7α-METHOXYLATION OF CEPHALOSPORINS

Katsuyoshi Iwamatsu, Koichi Shudo and Toshihiko Okamoto
Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-ku, Tokyo, Japan

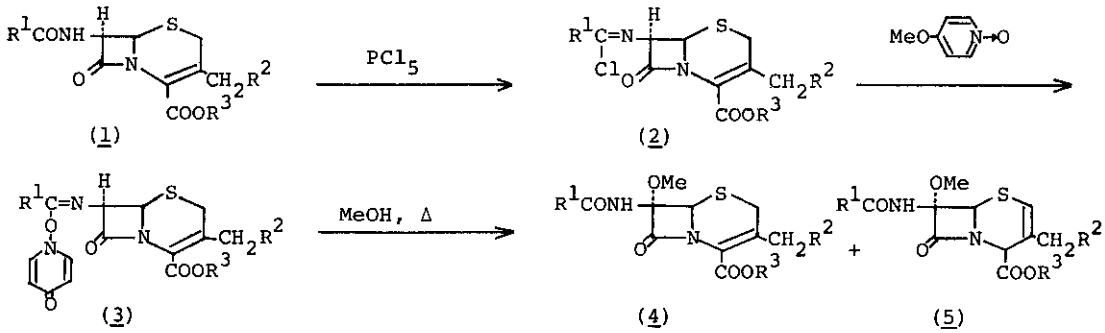
Abstract ——A method for 7α-methoxylation of cephalosporins is described. Treatment of the imidoyl chlorides of cephalosporins (2) with 4-methoxypyridine N-oxide afforded (4-pyrido-1-yl)oxyimino compounds (3), which were transformed to 7α-methoxycephalosporins (4) via thermal 1,4-elimination followed by addition of methanol.

The discovery of a new family of 7α-methoxycephalosporins and its high resistance to β-lactamase initiated extensive effort to search a method for introduction of a methoxy group at 7-position of cephalosporins, and various methoxylation methods have been reported.[1] In the previous paper,[2] we reported a new synthetic method for methoxylation on cephalosporins which involved the base catalyzed 1,4-elimination of the oxide-adducts obtained from the reaction of imidoyl chlorides of cephalosporins (2) with pyridine N-oxides in the presence of silver salt catalyst. As an extention of our studies, we found that 4-methoxypyridine N-oxide could couple with imidoyl chlorides (2) without using silver salt catalyst and afforded new type adducts, (4-pyrido-1-yl)oxyimino compounds (3) which underwent thermal 1,4-elimination to give 7α-methoxycephalosporins via 7-acylimine intermediate.
Treatment of imidoyl chloride (2a), which was obtained from methyl 7β-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (1a) and PCl_5, with 2.5 molar equivalents of 4-methoxypyridine N-oxide in 1,2-dichloroethane at 75° C for 7 hr under argon atmosphere afforded (4-pyrido-1-yl)oxyimino compound (3a) in 45 % yield. This was purified by silica gel chromatography by elution with $CHCl_3$-CH_3OH (30:1).[3]
The structure of 3a was consistent with the mass spectrum, showing a molecular ion peak at m/z 455 which corresponded to the molecular weight with loss of CH_3Cl from the adduct of 2a and 4-methoxypyridine N-oxide. In the NMR spectrum of 3a, the

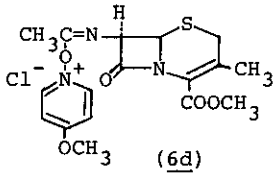
signal of the methoxy group on the pyridine ring was absent, and doublets at 6.30 and 7.25 ppm due to α and β-protons on the 4-pyridone moiety was observed.

The methoxylation was achieved by refluxing 3a in dry methanol without an oxydative reagent or catalytic base. Treatment of 3a with dry methanol at 120° C (in a sealed tube) for 30 min, followed by silica gel chromatography by benzene-ethyl acetate (5:2) as the developing solvent, afforded methyl 7α-methoxy-7β-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (4a), together with Δ^2-isomer (5a) in 41 % and 34 % yields, respectively.[4] The total yield of methoxylation was 75 %. The α-configuration of 7α-methoxy group of 4a was assigned by comparing the NMR spectrum with that of an authentic sample.[1a] This methoxylation method was analogously applied to other cephalosporins and the results were summarized in Table 1. No special effort was made to improve the yield.

Scheme 1.

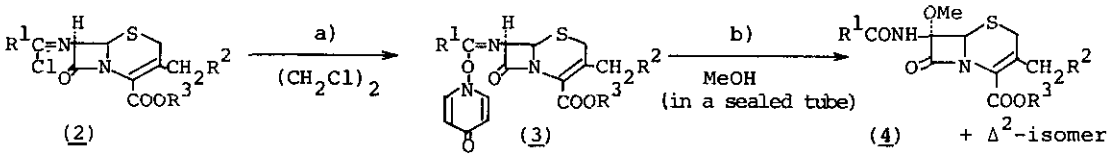


The reactivity of imidoyl chloride with 4-methoxypyridine N-oxide depended on the nature of the original 7β-substituent. When the dichloromethane solution of imidoyl chloride (2d) of methyl 7β-acetamido-3-methyl-3-cephem-4-carboxylate (1d) was treated with 4-methoxypyridine N-oxide, the reaction proceeded under cooling conditions (at 0° C for 30 min) and an intermediate (6d) was isolated successfully as white needles in 73 % yield after Sephadex LH-20 chromatography. The pyridinium structure of 6d was determined on the basis of the spectroscopic data and elemental analysis.[5] The empirical formula, $C_{17}H_{20}N_3O_5SCl\cdot H_2O$, was consisted with the proposed structure for 6d, and IR spectrum demonstrated the retention of the ⩾C=N- bond at



(6d)

Table 1.



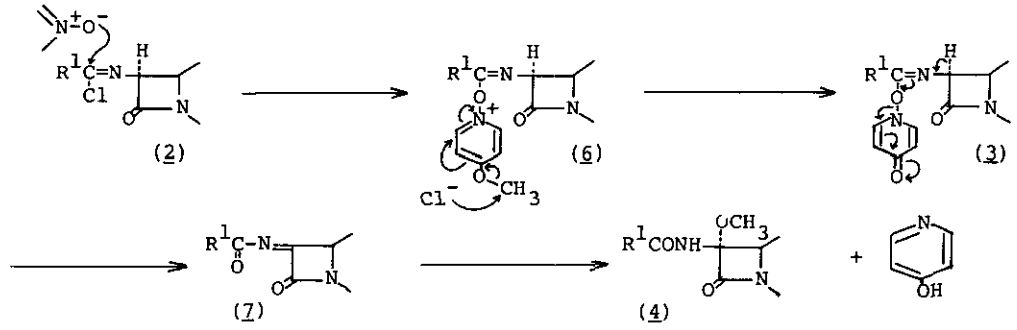
Entry	R^1	R^2	R^3	Conditions	Yield (%) (3)	(4)	(5)
a	$PhOCH_2$	H	CH_3	a) N-oxide 2.5 mol eq., 75°C, 7 hr b) 120°C, 0.5 hr	45	41	34
b	$PhOCH_2$	H	$CHPh_2$	a) N-oxide 3 mol eq., 70°C, 9 hr b) 120°C, 0.5 hr	18	30	20
c	$PhOCH_2$	STz	CH_3	a) N-oxide 2.5 mol eq., 70°C, 3 hr b) 120°C, 40 min	7	15	42
d	CH_3	H	CH_3	a) N-oxide 2.5 mol eq., 70°C, 1.5 hr b) 70°C, 1.5 hr	9	49	27

1625 cm^{-1}. NMR spectrum showed a singlet at 4.21 ppm (3H) due to the methoxy group on the pyridinium ring, and a more deshielded couple of doublets at 7.70 and 9.25 ppm compared to those of 4-methoxypyridine N-oxide (at 6.79 and 8.12), which were assigned to the protons of the pyridinium moiety of 6d.

Treatment of pyridinium intermediate 6d in 1,2-dichloroethane at 60° C for 4.5 hr resulted in demethylation of 4-methoxypyridinium moiety and gave (4-pyrido-1-yl)oxyimino compound (3d) in 35 % yield. Subsequent reaction of 3d with hot methanol afforded 4d, together with a reasonable amount of 4-hydroxypyridine which was purified by Sephadex LH-20 chromatography and identified with an authentic sample.

A reaction mechanism shown in Scheme 2 was proposed. The formation of (4-pyrido-1-yl)oxyimino derivative (3) from 6 could be explained by a nucleophilic attack of chloride on the methyl group of 6, which was formed by initial nucleophilic addition of the N-oxide on imidoyl chloride (2). Recently, Wachi and Terada proposed an

Scheme 2



analogous mechanism for the reaction of 4-chloro-2,2-dimethyl-2H-benzoxazine with 2- or 4-methoxypyridine N-oxide.[6] The generation of acylimine (7) from (4-pyrido-1-yl)oxyimino derivative (3) was realized via 1,4-elimination which may be triggered by thermal heterolytic cleavage of the N-O bond of 3. The N-O heterolytic reaction has been established.[7] Introduction of the methoxy group to 7-position occurs from α-side as usual.[1a]

REFERENCES AND NOTES

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3) 3a, nmr ($CDCl_3$) δ (ppm) 2.10 (3H, s, CH_3), 3.20 (2H, ABq, J=18Hz, C-2), 3.82 (3H, s, $COOCH_3$), 4.90 (1H, d, J=5Hz, C-6), 5.56 (1H, d, J=5Hz, C-7), 5.08 (2H, ABq, J=14Hz, OCH_2), 6.9-7.4 (5H, m, phenyl), 6.30 (2H, d, J=8Hz, pyridone), 7.25 (2H, d, J=8Hz, pyridone), ir (KBr) 1770 (lactam), 1720 (C=O), 1620 (⊃C=N-) cm^{-1}, mass (M^+:m/z 455).

4) 4a, nmr ($CDCl_3$) δ (ppm) 2.19 (3H, s, CH_3), 3.18 (2H, s, C-2), 3.58 (3H, s, OCH_3), 3.86 (3H, s, $COOCH_3$), 4.60 (2H, s, OCH_2), 5.08 (1H, s, C-6), 6.9-7.5 (6H, m, phenyl and CONH), ir (KBr) 1775 (lactam), 1720 (C=O), 1685 (CONH) cm^{-1}, mass (M^+:m/z 392). 5a, nmr ($CDCl_3$) δ (ppm) 1.90 (3H, bs, CH_3), 3.60 (3H, s, OCH_3), 3.84 (3H, s, $COOCH_3$), 4.62 (2H, s, OCH_2), 4.79 (1H, bs, C-4), 5.43 (1H, s, C-6), 5.88 (1H, bs, C-2), 6.9-7.5 (6H, m, phenyl and CONH), ir (KBr) 1770 (lactam), 1740 (C=O), 1690 (CONH) cm^{-1}, mass (M^+:m/z 392).

5) 6d, mp 103.5-104.5° C (dec), Anal. Calcd. for $C_{17}H_{20}N_3O_5SCl \cdot H_2O$: C, 47.28; H, 5.13; N, 9.73; S, 7.42; Cl, 8.21. Found: C, 46.99; H, 5.10; N, 9.97; S, 7.30; Cl, 8.34, nmr ($CDCl_3$) δ (ppm) 2.07 (3H, s, CH_3), 2.53 (3H, s, CH_3C=N-), 3.25 (2H, ABq, J=18Hz, C-2), 3.82 (3H, s, $COOCH_3$), 4.21 (3H, s, OCH_3), 4.88 (1H, d, J=5Hz, C-6), 5.37 (1H, d, J=5Hz, C-7), 7.70 (2H, d, J=7Hz, pyridinium), 9.25 (2H, d, J=7Hz, pyridinium), ir (KBr) 1760 (lactam), 1725 (C=O), 1625 (⊃C=N-) cm^{-1}, mass (M^+:m/z 378).

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