Facile Alkyl–Oxygen Ester Cleavage

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Sodium thiophenoxide has been used successfully in an inert solvent (dimethylformamide) at or below room temperature to effect cleavage, at the alkyl–oxygen bond, of certain selected ester functions (principally phenacyl) and to generate as products sodium salts of the corresponding carboxylic acids in good to excellent yields. It is suggested that this procedure is ideally suited for temporarily masking carboxyl functions in synthetic sequences involving sensitive molecules such as the penicillins and peptides.

In synthesis it is frequently desirable to "mask" a carboxyl function, cause a reaction or reactions to occur elsewhere in the molecule, and finally to regenerate selectively the carboxyl function under conditions which will not affect other sensitive features of the molecule. Very few general methods have been devised for accomplishing this sequence. In specific instance, sequences involving the hydrogenolysis of benzyl[2] or *p*-nitrobenzyl[3] esters, the selective saponification of methyl or ethyl esters,[2] and the cleavage under acidic conditions of *t*-butyl ester[4] functions have been successfully employed. More recently, Nefkens[5] has used the phthalimidomethyl group to protect carboxyl functions in a number of peptide syntheses. These methods are limited in scope[2] and generally suffer from the fact that the strong acid or base necessary to effect ester cleavage often destroys other sensitive molecular features. Use of the readily hydrogenolyzed benzyl esters avoids this difficulty; however, problems often arise due to the incompatibility of this method with molecules bearing groups—chiefly sulfur containing—sensitive to catalytic hydrogenation conditions.[2]

We have now developed a simple and effective procedure for the removal of protecting ester functions under very mild and essentially neutral conditions. Phenacyl, phthalimidomethyl,[5] and certain other "active" esters are cleaved at the alkyl–oxygen bond to the corresponding sodium carboxylates by the action of sodium thiophenoxide in an inert solvent at or below room temperature. The literature contains a number of reports[5,6] of formally analogous reactions involving ester cleavage at the alkyl–oxygen bond by nucleophilic agents. These reactions, however, generally require high temperatures and/or prolonged reaction times, conditions much too rigorous for use on highly sensitive molecules. Recently, for example, a series of ester cleavages by mercaptides at temperatures from 79 to 213° with reaction times up to 24 hr. has been reported.[15a] The yields obtained typically were less than 50%. In contrast, using our procedure, phenacyl benzylpenicillinate[16] was cleaved to sodium benzylpenicillinate[17] in 84% yield in 15 min. at room temperature.

In developing this procedure, esters of highly labile[18] benzylpenicillin were chosen as test compounds and the extremely nucleophilic, mildly basic thiophenoxide anion[19] was selected as the cleavage reagent. Dimethylformamide was found to be a satisfactory reaction solvent. Acetone, acetonitrile, and toluene were rejected chiefly owing to the considerably lower solubility of sodium thiophenoxide in these solvents. The methyl,[20] benzyl,[21] and phenacyl[16] esters of benzylpenicillin were prepared and their behavior in the presence of sodium thiophenoxide at various temperatures was studied. The results of these experiments are summarized in Table I.

An examination of the data in Table I demonstrates the critical nature of reaction temperature when dealing with systems containing the labile β-lactam structure. Thus, while no ester cleavage product could be detected when benzyl benzylpenicillinate (**2**) was stored in the presence of one molar portion of sodium thiophenoxide at 5° for 18 hr., 90% of the unchanged ester was recovered. However, after only 20 min. at 50° only 78% of the ester could be recovered, and after 15 min. at 100° no β-lactam-containing material could be detected. Similarly, phenacyl benzylpenicillinate (**3**) in the pres-

(1) National Institutes of Health Predoctoral Fellow, 1962–1964.

(2) For references see (a) M. Goodman and G. W. Kenner, *Advan. Protein Chem.*, **12**, 465 (1957); (b) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 928.

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(5) G. H. L. Nefkens, *Nature*, **193**, 974 (1962); G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. trav. chim.*, **82**, 941 (1963). The phthalimidomethyl ester is readily cleaved under the milder conditions described in this paper (see Table II).

(6) Lithium iodide[7] and other metal halides,[8-10] usually in the presence of a tertiary amine, have been successfully used to effect ester cleavage in a number of examples. Tertiary amines alone cleaved more labile phosphoric acid esters.[11] Fusion of carboxylic acid esters with pyridine hydrochloride[12] produced the corresponding pyridinium carboxylates. Cleavages at the alkyl–oxygen bond of β-lactones,[13] γ-lactones,[14] and certain alkyl esters[15] by alkyl and aryl mercaptides have been reported.

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TABLE I

$$RCOOR' + PhS^-Na^+ \longrightarrow RCOO^-Na^+ + PhSR'$$[a]

Ester	Mole ratio PhS^-Na^+/ ester	Reaction time, hr.	Reaction temp., °C.	Yield, %	% ester recovd.
Methyl benzylpenicillinate (1)	1	18	5	0	
Benzyl benzylpenicillinate (2)	1	18	5	0	90
	1	0.33	50	0	78
	1	0.25	100	0	0
Phenacyl benzylpenicillinate (3)	1	18	5	48	
	1	0.17	50	36	
	2	2	5	66	
	2	0.25	25	84	

[a] The isolation and identification of the sulfide coproduct has been previously accomplished.[15a]

ence of one molar portion of sodium thiophenoxide for 18 hr. at 5° was cleaved to the extent of 48%; yet after only 10 min. at 50° only 36% of cleavage product could be isolated. This is indicative of substantial decomposition of the β-lactam system at higher temperature.

In one case (**3**) an increase in the molar ratio of sodium thiophenoxide markedly increased the yield of reaction product. In other instances a one molar portion of sodium thiophenoxide was adequate to effect cleavage in good yield (see Table II). In general, the sodium carboxylate was isolated by the simple expedient of adding a large excess of acetone to the reaction mixture and after a short time collecting the usually crystalline product by filtration. In order to determine the stability of a sensitive product to the reaction conditions and at the same time to examine the efficiency of the isolation procedure, sodium benzylpenicillinate[17] was stored with one molar portion of sodium thiophenoxide at 5° for 24 hr. Recovery of 85% of unchanged material was achieved. After 10 min. at 25° a similar experiment yielded 88% of unchanged material. These results, when considered with the data in Table I, strongly suggest that the reaction may well be quantitative with the yield loss due to incomplete product isolation. It will be noted in Table II that in certain cases higher yields were obtained, apparently due to more favorable solubility characteristics of the products.

Table II lists several additional examples which help to delineate the scope and versatility of the reaction. While sodium thiophenoxide did not effect cleavage of the less activated benzyl ester (**4**) at 25°, at 100° cleavage to the extent of 64% was observed, whereas the highly hindered *t*-butyl ester[22] (**6**) was stable at 100° for 2 hr.

It is noteworthy that sodium thiophenoxide selectively removed phenacyl and similar esters from molecules containing the highly labile[23] phthalimido system (**8**, **9**, **10**, and **12**) often used for protection of amino functions.[24] Careful examination of the reaction products showed no contamination by material in which ring opening had occurred. That sodium thiophenoxide under mild conditions will effect cleavage of a variety of suitably chosen ester functions is further suggested

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(23) Ref. 2b, p. 1249.
(24) Ref. 2b, p. 901.

TABLE II

Ester	Mole ratio PhS^-Na^+/ ester	Reaction time, min.	Reaction temp., °C.	Yield of $RCOO^-Na^+$, %
Benzyl benzoate (**4**)	1	30	25	0
	1	30	100	64
Phenacyl benzoate (**5**)	1	30	25	84
	2	30	25	87
t-Butyl benzoate (**6**)	1	120	25	0
	1	120	100	0
Phenacyl 6-tritylaminopenicillanate (**7**)	1	30	25	81
Phenacyl 6-phthalimidopenicillanate (**8**)	1	30	25	76
Phenacyl phthaloylglycinate (**9**)	2	15	25	99
Benzoin phthaloylglycinate (**10**)	1	15	25	57
4,4′-Dimethoxybenzoin acetate (**11**)	1	30	25	91
Phthalimidomethyl acetate (**12**)	1	30	25	90

by the facile cleavages of benzoin phthaloylglycinate[25] (**10**) and 4,4′-dimethoxybenzoin acetate[26] (**11**).

Experimental[27]

Materials.—Sodium thiophenoxide was prepared by the addition of thiophenol to a molar portion of finely dispersed sodium in ether. After 72 hr. of vigorous stirring, sodium thiophenoxide was collected by filtration and stored in a vacuum desiccator until used. The sodium salts of phthaloylglycine,[28] 6-phthalimidopenicillanic acid,[29] and 6-tritylaminopenicillanic acid[29] were prepared by the slow addition of a molar portion of sodium thiophenoxide in a small volume of dimethylformamide to a stirred solution of the appropriate acid in dimethylformamide. When addition was complete, excess acetone[30] was added; after a few minutes the product was collected by filtration.

Action of Sodium Thiophenoxide on Phenacyl Benzylpenicillinate.[16]—A solution of 0.029 g. of sodium thiophenoxide and 0.050 g. of phenacyl benzylpenicillinate[16] in 0.2 ml. of dimethylformamide was allowed to stand at room temperature (25°) for 15 min. To this solution was then added 20 ml. of acetone. This solution was stirred mechanically for 10 min. during which time crystallization occurred. Filtration afforded 0.033 g. (84%) of sodium benzylpenicillin,[17] m.p. 226–227°. The identity of the product was confirmed by mixture melting point and comparison of infrared spectra.

All other ester cleavage reactions were similarly conducted with molar ratios, reaction times, and temperatures as indicated in Tables I and II. In some cases product precipitation occurred before the addition of acetone.[30] In all cases the products were compared spectrally with authentic material and where possible mixture melting points were taken.

Action of Sodium Thiophenoxide on Benzyl Benzylpenicillinate.[21]—A solution of 0.019 g. of sodium thiophenoxide and 0.061 g. of benzyl benzylpenicillinate[21] in 0.3 ml. of dimethylformamide was stored at 5° for 18 hr. To the cold solution was added 10 ml. of pH 7 buffer solution and the resulting solution was extracted three times with 25–50-ml. portions of ether. The dried (magnesium sulfate) ether extract was evaporated to yield 0.055 g. (90%) of a thick oil identified as starting material by infrared spectra.

After 20 min. at 50° a similar experiment yielded 78% of recovered benzyl benzylpenicillinate.[21]

Phenacyl 6-Phthalimidopenicillanate.—A solution of 0.100 g. of 6-phthalimidopenicillanic acid,[29] 0.292 g. (0.04 ml.) of triethylamine, and 0.070 g. of phenacyl bromide in 1 ml. of dimethyl-

(25) J. C. Sheehan and R. M. Wilson, unpublished results.
(26) A. McKenzie and D. J. C. Pirie, *Ber.*, **69**, 861 (1936).
(27) All melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 237 spectrophotometer. We are indebted to Dr. S. M. Nagy and his associates for the microanalytical data.
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(29) J. C. Sheehan and K. R. Henery-Logan, *ibid.*, **84**, 2983 (1962).
(30) In the case of 6-tritylaminopenicillanic acid, benzene was used to effect isolation.

formamide was refrigerated (5°) for 3 hr. During this time triethylamine hydrobromide crystallized. The mixture was triturated with 10 ml. of ice–water and the resulting precipitate was filtered and dried. This material was suspended in 25 ml. of petroleum ether (b.p. 40–60°) and stirred for 10 min. The crude product (0.117 g.) was then filtered and recrystallized from ethanol to give 0.051 g. of colorless needles, m.p. 144–145°. The infrared spectrum in methylene chloride had strong carbonyl maxima at 1710, 1730, 1760, 1780, and 1800 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{20}N_2O_6S$: C, 62.1; H, 4.32; N, 6.04. Found: C, 61.6; H, 4.35; N, 6.04.

Phenacyl 6-Tritylaminopenicillanate.—A mixture of 0.531 g. of 6-tritylaminopenicillanic acid diethylamine salt[29] and 0.199 g. of phenacyl bromide in 10 ml. of tetrahydrofuran was stirred at room temperature for 18 hr. The precipitated diethylamine hydrobromide (0.117 g., 76%) was removed and the filtrate was evaporated to dryness. The residue was triturated with petroleum ether; the solid material was removed by filtration and recrystallized from a mixture of methylene chloride and ethanol to yield 0.223 g. (39%) of fine colorless platelets, m.p. 184–185°. The infrared spectrum (methylene chloride) exhibits strong carbonyl maxima at 1710, 1760, and 1780 cm.$^{-1}$.

Anal. Calcd. for $C_{35}H_{32}N_2O_4S$: C, 72.7; H, 5.56; N, 4.86. Found: C, 72.6; H, 5.73; N, 5.23.

Phenacyl Phthaloylglycinate.—A mixture of 4.0 g. of phthaloylglycine,[28] 3.1 g. of phenacyl chloride, and 2.0 g. of triethylamine in 150 ml. of 95% ethanol was heated under reflux for 3 hr. and allowed to cool. The product which crystallized was collected and recrystallized from ethanol to yield 2.2 g. of colorless needles, m.p. 149–150°.

Anal. Calcd. for $C_{18}H_{13}NO_5$: C, 66.9; H, 4.02; N, 4.34. Found: C, 67.0; H, 4.01; N, 4.41.

Notes

The Synthesis and Configuration of *cis*- and *trans*-3-Hydroxystachydrine

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The mature fruit of *Courbonia virgata* has been shown to contain the two betaines of 3-hydroxyproline, *cis*- and *trans*-3-hydroxystachydrine.[2] These two isomers, distinguished by the letters a and b, had reported melting points of *ca.* 250° and 209–210°, respectively, with the latter being provisionally assigned the *cis* configuration "because of its greater solubility and slighter tendency to form crystalline salts."[2]

Recently, both *cis*- and *trans*-3-hydroxyproline have been synthesized in this laboratory and the configurations unambiguously assigned by conversion of a precursor, *trans*-3-methoxy-L-proline, to L-methoxysuccinamide.[3]

We have now synthesized *cis*- and *trans*-DL-3-hydroxystachydrine by treatment of the silver salts of *cis*- and *trans*-3-hydroxyproline with methyl iodide in methanol at room temperature. Under these mild conditions epimerization was not observed, in agreement with the analogous 4-hydroxyproline series.[4]

The comparison of the synthetic isomers with authentic samples of stereoisomers a and b revealed that isomer a corresponded to the *trans* configuration and isomer b corresponded to the *cis* configuration. Comparisons were made of melting points, infrared spectra, the relative electrophoretic mobilities, and by paper chromatography in three different solvent systems.

Experimental

Preparation of *cis*-3-hydroxy-DL-stachydrine.—A mixture of 50 mg. (381 μmoles) of *cis*-3-hydroxy-DL-proline, 100 mg. (433 μmoles) of silver oxide, and 125 μl. of water in a 3-ml. centrifuge tube was stirred occasionally at room temperature for 3.25 hr. Approximately one-half of the water was evaporated by means of a stream of nitrogen and 1.0 ml. of methanol was added followed by 50 μl. (113.5 mg., 800 μmoles) of methyl iodide. After 24 hr., an additional 37.5 μl. (85.5 mg., 602 μmoles) of methyl iodide was added and the mixture was stored at room temperature for 48 hr.

The liquor was withdrawn from the centrifuged suspension and the residue washed twice with methanol. Removal of the solvent gave a mixture of pale orange oil and colorless crystals which was triturated with a 2:1 mixture of ethyl alcohol and acetone. The crystalline material was washed twice with a 1:1 mixture of ethyl alcohol and acetone and then dried to give 125 mg. of *cis*-3-hydroxy-DL-stachydrine (41.3%). Two recrystallizations from ethyl alcohol gave small colorless elongated prisms, m.p. 222–222.5°.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 52.66; H, 8.46; N, 8.31.

Analogous treatment of *trans*-3-hydroxy-DL-proline yielded 47.2 mg. of *trans*-3-hydroxy-DL-stachydrine (77.6%). Recrystallization from ethanol gave colorless prisms, m.p. 232.5–233°.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 53.47; H, 8.64; N, 8.69.

By comparison, the melting point of isomer a was 251.5–252° dec. and of isomer b was 216.5–217° dec. All melting points were determined under nitrogen in sealed capillaries.

Comparison of *cis* and *trans*-3-Hydroxy-DL-stachydrine with Cornforth's Stereoisomers a and b.—The infrared spectrum of *trans*-3-hydroxy-DL-stachydrine was substantially identical with the spectrum of isomer a with peaks occurring at 3400, 1635, 1468 cm.$^{-1}$ and more than a score in the fingerprint region. The infrared spectrum of *cis*-3-hydroxy-DL-stachydrine was substantially identical with the spectrum of isomer b with peaks occurring at 3530, 1670, 1625, 1485 cm.$^{-1}$ and more than a score in the fingerprint region.

The relative mobilities of the compounds were as follows: paper electrophoresis[5] isomer a, 0.87; *trans*-3-hystach, 0.87; isomer b, 1.00; and *cis*-3-hystach, 1.00.

Paper chromatography was carried out in three different solvent systems [(a) *n*-butyl alcohol–acetic acid–water (4:1:5), 24.5 hr., Whatman No. 1 paper; (b) *n*-propyl alcohol–water (65:35), 19 hr., Whatman No. 1 paper; (c) ethyl alcohol–acetic acid–water (6:1:3), 15.5 hr., Whatman No. 1 paper] on isomer

(1) U. S. Public Health Service Ref. No. 1-F1-GM-14,275-01A1.

(2) J. W. Cornforth and A. J. Henry, *J. Chem. Soc.*, 597 (1952).

(3) J. C. Sheehan and J. G. Whitney, *J. Am. Chem. Soc.*, **84**, 3980 (1962); **85**, 3863 (1963).

(4) A. A. Patchett and B. Witkop, *ibid.*, **79**, 185 (1957).

(5) pH 1.9, 3 kv; 4 hr.