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An improved one pot procedure for preparation and isolation of cephalosporin intermediate: 7-amino-3-nor-3-cephem-4-carboxylic acid (7-ANCA)

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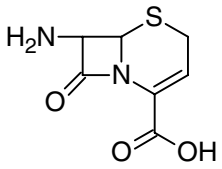
ABSTRACT

An efficient one pot synthesis of useful cephalosporin intermediate, 7-ANCA is described. The present process does not involve number of isolation step as well as purification and amenable to large scale synthesis.

Key words: One pot synthesis, Cephalosporin, large scale synthesis.

INTRODUCTION

7-amino-3-nor-3-cephem-4-carboxylic acid(1) is an intermediate of a parental broad spectrum fourth generation cephalosporin having high antibacterial activity against both gram negative and gram positive bacteria.



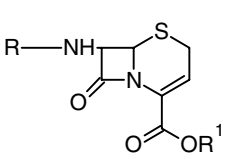
1

In the course of a project on the synthesis of some cephalosporin antibiotic, we have been engaged in the development of a cost effective and commercially viable process for the manufacturing of 1.During literature survey we found the synthesis of 3-unsubstituted-3-cephem rings(II)has been reported by several groups[1].First, Heusler and Feching synthesized 3-unsubstituted-3-cephem from a penicillin derivatives.[1] However, the preferred routes to the 3-unsubstituted derivatives(II) are either the 3-exomethylenecepham derivative(III)[2] or the 3-hydroxy-3-cephem derivatives(IV)[3].

The synthesis of 3-exomethylenecepham compound (III) has been achieved only under limited conditions because of the labile β-lactam structure of the molecule. So far, III has been synthesized from 3-substitutedthiomethyl-3-cephem compounds by reduction with Raney Nickel[2,4] or Zn-HCO_2H-dimethylformamide,[4] and from 3-acetoxymethyl-3-cephem compounds by reduction with Cr (II)[5], Hg(Al)[3] or electrolysis[6] compound III was also synthesized by ring expansion of penicillin sulfoxide [2,6].

Our synthetic plan was to lead to 1 via 7-amino-3-hydroxycepham-4-carboxylic acid (V) for the synthesis of 1. We intended to prepare V from 7-amino-3-methylenecepham-4-carbosylic acid (III) via ozonolysis followed by reduction of 7-aminoi-3-hydroxy-3-cepham-4-carboxylic acid (IV)

Another reported process in which reducing agents such as zinc powder acted on a 3-halocephem compound or 3- sulfonyloxycephem compound (VI), gave compound 1.



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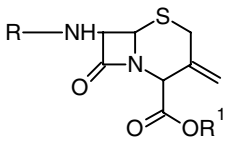

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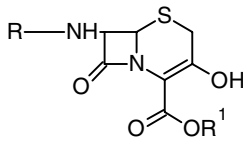

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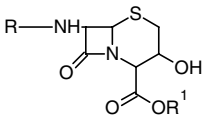
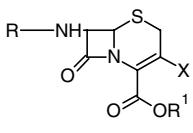
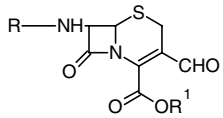


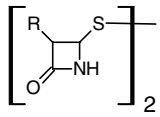
(V)



(VI)



(VII)



(VIII)

This process is, however, generally not suitable for a commercial scale due to the difficulty in preparing 3-halocephem compound or 3-sulfonyloxycephem compound, as a starting material.

Also, there has been reported a process for preparing 3-halocephem compound in which a 3-hydroxycephem compound is subjected to a catalytic hydrogenation to obtained a 3-hydroxycephem compound, followed by 1, 2-elimination using halo formic acid ester/base.

This process is, however, not a commercial process because of the two step of catalytic hydrogenation and 1, 2-elimination are required.

In addition, chemistry and biology of beta-lactum antibiotics penicillins and cephalosporins volume 1, p.170, disclosed a process in which a 3-formylcephem shown by the following reaction scheme (VII) is used as a starting material, and a process employing the witting reaction shown by the following scheme (VIII)

However, the above two processes have difficulties in obtaining their starting materials. In addition, the former requires rhodium complex that is expensive, while the latter has the problem that a large amount of phosphorus containing waste is formed as a by product by the witting reaction.

RESULTS AND DISCUSSION

The present method describes the one pot synthesis of 1. In first step compound i was reduced by sodium borohydride in presence of glacial acetic acid in methylene chloride used as a solvent. After completion of reaction, added Mesylchloride,triethylamine and diethyl amine to above reaction mass to formed the compound iii and used as such for desertification by using phenol in presence of few drops of hydrochloric acid. After proper workup organic layer used as such for the deacylation by using Penicillin G amidase to yield the compound 1 in 45% overall yield. During over optimization studies we carried out the reaction under different condition such as temperatute, different solvents and mixture of solvents. The results thereof are tabulated in table A. It is found that varying the ratio of methylene chloride /THF impacts the yield of 1 .The best result is obtained in methylene chloride/THF (10:1)(entry 4). The advantage of this method are its simplicity in terms of operation on commercial scale, workup, hardware and direct isolation of compound 1,thereby eliminating exhaustive workup, reaction as well as reaction time, hydrogenation and chromatographic techniques for isolation.

In conclusion, simplified, cost-effective consistence industrial process for synthesis and isolation of 1 with superior yield is descrided.This

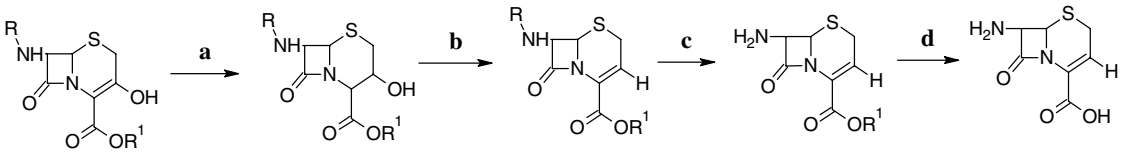
Table 1: Preparation of 7-ANCA (1) under different conditions

Entry	Solvents (times)	Reaction time (min)	yield (%)
1	CH_2Cl_2 (5)	60	33
2	CH_2Cl_2 (5)/methanol (5)	35	40
3	CH_2Cl_2 (10)	40	45
4	CH_2Cl_2 (10)/THF (1)	30	48
5	THF (2)/CH_2Cl_2 (5)	70	_b
6	THF (2)/CH_2Cl_2 (10)	70	35
7	acetonitrile (10)	85	22
8	acetonitrile (5)/methanol (5)	75	39
9	acetonitrile (5)/dioxane (5)	65	39
10	dioxane (10)	90	_b

[b]Isolation problem

process does not involve any chromatographic separation, monotonous workup and extensive reaction time/isolation.

Synthetic scheme



(a)Glacial acetic acid, Sodium borohydride, (b) Mesylchloride, Triethyl amine, Diethyl amine, (c) Phenol, (d) PenicillinG amidase.

temperature and stirrer to get a clear solution. Added 125 ml glacial acetic acid at ambient temperature. Reaction mass cooled to -50°C and added 5.0 gm sodium borohydride in equal two lots after 15min. followed by stir reaction mass at -45 to -50°C .Raise temperature slowly to -20°C.Reaction progress monitor by TLC.After completed the reaction added 250 ml 110% brine and extracted out organic layer.Againg add 250 ml 10% brine solution into organic layer for extraction .Add again 250 ml 10% brine in organic layer followed by adding 800 ml MDC and adjusted PH 7.0 by 20% sodium carbonate solution. Separate the organic layer. Dry organic layer with anhydrous sodium sulphate and decant it. Washed sodium sulphate with 200 ml Methylene chloride. Distilled off 250 ml methylene chloride out of 1500 ml and used as such for next step.

Step-1. GHYH (i) to Reduced compound (ii)

Charged 500 ml methylene chloride followed by adding 50 gm compound i at ambient

Step-2. Reduced compound (ii) to Protected nor compound (iii)

Above reaction mass cooled to 10°C and add Mesylchloride (28.5 gm).Reaction mass cooled to – 50°C. Add prechilled (- 50°C) triethyl amine (40 gm) at – 50°C into above cooled mixture. During triethyl amine addition high exothermicity observed i.e. -50° to -30°C. Raise temperature of reaction mass up to -10°C. Reaction mass stir for 25 min at – 10°C and reaction mass becomes clear. Reaction mass cooled to – 20°C and add diethyl amine(14.7 gm) at -20°C.Reaction mass stir for 25 min at -10°C.Add 500 ml 10% brine solution into above

reaction mass and adjust PH 1.0 by using 5% Hydrochloric acid solution. Separate the organic layer and hold it. Organic layer extracted again with 500 ml 10% brine solution and separate out organic layer followed dry the organic layer with anhydrous sodium sulphate.washed sodium sulphate with 50 ml methylene chloride. Distilled off the methylene chloride completely and used as such for desterification reaction.

Step-3. Desertification of protected nor compound (iv)

Charged phenol (250 ml) into above into above concentrated mass followed by adding 6 drops of concentrated hydrochloric acid. Stir the reaction mass for 5hrs at 48-50°C. Reaction mass cooled to ambient temperature and add 0°C pre cooled 750 ml n-butyl acetate under stirring. Reaction mass stir for 15 min at 25°C.Also add 630 ml 1.8% sodium bicarbonate in above mixture and adjust the PH of reaction mass 7 to 8.0.Separate the aq. Layer and organic layer again re-extracted with 1.8% sodium bicarbonate and separate out. Combined both aq. Layer and twice extracted with 250 ml n-butyl acetate and separate out aq. Layer.Aq. Layer used as such for deacylation in next step.

Step-4. Deacylation of desterified nor compound (1)

Added penicillin G amidage 105 gm wet into above aq. Layer which ph was 7.86 at 28-30°C and stir. Adjust ph by 20% sodium carbonate in between 8 to 8.33.Continously add sodium carbonate to adjust ph 8-8.22.Reaction completed 3-4 hrs. Filter the enzyme and kept in 50 ml water for recycle use. Add 7.0 gm carbon in filtered reaction mass followed by stirring for 15 min at 28-30°C. Filter the reaction mass and carbon bed washed with 15 mi DI water. Added 1200 ml precooled (-10°C) into above filtered reaction mass. Reaction mass cooled to 0-5°C and adjusted ph 5.0 to 5.2 by using 6N hydrochloric acid solution. Stir reaction mass 2 hrs at 0-5°C .Filtered the reaction mass and washed with 100 ml cooled(0°C) DI Water and finally washed with 70 ml precooled (0°C) acetone to yield compound 1 in 45% overall yield.

^{1}HNMR (CDCl3): δ 6.937 (1H, dd), 3.765 (1H, dd), 3.524 (1H, dd), 4.153 (1H, d), 5.555 (1H, d)

ACKNOWLEDGMENTS

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