Two ring transformations of 3-methyl-5-nitropyrimidin-4(3*H*)-one for the construction of azaheterocycles

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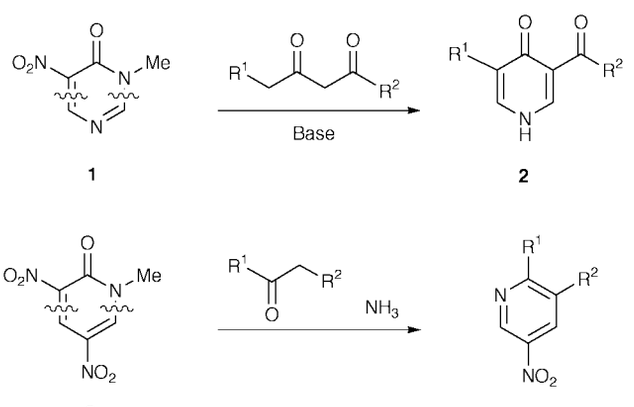
The reaction of 3-methyl-5-nitropyrimidin-4(3*H*)-one **1** with ketones in the presence of NH_3 afforded 4,5-disubstituted pyrimidines **5**. Use of ammonium acetate instead of NH_3 as the nitrogen source caused another ring transformation giving 5,6-disubstituted 3-nitro-2-pyridones **8** as well as **5**. Pyrimidinone **1** behaved as an activated diformylamine **6** in the former reaction and as the synthetic equivalent of α-nitroformylacetic acid **9** in the latter case. The ratio of **5** and **8** produced when using NH_4OAc varied with solvent. The reaction in acetic acid predominantly afforded pyrimidine **5**, but in methanol the reaction afforded pyridone **8**. The two types of ring transformations presented here are novel methods for the preparation of azaheterocycles.

Introduction

The ring transformation of heterocyclic compounds is one of the most useful tools for the construction of various skeletons.[1] Nitropyrimidine derivatives such as 5-nitropyrimidine and 5-nitrouracil have been employed to obtain polyfunctionalized compounds[2] since these substrates bear suitable structures for this purpose. 5-Nitropyrimidinones are also expected to be very useful in synthesis, however, only a few examples have been recorded.[2,3]

In our studies on electron deficient heterocyclic compounds, we have focused our attention on three isomeric compounds: *N*-methyl-5-nitropyrimidin-2(1*H*)-one, -4(1*H*)-one and -4(3*H*)-one.[4–9] Of these, 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**) was found to be one of the best skeletons for ring transformation. The reaction of **1** with enolate ions of 1,3-dicarbonyl compounds afforded 3,5-difunctionalized 4-pyridones **2** (Scheme 1).[6]



Scheme 1

Meanwhile 3,5-dinitro-2-pyridone **3**, deazaanalog of **1**, showed similar electron deficiency and reactivities to nitropyrimidinone **1**. 5,6-Disubstituted 3-nitropyridines **4** were effectively obtained by the ring transformation of pyridone **3** with ketones and NH_3 (Scheme 1).[10]

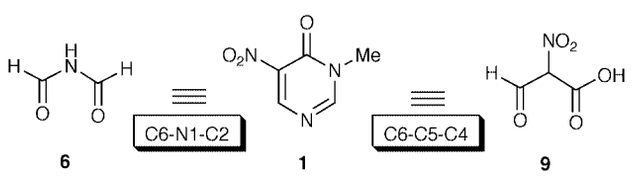


Fig. 1

These experimental facts allowed us to investigate the ring transformation of nitropyrimidinone **1** in the presence of a nitrogen source which leads to azaheterocycles following a novel synthetic strategy.

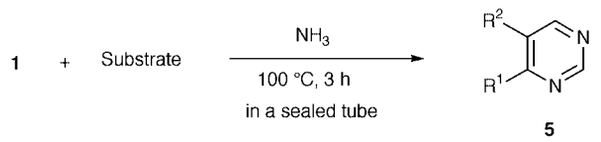
Results and discussions

Nitropyrimidinone **1** was heated at 100 °C with cyclohexanone in the presence of NH_3. Column chromatography of the reaction mixture gave 5,6,7,8-tetrahydroquinazoline **5a**[11] in 54% yield.[8] Pyrimidinone **1** behaved similarly to activated diformylamine **6**, composing the C2–N1–C8a moiety of **5a**, with the rest of **5a** being derived from NH_3 and cyclohexanone (Fig. 1).

Since pyrimidine derivatives are frequently used as functional materials, a great number of methods for the construction of the pyrimidine skeleton have been reported.[12] While the majority of them involve the condensation of a C–C–C unit (*e.g.*, malonaldehyde, malononitrile, diethyl malonate) and an N–C–N unit (*e.g.*, urea, guanidine), the general method involving a combination of C–N–C and N–C–C (or N and C–C) units is known only in a few cases.[13] Thus, the present ring transformation is an alternative method for the preparation of 4,5-disubstituted pyrimidines **5** (Table 1).

Acetonitrile (MeCN) and methanol (MeOH) were suitable solvents for this reaction. Use of 1-morpholinocyclohexene instead of cyclohexanone was also effective. Condensed pyrimidines **5b**[11] and **5c**[11] were prepared in a similar way, however, acetophenone gave only 6% of 4-phenylpyrimidine (**5d**)[11] even though severe conditions were employed. This disadvantage was overcome to some extent by using 1-morpholinostyrene. In each case, small amounts of β-carbamoylnitroenamines **7a** and/or **7b** were isolated (Fig. 2) after the aminolysis of pyrimidinone

Table 1 Ring transformation in the presence of NH_3



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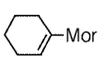
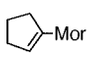
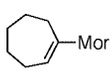
Substrate	Solvent	Product R^1	R^2		Yield (%)
	MeOH	—$(CH_2)_4$—		**a**	54
	MeCN				85
	MeOH				76
	MeCN				78
	MeCN	—$(CH_2)_3$—		**b**	31
	MeOH				30
	MeOH	—$(CH_2)_5$—		**c**	40
	MeOH[a]	Ph	H	**d**	6
	MeOH				35
	MeCN				25

[a] 120 °C Mor: Morpholino group

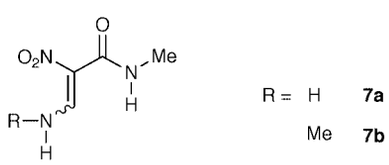


Fig. 2

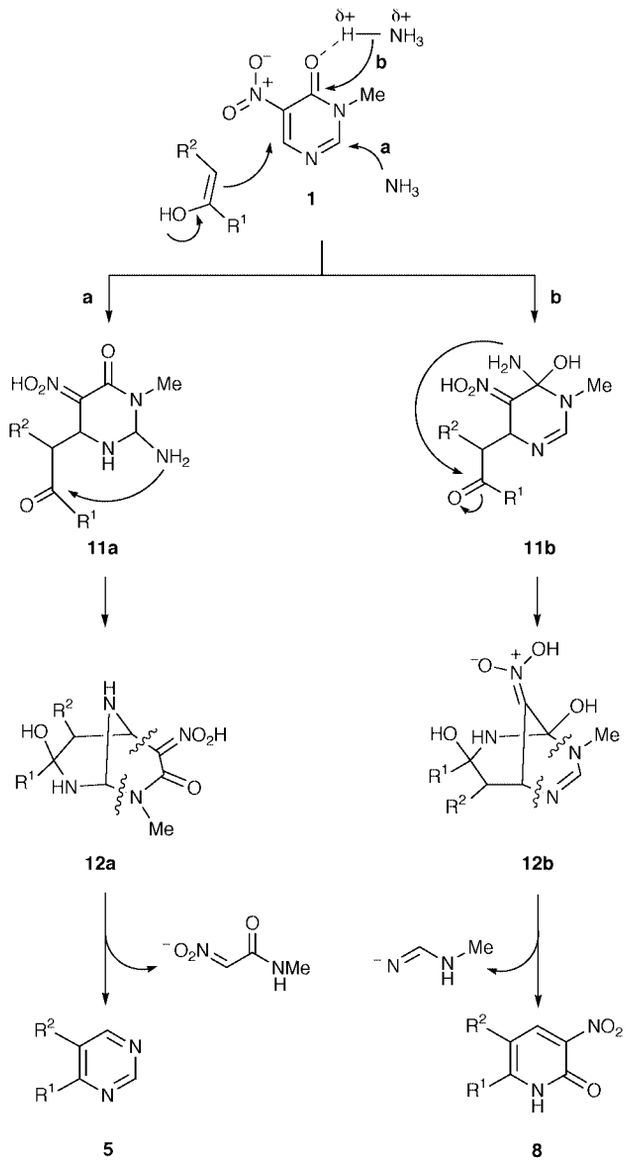
1.[7] The ring transformation was obviously affected by the decomposition of **1**, lowering the yields of pyrimidines **5**.

To avoid this unfavorable reaction, a less nucleophilic ammonium salt was employed as a nitrogen source.[9] Pyrimidinone **1** was heated with acetophenone in the presence of ammonium acetate (NH_4OAc). Ring transformation proceeded to give pyrimidine **5d** in a considerably improved yield under milder conditions compared with the yield in the reaction using NH_3. In addition to pyrimidine **5d** 3-nitro-6-phenyl-2-pyridone (**8d**)[14] was also isolated as yellow needles.

3-Nitro-2-pyridone **8** is the result of the ring transformation at the 4- and 6-positions of pyrimidinone **1**. In this case, **1** behaves as the synthetic equivalent of α-nitroformylacetic acid **9** to compose the C2–C3–C4 moiety of **8**. Since 3-nitro-2-pyridone derivatives have recently attracted attention as key compounds for drug design,[15] it is expected that this reaction will have significant synthetic applications.

Plausible mechanisms for the ring transformations are shown in Scheme 2. The bicyclic intermediates[6] **12a** and **12b** were formed by the intramolecular nucleophilic addition of adducts **11a** and **11b**, respectively. Elimination of anionic nitroacetamide[10] from **12a** leads to pyrimidine **5**, and that of the anionic amidine from **12b** gives 3-nitropyridone **8**.

The present reaction was applicable to other ketones affording the corresponding pyrimidines **5**[11] and/or nitropyridones **8**. The structures of pyridones **8** were confirmed by spectral and analytical data. In the ^1H NMR of **8d** and **8f**, the signal at the 3-position was broadened, probably due to the influence of tautomerism between the pyridone and the pyridinol forms. The IR spectra did not always reveal strong absorptions between



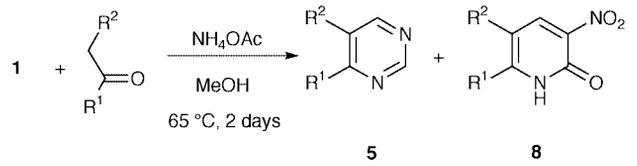
Scheme 2

1520 and 1570 cm^{-1}, and a strong absorption was observed at 1590 cm^{-1} that could not be confidently assigned to the nitro group. However, this was considered to be the characteristic absorption of the 3-nitro-2-pyridone skeleton after consultation with spectral data in the literature.[15a]

The ratios of **5**:**8** showed remarkable variation depending on both steric and electronic properties of the ketones used. When cycloalkanones were employed, the reaction was influenced by the ring size. Pyrimidines **5** were derived from the smaller ketone, and pyridones **8** from the larger one. In the reactions of **1** with acetophenone derivatives, the effect of the substituent on the product selectivity was also observed (Table 2). Electron donating groups increased the yields of pyridones **8e** and **8f**. On the other hand, *p*-nitroacetophenone furnished pyrimidine **5g**. We have not satifactorily rationalised the above results, hence a more detailed investigation into the dependency of the ratio of **5**:**8** on the structure of the ketone is in progress.

The synthetic value of nitropyrimidinone **1** will be improved if it is possible to control two competitive ring transformations resulting in selective preparations of desired compounds. The addition of acetic acid (AcOH) was studied with the aim of promoting the electrophilicity of pyrimidinone **1**. In the reaction of **1** (1 mmol) with acetophenone, the presence of 1 mmol of AcOH increased the yield of pyridone **8d** by 9%. The more AcOH added, the less pyrimidine **5d** was obtained. In each case,

Table 2 Ring transformation in the presence of NH_4OAc



R^1	R^2		Yield (%) 5	8
—$(CH_2)_4$—		**a**	51	0
—$(CH_2)_3$—		**b**	85	Trace
—$(CH_2)_5$—		**c**	11	79
Ph	H	**d**	47	48
p-MeC_6H_4	H	**e**	21	68
p-$MeOC_6H_4$	H	**f**	0	76
p-$NO_2C_6H_4$	H	**g**	72	17[a]
i-Pr	H	**h**	0	22

[a] **8g** was obtained as the ammonium salt.

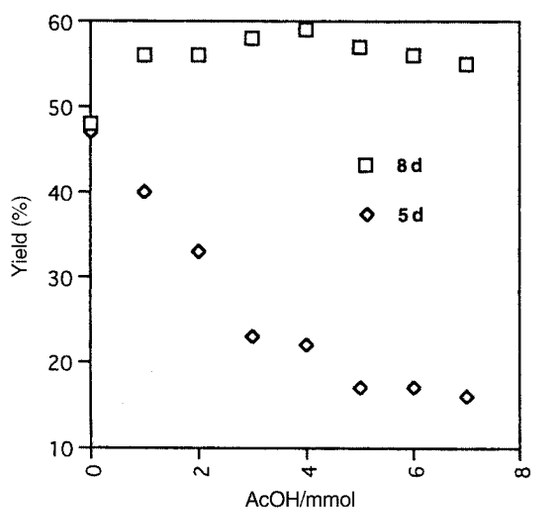


Fig. 3 Effects of AcOH on the yields of **5d** and **8d**.

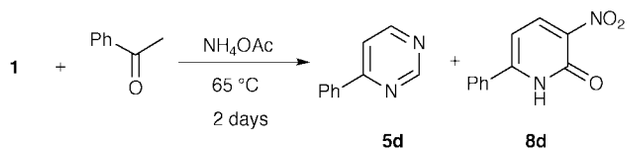
the yield of **8d** was almost constant, and no pyrimidinone **1** was recovered. Since isolated **5d** is stable under all conditions, the decrease in **5d** was considered to be due to decomposition of nitropyrimidinone **1** (Fig. 3).[16]

A dramatic change in the ratio of **5d**:**8d** was observed when larger amounts of AcOH were used. The ratio was inverted in the reaction employing mixed solvent (MeOH–AcOH = 3:1) although the reaction rate was somewhat slowed down. The reaction conducted in AcOH alone predominantly furnished pyrimidine **5d** (Table 3).

The above selectivity patterns prompted us to investigate the application to other substrates. Similar solvent effects were also observed in the reaction with cycloheptanone. Nitropyridone **8c** was the principal product in the reaction using MeOH. In contrast with this result, 6,7,8,9-tetrahydro-5*H*-cyclohepta[*d*]-pyrimidine (**5c**) was exclusively obtained from the reaction in AcOH (Scheme 3).

The 2- and 6-positions show high values for nucleophilic susceptibility.[17] This indicates that the ring transformation usually occurs between these positions. In the presence of NH_4OAc, the carbonyl group at the 4-position of **1** becomes active enough for participation in ring transformations. Addition of AcOH activates not only the 4-position but also the 2- and 6-positions. Excessive activation allows the attack of MeOH at the 2- or 6-positions causing the competitive ring opening reaction[16] of pyrimidinone **1**. In the reaction in AcOH, the ring transformation proceeds preferentially giving **5** because of the absence of the nucleophilic MeOH (Fig. 4).

Table 3 Effects of AcOH on the yields of **5d** and **8d**



Solv.	AcOH/ mmol	Yield (%) 5d	8d	Recovery (%) 1
MeOH	0	47	48	0
MeOH	1	40	56	0
MeOH	4	22	59	0
MeOH	7	16	55	0
MeOH–AcOH	(3:1)	24	9	21
AcOH	—	42	7	29
AcOH[a]	—	65	14	0

[a] 3 days.

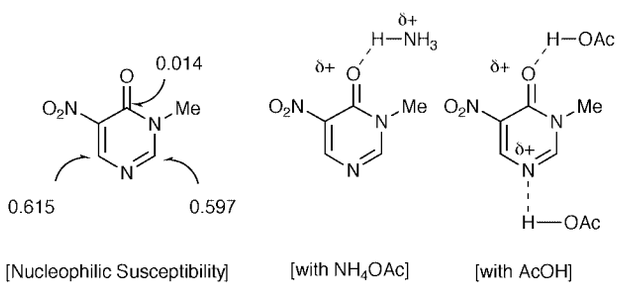
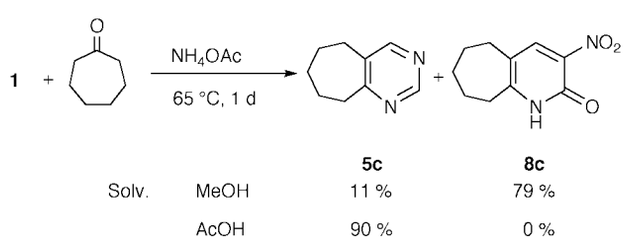


Fig. 4



Scheme 3

In summary, two types of ring transformations of nitropyrimidinone **1** were observed. Syntheses of 4,5-disubstituted pyrimidines **5** and 5,6-disubstituted 3-nitropyridones **8** were readily accomplished. The possibility of controlling the selectivity of products **5** or **8** was also shown. The reaction described here is a facile, novel procedure for the preparation of azaheterocycles.

Experimental

General

The melting points were determined on a Yanaco micro-melting-points apparatus, and are uncorrected. All the reagents and solvents were commercially available and used as received except for NH_4OAc. NH_4OAc was dried under reduced pressure and stored in a desiccator. ^1H NMR spectra were measured on a Bruker DPX-400 at 400 MHz with TMS as an internal standard. IR spectra were recorded on a Horiba FT-200 IR spectrometer. Elemental microanalyses were performed using a Yanaco MT-3 CHN-Corder.

3-Methyl-5-nitropyrimidin-4(3*H*)-one 1

Pyrimidinone **1** was obtained from 2-thiouracil by reduction,[18] methylation,[18] and nitration[8] with fuming HNO_3 in 18 M H_2SO_4 at 100 °C for 7 h in 43% overall yield.

Ring transformation in the presence of NH_3

To a solution of pyrimidinone **1** (155 mg, 1.0 mmol) in MeOH or MeCN (40 cm^3), ketone or enamine (2.0 mmol) and methanolic NH_3 (2 mol dm^{-3}, 4 cm^3, 8.0 mmol) were added. The solution was heated at 100 °C for 3 h in a sealed tube. After removal of solvent under reduced pressure, the mixture was extracted with benzene, and the extract was concentrated. The residual oil was column chromatographed on silica gel to give 4,5-disubstituted pyrimidine **5** (eluted with $CHCl_3$).

Ring transformation in the presence of NH_4OAc

To a solution of pyrimidinone **1** (155 mg, 1.0 mmol) in MeOH (20 cm^3), ketone (2.0 mmol) and NH_4OAc (154 mg, 2.0 mmol) were added. The mixture was heated at 65 °C for 2 d. During the reaction, 3-nitro-2-pyridone **8** precipitated. The precipitates were collected by filtration, which afforded satisfactory analytical data without purification. The filtrate was evaporated, and the residue was column chromatographed on silica gel to give pyrimidine **5** (eluted with $CHCl_3$).

1,5,6,7,8,9-Hexahydro-3-nitro-2*H*-cyclohepta[*b*]pyridin-2-one 8c. Colorless plates; mp 215–223 °C (decomp.); IR (Nujol) 1662, 1570, 1313 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.6–1.9 (m, 6H), 2.6–2.7 (m, 2H), 2.9–3.0 (m, 2H), 8.33 (s, 1H), 13.0–14.0 (br s, 1H). Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.68; H, 5.83; N, 13.39%.

3-Nitro-6-phenyl-2(1*H*)-pyridone 8d. Yellow needles; mp 275–276 °C (lit.[14] 276–277 °C); IR (Nujol) 1689, 1591, 1578, 1308 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 6.7–6.9 (br s, 1H), 7.4–7.6 (m, 3H), 7.7–7.9 (m, 2H), 8.50 (d, J = 8.1 Hz, 1H), 12.8–13.2 (br s, 1H). Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.24; H, 3.66; N, 13.02%.

6-(4-Methylphenyl)-3-nitro-2(1*H*)-pyridone 8e. Yellow needles; mp 195–197 °C; IR (Nujol) 1668, 1593, 1331 cm^{-1}; ^1H NMR (DMSO-d_6, 60 MHz) δ 2.42 (s, 3H), 6.84 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 8.62 (d, J = 8.2 Hz, 1H), 12.9–13.3 (br s, 1H). Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.68; H, 4.36; N, 12.24%.

6-(4-Methoxyphenyl)-3-nitro-2(1*H*)-pyridone 8f. Yellow needles; mp 226–230 °C; IR (Nujol) 1678, 1593, 1323 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.85 (s, 3H), 6.6–6.8 (br s, 1H), 7.10 (d, J = 8.9 Hz, 2H), 7.86 (d, J = 8.9 Hz, 2H), 8.49 (d, J = 8.2 Hz, 1H), 12.8–13.1 (br s, 1H). Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.65; H, 4.06; N, 11.23%.

Ammonium salt of 3-nitro-6-(4-nitrophenyl)-2(1*H*)-pyridone 8g. Yellow needles; mp 293–296 °C (decomp.); IR (Nujol) 1595, 1344 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.7–3.9 (br s, 4H), 6.82 (d, J = 7.9 Hz, 1H), 8.17 (d, J = 7.9 Hz, 1H), 8.2–8.4 (m, 4H). Anal. Calcd. for $C_{11}H_{10}N_4O_5$: C, 47.49; H, 3.62; N, 20.14. Found: C, 47.54; H, 3.64; N, 20.47%.

6-Isopropyl-3-nitro-2(1*H*)-pyridone 8h. Pale yellow plates; mp 175–183 °C (decomp.); IR (Nujol) 1675, 1601, 1560, 1317 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.21 (d, J = 6.9 Hz, 6H), 2.89 (septet, J = 6.9 Hz, 1H), 6.28 (d, J = 8.1 Hz, 1H), 8.40 (d, J = 8.1 Hz, 1H), 12.6–13.1 (br s, 1H). Anal. Calcd. for $C_8H_{10}N_2O_3 \cdot \frac{1}{8}H_2O$: C, 52.10; H, 5.60; N, 15.20. Found: C, 52.09; H, 5.59; N, 15.38%.

Ring transformation with addition of AcOH

To a solution of pyrimidinone **1** (155 mg, 1.0 mmol) in MeOH (20 cm^3), were added acetophenone (0.23 cm^3, 2.0 mmol), NH_4OAc (154 mg, 2.0 mmol) and AcOH (0.230 cm^3, 4.0 mmol). The mixture was heated at 65 °C for 2 d. During the reaction, pyridone **8d** was precipitated. Filtration of the reaction mixture afforded pure pyridone **8d** (127 mg, 0.59 mmol). The filtrate was evaporated, and the residue was column chromatographed on silica gel to give pyrimidine **5d** (34 mg, 0.22 mmol, eluted with $CHCl_3$).

Ring transformation using AcOH as the solvent

To a solution of pyrimidinone **1** (155 mg, 1.0 mmol) in AcOH (20 cm^3), were added acetophenone (0.23 cm^3, 2.0 mmol), NH_4OAc (154 mg, 2.0 mmol). The mixture was heated at 65 °C for 3 d. In this case, pyridone **8d** was not precipitated. The reaction mixture was concentrated, and washed with $CHCl_3$ (20 $cm^3 \times 3$) to give pyridone **8d** (30 mg, 0.14 mmol). The $CHCl_3$ solution was evaporated, and the residue was column chromatographed on silica gel to give pyrimidine **5d** (101 mg, 0.65 mmol, eluted with $CHCl_3$).

Acknowledgements

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