

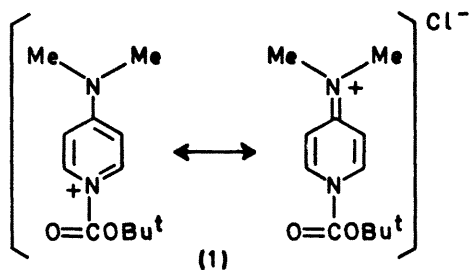
A Water-soluble Agent for the t-Butoxycarbonylation of Amines

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Summary 4-Dimethylamino-1-t-butoxycarbonylpyridinium chloride is a stable compound which reacts with amino-acid sodium salts in aqueous solution: at 25 °C the reaction is very fast and BOC-amino-acids (BOC = t-butoxycarbonyl) are isolated in good yields by solvent extraction.

ACYLPYRIDINIUM ions are very reactive species¹ which are stabilised by electron-donating substituents.^{1,2} We have found that 4-dimethylamino-1-t-butoxycarbonylpyridinium chloride (1) is a stable compound which reacts with amines in water.



The reagent is prepared by adding 4-dimethylamino-pyridine³ to an excess of the unstable t-butoxycarbonyl chloride⁴ in dry ether at 0°. The solid is collected and purified by precipitation by ether from a methylene chloride

solution; m.p. 50° (decomp.). It can be stored in the cold for several months.[†]

Spectral data for (1) are: ν_{\max} (Nujol) 1770 (C=O), 1645 and 1565 (C=C and C=N⁺), 1285 and 1220 (Bu^t) cm⁻¹; λ_{\max} (H₂O) 298 nm (log ϵ 4.25); δ (Me₂SO) 8.6 (d, 2, H _{α}), 7.05 (d, 2, H _{β}), 3.36 (s, 6, CH₃N), 1.62 (s, 9, CH₃C) p.p.m.

(1) is rapidly hydrolysed in aqueous solution at pH 5.5 ($t_{1/2}$ at 25° = 125 s). In alkali both hydrolysis and aminolysis are very fast, but selectivity, as in the case of acetylpyridinium chloride,¹ and the mass-law effect favour aminolysis at pH \leq 10.

We have studied the reaction of (1) with cyclohexylamine (the carbamate is formed in 90% yield) and with amino-acids. To a solution of 0.01 mol of the amino-acid in 10 ml of 1N-NaOH is added 0.01 mol of (1); 10 min later the solution is cooled to 0° and acidified to pH 3 (HCl). The N-BOC-amino-acid is extracted by ether, chloroform, or butanol[‡] and characterised by its m.p.⁵ and n.m.r. spectrum.

In this way we have prepared N-BOC-glycine (yield, 85%, solvent, CHCl₃), N-BOC-glutamic acid (70%, butanol), ϵ -BOC- α -L-lysine (Z = benzyloxycarbonyl, 80%, CHCl₃), N-BOC-serine (60%, butanol), N-BOC-glycine ethyl ester (90%, CHCl₃).

This method may be useful for the direct protection of free amino-groups of peptides in aqueous medium.

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[†] 4-Aminopyridine itself gives 4-amino-1-t-butoxycarbonylpyridinium chloride which is also a good t-butoxycarbonylating agent, but is slightly hygroscopic.

[‡] Butanol extracts some 4-dimethylaminopyridine hydrochloride. In this case butanol is removed by evaporation and the BOC-amino-acid extracted by CHCl₃.

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