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A mild and convenient method for the preparation of multi-isocyanates starting from primary amines

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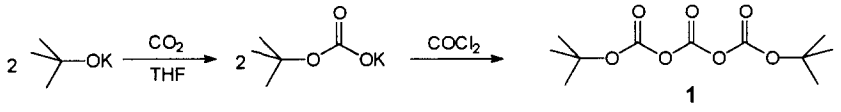
Abstract: A mild and convenient method for the synthesis and isolation of multi-isocyanates, obtained from the reaction of the corresponding primary amines with di-*t*-butyltricarbonate (**1**) is described.

Phosgene and triphosgene are reagents widely employed in the synthesis of isocyanates prepared from aromatic and aliphatic amines.[1] The relatively drastic conditions, the toxicity of phosgene, and the formation of gaseous hydrochloric acid during the conversions, have led to the development of sufficiently reactive phosgene analogs, as for example 1,1'-carbonyldiimidazole,[2-4] or alternatives such as the recently disclosed combination of di-*t*-butyldicarbonate and 4-*N*,*N*-dimethylaminopyridine.[5] For most, if not all, methods the synthesis of molecules bearing more than one isocyanate is strongly hampered by intramolecular reactions leading to ureas, e.g. in the case of 1,3-diaminopropane, where a six-membered urea ring is formed instead.

Here, we report on our finding that di-*t*-butyltricarbonate **1**[6-7] converts almost any primary amine quantitatively into its corresponding isocyanate in less than 5 minutes at room temperature. For the synthesis of multi-isocyanates **1** is the reagent par excellence, since the formation of cyclic ureas is suppressed. Tricarbonate **1** has already been reported for the synthesis of aromatic ureas,[6] however, the potential of this reagent has by far not been investigated to its full extent, despite the detailed report of its synthesis in Organic Syntheses.[7]



1

Scheme 1. Synthesis of di-t-butyltricarbonate, **1**.

The synthesis of **1** was first reported in 1969[7] and was later used commercially to prepare di-*t*-butyldicarbonate (BOC_2O). We followed the Organic Syntheses procedure, which starts with the insertion of CO_2 into potassium-*t*-butoxide and subsequent reaction with phosgene (Scheme 1). After crystallization from pentane, **1** was obtained in 84% yield. This compound should be stored below 4 °C in order to prevent the decomposition into CO_2, isobutene and *t*-butanol.[7]

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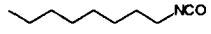
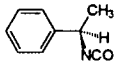
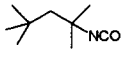
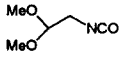
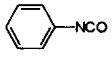
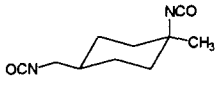
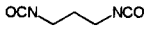
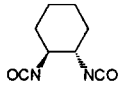
The conversion of the primary amines into the corresponding isocyanates was performed on a 5–10 mmol scale by the addition of a solution of the primary amine in freshly distilled CH_2Cl_2 to a solution of **1** in the same solvent at room temperature. The reaction leads to the formation of 2 equivalents of CO_2 and *t*-butanol.[7] The reaction is complete within 5 minutes and the yields of **2–8**, derived from a selection of primary amines, are good to excellent (Table 1). The yield of isocyanate purified by bulb-to-bulb distillation is sometimes lowered due to the similarities between boiling point of isocyanate and the side-product (BOC_2O). Both acid- and base-sensitive groups (**5** and **6**) can be tolerated. Aromatic amines (**7**) can be transformed as well, however, these should be of high enough nucleophilicity, since 2- or 3-aminopyridine and melamine are basic enough to transform **1** into BOC_2O.[7] Remarkably, the yields observed for compounds **9**[8] and **10** are relatively high. To the best of our knowledge this is the first time that these molecules have been made directly starting from their corresponding primary amines.

Table 1. Observed and isolated yields for isocyanates **2–10**.

	Isocyanate	Observed yield (%)	Isolated yield (%)
2		100	92
3		100	93
4		100	93
5	$MeO_2C(CH_2)_{10}NCO$	100	80
6		100	85
7		95	87
8		100	98
9		60[a]	48[a]
10		70[b]	20

[a] The cyclic urea is formed in a yield of 40%. After distillation, the product possesses an estimated purity of 94%.

[b] The cyclic area is formed in a yield of 30%.

In order to test the selectivity of this conversion, we subjected the poly(propylene imine) dendrimers[9] of all generations up to the fifth generation with 64 primary amine end groups to the reaction with tricarbonate **1** (Figure 1).

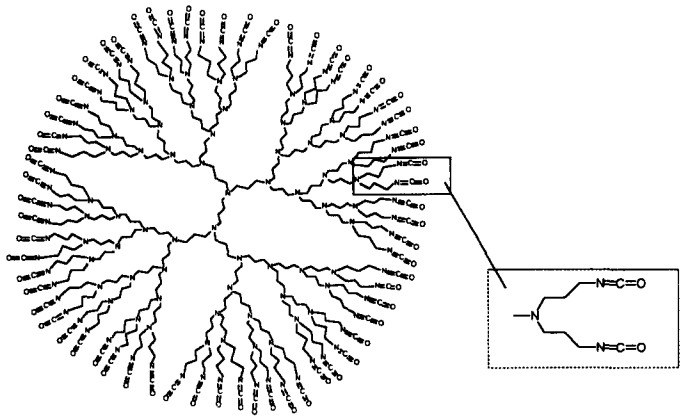
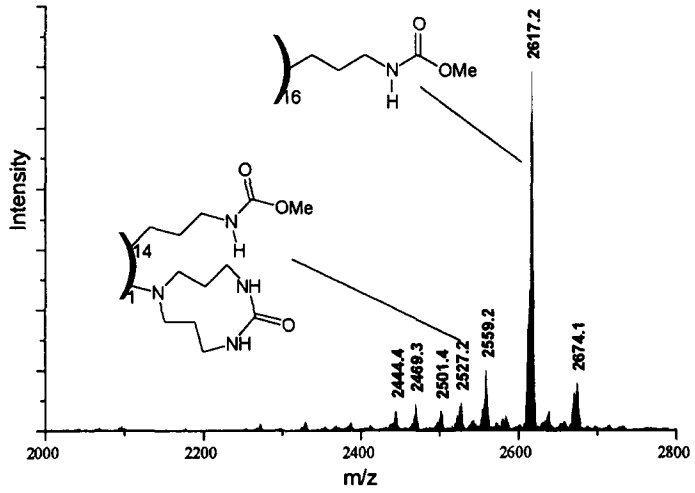


Figure 1. Fifth generation isocyanate functionalized poly(propylene imine) dendrimer.

All dendrimers were converted quantitatively into the multi-functional isocyanates, however, isolation proved to be difficult as upon evaporation of the solvent insoluble materials were obtained. Therefore, the dendritic isocyanates were converted *in situ* into urethanes and ureas using alcohols and amines, respectively. ^{1}H-NMR, ^{13}C-NMR, and IR spectroscopy of the urethanes of all generations did not show the presence of (cyclic) ureas formed by intra- or intermolecular reactions, within the experimental error of the technique. The defects present in the starting poly(propylene imine) dendrimers have been characterized in detail using ESI-MS.[9] For a more detailed study on the nature of possible defects accompanying the reaction, ESI-MS was measured on the methyl carbamate-functionalized dendrimer of the third generation (Scheme 2) with 16 end groups, as for this compound the parent amine dendrimer contains almost no defects.[9]



Scheme 2. ESI-MS of third generation methyl carbamate poly(propylene imine) dendrimer.

The mass spectrum indicates the presence of the $[M+H]^+$ peak at *m/z* 2617 (Calculated mass for $C_{120}H_{240}N_{30}O_{32}$: 2615.4 Da). The peaks at *m/z* 2674, 2559, 2501 and 2444 can be attributed to defects present in the parent dendrimer. Defect structures caused by the reaction with **1** are related to the intramolecular formation of cyclic urea and can be found at *m/z* 2527 (one defect) and 2469 (one end group missing and one defect). The amount of defects caused by the conversion to the dendritic isocyanates can be estimated from the ESI-MS spectrum and is approximately 0.5% per end group.

In conclusion, we have introduced a general and convenient method to transform primary amines into isocyanates using the easy accessible di-*t*-butyltricarbonate, **1**. The neutral and mild reaction conditions and the absence of side-products that are difficult to remove on the one hand and the ability to limit urea formation in the reaction of di- and multi-functional amines with **1** on the other hand, will make di-*t*-butyltricarbonate **1** the reagent *par excellence* for the formation of isocyanates starting from the corresponding primary amines.

Acknowledgements.

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