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LETTERS

A novel solid-phase chlorinating reagent for the synthesis of acyl chlorides

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Abstract—Cyanuric chloride was loaded onto a modified Wang resin, which was successfully used to convert carboxylic acids to their corresponding acyl chlorides. The formation of acyl chlorides were confirmed by condensation with various amines or alcohols to form the corresponding amides or esters. © 2002 Elsevier Science Ltd. All rights reserved.

Cyanuric chloride (2,4,6-trichloro[1,3,5]triazine) has long been used in different organic transformations, such as dehydration of amides to nitriles,[1] deoxygenation of sulfoxides,[2] activation of DMSO for the oxidation of alcohols,[3] and conversion of acids to acyl chlorides.[4] Some derivatives of cyanuric chloride, especially the dimethoxy analog (CDMT), have been employed as mild coupling reagents in the synthesis of amides with mixed anhydride intermediates.[5]

Over the last decade, polymer-supported reagents have found increasing applications in combinatorial, parallel or even multistep conventional organic synthesis.[6] Continued interest in the development of new solid-phase reagents[7] has greatly facilitated solution phase library synthesis with simplified purification procedures that are applicable to robotic protocols.[6] Recently, an amino resin-supported dichlorotriazine group (DCT) was reported to serve as a good coupling reagent between carboxylic acids and amines to produce amides.[8] This was the first example of a polymer-supported cyanuric chloride, which activates a carboxylic acid through the mixed anhydride intermediate. However, the amino group linked DCT was not active enough to directly convert carboxylic acids to the acyl chlorides, most likely due to the electron-donating ability of the amino group.

We were interested in a resin-bound chlorinating reagent capable of directly converting various carboxylic acids to acyl chlorides. Reasoning that one equivalent of cyanuric chloride could convert two equivalents of carboxylic acid to acyl chloride, and that the intermediate, 2-hydroxyl-4,6-dichloro[1,3,5]triazine, is still capable of transferring one chlorine,[4] we proposed that an oxygen instead of nitrogen linkage should be able to convert carboxylic acids to acyl chlorides other than simply serving as an activating group[8] (Fig. 1).

Because of its commercial availability and high loading, we first examined the Wang benzyl alcohol resin which has a hydroxy group for attachment of DCT. The loading of cyanuric chloride went smoothly on shaking the resin with excess cyanuric chloride and Et_3N in chloroform. Filtration followed by rinsing with solvents afforded resin **1** (Scheme 1).[9] The formation of resin **1** was verified by the disappearance of the hydroxyl IR stretching frequency (3200–3700 cm^{-1}), as monitored by single-bead IR (Fig. 2). Further experimental verification was provided by elemental analysis of the chlorine content (Table 1). More importantly, elemental analysis provided the relative loading amount of cyanuric chloride on the resin (Table 1).

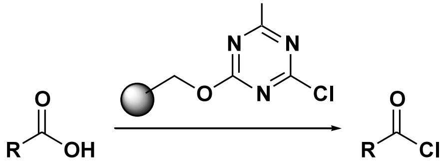

Figure 1. Preparation of acyl chlorides through resin-supported DCT.

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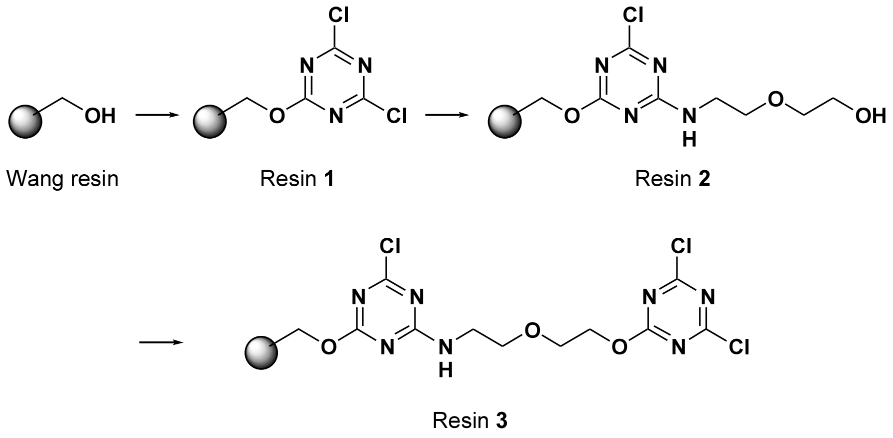


Scheme 1. Synthesis of different cyanuric chloride resins.

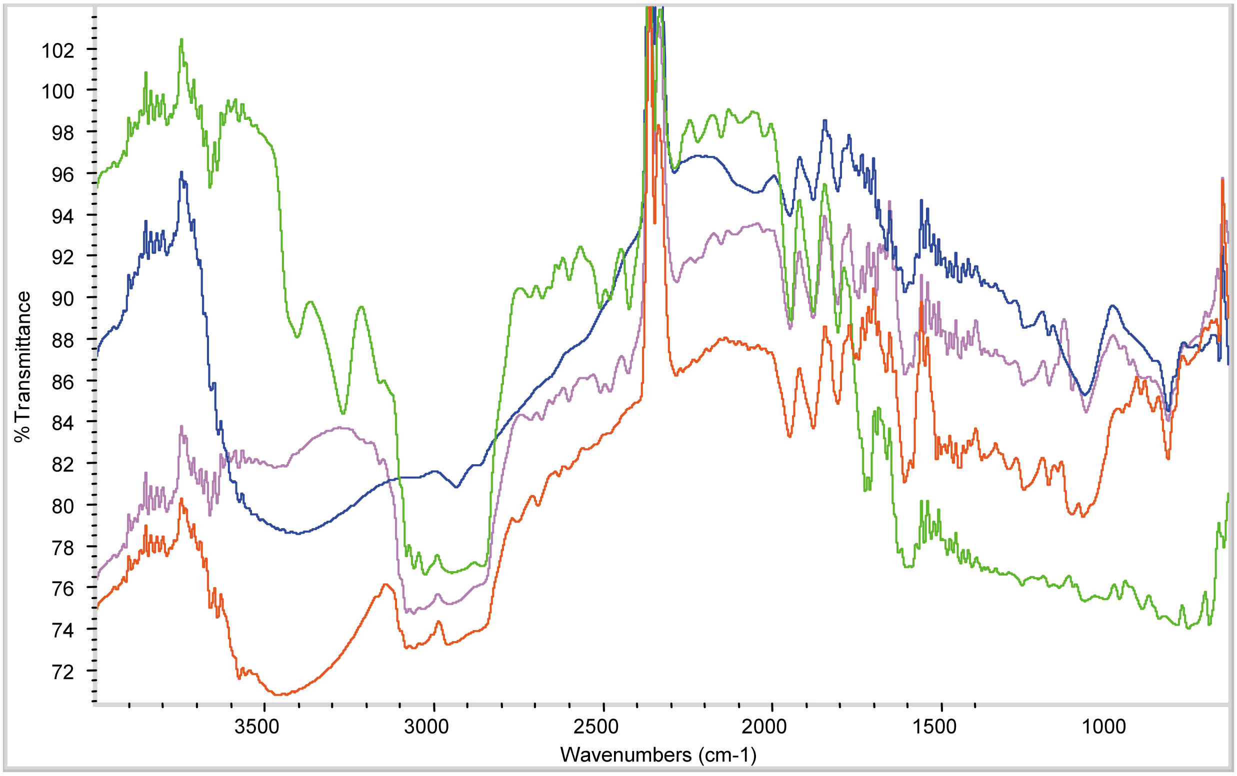


Figure 2. Single-bead IR (Nicolet Protégé 460) spectra of various resins. Red: Wang resin; purple: resin **1** (Wang loaded with DCT); blue: resin **2** (with linker); green: resin **3** (loaded with DCT).

Table 1. Chloride contents of resin **1**, **2** and **3**[a]

	Chlorine (%)	Loading (mmol/g)
Resin **1**	13.45	1.9 (DCT)
Resin **2**	3.00	0.85 (Cl)[b]
Resin **3**	20.87	1.96 (DCT)[c]

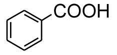
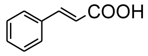
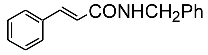
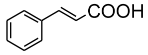
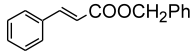
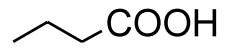
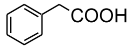
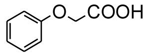
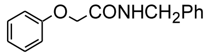
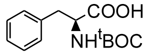
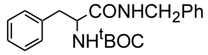
[a] Chloride content varies with different preparations.

[b] It cannot be ruled out that some DCT were bisaminated thus less chloride.

[c] Calculated based on monoamination linker.

To our disappointment, conversion of benzoic acid to benzoyl chloride effected by this resin was sluggish (only up to 30% conversion as monitored by HPLC) in either acetone or CH_2Cl_2, even with a large excess of resin **1**. Longer reaction times of 5 h resulted in the appearance of side products, presumably due to the instability of the benzyloxy linker of the resin. The sluggish reactivity is probably due to proximity and steric hindrance between the DCT units and the resin. To circumvent this problem, we intended to place spacer units between the resin and cyanuric chloride

Table 2. Synthesis of amide or ester via acyl chloride intermediate using resin **3**

Carboxylic acid	Amide or ester	Yield (%)[a]
		69
		81
		83
		88
		72
		78
		64[b]

a. The yield is based on purified product. b. Completely racemized by chiral HPLC analysis.

such that the reactive center was positioned further away from the resin surface (Scheme 1). Such an extension we felt would not only allow greater reactivity but also serve to protect the labile benzyloxy ether linkage of the Wang resin.

Direct extension of the spacer from the Wang resin is probably practicable but resin **1** itself provided a good starting point since it is a good electrophile. Towards this end, resin **2** was prepared by shaking resin **1** with excess 2-(2-aminoethoxy)ethanol. Analysis by single-bead IR (appearance of the hydroxyl group at 3200–3700 cm^{-1}) and elemental analysis confirmed the complete conversion of **1** to **2** (Fig. 2 and Table 1).[9] Resin **2** is stable and inert to moisture and could be stored at room temperature. Resin **2** was further converted to resin **3** by shaking with excess cyanuric chloride in the presence of Et_3N in chloroform.[9] Resin **3** was again characterized by IR (disappearance of the hydroxyl group) and elemental analysis (Fig. 2 and Table 1).

We were gratified to find that after benzoic acid was shaken with resin **3** (3 equiv.) and Et_3N in either CH_2Cl_2 or acetone for 3 h, benzoyl chloride was formed in 70–80% conversion without any noticeable side products as monitored by HPLC.[10] Encouraged by the results with resin **3**, we prepared a limited series of acyl chlorides using different carboxylic acids.[9] After removal of the resin by filtration, the acyl chlorides were converted to their corresponding benzyl amides or esters for characterization and calculation of the yields (Table 2).

From the isolated yields of the amide or ester, it can be inferred that the yields for the corresponding acyl chlorides are generally around 70–90%. However, a chiral amino acid was completely racemized under this resin treatment.

In summary, a new resin-supported chlorinating reagent based on cyanuric chloride has been developed and used in the facile preparation of acyl chlorides. Compared to the conventional synthesis of acyl chlorides using thionyl or oxalyl chloride, the solid-phase methodology is odorless, and the handling process is very convenient since purification can be affected by simple filtration.

Acknowledgements

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9. *Synthesis of resin **1***: To a suspension of Wang resin (250 mg, 1.5–2.0 mmol OH/g) and cyanuric chloride (369 mg, 2.0 mmole) in chloroform (6 mL) was added diisopropylethylamine (0.5 mmol). After shaking at rt for 18 h, the resin was then filtered, washed with chloroform (3×3 mL) and THF (3×3 mL), dried in vacuo and characterized by IR and elemental analysis.

   *Synthesis of resin **2***: To a solution of 6-amino-1-hexanol (293 mg, 2.5 mmol) in THF (8 mL), 250 mg of resin **1** was added followed by diisopropylethylamine (0.5 mmol). After shaking at rt for 18 h, the resin was filtered, washed with THF (5×2 mL), dried in vacuo and charaterized by IR and elemental analysis.

   *Synthesis of resin **3***: To a suspension of resin **2** (250 mg) and cyanuric chloride (553 mg, 3.0 mmol) in chloroform (12 mL) was added diisopropylethylamine (0.5 mmol). After shaking at rt for 18 h, the resin was then filtered, washed with chloroform (3×5 mL) and THF (3×5 mL), dried in vacuo and charaterized by IR and elemental analysis.

   Preparation of acyl chlorides: To a suspension of resin **3** (200 mg) in CH_2Cl_2 was added carboxylic acid (0.3 equiv. based on the loading of resin **3**) and Et_3N (0.5 equiv.). After shaking at rt for 3 h and monitoring the reaction by TLC, the resin was then filtered and the solution of the acyl chloride was directly carried onto the next reaction.

10. An analogous resin with a hexyl linker (prepared from 6-amino-1-hexanol) provided similar conversion in CH_2Cl_2 while little conversion in acetone.