72.
19 W. Szar and D. Shugar, *Acta Biochim. Pol.*, 1966, **13**, 177.
20 Z. Budésinsky, V. Bydzovsky, J. Kopecky, A. Sváb and J. Vavrina, *Cesk. Farm.*, 1961, **10**, 241.
21 Z. Budésinsky, J. Prikryl and E. Svátek, *Collect. Czech. Chem. Commun.*, 1964, **29**, 2980.
22 Z. Budésinsky, J. Prikryl and E. Svátek, *Collect. Czech. Chem. Commun.*, 1967, **32**, 1637.
23 A Novácek and M. Lisserová, *Collect. Czech. Chem. Commun.*, 1968, **33**, 1003.
24 T. Nishio, K. Katahira and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, 1981, 943.
25 M. R. Atkinson, M. J. Maguire, R. K. Ralph, G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1957, 2363.
26 Y. F. Shealy and C. A. O'Dell, *J. Heterocycl. Chem.*, 1976, **13**, 1041.
27 T. Joijima and S. Tamura, *Agric. Biol. Chem.*, 1966, **30**, 896.

Paper 9/05519C