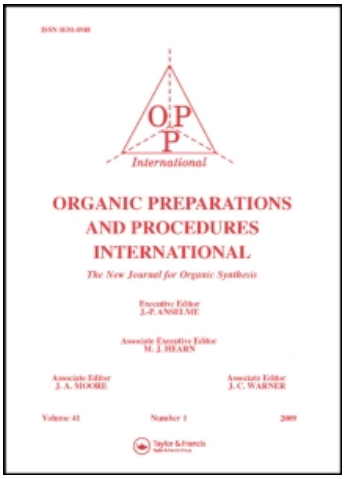

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SIMPLE AND CONVENIENT PROCEDURE FOR THE PREPARATION OF ACID CHLORIDES OF PENICILLINS

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SIMPLE AND CONVENIENT PROCEDURE FOR THE PREPARATION OF ACID CHLORIDES OF PENICILLINS

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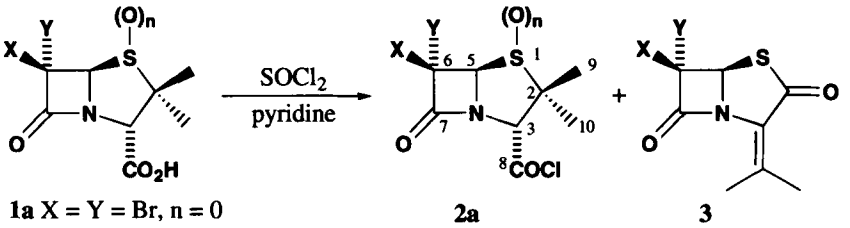
The acid chloride of penicillins are important chiral intermediates for the preparation of other 3α-substituted penam derivatives.[1] In particular, recent publications have highlighted the discovery of penicillanate esters[2] and amides[3] as inhibitors of human leukocyte elastase (HLE). These acid chlorides are normally synthesized from their corresponding acids by reaction with thionyl chloride in the presence of pyridine in yields ranging from 20-53%.[4] Thus, when we have used the literature conditions on 6,6-dibromopenicillanic acid (**1a**), the best result was a 70% yields of a mixture of 6,6-dibromo-3α-chlorocarbonyl-2,2-dimethylpenam (**2a**) and anhydro-6,6-dibromopenicillin (**3**),[5] in a ratio 5:1 (Scheme 1). Compound **3** was derived from a well-established rearrangement which is, however, supposed to occur *only* when a stronger base (triethylamine) is added to the reaction mixture.[4]

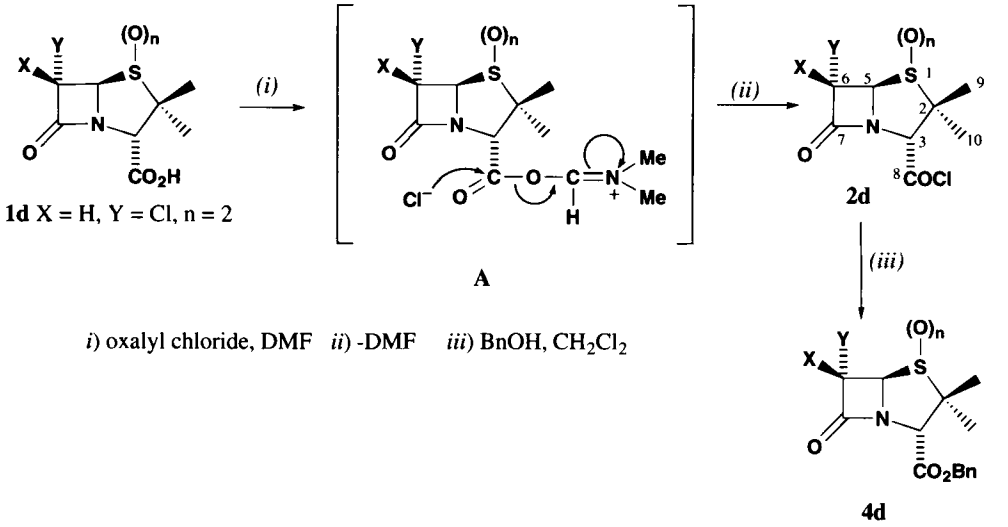


1a X = Y = Br, n = 0 **2a** **3**

Scheme 1

This communication reports that the reaction of penicillanic acid derivatives **1a-d** with oxalyl chloride and dimethylformamide[6] in chloroform or benzene at room temperature, affords the corresponding pure acid chlorides **2a-d** in very good yields with no traces of anhydropenicillin being detected in any case (Table). This reaction probably proceeds through the formation of a carboxymethyleniminium chloride salt intermediate **A**,[7] which then reacts with chloride ion to give the acid chloride (Scheme 2). The potential utility of this method for the synthesis of biologically active compounds is demonstrated by the preparation of benzyl 6α-chloropenicillanate sulfone (**4d**) in 62% yield from **2d** and benzyl alcohol. This compound has been reported in studies of human leukocyte elastase inhibition.[2,8]

In conclusion, we have described a simple and high yield method for the synthesis of acid chlorides **2**, useful intermediates in penicillin synthesis, overcoming the anhydropenicillin rearrangement, the major drawback of earlier procedures.



Scheme 2

Table. Synthesis of Acid Chloride of Penicillins

	Product			Method	Solvent	Time (hrs)	Yield (%)[a]
a	X = Br	Y = Br	n = 0	A	benzene	0.5	90
b	X = H	Y = H	n = 2	B	chloroform	1.5	78[b]
c	X = H	Y = Cl	n = 0	A	benzene	2	75
d	X = H	Y = Cl	n = 2	B	benzene	1	91

a) Isolated yields, unless otherwise stated. b) Along with 5% starting material by ^{1}H NMR, probably due to rapid hydrolysis of the product.

EXPERIMENTAL SECTION

Melting points were determined on a Ernst Leitz melting point apparatus and are uncorrected. IR spectra were taken on a Beckman Acculab 8 Spectrometer. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ on a Bruker WP 80 SY and AC 200, using TMS as an internal stanard. Low and high resolution mass spectra (electron impact, 70 eV) were obtained with a Varian MAT 112S. Flash column chromatography was performed over silica gel, according to the procedure described by Still *et al.*[9] Starting materials **1a**,[10]**1b**,[10] **1c**,[11] and **1d**[12] were synthesized as reported in the literature.

General Procedure. Method A.- To a stirred suspension of the corresponding acid **1** (2.8 mmol) in a mixture of anhydrous benzene (8.0 mL) and anhydrous dimethylformamide (0.15 mL, 1.9 mmol) at 20°, oxalyl chloride (0.29 mL, 3.3 mmol) was added dropwise while a slow stream of nitrogen was passed through the mixture. After the reaction proceeded, the insoluble starting material went into solution. After the reaction was complete, the solvent was evaporated *in vacuo* and the resulting crystalline residue was purified by passing through a short pad of silica gel using chloroform as eluent.

Method B.- Oxalyl chloride (0.07 mL, 0.78 mmol) was slowly added to a suspension of the acid **1**

(0.56 mmol) in benzene or chloroform (1.5 mL) and dimethylformamide (0.03 mL, 0.39 mmol) at room temperature. As the reaction was complete, the soluble phase was transferred to another flask and the solid washed with benzene or chloroform (2 x 1 mL). The combined organic phases were evaporated *in vacuo* to afford **2** as an oil.

6,6-dibromo-3α-chlorocarbonyl-2,2-dimethylpenam (2a), mp. 111-112° (from benzene-hexane). IR (KBr) 1810 (COCl)and 1790 cm^{-1} (β-lactam). ^1H NMR (80 MHz): δ 1.63 (s, 3H, Me), 1.69 (s, 3H, Me), 4.80 (s, 1H, H3), 5.81 (s, 1H, H5). ^{13}C NMR (20.15 MHz): δ 26.0 (C-10), 33.3 (C-9), 57.5 (C-6), 64.8 (C-2), 76.9 (C-3), 80.5 (C-5), 164.2 (C-7), 168.7 (C-8). MS (EI) *m/z*: 381 (0.4%), 379 (1), 377 (1.5), 375 (M^+, O.6), 261 (4.9), 259 (10.5), 220 (2), 218 (4.1), 216 (2), 202 (5), 200 (10), 198 (5), 114 (100). HRMS Calcd for $C_8H_8Br_2ClNO_2S$: 374.8332. Found: 374.8352.

3α-Chlorocarbonyl-2,2-dimethylpenam (2b)[13]: ^1H NMR (200 MHz): δ 1.53 (s, 3H, Me), 1.73 (s, 3H, Me), 3.53 (m, 2H, H6), 4.65 (s, 1 H, H3), 4.66 (m, 1H, H5).

6α-Chloro-3α-chlorocarbonyl-2,2-dimethylpenam (2c)[13]: IR (film) 1795 (COCl) and 1790 cm^{-1} (β-lactam). ^1H NMR (200 MHz): δ 1.63 (s, 3H, Me), 1.68 (s, 3H, Me), 4.81 (s, 1 H, H3), 4.81 (d, 1 H, J = 1.5Hz, H6), 5.37 (d, 1 H, J = 1.5Hz, H5). ^{13}C NMR (50 MHz): δ 25.70 (C-10), 33.28 (C-9), 62.75 (C-6), 65.02 (C-2), 70.81 (C-5), 76.68 (C-3), 166.34 (C-7), 169.14 (C-8).

6α-Chloro-3α-chlorocarbonyl-2,2-dimethylpenam S,S-dioxide (2d)[13]. ^1H NMR (200 MHz): δ 1.54 (s, 3H, Me), 1.73 (s, 3H, Me), 4.69 (s, 1H, H3), 4.71 (d, 1H, J = 1.6Hz, H6), 5.21 (d, 1H, J = 1.6 Hz, H5).

Synthesis of benzyl 6α-chloropenicillanate sulfone (4d).- To a solution of **2d** (129 mg, 0.45 mmol) in chloroform (1 mL) was added benzyl alcohol (0.104 mL, 1.01 mmol). The reaction mixture was stirred at room temperature for 3 hrs, poured into water (0.5 mL) and layers were separated. After washing with water (2 x 0.5 mL) and drying, solvent was evaporated *in vacuo* and the crude solid was purified by flash column chromatography (eluted with 85:15 hexane:ethyl acetate) to give **4d**[2,8] (100 mg, 62%), mp. 75.5-76° (from CH_2Cl_2-hexane). IR (KBr): 1805 (β-lactam), 1719 (ester), 1332 and 1118 (SO_2) cm^{-1}. ^1H NMR (200 MHz): δ 1.27 (s, 3H, Me), 1.54 (s, 3H, Me), 4.45 (s, 1H, H3), 4.63 (d, 1H, J = 1.5Hz, H6), 5.15 (d, 1H, J = 1.5Hz, H5), 5.25 (qAB, 2H, J = 12Hz, benzyl CH_2), 7.39 (s, 5H, aromatics). ^{13}C NMR (50 MHz): δ 16.45 (C-10), 19.73 (C-9), 55.35 (C-6), 62.98 (C-3), 63.12 (C-2), 66.29 (benzyl CH_2), 69.1 (C-5), 128.75, 128.99, 134.07 (aromatics), 165.74 (C-7), 165.85 (C-8).

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