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Alkoxy-5-nitrosopyrimidines: Useful Building Block for the Generation of Biologically Active Compounds

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Several alkoxy-5-nitrosopyrimidines were synthesised and high regioselective and sequential nucleophilic aromatic substitution of methoxy groups in 2-amino-4,6-dimethoxy-5-nitrosopyrimidine was observed. The approach was applied to the synthesis of valuable polyfunctionalised aminopyrimidines capable of mimicking fused heterobicyclic derivatives of biological interest. In addition, new compounds were evaluated as antivirals and their usefulness as synthetic intermediates was demonstrated.

Introduction

Aminopyrimidines constitute a class of biologically relevant molecules, as well as important intermediates for the design and synthesis of fused polycyclic pharmaceutical targets, such as purines, pteridines and nucleoside analogues.[1] The highly electron-deficient nature of the pyrimidine ring renders the nucleophilic aromatic substitution reaction (S_NAr) a general approach for the synthesis, both in solution[2] and more recently in the solid phase,[3] of a large number of aminopyrimidine derivatives, especially from readily available polyhalo-pyrimidines. Unfortunately from a synthetic point of view, the nucleophilic substitution reactions of 2,4- and/or 6-halopyrimidines are only moderately selective and a mixture of 2- and 4-monosubstituted products are frequently obtained.[4–6] In addition, once the first group has been introduced, the reactivity of the resultant 2/4-aminopyrimidine toward a second S_NAr is greatly diminished, thus restricting the use of poor nucleophiles, such as anilines, or requiring high temperatures for hours or days[7] and high concentrations of these nucleophiles to drive reactions to completion.[8] However, microwave irradiation can facilitate the synthesis of aminopyrimidines through microwave-assisted aromatic nucleophilic substitution.[9] In fact, we found that the treatment of pyrimidine **I** (Figure 1) with different primary amines led to aminolysis of the 2-methoxy group and to the corresponding 2-aminopyrimidine derivatives **II** in good to excellent yields in a short time at room temperature.[10] The easy substitution of a poor leaving group, such as methoxide, proved to be due to the strong electron deficiency that the 5-nitroso group imposes on the pyrimidine nucleus,[11] thus favouring nucleophilic substitution at the pyrimidine C(2) position.[12]

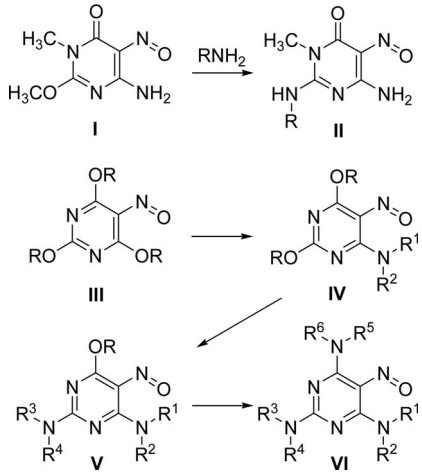

Figure 1. Derivation of pyrimidines through sequential alkoxy aminolysis.

These results encouraged us to explore similar aminolysis reactions with other 5-nitrosopyrimidines (**III**–**V**), carrying three or two alkoxy groups on C(2), C(4) and C(6), as an alternative to classical derivation of polyhalo-pyrimidines. Furthermore, multiple and sequential substitution of alkoxy groups in this kind of pyrimidine could lead to a great variety of valuable and conveniently functionalised 4-alkoxy-5-nitrosopyrimidine derivatives (Figure 2) some of which exhibit activity as inhibitors of cyclin-dependent kin-

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ases (CDKs)[13] and of the DNA-repair protein O(6)-alkylguanine-DNA-alkyltransferase (AGT),[14] leading to a renewed interest in the synthesis of these pyrimidine derivatives.

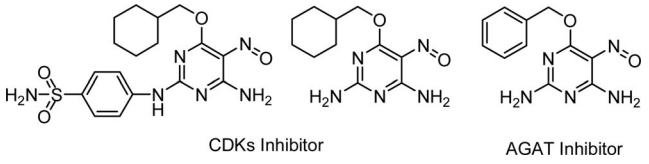


Figure 2. Biologically active 4-amino-5-nitrosopyrimidines.

With this idea in mind, several polyalkoxy-5-nitrosopyrimidines were synthesised[15] and then assayed against a range of amines. Here, we report on the very high activation towards aminolysis of methoxy groups found in symmetrical 2-amino-4,6-dimethoxy-5-nitrosopyrimidine (**1**).

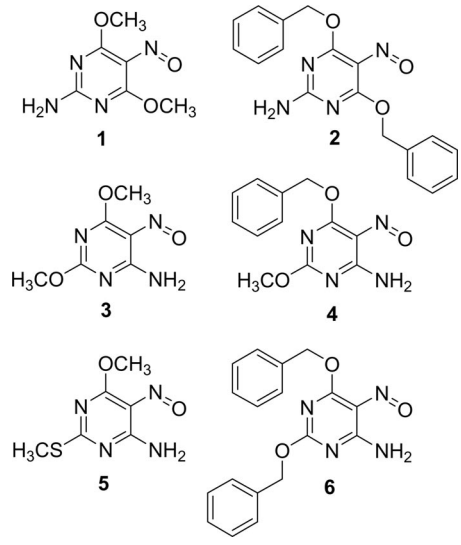


Figure 3. Dialkoxy-5-nitrosopyrimidines synthesised under neutral conditions with IAN and DMSO.

Results and Discussion

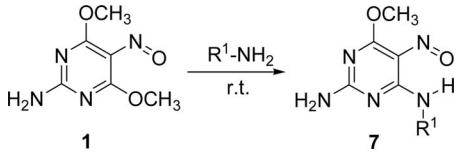
In a previous paper[10] we described how the treatment of several amino-dialkoxypyrimidines with a slight excess of isoamyl nitrite (IAN; 1.2 mol/mol pyrimidine) in dimethyl sulfoxide (DMSO) at room temperature, led to selective and clean C(5)-nitrosation of the pyrimidine nucleus. Isolation of the resulting 5-nitrosopyrimidines was accomplished through an easy work up consisting of water addition, followed by vacuum filtration, washing and vacuum drying, to afford the desired nitroso derivatives in good yields (65–75%). These results were considered particularly relevant because there is no general procedure reported in the literature to prepare such polyalkoxy-5-nitrosopyrimidines. The only known precedent is the preparation of 4-amino-2,6-dimethoxy-5-nitrosopyrimidine (**3**; Figure 3), which has been prepared by direct nitrosation of the corresponding pyrimidine with sodium nitrite in aqueous acid solution[16] but in a poor 14% yield, surely due to the propensity of the alkoxy groups to suffer hydrolysis under acidic conditions.[17] It is interesting to note that C(5)-nitrosation of 2,4,6-trimethoxypyrimidine was not achieved under any conditions. Thus, it may be concluded that the nitrosation procedure based on treatment with IAN in DMSO without any added acid extends the range of pyrimidine derivatives susceptible to C(5)-nitrosation from highly activated polyhydroxy or polyamino-pyrimidines to less active pyrimidines possessing only one amino substituent and two moderately π-electron-releasing substituents (alkoxy or alkylthio) on C(2) and/or C(4)/C(6) carbon atoms.

With several-5-nitrosopyrimidines to hand, preliminary aminolysis studies on pyrimidine **1** were undertaken to establish whether milder conditions could bring about the sequential displacement of methoxy groups. Thus, an equimolar mixture of **1** and *n*-butylamine was stirred in both protic and aprotic polar solvents at room temperature. After stirring for 30 min, TLC analysis revealed that two new, coloured compounds, resulting from the mono- and double-displacement of methoxy groups, were present, together with the starting material when water or methanol were used as solvent; the latter result suggested that lower selectivities were obtained when protic solvents were employed. No traces of di-substitution products were detected by TLC when anhydrous aprotic solvents such as DMSO, CH_2Cl_2 or CH_3CN were used and mono-substitution product **7a** (Table 1, entries 1–3) could be isolated by simple filtration without further purification after a short time. With the amine/methoxy displacement chemistry established, we then examined the scope of reaction of **1** with amines of diverse electron density and steric bulk (Table 1). These experiments were conducted under the same reaction conditions as described above, i.e., non-hydroxylic media at room temperature, however, some of the reactions were sluggish and required the addition of more amine or a protic solvent to achieve reasonable rates. All the reactions proceeded in suspension except when DMSO was used and, once the reaction was judged to be complete by TLC, the mixture was worked up and usually purified by simple filtration, wash-

Table 1. Synopsis of reaction conditions and yields for the aminolysis reaction of **1**.

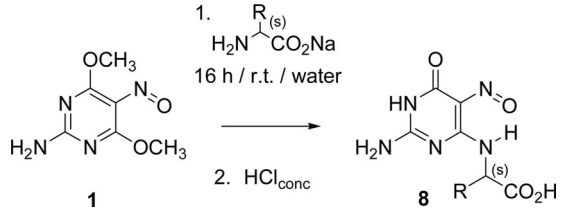
Entry	7	R^1	Solvent	Time [h]	Yield [%]
1	**a**	Bu	DMSO	1	75
2	**a**	Bu	CH_2Cl_2	24	65
3	**a**	Bu	MeCN	3	80
4	**b**	Cy	DMSO	3.5	80
5	**c**	Ad	H_2O/DMSO	36	87
6	**d**	$CH_2CH{=}CH_2$	CH_2Cl_2	20	66
7	**e**	CH_2CH_2OH	CH_2Cl_2	8	94
8	**f**	$(CH_2CH_2O)_2H$	MeCN	8	76
9	**g**	Bn	MeCN	7	70
10	**h**	Ph	H_2O	0.8	95
11	**i**	4-$HO_2CC_6H_4$	H_2O	20	95
12	**j**	3-ClC_6H_4	H_2O	48	50
13	**k**	CH_2CO_2Et	CH_2Cl_2	72	84
14	**l**	$CH_2CH_2CO_2Et$	DMSO	10	66
15	**m**	$CHCH_3CO_2Et$	EtOH	120	60
16	**n**	$CHBnCO_2Et$	H_2O	20	85

ing and recrystallisation. The simpler primary alkylamines (entries 1–9), all reacted selectively at room temperature, with only the highly hindered 1-adamantylamine requiring a larger excess of amine (1.5 mol/mol pyrimidine) and water as solvent to push the reaction to completion. The results were clean nucleophilic substitutions affording the corresponding 2,4-diaminopyrimidine derivatives **7a**–**g** in good to very good yields (65–94%) after reaction times ranging from 1 to 36 h (Scheme 1).



Scheme 1. Synthesis of 4-alkylamino-6-methoxy-5-nitrosopyrimidines **7**.

The less nucleophilic aromatic amines (entries 10–12) were unable to displace one methoxy group in aprotic solvents, however, this was achieved with excellent yield using a larger excess of amine (2.5 mol/mol pyrimidine) and water as solvent at room temperature. Like the reaction with 1-adamantylamine, in this case, neither contamination by disubstitution nor hydrolysis by-products were observed. A longer reaction time was required when less activated anilines were assayed (entries 11 and 12). Finally, reaction with α-amino esters (entries 13–16) offered the best results in a shorter reaction time when carried out in highly polar dimethyl sulfoxide solution. Water was also found to be a good solvent in some cases (entry 16), however, in general, long reaction times and high temperatures must be avoided to minimise ester hydrolysis by-products. α-Amino acid salts were also selectively linked to the nitrosopyrimidine nucleus after 16 h reaction at room temperature even in water as solvent. Unfortunately, all attempts to precipitate pyrimidinecarboxylate salts were unprofitable and controlled acidification of the reaction media led to a mixture of acids and methoxy-hydrolysed pyrimidine derivatives. Finally, the medium was acidified to induce total hydrolysis of the methoxy group in C(6) and to isolate only one product (Scheme 2). Single-crystal diffraction analysis of compound **8c** confirmed the predicted structure.[18]



Scheme 2. Synthesis of N^4-(6-oxopyrimidin-4-yl)-L-amino acids **8**. R and isolated yield (%): (a) R = H (90%); (b) R = Me (62%); (c) R = $CH(CH_3)Et$ (83%); (d) R = CH_2Ph (72%); (e) R = CH_2OH (40%); (f) R = CH_2CO_2H (76%).

A remarkable structural feature of compounds **7** and **8** is the strong intramolecular hydrogen bond that is established between the oxygen of the nitroso group and the hydrogen of the neighbouring NH group, which blocks the nitroso group rotation observed in the precursor[19] and results in the NMR signal of the involved NH proton being displaced up to 10.84–13.49 ppm ([D_6]DMSO, see Exp. Sect.). On the other hand, X-ray crystallographic analysis of compound **7c** (Figure 4) confirmed the predicted structure[20] and showed that, in the solid state, the molecule adopts a conformation in which the methoxy group is directed away from the nitroso group which, in turn, is turned towards the adamantyl substituent. The distance N(4)···O(5), and the angle N(4)–H(4)–O(5), were found to be 2.589 Å and 138°, respectively, indicating again that an intramolecular hydrogen bond exists between the oxygen of the nitroso group and the hydrogen of the adamantylamino group in **7c**. This strong hydrogen bond has been studied in several 4-amino-5-nitrosopyrimidine series[21] and it has been found that this link enables these compounds to mimic fused hetero-bicyclic systems such as purines to deliver new lead compounds of great biological interest with comparable pharmacological potency.[13d]

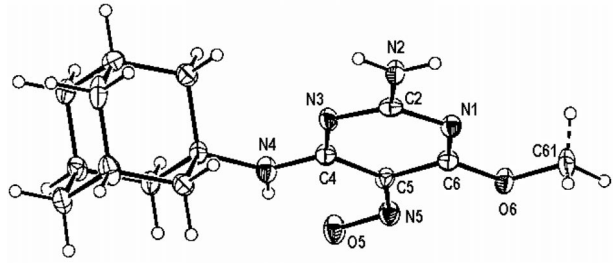
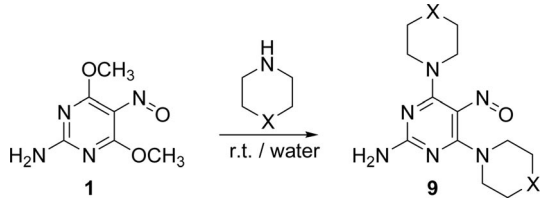


Figure 4. ORTEP drawing of **7c**.

Especially significant from a synthetic point of view is the fact that all the evaluated primary amines displaced the first methoxy group much faster than the second. Conversely, treatment of **1** with equimolar amounts of secondary amines (e.g., pyrrolidine, piperidine or morpholine) did not produce sequential displacement of their methoxy groups, and only starting material together with disubstitution products were detected by TLC and subsequently isolated after a very short reaction times, even for reactions in aprotic solvents (Scheme 3).



Scheme 3. Reaction of **1** with secondary amines to give **9**: (a) X = –, 0.2 h, 84%; (b) X = CH_2, 0.3 h, 64%; (c) X = O, 5 h, 65%.

This different selectivity of primary and secondary amines could be rationalised by considering the more nucleophilic character of secondary amines and the additional stability of nitrosopyrimidines **7** associated with planar delocalised structures A–E (Figure 5), which were deduced through X-ray analysis.[21e] In addition, it has been ob-

served that the planarity of the pyrimidine nucleus is lost when a secondary amine is introduced,[21c,21d] which means that charge delocalisation is not so effective as with primary amines and, therefore, the remaining methoxy group is more activated towards subsequent nucleophilic substitution.

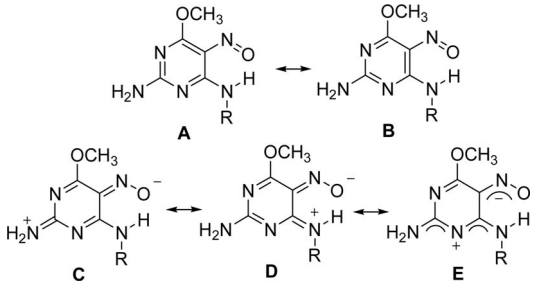
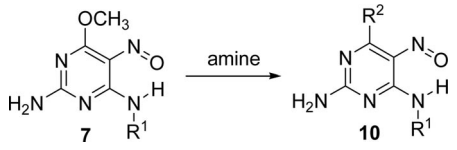


Figure 5. Resonance forms attributed to compounds **7** according to the results of X-ray analysis.

We next explored the ability of compounds **7** to undergo a second methoxy displacement to prepare symmetrical and non-symmetrical 2,4,6-tris(alkylamino)-5-nitrosopyrimidines, in which the different amines would be incorporated independently in a time-saving, one-pot procedure without requiring isolation or purification of the reaction intermediates (Scheme 4). When the reactions were carried out in the same aprotic solvents used for the first methoxy displacement, the substitution of the second methoxy group required rather long reaction times and the addition of a large excess (3–4 equiv.) of the second amine. Use of a protic solvent or heating the reaction medium was necessary to achieve complete displacement of the methoxy group in **7**. According to this understanding, symmetrical 2,4,6-tris(alkylamino)-5-nitrosopyrimidines were easily synthesised in one-pot by adding a slight excess of amine (2.2 mol/mol pyrimidine) to an aqueous suspension of pyrimidine **1** (Table 2, entries 17, 19, 22–24 and 29).



Scheme 4. Synthesis of 4,6-bis(alkylamino)-5-nitrosopyrimidines **10**.

The one-pot syntheses of non-symmetrical 2,4,6-tris(alkylamino)-5-nitrosopyrimidines were carried out by adding a protic solvent to crude **7** or, even better, by removing the original solvent (CH_2Cl_2 or MeCN) and adding water or a mixture of MeOH/H_2O (4:1, v/v) to gain solubility at room temperature. The influence of the amine bulk on the substitution rate is evident from the data shown in Table 2. In the most extreme case, the double displacement by the bulky 1-adamantylamine (entry 21) was not possible. Instead, the corresponding product obtained through monosubstitution and subsequent hydrolysis was isolated after two days in refluxing water. The same behaviour was observed when the secondary amines pyrrolidine and morpholine were used in an attempt to displace the second methoxy group from the monosubstituted products, i.e., C(6)-methoxy hydrolysis occurred instead of aminolysis. Nevertheless, the aminolysis products **10d** and **10i** (entries 20 and 25) were finally isolated in good yields after long reaction times in refluxing methanol. In this respect, the longer reaction time required by secondary amines in comparison to primary amines despite the more nucleophilic character of the former is worth noting.[22] Steric effects and the instability of non-planar reaction intermediates can be suggested as possible causes of this lower reactivity.[23] Finally, the monosubstituted aniline derivatives (entries 30–32) were reactive enough to undergo a second methoxy displacement by aliphatic amines as well as by α-amino esters, but not by less nucleophilic anilines. In this case, the less basic character of aniline had the result that the hydrolysis side reaction was not competi-

Table 2. Reaction conditions and yields of 4,6-bis(alkylamino)-5-nitrosopyrimidines **10**.

Entry	**10**	R^1	R^2	Conditions	Time [h]	Isolated yield [%]
17	**a**	Bu	NHBu	H_2O/r.t.	1.5	99
18	**b**	Bu	NHBn	H_2O/r.t.	24	80
19	**c**	Cy	NHCy	H_2O/r.t.	96	65
20	**d**	Cy	NPyr	MeOH/Δ	120	64
21	**e**	Ad	OH	H_2O/Δ	48	53
22	**f**	$CH_2CH{=}CH_2$	$NHCH_2CH{=}CH_2$	H_2O/r.t.	8	79
23	**g**	$(CH_2)_3NMe_2$	$NH(CH_2)_3NMe_2$	H_2O/r.t.	8	95
24	**h**	CH_2CH_2OH	$NHCH_2CH_2OH$	H_2O/r.t.	3.5	84
25	**i**	CH_2CH_2OH	NMor	MeOH/Δ	36	82
26	**j**	CH_2CH_2OH	NHBn	MeOH/Δ	0.75	87
27	**k**	Bn	NHMe	MeOH/H_2O/r.t.	4	67
28	**l**	Bn	NH*i*Pr	MeOH/H_2O/r.t.	4	86
29	**m**	Bn	NHBn	H_2O/r.t.	36	75
30	**n**	Ph	NHBu	MeOH/H_2O/r.t.	24	77
31	**o**	Ph	$NHCH_2CH_2CO_2Et$	DMF/80 °C	24	60
32	**p**	3-ClC_6H_4	NH*i*Pr	MeOH/H_2O/r.t.	48	76

tive enough and only the starting material was recovered even after prolonged heating in water, ethanol or dimethyl sulfoxide with a large excess of aniline.

^{1}H and ^{13}C NMR spectra of non-symmetrically substituted compounds **10** showed two sets of signals, indicating that, in solution, these compounds exist as two rotamers **10α** and **10β** in equilibrium (Figure 6). The ^{1}H NMR spectrum in $CDCl_3$ showed the α/β ratio of the equilibrium mixture to be 87:13 as determined by integration of $PhCH_2N$ and CH_3N signals in compound **10k**, however, this ratio changed to 50:50 in [D_6]DMSO (see Figures S85 and S87 in the Supporting Information). No significant changes in the ^{1}H NMR spectrum (i.e., broadening or coalescence of signals) were observed between 25 and 120 °C, which is consistent with a high rotational barrier around the C(5)–NO bond,[24] as a result of the high strength of the intramolecular, resonance-assisted, N=O···H–N hydrogen bonds existing in both rotamers. This might have significant consequences from a biological point of view since a non-symmetrically substituted nitrosopyrimidine **10** could be able to mimic two potentially active purines.

Aromatic nitroso compounds are characterised by a weak n→p* transition that appears in the visible region between 480 nm and 760 nm (ε = 40–70), which is sensitive to solvent polarity (Figure 7).[25] The spectrum of **10k** in methanol, for example, shows peaks at λ_{max} 295 (ε = 9060), 331 (ε = 15120), 507 nm (ε = 68), which is consistent with the presence of a nitroso group or a mixture of nitroso derivatives (**10α** and **10β**). On the other hand, in ethyl acetate, the compound absorbs at λ_{max} 278 (ε = 8540), 340 (ε = 15200) and 578 nm (ε = 67). Finally, no changes were observed when the spectra were recorded in methanol over a temperature range of +20 to –20 °C, in particular, the 507 nm band changed neither its position nor its intensity significantly.

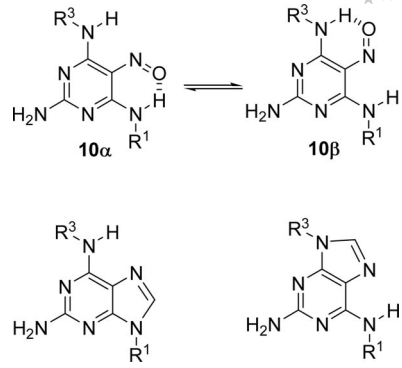
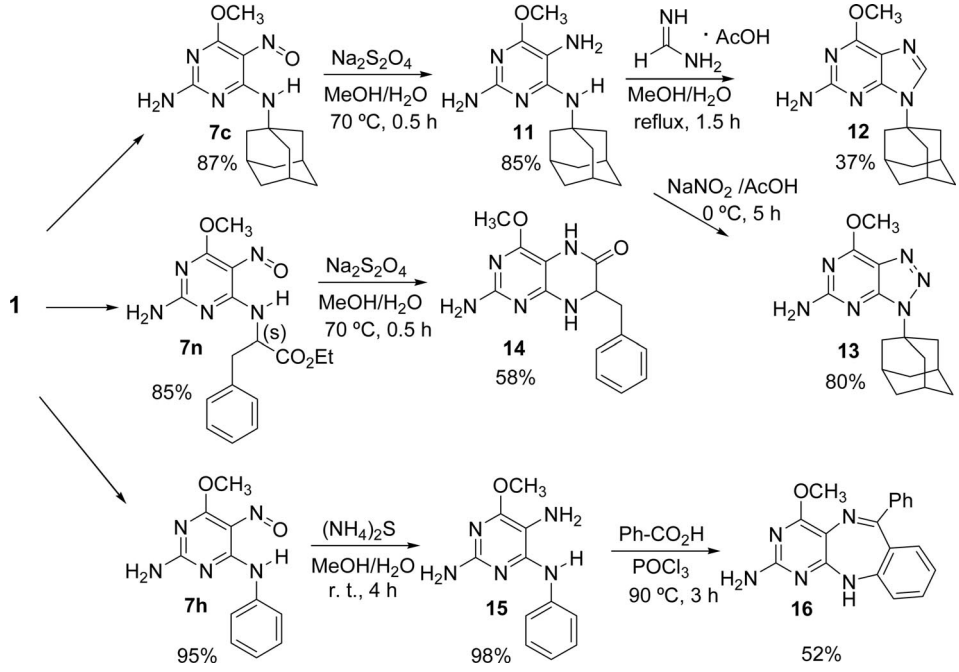


Figure 6. Rotamers of non-symmetrically substituted 5-nitrosopyrimidines **10** and mimicked purine analogues.

Figure 7. Solvent effect on the colour of 5-nitrosopyrimidine solutions.

Finally, to demonstrate the synthetic usefulness of amino-5-nitrosopyrimidines **7** as intermediates in the preparation of binuclear heterocycles of potential biological sig-



Scheme 5. Application of 5-nitrosopyrimidine aminolysis to the synthesis of fused polyazaheterocycles.

nificance, several fused pyrimidine derivatives were synthesised from the alkoxy-5-nitrosopyrimidines **7c**, **7n** and **7h**, following the routes depicted in Scheme 5.[26–29]

Antiviral Activity

Most of the compounds described herein were evaluated for antiinfluenza virus activity.[30] Convincing activity was noted for the reference compounds oseltamivir carboxylate (the active form of Tamiflu), ribavirin, amantadine and rimantidine (the latter two are only active against influenza A virus). Unfortunately, none of the test compounds displayed antiinfluenza virus activity at subtoxic concentrations or the highest concentration tested (100 μg/mL). Activity studies against other viruses are in progress and will be the subject of another report in the near future.

Conclusions

The introduction of a nitroso group on C(5) of a pyrimidine nucleus highly activates it towards nucleophilic substitution. This enables easy and selective displacement of methoxy groups in 2-amino-4,6-dimethoxy-5-nitrosopyrimidine by a large range of amines under mild conditions, allowing efficient, time-saving, one-pot preparations of symmetrical and non-symmetrical 2,4,6-tris(alkylamino)-5-nitrosopyrimidines, which are useful as intermediates in common synthetic routes to hetero-bicyclic systems of great biological interest such as purines, pteridines or diazepines. Unfortunately, none of the test compounds displayed antiinfluenza virus activity; nevertheless, additional activity evaluation of the synthesised compounds are in progress and, in accord with the initial results, further investigations to assess the applicability of the methoxy aminolysis strategy to automated solid-phase synthesis of large 5-nitrosopyrimidines libraries will be undertaken.

Experimental Section

General Procedure (A) for the Synthesis of Amino-dialkoxy-5-nitrosopyrimidines 1–6: The aminopyrimidine was dissolved in DMSO (2.5 mL/mmol pyrimidine) and isoamyl nitrite (1.1 mol/mol pyrimidine) was added. The reaction mixture was stirred at r.t. until the starting pyrimidine could no longer be detected by TLC (silica; CH_2Cl_2/MeOH, 9:1, v/v). Then, a double volume of water was added dropwise under continuous stirring and the suspension was stirred for 2 h. The product was isolated by vacuum filtration, washed several times with water and finally dried in a vacuum desiccator over potassium hydroxide pellets.

2-Amino-4,6-dimethoxy-5-nitrosopyrimidine (1): Following general procedure A, starting from commercial 2-amino-4,6-dimethoxypyrimidine (1.00 g, 6.44 mmol), compound **1** was obtained after 36 h of reaction time as a green solid (0.866 g, 75%). Crystals suitable for single-crystal X-ray diffraction were obtained by slow evaporation in acetone.[31] M.p. 190–192 °C (decomp.). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 8.33 (br. s, 2 H, NH_2), 3.98 (s, 6 H, 2 × OMe) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 173.0 (s), 163.5 (s), 141.9 (s), 54.9 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3328, 1673, 1586, 1402, 1255 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 184 (14) [M]$^{+\cdot}$, 96 (16), 69 (40), 57 (57), 43 (100). UV/Vis (MeOH): λ_{max} [logε] = 237 [3.91], 338 [4.41], 651 [1.77] nm. $C_6H_8N_4O_3$ (184.15): calcd. C 39.13, H 4.38, N 30.42; found C 39.06, H 4.52, N 30.46.

General Procedure (B) for the Synthesis of 2-Amino-4-alkylamino-6-methoxy-5-nitrosopyrimidines 7: To a suspension of **1** in a suitable solvent (10 mL/mol pyrimidine), amine (1.0 mol/mol pyrimidine) was added. When ethyl amino acid ester hydrochloride was used, Et_3N (2.0 mol/mol pyrimidine) was added to neutralised the hydrochloride. The mixture was stirred at r.t. and the reaction was monitored by TLC (silica; CH_2Cl_2/MeOH, 9:1, v/v) until no starting material was observed. The mixture was evaporated to dryness and the residue was suspended in water. The precipitate was filtered, washed with water and finally dried in a vacuum desiccator over potassium hydroxide pellets.

2-Amino-4-(butylamino)-6-methoxy-5-nitrosopyrimidine (7a): Following general procedure B, starting from pyrimidine **1** (184 mg, 1.00 mmol) and *n*-BuNH_2 in MeCN, **7a** was obtained after 3 h of reaction time as a violet solid (180 mg, 80%). M.p. 102–104 (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 11.65 (br. s, 1 H, NH), 5.66 (m, 2 H, NCH_2), 4.15 (s, 3 H, OMe), 3.46–3.40 (m, 2 H, CH_2), 1.62–1.52 (m, 2 H, CH_2), 1.45–1.35 (m, 2 H, CH_2), 0.93 (t, *J* = 7.3 Hz, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.3 (s), 163.6 (s), 151.0 (s), 139.2 (s), 54.9 (q), 39.5 (t), 30.9 (t), 20.1 (t), 13.7 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3333, 3159, 2934, 1650, 1582, 1211 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 225 (93) [M]$^{+\cdot}$, 208 (100), 179 (38), 154 (89), 127 (33), 68 (32), 57 (43), 43 (70). UV/Vis (MeOH): λ_{max} [logε] = 231 [3.86], 328 [4.36], 538 [1.83] nm. $C_9H_{15}N_5O_2$ (225.25): calcd. C 55.59, H 5.05, N 27.01; found C 55.64, H 5.06, N 26.68.

***N*-(2-Amino-6-methoxy-5-nitrosopyrimidin-4-yl)ethyl Glycinate (7k):** Following general procedure B, starting from pyrimidine **1** (184 mg, 1.00 mmol), GlyOEt·HCl and Et_3N in CH_2Cl_2, **7k** was obtained after 72 h of reaction time as a blue solid (220 mg, 84%). M.p. 150–152 °C (decomp.). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 11.22 (br. s, 1 H, NH), 8.07 (br. s, 1 H, NH_2), 8.01 (br. s, 1 H, NH_2), 4.19 (d, *J* = 5.6 Hz, 2 H, NCH_2), 4.12 (q, *J* = 7.1 Hz, 2 H, $COCH_2$), 4.07 (s, 3 H, OCH_3), 1.20 (t, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.1 (s), 169.0 (s), 163.2 (s), 150.0 (s), 138.9 (s), 60.8 (t), 54.4 (q), 41.3 (t), 14.0 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3426, 3296, 3162, 2976, 1729, 1643, 1214 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 255 (94) [M]$^{+\cdot}$, 166 (63), 154 (100), 127 (42), 57 (30), 43 (29). UV/Vis (MeOH): λ_{max} [logε] = 234 [3.85], 333 [4.39], 549 [1.84] nm. $C_9H_{13}N_5O_4$ (255.23): calcd. C 42.35, H 5.13, N 27.44; found C 42.42, H 5.14, N 27.39.

General Procedure (C) for the Synthesis of N^4-(2-Amino-1,6-dihydro-5-nitroso-6-oxopyrimidin-4-yl)-L-amino Acids 8: To a suspension of **1** (0.092 mg, 0.5 mmol) in MeCN (5 mL), a solution of L-amino acid (0.6 mmol) in Na_2CO_3 (1 M, 0.6 mL) was added. The total volume was increased by the addition of water (4.4 mL) and the final mixture was stirred at r.t. until the initial nitrosopyrimidine was no longer detected by TLC (silica; MeOH). The solvent was distilled off and the residue was suspended water (5 mL) and acidified with concentrated HCl to pH 2–3. The solvent was removed in a vacuum evaporator and the red residue obtained was suspended in water (5 mL), filtered off and finally dried in a vacuum desiccator over potassium hydroxide pellets.

***N*-(2-Amino-1,6-dihydro-5-nitroso-6-oxopyrimidin-4-yl)-L-isoleucine (8c):** Following general procedure C, starting from pyrimidine **1** and L-isoleucine, **8c** was obtained as a red solid (97 mg, 72%). Crystals suitable for X-ray diffraction were obtained by slow evaporation in water.[21] M.p. 190–192 °C (decomp.). ^{1}H NMR

(300 MHz, [D$_6$]DMSO, 25 °C): δ = 12.87 (d, J = 8.4 Hz, 1 H, NH), 10.94 (br. s, 1 H, NH), 8.29 (br. s, 1 H, NH$_2$), 7.01 (br. s, 1 H, NH$_2$), 4.70 (dd, J = 8.5, 4.5 Hz, 1 H, NCH), 1.98–1.85 (m, 1 H, CH), 1.51–1.37 (m, 1 H, CH$_2$), 1.27–1.13 (m, 1 H, CH$_2$), 0.91 (d, J = 7.3 Hz, 3 H, CH_3CH), 0.85 (q, J = 7.3 Hz, CH_3CH$_2$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.5 (s), 161.1 (s), 156.3 (s), 151.8 (s), 140.5 (s), 56.6 (d), 36.7 (s), 24.7 (t), 15.5 (q), 11.4 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3369, 1736, 1656 cm^{-1}. UV (H$_2$O): λ_{max} [logε)] = 267 [4.07], 320 [3.98] nm. $C_{10}H_{15}N_5O_4$·1/4H$_2$O (273.76): calcd. C 43.87, H 5.71, N 25.58; found C 43.87, H 5.81, N 25.44.

General Procedure (D) for the Synthesis of Symmetrically Substituted 2-Amino-4,6-bis(alkylamino)-5-nitrosopyrimidines 9–10: To a suspension of **1** in water (10 mL/mmol), the corresponding amine (2.2 mol/mol pyrimidine) was added. The mixture was stirred at r.t. and monitored by TLC (silica; CH_2Cl_2/MeOH, 9:1, v/v) until no starting material was observed. The mixture was evaporated to dryness and the residue was suspended in water (diethyl ether when secondary amines were used). The precipitate was filtered, washed and dried in a vacuum desiccator over potassium hydroxide pellets.

2-Amino-5-nitroso-4,6-bis(pyrrolidin-1-yl)pyrimidine (9a): Following general procedure D, starting from pyrimidine **1** (92 mg, 0.50 mmol) and pyrrolidine, **9a** was obtained after 0.2 h of reaction time as a red solid (110 mg, 84%). Red crystals suitable for X-ray diffraction were obtained by slow evaporation from CH_3CN.[21e] M.p. 192–195 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 6.99 (br. s, 2 H, NH$_2$), 3.87 (br. s, 2 H, NCH$_2$), 3.68 (br. s, 2 H, NCH$_2$), 3.46 (t, J = 6.7 Hz, 2 H, NCH$_2$), 3.08 (t, J = 6.3 Hz, 2 H, NCH$_2$), 1.91 (br. s, 4 H, 2CH$_2$), 1.88–1.74 (m, 4 H, 2CH$_2$) ppm. ^{13}C NMR (100, MHz, [D$_6$]DMSO): δ = 163.1 (s), 161.4 (s), 151.6 (s), 142.0 (s), 51.9 (t), 50.7 (t), 48.2 (t), 47.7 (t), 25.9 (t), 25.2 (t), 23.7 (t) ppm. IR (KBr): $\tilde{\nu}$ = 3341, 2975, 1651, 1577, 1352, 1074 cm^{-1}. MS (EI, 70 eV): m/z (%) = 262 (4) [M]$^{+\cdot}$, 245 (100), 203 (12), 174 (14), 55 (24), 41 (100). UV/Vis (MeOH): λ_{max} [logε] = 280 [4.17], 336 [4.26], 470 [1.97] nm. $C_{12}H_{18}N_6O$·1/2H$_2$O (271.15): calcd. C 53.12, H 7.06, N 30.97; found C 53.25, H 7.14, N 30.80.

2-Amino-4,6-bis(benzylamino)-5-nitrosopyrimidine (10m): Following general procedure D, starting from pyrimidine **1** (184 mg, 1.00 mmol) and BnNH$_2$, **10m** was obtained after 36 h of reaction time as a red solid (240 mg, 75%). Crystals suitable for single-crystal X-ray diffraction were obtained by slow evaporation in MeCN/DMSO (5:1, v/v).[21c] M.p. 160–162 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO, 25 °C): δ = 11.95 (t, J = 5.9 Hz, 1 H, NH), 9.26 (t, J = 6.4 Hz, 1 H, NH), 7.51 (br. s, 2 H, NH$_2$), 7.40–7.23 (m, 10 H, 2Ph), 4.89 (d, J = 6.4 Hz, 2 H, NCH$_2$), 4.62 (d, J = 5.9 Hz, 2 H, NCH$_2$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 164.3 (s), 163.0 (s), 150.6 (s), 139.3 (s), 138.1 (s), 136.1 (s), 128.4 (d), 128.1 (d), 127.5 (d), 127.3 (d), 127.0 (d), 126.6 (d), 42.9 (t), 42.1 (t) ppm. IR (KBr): $\tilde{\nu}$ = 3310, 1631, 1592, 1496, 1360, 1173 cm^{-1}. MS (EI, 70 eV): m/z (%) = 334 (7) [M]$^{+\cdot}$, 317 (45), 226 (40), 91 (100). UV/Vis (MeOH): λ_{max} [logε]: 231 [sh], 296 [sh], 329 [4.33], 504 [2.03]. $C_{18}H_{18}N_6O$ (334.38): calcd. C 64.66, H 5.43, N 25.13; found C 64.75, H 5.52, N 25.10.

General Procedure (E) for the Synthesis of Non-Symmetrically Substituted 2-Amino-4,6-bis(alkylamino)-5-nitrosopyrimidines 10: General procedure B for the synthesis of pyrimidines **7** was followed until compound **1** was no longer observed by TLC. The solvent was removed, the residue was suspended in a suitable solvent (ca. 10 mL/mmol pyrimidine) and a second amine (1.5 mol/mol pyrimidine) was added. The mixture was stirred until compound **7** was no longer observed by TLC (silica; CH_2Cl_2/MeOH, 9:1, v/v), then the precipitate was filtered, washed with water and dried in a vacuum desiccator over potassium hydroxide pellets.

2-Amino-4-benzylamino-6-methylamino-5-nitrosopyrimidine (10k): Following general procedure E, starting from pyrimidine **7g** (138 mg, 0.53 mmol) and MeNH$_2$ in MeOH/H$_2$O (4:1, v/v), **10k** was obtained as a red solid (92 mg, 67%). M.p. 160–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 12.01, 7.87 (br. s, 1 H, NH), 11.64, 7.62 (br. s, 1 H, NH), 7.33 (m, 5 H, Ph), 5.55 (br. s, 2 H, NH$_2$), 4.74, 4.64 (d, J = 6.0 Hz, 2 H, NCH$_2$), 3.09, 2.95 (d, J = 4.9 Hz, 3 H, NCH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9 (s), 163.7 (s), 152.0 (s), 137.6 (s), 136.4 (s), 128.8 (d), 128.7 (d), 127.5 (d), 44.6 (t), 26.1 (q) ppm. IR (KBr): $\tilde{\nu}$ = 3321, 3174, 1573, 1360, 1182 cm^{-1}. MS (EI, 70 eV): m/z (%) = 258 (9) [M]$^{+\cdot}$, 241 (100), 224 (32), 153 (32), 91 (71), 65 (30), 43 (28). UV/Vis (MeOH): λ_{max} [logε] = 228 [sh], 295 [sh], 331 [4.18], 507 [1.83]. $C_{12}H_{14}N_6O$ (258.28): calcd. C 55.80, H 5.46, N 32.54; found C 55.87, H 5.69, N 32.51.

Supporting Information (see also the footnote on the first page of this article): Material and methods, experimental procedures, characterisation data and copies of ^{1}H, ^{13}C, DEPT NMR spectra of all the synthesised compounds as well as the data for the antiinfluenza virus activity and cytotoxicity in MDCK cell cultures with some of synthesised compounds are available.

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