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Regioselective solid-phase 4-amino-de-chlorination of 2,4,6-trichloropyrimidine by resin-supported *N*-potassium carbamates

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Abstract—The first regioselective resin-anchoring reaction of 2,4,6-trichloropyrimidine has been achieved through 4-amino-de-chlorination by solid-supported Boc-like *N*-potassium carbamates. Excellent regioselectivities together with high coupling efficiency were obtained with aliphatic, aromatic and α-amino-ester derived carbamates. The scope and limits of the reaction are described with the view of its applications to the solid-phase synthesis of combinatorial libraries of aminopyrimidine-based structures.

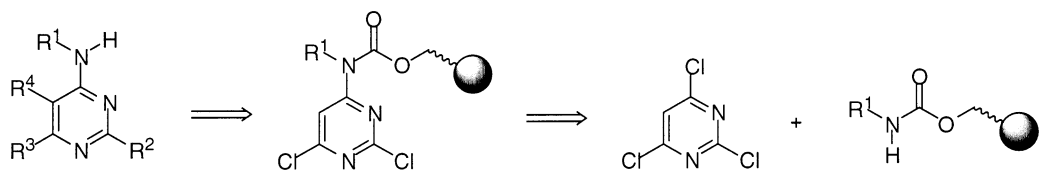
1. Introduction

Aminopyrimidines constitute a class of biologically relevant molecules, as well as important intermediates for the design and synthesis of fused polycyclic pharmaceutical targets, such as purines and quinazolines.[1] For these reasons, a number of syntheses of aminopyrimidines have been reported both in the solid phase[2] and in solution.[3] In principle, solid-phase amino-de-chlorination of commercially available and cheap 2,4,6-trichloropyrimidine (TCP) could represent a very convenient route to combinatorial libraries of the target compounds.[4] In fact, the amino-dichloropyrimidine initially formed could be further derivatized by displacement of the chlorine atoms and C-5 functionalization, introducing a considerable diversity on the scaffold (Scheme 1). However, the lack of regioselectivity is a serious drawback affecting this methodology because the production of nearly equimolar amounts of 2- and 4-amino-dichloropyrimidine isomers on the single resin beads in the first step of the synthesis leads to the formation of complex product mixtures during the next steps.[2] An overview of the literature revealed that regioselective amino-de-chlorination anchoring reactions of TCP for solid-phase synthesis are hitherto unavailable.

Recently, we reported the regioselective solution-phase 4-amino-de-chlorination of TCP by *N*-sodium carbamates.[5] We now report the successful, not trivial, adaptation of that methodology to the solid phase.

2. Results and discussion

A series of amines anchored to the polystyrene support via a Boc-like linker (**1**) was prepared according to a modification of the method of Hernández and Hodges.[6]



Scheme 1.

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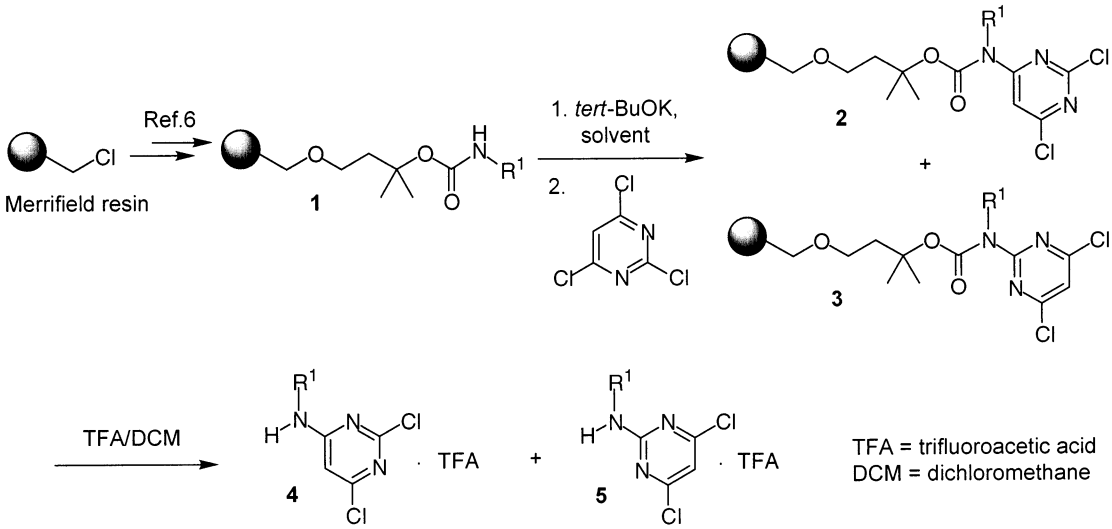

Scheme 2.

The first attempts to transfer the exact procedure for solution-phase 4-amino-de-chlorination of TCP to the solid phase proved to be very disappointing. In fact, treatment of a preformed mixture of **1a** and TCP (2–15 equiv.) in DMF with variable amounts of NaH (2–15 equiv.) at rt for up to 27 hours, or alternatively addition of TCP (15 equiv.) to a mixture of **1a** and NaH (2–5 equiv.) in DMF, shaken for 1–9 hours from rt to 60°C, did not produce the desired outcome. Both FT-IR analysis of the resulting polymer and NMR of the residue obtained upon treatment with TFA/DCM revealed either negligible loading of pyrimidine or intra resin cross-linking side reactions, particularly in the case of prolonged shaking at 60°C.[7] Repeating the reaction did not significantly enhance the pyrimidine content of the resin. Similarly, negative results were achieved using Cs_2CO_3 as a base.

The use of potassium *tert*-butoxide (3 equiv.) as a base proved to be much more rewarding. In fact, preliminary formation of resin-supported *N*-potassium carbamates from **1**, in dry THF or DMF for 1 hour at rt, followed by addition of TCP (10 equiv.), provided the target resin-bound dichloropyrimidines **2** and **3a**–**g** (Scheme 2 and Table 1) with excellent regioselectivities in favor of the 4-amino isomers **2**, and satisfactory coupling efficiencies. In order to assess unambiguously the products identities and ratios in the solid-phase reactions, the resins **2** and **3a**–**g** were treated with TFA/DCM, and the products **4** and **5a**–**g** released from the solid support were analyzed by NMR and HPLC. The same products **4** and **5a**–**g** were prepared in parallel via conventional solution-phase amino-de-chlorination of TCP with the corresponding amines,[5] followed by chromatographic purification, and treatment with TFA. Finally, their NMR and HPLC analyses were compared to those obtained in the solid phase.[8]

Better solid-phase regioselectivities were observed using DMF as a solvent, ranging from 4.9:1.0 achieved with **1a** and **1f** (entries 6 and 11) to 98:2 obtained with **1d** (entry 8). A very good coupling efficiency was observed with all the structurally diverse polymer-bound amines employed, such as benzylamine (**1a**, entries 1 and 2), phenethylamine (**1b**, entries 3 and 4), arylamines (**1d**,**e**, entries 7–10) and α-amino-*tert*-butylesters (**1f**,**g**, entries 11 and 12), with the exception of the *cyclo*-hexylamine **1c** which added quite sluggishly. Comparable purity of the released substrates **4** and **5** was observed with THF and DMF. In the case of glycine and L-phenylalanine derivatives, the use of methyl esters led to complex mixtures of products, probably arising from competitive reactions at the carboxyl function. Attempts to extend the procedure to less reactive heterocyclic chlorides, such as 2,4-dichloropyrimidine, by treatment with *N*-potassium-**1a**,**c**,**d** afforded largely incomplete amino-de-chlorinations. Also in this case, repeating the reaction did not significantly improve the situation.

In summary, we have developed the first regioselective anchoring procedure for the preparation of resin-bound 4-amino-2,6-dichloropyrimidines from TCP and polymer-supported *N*-potassium Boc-like carbamates. Due to its experimental simplicity and effectiveness, this methodology emerges as a valuable tool for the preparation of combinatorial libraries of compounds based on the aminopyrimidine scaffold. This issue is currently being addressed in our laboratories.

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Table 1. 4-Amino-de-chlorination of 2,4,6-trichloropyrimidine by resin-supported *N*-potassium carbamates[a]

Entry	Products	R^1	Ratio **4**/**5**[b]	Solvent	Coupling efficiency (%)[c]
1	**4** and **5a**	$PhCH_2$	89.7:10.3	THF	82.9
2	**4** and **5a**	$PhCH_2$	95.8:4.2	DMF	71.9
3	**4** and **5b**	$Ph(CH_2)_2$	78.7:21.3	THF	79.3
4	**4** and **5b**	$Ph(CH_2)_2$	93.9:6.1	DMF	75.0
5	**4** and **5c**	*cyclo*-Hexylamine	92.9:7.1	THF	44.5
6	**4** and **5c**	*cyclo*-Hexylamine	96.6:3.4	DMF	55.8
7	**4** and **5d**	Ph	96.8:3.2	THF	80.1
8	**4** and **5d**	Ph	97.8:2.2	DMF	74.3
9	**4** and **5e**	4-MeO-C_6H_4	91.3:8.7	THF	77.9
10	**4** and **5e**	4-MeO-C_6H_4	96.8:3.2	DMF	78.8
11	**4** and **5f**	CH_2CO_2H[d]	83.1:16.9	DMF	87.1
12	**4** and **5g**	L-$CH(Bn)CO_2H$[d]	92.3:7.7	DMF	75.0

[a] Purity spanned from 80 to 90% in all cases, the main impurity being the trifluoroacetate of unreacted R^1NH_2. The only exception was *cyclo*-hexylamine (entries 5 and 6), present in ca. 1:1 ratio with **4** and **5c**, due to incomplete amino-de-chlorination.
[b] Determined by HPLC after release from **2** and **3**, except for **4** and **5f**,**g** which were analyzed by ^1H NMR.
[c] Based on the chlorine content of **4** and **5**, as measured by combustion analysis.
[d] Prepared from the corresponding *tert*-butyl esters.

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6. Hernández, A. S.; Hodges, J. C. *J. Org. Chem.* **1997**, *62*, 3153–3157. Merrifield resin was reacted with the disodium alkoxide of 3-methyl-1,3-butanediol, prepared with NaH in dry DMF, providing the solid-supported tertiary alcohol **I**. This reaction was complete, as shown by a content of chlorine <500 ppm measured by combustion analysis of **I**. Reaction of **I** with CDI/DMAP afforded the resin-bound (*tert*-alkoxycarbonyl)imidazole **II**, which was transformed into the resin bound *tert*-alkyl carbamates **III** according to the literature method.
7. In that case, a resin having the following combustion analysis was obtained (%): C, 84.10; H, 7.62; N, 1.24; O, 3.81; Cl, 2.45. FT-IR analysis of the resin showed the diagnostic pyrimidine band at 1560 cm^{-1}. Unfortunately, negligible amounts of the desired aminopyrimidines **4** and **5a** were recovered after release by TFA/DCM, suggesting that some resin cross-linking might have occurred.
8. HPLC analyses of **4** and **5a**–**e** were carried out after washing with aqueous $NaHCO_3$ in order to neutralize TFA.