Registry No. **1a**, 136667-35-1; **1b**, 136667-54-4; **1c**, 33128-26-6; **1d**, 136667-55-5; **1e**, 101216-59-5; **1f**, 106510-41-2; **2a**, 136667-36-2; **2b**, 136667-49-7; **2c**, 136667-50-0; **2d**, 136667-51-1; **2e**, 136667-52-2; **2f**, 136667-53-3; **3**, 4526-07-2; **4**, 73084-25-0; **6a**, 78365-43-2; **6b**, 34508-57-1; **6c**, 136667-39-5; **6d**, 136667-40-8; **7a**, 136667-37-3; **7b**, 136667-41-9; **7c**, 136667-42-0; **7d**, 136667-43-1; **8a**, 136667-38-4; **8b**, 136667-44-2; **8c**, 136667-45-3; **8d**, 136667-46-4; **8e**, 136667-47-5; **8f**, 136667-48-6; 3-bromo-1-propanol, 627-18-9; 4-bromo-1-butanol, 33036-62-3; 7-bromo-1-heptanol, 10160-24-4; 11-bromo-1-undecanol, 1611-56-9; 1-iodoundecane, 4282-44-4; 1-iododecane, 2050-77-3; 1-iodoheptane, 4282-40-0; 1-iodopropane, 107-08-4; 1-iododecane, 4292-19-7.

Facile Chloride Substitution of Activated Alcohols by Triphosgene: Application to Cephalosporin Chemistry

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Functionalization of cephalosporins at C-3 has been instrumental in the development of a series of clinically useful β-lactam antibacterials.[1] Such structural manipulations are often carried out on halogenated intermediates; therefore, there exists a need for new and mild synthetic routes to these compounds. Whereas a number of reagents are available for halogenation of hydroxyl compounds, the vast majority are not useful for chemical conversions on cephalosporins. The primary problem is the lability of the β-lactam ring of cephalosporins to both acidic and basic conditions. Furthermore, the ability of ceph-3-ems to isomerize to the undesired ceph-2-ems, under even mildly basic conditions, complicates the problem.

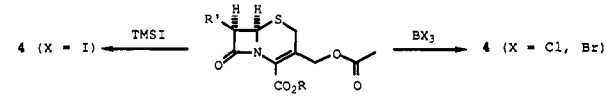
Bromination of 3-methylcephem sulfoxides with *N*-bromosuccinimide (NBS) in the absence[2] or presence[3] of photoinitiation has been reported (**1** → **2**). A complicating factor noted with the use of NBS is the possibility of overreaction at C-2 or at the C-7 substituent to give dibromo derivatives. It is significant that the reaction failed when applied to 1-oxocephems.[4]

1 **2**

A practical route to halogenated cephems is provided by the conversion of 3-*exo*-methylenecephams to ceph-3-em halides (**3** → **4**).[5] Compound **3** undergoes reaction with *tert*-butyl hypochlorite, bromine, or iodine under basic conditions to afford the chloro-, bromo- and iodocephems, respectively.

3 **4** (X = Cl, Br, I)

Reactions of boron trihalide[6] and iodotrimethylsilane[7] with cephems possessing ester functionalities at C-3 (**5**) provide additional entries into the corresponding halocephem derivatives. A principal drawback to this chemistry is the fact that acid labile protective groups such as the *tert*-butyl, benzhydryl, and *p*-methoxybenzyl functions, which are used widely in β-lactam chemistry, cannot be used with these reagents. Deacetylcephalosporins have been reported to undergo reaction in the presence of phosphorus pentachloride and pyridine to give the corresponding chloro analogues.[8] However, protection of the amide group typically found at C-7 of cephalosporins is required in this reaction, since the reagent (PCl_5/pyridine) facilitates the cleavage of this function in a competing reaction with chlorination at C-3.[8,9]



5

We report here on the chlorination of the cephem nucleus at the C-3 position using triphosgene (bis(trichloromethyl)carbonate). Deacetylcephalothin (**6**), a semisynthetic cephalosporin, and triphosgene undergo an exothermic reaction in the presence of pyridine at room temperature to give compound **4**. Two such cephalosporins, one with the *p*-methoxybenzyl and the other with the benzhydryl groups at the C-4 carboxylate, were prepared in 60–80% yields. Whereas some $\Delta^3 \rightarrow \Delta^2$ isomerization was noted when triethylamine was used in this reaction, no such undesired side reaction was detected in the presence of equimolar amounts of pyridine. The lactone **8** was the only other observed product. However **8** was readily separated from the cephem chloride by chromatography. In order to minimize the lactonization problem a 6-fold excess of triphosgene was used to speed up the chlorination reaction; however, the yield of the cephem chlorides improved only by 4–5%. The reaction is thought to proceed through an unstable cephem chloroformate (**7**); formation of chloroformates in reactions of hydroxy compounds with triphosgene is precedented.[10] In a typical reaction, we allow a solution of the alcohol and triphosgene (3:1 molar ratio) to stir in a minimum amount of THF or CH_2Cl_2. The progress of the reaction can be conveniently monitored by measuring CO_2 evolution by a manometer connected to the vessel. As shown in Table I, the reaction is applicable to benzylic, allylic and propargylic alcohols. The chlorides listed in Table I were each made from the corresponding alcohol in less than 15 min at room temperature, with the exception of propargyl chloride. Whereas the chloroformate of propargyl alcohol formed in less than 1 min, gentle warming was necessary to drive the reaction to completion to give propargyl chloride. It is significant that under these conditions with unactivated alcohols chloroformates are isolated readily without a trace

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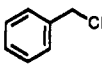
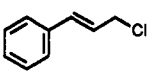
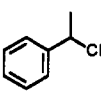
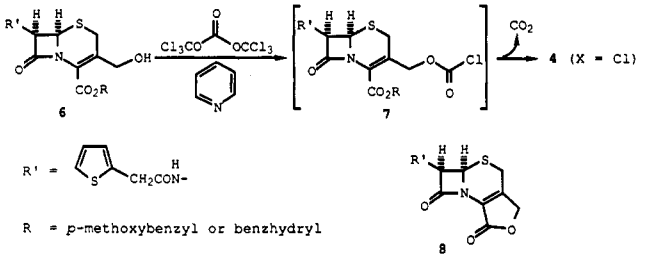
Table I. Chlorides Prepared from the Corresponding Alcohols[a]

product	yield,[b] %	IR,[c] cm^{-1}	^{1}H NMR,[d] δ	MS,[e] m/z
	90[f]	3034, 1497, 1454, 1269, 696, 560	7.35 (m, 5 H), 4.58 (s, 2 H)	128 (M + H, 3), 126 (M, 10), 91 (M - Cl, 50)
	65[g]	3130, 1450, 1223, 1019, 865, 750	5.06 (m, 1 H), 4.93 (m, 1 H), 4.00 (d, 2 H, J = 0.7 Hz), 1.84 (d, 3 H, J = 0.7 Hz)	91 (M, 4), 55 (M - Cl, 23)
	63[h]	3313, 2975, 1263, 958, 714, 641	4.06 (d, 2 H, J = 2.7 Hz), 2.51 (t, 1 H, J = 2.7 Hz)	76 (M + 2, 2) 74 (M, 5)
	80[i]	3074, 1475, 1464, 1226, 851, 619	7.41 (m, 2 H), 7.23 (m, 2 H), 5.43, 5.40 (dd, 1 H, J = 3.3, 6.9 Hz), 3.16 (m, 1 H), 2.88 (m, 1 H), 2.58 (m, 1 H), 2.35 (m, 1 H)	154 (M + 2, 2), 152 (M, 4), 117 (M - Cl, 31)
	85[j]	3086, 3065, 1651, 1496, 1248, 966	7.26–7.41 (m, 5 H), 6.68, 6.63 (d, 1 H, J = 15.9 Hz), 6.34, 6.29 (dt, J = 15.9, 7.0 Hz), 4.25, 4.23 (dd, 2 H, J = 7.0 Hz)	154 (M + 2, 3), 152 (M, 8), 117 (M - Cl, 32)
	86[k]	2978, 1494, 1453, 1049, 971, 698	7.36 (m, 5 H), 5.12 (q, 1 H), 1.88 (d, 3 H)	142 (M + 2, 2), 140 (M, 5), 105 (M - Cl, 25)

[a] 3:1 molar ratio of alcohol to triphosgene was used in each case. [b] Reactions were carried out as described for **4a** and isolated yields are reported. [c] Spectra were recorded in CCl_4 or in mineral oil. [d] 300 MHz, δ in ppm downfield from tetramethylsilane in $CDCl_3$. [e] Electron impact (EI) or chemical ionization (CI). [f] Dist. 62–66 °C (8 Torr). [g] Dist. 70–75 °C. [h] Dist. 56–62 °C. [i] Isolated as described for **4a**; 6% indene was detected in the crude mixture as well. [j] Dist. 107–111 °C (12 Torr). [k] Dist. 29–32 °C (0.6 Torr).

of the corresponding chloride; (−)-menthol chloroformate and *sec*-butyl chloroformate were made in 98% and 74% yields, respectively.



In analogy with the reaction of thionyl chloride with alcohols, which results in the formation of the corresponding chlorides, either an S_N2 or carbonium ion mechanisms (such as S_Ni and S_N1) could be invoked for the formation of chlorides from the intermediary chloroformates. The former mechanism would result in inversion, whereas the latter two would give retention and racemization of configuration at the site of reaction, respectively.[11] (*R*)-(+)-1-Phenylethanol ($[\alpha]^{20}_D$ = +45.7° (neat), 99% ee)[12] was converted to 1-(chloroethyl)benzene by this procedure. Polarimetric measurements of the product ($[\alpha]^{20}_D$ = −42.0° (neat)) revealed it to be a 3:7 molar ratio of (*R*)-(+)- and (*S*)-(−)-1-(chloroethyl)benzene, respectively.[13] Thus, the reaction proceeds primarily via S_N2, with some contribution by S_N1 and/or S_Ni mechanisms.

An example of the use of phosgene gas in chlorination of a benzylic alcohol was reported in 1939,[14] and a few variations of this reaction have also appeared in the literature.[15] This reaction has not received widespread attention, undoubtedly because of the toxicity of phosgene gas. However, the availability of triphosgene as a stable solid alternative to phosgene should make the reaction reported herein a practical and convenient route to a number of chlorinated compounds.

Experimental Section

Proton NMR spectra were obtained at 300 MHz using a Nicolet QE-300 spectrometer. Chemical shift values (δ) are given in ppm. Infrared and mass spectra were recorded on a Nicolet DX and a Kratos MS 80RFA spectrometer, respectively. Melting points were taken on a Hoover UniMelt apparatus and are uncorrected. Thin-layer chromatograms were made on silica gel. All other reagents, including triphosgene, were purchased from the Aldrich Chemical Co. Crystals of compound **4a** (vide infra) were grown from a THF solution by slow vapor diffusion of cyclohexane. X-ray diffraction data on compound **4a** was collected on a Nicolet R3 diffractometer at ambient temperature with monochromated MoKα radiation. The crystals were small thin colorless flat needles. A sample chosen for data collection was 0.16 × 0.08 × 0.14 mm^3, and although it was the best quality available, it was a poor diffractor with little diffraction greater than 15° in 2θ. The space group is $P2_1$; cell constants are a = 13.235 (6) Å, b = 4.816 (2) Å, c = 18.679 (6) Å, β = 100.1 (3)°, V = 1172.0 (0.8) Å^3, and Z = 2. The total number of reflections collected was 2517 of which 1223 had $I \geq 1.5\ \sigma(I)$. In the structure solution the thiophene ring is badly disordered, which could be due to either true crystalline disorder or twinning. The remainder of the molecule is well behaved. The weighted R value is 0.077.

***p*-Methoxybenzyl 7β-(2-Thienylacetamido)-3-(chloromethyl)-3-cephem-4-carboxylate (4a).** A solution of *p*-methoxybenzyl 7β-(2-thienylacetamido)-3-(hydroxymethyl)-3-cephem-4-carboxylate (750 mg, 1.6 mmol) and triphosgene (160 mg, 0.54 mmol) in 20 mL of dry THF was stirred at room temperature. Subsequently, dry pyridine (270 μL, 3.2 mmol) was added over 30 s; pyridinium hydrochloride precipitated immediately. The mixture was allowed to stir for 30 min, at which time the solution was evaporated to dryness and the residue was purified by column chromatography on silica gel (10% ethyl acetate in benzene). The title compound was isolated as a white solid (640 mg, 81%): mp 132–136 °C; IR (mineral oil) 1779, 1710, 1703, 1646, 1377 cm^{-1}; R_f 0.31 (1:9 ethyl acetate/benzene); ^{1}H NMR ($CDCl_3$) δ 3.41, 3.61 (2d, 2 H, C-2, J = 18.3 Hz), 3.80 (s, 3 H, methoxy), 3.83 (s, 2 H, side chain methylene), 4.40, 4.53 (2d, 2 H, C-3 chloromethyl, J = 11.7 Hz), 4.93 (d, 1 H, C-6, J = 4.8 Hz), 5.20 (s, 2 H, benzylic methylene) 5.83 (m, 1 H, C-7), 6.63 (d, 1 H, NH, J = 9.3 Hz), 6.89 (d, 2 H, phenyl, J = 8.4 Hz), 6.98 (m, 2 H, thienyl), 7.24 (m, 1 H, thienyl), 7.33 (d, 2 H, phenyl, J = 8.4 Hz); MS FAB$^+$ 492 (M + H, 0.5%).

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Benzhydryl 7β-(2-Thienylacetamido)-3-(chloromethyl)-3-cephem-4-carboxylate (4b). The reaction was carried out and the crude product was purified as outlined above to afford a pale yellow solid in 60% yield: mp 143-148 °C; IR (mineral oil) 1781, 1723, 1659, 1376 cm^{-1}; R_f 0.43 (1:9 ethylacetate/benzene); ^1H NMR ($CDCl_3$) δ 3.45, 3.60 (2d, 2 H, C-2, J = 18.6 Hz), 3.86 (s, 2 H, side chain methylene), 4.38 (s, 2 H, C-3 chloromethyl), 4.99 (d, 1 H, C-6, J = 5.1 Hz), 5.88 (m, 1 H, C-7), 6.34 (d, 1 H, NH, J = 9.0 Hz), 6.97 (s, 1 H, benzylic methine), 7.02 (m, 2 H, thienyl), 7.37 (m, 11 H, thienyl and phenyl); MS FAB⁻ 537.5 (M - H, 4.5).

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18-Crown-6 as a Catalyst in the Dialkylation of *o*-Nitrophenacyl Derivatives†

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α,α-Dialkyl *o*-nitrophenacyl derivatives (**3**, Scheme I) are intermediates in a facile synthesis of polysubstituted indolines and related heterocycles.[1] Previously reported syntheses of **3** are lengthy and give low overall yields.[2,3] Hence, it was of interest to develop an efficient, simple, and general synthesis of these compounds.

The use of enolate chemistry to alkylate the benzylic carbon of the *o*-nitrophenacyl moiety with a variety of carbon electrophiles should be relatively straightforward due to the acidity of the benzylic hydrogens. However, our attempts to dialkylate with alkylating agents such as ethyl iodide and benzyl bromide in the presence of bases such as sodium ethoxide, lithium diisopropylamide, and potassium *tert*-butoxide gave low yields of dialkylated products, along with impurities which were not successfully separated. Monoalkylated products **2** were obtained in excellent yields (83-98%) with 1.1 equiv of potassium *tert*-butoxide and alkyl halide. Attempts to dialkylate the monoalkylated products through the use of potassium *tert*-butoxide and *n*-butyllithium, however, gave inseparable mixtures of products.

Use of 18-crown-6 to increase the reactivity of bases and nucleophiles is well-known,[4,5] but there are very few examples of its use for alkylations.[6,7] We have found that dialkylated products **3** are obtained in good yields (60-97%) under 18-crown-6 catalysis. The dialkylations were carried out in one step on 1 equiv of 2-(2-nitrophenyl)-1-phenylethanone (**1a**),[8] methyl *o*-nitrophenylacetate (**1b**),[9] or *o*-nitrophenylacetonitrile (**1c**) with 2.2 equiv of potassium *tert*-butoxide and the alkyl halide in the presence of 0.25 equiv of 18-crown-6. The dialkylation also can be carried out in a stepwise manner on monoalkyl derivatives in good yields (85-97%) in the presence of 18-crown-6. The stepwise procedure permits the introduction of two different alkyl side chains. The monoalkyl derivatives **2** can be prepared with or without 18-crown-6 with no significant difference in yields. The results are summarized in Tables I-IV.

With the ketone **1a**, the steric limits of *C*,*C*-dialkylation appear to have been exceeded when ethyl iodide and allyl bromide were used as the electrophiles. The products showed the expected mass spectral molecular weights but had no carbonyl bands in the infrared spectra, suggesting that *C*,*O*-dialkylation had occurred. The ^1H NMR spectra suggest that the products are mixtures of *E* and *Z* enol *O*-alkylates **4a** and **4b**. It was possible, however, to monoalkylate first with a bulky substituent, followed by a second alkylation with a small (methyl) substituent, as illustrated by the stepwise preparation of an ethyl methyl derivative **3b** in 85% overall yield. The steric limitations observed in the dialkylation of **1a** did not occur with the ester **1b** or the nitrile **1c**, which readily afforded both the *C*,*C*-diethyl (**3c** and **3i**), *C*,*C*-diallyl (**3j**), and *C*,*C*-dibenzyl (**3f**) derivatives in excellent yield.

In summary, dialkylation with potassium *tert*-butoxide in the presence of 18-crown-6 has been shown to provide a versatile method for making a variety of α,α-dialkyl *o*-nitrophenacyl derivatives **3** in one or two steps from commercially available starting materials.

Experimental Section

All melting points were determined on Thomas Hoover capillary melting point apparatuses and are uncorrected. Infrared spectra (IR, liquids neat and solids in KBr) were determined on either a Perkin-Elmer Series 1600 FT IR or a Nicolet 5DXC FT IR. Nuclear magnetic resonance spectra (NMR, in $CDCl_3$) were determined either on a 200-MHz Bruker AC-200 or on a 300-MHz General Electric GN-OMEGA. Chemical ionization mass spectra (CIMS) were determined on a Finnigan 4000 spectrometer. All new compounds were characterized by IR, NMR, CIMS, and elemental analyses by either M-H-W laboratories, Phoenix, AZ, or Midwest Microlab, Indianapolis, IN.

General Procedures. Monoalkylation. The *o*-nitrophenacyl starting material **1a-c** (1.00 mmol), freshly distilled alkyl halide (1.10 mmol), and dry tetrahydrofuran (THF, 15 mL) were placed in a dry two-necked flask under an atmosphere of nitrogen. The resulting solution was stirred and cooled to -78 °C in a dry ice/acetone bath, and potassium *tert*-butoxide (1.10 mmol) was added. Stirring was continued for 2 h while the resulting mixture was allowed to warm to room temperature. The mixture was then cooled again to -78 °C and quenched by rapid addition of satu-

† Paper no. 261 presented at a Poster Session before the Organic Division at the Fourth Chemical Congress of North America and the 202nd National Meeting of the American Chemical Society, New York, NY, August 28, 1991, Abstract no. 261.

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