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NOTE

An Efficient Method for the Reduction of Cephalosporin Sulfoxide

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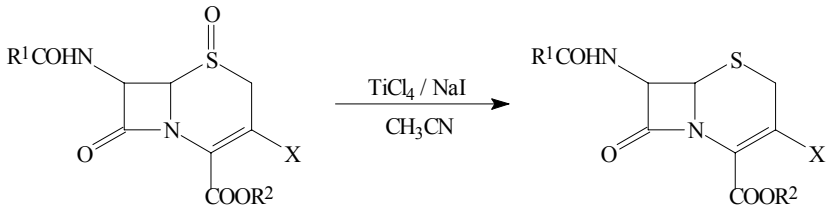
An efficient method for the reduction of cephalosporin sulfoxide to their corresponding sulfide using $TiCl_4$/NaI reagent system.

Key Words: Cephalosporin, Sulfoxide, Reduction.

Cephalosporin sulfoxide (**1**) is very useful and widely used intermediates for the preparation of the important antibacterial agents. The conversion of these sulfoxides to sulphide is an important step involved in the synthesis of cephalosporin antibiotics like cefaclor, cefrodaxine, *etc*. Of the several reduction methods available[1,2], only a few are suitable for reduction of cephalosporin sulfoxides. The problems associated with common methods are the use of DMF as solvent, longer reaction times where the yields are mainly depends on the dryness and purity of solvents[3,4]. Use of Lawesson reagent[5] and iodotrimethyl silane[6] were reported for this transformation. In a search for new method for the deoxygenation, we have investigated use of $TiCl_4$/NaI system[7] in acetonitrile for the reduction of cephem sulfoxide to corresponding sulphide. In cephalosporin chemistry, use of this reagent as a reducing agent is not reported earlier.

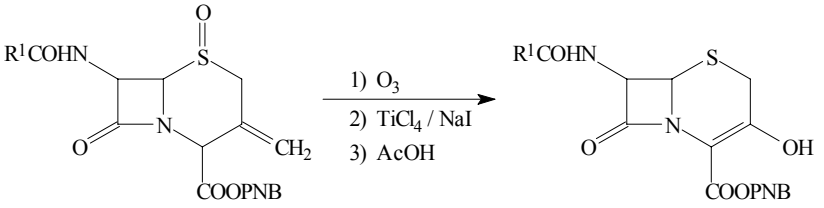
In this report, we describe the use of $TiCl_4$ and NaI in acetonitrile reagent system for the easy and convenient conversion of cepham/cephem sulfoxide to their corresponding sulphides. The deoxygenation using this reagent system is fast, clean, good yielding and the process is easily scalable. The product obtained needs no further purification by chromatography.

The hydroxyl compounds **2f** and **2g** are the intermediates for the synthesis of antibiotics[8] cefaclor and cefroxidine. The compounds **2f** and **2g** are synthesized from exomethylene sulfoxide (**1a**) and **1b**, respectively by an efficient single pot method involving ozonolysis followed by *in situ* deoxygenation with $TiCl_4$/NaI reagent and are isolated as acetic acid solvates (Table-1).



(1-a-g) **(2-a-g)**

Scheme-I



Scheme-II

TABLE-1

Entry	R^1	R^2	X	Yield (%)
2a	$PhCH_2$	PNB	CH_3	78
2b	$PhOCH_2$	PNB	CH_3	76
2c	$PhOCH_2$	PNB	Cl	72
2d	$PhCH_2$	PNB	Cl	82
2e	$PhCH_2$	$CHPh_2$	CH_3	78
2f	$PhCH_2$	PNB	OH	68
2g	$PhOCH_2$	PNB	OH	85

All the reagents and solvents were used as such without further purification. The progress of the reactions were monitored by TLC using silica gel plates (E. Merck). IR spectra were recorded on a ^{1}H NMR spectra on Bruker (300 MHz) spectrometer using TMS as the internal standard. The structure of the isolated reaction products shown in the table were confirmed by IR, ^{1}H NMR comparison with the authentic sample.

General procedure for the conversion of deoxygenation: To a suspension of cephalosporin sulfoxide (10 mmol) in acetonitrile (50 mL), $TiCl_4$ (20 mmol) was added drop wise at -10 to -5°C followed by NaI (30 mmol). The reaction mixture was stirred for *ca.* 1 h at 0-10°C (progress of

the reaction monitored by TLC). The reaction mixture was quenched with 2 % aq. KOH solution to neutral pH and then extracted with ethyl acetate (20 mL). The ethyl acetate layer was washed with 5 % aq. sodium thiosulphate solution (100 mL) and the solvent is removed under vacuum. The residue stirred with methanol (25-30 mL) to give cephalosporin sulfide.

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