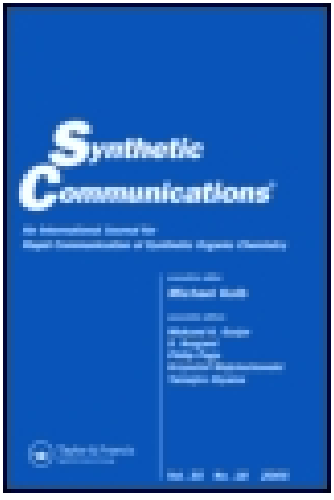

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An Efficient Method for the Reduction of Cephalosporin Sulfoxides

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AN EFFICIENT METHOD FOR THE REDUCTION OF CEPHALOSPORIN SULFOXIDES

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Abstract : An efficient and convenient method for the reduction of cephalosporin sulfoxides to their corresponding sulfides by Lawesson reagent is reported.

The reduction of cephalosporin sulfoxides (1) to their corresponding sulfides (2) is important owing to the biological activity associated with latter. β–Lactam sulfoxides, finding application as intermediates for antibiotics like Cefaclor, Cefroxidine, etc., need to be reduced to their corresponding sulfides at some stage of the process. Despite numerous methods[1] available for the reduction of sulfoxides, only a few are suitable for reduction of Cephalosporin sulfoxides. The problems associated with common methods are the use of DMF or DMAc as solvents, longer reaction times where the yields are mainly dependent on the dryness and purity of solvents[2,3] . In a hunt for new deoxygenation methods for cephalosporins sulfoxides, we

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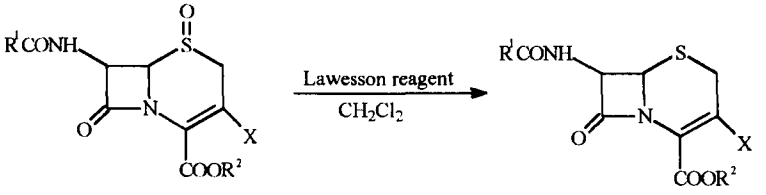
found Lawesson reagent[4,5] to be an excellent reducing agent. To the best of our knowledge use of this reagent as reducing agent in cephalosporin chemistry has not been reported earlier.

In this paper we describe the use of Lawesson reagent for the easy and convenient conversion of cepham / cephem sulfoxides to their corresponding cephem sulfides. The deoxygenation using this reagent is fast, clean and good yielding and the product obtained needs no further purification by chromatography.



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

Scheme 1

About 1.2 to 1.5 mol. eq. of reagent is needed for the reaction which goes to completion in 15-30 min time.

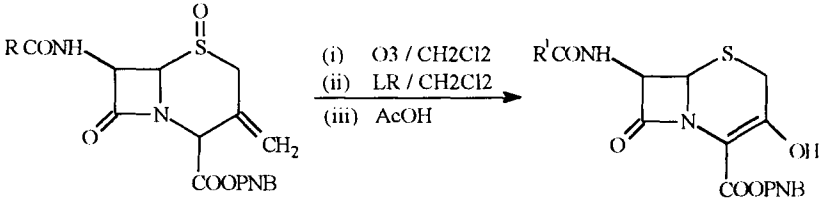
The results of this finding are summarised in the table.

Hydroxy compounds (2f) and (2g) were synthesized from exomethylene sulfoxides (1a) and (1b) respectively by an efficient single pot method involving ozonolysis followed by insitu deoxygenation with Lawesson reagent and isolation as acetic acid solvates.

Table

Entry**	R^1	R^2	X	Yield
2a	$PhCH_2$	PNB	CH_2	80%
2b	$PhOCH_2$	PNB	CH_2	78%
2c	$PhOCH_2$	PNB	Cl	72%
2d	$PhCH_2$	PNB	Cl	78%
2e	$PhCH_2$	$CHPh_2$	CH_3	70%
2f*	$PhCH_2$	PNB	OH	72%
2g*	$PhOCH_2$	PNB	OH	80%

PNB = p-Nitrobenzyl
* isolated as acetic acid solvates
**Compounds (2 a-g) were identified by comparison of their ^{1}HNMR, IR spectra with those of authentic samples.



(1a) $R^1 = PhCH_2$
(1b) $R^1 = PhOCH_2$

(2f) $R^1 = PhCH_2$
(2g) $R^1 = PhOCH_2$

Compounds (2f) and (2g) are important as they are key intermediates in the synthesis of major antibiotics Cefaclor and Cefroxidine.

Earlier reported method for (2f) and (2g) comprises laborious two step process involving ozonolysis[6], isolation of intermediate hydroxy sulfoxide and then its deoxygenation by PCl_3/ DMF[7].

Experimental :

All melting points were taken on electrothermal 9300 and are uncorrected. HPLC analyses were done on Hewlet-Packard model 1090 liquid chromatograph while 'HNMR and IR spectra were recorded on FT R-1500 and Perkin Elmer 16 PC-PT respectively. The structure of the isolated reaction products shown in table were confirmed by IR, ^{1}HNMR comparision with the authentic samples.

General Procedure :

The cephalosporin sulfoxide was dissolved in CH_2Cl_2 at r.t. followed by the addition of Lawesson reagent (1.2 - 1.5 mol. eq.). The contents were stirred for 15 - 30 min. at 35 - 37°C and completion of reaction was monitored by TLC. Reaction mixture was filtered and evaporated to dryness under vacuum. Addition of MeOH to the residue followed by stirring for 30 min., filtration, washing with MeOH and drying afforded pure, product.

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