Syntheses and uses of azetidiniminium salts

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Abstract : Tertiary amides are readily converted into iminium salts which
react with imines in the presence of triethylamine to give azetidiniminium
salts. Upon hydrolysis, thiolysis or aminolysis these are transformed into the
corresponding β-lactams, azetidinethiones or azetidinimines. Chiral azetidi-
niminium salts have been obtained in high optical purity from chiral iminium
salts and imines. A new application of the Baeyer-Villiger oxidation has been
found : it allows the conversion of azetidiniminium salts into oxazolidino-
nes. Preliminary results on a new potential asymmetric synthesis of amino
alcohols and amino acids are described.

INTRODUCTION

Several decades after the discovery of penicillin, the search for more effective
antibiotics still provides the incentive for continuing synthetic studies of new mono- and
bicyclic- β-lactams. Among a plethora of structural variations, only a few involve the
replacement of the carbonyl group of the β-lactam by related electrophilic groups (ref. 1).
Several years ago we felt that there was a need to develop practical synthetic approaches
toward these analogs of β-lactams. This lecture will summarise our present knowledge on the
synthesis and applications of azetidiniminium salts.

## SYNTHESES OF AZETIDINIMINIUM SALTS

The synthetic strategy for the preparation of azetidiniminium salts follows very
closely the one often utilised for β-lactams. It involves the reaction of an imine with
electrophilic reagents derived from tertiary amides (Scheme 1). These are readily converted

Scheme 1
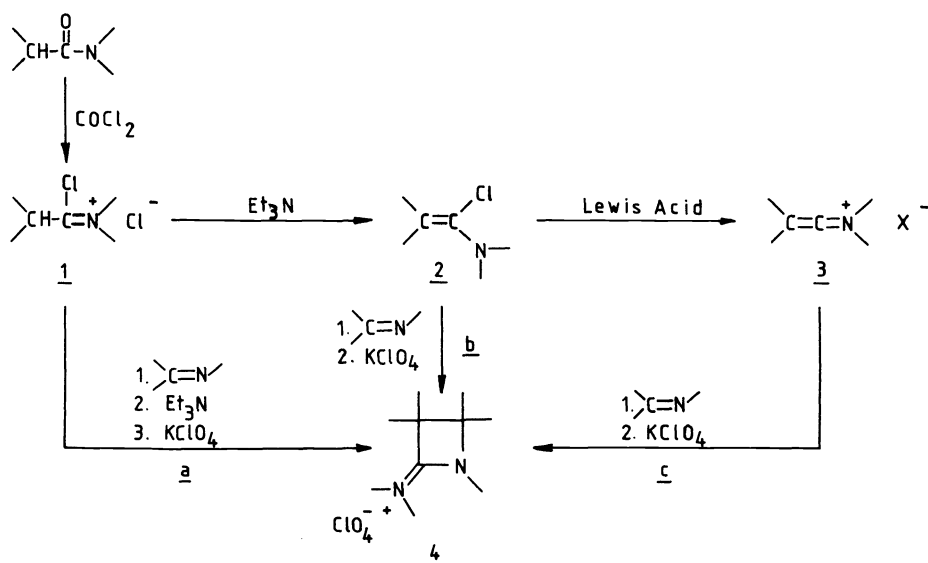
into the corresponding α-chloroiminium chlorides 1 by reaction with phosgene (ref. 2,3). α-Chloroiminium chlorides 1 react with imines in the presence of triethylamine to give azetidiniminium salts 4 (path a) (Ref. 4). Alternatively, α-chloroiminium chlorides 1 can be converted into α-chloroenamines 2, which can be isolated and purified when they bear no hydrogen atom on the β-carbon atom (ref. 2,3). They react as keteniminium chlorides and readily cycloadd to imines to give 4 (path b) (ref.4). Using these methods, we have been able to prepare more than 30 azetidiniminium salts which were usually purified as perchlorate salts. Representative structures are shown in Scheme 2.

Scheme 2

| 87% (a) | 66% (b) | 75% (b) | 40 % (b) |

| 50% (a) | 77% (b) | 0 % (a) ; 70% (c) | 83% (b) |
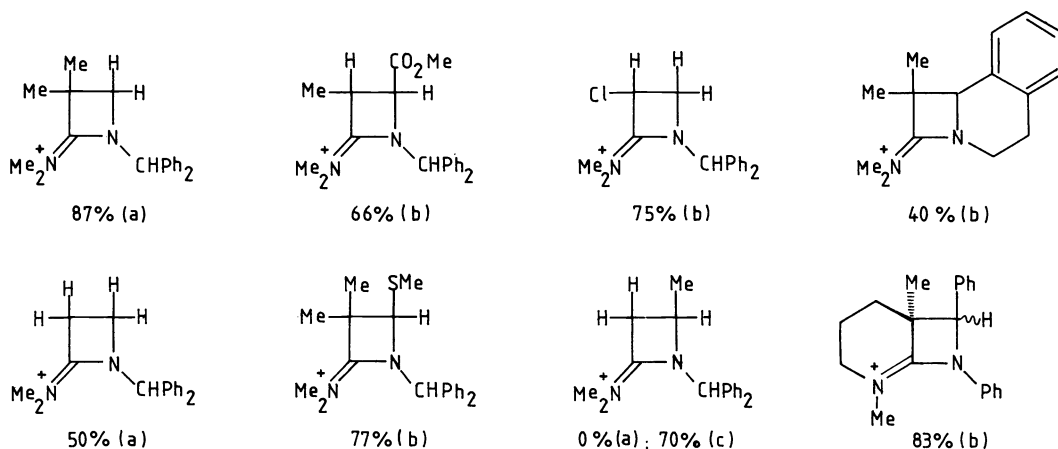
Paths a and b usually gave similar results. In general, however, path a is more practical since it does not involve the isolation of 2. However, neither path a nor path b allow for the preparation of 4-alkyl substituted azetidiniminium salts. They usually yield open-chain products. This problem could be solved by using the more electrophilic keteniminium salts 3 which can be prepared by reaction of α-chloroenamines 2 with Lewis acids (ZnCl$_2$, TiCl$_4$) (ref.2).

HYDROLYSIS OF AZETIDINIMINIUM SALTS

Are azetidiniminium salts precursors of β-lactams ? As amidinium salts, they are expected to regenerate an amide and an amine upon hydrolysis. However, the reaction of 4 with hydroxide ion generates a tetrahedral intermediate which can fragment in two ways (Scheme 3). The first pathway involves the cleavage of the exocyclic C-N bond and leads indeed to a β-lactam. Alternatively, cleavage of the endocyclic C-N bond, which is accompanied by a substantial relief of strain, would lead to an open-chain product.

Scheme 3
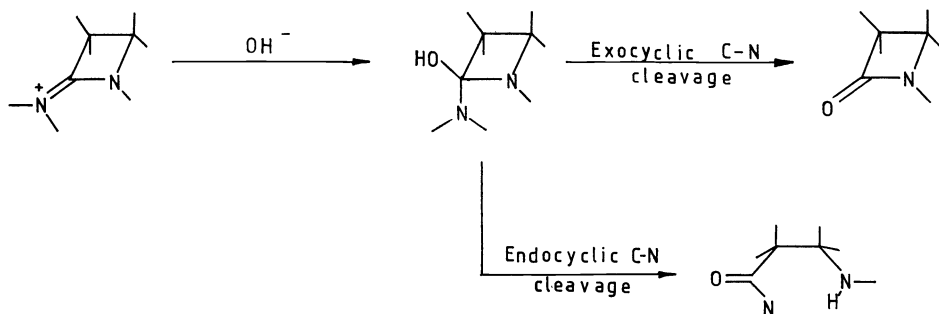
Experimentally, β-lactams were found to be the major hydrolysis products of 4 in a large number of cases (ref. 4). Thus, relief of strain does not appear to influence significantly the breakdown of the tetrahedral intermediate. This suggests that the transition state of the rate-determining step of the hydrolysis of 4 does not involve the cleavage of the C-N bond. In the light of extensive studies by Page et al. (ref. 5) of hydrolyses and aminolyses of β-lactams, one could consider the relative rate of protonation

of the endocyclic and exocyclic nitrogen atoms of the tetrahedral intermediate as a possible product-determining factor. This is being investigated in collaboration with Dr Page.

Azetidiniminium salts <u>4</u> can also be converted into a variety of derivatives such as azetidinethiones, -imines, -hydrazones and oximes (Scheme 4). Yields of imines derivatives

Scheme 4
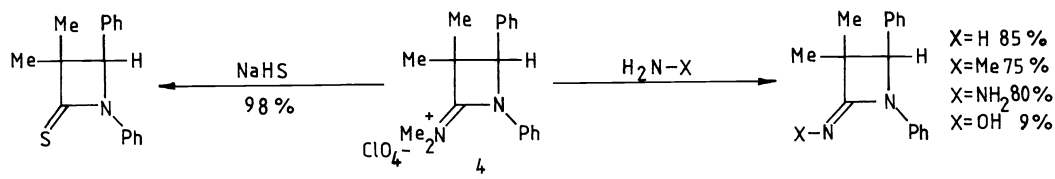
are high when the salts <u>4</u> bear no hydrogen at C-3. Otherwise the conversion of <u>4</u> into azetidinimines is best effected by first forming the corresponding azetidine-2-thione which is then treated with an amine in the presence of mercuric acetate (Scheme 5) (ref. 6).

Scheme 5
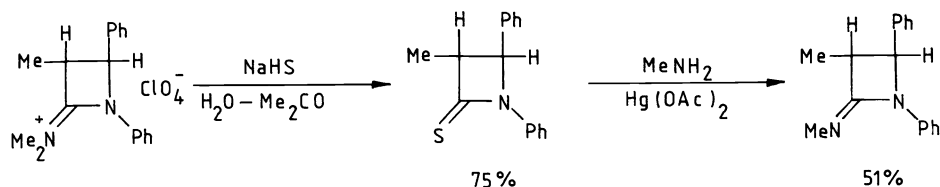
ASYMMETRIC SYNTHESES OF AZETIDINIMINIUM SALTS

The new methodology described above offered obvious possibilities for an asymmetric synthesis of β-lactams and β-lactam analogs. This idea was further supported by our earlier findings (ref. 7) that chiral keteniminium salts reacted with olefins to give cyclobutanones in high optical purities. In such an approach, the chiral auxiliary is present as the amine part of the starting amide and therefore can be easily varied. Furthermore, the chiral inductor should be easily recovered after hydrolysis, thiolysis or aminolysis of the resulting azetidiniminium salts. The validity of this approach was first demonstrated by Belzecki and Rogalska (ref. 8). Using amides derived from (S) 2-ethylpiperidine and from (S) N-methylamphetamine, they obtained β-lactams in enantiomeric excesses up to 76%.

In Louvain-la-Neuve we first selected (S) 2-(methoxymethyl) pyrrolidine as chiral inductor. This had proved to be efficient in the asymmetric cycloadditions of keteniminium salts with olefins (ref. 7). The "one pot" sequence for conversion of chiral amides <u>5</u> and imines into β-lactams is shown in Scheme 6. Some typical results are shown in Scheme 7. It can be seen that the bulk of the amide substituents R^1 and R^2 plays a decisive role on the
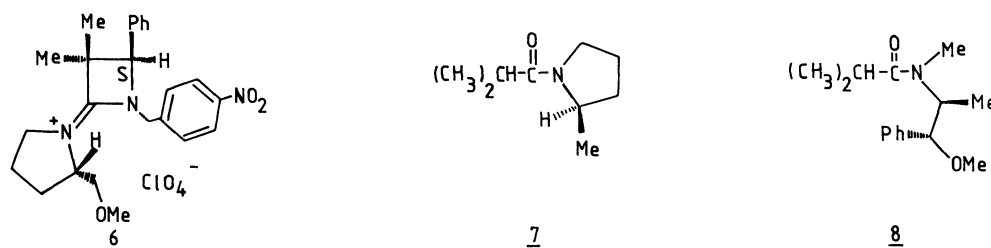
Scheme 6
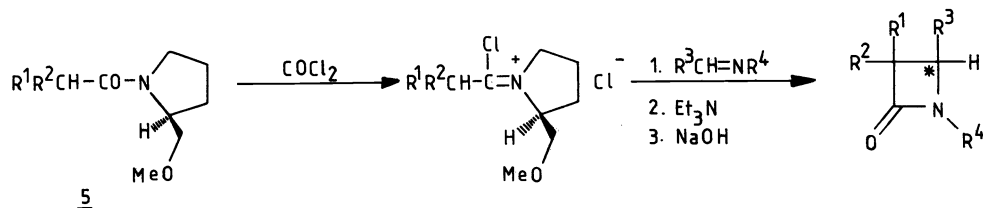
diastereoselectivity of the reaction. When R^1=Me and R^2= Me or Ph, β-lactams are obtained in high (≥95%) optical purities. When R^1=R^2=H the diastereoselectivity drops dramatically. On the other hand, the diastereoselectivity is rather independent of the imines substituents

Scheme 7

| Yield | 42 | 65 | 29 | 40 |
| ee | 98 | 99 | 97 | 4 |
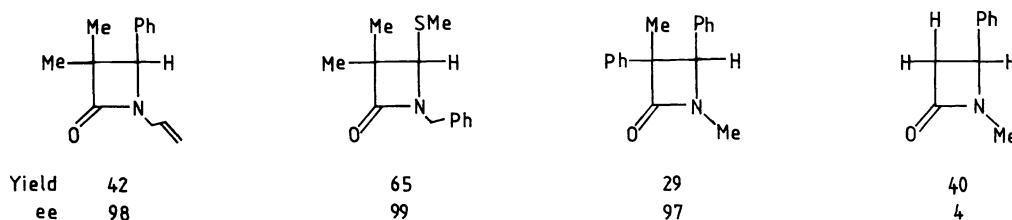
R^3 and R^4. Compound <u>6</u> was isolated in crystalline form suitable for X-ray diffraction analysis (ref. 9). The absolute configuration at C-4 was found to be (S) with the "chiral arm" oriented as shown in Scheme 8.
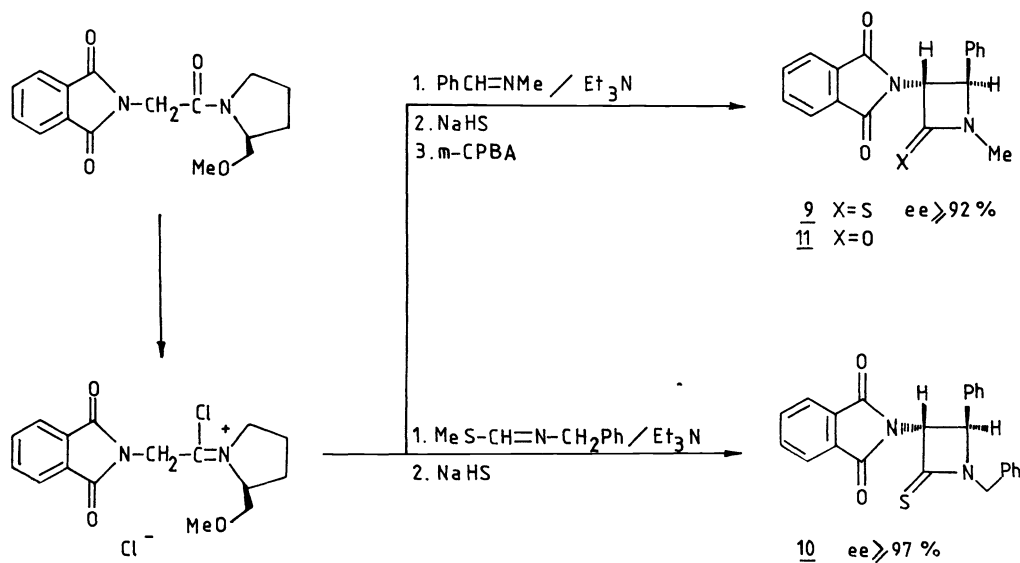
Scheme 8

We have also examined two other chiral isobutyramides <u>7</u> and <u>8</u>. Both gave β-lactams in high (≥96%) optical purities.

Using this method, it was also possible to prepare β-lactams bearing a protected amino side-chain at C-3 (Scheme 9). This required a slight modification of the general procedure

Scheme 9

<u>9</u> X=S ee≥92%
<u>11</u> X=O

<u>10</u> ee≥97%

because the basic conditions of the hydrolysis step destroys the intermediate azetidiniminium salts. Therefore, the crude salts were treated with sodium hydrogen sulphide (acetone, 20°C) to give azetidine-2-thiones in high enantiomeric excesses. Compound 9 could be readily transformed into the corresponding β-lactam by oxidation with mCPBA. Both reactions yielded only the trans-isomers. This is an obvious disadvantage with respect to the methods recently described in the literature (ref. 10).

EXPLORATORY STUDIES ON OXIDATION OF AZETIDINIMINIUM SALTS: POTENTIAL ROUTE TOWARDS 1,2-AMINO ALCOHOLS AND α-AMINO ACIDS

It is not yet clear whether this new asymmetric synthesis of β-lactams or their analogs described above will be applicable to the preparation of biologically interesting compounds. Nevertheless, a convergent and effective asymmetric synthesis of a strained heterocyclic ring represented a synthetic "bonus" which can be exploited in synthesis.

We found that azetidiniminium salts 12a and 12b readily reacted with bis-trimethylsilyl peroxide in the presence of fluoride ion to give the five-membered carbamates 13a and 13b (Scheme 10). These should be readily converted into the corresponding 1,2-amino alcohols by
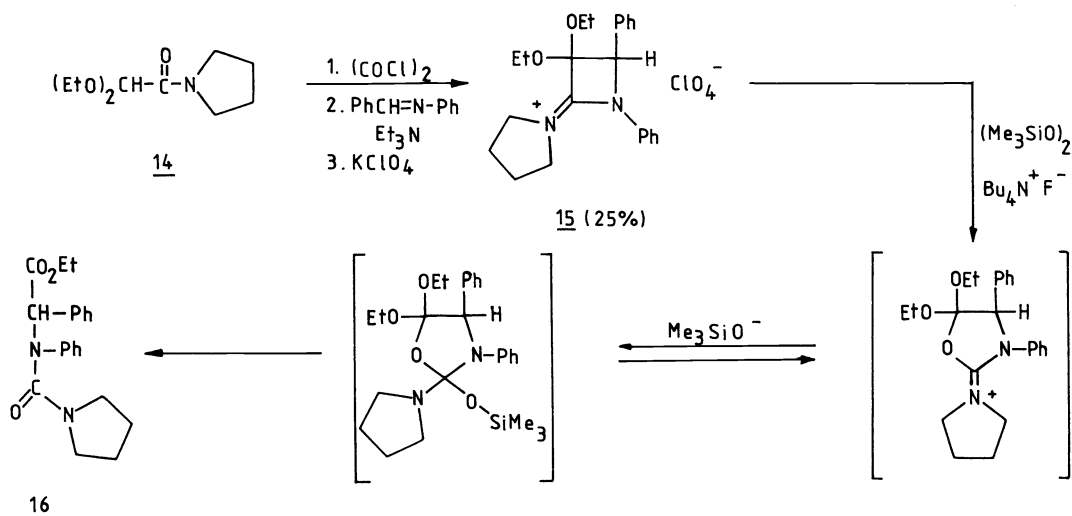
Scheme 10

12 a R=Ph
  b R=CHPh2

13 a 72%
  b 75%
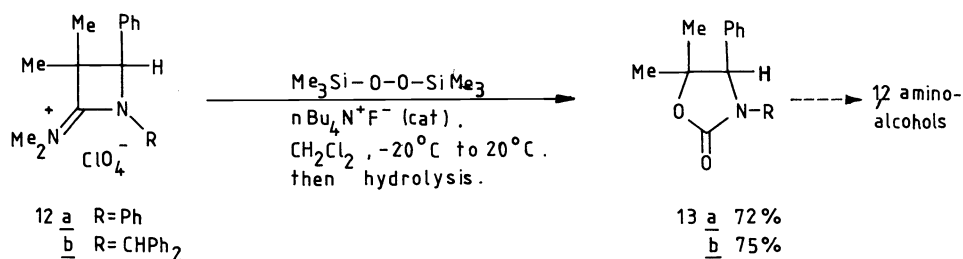
hydrolysis. Thus, optically active 1,2-amino alcohols should be accessible from a sequence of reactions involving the asymmetric synthesis of an azetidiniminium salt followed by its oxidation and subsequent hydrolysis of the resulting carbamate.

Preliminary results show that this methodology can be applied to the preparation of amino acids (Scheme 11). Amide 14 and oxalyl chloride yielded an iminium salt which reacted

Scheme 11

15 (25%)

16

with benzalaniline and triethylamine to give 15. Oxidation of 15 directly gave the amino acid derivative 16 probably by the mechanism shown in Scheme 11. These findings represent a potential asymmetric route towards amino alcohols and amino acids from imines and amides derived from chiral amines.

Acknowledgements

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