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CONVERSION OF IMIDOYL CHLORIDES TO IMINES. A NEW METHOD FOR THE ACYL EXCHANGE AND CLEAVAGE OF AMIDES

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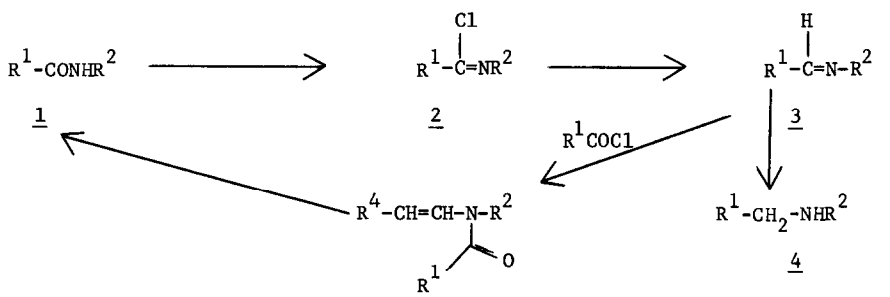
The breaking of the amide bond under mild conditions is an often encountered problem in natural product chemistry. In the field of β-lactam antibiotics an exchange of acyl groups is required.[1] The generally used fission method is the acid hydrolysis of the corresponding imino ethers.[2] This, however, is not applicable when the produced amine is not acid stable.[3]

In this paper we describe two new methods for the acyl exchange and mild cleavage of secondary amides based on the conversion of imidoyl chlorides to imines. In the first method, the imine (3), produced by partial reduction (2 → 3) was converted to a new amide (1) by acylation followed by hydrolysis (acyl exchange). In the second procedure, the imine (7), produced by reaction with a methyl cuprate, was hydrolyzed to the amine 9 at neutrality.

The acyl exchange method is illustrated by the following scheme:



a) R^1 = ethyl R^2 = cyclohexyl

b) R^1 = heptyl R^2 = cyclohexyl

c) R^1 = ∅ R^2 = cyclohexyl

Conversion of amides to imidoyl chlorides was carried out by known methods.[4] Two reagents were used in the past for the partial reduction of imidoyl chlorides to imines[5]: a) $SnCl_2$ in highly acidic medium, b) $CrCl_2$, which was reported to fail in some cases.[6] Clearly, these

reagents were not suitable for our purposes. We have found, however, that $LiAl(tBuO)_3H$ reduces imidoyl chlorides rapidly under very mild conditions.

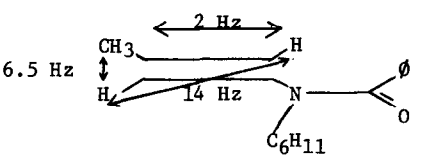
In a typical experiment, the solution of the reducing agent in THF was added to a cooled (-78°C) solution of the imidoyl chloride. After 30 minutes the mixture was allowed to warm to room temperature and the excess hydride was decomposed by the addition of a water or dil NaOH solution. The voluminous precipitate was removed by filtration[7] to afford a solution of the imine. The starting amide (1) and amine 4 were the main contaminants. Under these conditions, excess reducing agent can be used, since conversion to amine 4 required 24 hrs. exposure at room temperature to an excess of the reagent. The results are summarized below.

Reduction of Imidoyl Chlorides

Amide (1)	Excess of Reagent	Yield* of Imine (3)
1a R^1 = ethyl, R^2 = cyclohexyl	150%	62%
1a	300%	65%
1b R^1 = heptyl, R^2 = cyclohexyl	150%	60%
1c R^1 = ø, R^2 = cyclohexyl	120%	85%
1c	200%	85%

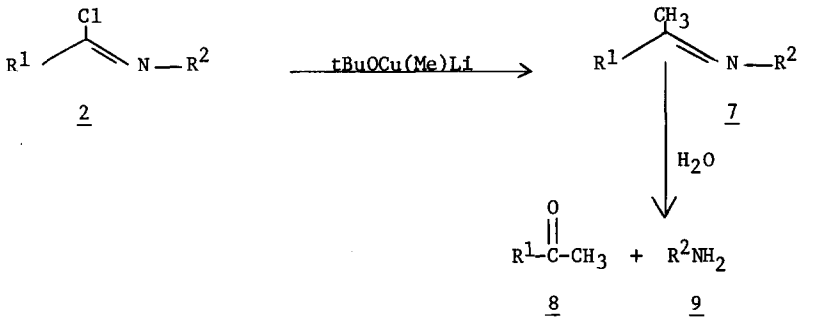
* Estimated by VPC in comparison with an authentic sample.

Acylation of imine 3a with octanoyl chloride and triethylamine according to the procedure of Breederveld[8] afforded enamine 5a (R = heptyl, R^4 = methyl) as a mixture of cis and trans isomers in 68% yield. The dominating trans isomer, isolated by chromatography, was a colorless oil and it showed a characteristic NMR spectrum: ($CDCl_3$) δ 1.78 (two d, CH_3), 5.5 (two qu, CH_3-C(H)=), 6.0 (two d, N-C(H)=). Similarly, benzoylation afforded 5 (R^1 = ø, R^4 = methyl) which showed analogous NMR spectrum with the following splitting constants.



The acyl enamines (5) were converted to the new amides 1 by two procedures: a) the isomeric mixture of 5 (R^1 = heptyl, R^4 = methyl) was allowed to stand overnight in 0.1N methanolic HCl to afford octanoyl cyclohexylamine 1b in 90% yield; b) the benzoyl analog 5 (R^1 = ∅, R^4 = methyl) was converted to benzoyl cyclohexylamine 1c on treatment with hydroxylamine hydrochloride in THF-water for 30 min at 40° (85% overall yield from 3a to 1c). This sequence represents an acyl exchange of amides under mild conditions.

The second method developed for the fission of the amide bond is based on the reaction of imidoyl chlorides with methylcuprates. Reaction of 2 with lithium t-butoxy (methyl) cuprate[9] at low temperature afforded ketimine 7 is good yield. During the aqueous work-up (pH 7.5), the imine hydrolyzed to the corresponding amine (9) and ketone (8).



2 7 8 9

In the case of benzoyl analog 2d, the hydrolysis was slow and imine 7 was the main product. In a typical procedure, the THF solution of 2 was added to a freshly prepared slurry of tBuOCu(Me)Li in THF at -78°. After 15 minutes reaction at -78°, pH 7.5 NH_4 Cl/$NaHCO_3$ buffer was added and the products were isolated by extraction with ethyl acetate.

Reaction Imidoyl Chlorides with t-BuOCu(Me)Li

Imidoyl chloride 2	Yield* of Imine (7)	Yield of Ketone (8)
2b R^1 = heptyl, R^2 = cyclohexyl	10%	63%
2d R^1 = ∅, R^2 = hexyl	55%	10%
2e R^1 = propyl, R^2 = ∅		55%

* estimated by VPC, in comparison with an authentic sample

The methods presented for the conversion of imidoyl chlorides to aldimines and ketimines could have many other applications in organic chemistry besides the mild cleavage of amide bonds. The cleavage of 7-methoxy cephalosporin amides by the methyl cuprate method is the subject of the next paper in this Journal.

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