4-Nitrophenyl Chloroformate: A Versatile Coupling Reagent

Compiled by Benedikt Sammet

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Introduction

4-Nitrophenyl chloroformate (4-NPC; CAS: 7693-46-1) is one of the most common reagents for the activation of alcohols, thiols and amines for the formation of carbonates and carbamates. It is a colorless, crystalline solid, which is easy to handle and well-storable. It was introduced into literature for the synthesis of t-butyl 4-nitrophenyl carbonate as a reagent for the Boc-protection of amines. Today, however, its range of application is very broad and has led to considerably safer chemistry, replacing phosgene in many reactions. The obtained 4-NP carbonates and carbamates are often stable and can be purified by column chromatography or recrystallization. Nevertheless, one-pot procedures for the in situ substitution of the 4-nitrophenyl moiety are regularly employed. Due to the increasing demand for bioconjugates containing different natural product classes, stable carbonate and carbamate linker systems are conveniently synthesized by applying this reagent. In addition, the substance is used for covalent protein immobilization on surfaces and polymer peptide linkages.

Abstracts

(A) In a typical procedure for 4-nitrophenyl carbamate and carbonate synthesis 4-NPC is added to the nucleophile in the presence of an excess amine base at room temperature. In the case of an in situ substitution of the obtained intermediate the second nucleophile is directly added to the system and stirred at room temperature for usually less than one hour.

(B) 4-Nitrophenyl chloroformate is used to block hydroxyl groups in nucleosides. 4-NPC was applied to synthesize 4-nitrophenyl-5′-O-tritylthymidine-3′-carbonate in 89% yield. The obtained compound is stable enough for phosphorylation reactions and the carbonate can be removed under mild basic conditions using imidazole in aqueous organic solvents.

(C) 4-NPC is applicable for the two-step synthesis of even more reactive corresponding isocyanates. The isocyanate is either synthesized in a refluxing solution of triethylamine in toluene or via a chlorosilane-induced cleavage of 4-nitrophenol. It was shown, that the latter method selectively activates 4-nitrophenyl carbamates in the presence of 4-methoxyphenyl carbamates.

(D) The conversion of a secondary benzylamine to a corresponding Boc amine in the presence of double bonds is often not trivial. In the example shown, this problem was solved by cleaving the benzyl group under addition of 4-NPC. The direct substitution of the 4-nitrophenyl moiety with potassium tert-butylate led to the product in 66% yield in a one-pot procedure.

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(E) In an effort to synthesize deuterated catechols, benzo[\textit{d}]-1,3-dioxoles and their derivatives, an N-methylpiperidine moiety was recently successfully demethylated by the addition of 4-NPC in a two-step procedure. After the formation of the 4-NP carbamate intermediate, aqueous hydrolysis and subsequent reprotonation gave the piperidinium salt in acceptable yield.\textsuperscript{10} The reported cleavage of similar methylated secondary amines by phenyl chloroformate was explained by the formation of an N-methylated phenyl carbamate cation, followed by the nucleophilic attack of the chloride anion at the methyl group.\textsuperscript{11}

(F) 4-Nitrophenyl chloroformate can also be used to synthesize thiolactones, thus providing a useful procedure for the synthesis of thiazolidinones in \textit{β}-lactam chemistry.\textsuperscript{12,13} The intramolecular substitution of the 4-nitrophenyl moiety by an ester enolate allowed the cyclization in 46\% yield.\textsuperscript{13}

(G) 4-NPC is applicable for the rapid conversion of carboxylic acids into their reactive nitrophenyl esters.\textsuperscript{14,15} These can be used for Pd-catalyzed decarboxylative olefination reactions with various olefins. High yields were often obtained.\textsuperscript{15}

(H) Resin activation with 4-NPC is a valuable method for the connection of the first residue in solid phase chemistry. The loading capacity of such a modified PEG-resin can be easily checked by basic cleavage and UV absorption measurement of the liberated 4-nitrophenol. Cleavage from the resin is accomplished by the strong non-nucleophilic base 1,1,3,3-tetramethylguanidine directly leading to a substituted cyclic hydantoin.\textsuperscript{16}

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\text{4-NPC, DIPEA} 
\text{toluene} 
\text{80 °C, 5 h, 49\%}

1. 2 M aq NaOH, dioxane 
\text{70 °C, 3 h}

2. 1 M HCl in Et\textsubscript{2}O, acetone 
\text{0 °C, 1 h, overall 41\%}

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