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Preliminary Communication

Reactions of Penicillin Esters and Related Compounds with 1-Chlorobenzotriazole*

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Recently we reported chlorinolysis of the carbon-sulfur bond in penicillins[1]. Depending on the amount of halogen used, two kinds of products are isolated. With 1 mole of chlorine, the reaction gives azetidinone sulfenyl chlorides III and with 2 moles of chlorine, olefinic azetidinone derivatives IV are formed.

As an extension of our studies of the reactions of penicillin esters with electrophiles, the use of 1-chlorobenzotriazole (CTBA) as an electrophile source was investigated. 1-Chlorobenzotriazole is an easily available, inexpensive and effective source of positive chlorine, and in addition reactions with this reagent are simple, clean and high-yielding under mild conditions.[2-5] The results reported in this paper fully corroborate all these advantages and also describe the utility of CBTA in preparing monocyclic azetidinone compounds from penicillins.

The reactions of *p*-nitrobenzyl 6-phthalimidopenicillanate (I) with 1 equiv of CBTA in methylene chloride at room temperature for 90 min yields the benzotriazol-1-yl sulfenamide II in 81% yield; ir ($CHCl_3$) 1801 (azetidinone C=O), 1787 and 1735 (phthalimido C=O) and 1750 cm^{-1} (ester C=O). The structure of II is revealed by elemental analysis and NMR data (see Table I).

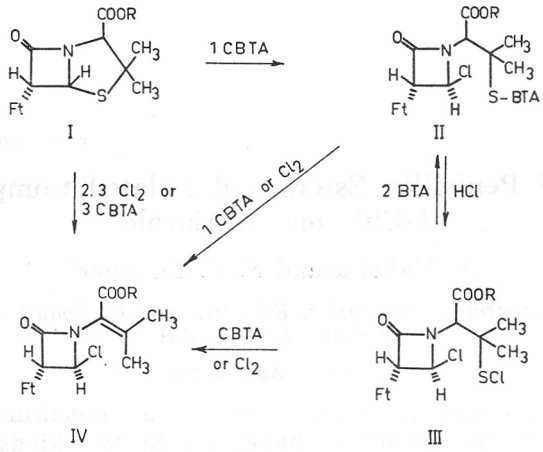
TABLE I

NMR Chemical Shift Values ($CDCl_3$)

Compound[a]	$C(CH_3)_2$	CHCOOR	$COOCH_2$-	Azetidinone H		Arom H
I	89; 111	287	322	338 (d, J = 4.5)	342 (d, J = 4.5)	472
II	93; 95	288	328	334 (d, J = 2)	385 (d, J = 2)	470
III	103.5	281	328	334 (d, J = 2)	367 (d, J = 2)	474
IV	128; 142	—	323	333 (d, J = 2)	370 (d, J = 2)	474

* Satisfactory elemental analyses were obtained for all compounds. Chemical shift and J values are in Hz.

* Azetidinone Antibiotics. IV.



BTA = benzotriazole; Ft = phthalimido; R = *p*-nitrobenzyl.

Evidence that the benzotriazolyl group is attached to the sulfur, and not to the C-2 of the azetidinone ring, is furnished unambigously by conversion of II with 1 equiv of Cl_2 or CBTA to the olefinic compound IV, and by synthesis of II from the corresponding sulfenyl chloride III and benzotriazole. When 2 *S*-chloro-1-(1′-*S*-*p*-nitrobenzyloxy-carbonyl-2′-chlorothio-2′methylpropyl) -3 *R*--phthalimidoazetidin-4-one (III) is treated with 2 equiv of benzotriazole in methylene chloride at room temperature for 1 hr, colorless benzotriazole hydrochloride is precipitated. After filtration of the salt, an amorphous product is isolated in 67% yield and is shown by spectral properties to be identical with compound II. An additional evidence in support of structure II is obtained by hydrolysis of the sulfenamide II to the sulfenyl chloride III with hydrochloric acid.[6] The benzotriazol-1-yl sulfenamide II is dissolved in methylene chloride and treated with dry hydrogen chloride at room temperature for 7 min. During this time the hydrochloride salt of benzotriazole is precipitated and subsequently removed by filtration. From the filtrate, sulfenyl chloride III is obtained in almost quantitative yield; ir ($CHCl_3$) 1800 (azetidinone C=O), 1785 and 1730 (phthalimido C=O) and 1750 cm^{-1} (ester C=O). Compound III is also prepared by chlorinolysis of penicillin ester I according to the method reported previously.[1] Characterization of III is made from spectral data (Table I) and analysis.

The successful application of 1-chlorobenzotriazole as a source of positive chlorine in preparation of II prompted us to extend its use to the olefin--forming reaction described previously.[1] When I is reacted with 3 equiv of 1-chlorobenzotriazole in methylene chloride at room temperature for 90 min, benzotriazole hydrochloride is obtained as a colorless precipitate. After filtration of the hydrochloride salt, 2 *S*-chloro-1-(1′-*p*-nitrobenzyloxycarbonyl--2′-methylprop-1′-enyl)-3 *R*-phthalimido azetidin-4-one IV is isolated in nearly quantitative yield; ir ($CHCl_3$) 1798 (azetidinone C=O), 1785 and 1733 (phthalimido C=O) and 1740 cm^{-1} (ester C=O). Compound IV also can be made from I, II, and III by the reaction with the appropriate amount of chlorine.

The mechanism of heterolysis of the sulfur-carbon bond in penicillin with CBTA is not clear. There is a question whether the reaction is an ionic or free-radical process, and in addition the role of the ambident benzotriazolyl anion also is not established. Since details of the reaction mechanism have not been investigated these questions cannot be answered on the basis of presently available data. Apparently, the previously postulated mechanism for the chlorinolysis of penicillins cannot explain adequately the formation of II.

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IZVOD

Reakcija penicilinskih estera i srodnih spojeva s 1-klorbenzotriazolom

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Opisana je reakcija *p*-nitrobenzil-6-ftalimidopenicilinata (I) s 1, 2 i 3 mola 1-klorbenzotriazola (CBTA). Izolirani su kao produkti cijepanja S_1—C_5 veza spojevi II, III i IV; njihova struktura potvrđena je na osnovu spektralnih svojstava (IR, NMR) kao i međusobnom interkonverzijom. Tako je II preveden u IV u prisustvu jednog mola klora ili CBTA, a III je dao u reakciji s benzotriazolom spoj II. Hidrolizom sulfenamidne grupe u spoju II s klorovodikom u metilenkloridu dobiven je sulfenil klorid III.

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