Solid-Phase Synthesis of 2,4,6-Triaminopyrimidines

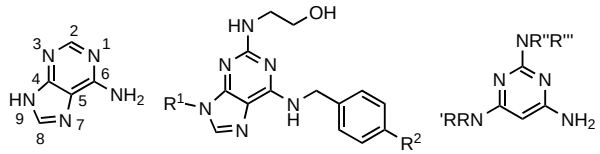
Fabrice Guillier,[a] Patrick Roussel,[a] Heinz Moser,[b] Peter Kane[c] and Mark Bradley*[a]

Abstract: Substituted pyrimidines are an important class of kinase inhibitors. We therefore developed a synthetic route suitable for the solid-phase synthesis of 2,4,6-triaminopyrimidines through displacement reactions on deactivated pyrimidines. Functionalising the pyrimidines was achieved using a range of primary and secondary amines and aniline and was realised on polystyrene resin with temperatures up to 140 °C. Two different amination reactions were performed following the anchoring of 4,6-dichloro-2-thiomethylpyrimidine (**4**) onto Rink-amide derivatised resin. The regio- and chemoselectivity for the displacement was studied for different leaving groups. The most consistent results were obtained when chlorine was used in 6-position and a methylsulfonyl group in the 2-position. A small library of substituted pyrimidines was prepared to ascertain the extent of the developed chemistry.

Keywords: amination · kinases · nucleophilic aromatic substitution · pyrimidines · solid-phase synthesis

Introduction

Protein kinases play critical roles in regulating the cell cycle, acting as enzyme activators by transferring the γ-phosphate group of ATP to a serine, threonine or tyrosine residue of an acceptor protein. This activation is important in many biological processes such as cell growth, DNA replication and cell division.[1–3] Specific inhibitors of kinases may have potential therapeutic utility in retarding tumour cell proliferation and synthetic attention has been focused almost entirely on inhibitors of the ATP binding site. Purine analogues of adenine **1** have been synthesised[4–8] while olomoucine **2a** competitively inhibits the cyclin-dependent kinase complex p33cdk2/cyclin A ($IC_{50} = 7$ μM).[9–11] A more potent compound **2b** ($IC_{50} = 0.6$ μM) was obtained by solid-phase synthesis and screening of combinatorial libraries based on modifications at the C-6, C-2 and N-9 positions of the purine scaffold.[6] It has been noticed by X-ray analysis that, although olomoucine binds in the adenine binding pocket of cdk2, the purine nucleus adopts an entirely different orientation than that observed for ATP.[12] The aromatic heterocyclic core is thus important for recognition but better ligands can still be found for more active antagonists. It is with this objective in mind that we describe herein the solid-phase synthesis of a range of aminopyrimidines **3**.



1 **2a** R^1=Me, R^2=H **3**
2b R^1=*i*Pr, R^2=OMe

Polyaminopyrimidines constitute the common entity of the potential kinase inhibitors described here. In order to study their structure–activity relationship, the preparation of a series of various polyaminopyrimidines was undertaken. Combinatorial chemistry has received much interest in the last decade as a result of its potential to accelerate the drug discovery process by enabling the production of a large number of compounds in a relatively short period of time.[13, 14] This methodology ideally enables the generation of "molecular diversity" through a careful choice of building blocks. In the particular case of template derivatisation, solid-phase synthesis appears to be the method of choice, if the template can be easily anchored onto a solid support and derivatisation achieved efficiently using various and "diverse" building blocks all with reliable chemistry. The synthesis of a large range of analogous polyaminopyrimidines (with primary, secondary amines and anilines derivatives) is perfectly integrated in this approach, as amines are one of the most readily available compound types allowing a range of hydro-

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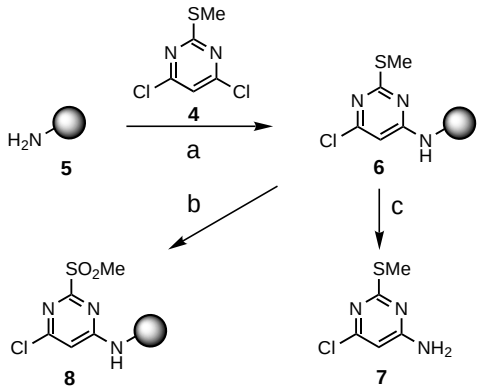
phobic, electronic and steric characters to be considered. One particular difficulty in combinatorial synthesis remains conciliating the dissimilarity with finding a general chemical reaction with reagents having different reactivity. Although a striking effort is concentrated on the development of a wide range of organic reactions on solid support,[15] their use in combinatorial chemistry is still restricted by subunit applicability and thus the diversity they can generate. In our particular case, another requirement was the necessary control of functionalisation in a chemo- and regioselective manner. In this work we present studies showing the functionalisation of the pyrimidine core by various amines. Particular attention was paid to the control of regio- and chemoselectivity in order to optimise yield and purity. Scaffold attachment of the starting commercially available trisubstituted pyrimidine on the resin was through a Rink "amine-generating" linker,[16] allowing two points of diversity to be realised on the template. Synthesis of polyamino-electron-deficient heterocycles is usually achieved by nucleophilic displacement at the different electrophilic centres.[17, 18] Selectivity is obtained as the reactivity decreases after each nucleophilic displacement. A library of polyaminotriazines has already been generated through successive substitution of dichlorotriazine[19] and trichlorotriazine[20] on the solid phase. However, pyrimidines are much less reactive towards nucleophilic displacement especially after the first and second replacement by electron-donating groups such as amines. Harsh conditions such as refluxing in neat amine are often required for displacement. The reactivity of different amines also plays a crucial role. Primary and not too hindered secondary amines are good nucleophiles and suitable for the first displacement reaction. However these groups provide a deactivating effect for the next substitution, although the reverse behaviour is expected for aniline derivatives. One of the aims of this project was to determine if the regioselectivity could be retained and diversity generated with a large range of amines.

Results and Discussion

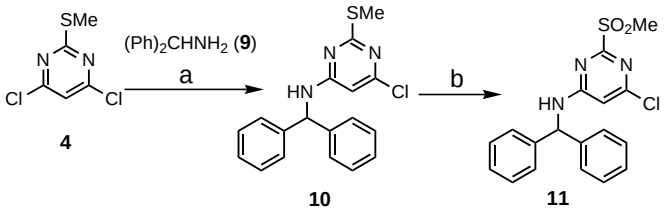
In order to prepare compounds **3** on the solid support, a functional group was required on the pyrimidine ring to link to the solid support. Despite some limitations in the use of one of the amine groups as an anchoring group, thus limiting the diversity, solid-phase synthesis was preferred rather than solution-phase as a result of the ease of purification of the reaction mixtures following the extreme conditions used for this chemistry. For example, purification when non-volatile neat amines are used under reflux would have lead to some problems when carried out in solution. Aminomethyl polystyrene resin was employed as the solid support.[21] Standard coupling conditions, diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBt) were used to anchor the Fmoc-Rink-amide linker[22] onto the aminomethyl polystyrene resin. Subsequent removal of the Fmoc protecting group with 20% piperidine in dimethylformamide (DMF) afforded the resin-bound Rink-amide linker **5**. Anchoring the template **4** was performed by reaction of **5** with five equivalents of the 4,6-dichloro-2-thiomethylpyrimidine (**4**), tetra-*n*-butylammonium bromide and diisopropylethylamine (DIEA) in DMF at 90 °C. Full substitution was achieved as indicated by the ninhydrin test.[23] The cleaved 4-aminopyrimidine (**7**) was of high purity (100%) as determined by HPLC (254 nm) and was recovered in 89% yield based on initial resin loading (Scheme 1).



Scheme 1. Anchoring and oxidation of template **4**: a) Chloropyrimidine **4**, DIEA, nBu$_4$NBr, DMF, 90 °C; b) *m*CPBA, dioxane, 1M NaOH, RT; c) TFA, H_2O, CH_2Cl_2 (90:5:5), 3 h (89%).

Oxidation of the thiomethyl group into the corresponding sulfone was performed in order to enhance the reactivity of pyrimidine **6** towards nucleophilic displacement. The functional interconversion of the sulfide into the sulfone group allows its displacement, while selectivity was expected to be retained as the resulting sulfone group should be a better leaving group than the 6-chloro moiety. The oxidation was realised with 10 equivalents of *m*-chloroperbenzoic acid (*m*CPBA) in dioxane and led to compound **8** (Scheme 1). 1M Aqueous sodium hydroxide was added to the reaction to avoid premature cleavage from the support during the reaction by generation of acidic by-products. Monitoring the oxidation of the sulfide was difficult as a result of the reactivity of **8** and the weak signals obtained by electrospray mass spectrometry (ES-MS) of the cleaved compound. Nevertheless reaction assessment could be achieved with on-bead infra-red spectroscopy.[24] This was performed by relative integration of the sulfone absorbance compared with a reference peak and allowed us to qualitatively monitor the conversion. For accuracy, standards of sulfide and sulfone were synthesised in solution in order to construct a calibration curve enabling quantitative studies. Refluxing diphenylmethylamine **9** (as a Rink-linker mimic) with 4,6-dichloro-2-thiomethylpyrimidine (**4**) in acetonitrile and triethylamine provided the aminosubstituted pyrimidine **10** in 75% yield. The oxidation step was performed with *m*CPBA in dichloromethane for two hours at room temperature and led to the sulfone **11** in 89% yield (Scheme 2).

Infra-red spectra of the starting sulfide **10** prepared in solution and **6** on the solid support showed many analogies despite the fact that on the solid support the spectrum is much broader which is a general feature of this technology (Figure 1). The same observations were repeated for the sulfones **11** and **8**.



Scheme 2. Solution-phase synthesis of sulfide **10** and sulfone **11** used as standards for IR quantification: a) Amine **9**, Et_3N, CH_3CN, reflux, 26 h (75%); b) *m*CPBA, CH_2Cl_2, 2 h, RT (89%).

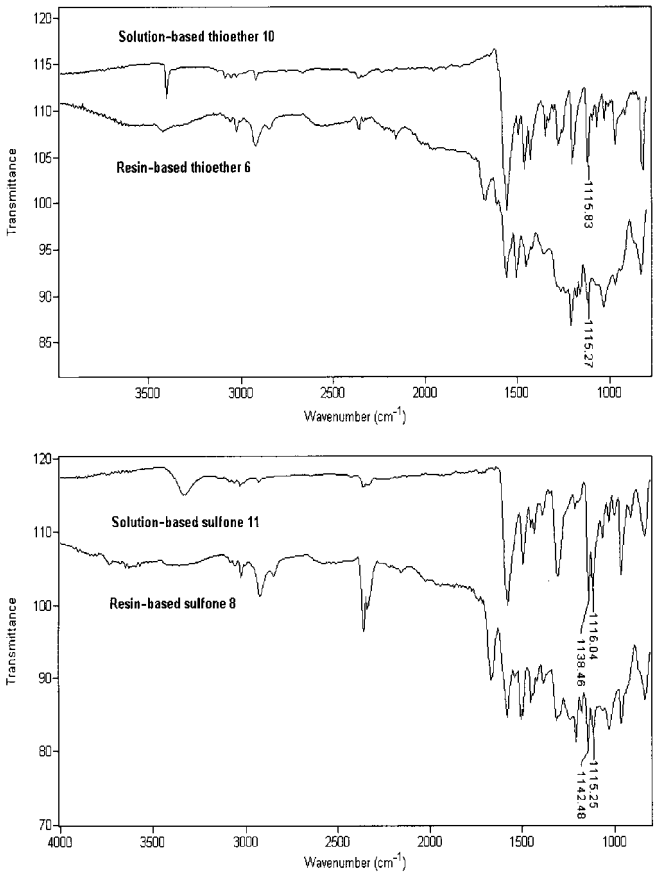


Figure 1. Infra-red spectra of starting sulfide **6** and sulfone **8** (with the solution equivalents **10** and **11**, respectively).

Evaluation of the sulfone IR peak (1138 cm^{-1}) for mixtures of known composition of **10** and **11** permitted selection of a reference peak at 1116 cm^{-1} with a good correlation between the relative integration of the sulfone peak and the composition of the mixture. Kinetic studies were then realised on the beads and the corresponding peak (1142 cm^{-1}) for compound **8**, characteristic of the sulfone group, was integrated relative to the reference peak at 1115 cm^{-1}. Thus, 200 mg of resin **6** and 10 equivalents of *m*CPBA were used during the kinetic studies and aliquots were removed, washed and dried before analysis. A graph was recorded displaying the oxidation of the sulfide group by the appearance of the 1142 cm^{-1} peak. The reaction was complete after two hours (Figure 2).

HPLC analysis was consistent with the IR data and confirmed that no starting material (RT = 12.0 min) or sulfoxide (RT = 6.5 min) were present. Selective displacement

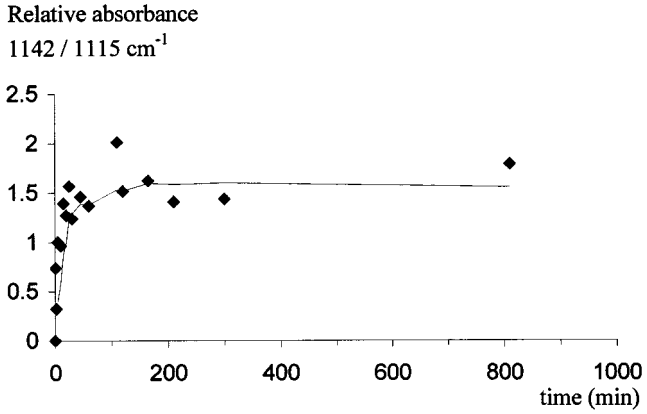


Figure 2. Kinetic IR studies for the oxidation of sulfide **6** into sulfone **8**. Relative integration of the IR sulfone's peak versus time.

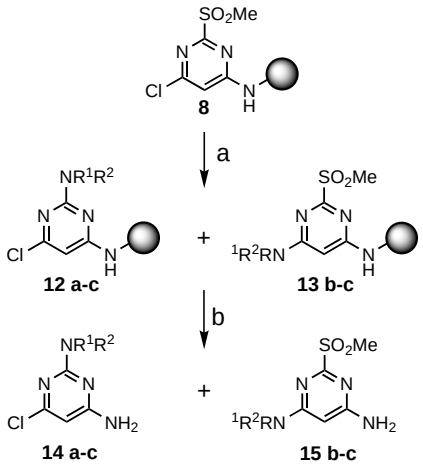
with primary amines took place smoothly at room temperature as a result of the activating effect of the sulfonyl group (Table 1, entry 1). This reaction required large excesses of

Table 1. HPLC and ES-MS analysis for substitution on resin **8** by primary and secondary amines.

Entry	R^1R^2NH	HPLC [%] **14/15**	Product	RT [min]	MS $[M+H]^+$
1	benzylamine	100/0	**14a**	11.6	235
2	diethylamine	40/60	**14b**	10.4	201
			15b	11.8	245
3	diethylamine[a]	30/70	**14b**	10.4	201
			15b	11.8	245
4	piperidine	45/55	**14c**	11.4	213
			15c	12.2	257

[a] Refluxing in DMSO as a 1:1 mixture with amine.

amines to go to completion and hence the amine was used as solvent. Cleavage from the resin under the usual conditions gave the diamine **14a** in 76% overall yield when benzylamine was used (Scheme 3). Displacement by secondary amines surprisingly led to loss of chemo- and regioselectivity as both leaving groups were displaced (Scheme 3; Table 1, entries 2, 3, 4). This particular behaviour can be explained by the fact that



Scheme 3. Nucleophilic substitution on chlorosulfonylpyrimidine **8** by primary and secondary amines: a) R^1R^2NH, 15 h, RT; b) TFA, H_2O, CH_2Cl_2 (90:5:5), 3 h.

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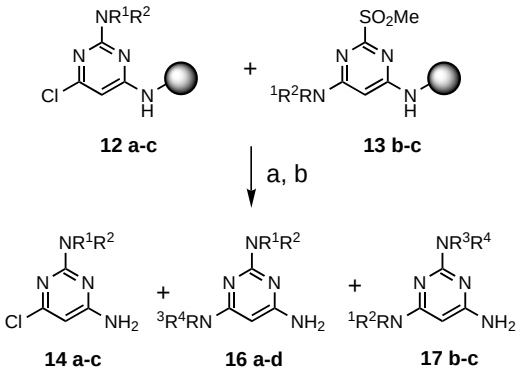
Table 2. HPLC and ES-MS analysis after second substitution carried out on mixtures of resins **12a–c** and **13b–c** (**14a–c** and **15b–c** after cleavage).

Entry	R^1R^2NH	HPLC [%] **14/15** Starting materials	R^3R^4NH	HPLC [%] **14/16/17** Products		RT [min]	MS $[M+H]^+$
1	benzylamine	100/0	benzylamine	10/90/0	**16a**	13.1	306
2	diethylamine	30/70	benzylamine	25/10/65	**16b**	12.8	272
					17b	13.3	272
3	piperidine	45/55	benzylamine	35/15/50	**16c**	12.6	284
					17c	13.4	284
4	benzylamine	100/0	cyclohexylamine	60/40/0	**16d**	13.9	298

both sites became equally reactive towards strong nucleophiles, with the better leaving group (the sulfone) being on the less electrophilic centre (C2) with the chlorine being on the more electrophilic position (C6). This mixture of products forced us to avoid the use of secondary amines with this pyrimidine. Displacement with anilines was unsuccessful as prolonged heating resulted in degradation of the chlorosulfonylpyrimidine.

Primary amine substituted compounds could then undergo a second displacement involving the chlorine. Stronger conditions than for the first displacement were required as a result of the deactivating effect of the two amine groups already on the pyrimidine ring and 140 °C or refluxing amine were used. However, upon cleavage, the reaction was observed not to be complete and some chloro derivative **14** remained (Table 2, entries 1 and 4). The nucleophilicity seemed to be sensitive to steric hindrance as only 40% conversion was observed when cyclohexylamine was employed compared with the benzylamine which gave 90% conversion. When the mixture of pyrimidines bearing a secondary amine in the 2- or 6-position was used (compounds **12** and **13**), displacement by the primary amine at 140 °C overnight was achieved for sulfone **13**, but compound **12** proved to be less reactive (Scheme 4; Table 2, entries 2 and 3). In this case the sulfone was displaced much more easily than the chlorine.



Scheme 4. Incomplete second amination then cleavage carried out on the mixture of pyrimidines **12** and **13**: a) R^3R^4NH, 15 h, 140°C; b) TFA, H_2O, CH_2Cl_2 (90:5:5), 3 h.

Despite the preparation of some pyrimidines **16** and **17** bearing three different amines in the 2,4,6-positions the diversity potential was low since the first displacement only works with primary amines without lost of regioselectivity. The second displacement was never totally achieved as a result of the low reactivity of the chlorine in the 6-position. It was believed that replacement of the chlorine residue by another sulfonyl group would enhance the reactivity for nucleophilic displacement. The regioselectivity was expected to follow the same rule described for 2,6-dihalopyrimidines,[17] that is the first displacement occurs in 6-position then the second in the 2-position. Thus the resin-bound 2,6-bismethylsulfonylpyrimidine (**20**) was preliminary generated from the 6-chloro-2-thiomethylpyrimidine (**6**) by displacement of the chloride by a thiomethylide group. Perfect solubilisation of sodium thiomethoxide and use of one equivalent of crown ether were crucial for achieving the reaction (Table 3). [Only

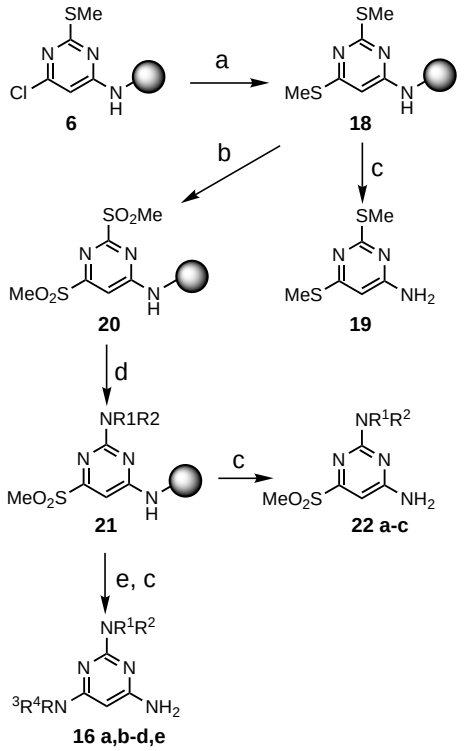
Table 3. Reaction optimisation for the synthesis of bismethylsulfide **19**.

Experimental conditions	HPLC [%] **19/7**
NaSMe, DMSO, 13 h, 100 °C	0/100
NaSMe, [15]crown-5, EtOH, DMF, 13 h, RT	0/100
NaSMe, [15]crown-5, EtOH, DMF, 13 h, 80 °C	75/25
NaSMe, [15]crown-5, EtOH, DMF, 13 h, 130 °C	100/0

starting materials were recovered when a Stille coupling, already described in solution with 6-chloropyrimidine with various tin derivatives[25], was attempted with tributyltinphenylsulfide[26] with conditions for the solid-phase reaction[27, 28] ([Pd_2dba_3], $AsPh_3$, NMP, N_2, overnight 80 °C)]. The bisthioether **18** was cleaved from the resin under the usual conditions and afforded 4-amino-2,6-dimethylthiosulfide (**19**) in high purity in 71% overall yield (Scheme 5).

The subsequent oxidation step was performed with *m*CPBA as described for compound **8**. No starting material or sulfoxide was recovered when 40 equivalents of *m*CPBA where employed, while HPLC and ES-MS monitoring were inconclusive as a result of the extreme lability of the disulfone containing pyrimidine. Nevertheless completion in the following displacement step demonstrated that the oxidation reaction worked satisfactorily. Displacement with various amines was performed at room temperature (Scheme 5). No regioselectivity problems were encountered with secondary amines and only compound **22** was obtained (Table 4).

It was initially expected that substitution had occurred at the 6-position of the pyrimidine ring since it is documented that pyrimidines bearing two chloro groups in the 2- and 6-positions are prone to substitution reactions at the 6-position.[17] However, the retention times obtained for 4-amino-2-diethylamino-6-sulfonylmethylpyrimidine (**22b**) and 4-amino-2-cyclohexylamino-6-sulfonylmethylpyrimidine (**22c**) (11.2 and 11.9 min) were different than those for 4-amino-6-diethylamino-2-sulfonylmethylpyrimidine (**15b**) and 4-amino-6-cyclo-



Scheme 5. Preparation of disulfonylmethylpyrimidine (**20**). Incomplete regioselective amination followed by cleavage: a) NaSMe, [15]crown-5, EtOH/DMF (1:4), 15 h, 130 °C; b) *m*CPBA, dioxane, 1M NaOH, RT; c) TFA, H_2O, CH_2Cl_2 (90:5:5), 3 h; d) R^1R^2NH, 15 h, RT; e) R^3R^4NH, 15 h, 140 °C.

Table 4. HPLC and ES-MS analysis after regioselective substitution on resin **20**.

R^1R^2NH	HPLC [%]	Product	RT [min]	MS $[M+H]^+$
benzylamine	91 %	**22a**	11.6	279
diethylamine	100 %	**22b**	11.2	245
cyclohexylamine	85 %	**22c**	11.9	271

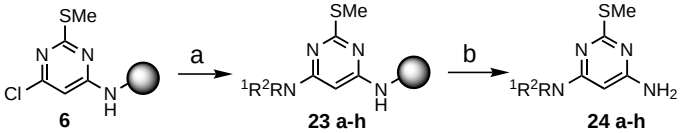
hexylamino-2-sulfonylmethylpyrimidine (11.8 and 13.1 min) which were obtained unambiguously by another route show that displacement had taken place at the 2-position. The displacement by aniline derivatives at room temperature was still unsuccessful and the starting material was entirely recovered. Prolonged heating did not afford any better result. The second displacement was then investigated with more vigorous conditions and was performed with neat amine at 140 °C. Incomplete conversion was observed (Table 5) and the sulphonyl group was not fully displaced during the second substitution reaction. Both the 2- and 6-position appeared to react differently and the 6-position seems to be less reactive than the 2-position.

Table 5. HPLC and ES-MS analysis after conversion of 6-sulfonyl resin **21** into triaminopyrimidine **16**.

R^1R^2NH	R^3R^4NH	HPLC [%] **16**/**22**[a]	Product	RT [min]	MS $[M+H]^+$
benzylamine	benzylamine	25/75	**16a**	13.1	306
diethylamine	benzylamine	30/40	**16b**	12.8	272
benzylamine	cyclohexylamine	20/65	**16d**	13.9	298
cyclohexylamine	benzylamine	30/10	**16e**	13.9	298

[a] Remaining percentage corresponds to unidentified residues.

Nevertheless, this pathway constituted an improvement for the preparation of triaminopyrimidines. The regioselectivity problem was suppressed for secondary amines as pure products were obtained for the first substitution. Some important drawbacks remained with the aromatic amines which were still unreactive and the low conversion of the second displacement. As a result of the failure of this new approach, the first displacement reaction was performed on the less activated 6-chloro-2-methylsulfanylpyrimidine (**6**). Supposedly the second displacement would occur at the sulfone group on the 2-position generated after the first displacement. This time, complete conversion for the second reaction would be expected. The first displacement was thus realised at 140 °C or at refluxing temperature with neat amines (Scheme 6). Under these conditions, primary and secondary amines gave good yields and high purities were obtained (Table 6, entries 1 to 7).



Scheme 6. Substitution of the chlorine group on resin **6** by primary, secondary and arylamines: a) R^1R^2NH, 15 h, 140 °C; b) TFA, H_2O, CH_2Cl_2 (90:5:5), 3 h.

Table 6. HPLC and ES-MS analysis after amination of **6** by primary, secondary and arylamines.

Entry	R^1R^2NH	*T* [°C]	HPLC [%] **24**/**7**[f]	Product	RT [min]	MS $[M+H]^+$
1	benzylamine	140[a]	98/0	**24a**	11.1	247
2	pentylamine	104[b]	100/0	**24b**	11.9	227
3	cyclohexylamine	134[b]	100/0	**24c**	11.8	239
4	ethanolamine	140[a]	100/0	**24d**	7.4	201
5	2-methoxyethylamine	95[b]	68/0	**24e**	8.5	215
6	4-morpholineethylamine	150[b]	86/0	**24f**	6.8	270
7	piperidine	106[b]	100/0	**24g**	10.9	225
8	aniline	140[a]	5/95	**24h**	11.1	233
9	aniline	100[c]	45/55	**24h**	11.1	233
10	anisidine	100[c]	20/80	**24i**	11.2	263
11	aniline	100[d]	0/100	**24h**	11.1	233
12	aniline	140[e]	100/0	**24h**	11.1	233
13	anisidine	140[e]	1/67	**24i**	11.2	263

[a] Overnight heating in neat amine with minimum amount of NMP for swelling. [b] Overnight heating at refluxing temperature in neat amine with minimum amount of NMP for swelling. [c] Overnight heating with amine (20 equiv), NaO*t*Bu (20 equiv), $[Pd_2dba_3]$ (0.2 equiv), P(*o*Tol)$_3$ (0.8 equiv) in refluxing dioxane. [d] Same condition as [c] but without palladium. [e] Overnight heating with KO*t*Bu (20 equiv), [18]crown-6 (10 equiv) in a mixture of amine/NMP 75:25. [f] Remaining percentage corresponds to unidentified compounds.

Neat anilines at refluxing temperature failed to react (Table 6, entry 8). The conditions developed by Buchwald for palladium-catalysed amination[29, 30] afforded us some reaction but total conversion was never achieved even with stoichiometric amounts of palladium (Table 6, entries 9 and 10). In fact, better results were obtained with just potassium *tert*-butoxide and [18]crown-6 without the palladium affording

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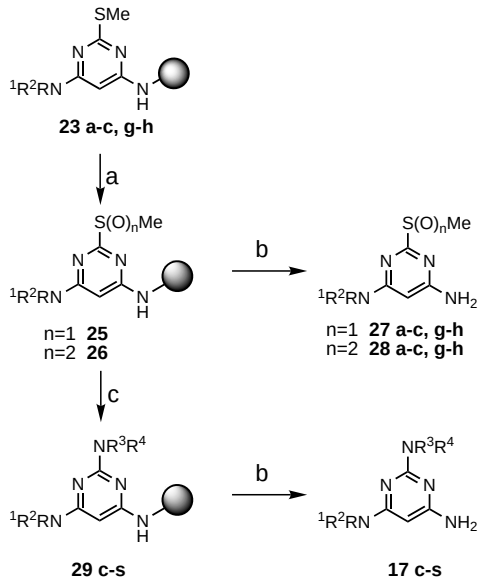
a quantitative transformation in one case (Table 6, entry 12). However, extrapolation towards other aniline derivatives was unsuccessful leading mainly to recovery of the starting material (Table 6, entry 13). Attempts at the oxidation of sulfide **23** were carried out with 10 equivalents of *m*CPBA in dioxane at room temperature. No starting material was recovered after 15 hours but the recovery of the sulfone **28** was found to be very low suggesting a loss of material during the oxidation reaction leading to premature cleavage or sensitivity to TFA. Rotella[31] recovered only modest yields of product after epoxidation of olefins loaded onto Wang linkers and suggested this was due to the oxidation sensitive nature of the linker.[32, 33] Specific oxidising agents such as sodium periodate were unsuccessful and starting material was entirely recovered. Magnesium monoperoxyphthalate (MMPP) was found to be the most versatile reagent and afforded the best compromise between the conversion of the sulfide and the minimisation of the sulfone formation (Scheme 7, Table 7). Attempts with 2.75 equivalents of MMPP for two hours at 0 °C afforded the best selectivity giving sulfoxide **27** (>79 %) and sulfone **28** (<15 %). A second cycle with one equivalent of MMPP at 0 °C for one hour permitted the consumption of all the starting material. In each case the sulfoxide was contaminated with sulfone but both would be displaced during the next reaction.

The second displacement was realised in neat amine at 140 °C or under reflux leading to the final triaminopyrimidine (**17**) in good purity (HPLC). Seventeen compounds were generated by parallel synthesis using 45 mg of resin **6** with a substitution of 0.60 mmol g^{-1}. Purification was performed by semipreparative RP-HPLC (Table 8).

We should note that after cleavage and the usual procedures (washing, freeze drying), the weight obtained for the crude products were considerably higher than expected (10 to 80 % higher). Monitoring at 254 nm gave good information for the conversion but was unable to detect the impurities thought to occur after prolonged exposure of the resin to 140 °C. Despite good analytical data (^{1}H, ^{13}C NMR, ES-MS, RP-HPLC) obtained after cleavage (Figure 3), a further purification step was required (silica gel column chromatography or semi-preparative RP-HPLC). Final overall yields were 11–52 % for the isolated products. These results can be considered as acceptable for a five-step synthesis with two steps at 140 °C on polystyrene resin. It should be noted that the support turns very dark in colour after each step performed at high temperature but still gave pure products.



Scheme 7. Formation of triaminopyrimidines **17** through oxidation of the methylsulfide group of resin **23** then amination: a) MMPP, EtOH/DMF 1:4, 2 h, 0 °C; b) TFA, H_2O, CH_2Cl_2 (90:5:5) 3 h; c) R^1R^2NH, 15 h, 140 °C.

Table 7. HPLC and ES-MS analysis of sulphoxides **27** and sulphones **28**.

R^1R^2NH	HPLC [%] **27**	HPLC [%] **27** + **28**	Product	RT [min]	MS $[M+H]^+$
benzylamine	80	90	**27a**	10.0	263
pentylamine	84	92	**27b**	10.6	243
cyclohexylamine	81	89	**27c**	10.3	255
piperidine	79	94	**27g**	9.5	241
aniline	86	95	**27h**	10.2	249

Table 8. Library of triaminopyrimidines **17**.

R^1R^2NH	R^3R^4NH	Product	RT [min]	MS $[M+H]^+$	HPLC [%][a]	Yield[b] [%]
piperidine	benzylamine	**17c**	13.4	284	88	28 (72 [c])
piperidine	pentylamine	**17d**	14.4	264	97	35
piperidine	ethanolamine	**17e**	11.0	252	>98	27
piperidine	4-(2-aminoethyl)morpholine	**17f**	8.5	307	82	40
piperidine	piperidine	**17g**	12.8	262	98	28
piperidine	pyrrolidine	**17h**	12.3	248	96	35
benzylamine	pentylamine	**17i**	13.9	286	92	52
benzylamine	ethanolamine	**17j**	9.8	260	44	11
benzylamine	benzylamine	**17k** = **16a**	13.1	306	90	21
benzylamine	cyclohexylamine	**17l** = **16e**	13.9	298	65	28
pentylamine	piperidine	**17m**	13.4	264	89	31
pentylamine	pyrrolidine	**17n**	12.7	250	89	21
pentylamine	cyclohexylamine	**17o**	14.7	278	72	44
cyclohexylamine	pentylamine	**17p**	14.7	278	78	22
cyclohexylamine	2-methoxyethanolamine	**17q**	11.6	266	71	14
cyclohexylamine	pyrrolidine	**17r**	12.6	262	94	32
cyclohexylamine	piperidine	**17s**	13.4	276	96	25

[a] HPLC Purity after cleavage from the solid support. [b] Overall yield of isolated compound after semipreparative HPLC calculated from resin **5**. [c] Yield of isolated compound after silica gel flash chromatography calculated from resin **5**.

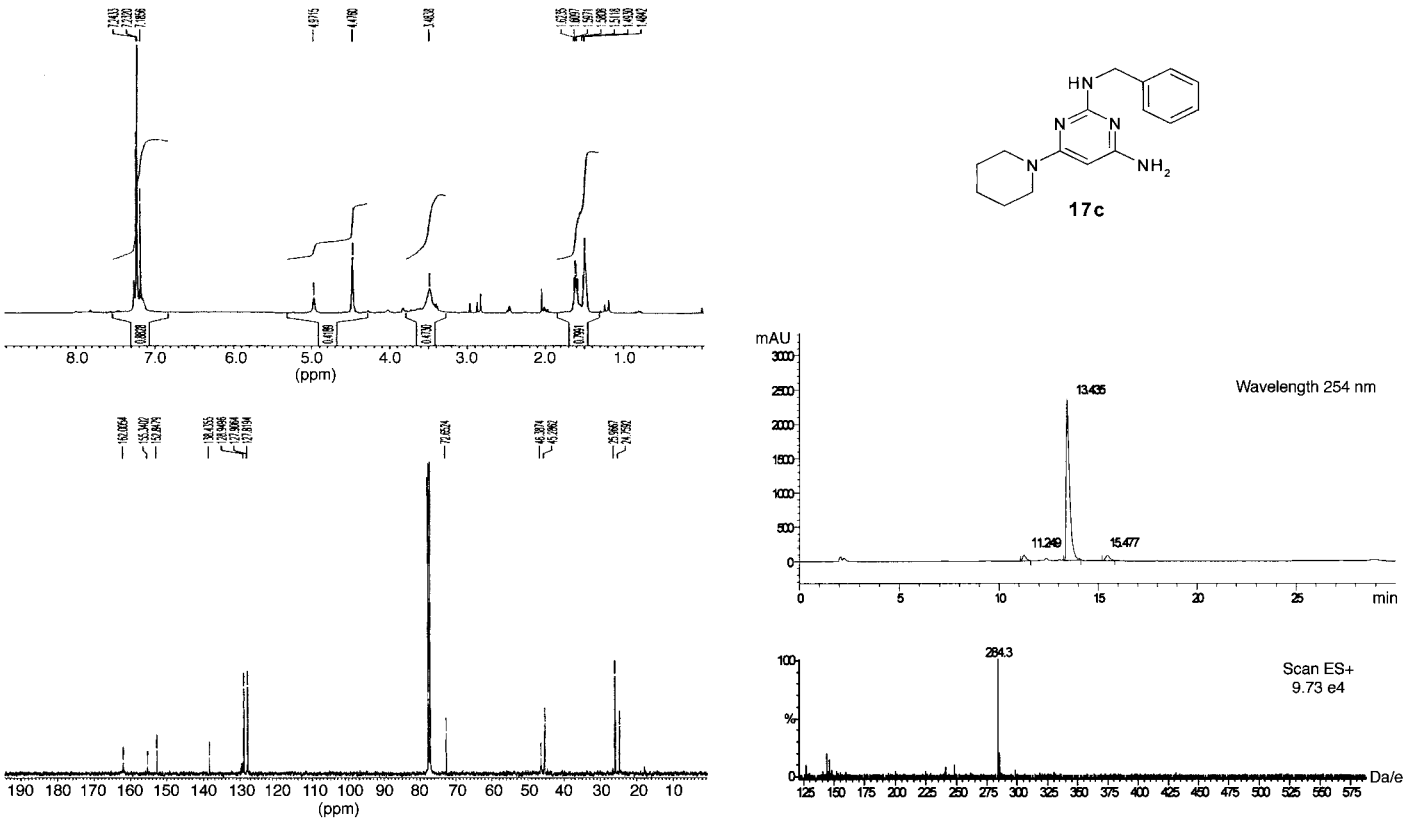


Figure 3. Analytical data (^{1}H, ^{13}C NMR, RP-HPLC, ES-MS) for compound **17c** obtained after cleavage from the solid support, prior to purification.

Conclusion

Methods have been developed for the solid-phase synthesis of 2,4,6-triaminopyrimidines through displacement reactions on deactivated pyrimidines. Extensive studies on the reactivity of a number of methylsulfonylaminopyrimidines and chloroaminopyrimidines towards nucleophilic displacements were carried out. The reactivity of the pyrimidine template functionalised with leaving groups in the 2- and 6-positions towards displacement varied in an unusual manner, with the electrophilic centre having greater importance than leaving group ability. The functionalisation of the pyrimidine was finally achieved with 6-chloro-2-methylsulfonyl activation. Two successive functionalisations by primary and secondary amines were regio- and chemoselective. The use of high temperatures (up to 140 °C) was not observed to be a limiting factor and allowed the preparation of triaminopyrimidines through nucleophilic substitution reactions. In one case, aniline successfully displaced the chlorine group of the resin bound 4-amino-6-chloro-2-methylsulfanylpyrimidine but extrapolation to other aryl amine derivatives failed. Using this methodology, seventeen 2,4,6-triaminopyrimidines have been prepared validating this synthetic strategy.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300, Bruker AM-360 or Bruker DPX-400 spectrometers. The chemical shifts are reported in ppm (δ) and were referenced to residual protonated solvent resonances. Mass spectra were obtained on a VG platform single quadrupole mass spectrometer in electrospray positive ionisation mode ES-MS or electronic impact EI-MS. Analytical RP-HPLC was performed on a Hewlett Packard HP 1100 chemstation equipped with a Phenomenex Prodigy reverse phase C18 column (150 × 3 mm) with a flow rate of 0.5 mL min^{-1}, monitoring at 254 nm and eluting with A) 0.1 % TFA in water and B) 0.042 % TFA in MeCN, gradient 0 % B to 100 % B in 20 min. Preparative HPLC was performed using a Luna C8 (60 × 21.2 mm) reverse-phase column with a flow rate of 20 mL min^{-1}, detection at 220 and 254 nm with a diode array detector and eluting with A) water and B) MeCN, gradient 10 % B to 95 % B in 4.5 min. Infra-red spectra were recorded on a Bio-Rad FTS 135 spectrometer equipped with the Golden Gate Single Reflection Diamond ATR. Starting materials were used as received. 4-Chloromethylated polystyrene resin (Merrifield resin) 200 – 400 mesh, substitution 1.34 mmol g^{-1} was obtained from Novabiochem. Room temperature small-scale (< 250 mg of resin) reactions as well as resin washing and drying procedures were carried out by using polypropylene filtration tubes (1, 3 or 6 mL) with polyethylene frits and a Visiprep solid-phase extraction vacuum manifold supplied by Supelco. Cleavage reactions for HPLC analysis were performed on approximately 5 mg of resin in polypropylene 1.9 mL microcentrifuge tubes (Eppendorf) and agitating with a blood-tube rotator SB1. Other reactions were performed in round-bottom flask with magnetic stirring carried out at the lowest speed.

General procedure for cleavage reactions: Resin (50 mg) was swollen in CH_2Cl_2 (250 μL). A solution of trifluoroacetic acid in water 95:5 (4.75 mL) was added and the mixture stirred for 3 hours at room temperature. The suspension was filtered, and the resin was washed with CH_2Cl_2 (2 × 5 mL), CH_3CN (2 × 5 mL) then CH_2Cl_2 (2 × 5 mL). The filtrates were combined and the solvents evaporated under reduced pressure. The residue was then taken up in a acetonitrile/water solution (2 mL, 1:1) then freeze-dried overnight. The resulting residue was then purified by silica gel chromatography or semi-preparative RP-HPLC.

Resin-bound 6-chloro-2-methylsulfanylpyrimidine (**6**): Resin **5** (4.01 g, 0.73 mmol g^{-1} loading, 2.93 mmol) was swollen in DMF (75 mL) for 30 min. 4,6-Dichloro-2-methylthiopyrimidine (**4**) (2.84 g, 14.6 mmol), tetra-*n*-butylammonium bromide (1.84 g, 5.7 mmol) and diisopropylethylamine (5.1 mL, 29.3 mmol) were added and the mixture gently stirred and heated overnight

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at 90 °C. The resin was then filtered, washed thoroughly with DMF (2 × 40 mL), CH_2Cl_2 (2 × 40 mL), MeOH (2 × 40 mL), DMF (2 × 40 mL), CH_2Cl_2 (2 × 40 mL), MeOH (2 × 40 mL) then Et_2O (2 × 40 mL). The resin was predried by passing air through the filter tube which was then placed under high vacuum. A negative ninhydrin test indicated full substitution. 4.33 g of resin **6** were obtained.

4-Amino-6-chloro-2-methylsulfanylpyrimidine (**7**): Cleavage from resin **6** (100 mg, 0.51 mmol g^{-1} loading, 0.051 mmol) and purification by silica gel chromatography (ethyl acetate/petroleum ether 1:1, $R_f = 0.69$) afforded white crystals of **7** (8 mg, 89 % yield from resin **5**). M.p. 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.16$ (s, 1 H, H^5), 5.00 (br s, 2 H, NH_2), 2.51 (s, 3 H, SCH_3); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 173.0$ (C^4), 165.7 (C^2), 159.1 (C^6), 99.4 (C^5), 13.9 (SCH_3); HR-MS EI-MS: $C_5H_6N_3S^{35}Cl$ $[M]^+$ calcd 174.9971, found 174.9964; analytical RP-HPLC, RT = 12.1 min, purity crude product before purification > 95 %.

Resin-bound 2-methylsulfanyl-6-piperidinopyrimidine (**23 g**): Resin **6** (130 mg, 0.51 mmol g^{-1} loading, 0.066 mmol) was swollen in the minimal amount of *N*-methylpyrrolidinone (1.5 mL) for 30 min. Piperidine (4 mL) was added and the mixture was stirred gently and refluxed overnight. The resin was then filtered, washed thoroughly with DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL) then Et_2O (2 × 5 mL). The resin was predried by passing air through the filter tube which was then placed under high vacuum. Resin **23 g** was obtained with a theoretical loading of 0.50 mmol g^{-1}.

4-Amino-2-methylsulfanyl-6-piperidinopyrimidine (**24 g**): Cleavage of resin **23 g** (126 mg, 0.50 mmol g^{-1} loading, 0.063 mmol) and purification by silica gel chromatography (ethyl acetate/petroleum ether 1:1, $R_f = 0.43$) afforded **24 g** as white crystals (11 mg, 78 % yield from resin **5**). M.p. 122 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.30$ (s, 1 H, H^5), 4.51 (br s, 2 H, NH_2), 3.54 (t, 4 H, $J = 5.2$ Hz, CH_2), 2.51 (s, 3 H, SCH_3), 1.62 (m, 6 H, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 170.0$ (C^6), 163.3 (C^4), 162.5 (C^2), 78.8 (C^5), 45.3 (CH_2), 25.6 (CH_2), 24.8 (CH_2), 14.1 (SCH_3); ES-MS: *m*/*z* (%): 225.1 $[M+H]^+$ (100); HR-MS EI-MS: $C_{10}H_{16}N_4S$ $[M]^+$ calcd 224.1086, found 224.1096; analytical RP-HPLC, RT = 10.9 min, purity crude product before purification: 100 %.

Resin-bound 2-methylsulfinyl-6-piperidinopyrimidine (**25 g**): Resin **23 g** (500 mg, 0.50 mmol g^{-1} loading, 0.25 mmol) was swollen in DMF (20 mL) for 30 min. The mixture was cooled to 0 °C and a solution of magnesium monoperoxyphthalate (MMPP) (212 mg, 0.34 mmol) in DMF (5 mL) was added dropwise and stirring continued for two hours at 0 °C. After the resin was washed and dried in usual manner, the product of a small aliquot of resin (5 mg) was cleaved off. RP-HPLC analysis indicated that 6 % starting material remained and a new oxidation cycle was performed with MMPP (0.14 mmol) for one hour at 0 °C. Analysis showed the total conversion of resin **23 g** into a mixture of sulfoxide **27 g** (79 %) and sulfone **28 g** (15 %). The theoretical loading of resin **25 g** (based on the sulfoxide) was 0.50 mmol g^{-1}.

Resin-bound 2-benzylamino-6-piperidinopyrimidine (**29 c**): Resin **25 g** (130 mg, 0.50 mmol g^{-1} loading, 0.065 mmol) was swollen in the minimal amount of *N*-methylpyrrolidinone (1.5 mL) for 30 min. Benzylamine (4 mL) was added and the mixture was stirred and heated overnight at 140 °C. The resin was then filtered, washed thoroughly with DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL) then Et_2O (2 × 5 mL). The resin was predried by passing air through the filter tube which was then placed under high vacuum. Resin **29 c** was obtained with a loading of 0.49 mmol g^{-1}.

4-Amino-2-benzylamino-6-piperidinopyrimidine (**17 c**): Cleavage of resin **29 c** (110 mg, 0.49 mmol g^{-1} loading, 0.054 mmol) and purification by silica gel chromatography (ethyl acetate/petroleum ether 1:1, $R_f = 0.14$) afforded **17 c** as pale brown foam (11 mg, 72 % yield from resin **5**). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$ (m, 5 H, Bn), 4.97 (s, 1 H, H^5), 4.48 (d, 2 H, $J = 5.9$ Hz, CH_2Bn), 3.48 (m, 4 H, CH_2), 1.48–1.62 (m, 6 H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 162.0$ (C^6), 155.3 (C^2), 152.8 (C^4), 72.6 (C^5), 46.4 (CH_2-Bn), 45.3 (CH_2), 25.9 (CH_2), 24.8 (CH_2); ES-MS: *m*/*z* (%): 284.3 $[M+H]^+$ (100); HR-MS EI-MS: $C_{16}H_{21}N_4Cl^{35}$ $[M]^+$ calcd 283.1797, found 283.1794; analytical RP-HPLC, RT = 13.4 min, purity crude product before purification: 88 %.

Resin-bound 6-chloro-2-methylsulfonylpyrimidine (**8**): Resin **6** (250 mg, 0.73 mmol g^{-1} loading, 0.182 mmol) and dioxane (3 mL) was swollen for 30 min. A solution containing 70 % *meta*-chloroperbenzoic acid (*m*CPBA) (448 mg, 1.8 mmol), 1 M aqueous NaOH (1.8 mL, 1.8 mmol) in dioxane (3 mL) was added at room temperature and the mixture stirred gently overnight. The resin was then filtered, washed thoroughly with DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL) then Et_2O (2 × 5 mL). The resin was predried by passing air through the filter tube which was then placed under high vacuum. Resin **8** was obtained with a loading of 0.71 mmol g^{-1}.

Resin-bound 2-benzylamino-6-chloropyrimidine (**12 a**): A 6 mL polypropylene filtration tube fitted with polyethylene frit was charged with resin **8** (120 mg, 0.71 mmol g^{-1} loading, 0.085 mmol) and CH_2Cl_2 (3 mL) added for 30 min. CH_2Cl_2 was removed by filtration and replaced by benzylamine (4 mL). The mixture was then shaken overnight at room temperature. The resin was filtered, washed thoroughly with DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL) then Et_2O (2 × 5 mL) and finally dried by passing air through the resin. Resin **12 a** was obtained with a loading of 0.70 mmol g^{-1}.

4-Amino-2-benzylamino-6-chloropyrimidine (**14 a**): Cleavage of resin **12 a** (120 mg, 0.70 mmol g^{-1} loading, 0.084 mmol) and purification by silica gel chromatography (ethyl acetate/petroleum ether 1:1, $R_f = 0.65$) afforded **12 a** as a white oil (15 mg, 76 % yield from resin **5**). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.28$ (m, 5 H, Bn), 5.78 (s, 1 H, H^5), 5.40 (br s, 1 H, NH_2), 4.72 (br s, 2 H, NH_2), 4.53 (d, 2 H, $J = 5.9$ Hz, CH_2Bn); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 165.6$ (C^4), 158.9 (C^2), 154.5 (C^6), 137.8 (CH-Bn), 130.1 (CH-Bn), 129.3 (CH-Bn), 129.2 (CH-Bn), 95.2 (C^5), 46.5 (CH_2-Bn); ES-MS: *m*/*z* (%): 235.1 $[M+H]^+$ (100); HR-MS EI-MS: $C_{11}H_{11}N_4Cl^{35}$ $[M]^+$ calcd 234.0672, found 234.0669; analytical RP-HPLC, RT = 11.6 min, purity crude product before purification > 95 %.

Resin-bound 2,4-bismethylsulfanylpyrimidine (**18**): Resin **6** (350 mg, 0.73 mmol g^{-1} loading, 0.255 mmol) was swollen in DMF (4 mL) for 30 min. A solution containing sodium thiomethoxide (537 mg, 7.67 mmol), [15]crown-5 (50 μL, 0.255 mmol) ethanol (4 mL) and DMF (12 mL) were added and the mixture heated overnight at 130 °C. The resin was filtered upon cooling, washed thoroughly with DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL), water (2 × 5 mL), DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), MeOH (2 × 5 mL) then Et_2O (2 × 5 mL). The resin was predried by passing air through the filter tube which was then placed under high vacuum. Resin **18** was obtained with a loading of 0.72 mmol g^{-1}.

4-Amino-2,6-bismethylsulfanylpyrimidine (**19**): Cleavage of resin **18** (115 mg, 0.72 mmol g^{-1} loading, 0.083 mmol) and purification by silica gel chromatography (ethyl acetate/petroleum ether 1:1, $R_f = 0.77$) afforded **19** as white crystals (11 mg, 71 % yield from resin **5**). M.p. 101 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.92$ (s, 1 H, H^5), 4.71 (br s, 2 H, NH_2), 2.45 (s, 3 H, SCH_3), 2.42. (s, 3 H, SCH_3); ES-MS: *m*/*z* (%): 188.0 $[M+H]^+$ (100); HR-MS EI-MS: $C_6H_9N_3S_2$ $[M]^+$ calcd 187.0238, found 187.0226; analytical RP-HPLC, RT = 8.8 min, purity crude product before purification > 95 %.

4-Chloro-6-diphenylmethylamino-2-methylsulfanylpyrimidine (**10**): Triethylamine (3.6 mL, 25.8 mmol) was added to a stirred suspension of aminodiphenylmethane hydrochloride salt (1.69 g, 7.7 mmol) in acetonitrile (20 mL). This solution was added dropwise onto a solution of 4,6-dichloro-2-thiomethyl-pyrimidine (**4**) (1 g, 5.13 mmol) in acetonitrile (20 mL). The reaction mixture was refluxed for 24 hours. Solvents were removed under reduced pressure and water (30 mL) was added. The solution was acidified with 2 M potassium hydrogenosulfate then extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried over magnesium sulfate and concentrated to afford a crude product which was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:9, $R_f = 0.50$) to give **10** as white crystals (1.34 g, 75 %). M.p. 120 °C; IR (neat) $\tilde{\nu} = 3331$ (NH), 1555 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 8.66$ (d, 1 H, $J = 8$ Hz, NH), 7.29 (m, 10 H, H^{arom}), 6.43 (s, 1 H, H^5), 6.33 (d, 1 H, $J = 7.4$ Hz, CH(arom)$_2$), 2.28 (s, 3 H, SCH_3); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta =$ 171.3 (C^4), 161.8 (C^2), 156.8 (C^6), 142.1 (CH-Bn), 128.6 (CH-Bn), 127.4 (CH-Bn), 127.3 (CH-Bn); 99.5 (C^5), 58.0 (CH(arom)$_2$), 13.5 (SCH_3); ES-MS: *m*/*z* (%): 342.0 $[M+H]^+$ (100); HR-MS EI-MS: $C_{18}H_{16}N_3S^{35}Cl$ $[M]^+$ calcd 341.0754, found 341.0736; analytical RP-HPLC, RT = 20.3 min.

4-Chloro-6-diphenylmethylamino-2-methylsulfonylpyrimidine (**11**): 50 % *m*-Chloroperbenzoic acid (3.78 g, 10.96 mmol) was added to a solution of 4-chloro-6-diphenylmethylamino-2-methylsulfanylpyrimidine (**10**)

(750 mg, 2.2 mmol) in CH_2Cl_2 (50 mL). The solution was stirred two hours at room temperature before adding an aqueous solution of 10% $Na_2S_2O_3$. The organic layer was then washed with an aqueous solution of 10% $Na_2S_2O_3$ (2×25 mL) then 1M $NaHCO_3$ (3×25 mL). The aqueous layer were combined and extracted with CH_2Cl_2 (3×50 mL). The organic layers were finally combined, dried over magnesium sulphate and concentrated to afford a crude product which was purified by silica gel column chromatography (ethyl acetate/petroleum ether 3:7, $R_f = 0.30$) to obtain **11** as a white foam (0.73 g, 89%). M.p. 156 °C; IR (neat) $\tilde{\nu} = 3331$ (NH), 1575 (C=N), 1138 (S=O) cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO): $\delta = 9.32$ (d, 1H, $J =$ 8 Hz, NH), 7.35 (m, 10H, H^{arom}), 7.02 (s, 1H, H^5), 6.35 (d, 1H, $J = 7.4$ Hz, $CH(arom)_2$), 3.13 (s, 3H, SO_2CH_3); ^{13}C NMR (75.5 MHz, [D_6]DMSO): $\delta =$ 168.8 (C^4), 165.2 (C^2), 162.6 (C^6), 141.4 (CH-Bn), 128.7 (CH-Bn), 127.5 (CH-Bn), 127.4 (CH-Bn), 106.5 (C^5), 58.4 ($CH(arom)_2$), 38.5 (SO_2CH_3); ES-MS: m/z (%): 374.0 $[M+H]^+$ (100); HR-MS EI-MS: $C_{18}H_{16}N_3O_2S^{35}Cl$ $[M]^+$ calcd 373.0652, found 373.0654; analytical RP-HPLC, RT = 17.1 min.

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