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A NEW SYNTHETIC METHOD FOR 7α-METHOXYCEPHALOSPORINS

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Summary: A new synthetic route for 7α-methoxy-7β-acylaminocephalosporins is described.

7α-Methoxycephalosporins are very effective antibiotics against many pathogenic microorganisms, particularly against resistant gram negative bacteria, [1] and many efforts have been made to provide new practical methods for introduction of the methoxy group into cephalosporins.[2]

Koppel and Koehler[3] has reported a one-step stereoselective methoxylation of 7β-acylaminocephalosporins (reagent: MeOLi and t-BuOCl). The intermediate of this reaction is thought to be acylimine, which undergoes Michael type addition of methanol. We now wish to report a new one-pot procedure for preparation of 7α-methoxycephalosporins which comprises a 1,4-elimination process to form the acylimine without use of t-butyl hypochlorite.

7β-Acylaminocephalosporin 1 was converted to imino chloride 2 by the usual method. Treatment of compound 2 with silver triflate (or tetrafluoroborate) and pyridine-N-oxide (or 4-methoxypyridine-N-oxide) in methylene chloride at -30°c for 2 hr gave the oxide adduct 3. Without isolation of this adduct 3, the reaction mixture was treated with methanol and triethylamine at -40°c to afford 7α-methoxy-7β-acylaminocephalosporin 5.[4),5)] 5a: IR ν_{max}^{nujol} 1780 cm^{-1}; mp 142.5 -143.5°(MeOH). NMR($CDCl_3$) δ: 2.22(3H, s), 3.21(2H, s), 3.55(3H, s), 4.61(2H, s), 5.08(1H, s), 5.25 and 5.43(2H, ABq, J=18Hz), 6.8-7.5(5H, m), 7.59(2H, d, J=8Hz), 8.20(2H, d, J=8Hz).

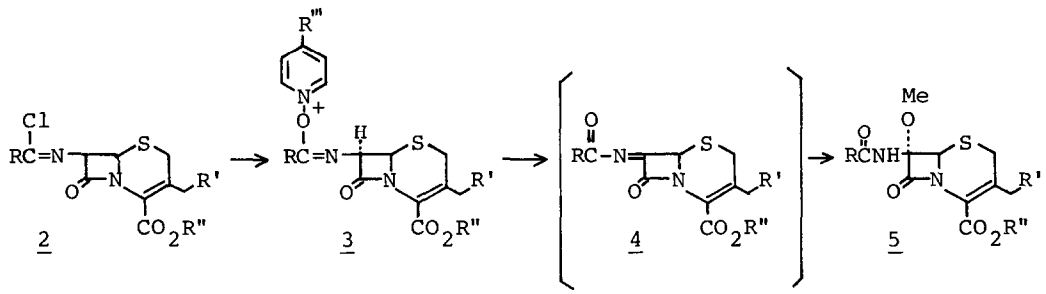
The starting cephalosporins 1, reagents and yields of 5 are summarised in the Table. A possible reaction process for the 7α-methoxylation is outlined in the Scheme deduced from the experimental procedure and the following experimental results.

The oxide adduct 3b was obtained by treatment of imino chloride 2b with silver tetrafluoroborate and 4-methoxypyridine-N-oxide followed by washing with cold water. This adduct 3b was purified by silica gel column chromatography (CH_2Cl_2-MeOH=20:1). 3b: IR ν_{max}^{film} 1775, 1725, 1630 cm^{-1}; F.D.Mass(Hitachi, M-80) M^+: 470; NMR($CDCl_3$) δ: 2.05(3H, s), 3.00 and 3.36(2H, ABq, J=18Hz), 3.76(3H, s) 4.13(3H, s), 4.84(1H, d, J=4Hz), 5.20(2H, s), 5.58(1H, d, J=4Hz), 6.90-7.45(5H,

m), 7.47(2H, d, J=8Hz), 8.50(2H, d, 8Hz).

When the oxide adduct 3b was treated with methanol and triethylamine at -15° c in N,N-dimethylformamide, 7α-methoxycephalosporin 5b was obtained (43% yield from 3b).

We are continuing to investigate the scope and limitation of this new procedure.



Compound	R	R'	R"	Reagent Oxide	Ag^+	Base	Yield %
a	$PhOCH_2$-	H	$CH_2C_6H_4NO_2$-p	PyO	AgOTf	i-Pr_2NEt	70
b	$PhOCH_2$-	H	Me	4-MeO·C_5H_4N-O	$AgBF_4$	NEt_3	35
c	$PhOCH_2$-	OAc	$CHPh_2$	PyO	AgOTf	NEt_3	46
d	$CH_2CH_2SCH_2$- (1) CO_2CHPh_2	OAc	$CHPh_2$	PyO	AgOTf	NEt_3	38
e	$PhOCH_2$-	STz	$CHPh_2$	PyO	AgOTf	NEt_3	20

References and Notes

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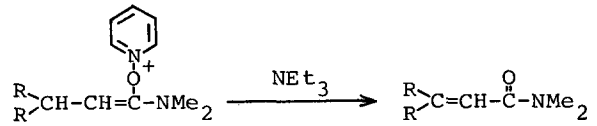
2) E.M.Gordon, H.W.Chang, B.Toeplitz and J.Z.Gougoutas., J. Am. Chem. Soc., 102, 1690 (1980). and references cited therein.
3) G.A.Koppel and R.E.Koehler., J. Am. Chem. Soc., 95, 2403 (1973).
4) The α-configuration of methoxyl at C-7 was confirmed by comparison of 5a with an authentic sample prepared by the route of Koppel and Koehler.
5) Pyridine-N-oxide has been used as an oxidising agent in few cases. But recently L.Ghosez has reported that pyridine-N-oxide adduct undergoes 1,4-elimination with the influence of triethylamine to give α,β-unsaturated t-amide. R.D.Costa, M.Gillard, J.B.Falmagne and L.Ghosez., J. Am. Chem. Soc., 101, 4381 (1979). See also, R.A.Abramovitch, G.Alvernhe, R.Bartnik, N.L.Dassanayake, M.N.Inbasekaran and S.Kato., J. Am. Chem. Soc., 103, 4558 (1981).



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