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Mild Preparation of Cephalosporin Allyl and p-Methoxybenzyl Esters Using Diazoalkanes

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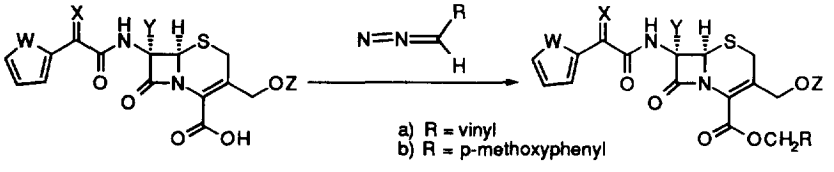
Abstract: Vinyl or p-methoxyphenyldiazomethane reacts rapidly with cephalosporins in ether/methylene chloride cosolvent to give the C-9 allyl and p-methoxybenzyl esters, respectively, in good yields, with no isomerization of the double bond to Δ-2.

For routine synthetic manipulations it is often necessary to protect the C-9 carboxylate of cephalosporins, and for this the allyl and p-methoxybenzyl groups are particularly useful.[1] Reaction of cephalosporin carboxylates with alkyl halides is problematic, however, due to the extreme base sensitivity of most cephems: the carboxylate itself is a sufficiently good base to cause isomerization of the double bond from Δ-3 to Δ-2.[2] Various means have been developed to overcome this problem, including sulfoxidation of the cephem dihydrothiazine ring,[3] phase transfer methods,[4] and other methods which limit the concentration of the carboxylate in solution,[2] but all suffer from modest yields, prolonged reaction times, or the necessity of multistep sequences. In an effort to develop a rapid, high yield synthesis of these esters, we investigated the use of vinyl and p-methoxyphenyldiazomethane.

Although both vinyl and p-methoxyphenyldiazomethane are known compounds,[5] they have been virtually unexploited as synthetically useful reagents for the formation of esters from carboxylic acids.[6] This is perhaps due to the perception that they are difficult to prepare and handle, or that they react too slowly with carboxylic acids of normal pK_a to be useful. As for the first point, we have found their preparation to be rapid and convenient from inexpensive starting materials, with no purifications required,[7] and as for the second, choice of solvent seems to be crucial for quick reaction and high yields.



	W	X	Y	Z
cephalothin **1**	S	H, H	H	$(CO)CH_3$
cefoxitin **2**	S	H, H	OMe	$(CO)NH_2$
cefuroxime **3**	O	$NOCH_3$	H	$(CO)NH_2$

Addition of an ethereal solution of the diazo compound to a solution or suspension of cephalothin (1) in another solvent (hereafter referred to as the cosolvent) produced dramatically different results depending on the nature of the cosolvent. For ether, ethyl acetate or acetone cosolvent the reaction was slow, as judged by

disappearance of the bronze color of the diazo compound, and the reaction did not go to completion despite addition of several equivalents of the diazo compound. For tetrahydrofuran and acetonitrile cosolvent, byproducts incorporating solvent were formed.[8] Methylene chloride cosolvent, however, gave excellent results. The reaction was nearly instantaneous: the bronze color of the diazomethane disappeared quickly until all starting material had been consumed (as judged by thin layer chromatography), allowing for convenient "titration" to a slight bronze color to judge completion of the reaction. For the case of vinyldiazomethane, aqueous workup and removal of solvent under reduced pressure afforded almost quantitative yields of material which was essentially pure as judged by proton NMR. For the case of p-methoxyphenyldiazomethane, aqueous workup followed by silica chromatography gave yields in the range of 90%.

The following table summarizes the reactions of the free acids of three commercial cephalosporins with vinyldiazomethane and p-methoxyphenyldiazomethane according to the protocol given in footnote 7.

	allyl ester	p-methoxybenzyl ester
	chromat.[a,b]	chromat.[b]
cephalothin 1	91%	89%
cefoxitin 2	83%	96%
cefuroxime 3	92%	80%

[a]The crude product from the allyl ester formation, isolated from the workup in essentially 100% yield, is sufficiently pure for most purposes and practically indistinguishable by proton NMR from the chromatographed material.

[b]Chromatography on silica. For cephalothin esters, elution was with 5.5 : 1 CH_2Cl_2/EtOAc. For cefoxitin and cefuroxime esters elution was with 1.5 : 1 CH_2Cl_2/EtOAc.

The utility of this method, which should be broadly applicable, is obviously not limited to cephalosporins. In terms of speed of reaction, purity of crude product, and yield, it is at least equal to and generally superior to other commonly used methods for the formation of allyl and p-methoxybenzyl esters of sensitive carboxylic acids. This, coupled with the ease of generating the diazo compounds from inexpensive starting materials, argues persuasively for its place as a method of choice in the synthetic arsenal.

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References and Notes

1. Both groups are conveniently removed using conditions under which the other cephem functions are unaffected. For instance, the allyl group can be conveniently removed using $(Ph_3P)_4Pd$ and 2-ethylhexanoic acid (see Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587), and p-methoxybenzyl can be removed using CF_3CO_2H/anisole (see Stewart, F. H. C. *Aust. J. Chem.* **1968**, *21*, 2543.)
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4. Ganboa, I.; Palomo, C. *Synthesis* **1986**, 52.

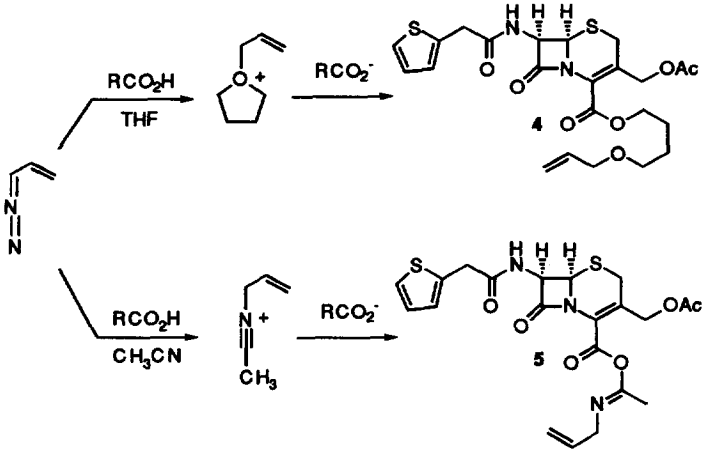
5. Vinyldiazomethane: a) Adamson, D. W.; Kenner, J. *J. Chem. Soc.* **1935**, 286. b) Hurd, C. D.; Lui, S. C. *J. Am. Chem. Soc.* **1935**, *57*, 2656. p-Methoxyphenyldiazomethane: c) Offord, R. E.; Storey, H. T.; Rees, A. R.; Hayward, C. F.; Johnson, W. H.; Pheasey, M. H.; Wightman, D. A. *Biochem. J.* **1976**, *159*, 480.

6. For example, neither reagent is listed in Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis, 2nd ed.* **1991**, John Wiley & Sons, New York, considered to be the standard work on protecting group chemistry. While early papers report the reaction of vinyldiazomethane with benzoic acid and p-nitrobenzoic acid (e. g., see 5b), a search of Chemical Abstracts by CAS number failed to reveal any paper in which this reaction was exploited in a synthetic context. A similar search of p-methoxyphenyldiazomethane (by CAS number) revealed only a relatively specialized use of the reagent in the esterification of peptides (ref. 5c).

7. A typical example of the preparation and use of vinyldiazomethane follows: To a solution of 0.978 g (7.58 mmol) of *N*-allyl-*O*-ethylcarbamate (prepared by reaction of allyl amine with ethyl chloroformate in methylene chloride/triethylamine) in 10 mL of ether was added a solution of 4.55 g (68.0 mmol) of $NaNO_2$ in 10 mL of water. Without stirring or cooling, 7.6 mL of 35% HNO_3 was added directly to the lower water layer over 1 hour. The organic layer was separated, washed with water, then four times with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and rotovapped to afford 1.004 g of *N*-allyl-*N*-nitroso-*O*-ethylcarbamate (83%). CAUTION: N-nitroso compounds as a class have been found to be potent carcinogens and should be handled only by skilled technicians taking proper precautions to avoid exposure. This material was quite pure as judged by ^1H NMR, and was used directly in the next step. To a solution of 3.3 mL of 2.6 M NaOMe/MeOH and 11 mL ether, stirred at -10 ° C, was added 528 mg (3.34 mmol) *N*-allyl-*N*-nitroso-*O*-ethylcarbamate in 7 mL of ether. After stirring for 2 hours, the reaction was diluted with ether and washed three times with 5% NaOH. The ether layer (volume approximately 30 mL) was dried over KOH pellets and contained about 0.6 mmol of vinyldiazomethane (19%), as judged by titration with cephalothin free acid, assuming quantitative conversion to ester. To a magnetically sitrred 50 mg sample of cephalothin free acid (0.13 mmol) in 10 mL of CH_2Cl_2 was added dropwise the above ethereal vinyldiazomethane solution. Each drop of bronze solution decolorized immediately. After the addition of 7 mL, the bronze color persisted and TLC (15 : 1 CH_2Cl_2/EtOAc) showed complete and clean formation of a single mid R_f spot corresponding to the allyl ester, with no starting material (baseline R_f) remaining. This solution was washed with dilute aq. AcOH, water, sat. aq. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and rotovapped to afford 55 mg (100%) of crude material which was judged by ^1H NMR to be pure enough for most purposes. Chromatography on silica eluting with 5 : 1 CH_2Cl_2/EtOAc gave the purified allyl ester of cephalothin (50 mg, 91% yield.) p-Methoxyphenyldiazomethane was prepared and used in the same manner, beginning with *N*-p-methoxybenzyl-*O*-ethylcarbamate. It was produced in 16-30% yield from the N-nitrosocarbamate, and

reacted with cephalothin free acid as above. The crude ester preparation was chromatographed on silica eluting with 5 : 1 CH_2Cl_2/EtOAc, and gave the purified p-methoxybenzyl ester of cephalothin in 89% yield.

8. Following the procedure given in footnote 7, but adding the ethereal vinyldiazomethane solution to a solution of the cephalothin free acid in tetrahydrofuran or acetonitrile gave rapid reaction and formation of two products, which could be separated by silica chromatography eluting with 6 : 1 CH_2Cl_2/EtOAc. The desired allyl ester was the first to elute in each case and was isolated in 44% (THF) and 40% (CH_3CN) yield. The slower moving compounds, isolated in 40% (THF) and 36% (CH_3CN) yield, were determined by ^1H and ^{13}C NMR and mass spectroscopy to have the structures shown below, and are proposed to have been formed by attack of the carboxylate on the transiently formed "onium" species, as illustrated:



single isomer of undetermined C=N-R stereochemistry

Spectral Data for **4**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (dd, J = 5.3, 2.4 Hz), 7.02 (dd, J = 5.1, 3.5 Hz), 6.99 (m), 6.35 (d, J = 9.2 Hz, NH), 5.91 (m), 5.78 (dd, J = 8.9, 4.8 Hz, H-7), 5.27 (dd, J = 17.1, 1.6), 5.18 (dd, J = 10.4, 1.6), 4.98 (d, J = 4.8 Hz, H-6), 5.08, 4.82 (two d's, J = 13.4 Hz, CH_2OAc), 4.29 (m, $CO_2CH_2CH_2$), 3.97 (dt, J = 5.5, 1.4 Hz), 3.87 (s. CH_2CON), 3.56, 3.36 (two d's, J = 18.6 Hz , H-3), 3.46 (t, J = 6.1 Hz, allylOCH_2), 2.36 (s, CH_3C=N), 2.09 (s, CH_3CO), 1.80 (quin, J = 6.7 Hz), 1.68 (m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 170.1, 164.5, 161.4, 135.0, 134.7, 128.0, 127.7, 126.2, 126.0, 125.1, 116.9, 71.9, 69.6, 66.3, 63.1, 59.3, 57.4, 37.2, 26.5, 26.2, 25.4, 20.8. Mass Spec: 531 (M + Na^+), 449* (M - AcO).

Spectral Data for **5**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (m), 7.01 (dd, J = 5.1, 3.4 Hz), 6.98 (m), 6.49 (d, J = 9.4 Hz, NH), 5.86 (m), 5.78 (dd, J = 9.4, 4.8 Hz, H-7), 5.21 (m), 5.18 (m), 4.97 (d, J = 4.8 Hz, H-6), 4.75, 4.55 (two d's, J = 13.0 Hz, CH_2OAc), 4.30 (m, C=NCH_2), 3.85 (s, CH_2CON), 3.59, 3.33 (two d's, J = 18.0 Hz , H-3), 2.36 (s, CH_3C=N), 2.07 (s, CH_3CO). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 170.6, 170.1, 164.7, 164.0, 134.7, 132.7, 130.2, 127.9, 127.7, 126.2, 117.2, 63.0, 59.5, 57.3, 48.0, 37.2, 26.1, 24.9, 20.8. Mass Spec: 478 (M + 1), 418* (M - AcO).

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