(15) The dinitrotrifluorobenzene was prepared as follows: 120 mL of 90% nitric acid was added to 180 mL of 30% fuming sulfuric acid with cooling; 52.8 g of 1,3,5-trifluorobenzene[12] was added dropwise with stirring at 10–15 °C and the mixture was warmed to 45–50 °C for 45 min; the cooled reaction mixture was poured onto ice and the precipitated product was immediately removed, washed with cold water, and dried in vacuo to give 79.5 g (90%), mp 47–52 °C; crystallization from dry carbon tetrachloride gave mp 51–53 °C (lit. mp 52–53 °C: G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6036 (1956)).

Azetidinone Antibiotics. 19. A Simple Method for the Removal of *p*-Nitrobenzyl Acid Protective Group[1]

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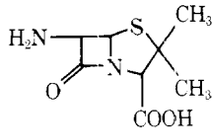
Received September 19, 1977

The chemistry of azetidinone antibiotics has undergone considerable progress during the last two decades.[3] This outstanding development has been largely possible due to the appropriate blocking of the amino and carboxyl groups in the nucleii **1** and **2**. In particular, the protection of the carboxyl



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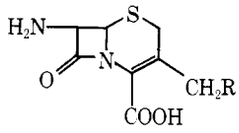

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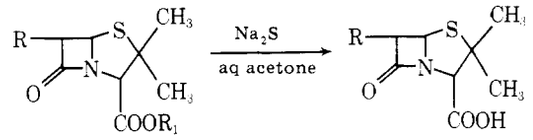
group from undesirable side reactions has been very beneficial. A wide variety of carboxyl protective groups, together with different methods for their selective removal, has been utilized. These include the *tert*-butyl, trichloroethyl, *p*-methoxybenzyl, phenacyl, 2-haloethyl, alkoxymethyl, benzyl, benzhydryl, *p*-nitrobenzyl, and others. Among these the *p*-nitrobenzyl (pNB) group has been frequently used in the chemical modifications of bicyclic azetidinones.[4] The pNB esters of penicillins and cephalosporins are easily prepared by treating the corresponding acid with *p*-nitrobenzyl bromide in the presence of base at temperatures between 0 and 20 °C. The significant advantage of the pNB protective group is relative stability to most acidic and basic reaction conditions. The additional advantage is that it can be selectively removed by catalytic or chemical reduction. Chemical reductions have been widely used in a number of circumstances. Catalytic hydrogenolysis has also been used although these sulfur-containing molecules occasionally caused a "poisoning" effect on hydrogenation catalysts.

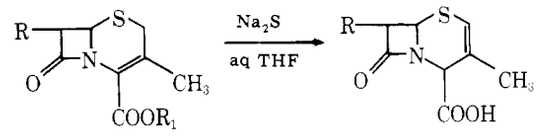
In connection with our work on the removal of the phthaloyl group,[5] a simple, rapid, and high-yield method for the removal of the *p*-nitrobenzyl group from highly sensitive azetidinone antibiotics has been found and our results are reported here.

We have observed that the pNB group can be removed easily by alkaline hydrolysis with sodium sulfide ($Na_2S·9H_2O$). The hydrolysis is performed in an aqueous THF, DMF, or acetone solution at ice-bath temperature within 25–35 min. The progress of hydrolysis can be followed by thin-layer chromatography. The expected acid is usually isolated by acidification of an aqueous portion and if desired recrystallized from the appropriate solvent.

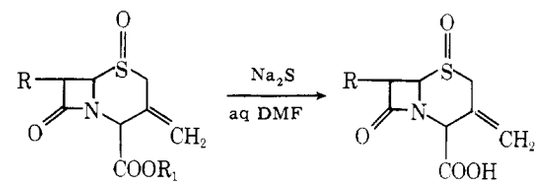
When this method was applied to *p*-nitrobenzyl esters of penicillin G and V (**3g** and **3v**), the corresponding penicillanic acids **4g** and **4v** were obtained in about 80% yield. A similar hydrolysis of deacetoxycephalosporin esters **5h, 5g,** and **5v** afforded 2-cephem acids **6h, 6g,** and **6v** in 75–83% yield. Apparently, in the case of pNB esters of 3-cephem derivatives, the ester group was hydrolyzed, and at the same time, the double bond was isomerized from the Δ^3 to the Δ^2 position. Accordingly, this is a very practical method for preparation of 2-cephem acids **6**.



3g or **3v** **4g** or **4v**



5h, 5g, or **5v** **6h, 6g,** or **6v**



7v **8v**

g, R = $PhCH_2CONH-$; **v**, R = $PhOCH_2CONH-$; **h**, R = NH_2, R_1 = *p*-nitrobenzyl (pNB)

However, an analogous hydrolysis of the pNB ester of 3-methylene cepham **7v** with $Na_2S·9H_2O$ in aqueous DMF resulted only in the removal of the ester group without isomerization of the exocyclic double bond. The acid **8v** was isolated in 45% yield.

The results described in this paper demonstrate that the hydrolysis of pNB esters of various azetidinone derivatives with $Na_2S·9H_2O$ is feasible, even with highly sensitive azetidinone antibiotics. Removal of the pNB group may be used as an alternative to chemical reduction and hydrogenolysis, although the simplicity, expediency, and high yields could be considered as being advantageous. Therefore, we believe that the hydrolysis with $Na_2S·9H_2O$ will find widespread application in the removal of the pNB group.

Experimental Section

Representative Hydrolyses of pNB Esters of Azetidinone Antibiotics. A. 6-Phenylacetamidopenicillanic Acid. A solution of 469 mg (1 mmol) of *p*-nitrobenzyl 6-phenylacetamidopenicillanate in 12 mL of THF and 6 mL of water was cooled in an ice bath, and a solution of 240 mg (1 mmol) of $Na_2S·9H_2O$ in 5 mL of water was added. The mixture was stirred at 0–5 °C for 25 min, 1 mL of 1 N HCl added, and THF was evaporated in vacuo. In order to remove the nonacidic material, 15 mL of ethyl acetate was added to the aqueous solution, pH adjusted to 8.5, and the organic layer was discarded. The pH of the aqueous solution was adjusted to 2.5 with 1 N HCl, and the desired acid was extracted with 20 mL of ethyl acetate. The extract was washed with brine and dried ($MgSO_4$). After evaporation of the solvent 270 mg (81%) of the corresponding acid was obtained. NMR, IR, and TLC of this material were in agreement with those of an authentic sample.

B. 7-Phenoxyacetamido-3-methyl-2-cephem-4-carboxylic Acid. A mixture of 4.83 g (10 mmol) of *p*-nitrobenzyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate, 100 mL of THF, 10 mL of water, and 2.4 g (10 mmol) of $Na_2S·9H_2O$ was stirred in an ice bath for 30 min.

HCl (10 mL, 1 N) was added and THF was evaporated on a rotavapor and the solution was extracted with 30 mL of ethyl acetate. The extract was discarded. The pH of the aqueous layer was adjusted to 3.2 with hydrochloric acid, and soon the oily product commenced to

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crystallize. The crystalline acid was filtered and dried in a vacuum oven overnight. Yield, 3.0 g (83%); NMR ($CDCl_3$ + DMSO-d_6) τ 8.02 (s, 3 H, CH_3), 5.4 (s, 2 H, $PhOCH_2$), 5.33 (bs, 1 H, C_4–H), 4.65 (d, J = 5.0, 1 H, C_6–H), 4.36 (q, J = 5 and 9, 1 H, C_7–H), 3.14–2.52 (m, 5 aromatic H), and 2.1 (d, J = 9.0 Hz, NH). Anal. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04; O, 22.96; S, 9.20. Found: C, 54.82; H, 4.74; N, 7.72; O, 22.79; S, 8.98.

C. 7-Phenoxyacetamido-3-methylenecepham-4-carboxylic Acid 1-Oxide. *p*-Nitrobenzyl 7-phenoxyacetamido-3-methylenecepham-4-carboxylate 1-oxide,[6] 1.5 g (3 mM) was dissolved in 36 mL of dimethylformamide and 20 mL of water and cooled in an ice–water bath for addition of sodium sulfide, 1.1 g (4.5 mM), in 10 mL of water. The reaction mixture was stirred in the cold for 30 min. The mixture was poured into a mixture of 5% HCl and ethyl acetate. The organic layer was separated and washed with 5% HCl and then water. The ethyl acetate solution was slurried with water; the pH was adjusted to 7. The aqueous layer was separated and slurried with ethyl acetate and the pH was readjusted to 2.5. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to dryness in vacuo. The amorphous residue weighed 600 mg and was made to crystallize by trituration with ether. Yield of pure product; 500 mg (46%); NMR ($CDCl_3$ + DMSO-d_6) τ 6.19 (s, 2 H, C2-H_2), 5.45 (s, 2 H, α-CH_2), 4.97–4.87 (d and s, 3 H, C4-H and C6-H), 4.60 and 4.30 (2s, 2 H, C3-CH_2), 4.09 (q, 1 H, C7-H), 3.14–2.52 (m, 5 H, aromatic H), and 0.21 (d, 1 H, amide-NH); IR (Nujol mull) 1668, 1735 and 1758 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.72; H, 4.54; N, 7.91.

D. 7-Amino-3-methyl-2-cephem-4-carboxylic Acid. A suspension of 798 mg (2 mmol) of *p*-nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate in 10 mL of THF and 8 mL of water was cooled in an ice bath and a solution of 480 mg (2 mmol) of $Na_2S \cdot 9H_2O$ in 4.0 mL of water was added. The mixture was stirred at 0–5 °C for 35 min, then 2.0 mL of 1 N HCl was added, and THF was evaporated in vacuo. The resulting aqueous solution (pH 8.5) was extracted with 20 mL of ethyl acetate, and the extract was discarded. The pH of the aqueous solution was adjusted to 3.9 with 1 N HCl while being cooled in an ice bath. After approximately 3 min, the precipitate began to form. After 30 min the solid was filtered and dried in a vacuum oven overnight. Yield of 6 h, 320 mg (75%); *m/e* 214. Anal. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08; O, 22.40; S, 14.97. Found: C, 44.90; H, 4.70; N, 13.94; O, 22.14; S, 15.17.

Registry No.—**3g,** 27487-21-4; **4g,** 61-33-6; **5h,** 29124-83-2; **5v,** 28974-31-4; **6h,** 56487-68-4; **6v,** 10209-07-1; **7v,** 63427-57-6; **8v,** 64811-71-8.

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(5) S. R. Lammert and S. Kukolja, *J. Am. Chem. Soc.*, **97,** 5583 (1975).
(6) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **98,** 5040 (1976).

Regiospecificity of Enol Ether Formation in the Catalyzed Decomposition of Ethyl Diazoacetate in the Presence of Unsymmetrical Ketones

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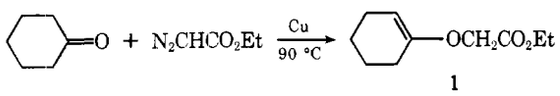
Received January 4, 1977

In 1953, Kharasch and co-workers[1] reported (among other products) the formation of ethyl (cyclohexen-1-oxy)ethanoate (1) in 43% yield from the reaction of excess cyclohexanone with ethyl diazoacetate in the presence of copper at 90 °C. We have found that the use of copper(I) chloride in place of copper gives similar results.



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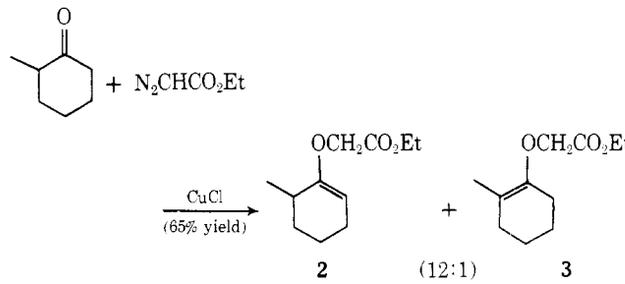
As part of an investigation of the reactions of carbenes and carbenoids with enolizable ketones, we report two examples of the decomposition of ethyl diazoacetate in the presence of copper(I) chloride and an excess of an unsymmetrical ketone which resulted in modest yields of the simple enol ether in which the least-substituted isomer dominated. For example, the use of 2-methylcyclohexanone results in a 65% yield of an isomer mixture in which approximately 92% is enol ether **2.**[2]



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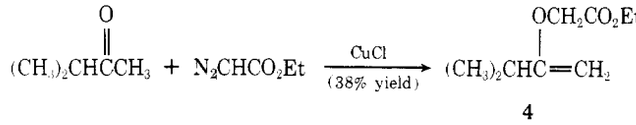
When the same reaction was carried out with 3-methyl-2-butanone, the only low-boiling product observed was enol ether **4.** The observed dominance of the least-substituted enol ether is consistent with simple steric and electronic considerations for the intramolecular proton abstraction required to get from the presumed intermediate carbonyl ylide **5** to the product.



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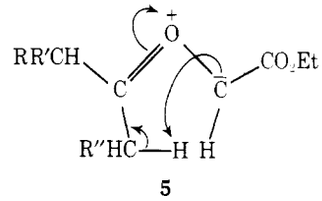

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Products which had a boiling point substantially higher than that of the simple enol ethers already described were not investigated for the reaction of 3-methyl-2-butanone and have been described previously by Kharasch[1] for the reaction with cyclohexanone.

Experimental Section

Elemental analyses were done by the Department of Medicinal Chemistry at the University of Kansas. Mass spectra were obtained on a Varian CH-5 mass spectrometer. Infrared spectra were obtained on a Beckman IR-8 (sodium chloride optics). Varian A-60 and T-60 spectrometers were used for determining NMR spectra of samples as solutions in chloroform-*d* containing an internal tetramethylsilane standard. An F&M Model 700 chromatograph (thermal-conductivity detector) was used for VPC analyses with the following columns: 10% QF-1 (a fluorosilicone; Dow Corning) on 80–100 mesh Gas Chrom Q (10 ft × 0.25 in. copper column) and 10% Hi-EEF 8 AP (a polycyclohexane–dicarbinol adipate; Applied Science Laboratory) on 60–80 mesh Gas Chrom Q (8 ft × 0.25 in. copper column).

Copper(I) chloride was prepared from copper(II) sulfate[4] and purified by washing several times each with glacial acetic acid, absolute ethanol, and anhydrous diethyl ether. Ethyl diazoacetate was prepared by the method of Searle.[5] All ketones were distilled prior to each reaction.

Cyclohexanone Reaction. A solution of ethyl diazoacetate (8.0 g, 0.0701 mol) and cyclohexanone (16 g, 0.163 mol) was added slowly (1.5–2.0 h) with stirring to a mixture of copper(I) chloride (0.10 g) and cyclohexanone (32.0 g, 0.326 mol) maintained at 90–95 °C (N_2 atmosphere). When the addition was complete and nitrogen evolution

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