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Palladium on Manganese ferrite: an efficient catalyst for one pot synthesis of primary amides from iodobenzene.
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Amidation of aryl halide in one pot is reported using Pd-MnFe$_2$O$_4$ as a catalyst. The catalyst was characterized by various techniques such as XRD, FEG-SEM, EDS, TEM, BET surface area and ICP AES. K$_4$[Fe(CN)$_6$] is used as non toxic cyanation reagent for in situ generation of benzonitrile and hydrolyzed as soon as it formed. The catalyst was found to be efficient and can be used for several cycles without loss in activity. Moderate to good yield of primary amides was obtained.

1. Introduction.
Primary amides are the most important functionality in pharmaceuticals, natural products, agrochemicals and biologically active molecules$^{13}$. Generally, primary amides are synthesized either by reaction of carboxylic acid or its derivative with ammonia or its equivalent$^2$. They are also synthesized by different methodologies such as catalytic rearrangement of aldoximes$^6$, reaction of aldehydes with ammonia$^7$, oxidation of benzylic alcohols in presence of ammonia$^8$ and catalytic oxidation of benzyl amines$^9$. Aminocarbonylation of aryl halide by using carbon monoxide and ammonia or ammonia equivalent is also reported as the efficient method for the synthesis of primary amides. However, this process involves handling of toxic gas and reduces its use at kilogram level$^5$. Aryl halides with ammonia in presence of metal carbonyls also have been used for the synthesis of primary amides, but it leads to release of toxic carbon monoxide gas and also the metal carbonyl complexes are volatile and unstable$^{10}$. Hydration of nitriles is an atom economical process and numbers of catalytic methods have been developed for nitrile synthesis$^{11}$. Hence preparation of nitriles as an intermediate for amide synthesis is of great importance. Nitriles are prepared by reaction of aryl halides with various nitrile sources such as alkali cyanide, CuCN, TMSCN and K$_4$[Fe(CN)$_6$]$^3$ salt in presence of transition metal catalyst. Among these K$_4$[Fe(CN)$_6$] is used as a less toxic and cheaper cyanide source for cyanation of aryl halides$^{12}$. Recently oxidation of benzyl amine to primary amide by using OMS-2 catalyst was reported$^{13}$. However, the reaction requires very high pressure (6 bars) and temperature (160°C) and also gives side products, where as we have reported general synthesis of primary amides at mild reaction conditions using magnetically retrievable catalyst.

Magentically separable catalyst has attracted much attention in the area of heterogeneous catalyst as it is easily separated by external magnet and can be used several times without losing its activity$^{13}$. Super paramagnetic materials, spinnel ferrites MFe$_2$O$_4$ (M= Ni, Co, Zn,) are one of the important advance materials used in drug delivery and biomedical applications such as MRI$^{14}$. Besides this, they are also found to be good support for transition metal catalysts$^{15}$. In particular, palladium supported on super paramagnetic material is the most important heterogeneous catalyst as it offers high surface area and easy separation. In continuation of our work with metal nano particles supported on super paramagnetic material$^{15b}$, herein we report palladium nanoparticles (PdNPs) supported on MnFe$_2$O$_4$ and its application in one pot synthesis of primary amides.

Manganese ferrite (MnFe$_2$O$_4$) nano crystals possess higher magnetization as compared to magnetite, CoFe$_2$O$_4$ and NiFe$_2$O$_4$ nanoparticles$^{15}$. Here we have carried out the tandem synthesis of primary amide from iodobenzene via in situ generation of benzonitrile in presence of DMSO: H$_2$O solvent system using Pd nano particles supported on MnFe$_2$O$_4$. This is the first report of the application of the heterogeneous catalyst for the synthesis of primary amide and that too using nontoxic nitrile source.

![General synthesis of primary amide.](image-url)

**Our Approach**

Manganese ferrite (MnFe$_2$O$_4$) nano crystals possess higher magnetization as compared to magnetite, CoFe$_2$O$_4$ and NiFe$_2$O$_4$ nanoparticles$^{15}$. Here we have carried out the tandem synthesis of primary amide from iodobenzene via in situ generation of benzonitrile in presence of DMSO: H$_2$O solvent system using Pd nano particles supported on MnFe$_2$O$_4$. This is the first report of the application of the heterogeneous catalyst for the synthesis of primary amide and that too using nontoxic nitrile source.
K₄[Fe(CN)₆]. Very good yields of the desired products were obtained.

2. Experimental

2.1 Catalyst preparation.
Catalyst was prepared by using ultrasound assisted coprecipitation method. FeCl₃・6H₂O (9.5 mmol, 50 mL) and MnCl₂・4H₂O (4.4 mmol, 50 mL) solutions were added in 250 mL round bottom flask followed by addition of 0.5 g KCl and PdCl₂ (60 mg). This mixture was placed in ultrasound bath for 5 min. Then pH of this mixture was adjusted at 12 by adding 3N NaOH followed by heating at 60 °C for 30 min. The obtained catalyst was filtered and washed with distilled water several times and then by ethanol to remove water. The catalyst was dried under vacuum at 60 °C for 24 h, and subsequently at 200 °C for 4h.

2.2 Characterization of material
The as synthesized catalyst was characterized by various techniques such as X-ray diffraction (XRD), Field emission gun Scanning electron microscopy (FEG-SEM), Transmission electron microscopy (TEM), FTIR, ICP-AES analysis, BET surface area analysis, Energy dispersive X-ray spectral analysis (EDS) image was recorded with an Oxford instrument at 10 kV. Beam intensity was kept high to get good response by the detector. Inductively coupled plasma Atomic Absorption spectrometry (ICP AES) analysis was performed on ARCS from M/s. Spectro, Germany. GC analysis is performed over PerkinElmer Clarus 480 instrument. GC-MS Spectra recorded over Shimadzu QP-2010 Instrument. 1H and 13C NMR spectra’s were recorded on Agilent 400MHz and 100MHz instrument respectively.

The XRD analysis was performed on Shimadzu XRD 2400 instrument using Cu Kα radiation (λ= 1.5406 Å) with scanning rate 2 degree per minute. TEM analysis was performed over PHILIPS 2200 instrument. FEG-SEM analysis was performed on TESCAN MIRA Instrument. The energy dispersive X-ray spectral analysis (EDS) image was recorded with an Oxford instrument at 10 kV. Beam intensity was kept high to get good response by the detector. Inductively coupled plasma Atomic Absorption spectrometry (ICP AES) analysis was performed on ARCS from M/s. Spectro, Germany. GC analysis is performed over PerkinElmer Clarus 480 instrument. GC-MS Spectra recorded over Shimadzu QP-2010 Instrument. 1H and 13C NMR spectra’s were recorded on Agilent 400MHz and 100MHz instrument respectively.

3. Results and Discussion
XRD analysis showed peak at 2θ = 30.1, 35.14, 43.41, 54.601, 57.0671 and 63.6651 which represent the Bragg reflections from the (220), (311), (400), (422), (511) and (440) planes respectively. The crystalline data matches with the JCPDS Card No. (74-2403). Palladium peaks at 40, 46° values were not observed because of the low loading of the palladium (Fig 2a).

Displacing value from XRD and TEM SEAD pattern is same and found to be 2A°. (Fig. 3 c and d)

The elemental analysis of Pd-MnFe₂O₄ was confirmed by EDS analysis as shown in (fig.2 b). The distribution of elements in Pd-MnFe₂O₄ was Mn =11.45%, Fe = 28.15%, O =59.31% and Pd=1.09%.

The TEM image of Pd-MnFe₂O₄ NPs. (Fig.3 c) clearly indicates that NPs are uniform in size with average particle size less than 45 nm. This is in accordance with the average crystallite size obtained by using the Debye–Scherrer equation. The image also exhibits that the Pd NPs on MnFe₂O₄ are well dispersed. Pd NPs size ranges from 2-10 nm.

From the N₂ adsorption–desorption isotherm of Pd-MnFe₂O₄ NPs, the BET surface area of the particles was found to be 24.9346m²/g and the adsorption average pore width was 315 Å. Single point surface area at P/Po = 0.254238207: 24.5190 m²/g (Fig.2 Supporting Information)

Reaction of iodobenzene with K₄[Fe(CN)₆] was treated as a...
model reaction and various reaction parameters were optimized for this reaction. Initially (1 mmol) of iodobenzene was treated with 0.25 mmol of K$_4$[Fe(CN)$_6$] in the presence of Pd-MnFe$_2$O$_4$ catalyst (30 mg, 1 mol% Pd), K$_2$CO$_3$ as a base in DMF :H$_2$O (1:1) solvent system, at 100°C, which offered 58% yield of benzamide (Table 1, entry 1). Series of experiments were performed to optimize the various reaction parameters such as solvent loading, solvent base and temperature of the reaction. Loading of the catalyst was also the important parameter and it was found that 1 mmol of the catalyst was enough to achieve the maximum yield of the desired product (Table 1 entry 4). Solvent study was the important part for this transformation. Various solvent systems such as DMF: H$_2$O, DMF: H$_2$O and NMP: H$_2$O were used out of which DMSO:H$_2$O (2:1) was found to be the most suitable solvent for this reaction. Initially (1 mmol) of iodobenzene was treated with 0.25 mmol concentration of K$_2$CO$_3$, which immediately gets hydrated to benzamide in the presence of water.

The reaction was also carried out with various inorganic and organic bases such as TEA, DBU, K$_2$CO$_3$, KOH and Cs$_2$CO$_3$, out of which K$_2$CO$_3$ was found to be the most efficient base giving maximum yield of the benzamide (Table 1 entry 8). The reaction was also carried out at various temperatures under optimized reaction conditions. The product yield increased dramatically from 19% to 90% when temperature increased from 90°C to 110°C whereas beyond 110°C no significant increase in the product yield with increase in temperature was observed (Table 1 entry 13-15).

We also studied the effect of concentration of K$_4$[Fe(CN)$_6$] salt on the product yield by increasing the amount from 0.1 mmol to 0.25 mmol. Conversion of aryl halide to benzonitrile was 100% at 0.25 mmol concentration of K$_4$[Fe(CN)$_6$] salt. The reaction was also carried out at various time intervals and 100% conversion was obtained in 18 h. For optimized reactionTON and 1TOF for amidation of iodobenzene was found to be 90 and 5 h$^{-1}$.

The applicability of the protocol was examined for various substituted aryl iodides (Table 2). It was found that electron rich substrate gave very good yield of the desired product.

**Table 2.** One pot synthesis of primary amides from aryl iodidesa.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodobenzene</th>
<th>Amide</th>
<th>Yield</th>
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<tr>
<td>2</td>
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<td>3</td>
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<td><img src="image6.png" alt="Image" /></td>
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<tr>
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<td><img src="image13.png" alt="Image" /></td>
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<td>8</td>
<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
<td>90</td>
</tr>
</tbody>
</table>

a.Reaction conditions: Aryl halide (1 mmole), K$_4$[Fe(CN)$_6$] (0.25 mmole), Time 12h, base (1.2 mmole), Isolated yield, time 18 h, 24 h, 3benzonitrile 92%
In case of p-NO₂ iodobenzene electron withdrawing effect was more prominent giving moderate yield of the desired products. However, in m-Nitro iodobenzene the yield was increased due to minimum electron withdrawing effect. Results are summarized in (Table 2, entry 6 and 12).

Donating substituents at ortho positions were well tolerated giving good yield of the corresponding primary amides. We further studied amidation of bromobenzene as well as chlorobenzene and observed that bromobenzene gave only 20% yield of the desired product where as chlorobenzene was unreactive with optimized reaction conditions (Table 2 entry 2 and 3). Heteroaryl iodide also gave good yield of corresponding amide (Table 2 entry 16).

**Heterogeneous test for the catalyst**

We also examined the heterogeneous nature of the catalyst by hot filtration test. The catalyst was separated from reaction mass after half of the reaction time and the filtrate was stirred for required time under same reaction conditions. The reaction did not proceed further, which indicated that there is no leaching of palladium during the reaction. We also carried out the ICP AES analysis to test the recyclability of the catalyst for first and fifth cycles which showed that the palladium leaching was below detectable level (0.01 ppm).

Plausible mechanism suggests that iodobenzene is oxidatively added to the catalyst and then in presence of K₄[Fe(CN)₆] salt gives benzonitrile which subsequently get hydrolyzed in presence of water and catalyst to give primary amide.

**Fig.4 Recycle study of the catalyst.**

**Fig.5 Plausible Mechanism of the reaction.**

**Fig.6 Magnetic separation of the catalyst a) before and b) after applying external magnet.**
Conclusions

In summary, we have developed the simple and practically applicable protocol for the synthesis of primary amides from aryl iodides. Pd-MnFe2O4 is the first heterogeneous catalyst for such transformation. Catalyst was found to be efficient for the transformation of iodobenzenes to respective amides. PdSMnFe2O4 is the first heterogeneous catalyst for such applicable protocol for the synthesis of primary amides from aryl iodides. The authors are very thankful to the UGCSSAP, New Delhi, India for awarding the fellowship.

Acknowledgements

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Notes and references

† Electronic Supplementary Information (ESI) available: [Experimental procedure, Characterization of the catalyst, Mass and 1H NMR spectrum of representative compounds are given]. See DOI: 10.1039/b000000x/
‡ TOF = [mol of product / (mol catalyst X h )].