Mild catalytic multiphase hydrogenolysis of benzyl ethers

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A preliminary study was conducted on the multiphase (aqueous KOH–isooctane–Aliquat® 336) hydrogenolysis of benzyl methyl ether using Pd/C, Pt/C and Raney-Ni as catalysts, under mild conditions ($T = 50$ °C, $pH_2 = 1$ atm). Using ethanol as solvent, the Pd/C system is very efficient, while the same catalyst under multiphase conditions is almost inactive. With Pt/C, the reaction is always sluggish, and ring hydrogenation kicks in under multiphase conditions. The Raney-Ni system has an opposite behavior, while debenzylation is slow in ethanol, under multiphase conditions the reaction is quite fast. Other *O*-benzyl protected substrates undergo debenzylation with Raney-Ni as well, with varying chemoselectivity.

Introduction

The multiphase system[1] made by hydrogen, an aqueous phase, isooctane, a phase transfer (PT) agent (*e.g.* Aliquat® 336, A336), and a heterogeneous catalyst (*e.g.* Pd/C, Pt/C) allows a variety of reduction reactions to be conducted under mild conditions ($T = 50$°C, $pH_2 = 1$ atm), *e.g.*; hydrodehalogenation of aryl halides,[2–6] hydrogenation of carbonyls,[7] hydrogenolysis of hydroxyls,[7] up to aromatic hydrogenation.[7,8] For substrates liable to multiple reductions, selectivity can be achieved by tuning the multiphase system, in order to favor one over the other of the possible reaction pathways.[9,10] Recently Raney-Ni was found to be active for hydrodehalogenation and hydrogenation reactions under multiphase conditions as well.[11] The multiphase system proves advantageous over monophasic ones, as demonstrated in a number of instances,[10] in particular for the case of Raney-Ni, where in the absence of A336, or of the alkaline aqueous phase, the reactions are inhibited.[11]
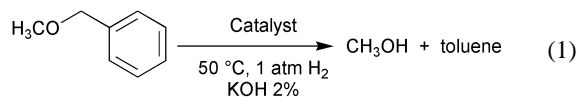
From the green chemistry standpoint, heterogeneous catalysis is an attractive synthetic tool, particularly: when it allows to selectively (chemo-, regio-, stereo-) conduct different transformations by tuning some simple reactions parameters, when the reaction conditions are easily accessible (*e.g.* low temperature and pressure), when the catalyst system can be conveniently recovered and recycled, and when the product can be easily separated. The positive features of heterogeneous catalysis can be improved by using an aqueous-organic biphasic solvent mixture.[12] Such mixtures provide a built-in method for product isolation and catalyst recycling (phase separation instead of distillation), resulting in fewer by-products. When the substrate forms a separate organic phase, the need for an organic solvent can be eliminated altogether, and aqueous–organic biphasic processes allow tuning of selectivity by proper manipulation of the pH of the aqueous phase. Further advantages for biphasic heterogeneous catalytic systems can be obtained by modifying the heterogeneous catalyst with phase transfer (PT) agents. In fact, in such a multiphase catalytic reduction system it is possible to conduct a variety of reduction reactions under mild conditions and with interesting chemo-, regio- and stereo-selectivities.

Results and discussion

To expand the synthetic applicability of this multiphase reduction system, we carried out a preliminary exploration of the hydrogenolysis of benzyl ethers, in view of its use for the selective deprotection of benzyl (Bn) protected alcohols. One common method for the cleavage of Bn protected hydroxyl groups is catalytic hydrogenolysis.[13] Palladium on charcoal (Pd/C)[14–17] and Raney-Ni[14,18] are among catalysts used, the solvent is generally ethanol, and the hydrogen pressures are often high for Raney-Ni.[14] Selectivity is an issue since other reduction-sensitive functional groups present in the molecule may be hydrogenated.

Benzyl methyl ether was chosen as the model substrate (eqn. (1)), to compare the activity of different catalysts (Pd/C, Pt/C, Raney-Ni), with and without A336, under the standard multiphase conditions.[10,11]

$$H_3CO \diagdown \bigcirc \xrightarrow[\substack{50\ °C,\ 1\ atm\ H_2 \\ KOH\ 2\%}]{\text{Catalyst}} CH_3OH + toluene \quad (1)$$

The results are reported in Table 1. In the usual hydrogenolysis conditions, with ethanol as solvent, Pd/C was very active for the debenzylation of benzyl methyl ether, and benzyl methyl ether was quickly and quantitatively reduced to toluene (entry 1). By contrast, using the multiphase conditions, with A336 and a basic aqueous medium, the reaction was practically inhibited (entry 2); while it was a little faster by removing A336 (entry 3). The trend was the same using Pt/C, although the reaction was slower in all cases; *i.e.* the reaction in ethanol

Green Context

Multiphase reaction systems have proven to be useful in a number of important synthetic transformations and those involving hydrogen have been shown to be effective under mild conditions. Here the multiphase hydrogenolysis of benzyl methyl ether with different catalytic systems is studied. Particularly significant is the observation that the relatively inexpensive Raney-Ni system is effective for debenzylation under such conditions while simpler systems require Pd/C as catalyst. The methodology enables difficult transformations to be carried out under mild conditions, with a less expensive catalytic system and allowing easy catalyst recovery and reuse. *JHC*

proceeded (entry 4), with the multiphase system it did not (entry 5), and with the multiphase system and no A336 it proceeded only very slowly (entry 6).

Ra-Ni behaved in a manner opposite to Pd/C. It reacted sluggishly in ethanol as solvent (entry 7) where, after almost 4 h, conversion was only 37%. In the multiphase system, without A336 the reaction appeared still inhibited (entry 9). By contrast, with A336, Ra-Ni promoted quick hydrogenolysis of benzyl methyl ether (entry 8), yielding complete conversion after 2.5 h, far better than Pd/C and Pt/C under the same multiphase conditions.

To explain this behavior, a surfactant type effect of A336, able to increase catalyst availability, was ruled out, since preceding studies had indicated that phase transfer agents, such as A336, do not act like surfactants. This was also verified by replacing A336 with sodium dodecyl sulfate (SDS), and observing that the reaction was once again slow (entry 10). These observations are in line with a preceding hypothesis on the mode of action of A336, where it coated the catalyst particles, causing a change of the catalytic environment in a way that promoted the activity and the chemoselectivity of the reactions.[1,9,19]

To explore whether chemo- and/or regio-selective deprotection of the benzyl group was possible with the Raney-Ni/A336 system, a series of available benzyl ethers were subjected to the conditions of entry 8 of Table 1. The results are reported in Table 2. The double bond of allyl benzyl ether was rapidly hydrogenated to benzyl propyl ether (entry 1), as could be expected due to its reactivity, followed by debenzylation, to yield propanol. Nopol benzyl ether instead, with a more hindered double bond respect to the preceding case, underwent faster debenzylation initially (entry 2), followed by double bond hydrogenation, to yield a 1:2 mixture of nopol and dihydronopol after 5 h. Tri-*O*-benzylglucal was totally debenzylated after 4 h (entry 3), as indicated by the production of three equivalents of toluene. No regioselectivity was observed in this case, and the product could not be identified.

Benzyl phenyl ether was very rapidly debenzylated to phenol (entry 4). Instead, *O*-benzyloxy-3-phenylpropanal first underwent slow carbonyl reduction, followed by even slower debenzylation (entry 5). The chemoselectivity was therefore totally towards carbonyl reduction.

However, BOC-*O*-benzylserine (BOC = benzyloxycarbonyl) could be chemoselectively deprotected to yield BOC-serine after 2.5 h (entry 6), showing that the BOC protecting group is stable under the reported multiphase conditions.

Previous studies had indicated that Pd/C is a more active reduction catalyst than Raney-Ni under multiphase conditions for the hydrodechlorination of chlorobenzenes,[5] while Raney-Ni is more active, provided A336 is present, in the hydrodebromination of bromobenzenes.[5] The observed activity of the Raney-Ni/A336 multiphase system for the hydrogenolysis of benzyl ethers, and the opposite behavior of Pd/C, is another case of changes in the chemoselectivity produced by modifications of a component of the catalytic multiphase system (in this case the catalyst).
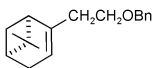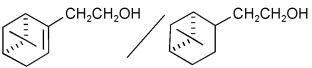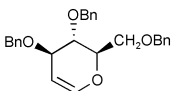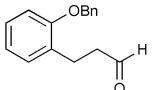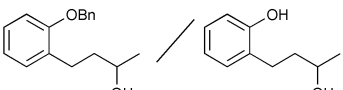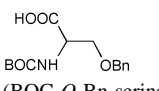
This study evinces that Raney-Ni is active in the hydrogenolysis of benzyl ethers under multiphase conditions, albeit not as active as Pd/C in ethanol. In particular, benzyl hydrogenolysis is possible in the presence of the BOC group, which is instead stable under the investigated conditions. Further studies will be aimed to determine whether the system could prove advantageous for the deprotection of other benzyl protected hydroxyl functions, where chemoselectivity is an

Table 1 Hydrogenolysis of benzyl methyl ether

Entry	Catalyst	Solvent system	PT agent	Time/min	Conv. (%)
1	Pd/C	Ethanol	None	30	100
2		Multiphase	A336	310	3
3		Multiphase	None	330	85
4	Pt/C	Ethanol	None	240	33[a]
5		Multiphase	A336	360	0
6		Multiphase	None	300	5[a]
7	Ra-Ni	Ethanol	None	230	37
8		Multiphase	A336	150	100
9		Multiphase	None	420	85
10		Multiphase	SDS	435	98

[a] Toluene was further reduced to methylcyclohexane.

Table 2 Hydrogenolysis of benzyl ethers with Ra-Ni and A336[a]

Entry	Substrate	Time/min	Product/s	Yield (%)
1[a]	OBn	30 180	*n*-PrOBn *n*-PrOH	100 100
2	(Nopol-*O*-Bn-ether)	320		20/40
3	(Tri-*O*-Bn-glucal)	240	[b]	100
4	OBn	30	Phenol	100
5[c]		240		90/10
6	(BOC-*O*-Bn-serine)	150	BOC-serine	100

[a] *Conditions*: 0.25 mmol A336, 250 mg Raney-Ni Actimet M®; 10 mL isooctane; 5.5 mL 2% aq. KOH; 0.7 mmol of substrate. Stirred at 1000 rpm and bubbled with H₂, at 50 °C. [b] The product was not identified, however three equivalents of toluene were produced indicating that debenzylation took place. [c] Reaction run in the absence of KOH (to avoid aldol condensation).

issue, *e.g.* in the presence of other reduction sensitive functional and/or of other protecting groups.

Experimental

All reactions were run in a 25 mL reactor thermostated at 50 °C, loaded with (in this order): 2.32 mL of a 5% isooctane solution (vv) of Aliquat 336 (0.25 mmol), the catalyst (250 mg wet Raney-Ni Actimet M® from Engelhardt, or 46 mg Pd/C 5%, or 84 mg Pt/C 5%); 7.7 mL isooctane; 5.5 mL 2% aqueous KOH; 50 mg (0.41 mmol) of benzyl methyl ether. The mixture was stirred at 1000 rpm and bubbled with hydrogen (≈ 5 mL min^{-1}). Samples were withdrawn at intervals, and were monitored for toluene concentration by GC using the internal standard (decane) technique. For the compounds of Table 2, structures were confirmed by GC-MS analyses by comparison with authentic samples.

Acknowledgments

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