Journal of Organometallic Chemistry, 122 (1976) C49–C53

Preliminary communication

1,1'-Ferrocenyldiacetic Acid Anhydride and its Use in the Preparation of Heteroannularly Substituted Ferrocenyl--penicillins and -cephalosporins.

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(Received October 13th, 1976)

Summary

1'1,-Ferrocenediacetic acid anhydride has been prepared and it has been shown to be useful in the preparation of new heteroannularly substituted ferrocenyl-penicillins and -cephalosporins; these compounds exhibit antibiotic activity.

As part of a study of ferrocene molecules that possessed pharmacological activity [1,2] we required a simple route to heteroannularly substituted ferrocenyl-penicillins and -cephalosporins. The reaction of heteroannularly bridged ferrocenyl-acid anhydrides with 6-aminopenicillanic acid or

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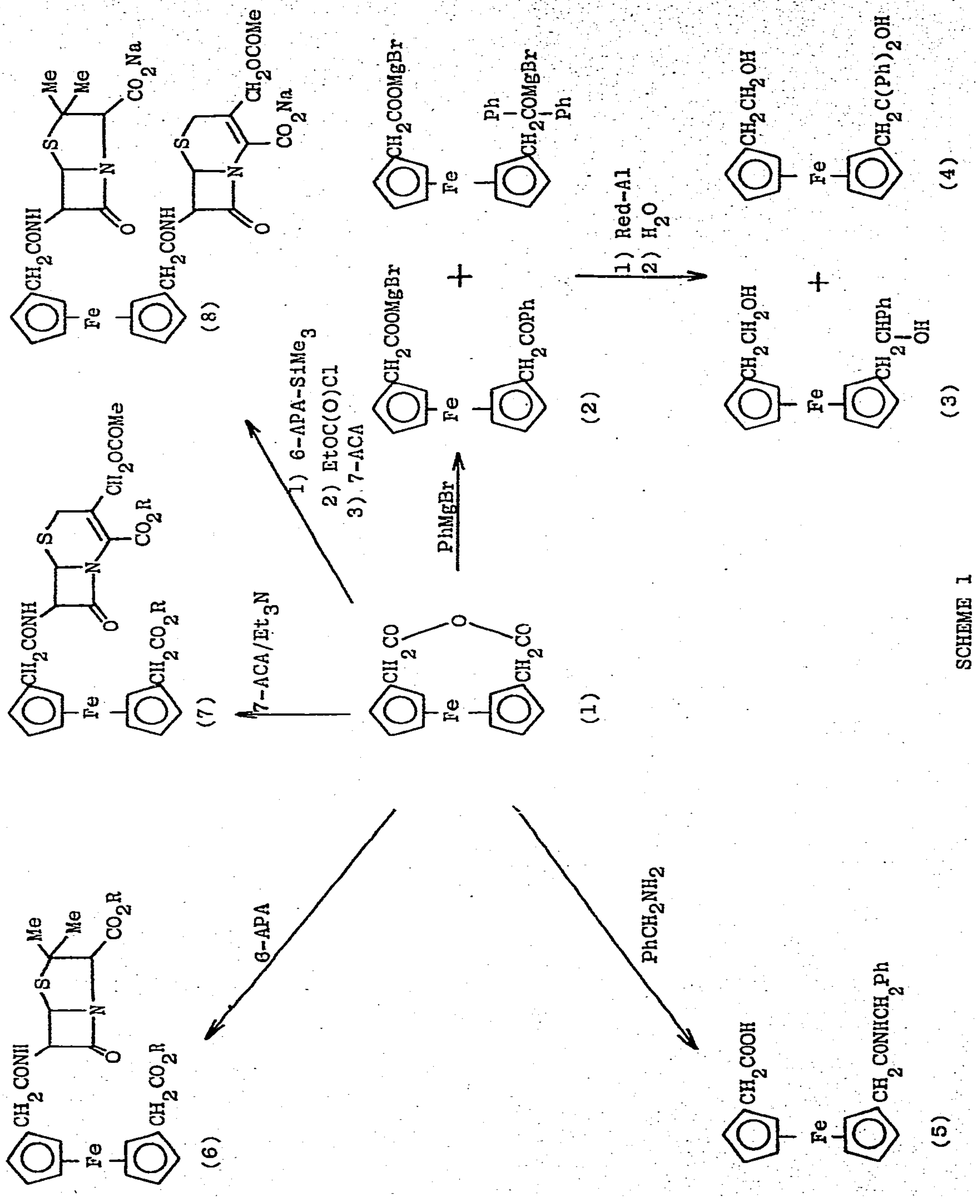
(1)
(2)
(3)
(4)
(5)
(6)
(7)
(8)
PhMgBr
1) Red-Al
2) H_2O
1) 6-APA-SiMe$_3$
2) EtOC(O)Cl
3) 7-ACA
7-ACA/Et$_3$N
6-APA
PhCH$_2$NH$_2$

SCHEME 1

7-aminocephalosporanic seemed to be the ideal route to these molecules[3]. However, ferrocenyl-acid anhydrides of this type have not been reported despite the extensive chemistry of the ferrocenophanes[4].

Attempts to effect the intramolecular cyclization of 1,1'-ferrocenedicarboxylic acid were unsuccessful and it may be significant that only the intermolecular dimer has been reported previously[5]. However, the treatment of 1,1'-ferrocenediacetic acid with dicyclohexylcarbodiimide in dichloromethane at room temperature gave the acid anhydride (1) in good yield (64%). The ferrocene derivative (1) behaved as a typical acid anhydride. Reduction with bis(2-methoxyethoxy)aluminium hydride (Red-al) gave 1,1'-bis(hydroxyethyl)ferrocene. Treatment of the anhydride with phenylmagnesium bromide followed by hydrolysis gave a mixture of carboxylic acids which could not be separated. The acids were characterised by reduction with Red-al to give two ferrocenyl-alcohols (3 and 4) (Scheme 1) which were separated by column chromatography on alumina. The tertiary alcohol (4) was formed presumably by reaction of the intermediate ketone (2) with excess Grignard reagent.

Treatment of the anhydride (1) with benzylamine gave the ferrocenylmethyl-amide (5) in good yield (64%). This ring opening reaction with an amine was utilized in the preparation of ferrocenyl-penicillins and cephalosporins. The reaction of the anhydride (1) with 6-aminopenicillanic acid (6-APA) and 7-aminocephalosporanic acid (7-ACA) in the presence of tri thylamine gave the ferrocenyl-penicillin (6;R=H) and the ferrocenyl-cephalosporin (7;R=H) respectively.

The ferrocenyl-penicillin (6;R=H) and -cephalosporin (7;R=H) were isolated as the disodium salts after treatment with sodium 2-ethyl-hexanoate. The infrared spectra of the sodium salts (6;R=Na) and (7;R=Na) exhibited strong absorptions characteristic of a β-lactam ring, at 1765 cm^{-1} and 1760 cm^{-1}, and a secondary amide carbonyl group, at 1660 cm^{-1} and 1665 cm^{-1} respectively.

Penicillins and cephalosporins both behave as antibiotics but as a general rule the penicillins are hydrolysed more readily under acid conditions and are more susceptible to attack by β-lactamases than cephalosporins. The combination of the penicillin and cephalosporin moieties within the same molecule is potentially very useful in the design of antibiotics which can be used under a wide variety of conditions against a range of bacteria[6]. The attachment of both the penicillin and cephalosporin nuclei to ferrocene was achieved via the anhydride (1). Treatment of the anhydride (1) with 6-APA trimethylsilylester followed by ethylchloroformate, formed the activated ester, and then 7-ACA gave 1-(6-acetamido--penicillanic acid)-1'-(7-acetamidocephalosporanic acid)ferrocene (Scheme 1)[6] which was isolated as the disodium salt (8).

The ferrocene derivatives (6 and 7;R=Na) and (8) all exhibited antibiotic activity against various strains of <u>Staphylococcus</u> <u>aureus</u>. Further work is in progress with other acid anhydrides to explore the general applicability of this route to the synthesis of new penicillins and cephalosporins All new compounds exhibited the requisite analytical and spectral properties and they were shown to be pure by thin layer chromatography.

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