A Convenient Synthesis of Esters of 6-Aminopenicillanic Acid[1]

M. S. MANHAS*, Kanti GALA, S. S. BARI, Ajay K. BOSE

Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey 07030, U.S.A.

6-Aminopenicillanic acid (**1**) is a readily available, optically active, low-priced organic compound which is an important intermediate for the manufacture of semi-synthetic penicillins and other β-lactam antibiotics. Potential uses of this chiral intermediate for large scale preparation of non-β-lactam compounds too can be foreseen[2]. For conducting reactions with this compound in organic solvents, it is convenient to convert it to an ester.

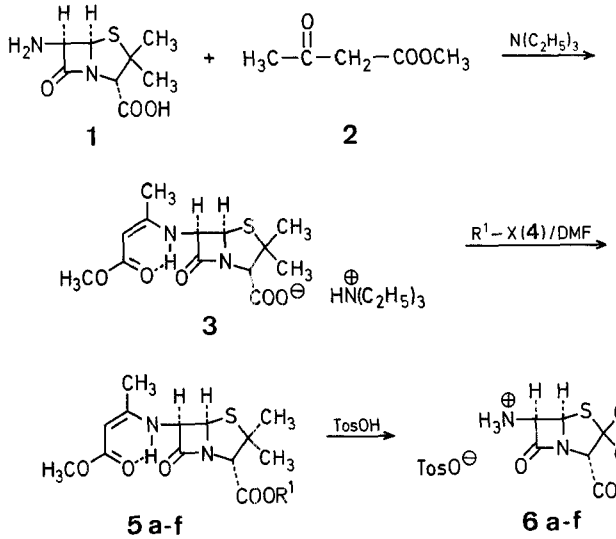
Methyl and benzyl esters of **1** have been prepared by reaction with diazomethane and phenyldiazomethane, respectively[3].

Diazoalkanes, however, are hazardous chemicals which cannot be used for large scale preparations. An alternative method[3] is to react **1** with a molar equivalent of benzyl bromide in presence of triethylamine, however, in this reaction *N*-benzylation can also take place unless the reaction conditions are carefully controlled. Under similar conditions allyl, acetonyl, and phenacyl esters have been prepared[3].

Gordon and coworkers[4] have used the benzhydryl ester of **1** to prepare 6α-methoxypenicillins with different amide side chains. In a recent publication, Jeffrey and McCombie[5] have described the advantages of working with allylic esters of β-lactam antibiotics. We describe here an economical and safe method for the preparation of a variety of esters of **1** which can be conducted on a large scale.

Dane and coworkers[6] have shown that the vinylamino protective group is a convenient way to mask the amino function of an α-amino acid for peptide synthesis. Maclaren[7] has used this approach to prepare esters from α-amino acids. In the course of our studies on the synthesis of penicillin and cephalosporin related compounds, we have developed a facile synthesis of α-amino-β-lactams[8,9] using the intermediacy of the Dane salt from glycine.

The preparation of a Dane salt involves the formation of the sodium or potassium salt of the amino acid by treatment with aqueous alkali and subsequent reaction with a β-keto ester. In the case of **1**, the use of sodium or potassium hydroxides leads quickly to scission of the β-lactam ring. Therefore, we have used triethylamine as the base and an organic solvent instead of inorganic hydroxides in water solution.

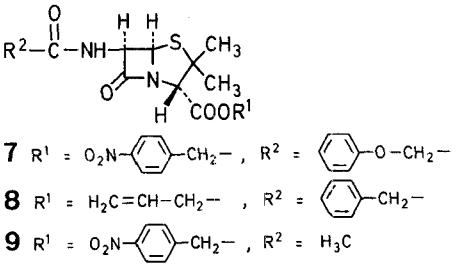


5,6	R^1	5,6	R^1
a	$H_2C=CH-CH_2-$	d	$C_2H_5O-\overset{O}{\overset{\|}{C}}-CH_2-$
b	$O_2N-C_6H_4-CH_2-$	e	$n\text{-}C_4H_9-$
c	$C_6H_5-CH_2-$	f	Cl_3C-CH_2-

When powdered **1** was suspended in dichloromethane and stirred with triethylamine[10] and methyl acetoacetate **(2)**, the quaternary ammonium salt **3** was gradually formed. Upon monitoring the reaction by N.M.R. spectroscopy, it was found that about 3 h were required for complete conversion of **1** to **3**. All volatile materials were then removed from the reaction mixture and the residue dissolved in dimethylformamide. This solution was stirred with an alkyl halide **4** for a few hours to convert **3** in high yield to the desired ester **5**. Since these esters are usually unstable liquids, we found it convenient to treat **5** with *p*-toluenesulfonic acid monohydrate to remove the amino-protective group; in most cases, the esters were isolated as the crystalline *p*-toluenesulfonate salts **6**.

In a recent publication, Dhaon and coworkers[11] have reported the esterification of benzyloxycarbonyl or *t*-butoxycarbonyl protected amino acids with an alcohol in the presence of 1-ethyl-3-[(3-dimethylamino)-propyl]carbodiimide hydrochloride and 4-(dimethylamino)-pyridine. We have found that this method could also be used for the esterification of **3**. Thus, the treatment of **3** with *n*-butanol or 2,2,2-trichloroethanol in the presence of the two reagents gave the corresponding esters **5e** and **5f** which were subsequently transformed to the crystalline *p*-toluenesulfonic acid salts **6e** and **6f**.

Salts of type **6** can be stored unchanged in a refrigerator for long periods of time. They are convenient starting materials for preparing penicillin esters. Thus, when the ester salt **6** was treated with an excess of triethylamine and an equivalent of phenoxyacetyl chloride, penicillin V *p*-nitrobenzyl ester **(7)** was obtained in good yield.



Earlier, we[12] have shown that a pathway to α-amido-β-lactams can be developed that takes advantage of the oxidazability of an enamine. Access to various amido side chains was achieved by using an appropriate β-keto ester for preparing the starting Dane derivative and subsequent oxidation with ruthenium tetroxide or ozonolysis followed by oxidative work up. This approach has been extended to derivatives of **1** - the ester **5b** was converted to **9** by ruthenium tetroxide oxidation.

Melting points are uncorrected. ^{1}H-N.M.R. spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane as internal standard with the downfield direction taken as positive. Mass spectra were taken with a CIMS - Biospect instrument. The I.R. spectra were recorded on a Perkin-Elmer 1310 Spectrophotometer. Microanalysis were performed by Schwarzkoff Microanalytical Laboratory, Inc., Woodside, New York.

Allyl 6-(1'-Methyl-2'-methoxycarbonylvinylamino)-penicillanate (5a); Typical Procedure for Method A using an Alkyl Halide 4:

To a stirred suspension of 6-aminopenicillanic acid (**1**; 2.16 g, 10 mmol) in dry dichloromethane (50 ml) at room temperature is added triethylamine (2.76 ml, 20 mmol) under nitrogen and stirring is continued till all the acid **1** has dissolved. Then methyl acetoacetate (**2**; 1.16 g, 10 mmol) is added dropwise. The reactants are stirred at room temperature for 3 h and concentrated under reduced pressure to leave **3** as an oil. A solution of **3** in dry dimethylformamide (25 ml) is stirred with allyl bromide (**4**; 0.95 ml, 11 mmol) for 3 h, the mixture is diluted with water (40 ml), and extracted with 5:1 ether/dichloromethane (4 × 40 ml). The extract is washed with water (2 × 30 ml), brine (2 × 20 ml), and dried with magnesium sulfate. Evaporation of the solvent under reduced pressure gives **5a** as a thick oil of sufficient purity (determined spectroscopically) for use in the next step; yield: 2.89 g (82%).

Table. Compounds **5** and **6** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. (KBr or neat) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	C.I.M.S. *m/e*
5b	70	112–114°	$C_{20}H_{23}N_3O_7S$[b] (449.5)	1775, 1735, 1650, 1600	1.48 (s, 3H); 1.66 (s, 3H); 2.20 (s, 3H); 3.64 (s, 3H); 4.57 (s, 1H); 4.67 (s, 1H); 5.23 (dd, J=4.5 Hz, 9 Hz, 1H); 5.37 (s, 2H); 5.68 (d, J=4.5 Hz, 1H); 7.93 (AB system, 4H); 9.89 (d, J=9 Hz, 1H)	NH_3 as reagent gas: 450 (M^++H)
5c	70	oil	$C_{20}H_{24}N_2O_5S$[b] (404.5)	1770, 1725, 1650, 1600	1.08 (s, 3H); 1.48 (s, 3H); 2.03 (s, 3H); 3.66 (s, 3H); 4.57 (s, 1H); 4.70 (s, 1H); 5.22 (dd, J=4.5 Hz, 9 Hz, 1H); 5.33 (s, 2H); 5.64 (d, J=4.5 Hz, 1H); 7.93 (AB system, 4H); 9.10 (d, J=9 Hz, 1H)	CH_4 as reagent gas: 404 (M^++H)
5d	78	oil	$C_{17}H_{24}N_2O_7S$[b] (400.5)	1775, 1735, 1650, 1600	1.30 (t, J=7 Hz, 3H); 1.63 (s, 3H); 1.70 (s, 3H); 2.03 (s, 3H); 3.66 (s, 3H); 4.26 (q, J=7 Hz, 2H); 4.56 (s, 1H); 4.70 (s, 2H); 4.75 (s, 1H); 5.16 (dd, J=4.5 Hz, 9 Hz); 5.63 (d, J=4.5 Hz, 1H); 9.1 (d, J=9 Hz, 1H)	NH_3 as reagent gas: 418 (M^++18)
5f	55	oil	$C_{15}H_{19}Cl_3N_2O_5S$[b] (445.7)	1775, 1755, 1650, 1600	1.58 (s, 3H); 1.71 (s, 3H); 2.00 (s, 3H); 3.64 (s, 3H); 4.60 (s, 1H); 4.65 (s, 1H); 4.76 (s, 2H); 5.14 (dd, J=4.5 Hz, 9 Hz, 1H); 5.62 (d, J=4.5 Hz, 1H); 9.02 (d, J=9 Hz, 1H)	CH_4 as reagent gas: 447 (M^++H)
6b	91	139–140°	$C_{22}H_{25}N_3O_8S_2$ (523.6)	1770, 1735	1.30 (s, 3H); 1.44 (s, 3H); 2.30 (s, 3H); 4.47 (s, 1H); 5.00 (d, J=4.5 Hz, 1H); 5.20 (s, 2H); 5.44 (d, J=4.5 Hz, 1H); 7.44 (AB system, 4H); 7.83 (AB system, 4H); 7.35 (br. s, 3H)	—
6c	72	156–157°	$C_{22}H_{26}N_2O_6S_2$ (478.6)	1770, 1720	1.35 (s, 3H); 1.47 (s, 3H); 2.30 (s, 3H); 4.40 (s, 1H); 4.88 (d, J=4.5 Hz, 1H); 5.10 (s, 2H); 5.45 (d, J=4.5 Hz, 1H); 5.73 (br. s, 3H); 7.30 (s, 5H); 7.35 (AB system, 4H)	—
6d	81	134–135°	$C_{19}H_{26}N_2O_8S_2$ (474.6)	1770, 1755, 1730	1.20 (t, J=7 Hz, 3H); 1.50 (s, 6H); 2.35 (s, 3H); 4.30 (q, J=7 Hz, 2H); 4.53 (s, 1H); 4.65 (d, J=4.5 Hz, 2H); 5.00 (d, J=4.5 Hz, 1H); 5.45 (d, J=4.5 Hz, 1H); 7.50 (AB system, 4H); 7.67 (br. s, 3H)	—
6e	78	144–145°	$C_{19}H_{28}N_2O_6S_2$ (444.6)	1775, 1730	0.90 (t, 3H, J=6 Hz); 1.3–1.7 (m, 10H); 1.36 (s, 3H); 1.46 (s, 3H); 2.33 (s, 3H); 4.10 (t, J=6 Hz, 2H); 4.40 (s, 1H); 4.95 (d, J=4.5 Hz, 1H); 5.37 (d, J=4.5 Hz, 1H); 7.2–7.8 (AB system, 4H); 8.70 (br. s, 3H)	—
6f	83	175–176°	$C_{17}H_{21}Cl_3N_2O_6S_2$ (519.9)	1790, 1730	1.46 (s, 3H); 1.63 (s, 3H); 2.25 (s, 3H); 4.51 (s, 1H); 4.74 (s, 2H); 4.90 (d, J=4.5 Hz, 1H); 5.47 (d, J=4.5 Hz, 1H); 7.1–7.7 (AB system, 4H)	—

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.23, N ±0.15; exceptions: **6b**, N −0.55; **6e**, N −0.53.
[b] Not analyzed.

$C_{16}H_{22}N_2O_5S$ (354.4)

I.R. (neat): ν=1770, 1730, 1660, 1600 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ=1.50 (s, 3H); 1.64 (s, 3H); 2.05 (s, 3H); 3.65 (s, 3H); 4.50 (s, 1H); 4.64 (br. d, 3H); 5.30 (dd, J=4.5 Hz, 9 Hz, 1H); 5.60 (d, 1H, J=4.5 Hz); 5.2–6.1 (ABX system, 3H); 9.05 ppm (d, J=9 Hz, 1H).

C.I.M.S. (NH_3 reagent gas): m/e=355 (M^++H).

***n*-Butyl 6-(1′-Methyl-2′-methoxycarbonylvinylamino)-penicillanate (5e); Typical Procedure for Method B using an Alcohol 4:**

A solution of **3** (3.45 g, 8.3 mmol) prepared as in Method A, 4-(dimethylamino)-pyridine (0.15 g, 1.22 mmol), and *n*-butanol (**4**; 0.70 g, 9.5 mmol) in dry dichloromethane (150 ml) is cooled with stirring in an ice/salt bath. 1-Ethyl-3-[(3-dimethylamino)-propyl]carbodiimide (2.04 g, 10.6 mmol) in dichloromethane (50 ml) is added dropwise and the mixture is stirred at 0–10 °C for 2 h. The progress of the reaction is monitored by T.L.C. After additional stirring for 2 h at room temperature, the mixture is washed with water (2×25 ml), brine (25 ml), and dried with magnesium sulfate. Removal of the solvent under reduced pressure gives **5e** as an oil which is purified by column chromatography on silica gel (100–200 mesh) eluting with 10:1 chloroform/ethyl acetate; yield: 1.6 g (53%).

$C_{17}H_{26}N_2O_5S$ (370.5)

I.R. (neat): ν=1775, 1735, 1655, 1605 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ=0.87 (t, J=6 Hz, 3H); 1.2–1.8 (m, 10H); 2.07 (s, 3H); 3.65 (s, 3H); 4.02 (q, J=6 Hz, 2H); 4.48 (s, 1H); 4.70 (s, 1H); 5.11 (dd, J=4.5 Hz, 9 Hz, 1H); 5.58 (d, J=4.5 Hz, 1H); 9.10 ppm (d, J=9 Hz, 1H).

C.I.M.S. (NH_3 as reagent gas): m/e=371 (M^++H).

Allyl 6-Aminopenicillinate *p*-Toluenesulfonic Acid Salt (6a); Typical Procedure:

To a solution of **5a** (2.83 g, 8 mmol) in dry acetone (4 ml) is added *p*-toluenesulfonic acid monohydrate (1.71 g, 9.9 mmol) and the reactants stirred at room temperature. The salt precipitates out after 5 min and the suspension is stirred for additional 5 min. The mixture is then diluted with dry ether (20 ml) while stirring. The crude salt is filtered, washed twice with dry ether, and recrystallized from dichloromethane/ether to give the spectroscopically pure product; yield: 2.4 g (80%); m.p. 149–150 °C.

$C_{18}H_{21}N_2O_6S_2$ (428.5)	calc.	C 50.45	H 5.64	N 6.53
	found	50.46	5.48	6.41

I.R. (KBr): ν=1770, 1730 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.37$ (s, 3H); 1.45 (s, 3H); 2.32 (s, 3H); 4.43 (s, 1H); 4.58 (d, $J = 6$ Hz, 2H); 4.65 (d, $J = 4.5$ Hz, 1H); 5.2–6.1 (ABX system, 4H); 7.48 (AB system, 4H); 7.80 ppm (br. s, 3H).

Penicillin V *p*-Nitrobenzyl Ester (7):
To a stirred solution of **6b** (420 mg, 0.8 mmol) in dichloromethane (50 ml) is added triethylamine (0.14 ml, 1 mmol) under anhydrous conditions. The formation of the free amine is monitored by T.L.C. After about 2 h of stirring, additional triethylamine (0.14 ml) is added. The solution is cooled to ice-salt temperature and phenoxyacetyl chloride (140 mg, 0.82 mmol) in dichloromethane (20 ml) is then added dropwise. The reaction mixture is allowed to warm to room temperature and stirring is continued for 2–3 h while the progress of the acylation is monitored by T.L.C. The mixture is then washed with 3% sodium hydrogen carbonate solution (20 ml), water (20 ml), and dried with magnesium sulfate. Evaporation of the solvent affords the product as an oily liquid; yield: 0.34 g (81%).

I.R. (neat): $\nu = 3390$, 1775, 1735, 1675 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.40$ (s, 3H); 1.45 (s, 3H); 4.28 (s, 3H); 5.20 (s, 2H); 5.45 (d, $J = 6$ Hz, 1H); 5.65 (dd, $J = 6$ Hz, 9 Hz, 1H); 7.1 (m, 6H); 7.80 ppm (AB system, 4H).

C.I.M.S. (NH_3 as reagent gas): $m/e = 503$ ($M^+ + NH_4$).

Penicillin G Allyl Ester (8)[5]:
Prepared similarly by acylation of **6a** with phenylacetyl chloride; yield: 84%; thick oil.

$C_{19}H_{22}N_2O_4S$ (374.5)

I.R. (neat): $\nu = 3300$, 1775, 1730, 1650 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.41$ (s, 6H); 3.57 (s, 2H); 4.34 (s, 1H); 4.60 (br. s, $J = 6$ Hz, 2H); 5.2–6.2 (m, 5H); 6.20 (br. d, 1H); 7.28 ppm (s, 5H).

C.I.M.S. (NH_3 as reagent gas): $m/e = 392$ ($M^+ + NH_4$).

***p*-Nitrobenzyl 6-Acetamidopenicillanate (9):**
To a cooled solution of sodium metaperiodate (1 g, 4.6 mmol) in acetone/water (15 + 15 ml) is added ruthenium dioxide (20 mg, 0.15 mmol) and the contents stirred for about 45 min till all the RuO_2 is oxidized to RuO_4 (solution develops yellow color). This solution is added dropwise to a solution of **5b** (1 g, 2.2 mmol in acetone (10 ml) and stirred for 3 h. The progress of the reaction is monitored by T.L.C. After completion of the reaction, the contents are filtered. The filtrate is evaporated to remove acetone. The resulting aqueous solution is extracted with dichloromethane (50 ml). The extract is washed with sodium hydrogen carbonate solution (20 ml), brine (20 ml), dried with magnesium sulfate, and evaporated to afford the title compound as a thick oil which crystallizes on trituration with ether; yield: 280 mg (16%); m.p. 120–121° (dichloromethane, ether petroleum ether).

The above reaction conditions are not optimal; the product has also been prepared by acylation of **6b** with acetyl chloride; yield: 80%.

$C_{17}H_{19}N_3O_6S$	calc.	C 51.90	H 4.86	N 10.68
(393.4)	found	51.42	4.63	10.64

I.R. (KBr): $\nu = 1770$, 1735, 1655 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.43$ (s, 3H); 1.63 (s, 3H); 2.06 (s, 3H); 4.46 (s, 1H); 5.26 (s, 2H); 5.50 (d, $J = 4.5$ Hz, 1H); 5.66 (d, $J = 9$ Hz, 4.5 Hz, 1H); 6.20 (br. d, $J = 9$ Hz, 1H); 7.86 ppm (AB system, 4H).

C.I.M.S. (NH_3 as reagent gas): $m/e = 411$ ($M^+ + NH_4$).

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[1] Part 67 in the series Studies on Lactams. For part 66 see D. P. Sahu, P. Mashava, M. S. Manhas, A. K. Bose, *J. Org. Chem.* **48,** in press (1983).

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