An Effective Acylation of Cephalosporins Using 1-Methanesulfonyloxy-6-trifluoromethylbenzotriazole†

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A new coupling agent, 1-methanesulfonyloxy-6-trifluoromethyl-benzotriazole (**3**), was prepared by the reaction of 1-hydroxy-6-trifluoromethylbenzotriazole (**1**) and methanesulfonyl chloride. **3** was reacted with 2-(2-amino-4-thiazolyl)-2-synalkoxyi minoacetic acid (**4**) to give a mixture of active intermediates (**5** and **6**), which was treated with 7-aminocephalosporanic acid derivatives (**10**) to afford cephalosporin derivatives (**11**) in short reaction time with high yields.

Introduction

Acylation is one of the most important reactions which are frequently used in the synthesis of β-lactam antibiotics, and considerable progress has been made in the development of various mild acylation methods.[1]

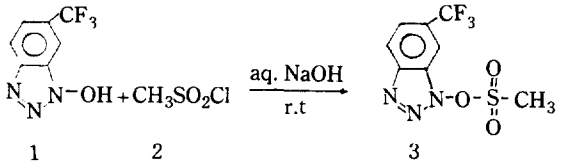
It has been well known that the utilization of 1-hydroxybenzotriazole (HOBT) as an activating reagent of carboxylic acid has provided an useful method for the formation of semisynthetic cephalosporins. Because of disadvantage of dicyclohexylcarbodiimide which causes side reaction[2] and purification problem. Various coupling agents have been developed such as p-toluenesulfonyloxy-benzotriazole[3], 1,1'-di[benzotriazolo]oxalate[4], 1,1'-bis[benzotriazolyl]carbonate[5] and benzotriazolyl diethyl phosphate[6], and have been widely used in the preparation of cephalosporins[7]. But these coupling agents still reguire comparatively long reaction times.[8]

Recently, It was reported that 1.1'-bis [6-(trifluoromethyl) benzotriazolyl]oxalate was an excellent coupling agent for the preparation of dipeptides, esters, and thioesters.[10] This led us to attempt the synthesis of several coupling agents from 1-hydroxy-6-(trifluoromethyl) benzotriazole (FOBT, **1**) which might be expected to function as efficient coupling agents with a wide range of preparative applications in acylation.

We now wish to report a new and effective method for acylation on the 7-aminocephalosporanic acid (7-ACA) derivatives using new coupling agent, 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS, **3**).

Results and Discussion

Synthesis of FMS(3). FMS is easily prepared from FOBT (**1**) and methanesulfonylchloride in aqueous sodium hydroxide solution at room temperature (Scheme 1).

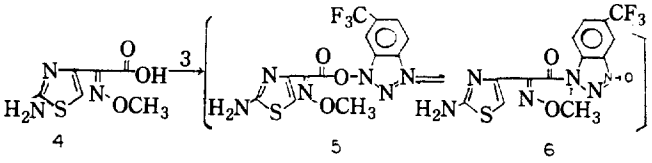


Scheme 1

†This article is dedicated to professor *Yoon Nung Min* for his 60th birthday.

FMS(**3**) is a white crystalline material melting at 98-100°C which can be stored for several months in refrigerator, and is generally used without further purification.

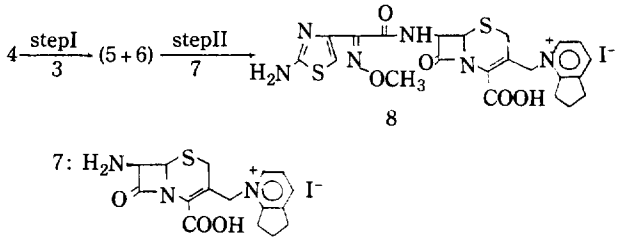
Reaction of FMS (3) with carboxylic acid. In order to demonstrate the simplicity and versatility, FMS (**3**) is directly reacted with 2-(2-amino-4-thiazolyl)-2-syn-methoxyiminoacetic acid (ATA, **4**) with unprotected amino group. Activation of carboxylic acid of ATA (**4**) is successfully carried out by the treatment of one equivalent of FMS in the presence of tertiary organic base to afford the mixture of active ester (**5**) and active amide (**6**) (Scheme 2).



Scheme 2

Each of these intermediates (**5** and **6**) is carefully separated by flash column chromatography and identified by its spectroscopic properties. Compound with higher R_f value has characteristic IR spectra at ca. 1850 cm^{-1} which shows O-acylated product (**5**) and that of lower R_f value has N-acylcarbonyl component (**6**) which showed characteristic IR spectra at ca. 1725 cm^{-1}. These active intermediates are predicted as highly reactive species toward aminolysis because of their unstability in the isolated forms. Therefore, It is more convenient to carry out the reaction in a one-pot procedure.

Acylation of 7-ACA derivatives. When the mixture of (**5**) and (**6**) is treated with 7-ACA derivatives, acylation is accomplished in several minutes to give acylated cephalosporin derivatives. To determine the optimum condition, first we study the synthesis of Cefpirome HI (**8**).



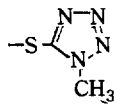
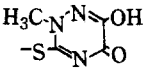
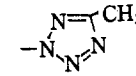
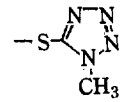
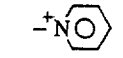
Scheme 3

Table 1. Preparation of Cepirome-HI under Various Conditions[a]

Ratio				Solvent	Base	Yield[c](%)
3	Base	**4**	**7**			
1	1	1	1	DMF	Et_3N	84
1	1	1	1	DMAC	Et_3N	80
1	1	1	1	NMP	Et_3N	78
1	1	1	1	DMF	pyridine	83
1	1	1	1	DMF	DMA[b]	80
1.2	1.1	1	1	DMF	Et_3N	91
1.2	1.1	1	0.8	DMF	Et_3N	94

[a] Activation reaction is carried out at ice-bath temperature, for 0.5 h using 10 mmol of **4** in 50 m*l* of solvent and acylation reaction is carried out at room temperature for 1 h. [b] N,N-Dimethylaniline. [c] Isolated yield based on **7** used.

Table 2. Preparation of Cephalosporin Derivatives (11) by FMS (3)

R	X	Z	M	Rxn Time[a](hr) Step I	Step II	Yield[b](%)
CH_3	CH		H	0.5	0.5	90
"	"		H	0.5	1.0	90
"	"		H	0.5	0.5	92
C_2H_5	N		H	1.0	0.5	88
CH_2COO-t-Bu	CH		-	0.25	1.0	91[c]

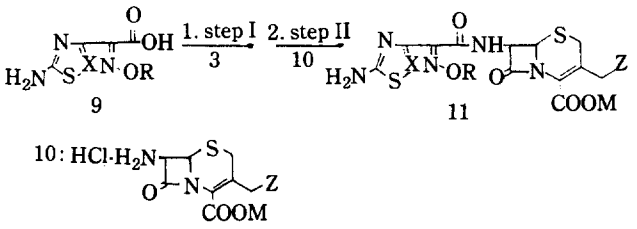
[a] see footnote on **Table 1.** [b] Isolated yield based on **10** used. [c] Obtained as a form of 2·HCl salt.

ATA (**4**) is dissolved in polar solvent such as DMF, N,N-dimethylacetamide (DMAC) and N-methylpyrrolidinone (NMP), and activated by FMS (**3**) in the presence of organic bases. The effect of solvents, bases and molar ratio of reactants is studied. As shown in Table 1, the best yield is obtained where 1.2 equiv of FMS to ATA is employed in DMF solvent in the presence of triethylamine. The activation reaction (step I) is complete within 15 minutes at ice-bath temperature and acylation reaction (step II) is accomplished within one hour by adding **7** and stirring at room temperature. The desired product (**8**) is isolated in the ordinary manner.[9]

These reaction conditions have applied to the preparation of several cephalosporins containing 2-aminothiazolyl and 2-aminothiadiazolyl group at C-7 position and the results are summarized in Scheme 4 and Table 2.

FMS has various advantages that it is easily handled and has no danger, and that the reaction can be carried out without undesirable side reactions to give desired cephalosporin derivatives in shorter time than HOBT derivatives[9]

In conclusion, we have found that FMS is one of the most useful coupling agents for the preparation of cephalosporin



Scheme 4

derivatives.

Experimental

Malting points were uncorrected. ^{1}H-NMR spectra were recorded at 80 MHz on a VARIAN FT-80A spectrophotometer. IR spectra were obtained using potassium bromide pellets with PERKIN-ELMER IR-283 spectrophotometer. Column chromatography was performed with Merck silica gel 60 (230-400 mesh). Properties (MP, IR, and NMR) of compounds synthesized were compared with those of literature. FOBT was prepared by usual procedure[10] using 4-chloro-3-nitro-α,α,α-trifluorotoluene which was purchased form Aldrich Chemicals. Aminothiazolyl derivatives (4 and 9) was purchased from Lonza chemical company.

1-Methanesulfonyloxy-6-trifluoromethylbenzotriazole(3). To a stirred solution of **1** (6.8 g, 33.5 mmol) in 1N aqueous sodium hydroxide (36 m*l*) was slowly added methanesulfonyl chloride (2.8 m*l*, 36.2 mmol) at ice-cold temperature and further was added thereto ethyl actate (20 m*l*) and water (100 m*l*). After the mixture was stirred at room temperature for 2 h, ethyl acetate layer is separated. The aqueous layer was extracted with ethyl acetate (20 m*l*×2) and combined ethyl acetate layer was dried over magnesium sulfate. After evaporation of ethyl acetate, the residue was triturated with petroleum ether to afford a white solid of **3** (8.8 g 93%); mp 98-100°C; IR (KBr, cm^{-1}) 1300 (S=o); ^{1}H-NMR (DMSO-d6,δ) 2.65 (3H,s), 7.60-7.80 (1H,m), 8.00-8.30 (2H,m).

2-(2-Amino-thiazolyl)-2-syn-methoxyiminoacetic acid-5-trifluoromethanşulfonyl-1H-benzotriazol-1-yl ester(5) and syn-1-[(2-amino-4-thiazolyl)-methoxyimino) acetyl]-3-hydroxy-5-trifluoromethyl-1H-benzotriazolium hydroxide inner salt (6). To a solution of **4**(2.0 g, 10 mmol) dissolved in DMF (20 m*l*), triethylamine (1.53 m*l*, 11 mmol) was added dropwise under ice-cooling and **3**(3.3 g 12 mmol) was added in one portion. After stirring for 30 minutes at ice-bath temperature, The mixture was poured into ice water. The precipitates were collected by filtration and then dried in vacuo to obtain a mixture of **5** and **6** (3.6 g, 92%) in the form of crystals. Parts of this mixture were separated by flash column chramatography [Merck silica gel 60 (230-400mesh); developing solvent, toluene: ethyl acetate=7:3 by volume] to afford **5**; mp 198°C (dec) and 6; mp 205 (dec), respectively.

5: IR (KBr, cm^{-1}) 1850 (ester); ^{1}H-NMR (DMSO-d6,δ) 3.90 (3H.s), 6.84 (1H,s), 7.56-8.25 (3H.m).

6: IR (KBr, cm^{-1}) 1725 (amide); ^{1}H-NMR (DMSO-d6,δ) 3.80 (3H.s), 6.78 (1H,s), 7.50-8.50 (3H,m).

Acylation of 7-aminocephalosporanic acid derivatives. General procedure. To a stirred solution of **9** (10 mmol) in DMF (50 m*l*) were added triethylamine (1.5 m*l*, 11 mmol) and **3**(3.4 g, 12 mmol) under ice-cooling. After the

stirring for 0.5 h, 7-aminocephalosporanic acid derivatives of **10** (8 mmol) was added to this mixture under ice-cooling. The mixture was stirred for several minutes at room temperature and then worked up as usual method to afford **11**.

Cefpirome-HI salt (8). **3** (3.4 g, 12 mmol) was added with stirring to a mixture of **4** (2.0 g, 10 mmol) and triethylamine (1.5 m*l*, 11 mmol) in DMF (50 m*l*) at ice-cold temperature. After 0.5 h, **7** (3.8 g, 8 mmol) was added to this mixture. After stirring for 0.5 h at room temperature, the insoluble meterial was filtered off. DMF was removed by distillation under reduced pressure (2 mmHg), and then isopropyl alcohol (20 m*l*) was added to the residue to crystalize. After stirring for 0.5 h under ice-bath temperature, The mixture was filtered and dried in vacuo to obtain yellowish crystal of **8** (4.8 g, 93.4%); mp 178-180°C (dec); IR (KBr, cm^{-1}) 1785 (lactam c=o); ^{1}H-NMR (CF_3COOD, δ) 2.30-2.85 (2H. m), 3.10-4.05 (6h, m) 4.4 (3H.s) 5.21-6.23 (4H.m) 8.11 (1H.s) 7.65-8.70(3H,m).

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References and Notes

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Remarks on Single-Frequency Two-Photon Absorption†

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The single-frequency two-photon absorption tensor is carefully rederived and examined. It is pointed out that the conventionally used tensor, which has been formally deduced from the different-frequency two-photon absorption tensor, can give an incorrect absolute two-photon absorption rate. The identity forbidden selection rule and the polarization ratio expressions are also examined with the new tensor.

Introduction

The expression for the two-photon absorption (TPA) tensor (of rank 2) or the two-photon absorption cross section, is often derived by applying the perturbation technique to the time-dependent Schrödinger equation at the electric-dipole approximation.[1,2] For TPA using two different frequencies (different-frequency two-photon absorption, DFTPA), each Cartesian tensor element contains two terms, each of which is a sum over intermediate states of the product of two dipole transition moments and an energy denominator.[1-5] Since molecular symmetry requires certain relations between the 9 Cartesian tensor elements,[2-4] two-photon transitions can often described by less than 9 independent tensor elements. For example, a transition from the A_{1g} ground state to an A_{2g} vibronic state (one quantum of a b_{1u} vibrational mode in the B_{2u} electronic state) in benzene belonging to the D_{6h} poing group can be described by a single tensor element (the xy or yx element) because the two non-vanishing elements have to be equal in magnitude and opposite in sign.[2-6] Thus, the TPA tensor for the A_{1g}-A_{2g} transition in benzene is traceless and antisymmetric.

When the frequencies of the applied radiation field used in two-photon absorption become identical (single-frequency two-photon absorption, SFTPA), the two-photon absorption tensor expressions are conventionally obtained by simply setting the two frequencies identical in the energy denominators of the DFTPA tensor.[2-4] The conventional Cartesian SFTPA tensor derived in this fashion should be symmetric because the two terms in the tensor element share the same energy denominator.

When the DFTPA tensor is traceless and antisymmetric as for the A_{1g}-A_{2g} two-photon transition in benzene, the conventional SFTPA tensor must vanish because of the additional symmetry requirement of the conventional SFTPA tensor. Therefore, such transitions become formally forbidden when the two frequencies are identical. This type of two-photon transitions is known as the *identity forbidden* transitions and the above mentioned A_{1g}-A_{2g} transition in benzene is a well-known example of such transtions.[2-6] This transi-

† Dedicated to Professor Nung Min Yoon on the occasion of his 60th birthday.