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Studies on the oxidation of 2,2,4-trisubstituted 3-pyrrolines

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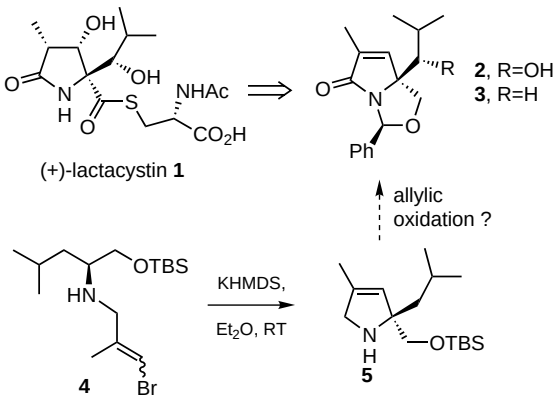
Abstract—As part of our studies directed towards a total synthesis of lactacystin, we have developed a reliable and environmentally acceptable method to oxidise 2,2,4-trisubstituted 3-pyrrolines to the corresponding 3-pyrrolin-2-ones. Several protocols were examined and the two-step (i) TPAP/NMO; (ii) sodium hypochlorite allylic oxidation was found to be the most satisfactory. Catalytic oxidation of the 3-pyrroline afforded the corresponding cyclic imine in high yield, and subsequent oxidation with NaOCl afforded the *N*-chloro-3-pyrrolin-2-one. The *N*-chloro-substituent was removed by a simple acid treatment. © 2002 Published by Elsevier Science Ltd.

(+)-Lactacystin **1** is a selective inhibitor of the mammalian 20S-proteasome[1] and has stimulated a considerable amount of synthetic interest over recent years.[2] Furthermore, it has been shown that a number of synthetic analogues of **1** are also inhibitors of the 20S-proteasome, and some of these show promise as potential therapeutic agents.[2,3] During their total synthesis of **1**, Baldwin et al.[4] used a suitably protected 3-pyrrolin-2-one **2** as a key synthetic intermediate and we felt that molecules of this general type could serve as excellent precursors to a range of novel lactacystin analogues. As a result of this, and as part of our own studies towards a total synthesis of **1**, we became interested in methods for the efficient construction of 3-pyrrolines and 3-pyrrolin-2-ones.

We have shown recently that a range of 3-pyrrolines (e.g. **5**) can be synthesised using an alkylidene carbene 1,5-CH insertion reaction as a key step,[5] and that 2,2-disubstituted 3-pyrrolines can be accessed in an enantioselective fashion using this methodology. In order for us to exploit this chemistry in the context of a synthesis of **1**, we next needed to find suitable conditions for oxidation of the C2-methylene of 3-pyrrolines and we chose **5** as a model substrate on which to study this process.

At the outset of this work we were optimistic that this transformation would prove straightforward as a number of well known methods for allylic oxidation were available. Reported conditions for one-pot allylic oxidations of this type commonly involved the use of chromium (e.g. CrO_3/3,5-dimethylpyrazole)[6] and selenium (e.g. SeO_2)[7] based reagents, and we started our study by examining the use of these for the oxidation of 3-pyrroline **5** (Scheme 1).



To our initial disappointment, we found that we were unable to find reliable and repeatable conditions to effect the desired oxidation of **5**, or protected versions of **5**, using either CrO_3/3,5-dimethylpyrazole[8] or SeO_2 based reagent systems. In most cases we observed consumption of the starting material, but the product mixtures were often found to be complex and contained only small amounts of the desired lactam oxidation products. It therefore became clear at an early stage in this work that an alternative oxidation protocol had to be found. Whilst working with the chromium and selenium based reagents, we were aware that it would

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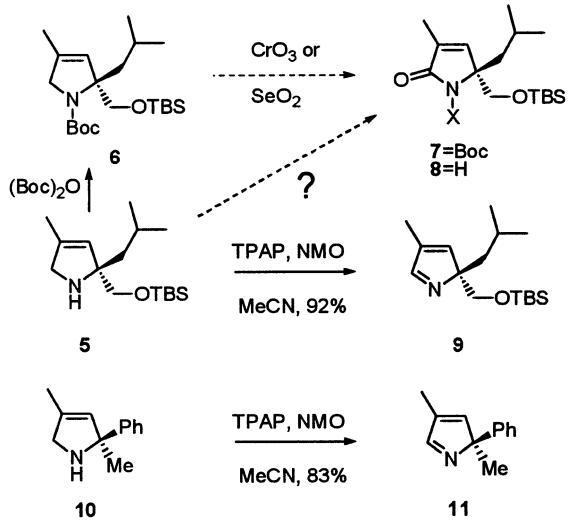


Scheme 1.

be preferable to find a more environmentally acceptable oxidation method, and if potentially harmful reagents were to be used, then these should be used in sub-stoichiometric amounts.

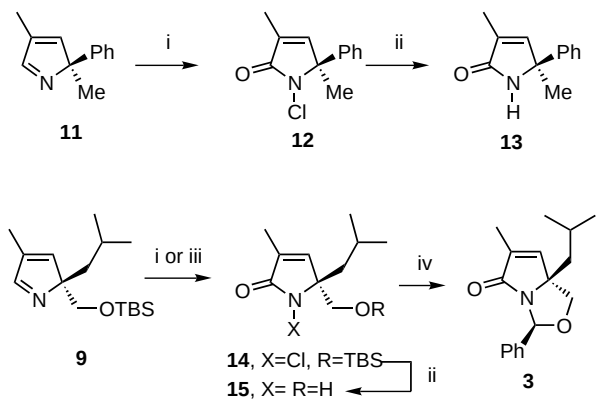
Upon further examination of the literature, we were struck by a report by Goti et al.,[9] who described the use of the well known TPAP/NMO catalytic system[10] for the oxidation of amines to imines. We felt that if this methodology could be used to oxidise 3-pyrrolines to the corresponding cyclic imines, then we may be able to oxidise these materials further to the lactams with other readily available oxidants. Pleasingly, we found that the 2,2-disubstituted 3-pyrroline **5** was oxidised to the corresponding imine **9** using the TPAP (5 mol%)/NMO (3.0 equiv.) conditions, as described by Goti, and the crude reaction mixture consisted largely of the expected imine (as judged by TLC and ^{1}H NMR) and the isolated yield of the desired product was high (92%). In a similar fashion, the enantiomerically enriched 3-pyrroline **10** was also oxidised using these reaction conditions and the imine **11** was produced in 83% yield (Scheme 1).

We next surveyed a range of oxidants for the remaining imine to amide functional group interconversion, and found that sodium hypochlorite gave the most promising results. Treatment of methanolic solutions of the imines **9** and **11** with an excess of NaOCl (13% aq., 10 equiv.) effected the desired imine oxidation, but it was clear from mass spectrometry and ^{1}H NMR data of the crude reaction mixtures that the *N*-chlorolactams **12** and **14** were produced as the major products (Scheme 2). Unsurprisingly, these materials proved to be unstable to purification by column chromatography and varying amounts of the dechlorinated lactams **8** and **13** could be recovered from these purification attempts. It is well documented that competitive HCl-mediated dechlorination is a side reaction in the photochemical generation of amidyl radicals from *N*-chloroamides,[11] and the formation of **8** and **13** from **14** and **12** can be rationalised by invoking a similar decomposition on the acidic silica gel used in the column chromatography.

As the synthesis of lactams corresponding to **8** and **13** was the initial goal of this work, we were not too disappointed by this finding and decided to exploit this acid-mediated dechlorination strategy. Thus, treatment of methanolic solutions of the crude reaction mixtures of the *N*-chlorolactams **12** and **14** with anhydrous HCl (generated in situ from the action of AcCl on MeOH) resulted in the exchange of the *N*-Cl atom for a proton. The lactam **13** was formed in 59% overall yield from the imine **11**, and in the case of *N*-chlorolactam **14**, the dechlorination reaction was accompanied by removal of the TBS-protecting group to afford the hydroxymethyl-lactam **15** in 49% yield from the imine **9**. Oxazolidine **3**, which is very similar to the intermediate **2** used in Baldwin's synthesis of lactacystin, was produced in excellent yield (85%) from **15** under standard aminal forming conditions, and this material was produced as a single diastereoisomer.[12]

Oxidation of the imines **9** and **11** likely proceeds via an initial *N*-chlorination, followed by addition of hypochlorite to the electrophilic *N*-chloroimmonium species **16** (Scheme 3). Elimination of HCl from **17** then completes the oxidation process to afford the observed *N*-chlorolactams. Evidence for this reaction pathway comes from the fact that products (e.g. **18**) formed by partial oxidation of the imines can be isolated from reaction mixtures when fewer equivalents of NaOCl are used. In these cases, none of the lactams **13** and **8** could be detected, thus, suggesting *N*-chlorination occurs before lactam formation.

Of the other oxidants screened for the imine to lactam conversion, only buffered sodium chlorite and *m*CPBA gave potentially useful results. Firstly, exposure of imine **9** to an excess of sodium chlorite, under the standard conditions used for the oxidation of an aldehyde to an acid,[13] resulted in the formation of the *N*-chlorolactam **14** in good yield (Scheme 2). Although we were pleased to achieve a clean oxidation reaction, we were surprised to observe **14** as the major product as we were hoping that the desired lactam **8** would be

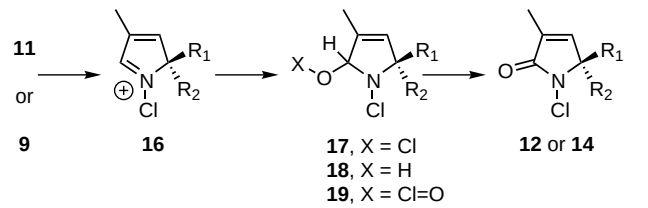


Scheme 2. *Reagents and conditions*: (i) NaOCl, MeOH, rt; (ii) AcCl, MeOH, 0°C→rt; (iii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^{t}BuOH/H_2O; (iv) $PhCH(OMe)_2$, PPTS, PhMe, Δ.

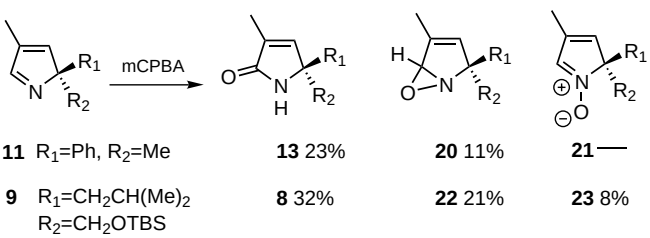
formed under these conditions. We attribute the formation of the *N*-chloro product **14** to the fact that the HOCl produced during the course of the reaction facilitates *N*-chlorination to produce an *N*-chloroimmonium species **16**, which is then oxidised to **14**, via the adduct **19** (Scheme 3). Evidence for this reaction pathway comes from the fact that only **14** and unreacted imine **9** are observed when fewer equivalents of $NaClO_2$ are used in this oxidation reaction. Attempts to scavenge the HOCl by using a large excess of 2-methyl-2-butene (40 equiv.) failed to stop the *N*-chlorination reaction. The lactam **14** produced in this reaction could be converted into the hydroxymethyl-lactam **15** in 53% overall yield from **9** by treatment with methanolic HCl, as described previously (vide supra).

Treatment of the imines **9** and **11** with *m*CPBA in CH_2Cl_2 resulted in the formation of the corresponding lactams **8** (32%) and **13** (23%), respectively. A number of additional oxidation products were isolated from these reactions, and these were identified as being the oxaziridines **20**/**22** and the nitrone **23**.[14] Although it is known that nitrones and oxaziridines can be converted into the isomeric amides, we were unable to optimize this particular set of transformations to afford synthetically useful yields of the desired lactam products (Scheme 4).[15]

In summary, we have found that 2,2-dialkyl-3-pyrrolines can be oxidised to 3-pyrrolin-2-ones, via their corresponding cyclic imines, in moderate to good yield using a convenient and reliable two-step procedure. Initial oxidation of the 3-pyrrolines with TPAP/NMO and subsequent exposure of the resulting imine to NaOCl/MeOH affords the *N*-chlorolactam product. Acid-mediated dechlorination then provides the desired 3-pyrrolinone products. We have shown that this method can be applied to the synthesis of the bicyclic lactam **3**, and we are now examining its application to a total synthesis of (+)-lactacystin **1** and these studies will be reported in due course.



Scheme 3.



Scheme 4.

Typical procedure for the TPAP-NMO oxidation of 3-pyrrolines

According to Goti's procedure:[9] NMO (165 mg, 1.40 mmol) and TPAP (12 mg, 0.04 mmol) were added sequentially to a stirring solution of 3-pyrroline **5** (200 mg, 0.70 mmol) in dry acetonitrile (2 mL) and 4 Å powdered molecular sieves under a nitrogen atmosphere. After 4 h, the acetonitrile was removed in vacuo and the crude material was filtered through a pad of Celite and silica using EtOAc as eluant. The filtrate was concentrated in vacuo and the crude material was purified by flash column chromatography (SiO_2, petrol:Et_2O (1:1)) to give the imine **9** (181 mg, 92%) as colourless oil. ν_{max}/cm^{-1} (film) 2954, 2928, 2858, 1686, 1520, 1471, 1384, 1363, 1256, 1006, 937, 837 and 776; δ_H (250 MHz; $CDCl_3$) 7.89 (1H, s, C*H*=N), 6.94 (1H, m, C*H*C=C), 3.91 (1H, d, *J* 9, C*H*HO), 3.07 (1H, d, *J* 9, CH*H*O), 2.00 (3H, d, *J* 1.5, CH_3C=C), 1.85 (1H, dd, *J* 14 and 6, C*H*HCH), 1.83 (1H, dd, *J* 14 and 6, CH*H*CH), 1.43–1.24 (1H, m, C*H*(CH_3)$_2$), 0.88 (9H, s, SiC(CH_3)$_3$), 0.81 (3H, d, *J* 6.5, CH_3CH), 0.79 (3H, d, *J* 6.5, CH_3CH), 0.03 (6H, s, 2×Si(CH_3)$_2$; δ_C (67 MHz; $CDCl_3$) 167.4 (CH), 152.1 (CH), 136.4 (C), 87.6 (C), 68.2 (CH_2), 41.4 (CH_2), 25.8 (CH_3), 24.8 (CH_3), 24.5 (CH_3), 24.2 (CH), 18.2 (C), 11.8 (CH_3), −6.0 (CH_3); *m*/*z* (ES^+) 282 (M^++1); ($C_{16}H_{32}NOSi$ requires 282.2253. Found 282.2267).

Typical procedure for the NaOCl oxidation of imines to *N*-chlorolactams and subsequent dechlorination

Sodium hypochlorite (2.5 mL of a 13% aqueous solution, 4.3 mmol) was added to a stirring solution of imine **9** (123 mg, 0.43 mmol) in MeOH (4 mL) at room temperature. After 2 h, water (5 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3×5 mL). The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the *N*-chlorolactam **14** in crude form. ν_{max}/cm^{-1} (film) 2954, 2926, 2780, 1716, 1470, 1257, 1121, 839 and 777; δ_H (400 MHz; $CDCl_3$) 6.67 (1H, m, C*H*C=C), 3.59 (2H, app s, CH_2O), 1.96 (3H, d, *J* 1.5, CH_3C=C), 1.70–1.50 (3H, m, CH_2CH and C*H*(CH_3)$_2$), 0.89 (3H, d, *J* 7.5, (CHCH_3), 0.86 (3H, d, *J* 6, (CHCH_3), 0.84 (9H, s, SiC(CH_3)$_3$), 0.02 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3); *m*/*z* (EI) 274 (100%, M^+−57); ($C_{12}H_{21}{}^{35}ClNO_2Si$ requires 274).

To effect dechlorination, the crude lactam **14** was dissolved in MeOH (4 mL), cooled to 0°C and acetyl chloride (0.13 mL, 1.72 mmol) was added dropwise. After 30 min the reaction was allowed to warm to room temperature. After stirring for 2 h, the solvent was removed in vacuo and the crude material was purified by flash column chromatography (SiO_2, EtOAc:MeOH (99:1)) to give the amide **15** (39 mg, 49%). ν_{max}/cm^{-1} (film) 3289 (br), 2954, 2925, 2869, 1682, 1644, 1467, 1365, 1237, 1168, 1068, 996 and 856; δ_H (400 MHz; $CDCl_3$) 7.73 (1H, br s, NH), 6.56 (1H, m, C*H*C=C), 3.66 (1H, d, *J* 11, C*H*HO), 3.45 (1H, d, *J* 11, CH*H*O), 1.84 (3H, d, *J* 1, CH_3C=C), 1.71–1.66 (1H, m, C*H*(CH_3)$_2$), 1.58–1.45 (2H, m, CH_2CH), 0.85 (3H, d, *J* 6.5, (CHCH_3), 0.84 (3H, d, *J* 6.5, (CHCH_3); δ_C (100

MHz; $CDCl_3$) 174.9 (C), 145.3 (CH), 135.1 (C), 77.3 (C), 67.3 (CH_2), 41.7 (CH_2), 24.7 (CH_3), 24.4 (CH_3), 23.9 (CH), 10.7 (CH_3); m/z (EI) 183 (M^+); ($C_{10}H_{17}NO_2$ requires 183.1259. Found 183.1248).

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15. Both thermal and photochemical (500 W lamp) methods were examined for this transformation, and although conversion of the nitrone **23** and the oxaziridine **22** to the lactam **8** was observed, we were unable to develop a reliable procedure suitable for work on a preparative scale.