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Hydrogenolysis of amide acetals and iminium esters.

Renat Kadyrov*

Abstract: Amide acetals and iminium esters were hydrogenated into amines under very mild reaction conditions over common hydrogenation catalysts. This finding provide new strategy for selective amide reduction. The synthetic utility of this approach was demonstrated by selective reduction of amides bearing ester and nitrile groups.

The reduction of amides with alumina- and borohydrides is one of the most frequently used methods for production of amides and often is a key step in the synthesis of natural products and pharmaceutical ingredients. [1, 2] The development of catalytic reduction with hydrogen [3] continues to be one of the greatest challenges as many publications over the last few years show. [4]

In the course of our studies on reductive amination we have concluded that the reactions proceed mainly via hydrogenolysis of the intermediary formed hemiaminals. [5] Therefore it appears likely that hydrogenolysis of the amide acetals should proceed at significantly milder conditions than direct hydrogenation of amides. In fact, the first experiments showed that commercially available N,N-dimethyl-formamide and acetamide dimethyl acetals could be efficiently converted into trimethylamine and dimethyl-ethylamine over most hydrogenation catalysts. The generality of this approach was proven by smooth hydrogenolysis of the easily available amide acetals and iminium esters under mild conditions (5 bar H₂ pressure, ambient temperature, 30 min) over common hydrogenation catalysts such as Pd/C, Pd/Al₂O₃, Pd/CaCO₃, Pt/C, Ru/Al₂O₃ and [(dppb)Rh(cod)]BF₄. For example, N-methyl-2,2-dimethoxy-pyrrolidine (**3**) and 2-ethoxy-2-methyl-3-benzyl-oxazolidine (**5**) could be efficiently converted into N-methylpyrrolidine (**4**) and N-benzyl-2-(ethylamino)ethanol (**6**), using Pd-, Pt-, Ru and Rh-based catalysts. It should be noted, that the hydrogenation completed in all reactions given in Table 1. The yields of amines obtained after 30 min of hydrogenation illustrate some differentiation in the catalyst performance. Although amide acetals are known since decades they have been reduced in the past with complexes hydrides. [6] In contrast to reduction with hydrides the hydrogenation of the amide acetals lead almost always to reduction of the amide function only, however nitro-group and in some cases double bond are also reduced at these conditions.

In view of the moisture sensitive nature of the amide acetals the wet catalysts should be dried before use. It was found in the hydrogenolysis of N-methyl-2,2-dimethoxy-pyrrolidine (**3**) that

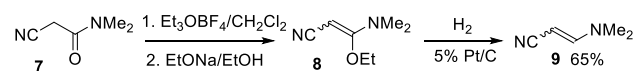
Pd/C catalysts were recyclable with no appreciable loss of activity for three repeated runs, indicating that the catalyst is not only reusable but also has a low level of catalyst leaching. The metal content measured in the reaction medium in all cases was below detection limit and no hydrogen uptake was observed if to the filtered solution from previous run fresh imide acetale was added and so obtained solution was pressurized with hydrogen. These facts clearly prove that the reaction runs over heterogeneous catalysts.

Table 1. Yields of amines after 30 min hydrogenation [a]

Acetal	MeC(OMe) ₂ NMe ₂ 1	 3	 5
Product	EtNMe ₂ 2	 4	BnEtN-CH ₂ -CH ₂ -OH 6
5%Pd/C	91	92	90
5%Pd/Al ₂ O ₃	96	74	60
5%Pd/CaCO ₃	93	69	45
5%Pt/C	92	96	92
5%Ru/Al ₂ O ₃	80	76	42
[(dppb)Rh(cod)]BF ₄	96	95	97

[a] Conditions: Amide acetal (20mmol), catalyst (1 mol%), 20 mL MeOH or EtOH, 5 bar H₂, 25 °C, 30 min. Amines (**2**) and (**4**) were isolated as hydrochlorides, N-benzyl-N-ethyl-amonoethanol (**6**) was isolated by distillation in vacuum.

Iminium salts derived from amides which contain acidic α-CH groups readily undergo elimination by the addition of alkoxides with the formation of ketene O,N-acetals. [7] When 3-dimethylimino-3-ethoxyacrylonitrile (**8**) prepared from N,N-dimethylcianoacetamide (**7**) according to the known procedure [7a] was hydrogenated over Pt/C enamine (**9**) was obtained in practical yield under maintenance of nitrile functional group (Scheme 1)



Scheme 1. Reduction of N,N-dimethylcianoacetamide.

Remarkably imidoesters could be transferred also into amines directly (Table 2). The catalyst screening showed that for hydrogenolysis of imidoesters the platinum based catalysts are the catalysts of choice. It is interesting to note, that hydrogenolysis of imidoesters derived from primary amides delivers a secondary amine as the main product.

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Table 2. Yields in the Hydrogenolysis of Imidates. [a]

Imidate	Amine	Yield, %
		86
		84
		85
		60
		19
	$(C_5H_{11})_2NH$ 20	68
	$(C_5H_{11})_3N$ 21	20
	Bn_2NH 23	85

[a] Conditions: Imidoester (20 mmol), 5% Pt/C (1 mol%), 20 mL MeOH or EtOH, 10 bar H_2 , 25 °C, 16 h.

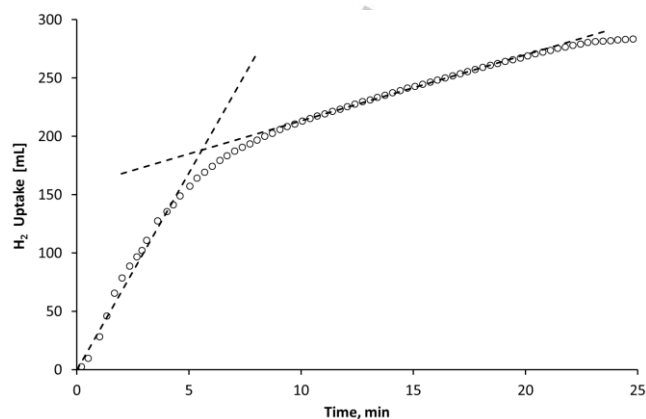
Next amides **24**, **26** and **28** were transformed into alkoxyiminium salts by O-alkylation with $(Et_3O)BF_4$ and amide acetals were generated "in situ" by mixing with alcoholic EtONa solution. In the case of amide **28** bearing nitrile-group, the reaction with EtONa should be done under alcohol-free conditions. Obtained solutions were directly hydrogenated without time-consuming procedure for isolation of amide acetals. The hydrogenation over 5% Pt/C proceeds well delivering amines in practical yields (Table 1), under maintenance of ester and nitrile moieties.

Table 3. Isolated Yields in the Reduction of Amides. [a]

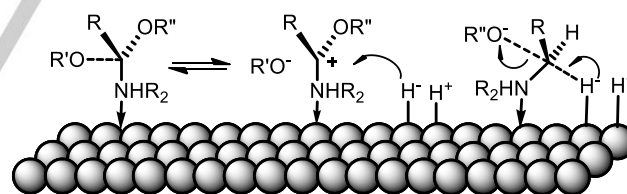
Amide	Amine	Conditions	Yield, %
		A	68
		A	51
		B	44

[a] Conditions: A: amide (20 mmol), $(Et_3O)BF_4$ (21 mmol), CH_2Cl_2 , 16 h, 5% Pt/C (1 mol%), EtONa (20 mmol), EtOH, 10 bar H_2 , 25 °C, 16 h; B: amide (50 mmol), $(Et_3O)BF_4$ (55 mmol), CH_2Cl_2 ; 16 h, EtONa (50 mmol), Et_2O ; 5% Pt/C (0.2 mol%) 10 bar H_2 , 25 °C, 16 h;

Figure 1 illustrates the hydrogen uptake as a function of time in the hydrogenolysis of N-methyl-2,2-diethoxyproline (**30**) over Pt/C at 25 °C and 5 bar of hydrogen pressure. Generally, the hydrogenolysis of amide acetals over heterogeneous catalysts follows almost zero order kinetics. Zero-order reactions are typically observed when a surface of the catalyst is saturated by the reactants. [8]

**Figure 1.** Hydrogen uptake in the hydrogenolysis of N-methyl-2,2-diethoxyproline (**30**) (6 mmol) in 6 mL of EtOH over 5% Pt/C (1 mol%) at 5 bar.

By acetalization, the amide function is transformed into an amine which exhibits a high affinity to metal complexation. Therefore it is likely that hydrogenolysis takes place on the metallic surface as a nucleophilic substitution. (Figure 2) In this process each alkoxy group is substituted by a hydride-ion in two subsequent steps. It is noticeable that the second step – hydrogenolysis of N,O-acetale – proceeds much slower than the first step on platinum surface. The first step is facilitated largely by dissociation of the amide acetals [9] (Figure 2). This explains why the hydrogenolysis of imidoesters derived from primary amides over platinum deliver mainly secondary amines.

**Figure 2.** Two steps in the hydrogenolysis of the amide acetal over hydrogenation catalysts.

For the first time it was demonstrated that amide acetals and iminium esters could be hydrogenated to amines at very mild conditions (at ambient temperature, the hydrogenation completed in 10–120 min at 5–10 bar hydrogen pressure) over commercially available hydrogenation catalysts. Amide acetals and iminium esters are easily available via O-alkylation of acid amides. [10] Taking advantage of a new approach established by this research effort, a simple and general method is now available for highly selective conversion of amides into amines.

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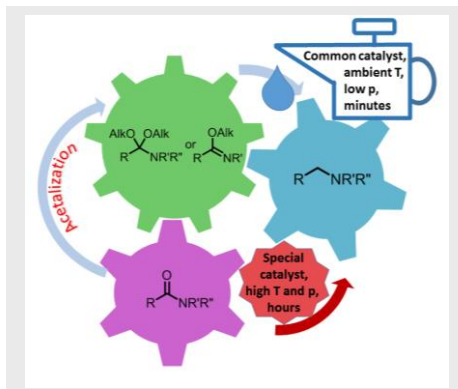
Keywords: Amide • Amine • Hydrogenation • Amidacetale • Imidoester

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Entry for the Table of Contents

COMMUNICATION

Amide acetals and iminium esters were hydrogenated into amines under very mild reaction conditions over common hydrogenation catalysts. Taking advantage of this approach and applying known procedures for the formation of amide acetals and iminium esters by O-alkylation of amides, a simple and general approach is now available for highly selective conversion of amides into amines.



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Page No. – Page No.

Reduction of amides I.
Hydrogenolysis of amide acetals and iminium esters