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A MILD AND EFFICIENT METHOD FOR THE ESTERIFICATION OF CEPHALOSPORANIC ACIDS

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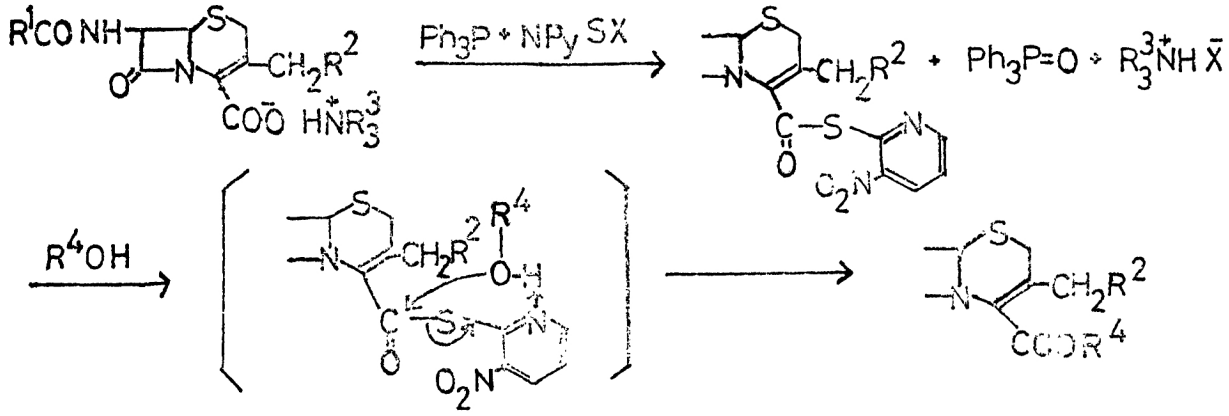
A mild and efficient method for the preparation of esters of cephalosporanic acids via the 3-nitro-2-pyridinethiol ester, easily prepared by the reaction of cephalosporanic acid salt with 3-nitro-2-pyridinesulfenyl halide and triphenylphosphine, is reported. Pure Δ^3-esters of various cephalosporanic acids were prepared in good yields by this method without accompanying isomerization of the thiazine ring.

In the preceding report[1], it has been shown that 3-nitro-2-pyridinesulfenyl halide (NPySX) is extraordinarily stable and safely stored, so that it can be used as a chemical reagent.

In the present communication, esterification of cephalosporanic acid was studied as an application of NPySX to synthetic techniques and the author would like to report a mild and efficient method for the preparation of esters of cephalosporanic acids via the 3-nitro-2-pyridinethiol ester which is easily prepared by the reaction of cephalosporanic acid salt with NPySX and triphenylphosphine.



Attempts to esterify cephalosporanic acid using acid chloride, carbodiimide, mixed anhydride or hydroxyphthalimide ester techniques have generally failed[2)-a] and the esterification of cephalosporanic acid salt with activated alkyl halide usually give a mixture of Δ^3- and Δ^2-esters except in a recently reported reaction using liquid sulfur dioxide[3]. Fractional crystallization, laborious chromatographic procedures or conversion of Δ^2-esters to Δ^3-esters via the sulfoxides are necessary to obtain pure Δ^3-esters[2)-c].

As to the mechanism of the formation of Δ^2-esters, the generation of a ketene intermediate[2)-c] or promotion of isomerization of the Δ^3-ester to the Δ^2-ester by a carboxylate anion or base[2)-a] have been proposed. It has been considered that the formation of Δ^2-esters could be prevented if cephalosporanic acid salt was activated into a stable intermediate without accompanying Δ^2-isomer and the esterification step was carried out under neutral conditions in the absence of carboxylate ion or base. As an activated intermediate, 3-nitro-2-pyridinethiol ester was studied with the expectation that it would be prepared without the formation of Δ^2-isomer using NPySX as an oxidant as in the recently shown oxidation-reduction condensation for pyridinethiol ester synthesis[5)]. This reaction causes no detectable racemization in peptide synthesis and has been extensively used for macrolide synthesis by E.J. Corey *et al*[6)] and H. Gerlach *et al*.[7)]

The present esterification method was studied and applied to isomerization sensitive[8)] 7β-(cyanomethylthioacetamido)-7α-methoxy-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid[9)] (generic name Cefmetazole) which has been developed in our laboratories as a very strong and versatile antibiotic cephalosporanic acid and favorable results were obtained. In a typical experiment, 3-nitro-2-pyridinesulfenyl chloride (1.905 g, 10 mmol) in 50 ml of methylene chloride was added with stirring at 0~-5°C to a mixture of N-methylmorpholine salt of Cefmetazole (5.12 g, 10 mmol) and triphenylphosphine (2.62 g, 10 mmol) in 200 ml of methylene chloride and stirring continued for 1.5 hr. The reaction mixture was washed with sat. $NaHCO_3$, water and dried over Na_2SO_4. The reaction mixture was condensed *in vacuo* and addition of ether gave crude product. Crystallization from methylene chloride-ether gave pure 3-nitro-2-pyridinethiol ester of Cefmetazole (I): 5.36 g (88.5%); mp 93~5°; nmr (δ in $CDCl_3$) 3.52~3.73 (9H, not clear due to overlapping, 7-NHCOC$\underline{H}_2$-S-C$\underline{H}_2$-, 7-OC$\underline{H}_3$ and 2-C$\underline{H}_2$-), 3.93 (3H, s, 3-N-C$\underline{H}_3$), 4.33 and 4.52 (2H, AB-q, J=14 Hz, 3-C$\underline{H}_2$-S-), 5.71 (1H, s, H-6), 7.60 (1H, b, 7-N$\underline{H}$-CO-), 7.65 (1H, dd, J=5 and 8 Hz, H-5 of pyridine), 8.47 (1H, dd, J=1.5 and 8 Hz, H-4 of pyridine), 8.98 (1H, dd, J=1.5 and 5 Hz, H-6 of pyridine). Found: C, 39.34; H, 3.09; N, 20.36; S, 20.82%. Calcd for $C_{20}H_{19}N_9O_6S_4$: C, 39.40; H, 3.14; N, 20.68; S, 21.04%. This thiol ester was also prepared in good yield by the same procedure starting from the sodium salt of Cefmetazole in place of its N-methylmorpholine salt, but an attempt to synthesize it using the free acid of Cefmetazole, 3-nitro-2-pyridinethiol and N,N'-dicyclohexylcarbodiimide gave a poor yield and resulted largely in the formation of the Δ^2-isomer.

This thiol ester was easily converted into the desired esters without isomerization by the reaction with alcohol, stirring at room temperature or allowing to stand for a few days in a refrigerator. For example, ethanol (0.184 g, 4 mmol) was added to (I) (1.218 g, 2 mmol) in 100 ml of methylene chloride and was stirred overnight at room temperature. The reaction mixture was washed with sat. $NaHCO_3$ to remove 3-nitro-2-pyridinethiol produced in the reaction[10)], washed with water and dried over Na_2SO_4. The reaction mixture was condensed and addition of petroleum ether gave ethyl ester of Cefmetazole: 0.635 g (71.7%, total yield of 63.8% from Cefmetazole salt), mp 117~9°C. This transesterification reaction was found to proceed without the formation of Δ^2-ester which was produced in ordinary methods as shown in Table I.

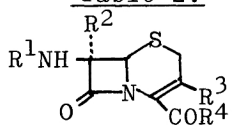
Table I. Preparation of Ethyl Ester of CS-1170

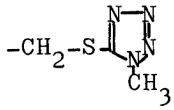
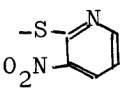
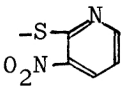
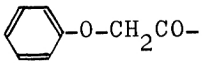
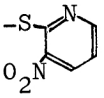
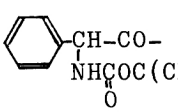
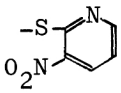
Esterification Conditions	Yield %	Δ^3/Δ^2 Ratios[1]
Cefmetazole free acid + EtOH + N,N'-dicyclohexylcarbodiimide in CH_2Cl_2, 24 hr	31	1/8[2]
Cefmetazole sodium salt + EtBr (1.5 eq) in DMF, 5 hr	38	2/5
The present method	64	1/0 (Δ^2 was not detected)[3]

1) Δ^3/Δ^2 ratios were determined by nmr analysis of the product with the comparison of signals of δ 5.11 of H-6 in Δ^3-isomer with δ 6.46 of H-4 in Δ^2-isomer.
2) The ester was found to be so sensitive to isomerization that the contact with silica gel during chromatography caused isomerization and then the product was purified by Sephadex LH-20 column in EtOH.
3) No Δ^2-isomer was detected in isolated ester, mother liquor and crude product by nmr analysis.

In a similar way, various esters of cephalosporanic acids were prepared in good yields and the results are shown in Table 2.

Table 2.



	R^1	R^2	R^3	R^4	Yield %[1]	M.P. °C
1	$NCCH_2SCH_2CO-$	$-OCH_3$			88	93~5
2	"	"	"	$-OC_2H_5$	72	118~9
3	"	"	"	$-OCH_2CH_2CH_2CH_3$	75	131~4
4	"	"	"		80	143~5
5	"	"	"		65	106~8
6	"	"	"		62	90~93
7		H	$-CH_2OAc$		79	85~7
8	"	"	"	$-O-CH_2-CH(OH)CH_2OH$	77	144~7 (lit.[11] 111~2)
9		"	CH_3		81	89~91
10	"	"	"	$-O-CH_2-CH(OH)CH_2OH$	63[2]	66~8
11	D- 	"	"		86	107~9
12	"	"	"	$-O-CH_2-CH(OH)CH_2OH$	61[2]	130~2

1) Yields of esters except thiol esters were calculated from thiol esters and yields of thiol esters were calculated from cephalosporanic acid salts. All esters had satisfactory analytical and spectroscopic data.
2) Transesterification reaction of 3-nitro-2-pyridinethiol ester was not so fast in the case of 3-methyl-type derivatives which are comparatively resistant to isomerization but the reaction was accelerated by the addition of mercaptan scavengers. (see, T. Mukaiyama, R. Matsueda, M. Ueki, and H. Maruyama, J. Amer. Chem. Soc., 91, 1554 (1969). H. Gerlach and A. Thalmann, Helv. Chim. Acta, 57, 2661 (1974)). The reactions were carried out by the addition of equivalent amounts of mercuric salt of succinimide or mercuric acetate for 3 hr at room temperature.

A special practical merit of this method is that pure Δ^3-esters with functional groups such as glyceryl, N-succinimidoyl and N-oxo-3-pyridyl esters are prepared in good yields. The glyceryl ester of Cephalothin (experimental number, 8) which could not be prepared by ordinary means[11] and is difficult to be prepared by the activated alkyl halide method was easily prepared by the present method without formation of the Δ^2-isomer.

In conclusion, it is noted that 3-nitro-2-pyridinethiol esters of various cephalosporanic acids are easily prepared by the reaction of cephalosporanic acids with NPySX and triphenylphosphine and they are converted into the desired esters by the reaction with alcohols under mild conditions in good yields without accompanying isomerization.

References and Notes

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2) a) "Cephalosporins and penicillins", ed. E.H. Flynn, Academic Press, New York, p 172 (1972). b) ibid., p 554. c) ibid., p 147.
3) S. Seki, S. Nakabayashi, K. Nishihata, N. Ito, and S. Fukatsu, Tetrahedron Lett., 2915 (1977).
4) P.H. Bentley, G. Brooks, and I.I. Zomaya, Tetrahedron Lett., 3739 (1976).
5) T. Mukaiyama, M. Ueki, R. Matsueda, and H. Maruyama, Japanese Patent No. 68,7121 (1972). see also, T. Mukaiyama, M. Araki, and H. Takei, J. Amer. Chem. Soc., 95, 4763 (1973).
6) E.J. Corey and K.C. Nicolaou, J. Amer. Chem. Soc., 96, 5614 (1974). E.J. Corey, K.C. Nicolaou, and L.S. Melvin, Jr., ibid., 97, 653, 97, 654(1975). E.J. Corey, K.C. Nicolaou, and T. Toru, ibid., 97, 2287 (1975).
7) H. Gerlach, K. Oertle, A. Thalmann, and S. Servi, Helv. Chim. Acta, 58, 2036 (1975).
8) It is well known that cephalosporanic acids with strong antibiotic activities often have electron withdrawing substituents at the 3-methyl position[2)-b] and are often easily isomerized in the esterification reactions[2)-c].
9) H. Nakao, H. Yanagisawa, B. Shimizu, M. Kaneko, M. Nagano, and S. Sugawara, J. Antibiotics, 29, 554 (1976).
10) 3-Nitro-2-pyridinethiol is converted into NPySCl quantitatively by the oxidation with $K_3Fe(CN)_6$ and the reaction with chlorine gas as described in the preceding report[1)] and it can be recycled in the esterification reactions.
11) R.R. Chauvette and E.H. Flynn, J. Med. Chem. 9, 741 (1966). A nearly equal mixture of Δ^2 and Δ^3-esters was obtained by mixed anhydride method.

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