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Bifunctional Chiral Auxiliaries 2: The Synthesis of 1,3-Diacylimidazolidin-2-ones from 1,2-Diamines

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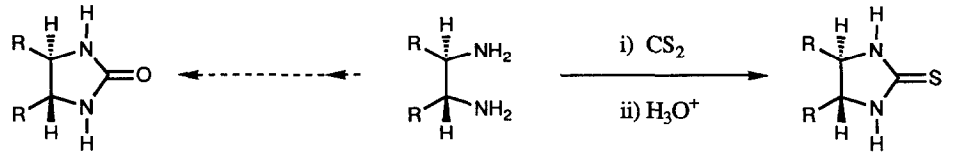
Summary: The title compounds are readily prepared in three steps *via* the corresponding 1,3-diacylimidazolidine-2-thiones. The final step involves the novel use of mercury (II) acetate for the conversion of thioureas to ureas.

Our desire to develop a novel series of bifunctional chiral auxiliaries, requires the synthesis of C_2 symmetric 1,3-diacylimidazolidin-2-ones[1]. The availability of *trans*-1,2-diamines such as *trans*-1,2-diaminocyclohexane **1a**[2] and *trans*-1,2-diphenyl-1,2-diaminoethane **1b**[3], coupled with the ease of their resolution[4], indicated their suitability as starting materials for such a synthesis. Such an approach would therefore be analogous to the preparation of N-acyl oxazolidinones from β-aminoalcohols *via* initial introduction of the oxazolidinone carbonyl group and subsequent N-acylation[5].

It was found that the reaction of *trans*-1,2-diaminocyclohexane **1a** with either phosgene or phosgene equivalents such as 1,1-carbonyl di-imidazole, urea, dimethyl carbonate or methyl chloroformate did not give the desired imidazolidin-2-one **2a**, but rather an oligomeric product. This indicates that the intermolecular reaction competes effectively against the intramolecular cyclisation, a result that has some precedent in the reaction of 1,2-diaminoethane (ethylene diamine) with urea[6]. However, the use of water as a solvent, advanced by this earlier study, did not improve the process sufficiently for its use in this approach.

An alternative approach was the introduction of a thiocarbonyl group, to give the imidazolidine-2-thione, followed by acylation and finally, dethionation to the 1,3-diacylimidazolidin-2-one. This approach was particularly attractive since 1,3-diacylimidazolidine-2-thiones are intrinsically interesting as chiral auxiliaries in their own right. The reaction of 1,2-diaminoethane with carbon disulphide has been reported[7] and repeating these conditions with diamines **1a**, **1b** gave the desired imidazolidine-2-thiones **3a**, **3b** in excellent yield. Furthermore, the reaction may be performed on a 0.5mol scale with comparable yield.



2a R = -$(CH_2)_4$-

1a R = -$(CH_2)_4$-
1b R = Ph

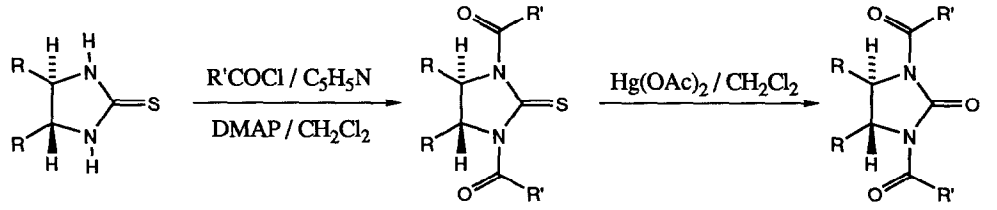
3a R = -$(CH_2)_4$- 94%
3b R = Ph 90%

Diacylation of imidazolidine-2-thiones has been reported by Kohn[8] using pyridine and the requisite acyl halide with a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane at ambient tenperature. Using the same conditions, a range of diacylated derivatives of the parent imidazolidine-2-thiones **3a**, **3b** was prepared in good yield, the details being shown in the Table below. The preparation of compounds with unsaturated acyl sidechains was found to be possible only when nucleophilic attack on the Michael acceptor was disfavoured. Thus, although the cinnamoyl derivatives **4h** and **4q** could be prepared in moderate yield, all attempts to prepare the acryloyl and crotonyl compounds failed due to the thiocarbonyl group acting as a nucleophile towards the double bond *via* an intramolecular conjugate addition.

The conversion of thiocarbonyl compounds to their oxocarbonyl analogues, although less well studied than the reverse reaction, has been achieved using a variety of conditions[9]. However, those reagents which seemed most suitable for the dethionation of 1,3-diacylimidazolidine-2-thiones **4a-4p** failed to give the desired product. Some earlier approaches had sought to effect the reaction by improving the leaving group ability of sulphur by coordinating it to a metal[10]. Developing this logic further, it was reasoned that mercury (II) acetate should be able to enhance the leaving group ability of the sulphur, due to its high thiophilicity, while the attached acetate anions should be able to act as suitable oxygen nucleophiles[11]. Treatment of a dichloromethane solution of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidine-2-thione **4b** with a stoicheiometric amount of mercury (II) acetate for 12 h at ambient temperature gave the corresponding imidazolidin-2-one **5b** in a yield of 88%. It was found expedient to modify the procedure such that the imidazolidine-2-thione was treated sequentially with two batches of mercury (II) acetate (1.0eq and 0.3eq) as this guaranteed the reaction going to completion.

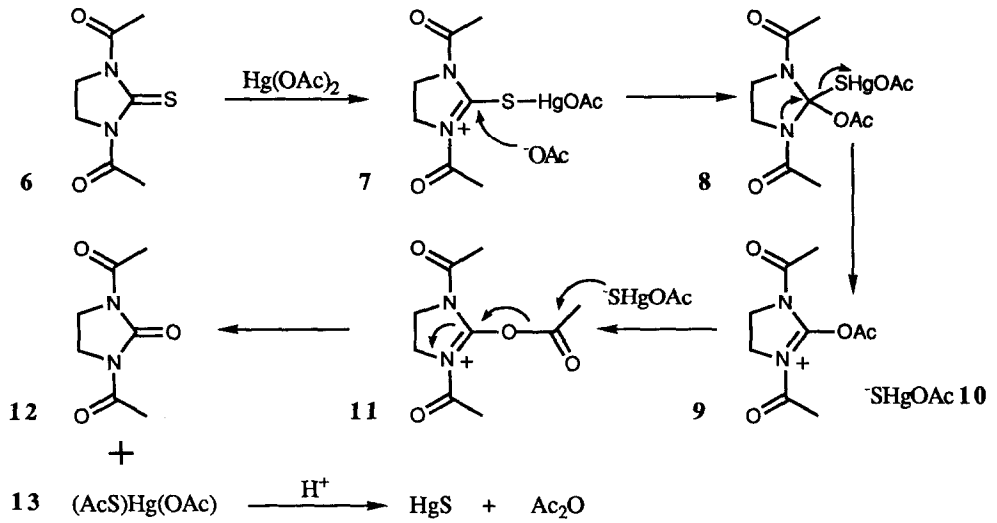
R	R'	Diacylation		Dethionation	
$-(CH_2)_4-$	Me	71%	**4a**	76%	**5a**
$-(CH_2)_4-$	Et	85%	**4b**	88%	**5b**
$-(CH_2)_4-$	n-Pr	83%	**4c**	70%	**5c**
$-(CH_2)_4-$	CH_2CH_2Ph	75%	**4d**	82%	**5d**
$-(CH_2)_4-$	CH(Me)Et	78%	**4e**	99%	**5e**
$-(CH_2)_4-$	$CH(Me)CH_2Ph$	94%	**4f**	84%	**5f**
$-(CH_2)_4-$	$CH(Et)CH_2Ph$	85%	**4g**	73%	**5g**
$-(CH_2)_4-$	CH=CHPh	48%	**4h**	78%	**5h**
$-(CH_2)_4-$	$C_{17}H_{35}$	97%	**4i**	97%	**5i**
Ph	Me	94%	**4j**	93%	**5j**
Ph	Et	88%	**4k**	91%	**5k**
Ph	n-Pr	88%	**4l**	87%	**5l**
Ph	CH_2CH_2Ph	68%	**4m**	93%	**5m**
Ph	CH(Me)Et	79%	**4n**	84%	**5n**
Ph	$CH(Me)CH_2Ph$	87%	**4o**	83%	**5o**
Ph	$CH(Et)CH_2Ph$	92%	**4p**	81%	**5p**
Ph	CH=CHPh	42%	**4q**	99%	**5q**

Employing this modified procedure, it was possible to prepare a wide range of 1,3-diacylimidazolidin-2-ones in uniformly high yield as can be seen from the Table above. It was also found that the reaction occurred cleanly on those compounds bearing unsaturated acyl sidechains **5h** and **5q**, and more recently it has been discovered that β-hydroxy substituents are also tolerated.



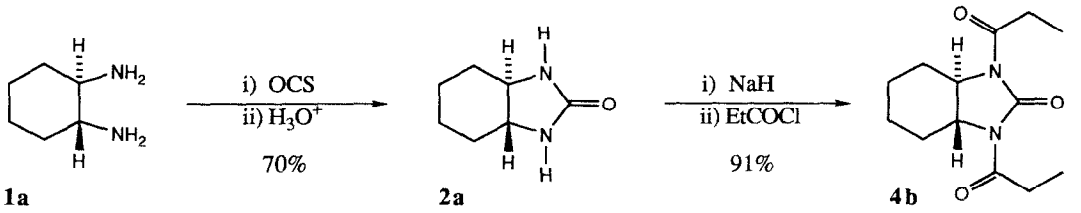
3 4 5

The development of this simple method for the conversion of 1,3-diacylimidazolidine-2-thiones **4a-4q** to the corresponding 1,3-diacylimidazolidin-2-ones **5a-5q** allows the latter type of compound to be synthesised from 1,2-diamines in three steps in an overall yield of 70-80% depending on the particular substituents. It was however, of interest to try and understand the mechanism of this novel functional group interconversion. The reaction was found to deliver the mercury by-product in two forms depending on the pH of the reaction. Under normal conditions the mercury was recovered as Hg(OAc)(SAc) **13** but if the reaction mixture was slightly acidic (due either to the use of fresh mercury (II) acetate or due to contamination with carboxylic acid residues from the previous stage), a black insoluble precipitate of mercury (II) sulphide was obtained together with acetic anhydride. Decomposition of Hg(OAc)(SAc) **13** under acidic conditions would give these latter products and it seems likely that the former is the first formed. That this species is a significant by-product of the reaction is emphasised by the observation that other mercury (II) salts, such as HgO and $HgCl_2$, fail to give the desired reaction. It is also important to note that an independent hydrolysis is not required and the reaction may be worked-up merely by filtering the reaction mixture through celite to remove the mercury salts. The proposed mechanism, shown below, is consistent with all these observations.



6 7 8 9 11 12

Despite the high yields associated with this three step approach, it was felt that a shorter route could be developed if carbon disulphide were to be replaced with carbonyl sulphide (OCS) in the initial step as this should give the imidazolidin-2-one directly. The use of carbonyl sulphide for the synthesis of medium ring ureas has been reported previously[12] and it was found that *trans*-1,2-diaminocyclohexane **1a** could be converted to *trans*-4,5-tetramethyleneimidazolidin-2-one **2a** which could then be acylated in high yield. Although the yield for the first step is only 70%, this has not been optimised and the method offers an attractive alternative to that described above.



1a **2a** **4b**

In conclusion, we have demonstrated short and efficient synthetic routes to 1,3-diacylimidazolidin-2-ones which are highly effective bifunctional chiral auxiliaries[1]. Further synthetic applications of mercury (II) acetate for the selective synthesis of carbonyl compounds from their thiocarbonyl analogues is under investigation.

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