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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

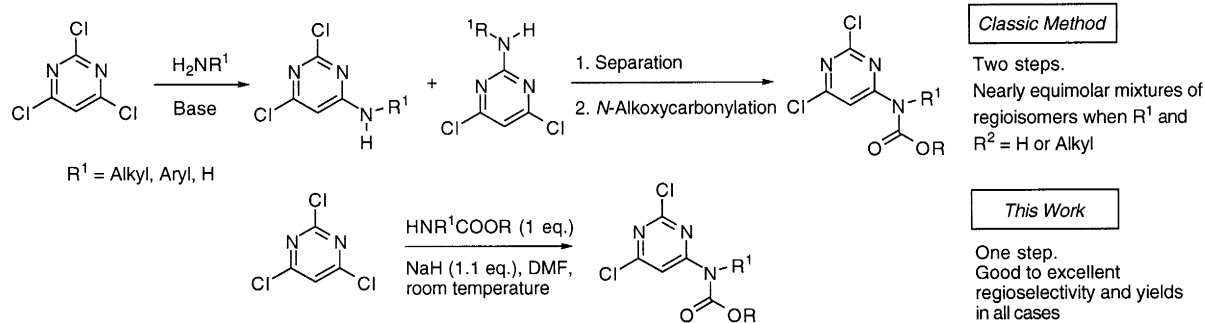
4-*N*-Alkoxy carbonyl-2,6-dichloropyrimidines have been synthesized with good to excellent regioselectivity and yields from 2,4,6-trichloropyrimidine and *N*-sodium carbamates in DMF, at room temperature, in 15–30 minutes. © 2000 Elsevier Science Ltd. All rights reserved.

**Keywords:** pyrimidines; carbamates; amination; regioselection.

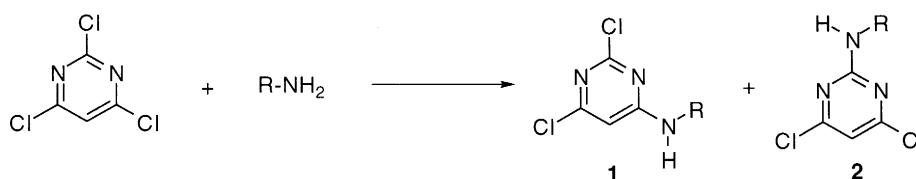
Aminopyrimidines are biologically important molecules (remarkable examples are cytosine, thiamine and vitamin B-1) and valuable heterocyclic nuclei for the design of pharmaceutical agents.<sup>1</sup> Recently, we became interested in preparing *N*-alkoxy carbonylamino-dichloropyrimidines from commercially 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.<sup>2</sup> Herein we disclose a tailor-made procedure, featuring all the requirements above, to perform the one-step synthesis of 4-*N*-alkoxy carbonylamino-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*-alkoxy carbonylation. 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).<sup>3</sup> Ammonia<sup>4</sup> and alkylamines, like benzylamine,<sup>5</sup> cyclopropylamine and ethanolamine,<sup>6</sup> 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).<sup>7</sup>

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Scheme 1.



Scheme 2.

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

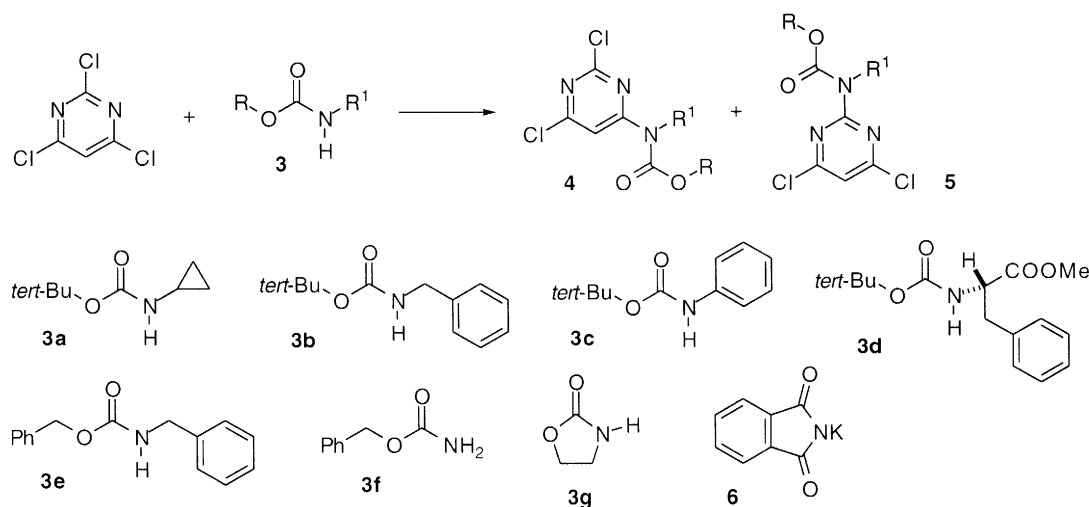
| Entry | Amine                                                     | Ratio 1/2          | Overall Yield (%) | Conditions                                                      |
|-------|-----------------------------------------------------------|--------------------|-------------------|-----------------------------------------------------------------|
| 1     | NH <sub>3</sub>                                           | ca. 1:2            | ca. 60            | EtOH/NH <sub>3</sub> , r.t., few hrs (Ref. 4)                   |
| 2     | PhCH <sub>2</sub> NH <sub>2</sub> (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 <sup>a</sup> | > 98 <sup>a</sup> | Ethanol, Na <sub>2</sub> CO <sub>3</sub> , r.t., 5.5 hrs        |
| 5     | HOCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub> (2 eq.) | 2:1                | 68                | THF, r.t., overnight (Ref. 6)                                   |
| 6     | C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>             | 91:9               | 99.2              | Ethanol, Na <sub>2</sub> CO <sub>3</sub> , r.t. to 80 °C, 1 day |
| 7     | C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub> (2 eq.)     | 61:39              | 93.1              | C <sub>6</sub> H <sub>6</sub> , r.t. to 60 °C, 1 day            |

Key: <sup>a</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.

However, we found that replacement of ethanol/Na<sub>2</sub>CO<sub>3</sub> with THF/C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub> induces a dramatic drop in regioselectivity (entry 7). Concerning the second step, our experiments, supported by analogous literature reports,<sup>8</sup> evidenced that *N*-acylation of aminodichloropyrimidines under standard conditions (acyl chloride, pyridine, CH<sub>2</sub>Cl<sub>2</sub>) 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,<sup>9</sup> 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).<sup>10,11</sup> 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**)

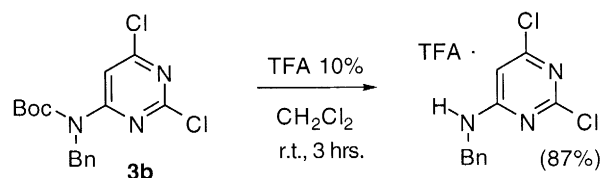
| Entry | Carbamate | Ratio 4/5 <sup>a</sup> | Overall yields (%) <sup>b</sup> | Conditions                                                      |
|-------|-----------|------------------------|---------------------------------|-----------------------------------------------------------------|
| 1   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

Key: <sup>a</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>b</sup> Isolated, unless otherwise stated. <sup>c</sup> Reaction time 15-30 min. <sup>d</sup> Several unidentified by-products formed (<sup>1</sup>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.<sup>12</sup> 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.<sup>13</sup> Disappointingly, attempts to react TCP with  $\delta$ -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<sub>4</sub>Cl 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 <sup>1</sup>H and <sup>13</sup>C NMR, FT IR and mass spectrometry.
11. The proton H-5 of 4-alkoxycarbonylamino-2,6-dichloropyrimidines **4** resonates at extraordinarily low fields ( $\delta$  7.8–8.3). This could be explained by an intramolecular C–H $\cdots$ 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<sub>3</sub>) = –77.8.
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