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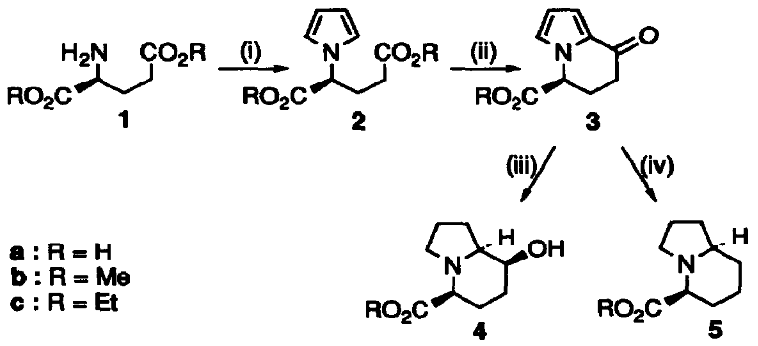
The Origins of Chemoselectivity in the Hydrogenation of Indolizidine Precursors

Timothy J. Bond, Robert Jenkins and Paul C. Taylor*

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK.

Abstract: It is proposed that the result of the hydrogenation of α-ketopyrrole **3b** depends on the relative rates of (a) hydrogenation of and (b) iminium ion formation from intermediate alcohol **8**.

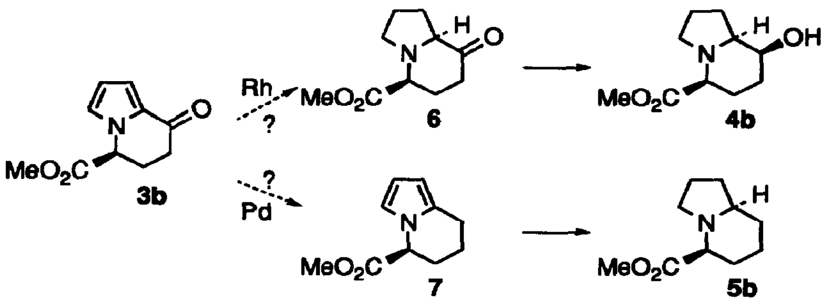
Optically pure building blocks **4** and **5**, for the synthesis of 5-substituted and 5,8-disubstituted indolizidines are now readily accessible in three steps from L-glutamic acid **1a**, or its commercially available alkyl ester hydrochlorides **1b** and **1c**, *via* a procedure developed independently by ourselves[1] and the group of Jefford.[2] We have found the conditions described by Jefford superior in avoiding racemisation in the first step,[3] but find TMSOTf more reliable for the intramolecular acylation of **2b** in the second step (this may not apply to **2c**). Both groups have found that palladium-on-carbon under acidic conditions catalyses highly diastereo- and chemo-selective hydrogenation of **3** to yield **5**. Furthermore, we have discovered that rhodium-on-alumina as catalyst, *in the absence of acid*, permits equally diastereo- and chemo-selective synthesis of the alternative hydrogenation product **4b**.



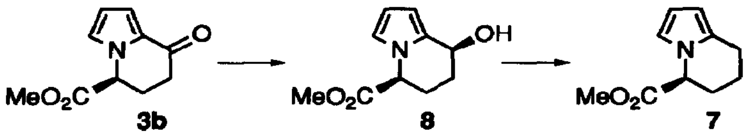
Scheme 1 *Reagents :* i, 2,5-dimethoxytetrahydrofuran;[1-3] ii, for R = H, HCl, MeOH, for R = Me, TMSOTf or BBr_3, for R = Et, BBr_3;[1,2] iii, H_2, Rh / Al_2O_3;[1] iv, H_2, Pd / C, H_2SO_4 or AcOH[1,2]

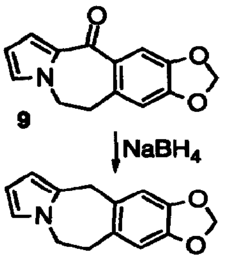
Although the high diastereoselectivity in the hydrogenation of compounds **3** was expected from literature precedent,[4] we were intrigued by the high degree to which the hydrogenation could be controlled by changing from palladium-on-carbon with acid to rhodium-on-alumina without acid. Our conclusions on the origins of this chemoselectivity are presented below. It is noteworthy that the group of Muchowski also found our palladium-on-carbon procedure[1] effective in fully reducing an α-ketopyrrole.[5]

Inspection of the hydrogenation products **4** and **5** led us to suspect that they arose from entirely different reaction pathways. We first proposed that with palladium, the ketone, while in conjugation with the pyrrole, was hydrogenolysed to the methylene compound **7** with subsequent hydrogenation of the pyrrole yielding **5b**. With rhodium we reasoned, reduction of the pyrrole might occur first, as the non-conjugated ketone of **6** would be most unlikely to be hydrogenolysed to **5b** but would instead proceed simply to the corresponding alcohol **4b**. To test this hypothesis we prepared the proposed intermediates **6** and **7** and submitted them to the hydrogenation conditions.



Swern oxidation of alcohol **4b** proceeded smoothly to yield proposed intermediate **6**.[6] As alcohol **8** was also an attractive substrate for our studies, we decided to prepare **7** *via* **8**. However, borane / dimethylsulfide reduction of **3b** was found to proceed directly to the methylene compound **7**.[7] A similar result was also found for sodium borohydride reduction of a seven-membered analogue **9**,[8] but reduction of the five-membered analogue **10** did stop at the alcohol stage.[9] These results can be rationalised if it is assumed that the second step of the reduction (CHOH to CH$_2$) proceeds from intermediate iminium ions **11**.[10] In the case of the five-membered analogue **10** strain would prohibit formation of the iminium ion.

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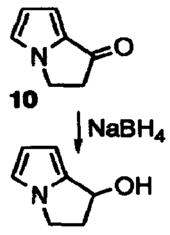
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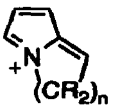
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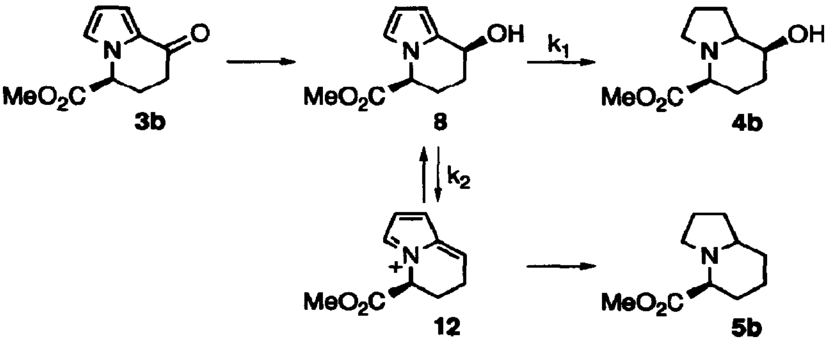
n = 2-4

The proposed intermediate **6** was not affected by our usual hydrogenation conditions with either catalyst. The other proposed intermediate **7** was partially reduced to **5b** with both rhodium-on-alumina (no acid) and palladium-on-carbon (with H_2SO_4) but much more slowly than with **3b** as substrate. We therefore conclude that neither compound **6** nor **7** is a likely intermediate in the hydrogenation of **3b** with either catalyst system. This information, along with the discovery that an iminium ion is a probable intermediate in the facile reduction of **3b** to **7**, led us to propose the following hypothesis.



With both catalysts, the first step is reduction of the ketone of **3b** to yield **8**. Alcohol **8** can undergo either reduction of the pyrrole to produce **4b** or elimination to produce the iminium ion **12**, the latter subsequently being further reduced to produce **5b**. We propose that k_1 is greater with rhodium-on-alumina than with palladium-on-carbon. The rate of elimination k_2 will clearly be accelerated in the presence of acid. This hypothesis is consistent with the observations that mixtures of **4b** and **5b** result both (a) when rhodium-on-alumina is used with acid and (b) when palladium-on-carbon is used without acid. The higher rate k_1 with rhodium-on-alumina is consistent with the known reluctance of palladium to reduce aromatic systems.[11]

We thus conclude that to selectively obtain **4** it is necessary to maximise k_1 (*ie*. use rhodium) and minimise k_2 (avoid acid) whereas if **5** is required one should minimise k_1 (use palladium) and maximise k_2 (use acid).

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3. Although it had originally been claimed that no racemisation occured during preparation of compounds **2** and their analogues (Kashima, C., Maruyama, T., Harada, K., Hibi, S., Omote, Y. *J.Chem.Res.*, **1988**, (*S*) 62; (*M*) 601), we remark that the optical purity of compounds **2a** and **2b**, when prepared using essentially the same conditions (ref. 1), varies from run to run (65% to >95% optical purity). We therefore recommend the aqueous conditions described in ref. 2.

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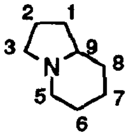
6. Compound **6** was prepared using a standard Swern oxidation (Omura, K., Swern, D. *Tetrahedron Lett.*, **1978**, *34*, 1651) in 55% yield: δ_H (CDCl$_3$ / 250MHz) 3.74 (3H, s, CO$_2$CH$_3$), 3.29 (1H, dd, J = 9.9, 3.8Hz, C(5)H), 3.21 (1H, dt, J = 8.1, 2.6 Hz, C(3)H$_{eq}$), 2.77 (1H, t, J = 7.8, C(9)H), 2.58-1.60 (9H, m, other CH$_2$ protons); δ_C (CDCl$_3$) 205.48, 172.30, 69.71, 64.31, 52.42, 37.91, 28.75, 22.68, 20.45 ppm.



7. Compound **7** was prepared using a literature method (Brown, H.C., Choi, Y.M. *Synthesis*, **1981**, 439) with dichloromethane (rather than THF) as solvent. The yield after column chromatography (silica gel, ethyl acetate: pet. ether 1:1) was 80%: δ_H (250MHz, CDCl$_3$) 6.51 (1H, m, C(3)H), 6.16(1H, m, C(1)H), 5.88 (1H, m, C(2)H), 4.76 (1H, m, C(5)H), 3.75 (3H, s, CO$_2$CH$_3$), 2.79 (2H, m, C(8)CH$_2$), 2.25 (2H, m, C(7)CH$_2$); δ_C (CDCl$_3$) 172.34, 128.85, 119.13, 108.22, 104.39, 57.11, 52.51, 27.24, 23.30, 18.82 ppm.

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