Novel 7-Pyrrolocephalosporins

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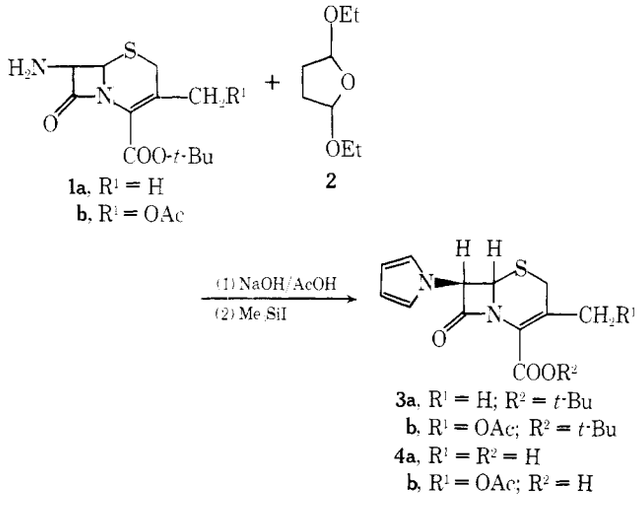
In the search for novel analogues of the naturally occurring β-lactam antibiotics, a large number of modifications have been carried out at positions 6 of the penicillins and 7 of the cephalosporins.[1] With the discovery of a family of the cephamycins, a renewed effort has been directed at the development of methods for the introduction of substituents at positions 6 and 7 of penicillins and cephalosporins, respectively.[2]

The modifications carried out have reported the introduction of alkyl, halogen, alkoxy, hydroxy, and azido groups. The naturally occurring amide function has, in turn, been converted into amino, amido, imino, and imido groups. We report here the first 7-heteroaromatic-substituted cephalosporins.

When the *tert*-butyl esters[3] of 7-aminocephalosporanic and 7-aminodesacetoxycephalosporanic acids (**1**) are treated with 2,5-diethoxytetrahydrofuran[4] (**2**) novel 7-pyrrolocephalosporins (**3**) are obtained.

In order to test compounds **3** for antibacterial properties, it was necessary to remove the *tert*-butyl ester group. The standard procedure for *tert*-butyl ester hydrolysis required acid catalysis. The instability of pyrroles to strongly acidic conditions brought about the decomposition of the compounds when subjected to trifluoroacetic acid. Even 1 equiv of trifluoroacetic acid in chloroform caused immediate and extensive decomposition. The *tert*-butyl ester groups of **3** were



1a, R^1 = H
b, R^1 = OAc

2

3a, R^1 = H; R^2 = *t*-Bu
b, R^1 = OAc; R^2 = *t*-Bu
4a, R^1 = R^2 = H
b, R^1 = OAc; R^2 = H

successfully removed upon treatment with trimethylsilyl iodide by the recently reported method of Jung and Lyster.[5] The great selectivity of this reagent was witnessed by the removal of the *tert*-butyl group of **3a**, leaving the acetate group intact. The acids **4a,b** showed weak antibacterial properties with MIC of ≥100 μg/mL against Streptococcus pneumoniae D137 and Streptococcus pyogenes ST 139.

Experimental Section

All new compounds gave satisfactory elemental analyses.

1,1-Dimethylethyl 3[(Acetyloxy)methyl]-8-oxo-7-(1*H*-pyrrol-1-yl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (3b). To a boiling solution of sodium acetate (0.25 g, 3 mmol) in acetic acid (10 mL) was added 7-ACA *tert*-butyl ester (**1a**) (1.64 g, 5 mmol) followed by 2,5-diethoxytetrahydrofuran (**2**) (0.8 g, 5 mmol). The solution was further boiled for about 1 min and was then poured into ice. A yellow solid was obtained which was chromatographed on 15 g of silica gel eluted with ether to give 250 mg (15%) of **3b**: mp 150–153 °C; IR (KBr) 1765 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 1.58 (s, 9), 2.10 (s, 3), 3.45 (q, 2), 4.7–5.3 (superimposed q and d, 3), 5.91 (d, 1, J = 5 Hz), 6.78 (t, 2), and 6.80 (t, 2).

1,1-Dimethylethyl 3-Methyl-8-oxo-7-(1*H*-pyrrol-1-yl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (3a). The title compound was obtained in 46% yield, as described for **3b** using the appropriate 7-ADCA *tert*-butyl ester **1b**: mp 160–161 °C; IR (KBr) 1765 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 1.60 (s, 9), 2.10 (s, 3), 3.27 (q, 2), 5.0 (d, 1), 5.79 (d, 1, J_{AB} = 5 Hz), 6.14 (t, 2), and 6.66 (t, 2).

3-Methyl-8-oxo-7-(1*H*-pyrrol-1-yl)-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic Acid (4a). To a solution of **3a** (0.8 g, 2.5 mmol) in 10 mL of dry chloroform was added trimethylsilyl iodide[5] (1 g, 5 mmol). The solution was stirred at room temperature for 40 min while protected from light and was then poured into 5% aqueous sodium bicarbonate. The aqueous phase was washed with ethyl acetate, cooled, acidified to pH 3 with dilute hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried and evaporated to give **4a**, 0.3 g (45%), as a yellow powder: IR (KBr) 1750 cm^{-1} (β-lactam); NMR (Me_2SO) δ 2.02 (s, 3), 3.44 (q, 2), 5.13 (d, 1), 6.0 (t, 2), 6.18 (d, 1, J_{AB} = 5.5 Hz), and 6.64 (t, 2).

3-(Acetyloxy)methyl-8-oxo-7(*H*-pyrrol-1-yl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (4b). The title compound was obtained in 50% yield as described for **4a** from the corresponding **3b**: IR (KBr) 1760 cm^{-1} (β-lactam); NMR (Me_2SO) δ 2.02 (s, 3), 3.52 (q, 2), 4.8 (q, 2), 5.22 (d, 1), 6.06 (t, 2), 6.36 (d, 1), and 6.69 (t, 2)

Registry No.—**1a**, 33610-06-9; **1b**, 6187-87-7; **2**, 3320-90-9; **3a**, 66967-02-0; **3b**, 66967-03-1; **4a**, 66967-04-2; **4b**, 66967-05-3.

References and Notes

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Convenient Preparation of α,β-Unsaturated Aldehydes

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A number of methods designed to convert carbonyl compounds into homologated α,β-unsaturated aldehydes have been reported.[1] All of these techniques possess variable degrees of utility and indeed have found widespread use. In 1969, Nagata[2] described the preparation of the phosphonate imine **1** and its ability to convert carbonyl compounds into α,β-unsaturated aldehydes **2**. This process is in effect a combination of the Wadsworth–Emmons[1d] olefination and the Wittig directed aldol condensation.[1g] We wish to describe in this report a simple and efficient procedure, beginning with the *N-tert*-butylimine of acetaldehyde **3**, leading to **2** without isolation of any of the intermediates. This method precludes the preparation of Nagata's reagent **1**,[2] which required three

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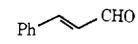
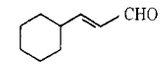
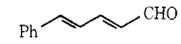
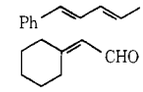
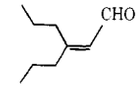
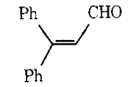
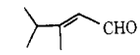
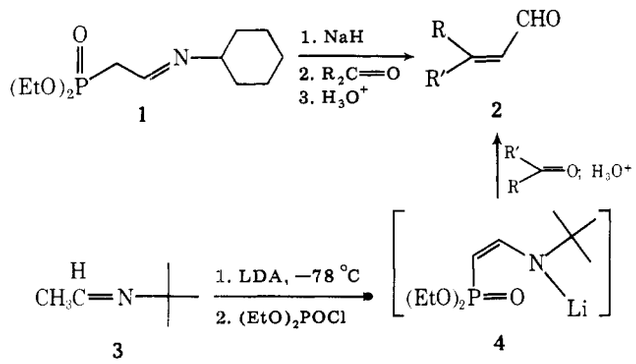
Table I. α,β-Unsaturated Aldehydes 2

carbonyl R	carbonyl R′	registry no.	product	registry no.	% yield[a,b]
Ph	H	100-52-7			70[c]
$Ph(CH_2)_2$	H	104-53-0		33046-84-3	73[d]
	H	2043-61-0		935-03-5	76[e]
PhCH=CH−	H	104-55-2		13466-40-5	67[c]
		108-94-1		1713-63-9	94[c]
		123-19-3		34626-45-4	53[c]
$Ph_2C=O$		119-61-9		1210-39-5	71[c]
		563-80-4		57398-52-4	72[f,g]

[a] Isolated yields by distillation or PTLC. [b] All compounds gave satisfactory spectral data and were identical with authentic samples. [c] A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973). [d] K. Hirai and Y. Kishida, *Tetrahedron Lett.*, 2743 (1972). [e] J. H. van Boon, P. P. Montijn, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays Bas*, **84**, 31 (1965). [f] M. Julia and B. Badet, *Bull. Soc. Chim. Fr.*, 1363 (1975). [g] *E/Z* ratio, as determined by NMR, is 6:4.



steps from commercial materials. Metalation of **3** with excess lithium diisopropylamide followed by introduction of diethyl chlorophosphate furnished in situ the lithioenaminophosphonate **4**. Addition of the carbonyl components and then an aqueous oxalic acid solution afforded, after workup, the α,β-unsaturated aldehydes **2** in satisfactory yields (Table I). Thus, in a single reaction vessel, starting with the imine **3**, the entire sequence is carried out to the final product.

Experimental Section

Cinnamaldehyde, General Procedure for all Aldehydes, 2. To a cooled solution (−78 °C) of lithium diisopropylamide [from 0.84 mL (6.0 mmol) of diisopropylamine and 2.73 mL (6.0 mmol) of butyllithium in hexane] in 8 mL of tetrahydrofuran was added acetaldehyde *N*-*tert*-butylimine[3] (0.4 mL, 3.0 mmol) and the mixture was stirred for 30 min. Diethyl chlorophosphate (518 mg, 3.0 mmol) was added and the solution was stirred at −78 °C for 2 h, allowed to warm to −10 °C over a period of 3 h, and recooled to −78 °C. Benzaldehyde (0.2 mL, 2.0 mmol) was added to the yellow solution and the mixture was stirred for 30 min and allowed to warm to ambient (usually overnight). The mixture was then treated with oxalic acid (6 mmol in 20 mL of water) and then 20 mL of benzene was added. The two phase system was stirred overnight at room temperature and the layers separated. The aqueous layer was extracted with ether (2 × 30 mL) and the organic layers were combined and washed successively with 5% oxalic acid, 15% sodium bicarbonate, and brine. Drying (K_2CO_3) and concentration of the organic phase followed by purification of the residue (distillation or preparative TLC, silica gel, 30% ethyl acetate–hexane) gave 185 mg of cinnamaldehyde, 70%.

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Registry No.—**3**, 7020-80-6.

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