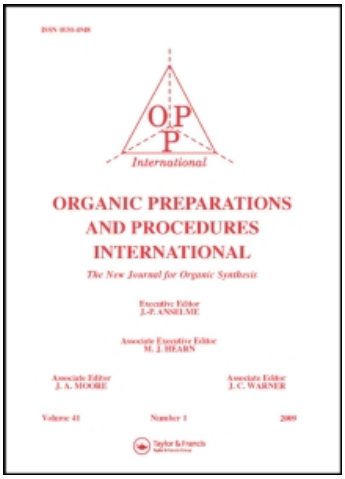

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A SIMPLE AND EFFICIENT PREPARATION OF METHOXYMETHYL ESTERS OF PENICILLINS AND CEPHALOSPORINS

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A SIMPLE AND EFFICIENT PREPARATION OF METHOXYMETHYL ESTERS OF PENICILLINS AND CEPHALOSPORINS

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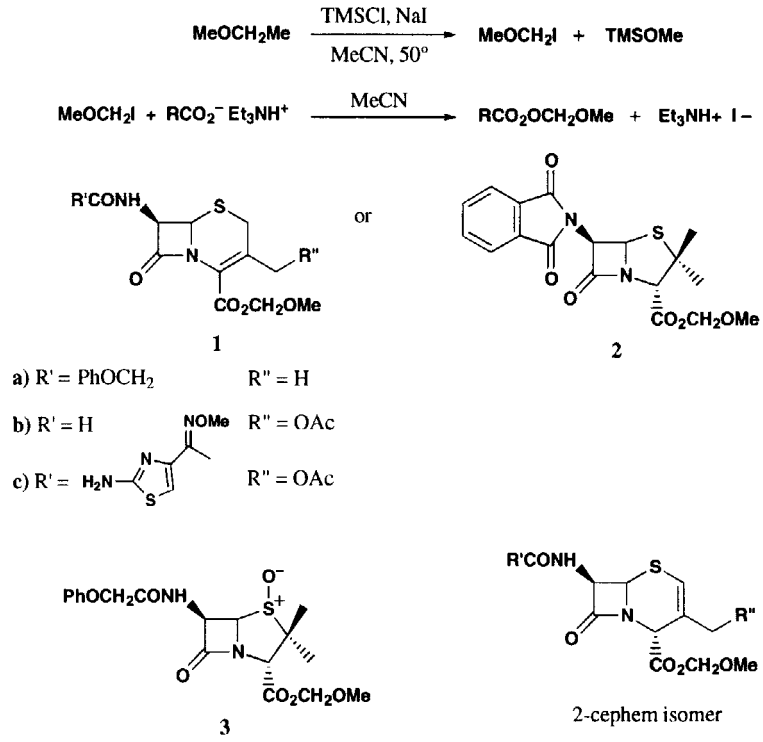
Methoxymethyl esters of penicillins and cephalosporins are important intermediates in synthetic transformations and potential pro-drugs for oral administration of β-lactams **1** antibiotics.[1] Such esters are sufficiently labile to be hydrolyzed both in the human body and *in vitro* under mildly acidic conditions. The ability of these esters to be deprotected in nonalkaline medium is crucial in the synthesis of cephalosporin derivatives, which easily isomerize to form 2-cephem derivatives even in the presence of weak bases. Although methoxymethyl esters of carboxylic acids are usually readily obtained *via* alkylation of the acid salts with chloromethyl methyl ether,[2] they are seldom used in chemistry of penicillins and cephalosporins. The main disadvantage of the alkylation procedure is the formation of isomerized ester,[2a,3] although the toxicity and carcinogenicity of chloromethyl methyl ether reagent are also major considerations. This paper describes a general method of synthesis of methoxymethyl esters of satisfactory purity, in which chloromethyl methyl ether is not employed.

The chemical reactivity of iodomethyl methyl ether is higher than its chloro analogue; however, the use of this material may be advantageous only if it could be readily prepared *in situ*. In order to obtain iodomethyl methyl ether we used the known procedure,[4] namely treatment of formaldehyde dimethyl acetal in methylene chloride with iodotrimethylsilane. The initial result of the alkylation of triethylammonium salt of 7-formylaminocephalosporanic acid in acetonitrile and methylene chloride mixture was promising, the product being obtained in good yield without admixture of detectable amount of 2-cephem isomer. Since iodotrimethylsilane is expensive and difficult to handle, it was replaced with chlorotrimethylsilane-sodium iodide-acetonitrile. It was found that an excess of these reagents is necessary in order to improve the yield of the final methoxymethyl ester. The results of the reactions carried out in neat acetonitrile are summarized in the Table.

The crucial improvement of this methodology lies in the combination of the highly reactive electrophile with the proper solvent. The use of more polar solvents, *e.g.* dimethylformamide, leads to the formation of the partially isomerized product. Good solubility of the ammonium salts of penicilins



and cephalosporins in acetonitrile and the availability of iodomethyl methyl ether from formaldehyde dimethyl acetal in the same solvent make acetonitrile a unique medium for methoxymethylation of these β-lactam derivatives.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were obtained on Varian Gemini (200 MHz) instrument with TMS as internal standard. The mass spectra were measured with a AMD-604 (AMD Intectra GmbH, Harpsted, Germany) double-focusing mass spectrometer with BE geometry, the ion source is equipped with Cs^+ gun. Energy of a Cs^+ ions - 12 keV. The liquid SIMS method was applied using *m*-nitrobenzyl alcohol as a matrix and a reference. HPLC analyses were done at 254 mm on a Shimadzu HPLC system equipped with a 250 x 4 mm reverse-phase column (Rp 18). Acetonitrile was distilled from phosphorus pentoxide. Sodium iodide was dried in oven at 120° for 3 hrs and stored over phosphorus pentoxide. Triethylamine was dried over potassium hydroxide. Chlorotrimethylsilane (Fluka) and formaldehyde dimethyl acetal (Merck, 92% purity; also contains 7% methanol and 0.3% water determined by the Fischer method) were used without purification.

Methoxymethyl-7-phenoxyacetylamino-8-oxo-3-methyl-5-thia-1-azabicyclo[4.2.0]oct.-2-ene-2-carboxylate (1a). General Procedure.- To a stirred mixture of dry sodium iodide (7.5 g, 50 mmol) and formaldehyde dimethyl acetal (4.4 mL, 50 mmol) in dry acetonitrile (30 mL) at *50-60°*, chlorotrimethylsilane (7.6 mL, 60 mmol) was added. The reaction was stirred at 50-60° for 2 hrs and cooled to room temperature.[5]

TABLE

Cmpd	Yield[a] (Purity)[b]	mp. (°C)	HRMS /M+H$^+$ (Found)	Elemental Analysis (Found)	^{1}H NMR (acetone-d_6). δ, J (Hz)
1a	86% (97%)	106-108.5 (THF-heptane)	393.11203 (393.11209)	C, 55.09 (54.78) H, 5.14 (5.01) N, 7.14 (7.01)	2.13 (s, 3H), 3.47 (s, 3H), 3.42 and 3.65 (ABq, 2H, J = 18.1), 4.64 (s, 2H), 5.16 (d, 1H, J = 4.7), 5.31 and 5.40 (ABq, 2H, J = 6.0), 5.83 (dd, 1H, J = 4.7, J = 9.0), 6.94-7.05 (m, 3H), 7.26-7.36 (m, 2H)
1b	84% (98%)	139-140.5 (acetone-THF-heptane)	345.07565 (345.07581)	C, 45.36 (45.79) H, 4.69 (4.93) N, 8.14 (7.76)	2.04 (s, 3H), 3.48 (s, 3H), 3.57 and 3.76 (ABq, 2H, J = 18.4), 4.80 and 5.09 (ABq, 2H, J = 13.3), 5.21 (d, 1H, J = 5.0), 5.36 and 5.42 (ABq, 2H, J = 6.0), 5.98 (dd, 1H, J = 5.0, J = 9.2), 8.09 (bd, 1H, J = 9.2), 8.29 (s, 1H)
1c	75%[c] (90%)	decomp. >70	500.09098 (500.09148)	[d]	1.97 (s, 3H), 3.50 (s, 3H), 3.57 and 3.76 (ABq, 2H, J = 18.4), 3.91 (s, 3H), 4.80 and 5.09 (ABq, 2H, J = 13.2), 5.26 (d, 1H, J = 4.9), 5.36 and 5.44 (ABq, 2H, J = 6.0), 6.00 and 6.05 (dd, 1H, J = 4.9, J = 8.8), 6.77 (bs, 2H), 6.83 (s, 1H), 8.49 (bd, 1H, J = 8.8)
2	79% (98%)	112-116 (EtOAc)	391.0964 (391.0963)	C, 55.37 (55.15) H, 4.65 (4.68) N, 7.18 (7.16)	1.55 (s, 3H), 1.81 (s, 3H), 3.52 (s, 3H), 4.61 (s, 1H), 5.36 and 5.40 (ABq, 2H, J = 6.0), 5.67 (d, 1H, J = 4.1), 5.81 (d, 1H, J = 4.1), 7.92 (s, 4H)
3	78% (98%)	107-108.5 (trit.-Et_2O)	433.10452 (433.10427) M+Na$^+$	C, 52.67 (52.65) H, 5.40 (5.54) N, 6.83 (6.72)	1.33 (s, 3H), 1.74 (s, 3H), 3.52 (s, 3H), 4.61 (s, 1H), 4.56 and and 4.64 (ABq, 2H, J = 15.1), 5.34 and 5.44 (ABq, 2H, J = 6.0), 5.46 (d, 1H, J = 4.8), 6.10 (dd, 1H, J = 4.8, J = 10.5), 6.97 7.07 (m, 3H), 7.28-7.40 (m, 2H), 8.29 (bd, 1H, J = 10.5)

a) Yields were not optimized; b) Reported purities were HPLC chromatogram area percent; c) Cefotaxime acid ethyl acetate solvate as a starting material; d) Satisfactory microanalyses could not be obtained due to decomposition of **1c**.

In a separate flask 7-phenoxyacetylamino-8-oxo-3-methyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (8.7 g, 25 mmol) was suspended in dry acetonitrile (40 mL)[6] and dry triethylamine (4 mL, 28 mmol) was added. The mixture was stirred at room temperature until the initial solid

disappeared, and then added dropwise to the suspension containing iodomethyl methyl ether prepared above. The reaction was stirred for 30 minutes and poured into a saturated aqueous solution of sodium hydrogen carbonate (50 mL) containing sodium thiosulfate (0.25 g, 1 mmol). Brine was added and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 8.4g of product of satisfactory purity (97% by HPLC area percent ratio). A portion of the compound (1.7 g) was dissolved in acetone and filtered through a pad of neutral alumina. The solution was concentrated *in vacuo*, diluted with tetrahydrofuran (10 mL) followed by dropwise addition of *n*-heptane (10 mL). Upon cooling in a freezer (-20°), a precipitate formed was collected and dried *in vacuo* (1-2 g).

REFERENCES

1. E. H. Flynn, in *Cephalosporins and Penicilins,* p.171, Academic Press, New York, 1972; R. B. Morin, M. Gorman, in *Chemistry and Biology of β-Lactam Antibiotics,* Vol.3, p.379, Academic Press, New York, NY, 1982.

2. a) A. B. A. Jansen, T. J. Russell, *J. Chem. Soc.,* 2127 (**1965**); b) R. R. Chauvette, E. H. Flynn, *J. Med. Chem.,* **9**, 741 (1966).

3. S. Mobashery, M. Johnston, *J. Org. Chem.,* **51**, 4723 (1986).

4. M. E. Jung, M. A. Mazurek, R. M. Lim, *Synthesis,* 588 (**1978**).

5. The alkylation of penicilins is accompanied by a strong exotherm. In the case of 2 and 3, the reaction mixtures were cooled to -10°.

6. Since cefotaxime triethylammonium salt is less soluble in acetonitrile compared to other cephalosporins, it is neccesary to increase of the amount of solvent to 150 mL.

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