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Efficient and regioselective 4-amino-de-chlorination of 2,4,6-trichloropyrimidine with *N*-sodium carbamates

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Abstract

4-*N*-Alkoxycarbonyl-2,6-dichloropyrimidines have been synthesized with good to excellent regioselectivity and yields from 2,4,6-trichloropyrimidine and *N*-sodium carbamates in DMF, at room temperature, in 15–30 minutes.

Keywords: pyrimidines; carbamates; amination; regioselection.

Aminopyrimidines are biologically important molecules (remarkable examples are cytosine, thiamine and vitamin B-1) and valuable heterocyclic nuclei for the design of pharmaceutical agents.[1] Recently, we became interested in preparing *N*-alkoxycarbonylamino-dichloropyrimidines from commercially available and cheap 2,4,6-trichloropyrimidine. Desired properties of this synthesis include: high regioselectivity, high yields, general applicability, extreme experimental simplicity, and one-pot introduction of the protected amine function. Surprisingly, an overview of the literature revealed that a general and efficient methodology to prepare *N*-acylamino dichloropyrimidines was not available.[2] Herein we disclose a tailor-made procedure, featuring all the requirements above, to perform the one-step synthesis of 4-*N*-alkoxycarbonylamino-2,6-dichloropyrimidines from 2,4,6-trichloropyrimidine (TCP) and the corresponding carbamates (Scheme 1).

The known approach to the target compounds 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 (Scheme 2 and Table 1).[3] Ammonia[4] and alkylamines, like benzylamine,[5] cyclopropylamine and ethanolamine,[6] invariably provide nearly equimolar ratios of the two possible regioisomers **1** and **2**, under different experimental conditions (entries 1–5). Interestingly, aniline in ethanol (Na_2CO_3 as base) gives rise to a regioselective chlorine displacement, producing 4-anilino-2,6-dichloropyrimidine (entry 6).[7]

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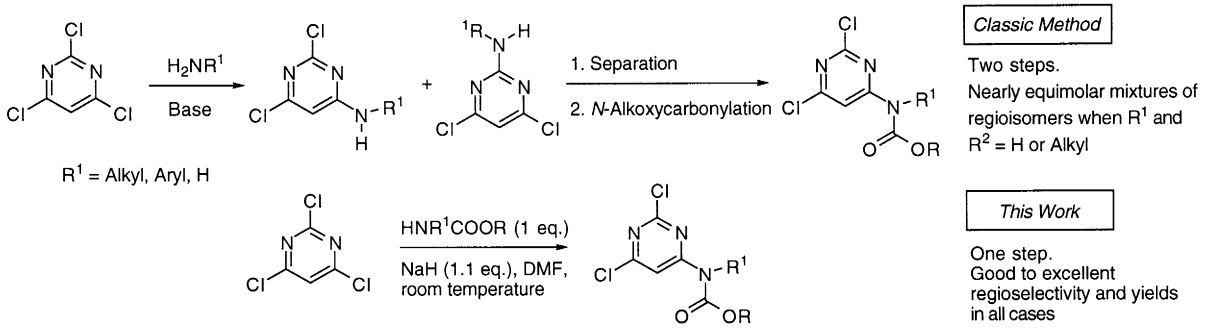
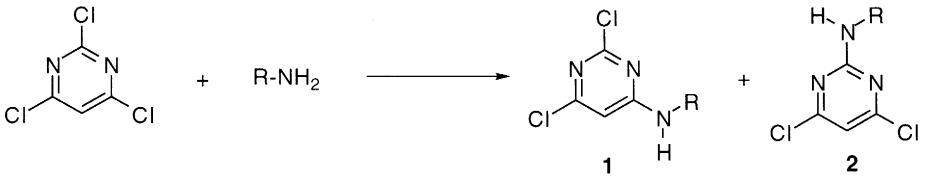


Scheme 1.



Scheme 2.

Table 1
Reaction of 2,4,6-trichloropyrimidine with free amines

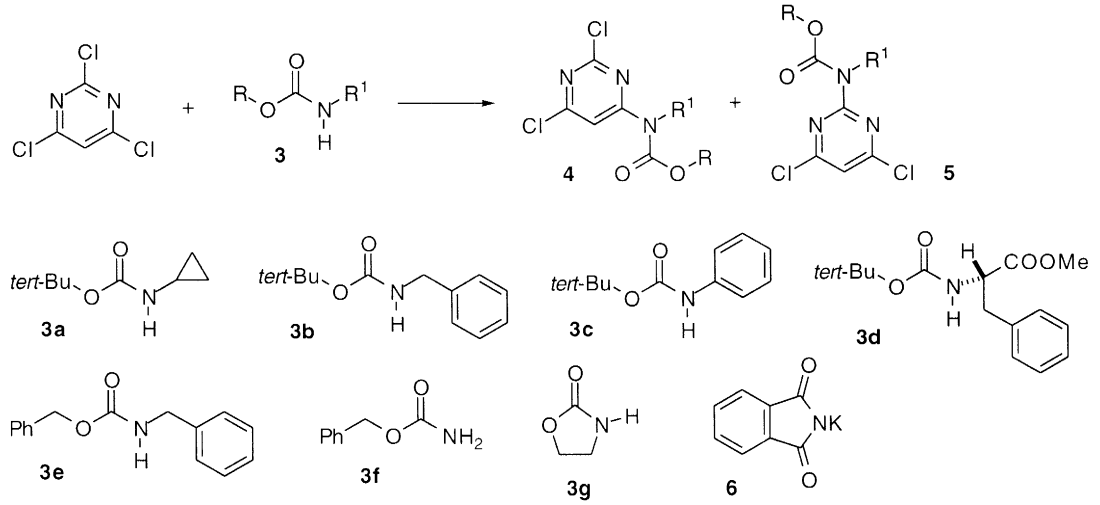
Entry	Amine	Ratio 1/2	Overall Yield (%)	Conditions
1	NH_3	*ca.* 1:2	*ca.* 60	EtOH/NH_3, r.t., few hrs (Ref. 4)
2	$PhCH_2NH_2$ (2 eq.)	*ca.* 6:4	75	EtOH, r.t., 3 hrs (Ref. 5)
3	Cyclopropylamine (2 eq.)	59:41	91.3	THF, 0 °C to r.t., 2.5 hrs
4	Cyclopropylamine	66:34[a]	> 98 [a]	Ethanol, Na_2CO_3, r.t., 5.5 hrs
5	$HOCH_2CH_2NH_2$ (2 eq.)	2:1	68	THF, r.t., overnight (Ref. 6)
6	$C_6H_5NH_2$	91:9	99.2	Ethanol, Na_2CO_3, r.t. to 80 °C, 1 day
7	$C_6H_5NH_2$ (2 eq.)	61:39	93.1	C_6H_6, r.t. to 60 °C, 1 day

Key: [a] Determined by ^1H NMR analysis of the crude reaction mixture.

However, we found that replacement of ethanol/Na_2CO_3 with THF/$C_6H_5NH_2$ induces a dramatic drop in regioselectivity (entry 7). Concerning the second step, our experiments, supported by analogous literature reports,[8] evidenced that *N*-acylation of aminodichloropyrimidines under standard conditions (acyl chloride, pyridine, CH_2Cl_2) is unsatisfactory, due to the low nucleophilicity of the amine function. For example, acetyl chloride gave rise to a largely incomplete reaction and massive formation of by-products upon reaction forcing.

We therefore turned our attention to the reaction of TCP with carbamates (Scheme 3). To the best of our knowledge a single example of nucleophilic hetero-aromatic substitution of chlorine by action of a *N*-metalated carbamate has been described,[9] therefore almost no data on the feasibility, regioselectivity and synthetic potential of this reaction were available. Satisfactorily, this approach proved to be very efficient, operatively simple, regio- and chemo-selective, since *O*-substitution was never found to be competitive. Portion-wise addition of solid NaH (60%) (usually 1.1 equiv., see Table 2) 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 2).[10,11] The method is general,

as witnessed by the fact that alkylamino, arylamino and even ammonia-derived carbamates underwent the reaction smoothly.



Scheme 3.

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

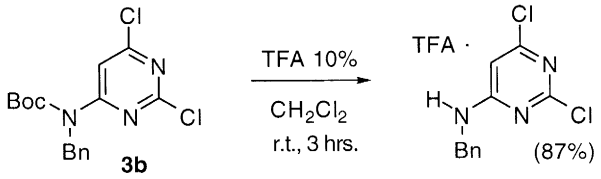
Entry	Carbamate	Ratio 4/5[a]	Overall yields (%)[b]	Conditions
1	**3a**	88:12	97.6	NaH (1.1 eq.), DMF, r.t.[c]
2	**3a**	91:9	66[a]	KO-*tert*-Bu, DMF, r.t., 30 min[d]
3	**3a**	50:50	33[a]	NaH (1.1 eq.), THF, r.t., 16 hrs[d]
4	**3a**	88:12	87.8	NaH (1.1 eq.), DMF, -25 °C to r.t., 1.5 hrs
5	**3b**	92:8	76.0	NaH (1.1 eq.), DMF, r.t.[c]
6	**3c**	95:5	99.8	NaH (1.1 eq.), DMF, r.t.[c]
7	**3d**	91:9	99.9	NaH (1.0 eq.), DMF, r.t.[c]
8	**3e**	86:14	80[a]	NaH (1.1 eq.), DMF, r.t., 1 hr
9	**3f**	74:26	94.3	NaH (2.2 eq.), DMF, r.t.[c]
10	**3g**	80:20	74.0	NaH (1.1 eq.), DMF, r.t.[c]
11	**3g**	83:17	82[a]	Cs_2CO_3 (1 eq.), DMF, r.t., 22 hrs
12	**3g**	32:68	48.8	NaH (1.1 eq.), THF, r.t., 1 hr
13	**3g**	> 10:1	< 20[a]	*n*-BuLi (1.0 eq.), THF, 0 °C to r.t., 2 hrs[d]

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

N-Sodium carbamates of alkylamines **3a**,**b**,**e** (entries 1, 5 and 8), ammonia **3f** (entry 9) and ethanolamine **3g** (entry 10) added regioselectively to 2,4,6-trichloropyrimidine, in contrast with the parent free amines (see Table 1). Very efficient reaction was achieved also with aniline carbamate **3c** (entry 6). A functionalized and chiral non-racemic carbamate, like *N*-Boc-L-phenylalanine methyl ester **3d** (entry 7), afforded remarkably good results as well.[12] 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

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 from 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. Attempts to employ EtN(*i*-Pr)$_2$ as base in the reaction of TCP with **3f** (benzene, 20 h, reflux) did not afford any detectable trace of the corresponding products **4**,**5f**. The order of addition of reagents and substrates was also found to play a key-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**. To extend the scope of the reaction, commercial *N*-potassium phthalimide **6** was also tested under identical conditions: the corresponding 4-phthalimido and 2-phthalimido-dichloropyrimidines were formed in 85:15 ratio and ca. 70% overall yield after 24 h at rt.[13] Disappointingly, attempts to react TCP with δ-valerolactam using NaH or Cs_2CO_3 under the optimized conditions afforded complex mixtures of products. 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-2,6-dichloropyrimidines. Indeed, treatment of **3b** with trifluoroacetic acid produced 4-benzylamino-2,6-dichloropyrimidine trifluoroacetate in 87% yield (Scheme 4).



Scheme 4.

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

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10. General experimental. To a solution of TCP and carbamate **3** (1.42 mmol both) in dry DMF (5 mL) solid NaH (60%) (1.56 mmol) was added portionwise over 5 min at rt. The resulting slurry was kept under stirring for 15–30 min at rt. The reaction was quenched with a saturated aqueous NH_4Cl solution, extracted three times with diethyl ether, the collected organic layers were washed twice with water, dried over anhydrous sodium sulfate, filtered and solvent removed in vacuo. Pure products **4** were obtained via silica gel chromatography, generally using *n*-hexane:ethyl acetate 9:1 as eluant. In the case of the primary carbamate **3f** (entry 6) 2.2 equiv. of NaH were used, since the corresponding products **4**,**5f** also undergo *N*-metalation. All new compounds were characterized by ^{1}H and ^{13}C NMR, FT IR and mass spectrometry.
11. The proton H-5 of 4-alkoxycarbonylamino-2,6-dichloropyrimidines **4** resonates at extraordinarily low fields (δ 7.8–8.3). This could be explained by an intramolecular C–H···O=C–N hydrogen bonding, which is confirmed by preliminary X-ray diffraction experiments.
12. Although the ee of the product **4d** was not measured, a high value of optical activity was recorded: $[\alpha]_D^{20}$ (c 1.0, $CHCl_3$)=−77.8.
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