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HYDROGEN TRANSFER REDUCTION OF ISOFLAVONES

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Abstract —— Hydrogen transfer reduction of isoflavones using ammonium formate and palladium charcoal provides an easy access to polyoxyisoflavanones and also to isoflavan-4-ols without the need for protection of the hydroxy groups. Optimized reaction conditions for improved isoflavanone yields are also discussed.

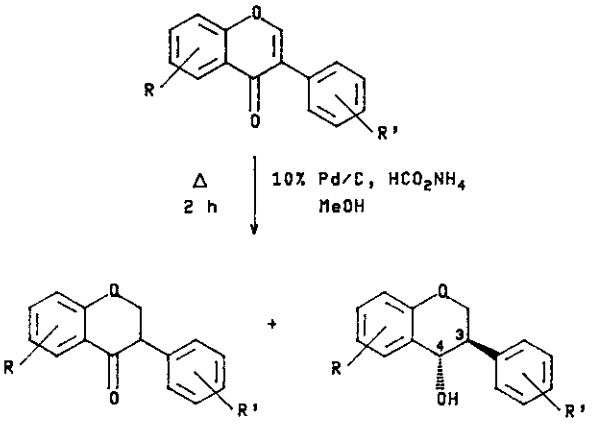
Reductions of isoflavones have usually been carried out using catalytic hydrogenation but those reactions seem to be difficult to control. Isoflavanones, isoflavenes, occasionally both cis- and trans-isoflavan-4-ols, and isoflavans may be formed, the latter usually as the main products. The effect on selectivity of solvent, pH and catalyst carrier has been thoroughly studied, certain selectivity being attainable for example by the utilisation of the slow reaction rate in dioxane solution. The results published by various workers are however contradictory to a large extent.[1-6]

Catalytic hydrogenation apparently requires the protection of phenolic hydroxyl groups but Krishnamurty and Sathyanarayana[7] have recently published a method for the hydrogen transfer reduction of unprotected hydroxyisoflavones using 10% Pd/C catalyst and ammonium formate as the hydrogen source. The reduction is reported to give a ~50% yield of the isoflavanone and ~50% of recovered starting material after refluxing for 3-4 h in methanol. The ratio of products remained the same despite the fact that excess catalyst, donor or a high temperature was used in some experiments.

In our hands this reaction behaved somewhat differently.[8] Using a number of substituted isoflavones, we found that even after a very short reaction time, also at room temperature, there was no starting material left. In addition to the isoflavanone, always the major product, there was in each case a byproduct present with a similar R_F to the starting isoflavone. However, phosphomolybdic acid staining and other visualisation techniques indicated that this compound was not the starting isoflavone. The byproducts are trans-isoflavan-4-ols (Scheme 1), as characterized by HRMS, ^{1}H nmr ($J_{3,4}$= 7 Hz[9]) and ms (M^+ weak, $M-H_2O$, and RDA fragmentation giving the base peak). These compounds are readily autoxidized and undergo a range of degradation reactions making the isoflavanols quite difficult to isolate.

A moderate temperature and a short reaction time give best isoflavanone yields. Reduction of polyoxyisoflavones proceed considerably faster than that of less substituted isoflavones. Reducing 7-hydroxy-4'-methoxy-, 5,7,4'-trihydroxy- or 5,7-dihydroxy-4'-methoxyisoflavone at room temperature affords the corresponding isoflavanone in about 90% yield. Upon prolonged refluxing the isoflavanol byproducts disappear to give rise to the ring opened ketones, possibly by a hydride shift mechanism (Scheme 2).

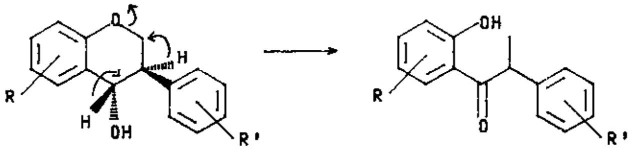
We also established that isoflavanones are stable under the hydrogen transfer reduction conditions. Therefore it seems that the isoflavanol can only arise by way of the isoflav-2-en-4-ol, presumably reduced as fast as formed and hence unisolable. This transfer hydrogenation reaction pathway is unusual as it implies that the carbonyl group is in this instance reduced in preference to the double bond, possibly because of the enol ether nature of the latter.



Starting material	Isoflavanone	Isoflavanol
	Yield % [a]	Yield % [a]
7-Hydroxyisoflavone	60 (53)[b]	19
7,4'-Dihydroxyisoflavone	52	13
7-Hydroxy-4'-methoxyisoflavone	53	14
7,4'-Dihydroxy-3'-methoxyisoflavone	53	16
5,7,4'-Trihydroxyisoflavone	59	21

a: Isolated yield.
b: lit. yield (7).

Scheme 1.



Scheme 2.

ACKNOWLEDGEMENT

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8. An isoflavone (1 mmol) was dissolved in methanol (20 ml). To this was added 10 % Pd/C (Fluka, 0.255 g) and ammonium formate (4 mmol). The mixture was then stirred at room temperature or refluxed. The reaction was monitored by TLC and/or nmr. After the reduction the Pd/C was removed by filtration and the solvent evaporated, furnishing the corresponding isoflavanone, or a mixture of the isoflavanone and the isoflavan-4-ol. Mixtures were separated by flash chromatography on silica gel.
9. Cis-isoflavan-4-ol $J_{3,4}$= 2.9-3.2 Hz and trans-isoflavan-4-ol $J_{3,4}$= 5.0-7.4 Hz. S. Yamaguchi, S. Ito, A. Nakamura, and N. Inoue, Bull. Chem. Soc., Japan, 1965, 38, 2187 and J.W. Clark-Lewis, Aust. J. Chem., 1968, 21, 2059.

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