A Convenient and Rapid Synthesis of Potassium Penicilliantes using EEDQ (1)

A. Nelson Voldeng, Janet T. Fifer and D. Ray Brown

College of Pharmacy, The University of Arkansas for Medical Sciences Campus, Little Rock, Arkansas 72201

Received October 20, 1978

N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ, **1**) has been utilized as a coupling reagent to attach sterically unhindered acids to the potassium salt of 6-aminopenicillanic acid (**4**) at room temperature.

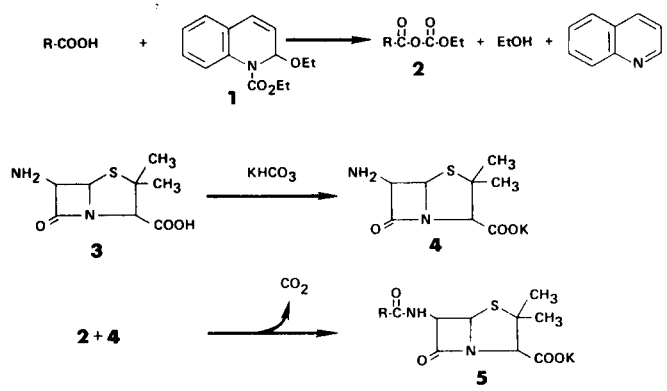
The excellent yields and rapidity of the reaction illustrate the convenience of utilizing **1** as the coupling reagent to directly prepare the potassium salt of certain penicillins.

J. Heterocyclic Chem., **16**, 621 (1979).

Introduction.

The literature (2a) contains many procedures for syntheses of penicillins utilizing a variety of reagents to couple acids with 6-aminopenicillanic acid (6-APA, **3**). These methods generally require sub-zero reaction temperatures, masking of the carboxyl group of **3** *via* inorganic or organic salts and esters, and several purification steps before isolation of the potassium penicillinate **5**. The relatively new peptide coupling reagent EEDQ (**1**) has been utilized by several groups to acylate the amino function of a carboxyl-protected cephalosporin nucleus (2b,c). Hydrogenolysis or hydrolysis of the carboxyl-protecting group afforded the cephalosporin derivative in 30-50% yield. We report herein a facile method for acylation of potassium 6-aminopenicillinate (**4**) utilizing EEDQ (**1**), and the isolation of potassium penicillinates directly from the reaction mixture.

Scheme 1



A mixed anhydride **2** of a sterically unhindered acid was prepared *in situ* utilizing **1**, and allowed to react with potassium 6-aminopenicillinate (**4**) to give penicillins **5** (Scheme 1). Potassium salts of the penicillins **5** prepared by this method were recrystallized from methanol-ether, and characterized by comparing their melting point and infrared spectra to authentic penicillins. Yields are reported in Table I.

We found the use of EEDQ to be advantageous as a coupling reagent to prepare certain penicillins. First, the reaction course can be followed by monitoring the evolution of carbon dioxide. If evolution of carbon dioxide occurs while stirring a solution of a carboxylic acid and EEDQ, either the solvent or impurities in the acid must be decomposing the mixed anyhydride **2**. If no evolution of carbon dioxide occurs while stirring the acid-EEDQ solution, but addition of an aqueous solution of **4** causes liberation of gas, then the mixed anhydride formed, reacted with **4** to liberate carbon dioxide, and **5** should be obtained.

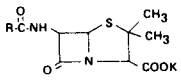
If vigorous gas evolution does not occur while stirring the acid-EEDQ solution, or after addition of **4**, the mixed anhydride **2** did not form. This was the situation when attempts were made to couple sterically hindered acids, such as 2,6-dimethoxybenzoic or 2-phenylbenzoic acid, with **4**. Furthermore, use of longer reaction times to prepare **2** or longer reaction times following addition of **4** did not effect coupling with these sterically hindered acids.

Product cleanliness and rapidity of the sequence represent additional advantanges of this method, since the potassium penicillinates **5** were isolated directly from the reaction. Furthermore, analogous reactions using acid chlorides, dicyclohexylcarbodiimide, or chloroformates, required sub-zero reaction temperatures, several purification steps, and generally provided poorer yields of less pure potassium pencillinates compared to the use of EEDQ.

As shown in Table I, excellent yields of penicillin potassium salts were obtained when **1** was utilized as the coupling reagent. Lower yields of α-phenoxyethyl (**5c**) and α-phenoxypropyl (**5d**) penicillins, compared to phenoxymethylpenicillin (**5b**), appear to be due to steric influence of the *alpha*-alkyl group which restricts mixed anhydride formation.

0022-152X/79/030621-02$02.25

Table 1
Yields of Potassium Penicillinates Prepared via EEDQ



Compd	Penicillin	R	Solvent System[a]	% Yield
5a	benzyl	$PhCH_2$	A	67[b]
			B	60
			C	62
5b	phenoxymethyl	$PhOCH_2$	A	88[c]
			B	86
			C	85
5c	α-phenoxyethyl	PhOCH(Me)	A	78[d]
			B	70
			C	64
5d	α-phenoxypropyl	PhOCH(Et)	A	53[e]
			B	28
			C	47

[a] A = methylene chloride-water-ethanol, B = acetonitrile-water-ethanol, C = acetonitrile-water. [b] mp 217-18°C dec. (lit. mp 214-15°C dec.): ref. 4. [c] mp 232-33°C dec. (lit. mp 244°C dec.): ref. 5. [d] mp 228-30°C dec. (lit. mp 230-32°C dec.): from ref. 3. [e] mp 215-17°C dec. (lit mp 195-97°C dec.): from ref 3.

We intend to prepare other beta-lactam antibiotics utilizing this technically simple reaction sequence.

EXPERIMENTAL

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide pellets on a Beckman Acculab-4 spectrometer. All products had strong ir absorption in the region 1755-1770 cm^{-1} corresponding to the β-lactam system. Infrared spectra from Sadtler Research Laboratories, and Abbott Laboratories were used for comparative purposes. All reagents were purchased from Aldrich Chemical Company. The three procedures described below are typical for preparation of potassium penicillinates, all of which are summarized in Table I.

Potassium benzylpenicillinate (**5a**).

Solvent System A.

Phenylacetic acid (68 mg., 0.5 mmole) was dissolved in a solution of EEDQ (124 mg., 0.5 mmole) in 4 ml. of dry methylene chloride by stirring at room temperature for 30 minutes. To a solution of 6-APA (108 mg., 0.5 mmole) and potassium bicarbonate (53 mg., 0.53 mmole) in 0.4 ml. of water was added 0.5 ml. of absolute alcohol. The aqueous-alcohol solution of **4** was quickly added to the rapidly stirred methylene chloride solution containing **2**; effervesing was immediate. The flask was rinsed with 0.5 ml. of absolute alcohol which was added to the reaction solution. After stirring for 30 minutes, the solvents were evaporated at room temperature *in vacuo*. Addition of acetone (5 ml.) to the residue followed by stirring in an ice bath afforded a white precipitate. Filtration and rinsing with acetone yielded 125 mg. (67%), m.p. 209-210° dec. Recrystallization from methanol-ether gave **5a**, m.p. 217-218° dec., [lit. (4) m.p. 214-215° dec.]. The ir spectrum was identical to the Sadtler spectrum for **5a**.

Solvent System B.

Acetonitrile (4 ml.) was used instead of methylene chloride. The same reagents and procedure described above were used, affording **5a**, 111 mg. (60%), m.p. 216-220° dec. Recrystallization from absolute methanol-ether afforded white crystals, m.p. 217-218° dec., identical to that reported above.

Potassium phenoxymethylpenicillinate (**5b**).

Solvent System C.

Phenoxyacetic acid (76 mg., 0.5 mmole) was dissolved in a solution of EEDQ (128 mg., 0.5 mmole) in 2 ml. acetonitrile by stirring at room temperature 30 minutes. A solution of 6-APA (108 mg., 0.5 mmole) and potassium bicarbonate (53 mg., 0.53 mmole) in 0.6 ml. water was added to the rapidly stirred acetonitrile solution, and effervesing was immediate. The flask was rinsed with 0.4 ml. water which was added to the reaction mixture. After stirring for 30 minutes the solvents were evaporated at room temperature *in vacuo*. Work-up as previously described and recrystallization from absolute methanol-ether afforded **5b**, 165 mg. (85%), m.p. 232-233° dec. [lit. (5) m.p. 244° dec.]. The infrared spectrum was identical to the Sadtler spectrum for **5b**.

Acknowledgement.

The authors are grateful to Abbott Laboratories for support of this work.

REFERENCES AND NOTES

(1) Presented at the 33rd Southwest Regional Meeting, American Chemical Society, Medicinal Chemistry Division, Little Rock, Arkansas, Dec. 6, 1977.

(2a) G. V. Kaiser and S. Kukolja, in "Cephalosporins and Penicillins, Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972, p. 74; (b) A. Nudleman, H. Karoly, F. Braun, E. H. W. Bohme and R. C. Erickson, *J. Med. Chem.*, **21**, 962 (1978); (c) T. T. Conway, G. Lim, J. L. Douglas, M. Marcel, T. W. Doyle, P. Rivest, D. Horning, L. R. Morris and D. Cimon, *Can. J. Chem.*, **56**, 1335 (1978).

(3) Y. G. Peron, W. F. Minor, C. T. Holdrege, W. J. Gottstein, J. C. Godfrey, L. B. Crast, R. B. Babel and L. C. Cheney, *J. Am. Chem. Soc.*, **82**, 3934 (1960).

(4) "Dictionary of Organic Compounds," 4th Ed., Vol. 1, Oxford University Press, New York, N. Y., 1965, p. 380.

(5) "Dictionary of Organic Compounds," 4th Ed., Vol. 4, Oxford University Press, New York., N. Y., 1965, p. 2664.