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A Convenient Method for the Production of 6-Oxopenicillinates and 7-Oxocephalosporinates

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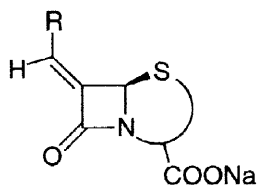
Abstract: A convenient and economical method for the preparation of 6-oxopenicillinates and 7-oxocephalosporinates from the corresponding amines is presented. These ketones are key intermediates in the synthesis of inhibitors of β-lactamase and elastase. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Penicillins; Cephalosporins; Diazo compounds, Oxidation

Several compounds of general structure **1**, including penams,[1] penems,[2] and cephems,[3] have displayed potent enzymatic inhibitory activity. Most often the targets of these inhibitors are the serine classes of β-lactamase, but elastase inhibitors have also been prepared.[3c] The mechanism of inhibition of the penem has been evaluated by kinetic and modeling experiments.[4]

These unsaturated compounds are prepared in two ways: 1) a Wittig reaction of the appropriate ylide with the corresponding bicyclic α-oxo-β-lactam; and 2) formation of the α-metallated-β-lactam and reaction with an appropriate aldehyde, followed by derivatization and elimination.[5] Especially from an industrial standpoint, both approaches are inefficient. The latter often produces mixtures of diasteriomers, poor yields, and can require exacting experimental conditions including very short reaction times at low temperatures. In the former case, reported preparations of α-oxo-β-lactams[6] can involve multiple steps, expensive reagents, and, in our experience, produce highly irregular yields, especially when performed on a large scale. Such synthetic difficulties limit the potential industrial application of this valuable class of inhibitors. We would now like to present a convenient, reproducible, and easily scaleable procedure for the preparation of bicyclic α-oxo-β-lactams.



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A straightforward approach to their synthesis involves conversion of the (6- or 7-position) amine to the corresponding diazo compound, followed by oxidation of the diazo group to the corresponding ketone. Especially in the cephalosporin series, this oxidation is problematic due to the presence of the easily oxidizable sulfide in the second ring (6-oxopenicillinate sulfoxides and 7-oxocephalosporin sulfoxides are unknown, and presumably unstable) and the propensity for α-oxo-β-lactams to undergo Baeyer-Villiger oxidation.[7] In an effort to find a general reagent to effect this transformation, we unsuccessfully explored several oxidizing agents including mCPBA, ozone, and dimethyldioxirane. An efficient protocol was eventually developed employing a rarely utilized[8] rhodium-catalyzed oxidation of the diazo in the presence of an epoxide.

The procedure is as follows: To a solution of benzhydryl 7-aminocephalosporanate (**3a**, 0.5 g, 1.15 mmol) in EtOAc (5 mL) were added isoamylnitrite (0.162 g, 1.37 mmol) (or isopropylnitite) and trifluoroacetic acid (6.5 mg, 0.05 mmol) and the stirring continued for 1h at rt. The reaction mixture was concentrated under reduced pressure (see caution below) and redissolved in benzene (5 mL). To this solution was added propylene oxide (6.7 g, 0.114 mol) followed by rhodium octanoate dimer (2 mg) and stirring continued for 15 min (nitrogen and propylene were evolved). Volatiles were removed to produce **5a** (0.5 g, 90% pure).

In each case studied, the oxidation is nearly quantitative by NMR. The product was used without purification, since, in our experience, these ketones degrade during chromatography. This procedure has been reproduced on a range of cephems and penams on a scale of from 0.5 to 40 g without alteration of the yield.

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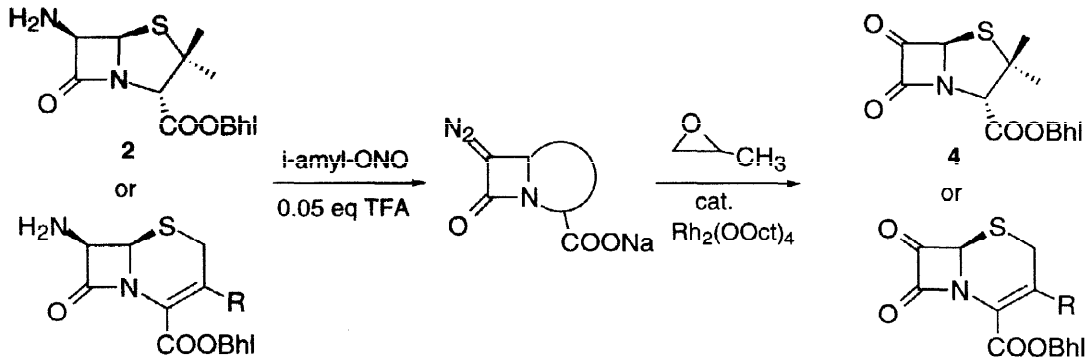
In all but one case, the intermediate diazo compounds were found (through several repetitions) to be isolable, easily handled solids at room temperature. These intermediates can also be stored at -20 for several days. However, diazocephalosporin **3c** was susceptible to a mildly exothermic decomposition which could be initiated by physical disturbance (such as scratching the dried solid). It is recommended that this particular diazocephem be handled with caution.



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