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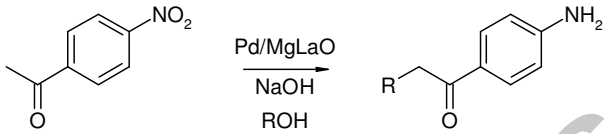

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Palladium-catalysed transfer hydrogenation of aromatic nitro compounds – an unusual chain elongation

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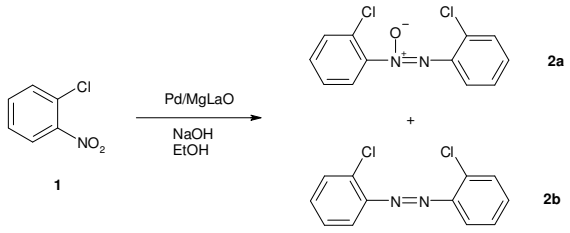
ABSTRACT

Aromatic nitro compounds are reduced via transfer hydrogenation in the presence of palladium on magnesium-lanthanum mixed oxide support in ethanol yielding the corresponding amines. With several acetophenone derivatives, the reduction was accompanied by chain elongation while the carbonyl group remained intact.

Palladium-catalysed cross-coupling reactions[1-6] have become very important synthetic tools for the preparation of functionalised aromatic compounds. A number of palladium complexes as well as ligands have been reported for this purpose.[7] Besides homogeneous methods, heterogeneous examples are very important, since in these cases the catalysts can be removed easily. They can often be reused, and in some cases the addition of ligands – the separation of which from the products is sometimes tedious – is not necessary.[8-10]

In the course of our research in the field of heterogeneous catalysis a new supported metal catalyst was developed. This Pd^0 on Mg-La mixed oxide (Pd/MgLaO) was successfully applied in Heck,[11] Sonogashira[12] and Suzuki[13] reactions. No measurable leaching of Pd was observed and the catalyst could be reused several times.

Continuing this work we investigated another known Pd-catalysed cross-coupling reaction, the Hiyama-coupling. Good results were obtained only when aryl iodides in THF and tetrabutylammonium fluoride (TBAF) as the base were used. When the base was replaced with NaOH, instead of the expected coupling, dehalogenation of the aryl halide was observed. Moreover, in the reaction of 2-chloronitrobenzene (**1**) in ethanol in the presence of NaOH, reduction of the nitro group occurred. Depending on the reaction conditions, the known intermediates,[14,15] 2,2'-dichloroazoxybenzene (**2a**) and 2,2'-dichloroazobenzene (**2b**) (Scheme 1) or 2-chloroaniline were obtained.



Scheme 1. Transfer hydrogenation of 2-chloronitrobenzene.

As aromatic amines can be useful intermediates for the synthesis of important organic compounds, and a simple method for their preparation is via the reduction of aromatic nitro compounds, these results led us to examine this reaction further. From the reaction conditions used, a transfer hydrogenation process would be expected. To check this hypothesis, nitrobenzene was refluxed in ethanolic sodium hydroxide in the presence of Pd/MgLaO and the reaction mixture was subjected to GC-MS analysis. The trace showed aniline, azoxybenzene,

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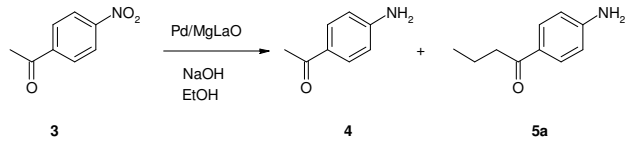
azobenzene, acetic acid, and some other compounds which could have originated from base-catalysed reactions of acetaldehyde. This evidently proved a transfer hydrogenation reaction had occurred where the alcohol solvent served as the hydrogen source and was oxidised to the aldehyde and further to the acid. In the literature, examples can be found of dehalogenation reactions in which an alcohol served as the hydrogen source in a transfer hydrogenation process.[16-20]

We next examined the reactions of different substituted nitrobenzenes. Surprisingly, in the reaction of 4-nitroacetophenone (**3**) in boiling ethanol, in the presence of three equivalents of NaOH a new compound was also formed. Based on the mass spectrum and ^{1}H NMR spectroscopic examination this compound was 4-aminobutyrophenone (**5a**) (Scheme 2). This indicated that the nitro group was reduced and the alkyl chain of the acetophenone was extended with two carbon atoms whilst the carbonyl function remained intact. The obtained yield of this new compound depended strongly on the amount of alcohol and the reaction time (Table 1).



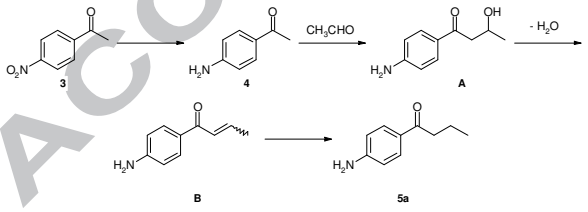
Scheme 2. Reaction of 4-nitroacetophenone in ethanol.

Table 1. Reaction of 4-nitroacetophenone in ethanol.[a]

Entry	Ethanol (ml)	Time (h)	Yield (%)[b]
1	3	6	**4** (29), **5a** (61)
2	3	12	**4** (48), **5a** (46)
3	3	24	**4** (69), **5a** (21)
4	10	24	**5a** (~100)

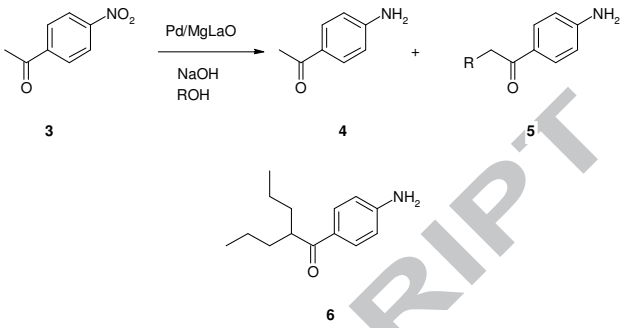
[a]5 mmol **3**, 0.2 g catalyst, 0.6 g NaOH, reflux
[b]Based on GC-MS analysis of the reaction mixture

The following mechanism is proposed for this reaction (Scheme 3). After the reduction of the nitro group, an aldol-type reaction of the acetophenone and the aldehyde derived from the alcohol occurs. This is followed by the dehydration of intermediate β-keto-alcohol (**A**), and the final product is formed by reduction of the olefinic double bond of **B**. In the GC-MS spectra of the reaction mixture, a small amount of **B** was found, which further supported this mechanism.



Scheme 3. Proposed mechanism for the reduction and chain elongation.

On examining other alcohols[21] (Table 2) in this reaction, we obtained good results with primary alcohols having at least two carbon atoms. In methanol or isopropanol, 4-aminoacetophenone (**4**) was obtained. In *n*-propanol, a significant amount of 1-(4-aminophenyl)-2-propylpentan-1-one (**6**) (Scheme 3) was formed via the addition of two propyl groups onto 4-aminoacetophenone. In *n*-butanol and *i*-butanol the respective chain-elongated products were obtained in good yields. In longer-chain alcohols, reduction of the nitro group occurred, but the chain-elongated products were not observed.



Scheme 3. Reaction of 4-nitroacetophenone in different alcohols.

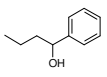
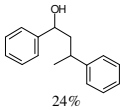
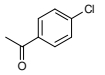
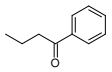
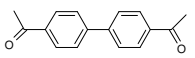
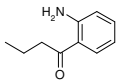
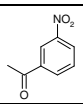
Table 2. Reaction of 4-nitroacetophenone with different alcohols.[a]

Entry	ROH	Time (h)	Yield (%)[b]
1	MeOH	24	**4** (84), **5b** (16)
2	*n*PrOH	24	**4** (20), **5c** (42), **6** (33)
3	*i*PrOH	12	**4** (~100)
4	BuOH	24	**4** (25)**, 5d** (73)
5	*i*BuOH	24	**4** (16)**, 5e** (75)

[a]5 mmol **3**, 0.2 g catalyst, 0.6 g NaOH, 10 ml alcohol, reflux
[b]Based on GC-MS analysis of the product

We also investigated the reactions of other acetophenones as well as benzaldehyde derivatives. The results are summarized in Tables 3 and 4, respectively.

Table 3. Reactions of different acetophenones with ethanol.[a]

Entry	Ketone	Product[b]		
1		 26%	 15%	 24%
2		 10%	 65%	 19%
		 <5%		
3		 6%	 67%	 27%
4		-[c]		

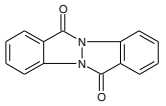
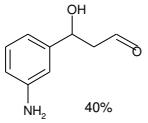
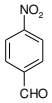
[a]5 mmol ketone, 0.2 g catalyst, 0.6 g NaOH, 10 ml ethanol, 24 h, reflux
[b]Relative yields based on GC-MS analysis
[c]No identifiable product was obtained

In the reaction of acetophenone, mainly 1-phenyl-1-butanol, 1-phenylethanol and the acetophenone dimer, 1,3-diphenylbutan-1-ol (Table 3, entry 1) were obtained. 4-Chloroacetophenone gave only dehalogenated products: acetophenone, 1-phenylethanol, and small amounts of the chain-elongated ketone

and C-C coupled 1-[4'-acetyl(1,1'-biphenyl)-4-yl]ethanone (Table 3, entry 2). 2-Nitroacetophenone gave mainly 2-aminoacetophenone and a small amount of the desired product (6%) and 4-methylquinoline (Table 3, entry 3). In the reaction of 3-nitroacetophenone no isolable product was obtained.

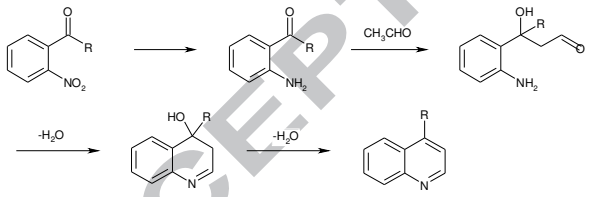
Aldehydes did not give the corresponding chain-elongated products. In the reaction of 2-nitrobenzaldehyde the dimer of 2-aminobenzaldehyde was obtained as the major product, along with quinoline (Table 4, entry 1). From the reaction of 3-nitrobenzaldehyde only the addition product of 3-aminobenzaldehyde and acetaldehyde could be identified (Table 4, entry 2). 4-Nitrobenzaldehyde gave an undefiniable product mixture.

Table 4. Reaction of different nitrobenzaldehydes with ethanol.[a]

Entry	Aldehyde	Product[b]	
1		 82%	 18%
2		 40%	
3		- [c]	

[a] 5 mmol aldehyde, 0.2 g catalyst, 0.6 g NaOH, 10 ml ethanol, 24 h, reflux
[b] Relative yield based on GC-MS analysis of the product
[c] No identifiable product was obtained

The formation of the quinoline derivatives can be explained by the reaction of the intermediate amino-carbonyl compound with acetaldehyde, to give an aldehyde which undergoes intramolecular cyclization (Scheme 4). This mechanism is supported by the product obtained in the reaction of 3-nitrobenzaldehyde (Table 4, entry 2).



Scheme 4. Proposed mechanism for the formation of quinoline derivatives.

Taking into account that the quinoline derivatives were obtained in only small amounts, their formation does not contradict the mechanism depicted in Scheme 2.

In conclusion, we have described an interesting heterogeneous catalytic method for the chain elongation of 4-nitroacetophenone with simultaneous reduction of the nitro group. The carbonyl group remained intact under the reported reaction conditions.

References and notes

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21. Reduction and chain elongation: A mixture of 4-nitroacetophenone (0.83 g, 5 mmol), NaOH (0.6 g), Pd/MgLaO (0.2 g) and the appropriate alcohol (10 ml) were stirred at 120 °C (bath temperature) for 24 hours. The mixture was filtered, the solid washed with MeOH and the filtrate concentrated in vacuum. The residue was dissolved in Et_2O and H_2O. Dilute HCl (25%) was added until pH 1. The two phases were separated and the aqueous phase basified to pH 8 by adding $NaHCO_3$. The aqueous phase was extracted with Et_2O (2 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuum. The products were purified by column chromatography (Kieselgel, hexane:acetone, 4:1). All products exhibited satisfactory spectral data (^{1}H NMR, mass spectra).[22]
22. Selected spectroscopic data: 1-(4-aminophenyl)butan-1-one (**5a**): ^{1}H NMR ($CDCl_3$, 300 MHz): 0,9 (t, *J*=7.6 Hz, 3H), 1,66 (m, 2H), 2,76 (t, *J*=7.6 Hz, 2H), 3,91 (br s, 2H), 6,56 (d, *J*=8.6 Hz, 2H), 7,73 (d, *J*=8.6 Hz, 2H); MS *m/z*(%):163 (M^+, 15), 135 (80%), 120 (100%), 92 (27%), 65 (22%); 1-(4-Aminophenyl)hexan-1-one (**5d**): ^{1}H NMR ($CDCl_3$, 300 MHz): 0.88 (t, *J*=7.6 Hz , 3H), 1.33 (m, 2H), 1.69 (m, 2H), 2.83 (s, 2H), 4.02 (br s, 2H), 6.62 (d, *J*=8.6 Hz, 2H), 7.79 (d, *J*=8.6 Hz, 2H); MS *m/z* (%):191 (M^+, 2), 148 (3), 135 (80), 120 (100), 92 (25), 65 (22); 1-(4-Aminophenyl)-2-propylpentan-1-one (**6**): ^{1}H NMR ($CDCl_3$, 300 MHz, crude product): 0.92 (t, *J*=7.5 Hz, 6H), 1.38 (m, 4H), 1.85 (m, 4H), 3.52 (m, 1H), 4,05 (br s, 2H), 6.64 (d, *J*=8.6 Hz, 2H), 7.75 (d, *J*=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz): 14.9, 22.8, 26.7, 36.1, 128.8, 133.1, 138.2, 150.6, 201.4; MS *m/z* (%): 219 (M^+, 1), 148 (9), 135 (100), 120 (85), 92 (22), 65 (18).