

The Use of a Nicotinoyl Group as a Protective Group for
Hydroxyl and Amino Functions

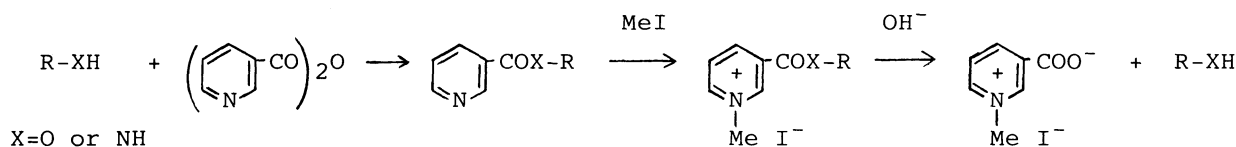
Satoshi USHIDA

Faculty of Home Economics, Mukogawa Women's University, Ikebiraki-cho,
Nishinomiya, Hyogo 663

The effective use of a nicotinoyl group as an easily introducible and cleavable protective group for hydroxyl and amino groups is described. Deprotection by alkaline hydrolysis is performed after activation by quarternization of pyridine moiety with methyl iodide.

Acyl groups are good protective groups for hydroxyl and amino functions from the viewpoint that the protected substrates are stable. This means, however, that deprotection sometimes must be carried out under drastic conditions.¹⁾ To facilitate the removal of acyl groups several methods by converting the acyl moieties into more labile groups toward the deprotection reaction have been reported. For example, protective groups containing functional groups such as nitro and carbonyl groups which can assist the deprotection after being converted into another functions²⁾ and those containing pyridine moieties such as 2-(2- or 4-pyridyl)ethoxycarbonyl³⁾ and 2-(4-pyridylethyl)⁴⁾ groups which can be activated by quarternization have been developed. This paper describes the results from the examination to use a nicotinoyl group for the protection of hydroxyl and amino groups. Nicotinic esters and amides can be converted into pyridinium salts which are more susceptible to alkaline hydrolysis than the original neutral molecules.

A nicotinoyl group was readily introduced by the reaction of an alcohol or an amine with an equimolar amount of nicotinic anhydride⁵⁾ in dry pyridine. Thus obtained esters or amides were subjected to the Menshutkin reaction in methyl iodide at room temperature. After stirring for a day quarternary salts produced as precipitates were separated. Deprotection was carried out in 0.5 mol dm⁻³ NaHCO₃ for esters or in 0.5 mol dm⁻³ NaOH for amides at room temperature. The deprotected substrates were extracted with ether, characterized and quantitatively determined with gas chromatography. Yields of protection and deprotection steps and the time required for the hydrolysis of 50% of the substrate are shown in Table 1.



Quarternized nicotinic esters and amides permitted easy alkaline hydrolyses. This enabled the selective cleavage of the nicotinoyl group. The intramolecular ester functions were not affected during the course of introduction and removal of the nicotinoyl group as seen for phenyl salicylate and methyl lactate. Other advantages of the present protective group are as follows; 1) Since quarternized protected substrates are water-soluble crystalline solids, they are readily isolated from the reaction mixture and purified by recrystallization. 2) Deprotected substrates are readily separated from the removed N-methylnicotinate by simple extraction by virtue of the difference in solubility.

The author thanks Professor A. Ohno of Kyoto University for helpful discussions.

Table 1. Introduction and removal of nicotinoyl group

Substrate	Introduction	N-Methylation	Alkaline hydrolysis	
	Yield/%	Yield/%	Yield/%	Time for 50% hydrolysis
Phenol	98	94	98	9 min
Benzyl Alcohol	92	93	94	2 h
2-Phenylethanol	96	95	98	2 h
1-Hexanol	95	94	95	3 h
Phenyl Salicylate	99	95	89	7 min
Methyl Lactate	93	90	85	2 min
Aniline	99	81	86	18 h
4-Chloroaniline	98	77	96	55 h
Benzylamine	99	93	55	2 h

References

- 1) T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, Inc., New York (1981).
- 2) I. D. Entwistle, *Tetrahedron Lett.*, 1979, 555; A. Hassner, G. Strand, M. Rubinstein, and A. Patchornik, *J. Am. Chem. Soc.*, 97, 1614 (1975).
- 3) H. Kunz and R. Barthels, *Angew. Chem., Int. Ed. Engl.*, 22, 783 (1983); H. Kunz and S. Birnbach, *Tetrahedron Lett.*, 25, 3567 (1984).
- 4) A. R. Katritzky, G. R. Khan, and O. A. Schwarz, *Tetrahedron Lett.*, 25, 1223 (1984); A. R. Katritzky, I. Takahashi, and C. M. Marson, *J. Org. Chem.*, 51, 4914 (1986).
- 5) A. W. Schrecker and P. B. Maury, *J. Am. Chem. Soc.*, 76, 5803 (1954).

(Received September 26, 1988)