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Deprotection of 4-Methoxybenzyloxycarbonyl Group with *p*-Toluenesulfonic Acid in Acetonitrile. Application to a Large-scale Preparation of 7-[D-2-Amino-2-(4-hydroxyphenyl)acetamido]cephalosporanic Acid

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Synopsis. The 4-methoxybenzyloxycarbonyl group of 7-[D-2-(4-hydroxyphenyl)-2-(4-methoxybenzyloxycarbonylamino)acetamido]cephalosporanic acid was effectively removed with *p*-toluenesulfonic acid in acetonitrile. The mechanism of the deprotection is discussed and the role of acetonitrile can reasonably be explained in terms of the Ritter reaction.

In a previous report1) of our screening study, we reported that the 4-methoxybenzyloxycarbonyl group [Z(OMe)] of 7-[D-2-(4-hydroxyphenyl)-2-(4-methoxybenzyloxycarbonylamino)actamido]cephalosporanic acid (**1**) could be successfuly removed by trifluoroacetic acid without adverse effect on the compound. Trifluoroacetic acid is conveniently used in laboratory synthesis, but its use for a large-scale preparation is undesirable because of its irritation on mucous membrane.

We now report a practical deprotection of the Z(OMe) group of **1** which has given a solution to this problem. The deprotection is accomplished by treatment of **1** with *p*-toluenesulfonic acid or methanesulfonic acid in

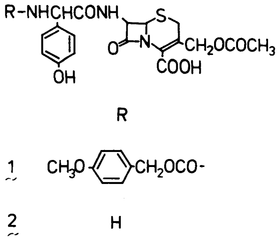


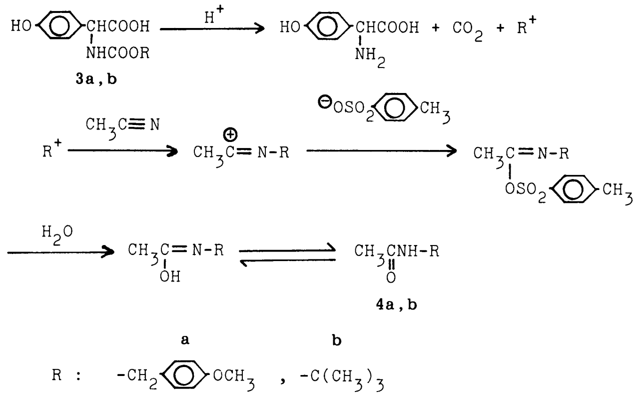
TABLE 1. CONDITIONS FOR REMOVAL OF Z(OMe) GROUP AND RATIOS OF **1** AND **2**

Sulfonic acid a) (molar ratio)	Solvent a) System & composition		Temperature °C	Reaction Time/min	Molar ratio/% 1	2
PTS (2 equiv)	MeCN-ACT		10	60	32	68
		9 : 1 b)	20	30	5	95
				60	0	100
		4 : 1		60	3	97
		1 : 1			19	81
	MeCN-Dioxane	9 : 1	20	60	2	98
		4 : 1			7	93
		1 : 1			36	64
	MeCN-H_2O	4 : 1	20	60	100	0
	ACT	—	25	60	39	61
	Dioxane	—			84	16
	EtOH	—			96	4
	DMF	—			100	0
PTS (1 equiv)	MeCN-ACT	9 : 1	20	30	61	39
				60	48	52
MSA (2 equiv)				60	23	77

a) Abbreviations: PTS, *p*-toluenesulfonic acid monohydrate; MSA, methanesulfonic acid; ACT, acetone; DMF, *N*,*N*-dimethylformamide. b) By volume.

acetonitrile. The deprotection extremely depended on the nature of solvents tested and acetonitrile was found to be the most effective solvent (Table 1). Removal of the Z(OMe) group of **1** was completed within 60 min by using two equivalents of *p*-toluenesulfonic acid at 20—25 °C in acetonitrile–acetone (9:1, v/v). Addition of acetone or dioxane to acetonitrile in a small ratio was useful for preventing deposits from separating out of reaction mixtures as the removal reaction proceeded, but their addition in increased ratios slowed down the reaction. The reaction was also slowed down when smaller amounts of *p*-toluenesulfonic acid or lower reaction temperatures were used. Addition of excess water to acetonitrile interfered with the deprotection. Methanesulfonic acid also removed the Z(OMe) group, but a slightly longer reaction time was required than for the use of *p*-toluenesulfonic acid.

The role of acetonitrile was made clear as follows: A treatment of *N*-Z(OMe)-*p*-hydroxyphenylglycine (**3a**) with *p*-toluenesulfonic acid in acetonitrile gave *N*-(4-methoxybenzyl)acetamide (**4a**) in 49% yield as well as *p*-hydroxyphenylglycine *p*-toluenesulfonic acid salt in 93% recovery. This result suggests that the Ritter reaction occurs in this deprotection. Chauvette *et al.*[2] reported that a Boc group was effectively removed in acetonitrile by treatment with *p*-toluenesulfonic acid. But the mechanism was not cleared. A treatment of *N*-Boc-*p*-hydroxyphenylglycine (**3b**) under similar conditions also gave the corresponding acetamide **4b** in 51% yield. In both cases, the role of acetonitrile can reasonably be explained on the basis of the mechanism shown in Scheme 1, although the yields of **4a** and **4b** were not quantitative.



Scheme 1.

This deprotection has successfully been applied to a several-hundred-gram scale preparation of cefpiramide,[3] a new broad-spectrum cephalosporin with anti-pseudomonal activity.

Although acetonitrile has not been a common solvent in peptide synthesis, this procedure using acetonitrile may be recommended for efficient deprotection of a Z(OMe) or a Boc group.

Experimental

Melting points were determined in open capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX-90Q (90 MHz) spectrometer with TMS used as internal standard; all chemical shifts are reported in δ values. Separation and quantitative analysis were performed with a high performance liquid chromatograph (Model No. ALC/GPL 204, Japan Waters, Ltd.) equipped with a LiChrosorb RP-8 column (10 μm particle size, 30 cm by 4 mm).

*Removal of a Z(OMe) Group of 7-[*D*-2-(4-Hydroxyphenyl)-2-(4-methoxybenzyloxycarbonylamino)acetamido]cephalosporanic Acid (1).* A mixture of compound **1**[1] (0.5 g), solvent (5 ml), and *p*-toluenesulfonic acid or methanesulfonic acid was stirred under the conditions given in Table 1. A part of the reaction mixture was sampled and analyzed by HPLC. The mobile phase used was a mixture of 0.01 M (1M=1 mol dm^{-3}) phosphate buffer (pH 6.8) and MeOH (6:4 by volume). The ratios of **1** and **2** in Table 1 were determined from each peak area corrected for the UV sensitivity of each compound.

Removal of a Z(OMe) Group of D*-2-(4-Hydroxyphenyl)-2-(4-methoxybenzyloxycarbonylamino)acetic Acid (3a).* To a solution of **3a** (1.0 g, 3 mmol) in MeCN (40 ml) was added a solution of *p*-toluenesulfonic acid monohydrate (1.15 g, 6 mmol) in MeCN (15 ml). The mixture was stirred at room temperature for 3.5 h. The *p*-hydroxyphenylglycine *p*-tolenesulfonic acid salt precipitated was collected by filtration, washed with MeCN (10 ml) and dried *in vacuo*: yield 0.95 g (93%); mp 222—223 °C (dec.) (lit,[6] 229 °C).

The combined filtrate and washings were concentrated *in vacuo*. To the residue was added a solution of sodium bicarbonate (0.507 g) in water (15 ml) and the mixture was extracted successively three times with diethyl ether (15 ml) and twice with ethyl acetate (15 ml). The extracts were combined, dried over $MgSO_4$, and the solvent removed *in vacuo*, leaving a yellow solid. It was chromatographed on a thin layer (Merck; pre-coated TLC plate Silica Gel $60F_{254}$, 20×20 cm, of layer thickness 0.50 mm) with EtOAc to give *N*-(4-methoxybenzyl)acetamide (0.195 g, 36.0%): mp 95—96 °C (lit,[4] 95—97 °C). The content of this compound in the reaction mixture was 0.27 g (49%) as determined by an HPLC analysis using a mobile phase consisting of 0.01 M phosphate buffer (pH 6.8) and MeOH (1:1 by volume).

A similar treatment of D-*N*-Boc-*p*-hydroxyphenylglycine (**3b**) with *p*-toluenesulfonic acid in acetonitrile gave *N*-(*t*-butyl)acetamide in 51% yield, which was identified by elemental analysis and by comparison of its melting point and ^{1}H NMR spectrum with those of an authentic sample.[5]

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