Formation and evaluation of novel silica supported secondary amines via an effective 'in-situ' reduction of silica supported imines

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Abstract

An effective method for the reduction of silica supported imines has been developed. This represents a useful approach to the selective preparation of silica supported secondary amines. The resultant modifications have produced effective catalysts, which are more hydrolytically stable than the corresponding imines. There is a large spread of different activities in the resulting catalysts, some of which are considerably more active than the simple primary amine, aminopropylsilica (AMPS). The nature of the alkyl group introduced in this technique thus plays a critical role in the catalyst activity. The nitroxyl radical, tetramethylpiperidinyloxy (TEMPO) has also been attached using this methodology, indicating that this approach may be of use in selectively functionalising AMPS leading to a wide range of supported species, bound via a hydrolytically stable linkage. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Silica supported primary amines and imines are well known heterogeneous catalysts [1–8]. Both are capable of catalysing a range of reactions including the Knoevenagel condensation and the Michael addition reactions. Supported secondary (RNHMe) amines are poor Knoevenagel and Michael catalysts [9], but tertiary amines are excellent catalysts for the Michael reaction [10]. In an attempt to improve the lifetime of typical primary amine catalysts, which are poisoned by amide formation in the Knoevenagel reaction, we have prepared and studied imines supported on silica [4]. Whilst these are very effective catalysts, they are not sufficiently hydrolytically stable, and can cleave under reaction conditions, or during reactivation. Thus, we have investigated the reduction of the silica supported imine group to the corresponding secondary amine. The resultant amines are of well-defined structure, avoiding the problems of poly-*N*-alkylation of amines and liberation of free amine encountered during alkylation using haloalkanes. We have shown that at least some of these materials are effective catalysts for the Knoevenagel reaction, and are stable towards leaching, even under hydrolytic conditions. Catalytic activity in the Knoevenagel reaction varies dramatically as a function of activity, and can be better than the primary amines, which are normally considered to be the most active. The new basic site (a secondary amine), is furthermore less likely to be susceptible to amide formation than a primary amine. The reducing agents, which have been used for a range of homogeneous imine

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reductions, include a range of hydride complexes with the emphasis in the literature being on sodium borohydride and lithium aluminium hydride [11–15].

The reductions were carried out on a variety of silica supported imines, using sodium borohydride, in two different solvent systems to determine the most effective method. In order to extend the scope of the method, the preparation of a reduced silica supported 4-oxo-2,2,6,6-tetramethylpiperidinyloxy (TEMPO) catalyst was also achieved. This moiety has previously been supported by different methods and has been shown to be a valuable metal-free oxidation catalyst [16–18].

2. Experimental

All reagents were purchased from Aldrich Chemical Company, Fluorochem and Lancaster Chemicals and used as received. All solvents were AR grade. Infrared spectroscopy was carried out using a Bruker Equinox 55 IR Spectrometer. Thermal analysis was carried out using a Stanton STA 625 machine and solid proton-decoupled MAS NMR was carried out using a Bruker Avance 400 digital NMR. Product yields were calculated by GC, using internal standards, using an HP 5890 series GC system with an HP1 column.

2.1. Catalyst preparation

Preparation of all the catalyst precursors (AMPS and imines derived therefrom) was carried out using the same method using Merck Kieselgel 100, 3-aminopropyl trimethoxysilane and the sodium salt of 3-hydroxybenzaldehyde (**1**), benzaldehyde (**2**), *n*-hexanal (**3**), 2-naphthaldehyde (**4**), 2,2-dimethylpropanal (**5**), pentafluorobenzaldehyde (**6**), 2,4,6-trimethylbenzaldehyde (**7**), 2-ethylbutanal (**8**), 2-ethylhexanal (**9**) [4], except for the 4-oxo TEMPO catalyst (**10**). This catalyst was prepared by the addition of 4-oxo TEMPO (3 mmol, 0.51 g) to 3-aminopropyl trimethoxysilane (3 mmol, 0.54 g) in methanol (50 ml), with stirring. After 4 h, K100 silica (3 g, not pre-activated) was added and the slurry left to stir at room temperature overnight. The mixture was filtered and the solid was washed with methanol (100 ml) and finally dried at 100 °C. Reduction procedure **a** was used for this particular material.

The reduction procedures **a** and **b** used sodium borohydride in specified quantities; the reduction scheme can be seen in Fig. 1, all of the catalysts prepared are listed in Fig. 2.

2.1.1. Reduction procedure a

The catalyst to be reduced (1 g), corresponding to ca. 1 mmol imine in each case, was added with stirring to diethyl ether (25 ml). When the catalyst was dispersed, sodium borohydride (as a 0.5 M solution in 2-methoxyethylether, available from Aldrich) was added (3 mmol). The reaction was left for 24 h. The catalyst was then filtered and washed with diethyl ether (50 ml). The catalysts were then added to water (50 ml) with stirring and left for another 24 h. The reduced catalyst was
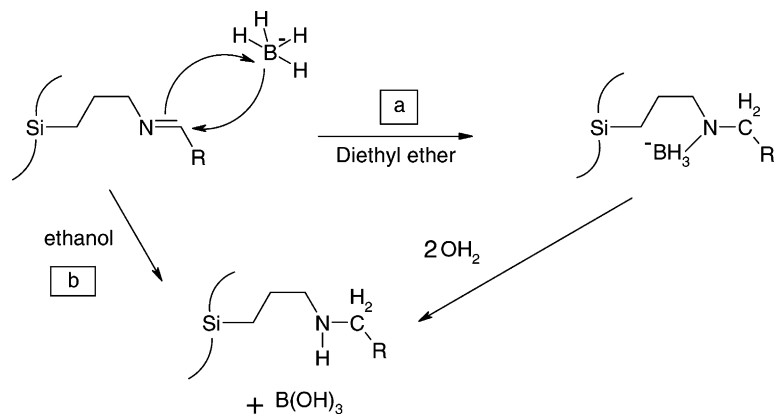

Fig. 1. Reduction scheme for silica supported imine catalysts.

where R =

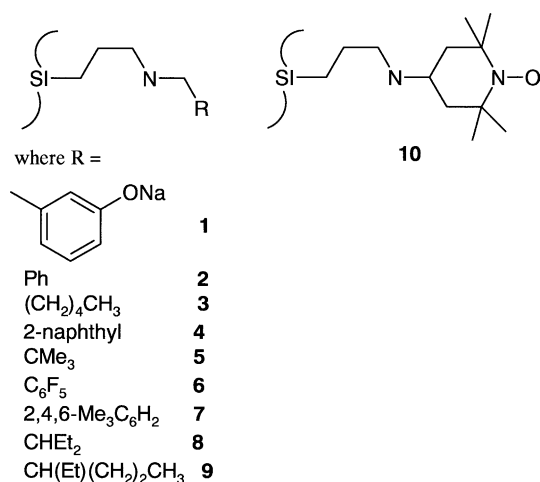|	
ONa (3-substituted phenolate)	**1**
Ph	**2**
$(CH_2)_4CH_3$	**3**
2-naphthyl	**4**
CMe_3	**5**
C_6F_5	**6**
$2,4,6\text{-}Me_3C_6H_2$	**7**
$CHEt_2$	**8**
$CH(Et)(CH_2)_2CH_3$	**9**

Fig. 2. Secondary amine catalysts prepared in this study by the reduction of the corresponding imine.

then filtered, washed with water (50 ml) and dried at 100 °C.

2.1.2. Reduction procedure b

The catalyst to be reduced (1 g) was added to ethanol (50 ml) with stirring. Solid sodium borohydride was added (3 mmol, 0.11 g) with stirring and left for 24 h. The catalyst was then filtered, washed with ethanol (150 ml) and dried at 100 °C.

2.2. Catalytic procedures

The catalysts were evaluated in the Knoevenagel condensation reaction between 3-pentanone (0.86 g, 10 mmol) and ethyl cyanoacetate (1.13 g, 10 mmol), Fig. 3. The reaction was carried out in refluxing cyclohexane (15 ml) with a Dean Stark trap to remove water. In all cases biphenyl was employed as an internal standard (0.15 g, 1 mmol) and 0.25 g (equivalent to 0.25 mol% active sites) of each catalyst was used.
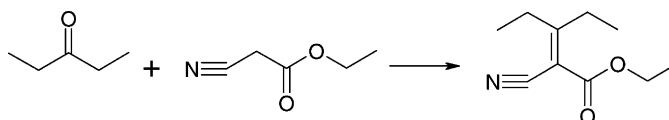
3. Results and discussion

3.1. Characterisation of the catalysts

The infrared spectra of the imine bonded catalysts showed typical imine stretches in the range of 1690–1640 cm^{-1}. Other bands could be assigned to the particular R groups, confirming their presence. When the catalysts were reduced via procedure **a**, prior to addition of water, it was seen that the imine band was no longer present, and, in addition to the loss of the imine band, four new bands were seen. These were due to the BH_3^- complex formed with the nitrogen on the surface of the catalyst, and possibly to free $NaBH_4$ on the surface. Interestingly, these bands remain unchanged even after several months storage in a dessicator. Three characteristic bands were seen due to the B–H bonds at 2200, 2275 and 2375 cm^{-1} and another band due to the B–N bond at 1600 cm^{-1}. This complex was destroyed and the boric acid formed was washed off the surface of the catalyst by washing with water to leave the free secondary amine. This is illustrated for phenolate catalyst **1** in Fig. 4.

When the catalysts were reduced using reduction procedure **b** the imine band was also lost; this time no intermediate complex could be isolated, due to the reaction of the B–H bonds with the alcoholic solvent. When a smaller quantity of borohydride was used a residual amount of imine was seen in the infrared spectra. However, in these cases there were no vibrations corresponding to B–H complexes, indicating that the complex is destroyed in situ as expected.

Condensation of 4-oxo TEMPO directly to AMPS proved to be of limited success, with even forcing conditions failing to give more than a few percent conversion to imine. Therefore, an alternative approach had to be attempted. The 4-oxo TEMPO based catalyst also showed a characteristic imine stretch (and no carbonyl band) after reaction of the 4-oxo-TEMPO with the free aminopropylsilane, indicating that condensation to form the imine was complete. This band was

Fig. 3. Knoevenagel condensation reaction between ethyl cyanoacetate and 3-pentanone.
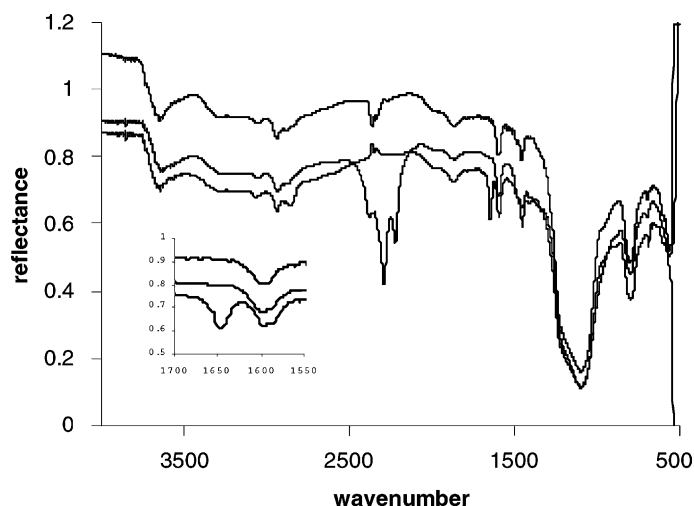
Fig. 4. Infra-red Spectra of supported imine corresponding to **1** (bottom spectra), aminoborane complex intermediate (middle spectrum) and final amine product **1** (top spectrum). Inset shows the imine stretching region from 1700–1550 cm^{-1}, and clearly shows the loss of imine (disappearance of the band at 1648 cm^{-1}).

then lost on reduction, as for the other catalysts. ESR spectroscopy confirmed the presence of the nitroxyl radical for both the imine material and its reduced form (Fig. 5). This provides a material with prospective oxidation catalyst possibilities [16–18], and work is progressing in this direction.

Thermal analysis showed there to be little difference between the phenolate catalyst **1** and its reduced counterpart. A small weight loss was seen at around 80 °C due to residual solvent and then a gradual loss over the

Fig. 5. ESR spectra of silica supported TEMPO before and after reduction with sodium borohydride.

remaining temperature range to 625 °C relating to decomposition of the organics. An overall weight loss of 10% was seen for both catalysts. Similar trends were noted for other catalysts.

Solid MAS NMR spectroscopy indicated that there were changes from the original phenolate catalyst **1** to the reduced form. In particular the imine resonance at 160 ppm and the CH$_2$–N=C peak at 61 ppm have reduced dramatically in intensity, to be replaced by peaks at 40 and 51 ppm, for the alkyl CH$_2$N group and the benzylic CH$_2$, respectively.

Thus, the characterisation of the catalysts shows that the imine bonded groups are effectively and cleanly reduced to their respective secondary amines using sodium borohydride. Using diethyl ether as a solvent requires a two step process due to the borohydride complex not being destroyed under the non-hydroxylic conditions of the reduction. However, it is interesting to note that the borohydride complexes formed are stable on a silica surface for considerable periods of time, despite the hydroxylic nature of the surface. Such complexes may find use as solid phase reducing agents [19], but we have not yet developed this aspect of the work, and results obtained will be reported elsewhere. The advantage of using alcoholic solvents is then apparent, as the second step is rendered unnecessary.
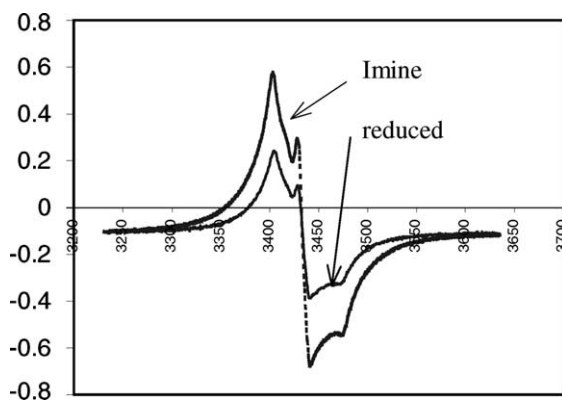
3.2. Catalytic results

All of the amine catalysts were compared in the Knoevenagel condensation reaction of 3-pentanone and ethyl cyanoacetate, Fig. 3. No differences were seen between catalysts of the same R group, prepared via method **a** or **b**. The catalytic activity of some of the imine catalysts has been previously reported [4] and it has been discussed that the order of reactivity of these catalysts is due to an interplay of both the mesomeric and inductive effects of the end groups themselves as well as to steric effects. In broad comparison to this work, the amines are less active than the corresponding imines, and the order of reactivity as a function of R has changed, probably due to the lack of resonance effects which can be transmitted from the aryl groups through the imine double bond, but not via the reduced link. It is apparent that these results are consistent with the conclusions of a previous paper [4] in that the imine group is in fact a stronger basic site than an amine in such catalysts. However, one important difference is that no hydrolytic cleavage is obtained with the amine catalysts in contrast with the observed cleavage of the imine catalysts in the presence of water.

The possibility that adsorbed sodium ions (associated with basic species such as SiO-) might be responsible for the catalysis was checked by reaction of sodium borohydride with AMPS followed by washing with ethanol. No change in activity was seen. Similarly, borohydride treated silica had negligible activity in the reaction under test. It is also known that the phenoxide site on supported catalysts such as **1** is inactive in Knoevenagel reactions [4].

Reaction profiles of the secondary amine catalysts are shown in Fig. 6, and are compared to the standard AMPS catalyst.

It is very interesting to compare the relative reactivities of the catalysts as a function of the alkyl group R. While there may be many factors influencing the structure–activity relationships in a series of catalysts, it can be seen that the bulkiness of the alkyl groups plays an important role in the activity of each individual catalyst, Fig. 6. This can be seen more clearly when the alkyl substituted catalysts and the aryl-containing catalysts are looked at separately. In the alkyl series, the catalyst with the highest activity contains a bulky tertiary alkyl group, followed by
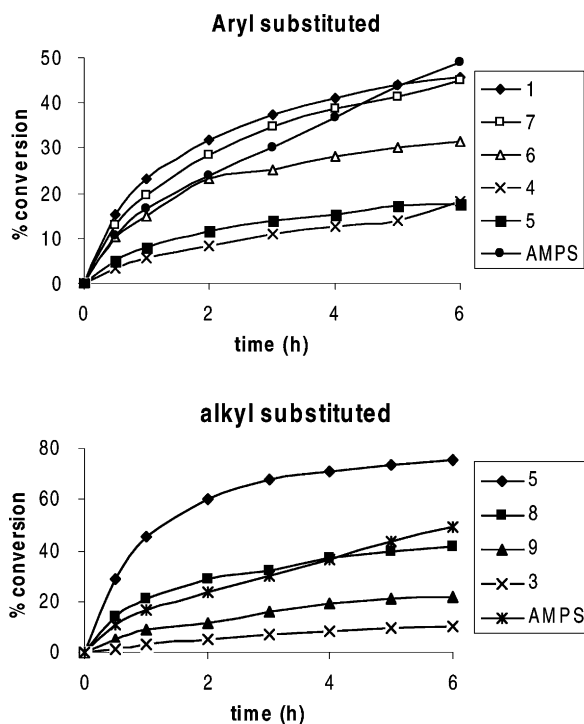

Fig. 6. Catalytic comparison of secondary amine catalysts in the Knoevenagel reaction between ethyl cyanoacetate and 3-pentanone: (upper graph) aryl-substituted amines compared with AMPS; (lower graph) alkyl substituted amines compared to AMPS.

those with secondary and primary alkyl substituents, respectively in the order of activity. The most active catalyst here is considerably more active than the standard primary amine AMPS. A similar trend is also seen in the benzylic systems, the more bulky the groups on the ring the better the activity.

While it is not clear as yet why this is the case, it is possible that bulky alkyl groups will reduce the NH–SiOH interaction at the surface, an interaction which might be expected to reduce the basicity and availability of the basic sites.

Additionally, the increased hydrophobicity of the larger groups is also likely to have a positive effect on the activity, although the size of the organic group appears to be less important than its bulkiness, and polar groups have a similar effect to similarly bulky non-polar systems. Such positive effects of hydrophobisation may play a positive role, as they are well known to do in similar, silica-based systems

[20–22] where the passivating group must usually be introduced by an additional silylation step. In aminopropyl-based systems, we have noticed that classical silylation procedures do not result in a positive effect on activity; indeed a negative effect is often seen.

It can be seen that the profile for AMPS is often different to that of some of the secondary amines, appearing to remain active for longer. Some of the secondary amines thus seem to lose activity early (e.g. **7**). This behaviour may be a consequence of the low activity of some of the catalysts, leading to an apparently "flat" rate profile, but may be real for some of the others. Since the most active catalysts do not display this behaviour, we have not concentrated on explaining it. However, several possibilities exist: there is a more rapid poisoning of these catalysts; diffusional (or non-irreversible adsorption/desorption) problems develop earlier, or that a change in mechanism is taking place. The Knoevenagel reaction mechanism is known to be very sensitive to subtle changes in environment [23] and the possibility of in-situ imine formation in these systems would be much more favoured in the case of a primary amine.

4. Conclusions

Silica supported imine catalysts are effectively reduced 'in situ' using sodium borohydride in two different solvent systems and in turn are less susceptible to hydrolysis. These new materials have higher stability and lower activity than imines, and display higher activity and similar stability to primary amines in the Knoevenagel condensation reaction. It has also been shown that other imine-bonded systems, such as TEMPO, can also be successfully reduced using this reduction method, leading to robustly bound silica supported oxidation catalysts. It is likely that this reduction methodology could be applied to a range of imines, leading to well-defined and robustly linked groups for a variety of applications.

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