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Regioselective 4-amino-de-chlorination of trichloro- and dichloro-pyrimidines with *N*-sodium carbamates

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Abstract—4-*N*-Alkoxycarbonylamino-2,6-dichloro- and -2-chloro-pyrimidines have been synthesized in good to excellent regioselectivity and yields from *N*-sodium carbamates and, respectively, 2,4,6-trichloropyrimidine and 2,4-dichloropyrimidine, in DMF, rt, 15–30 min. The reaction is effective also with 4,6-dichloropyrimidine, producing 4-*N*-alkoxycarbonylamino-6-chloropyrimidines in good yields. Some conformational features of 4-*N*-alkoxycarbonylamino-2,6-dichloro-pyrimidines have been investigated by X-ray diffraction and ^{1}H NMR spectroscopy. © 2002 Published by Elsevier Science Ltd.

1. Introduction

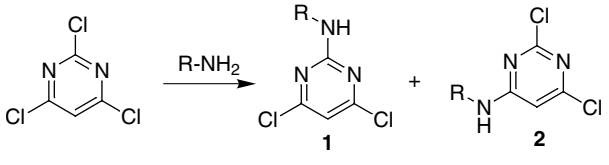
Aminopyrimidines are biologically important molecules and valuable heterocyclic nuclei for the design of pharmaceutical agents.[1] Recently, we undertook a research programme aiming at the synthesis of *N*-alkoxycarbonyl-amino-chloropyrimidines from commercially available chloropyrimidines, such as 2,4,6-trichloropyrimidine (TCP), 2,4-dichloropyrimidine (2,4-DCP) and 4,6-dichloro-pyrimidine (4,6-DCP). Desired properties of this synthesis include: high regioselectivity, high yields, general applic-ability, extreme experimental simplicity, and one-pot intro-duction of the protected amine function. Surprisingly, an overview of the literature revealed that a general and efficient methodology to prepare *N*-alkoxycarbonylamino chloropyrimidines was not available.[2] Herein, we describe in full details a tailor-made procedure, featuring all the above-mentioned requirements, to perform the one-step synthesis of 4-*N*-alkoxycarbonylamino-2,6-dichloro-, 2-chloro-, and 6-chloro-pyrimidines from, respectively, TCP, 2,4-DCP, 4,6-DCP and the corresponding carbamates.[3,4]

2. Results and discussion

The known approach to 4-*N*-alkoxycarbonylamino-2,6-dichloropyrimidines is in two steps: aromatic nucleophilic substitution (S_NAr) of TCP with free amines, followed by *N*-alkoxycarbonylation. Unfortunately, the former step is generally not regioselective, as witnessed by literature data as well as by our own experience.[5] In fact, ammonia[6a] and alkylamines, like benzylamine,[6b] cyclopropylamine and ethanolamine,[6c] invariably provide nearly equimolar ratios of the two possible regioisomers **1** and **2** (Scheme 1), under different experimental conditions. Interestingly, anilines give rise to a regioselective chlorine displacement in polar solvents such as ethanol, producing the corresponding 4-anilino-2,6-dichloropyrimidines, although we and others[3,7] noticed that replacement of ethanol with benzene or other low-polarity solvents induces a dramatic drop of regioselectivity.[8]

Similar results were observed for the much less studied amino-de-chlorination of 2,4-DCP which appears to be only moderately stereoselective toward the formation of the 4-amino-isomer.[9,10]

Concerning the second step, our experiments supported by analogous literature reports[11] evidenced that *N*-acylation of



Scheme 1.

Keywords: pyrimidines; carbamates; amination; regioselection.

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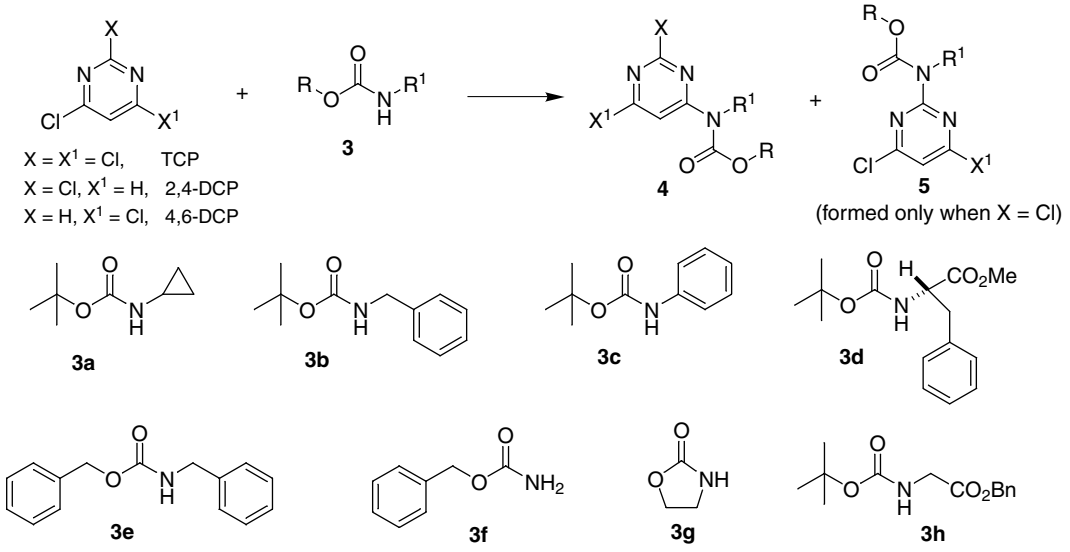
aminodichloropyrimidines under standard conditions (acyl or alkoxycarbonyl chloride, pyridine, CH_2Cl_2) is unsatisfactory, due to the low nucleophilicity of the amine functions.

We therefore turned our attention to the reaction of chloropyrimidines with carbamates (Scheme 2 and Table 1). To the best of our knowledge, a single example of nucleophilic heteroaromatic substitution of chlorine by action of a *N*-metalated carbamate has been described,[12] therefore, almost no data on the feasibility, regioselectivity and synthetic potential of this reaction were available at the beginning of our study. Satisfactorily, this approach proved to be very efficient, operatively simple, regio- and chemoselective (since *O*-substitution was never found to be competitive), and provided some modification, compatible with solid-phase chemistry.[4]

2.1. Reactions with TCP

Portion-wise addition of solid NaH (60%) (usually 1.1 equiv., see Table 1) to an equimolar mixture of carbamate **3** and TCP in dry DMF at rt afforded in all cases high yields of the corresponding 4-alkoxycarbonylamino-2,6-dichloropyrimidines **4** within 15–30 min. (Table 1). The method is general, as witnessed by the fact that alkylamino, arylamino and even ammonia-derived carbamates, underwent reaction smoothly. *N*-sodium carbamates of alkylamines **3a**,**b**,**e** (entries 1,5,8), ammonia **3f** (entry 9) and



Scheme 2.

Table 1. Reaction of 2,4,6-trichloropyrimidine with *N*-sodium carbamates (**3**)

Entry	Product	Carbamate	X	X^1	Ratio 4/5[a]	Yields (%)[b]	Conditions[c]
1	**4,5a**	**3a**	Cl	Cl	88:12	97.6	NaH (1.1 equiv.), DMF, rt
2	**4,5a**	**3a**	Cl	Cl	91:9	66[a]	KO-*tert*-Bu, DMF, rt[d]
3	**4,5a**	**3a**	Cl	Cl	50:50	33[a]	NaH (1.1 equiv.), THF, rt, 16 h[d]
4	**4,5a**	**3a**	Cl	Cl	88:12	87.8	NaH (1.1 equiv.), DMF, −25°C to rt, 1.5 h
5	**4,5b**	**3b**	Cl	Cl	92:8	76.0	NaH (1.1 equiv.), DMF, rt
6	**4,5c**	**3c**	Cl	Cl	95:5	99.8	NaH (1.1 equiv.), DMF, rt
7	**4,5d**	**3d**	Cl	Cl	91:9	99.9	NaH (1.0 equiv.), DMF, rt
8	**4,5e**	**3e**	Cl	Cl	86:14	80[a]	NaH (1.1 equiv.), DMF, rt, 1 h
9	**4,5f**	**3f**	Cl	Cl	74:26	94.3	NaH (2.2 equiv.), DMF, rt
10	**4,5g**	**3g**	Cl	Cl	80:20	74.0	NaH (1.1 equiv.), DMF, rt
11	**4,5g**	**3g**	Cl	Cl	83:17	82[a]	Cs_2CO_3 (1 equiv.), DMF, rt, 22 h
12	**4,5g**	**3g**	Cl	Cl	32:68	48.8	NaH (1.1 equiv.), THF, rt, 1 h
13	**4,5g**	**3g**	Cl	Cl	>10:1	<20[a]	*n*-BuLi (1.0 equiv.), THF, 0°C to rt, 2 h[d]
14	**4,5h**	**3b**	Cl	H	92:8	21	NaH (1.1 equiv.), DMF, rt, 3 h
15	**4,5i**	**3c**	Cl	H	95:5	73	NaH (1.1 equiv.), DMF, rt, 3 h
16	**4,5j**	**3f**	Cl	Cl	60:40	62	NaH (2.2 equiv.), DMF, rt, 3 h
17	**4,5k**	**3g**	Cl	Cl	86:14	>98[a]	NaH (1.1 equiv.), DMF, rt, 3 h
18	**4,5l**	**3h**	Cl	Cl	>95:5	26	NaH (1.1 equiv.), DMF, rt, 3 h
19	**4m**	**3b**	H	Cl	Only **4**	28	NaH (1.1 equiv.), DMF, rt, 3 h
20	**4n**	**3c**	H	Cl	Only **4**	61	NaH (1.1 equiv.), DMF, rt, 3 h
21	**4o**	**3g**	H	Cl	Only **4**	>98[a]	NaH (1.1 equiv.), DMF, rt, 3 h

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Overall isolated yields, unless otherwise stated.
[c] Reaction time 15–30 min, unless otherwise stated.
[d] Several unidentified by-products formed (^{1}H NMR of the crude mixture).

ethanolamine **3g** (entry 10) added regioselectively to 2,4,6-trichloropyrimidine, in contrast with the parent free amines (see Ref. 3). A very efficient reaction was also achieved with aniline carbamate **3c** (entry 6). A functionalised and chiral non-racemic carbamate, like *N*-Boc-L-phenylalanine methyl ester **3d** (entry 7), afforded remarkably good results as well.[13] Different alkoxycarbonyl residues were tested, namely Boc (**3a**–**d**), Cbz (**3e**,**f**) and the oxazolidinone (**3g**). The best results, both in terms of yields and in terms of regioselectivity, were obtained with Boc-carbamates. The influence of several experimental parameters like solvent, temperature and counter-ion was investigated.

Use of THF (entries 3,12,13) instead of DMF produced much slower reactions and lower yields. Below 0°C no reaction was observed; moreover, the regioselectivity was found to be independent of the temperature (entry 4). Interestingly, the regiocontrol was found to be superior with K^+ (entry 2), Li^+ (entry 13) and Cs^+ (entry 11) as counter-ions. Unfortunately, a remarkable drop of yields was experienced in the first two cases. Good yields were obtained in the case of Cs^+, but the longer reaction time and the high cost of Cs_2CO_3 as compared with NaH, represent two drawbacks of this protocol.[14] Attempts to employ $EtN(i\text{-}Pr)_2$ as base in the reaction of TCP with **3f** (benzene, 20 h, reflux) did not afford any detectable amount of the corresponding products **4**,**5f**. The order of addition of reagents and substrates was also found to play an important role. Slow addition of TCP to preformed *N*-sodium carbamate **3e** afforded a complex mixture of products, containing minor amounts of **4**,**5e**. Otherwise, inverse addition of *N*-sodium **3e** to TCP gave rise to a clean but largely incomplete formation of **4**,**5e**. Disappointingly, attempts to react TCP with δ-valerolactam using NaH or Cs_2CO_3 under the optimised conditions afforded intractable mixtures of products.

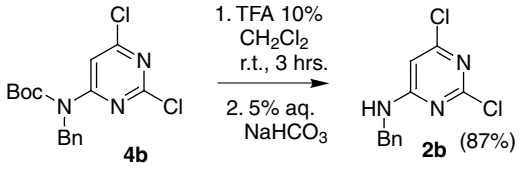
2.2. Reactions with 2,4-DCP

Although less reactive than TCP due to the presence of just two chlorine substituents, 2,4-DCP was nonetheless found to be a suitable substrate for the 4-amino-de-chlorination by sodium-carbamates (Scheme 2 and Table 1, entries 14–18). In fact, good to excellent regioselection was observed with carbamates **3b**,**c**,**f**,**g**,**h** using the optimised conditions [NaH (1.1 equiv.), DMF, rt], but good yields were obtained only for the formation of **4i**,**j**,**k**, while the reactions leading to **4h** and **l** were slow and still largely incomplete after 3 h at rt.

2.3. Reactions with 4,6-DCP

A reactivity comparable with that of 2,4-DCP was found for 4,6-DCP, but in this case, obviously a single product **4** could form. Thus, good yields were obtained for the reactions with *N*-sodium carbamates derived from **3c** and **g** (entries 20 and 21), leading to **4n** and **o**, but slow reaction and low conversion was achieved in the formation of **4m** from **3b** (entry 19).

Since Boc and Cbz are easily removable protecting groups, the present methodology also represents a useful and regioselective protocol to the synthesis of *N*-monosubstituted 4-amino-chloropyrimidines. Indeed, treatment of **4b** with trifluoroacetic acid produced 4-benzylamino-2,6-dichloropyrimidine in 87% yield (Scheme 3).



Scheme 3.

2.4. Structural features of 4-alkoxycarbonylamino-chloropyrimidines

An important structural feature of 4-*N*-alkoxycarbonyl-amino 2,6-dichloropyrimidines **4** is the presence of an intramolecular C–H···O hydrogen bond, involving the pyrimidine-ring hydrogen and the carbonyl oxygen, in the solid-phase,[15] as clearly shown by X-ray diffraction of suitable single crystals of the oxazolidin-2-one derivative **4g**. A view of **4g** is shown in Fig. 1 and selected molecular dimensions are reported in Table 2. Bond lengths and angles fall in the expected range.[16] The molecules shown in Fig. 1 are not related by any symmetry operation. In both the molecules, the presence of an intramolecular hydrogen bond involving, respectively, O(2) and H(5) (O···H 2.257 Å; O···H–C 119.3°), and O(4) and H(10) (O···H 2.278 Å; O···H–C 118.5°) is evident.

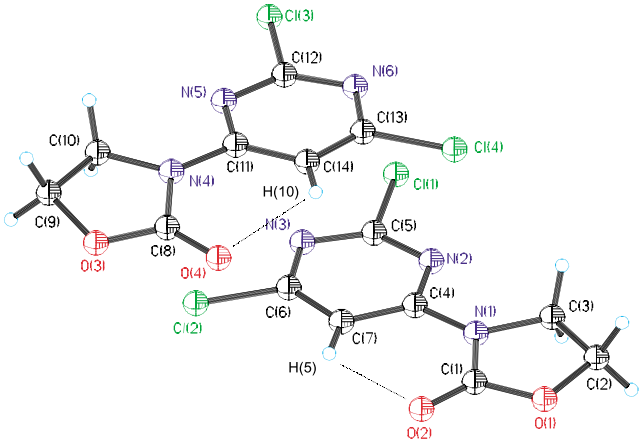


Figure 1. ORTEP view of **4g** showing the atomic labelling scheme. 30% Thermal ellipsoid for non-hydrogen atoms are shown.

Table 2. Selected molecular dimensions of **4g**

Bond lengths (Å)		Bond angles (°)	
N(1)–C(1)	1.365(5)	N(1)–C(1)–O(1)	109.4(3)
N(1)–C(3)	1.471(4)	N(1)–C(1)–O(2)	128.3(3)
N(1)–C(4)	1.376(4)	O(1)–C(1)–O(2)	122.2(4)
N(4)–C(8)	1.393(5)	N(4)–C(8)–O(3)	108.9(4)
N(4)–C(10)	1.466(4)	N(4)–C(8)–O(4)	126.1(4)
N(4)–C(11)	1.381(4)	O(3)–C(8)–O(4)	124.9(4)
C(1)–O(1)	1.346(4)		
C(1)–O(2)	1.196(4)		
C(8)–O(3)	1.330(5)		
C(8)–O(4)	1.199(5)		

The same rotamers with *s-trans* arrangement between the oxazolidinone C═O and the pyrimidine C═N seem to be predominant in $CDCl_3$ solution, as a likely result of highly unfavourable C═O/C═N dipole interactions affecting the *s-cis* conformation. Note added in proof: we thank the referee who suggested to us this hypothesis. In fact, ^{1}H NMR of **4** showed that the H-5 signals are extraordinarily down-field shifted with respect to the parent molecules **2**,[3–8] ranging from 7.79 (**4a**) to 8.21 ppm (**4g**), with a $\Delta\delta$ ranging from 1.17 to 1.91 ppm (for **4a** and **e**, respectively) (Section 3). Such a huge effect cannot be ascribed solely to the presence of the moderately electron-withdrawing (EW) *N*-alkoxycarbonyl group,[17] but is likely due to the deshielding anisotropic effect exerted on H-5 by the nearly planar C═O.[18] An additional stabilising effect due to a weak H-bond similar to that observed in the crystal structure cannot be a priori ruled out.

In summary, a regioselective, high yielding and practical 4-amino-de-chlorination of 2,4,6-trichloropyrimidine, 2,4- and 4,6-dichloropyrimidine has been disclosed and optimised. Its application for the combinatorial synthesis of a library of aminopyrimidines as well as its extension to other activated aromatic and heteroaromatic chlorides is currently in progress.

3. Experimental

3.1. General

Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Coupling constants (*J*) are reported in Hertz (Hz). Me_4Si was used as internal standard (δ_H and δ_C=0.00) for ^{1}H and ^{13}C nuclei, for ^{19}F nuclei as external standard (δ_F=162.90) for ^{19}F nuclei. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; etc. Anhydrous solvents were obtained by distillation from sodium (THF, benzene) or from calcium hydride (dichloromethane, diisopropylamine). In all other cases, commercially available reagent-grade solvents were employed without purification. Reactions performed in dry solvents were carried out under nitrogen atmosphere. Melting points are uncorrected and were obtained on a capillary apparatus. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230–400 ASTM mesh) was employed for flash chromatography (FC).

3.2. General procedure for the synthesis of 4,5

A solution of chloropyrimidine (1 mmol) and *N*-alkoxycarbonyl-amine **3** (1 mmol), in 5 ml of dry DMF, was treated with sodium hydride (1.1 mmol) (60% dispersion in mineral oil). The resultant mixture was stirred at rt for the appropriate time (Table 1), quenched with a saturated aqueous NH_4Cl solution and extracted in ether or ethyl acetate. The collected organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The solid products were purified by flash chromatography and then crystallised from the appropriate hot solvent or mixture of solvents. Yields are reported in Table 1. Some of the minor 2-aminopyrimidines **5** could not be isolated and characterized, but some of their signals could be observed by ^{1}H NMR of the crude reaction mixtures.

3.2.1. Cyclopropyl-(2,6-dichloro-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4a). R_f 0.37 (9/1 Hex/Et_2O); ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1H), 2.95–2.86 (m, 1H), 1.55 (s, 9H), 1.14–1.05 (m, 2H), 0.62–0.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.2, 161.4, 158.9, 153.5, 112.0, 83.4, 29.1, 28.0, 10.7; FT-IR (CsI) 3148, 2980, 1730, 1559, 1524, 1417, 1365, 1304, 1256, 1236, 1155 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 304. Anal. calcd for $C_{12}H_{15}Cl_2N_3O_2$: C, 47.38; H, 4.97; N, 13.81. Found: C, 47.76; H, 4.92; N, 13.66.

3.2.2. Cyclopropyl-(4,6-dichloro-pyrimidin-2-yl)-carbamic acid *tert*-butyl ester (5a). R_f 0.25 (9/1 Hex/Et_2O); mp 46–48°C; ^{1}H NMR ($CDCl_3$) δ 7.11 (s, 1H), 3.03–2.94 (m, 1H), 1.51 (s, 9H), 1.11–0.95 (m, 2H), 0.69–0.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.5, 161.4, 153.4, 116.2, 82.5, 29.8, 28.1, 9.4; FT-IR (CsI) 3101, 2979, 1734, 1558, 1527, 1419, 1366, 1294, 1263, 1224, 1155, 1117 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 304. Anal. calcd for $C_{12}H_{15}Cl_2N_3O_2$: C, 47.38; H, 4.97; N, 13.81. Found: C, 47.69; H, 4.91; N, 13.77.

3.2.3. Benzyl-(2,6-dichloro-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4b). Solid; R_f 0.28 (6/4 Hex/CH_2Cl_2); mp 65–67°C; ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.32–7.20 (m, 5H), 5.23 (s, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.3, 162.0, 158.8, 152.6, 137.5, 128.3, 127.4, 127.3, 110.0, 84.1, 48.8, 27.8; FT-IR (CsI) 3154, 2980, 2933, 1731, 1556, 1522, 1455, 1420, 1369, 1351, 1253, 1236, 1150 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 354. Anal. calcd for $C_{16}H_{17}Cl_2N_3O_2$: C, 54.25; H, 4.84; N, 11.86. Found: C, 54.36; H, 4.96; N, 11.81.

3.2.4. Benzyl-(4,6-dichloro-pyrimidin-2-yl)-carbamic acid *tert*-butyl ester (5b). Solid; R_f 0.16 (6/4 Hex/CH_2Cl_2); mp 50–52°C; ^{1}H NMR ($CDCl_3$) δ 7.42–7.20 (m, 5H), 6.99 (s, 1H), 5.16 (s, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 161.5, 160.0, 152.8, 137.7, 128.3, 127.7, 127.2, 115.0, 83.0, 50.6, 28.0; FT-IR (CsI) 3110, 2979, 2931, 1724, 1560, 1526, 1447, 1419, 1368, 1245, 1147 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 354. Anal. calcd for $C_{16}H_{17}Cl_2N_3O_2$: C, 54.25; H, 4.84; N, 11.86. Found: C, 54.63; H, 4.91; N, 11.61.

3.2.5. (2,6-Dichloro-pyrimidin-4-yl)-phenyl-carbamic acid *tert*-butyl ester (4c). Solid; R_f 0.43 (9/1 Hex/Et_2O); mp 97–99°C; ^{1}H NMR ($CDCl_3$) δ 8.04 (s, 1H), 7.49–7.34 (m, 3H), 7.15–7.07 (m, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.2, 162.0, 159.0, 152.4, 138.9, 129.1, 128.3, 128.0, 109.8, 83.9, 27.8; FT-IR (CsI) 3150, 2980, 2933, 1735, 1557, 1527, 1413, 1369, 1344, 1299, 1249, 1151, 1124 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 340 (M^+). Anal. calcd for $C_{15}H_{15}Cl_2N_3O_2$: C, 52.96; H, 4.44; N, 12.35. Found: C, 52.98; H, 4.50; N, 12.46.

3.2.6. L-2-[*tert*-Butoxycarbonyl-(2,6-dichloro-pyrimidin-4-yl)-amino]-3-phenyl-propionic acid methyl ester (4d). Oil; R_f 0.35 (9/1 Hex/AcOEt); $[\alpha]_D^{20}$=−77.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.88 (s, 1H), 7.25–7.08 (m, 5H), 5.89 (dd, 1H, *J*=5.31, 9.99 Hz), 3.75 (s, 3H), 3.56 (dd, 1H, *J*=4.98, 14 Hz), 3.25 (dd, 1H, *J*=9.66, 14 Hz),

1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.2, 162.0, 161.3, 158.0, 151.4, 136.8, 129.3, 128.2, 126.7, 110.0, 84.8, 58.9, 52.3, 35.9, 27.7; FT-IR (CsI) 3156, 2980, 2950, 1739, 1559, 1527, 1418, 1371, 1338, 1235, 1149, 1120 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 426. Anal. calcd for $C_{19}H_{21}Cl_2N_3O_4$: C, 53.53; H, 4.97; N, 9.86. Found: C, 53.28; H, 4.80; N, 9.40.

3.2.7. Benzyl-(2,6-dichloro-pyrimidin-4-yl)-carbamic acid benzyl ester (4e). Solid; R_f 0.34 (9/1 Hex/AcOEt); mp 85–87°C; ^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1H), 7.52–7.20 (m, 10H), 5.32 (s, 2H), 5.27 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 162.3, 161.9, 158.9, 153.8, 136.8, 134.5, 128.6, 128.4, 128.3, 127.7, 127.5, 127.2, 110.2, 69.0, 48.7; FT-IR (CsI) 3152, 3065, 3033, 2964, 1732, 1559, 1525, 1421, 1351, 1254, 1218, 1133, 1081 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 388. Anal. calcd for $C_{19}H_{15}Cl_2N_3O_2$: C, 58.78; H, 3.89; N, 10.82. Found: C, 58.68; H, 3.84; N, 10.85.

3.2.8. (2,6-Dichloro-pyrimidin-4-yl)-carbamic acid benzyl ester (4f). Solid; R_f 0.32 (9/1 Hex/AcOEt); mp 86–88°C; ^{1}H NMR ($CDCl_3$) δ 8.28 (bs, 1H), 7.97 (s, 1H), 7.50–7.25 (m, 5H), 5.24 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 162.92, 159.89, 159.26, 151.82, 134.46, 128.68, 128.54, 128.31, 106.48, 68.25; FT-IR (CsI) 3274, 3144, 3065, 1749, 1567, 1557, 1506, 1456, 1370, 1347, 1261, 1226, 1199, 1120, 980 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 164 (M^++1−COOBn). Anal. calcd for $C_{12}H_9Cl_2N_3O_2$: C, 48.35; H, 3.04; N, 14.09. Found: C, 48.09; H, 3.04; N, 13.98.

3.2.9. (4,6-Dichloro-pyrimidin-2-yl)-carbamic acid benzyl ester (5f). Solid; R_f 0.17 (9/1 Hex/AcOEt); mp 90–92°C; ^{1}H NMR ($CDCl_3$) δ 7.93 (bs, 1H), 7.50–7.28 (m, 5H), 7.04 (s, 1H), 5.23 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 162.4, 156.7, 150.4, 135.0, 128.5, 128.5, 128.4, 115.6, 67.8; FT-IR (CsI) 3258, 3115, 3065, 1744, 1554, 1508, 1419, 1382, 1219, 1185 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 164 (M^++1−COOBn). Anal. calcd for $C_{12}H_9Cl_2N_3O_2$: C, 48.35; H, 3.04; N, 14.09. Found: C, 48.53; H, 3.28; N, 14.02.

3.2.10. 3-(2,6-Dichloro-pyrimidin-4-yl)-oxazolidin-2-one (4g). Solid; R_f 0.35 (7/3 Hex/AcOEt); mp 149–152°C; ^{1}H NMR ($CDCl_3$) δ 8.21 (s, 1H), 4.64–4.51 (m, 2H), 4.34–4.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 162.5, 159.6, 159.0, 153.6, 106.8, 62.6, 43.6; FT-IR (CsI) 3138, 1768, 1557, 1524, 1445, 1390, 1357, 1278, 1194, 1151 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 234. Anal. calcd for $C_7H_5Cl_2N_3O_2$: C, 35.92; H, 2.15; N, 17.95. Found: C, 35.90; H, 2.41; N, 18.06.

Crystal data. $C_7H_5Cl_2N_3O_2$, f.w. 234.04, orthorhombic, space group $P2_12_12_1$, a=6.9360(3) Å, b=14.3180(9) Å, c=18.647(1) Å, V=1851.8(3) Å^3, Z=8, D_c=1.68 g/cm^3, μ=0.675 mm^{-1}, F(000)=944.

Data collection. X-Ray diffraction data were collected from a colourless prismatic crystal of NAME (size 0.20×0.20×0.14), with graphite monochromated Mo Kα radiation (λ=0.71073 Å) on a KappaCCD diffractometer (phi scan technique). Seventy-nine frames were collected (115 s/frame, delta phi=2.3°): each frame was measured two times. Detector to crystal distance: 32 mm. 13,521 reflections were collected ($2.5<\theta<32.99$; $+h,+k,+l$ and $-h,-k,-l$), (3420 unique). No significant decay was detected. No empirical absorption correction was applied.

Structure analysis and refinement. The structure was solved by direct methods using SIR[19] and refined by full-matrix least squares on F using LSFM OpenMoleN.[20] Non-hydrogen atoms were refined anisotropically. All hydrogen atoms have been included at calculated positions and refined with group temperature factors. Final values of the residual R and wR were 0.031 and 0.039, respectively. The highest peak and hole in the final difference-Fourier map were 0.179 and −0.184 e Å^3. The refined value of Flack's parameter[21] was 0.13(8).

3.2.11. 3-(4,6-Dichloro-pyrimidin-2-yl)-oxazolidin-2-one (5g). Solid; R_f 0.18 (7/3 Hex/AcOEt); mp 106–108°C; ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 1H), 4.55–4.43 (m, 2H), 4.33–4.19 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 162.4, 156.2, 151.8, 115.8, 61.6, 44.7; FT-IR (CsI) 3106, 2922, 1786, 1559, 1528, 1447, 1389, 1270, 1217, 1159, 820 cm^{-1}; MS (DIS EI 70 eV) *m/z* (%): 234. Anal. calcd for $C_7H_5Cl_2N_3O_2$: C, 35.92; H, 2.15; N, 17.95. Found: C, 36.03; H, 2.17; N, 17.53.

3.2.12. Benzyl-(2-chloro-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4h). Solid, mp 60–62°C (Hex); R_f 0.37 (4/1 Hex/Et_2O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49 (s, 9H), 5.26 (s, 2H), 7.25–7.32 (m, 5H), 8.00 (d, 1H, J=6 Hz), 8.36 (d, 1H, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ 28.0, 48.5, 83.7, 111.0, 127.3, 127.6, 128.3, 138.0, 158.9, 159.8, 161.8, the pyrimidine C-2 signal was obscured due to its low intensity; FT-IR (KBr) 3423, 1720, 1576, 1423, 1150 cm^{-1}; MS (CI, 70 eV) *m/z* (%): 320 (M^++1, 95), 264 (100) and 220 (25). Anal. calcd for $C_{16}H_{18}ClN_3O_2$: C, 60.09; H, 5.67; N, 13.14. Found: C, 59.78, H, 5.79; N, 13.10.

3.2.13. Phenyl-(2-chloro-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4i). Solid, mp 85.4–87.3°C (Hex); R_f 0.53 (3/1 Hex/Et_2O); ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 7.10–7.16 (m, 2H), 7.35–7.45 (m, 3H), 7.88 (d, 1H, J=6 Hz), 8.42 (d, 1H, J=6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.6, 84.2, 111.6, 128.5, 129.2, 129.8, 140.0, 153.4, 159.8, 160.6, 163.5, the pyrimidine C-2 signal was obscured due to its low intensity; FT-IR (KBr) 3449, 1725, 1571, 1293, 1151 cm^{-1}; MS (CI, 70 eV) *m/z* (%): 306 (M^++1, 70), 250 (100) and 205 (40). Anal. calcd for $C_{15}H_{16}ClN_3O_2$: C, 58.92; H, 5.27; N, 13.74. Found: C, 59.08; H, 5.59; N, 13.21.

3.2.14. Phenyl-(4-chloro-pyrimidin-2-yl)-carbamic acid *tert*-butyl ester (5i). R_f 0.32 (3/1 Hex/Et_2O); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 7.10–7.16 (m, 2H), 7.06 (d, 1H, J=5 Hz), 7.20–7.40 (m, 5H) 8.47 (d, 1H, J=5 Hz); ^{13}C NMR ($CDCl_3$) δ 28.7, 83.4, 118.2, 128.6, 129.6, 129.8, 131.6, 151.4, some of the quaternary pyrimidine carbons are obscured due to their low intensity; MS (CI, 70 eV) *m/z* (%): 306 (M^++1, 100), 250 (40) and 205 (20).

3.2.15. (2-Chloro-pyrimidin-4-yl)-carbamic acid benzyl ester (4j). Solid, mp 126.6–127.1°C; R_f 0.34 (7/3 Hex/Et_2O); ^{1}H NMR ($CDCl_3$) δ 5.25 (s, 2H), 7.39 (s, 5H), 7.91 (d, 1H, J=5 Hz), 8.46 (d, 1H, J=5 Hz); ^{13}C NMR ($CDCl_3$) δ

68.8, 107.6, 129.1, 135.5, 152.8, 160.0, 160.9, 163.4; FT-IR (KBr) 3199, 3048, 2926, 1748, 1570, 1363, 1235 cm^{-1}; MS (CI, 70 eV) *m/z* (%): 266 (33), 264 (M^++1, 100) and 220 (10).

3.2.16. (4-Chloro-pyrimidin-2-yl)-carbamic acid benzyl ester (5j). Solid, mp 60.2–62.1°C; R_f 0.47 (7/3 Hex/Et_2O); ^1H NMR ($CDCl_3$) δ 5.43 (s, 2H), 6.71 (d, 1H, *J*=6 Hz, CCH), 7.30–7.48 (m, 5H), 8.31 (d, 1H, *J*=6 Hz, NCH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 69.2, 107.4, 128.6, 128.7, 134.6, 158.9, 160.2, 162.1, 170.2; FT-IR (KBr) 3034, 2924, 1732, 1571, 1331, 1230 cm^{-1}; MS (CI, isobutane, 70 eV) *m/z* (%): 263 (M^+, 100).

3.2.17. 3-(2-Chloro-pyrimidin-4-yl)-oxazolidin-2-one (4k). Solid, mp 175.5–177.0°C (Hex/AcOEt ca. 9/1); R_f 0.28 (3/7 Hex/Et_2O); ^1H NMR ($CDCl_3$) δ 4.28 (t, 2H, *J*=8 Hz), 4.57 (t, 2H, *J*=8 Hz), 8.15 (d, 1H, *J*=6 Hz), 8.47 (d, 1H, *J*=6 Hz); ^{13}C NMR ($CDCl_3$) δ 43.4, 62.6, 107.3, 154.0, 158.5, 159.4, 160.3; FT-IR (KBr) 3448, 1775, 1579, 1446, 1179 cm^{-1}; MS (CI, 70 eV) *m/z* (%): 200 (M^++1, 100). Anal. calcd for $C_7H_6ClN_3O_2$: C, 42.12; H, 3.03; N, 21.05. Found: C, 42.64; H, 3.19; N, 20.50.

3.2.18. 2-[*tert*-Butoxycarbonyl-(2-chloro-pyrimidin-4-yl)-amino]-acetic acid benzyl ester (4l). Oil, R_f 0.16 (8/2 Hex/Et_2O); ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 4.82 (s, 2H), 5.21 (s, 2H), 7.36 (brs, 5H), 8.06 (d, 1H, *J*=6 Hz), 8.39 (d, 1H, *J*=6 Hz); ^{13}C NMR ($CDCl_3$) δ 27.9, 46.6, 67.1, 84.3, 110.6, 128.3, 128.5, 128.6, 135.4, 152.1, 159.1, 159.5, 161.1, 168.8; MS (CI, isobutane, 70 eV) *m/z* (%): 378 (M^++1, 20), 322 (M^++1−C_4H_8, 10), 277 (15).

3.2.19. Benzyl-(6-chloro-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4m). Wax, mp 38.1–40.7°C; R_f 0.55 (4/1 Hex/Et_2O); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 5.29 (s, 2H), 7.22–7.31 (m, 5H), 8.18 (s, 1H), 8.67 (s,1H); ^{13}C NMR ($CDCl_3$) δ 28.6, 49.4, 84.2, 113.0, 127.6, 127.7, 129.0, 138.8, 153.8, 158.1, 161.8, 161.9, 163.6; FT-IR (KBr) 2975, 1723, 1567 cm^{-1}; MS (CI, 70 eV) *m/z* (%): 320 (M^++1, 95), 264 (100) and 220 (25).

3.2.20. Phenyl-(6-chloro-pyrimidin-4-yl)-carbamic acid *tert*-butyl ester (4n). Solid, mp 121–122°C (Hex); R_f 0.30 (78/22 Hex/Et_2O); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 7.10–7.17 (m, 2H), 7.37–7.49 (m, 3H), 8.13 (s, 1H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9, 83.5, 112.2, 127.9, 128.5, 129.2, 139.6, 152.7, 157.7, 161.3, 162.1, the pyrimidine C-2 signal was obscured due to its low intensity; FT-IR (KBr) 3427, 1721, 1561, 1286, 1153 cm^{-1}; MS (CI, 70 eV) *m/z* (%): 306 (M^++1, 100), 250 (60) and 205 (10). Anal. calcd for $C_{15}H_{16}ClN_3O_2$: C, 58.92; H, 5.27; N, 13.74. Found: C, 58.85; H, 5.35; N, 13.72.

3.2.21. 3-(6-Chloro-pyrimidin-4-yl)-oxazolidin-2-one (4o). Solid, mp 138.2–139.6°C (*i*-Pr_2O/AcOEt ca. 9/1); R_f 0.55 (6/4 Hex/AcOEt); ^1H NMR ($CDCl_3$) δ 4.28 (t, 2H, *J*=8 Hz), 4.57 (t, 2H, *J*=8 Hz), 8.26 (s, 1H), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 43.6, 62.6, 108.7, 154.2, 157.7, 158.0, 161.6; FT-IR (KBr) 3438, 1764, 1562, 1460, 1398, 1188, 1140 cm^{-1}; MS (CI, 70 eV) *m/z* (%): 200 (M^++1, 100), 155 (M^+−CO_2, 5). Anal. calcd for $C_7H_6ClN_3O_2$: C, 42.12; H, 3.03; N, 21.05. Found: C, 42.26; H, 3.13; N, 20.75.

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