CHEMoseLECTiVE REDUCTION OF LACTAMS TO TERTIARY AMiNES USING TRiBUtyLTiN HYDRiDE

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Abstract - The piperidone carbonyl in the tetracyclic oxindolic derivatives (1a-d) was chemoselectively deoxygenated in good to fair yields by reacting the derived alkylthioiminiums (3a-d) with tributyltin hydride.

The widely used reduction of lactams to amines with lithium aluminium hydride is strongly limited through lack of chemoselectivity of the reagent. There has been then proposed numerous alternative methods, which use milder reducing agents such as mixed aluminohydrides, boranes, borohydrides, or silanes. In another set of procedures, lactam is transformed into a more reducible group; apart from the reduction of thiolactams with Raney nickel or Al-Hg, most of these methods rest on preparation of a chloroimine, of an imino ether, or of a thioimino ether, followed by hydride reduction.

The aim of this work was to reduce the C-3 carbonyl group in compounds (1a-d) (Table) which are intermediates in the synthesis of aspidosperma alkaloids without affecting the other carbonyl functions present in the molecules. The problem is complicated by the easy overreduction of 4 to 5, due to a Grob fragmentation (arrows on 4) followed by reduction of the resulting iminium, and this constraint prohibits any reducing reagent with ionic character. The problem was solved in one case by Pakrashi through the Raney nickel reduction of a thiolactam (1e → 4e); under the conditions used in this work the oxindolic lactam group was not affected by sulfauration with Lawesson's reagent. In our hands however, while the closely related oxindole thiolactam (2c) with a free NH group was also easily prepared from 1c, it resisted to desulphurization with Raney nickel or with Al-Hg.
No example of reduction proceeding from a radical mechanism was apparently known in the literature; actually transformation into an alkylthioiminium followed by reaction with tributyltin hydride (TBTH)\textsuperscript{15} - a reagent known to reduce iminiums\textsuperscript{16} and to cleave C-S bonds\textsuperscript{17} - was found a highly chemoselective means of reducing piperidone lactam group in this series of compounds.

In a typical procedure, thiolactam (2a), obtained from 1a (Lawesson's reagent,\textsuperscript{19} 3 eq, benzene, refl, 3 h, 84%) is S-alkylated to imino thioether (3a) (Me\textsubscript{3}O BF\textsubscript{4}\textsuperscript{-}, 1 eq, CH\textsubscript{2}Cl\textsubscript{2}, 3 h, evapn, 100%), which is submitted to the reduction process without further purification. The reaction is completed in 15 h in refluxing THF in the presence of TBTH (2 eq) and of a catalytic amount of AIBN, to yield 4a (90%, calc. from 2a).\textsuperscript{20} In all experiments, the scale was 0.05 to 2 mmol units.

All four compounds (1a-d) gave good yields of thiolactams (2a-d). Their S-alkylation could be made faster (1 h) by using 3 eq of Meerwein's reagent. However, this variation could not be applied to 2d, as it induced some debenzylation of the ether group. In no case was O-alkylation of the much less reactive oxindole carbonyl observed.

Two eq of TBTH in THF were found necessary to perform the reduction of the alkylthioiminiums, in periods of time ranging from 4 to 15 h. With smaller quantities, the reaction was sluggish, while a larger excess paradoxally resulted in isolation of the starting lactam and of the intermediate thiolactam as by-products, thus revealing the intervention of a competitive non reductive process. The yields of the reduction of 3a-b and 3d were fairly good. In the c-series, the lower yield probably results from difficulties in extraction of the product.

It must be emphasized that these reactions always gave a mixture of interconvertible stereoisomers at C-7 and C-21, due to the already mentioned fragmentation.

Overcrowding of the piperidone carbonyl as in oxindole (6)\textsuperscript{11c} expectedly hindered its reduction by the above sequence: the thiolactam (7) was obtained in modest yield (52%) under forced conditions only (toluene, refl, 18 h). Larger times of reaction gave a mixture of 7 and of disulfurated derivative (8).\textsuperscript{22} Alkylthioiminium (9) could be prepared from 7, as evidenced by nmr, but it was not reduced by TBTH under the above conditions; here again, an excess of reagent regenerated the starting thiolactam (7).

In conclusion, reaction of alkylthioiminiums with TBTH and AIBN appears an efficient means of reducing a lactam group to a tertiary amine in the presence of an oxindolic ring system and of other functional groups such as an olefin, an ester or a benzylic ether. With regard to the high degree of chemoselectivity required by the model compounds used in this study, it is thought that the sequence will be useful in a number of other instances.
Table: Results

<table>
<thead>
<tr>
<th></th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Starting material 1</th>
<th>Thiolactams 2 (yield %)</th>
<th>Products 4 (isolated yields from 2)</th>
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<tr>
<td>a</td>
<td>H</td>
<td>Et</td>
<td>Et</td>
<td>1a&lt;sup&gt;18&lt;/sup&gt;</td>
<td>2a&lt;sup&gt;(84)&lt;/sup&gt;</td>
<td>4a&lt;sup&gt;(90)&lt;/sup&gt;, 1a&lt;sup&gt;(trace)&lt;/sup&gt;</td>
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<tr>
<td>b</td>
<td>H</td>
<td>Et</td>
<td>CH₂CH₂</td>
<td>1b&lt;sup&gt;21a&lt;/sup&gt; (*)</td>
<td>2b&lt;sup&gt;(90)&lt;/sup&gt;</td>
<td>4b&lt;sup&gt;(95)&lt;/sup&gt;, 2b&lt;sup&gt;(trace)&lt;/sup&gt;</td>
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<td>c</td>
<td>H</td>
<td>Et</td>
<td>(CH₂)&lt;sub&gt;2&lt;/sub&gt;CO₂Me</td>
<td>1c&lt;sup&gt;18&lt;/sup&gt; (*)</td>
<td>2c&lt;sup&gt;(86)&lt;/sup&gt;</td>
<td>4c&lt;sup&gt;(46)&lt;/sup&gt;, 2c&lt;sup&gt;(trace)&lt;/sup&gt;</td>
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<tr>
<td>d</td>
<td>H</td>
<td>(CH₂)&lt;sub&gt;2&lt;/sub&gt;O Buchanan</td>
<td>(CH₂)&lt;sub&gt;2&lt;/sub&gt;CO₂Me</td>
<td>1d&lt;sup&gt;21b&lt;/sup&gt; (*)</td>
<td>2d&lt;sup&gt;(77)&lt;/sup&gt;</td>
<td>4d&lt;sup&gt;(99)&lt;/sup&gt;</td>
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<td>e</td>
<td>Me</td>
<td>Et</td>
<td>(CH₂)&lt;sub&gt;2&lt;/sub&gt;CO₂Me</td>
<td>1e&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2e&lt;sup&gt;13&lt;/sup&gt;</td>
<td>4e&lt;sup&gt;13&lt;/sup&gt;</td>
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</table>

(*) : mixture of stereoisomers.
REFERENCES AND NOTES

14. Although the transformation 1c → 4c is reported (E.Ali, P.K.Chakraborty, and S.C.Pakrashi, *Heterocycles*, 1982, 19, 1367) through borohydride reduction of a chloroimine7, in our hands led
to 5c (50%), as the major product of the reaction.


20. Selected spectral data :
   2a : Ms (m/z) : 328(M+., C_{19}H_{24}ON_{2}S, 55%), 299(M+.C_{2}H_{5}, 100%) : uv \( \lambda_{\text{max}}{(\text{MeOH})} : 210, 270 \text{ nm} \); ir (neat) : 3200, 1700, 1610 cm\(^{-1}\); \(^1\)H nmr(300MHz, CDCl\(_3\), ppm) : 4.2,s,1H (C(21)-H); \(^{13}\)C nmr(75MHz, CDCl\(_3\), ppm) : 196.7(C-3), 179.7(C-2), 72.3(C-21).
   3a : \(^1\)H nmr(DMSO-d\(_6\), ppm) : 4.5,s,1H (C(21)-H), 2.9,s,3H (S-CH\(_3\));
   \(^{13}\)C nmr(DMSO-d\(_6\), ppm) : 74.7(C-21), 15.0(S-CH\(_3\)).
   4a : Ms (m/z) : 298(M+., C\(_{19}\)H\(_{25}\)ON\(_2\), 35%), 124 (100%) ;
   uv \( \lambda_{\text{max}}{(\text{MeOH})} : 215, 255, 285 (sh) \text{ nm} \).

21. Tetracyclic oxindoles (1b and 1d) were prepared as follows according to a modification of the general procedure by Harloe-Mason (L.Castedo, J.Harley-Mason, and M.Kaplan, *J.Chem.Soc.,Chem.Commun.*, 1969, 1444). 2-HT = 2-hydroxytryptamine

(a) for 1b :

(b) for 1d :

22. 2 : Ms (m/z) : 458 (M+., C\(_{24}\)H\(_{30}\)N\(_2\)O\(_5\)S, 80%), 430 (60%), 386(100%) ;
   uv \( \lambda_{\text{max}}{(\text{MeOH})} : 210, 280 \text{ nm} \); ir (neat) : 1720, 1710, 1610 cm\(^{-1}\);
   \(^{13}\)C nmr (CDCl\(_3\), ppm) : 198.4 (C-3), 178.5 (C-2), 70.6(C-21).
   8 : Ms (m/z) : 474 (M+., C\(_{24}\)H\(_{30}\)N\(_2\)O\(_4\)S\(_2\), 60%), 401 (40%), 300 (100%) ;
   uv \( \lambda_{\text{max}}{(\text{MeOH})} : 205, 235, 285, 325 \text{ nm} \); ir (neat) : 1725, 1610, 1460, 1430 cm\(^{-1}\);
   \(^{13}\)C nmr (CDCl\(_3\), ppm) : 206.0 (C-2), 199.1 (C-3), 72.2(C-21).

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