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Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 847

www.rsc.org/greenchem

PAPER

Nano rod-shaped and reusable basic Al_2O_3 catalyst for *N*-formylation of amines under solvent-free conditions: A novel, practical and convenient 'NOSE' approach†

Vijay Kumar Das,[a] Rashmi Rekha Devi,[b] Prasanta Kumar Raul[b] and Ashim Jyoti Thakur*[a]

Received 18th August 2011, Accepted 16th December 2011
DOI: 10.1039/c2gc16020j

An expeditious, simple, highly efficient, practical and green protocol for the *N*-formylation of alkyl/aryl amines and indole derivatives catalyzed by novel nano rod-shaped basic Al_2O_3 under solvent-free conditions has been developed. The catalyst is efficiently recycled up to the 5th run, an important point in the domain of green chemistry. The methodology provides cleaner conversion, shorter reaction times and high selectivity which makes the protocol attractive.

Introduction

In the wake of increasing awareness in environmentally benign techniques during the past few years, organic synthesis under solvent-free conditions has gained much popularity.[1] In this regard, the synthesis of N-bonded compounds has received considerable attention from the sight of green chemistry.[2] There is a growing appreciation for *N*-formylation of primary or secondary amines into formamides which is a common methodology in synthetic organic chemistry. The reaction product, formamides serve either as a polar solvent or as an important intermediate in several organic transformations since their skeletons exist in pharmaceutically valuable compounds such as fluoroquinolines,[3] imidazoles,[4] 1,2-dihydro quinolines,[5] nitrogen-bridged heterocycles,[6] oxazolidinones[7] and cancer chemotherapeutic agents.[8] They have also found significant applications as Lewis base catalysts in various organic transformations,[9–14] synthesis of formamidines,[15] isocyanides[16] and as *N*-formylating agents in histone proteins as a secondary modification arising from oxidative DNA damage.[17]

The literature is enumerated with several strategies[18–28] prescribed for *N*-formylation of amines. Regardless of the existing methodologies, most of them suffer from different drawbacks such as thermal instability, sensitivity to moisture, application of toxic and expensive formylating agents and catalysts, poor atom economy, high temperatures, prolonged reaction times, harsh reaction conditions, formation of undesirable by-products, low yields, while also leading to diformylation and/or lack of regioselectivity and tedious work up. Therefore, the synthesis of formamides still remains an active research area in terms of operational simplicity and economic viability. In the recent years, formic acid[29–33] has been continually accepted as a potent formylating agent owing to its lower toxicity, inexpensivity and easy practical applicability.

With the nanotechnology now available to the scientists, of late, Somorjai *et al.* emphasizes that catalysis by transition metal nanoparticles is the central field of nanoscience and nanotechnology,[34] which are the frontiers between homogeneous and heterogeneous catalysis.[35] The growing interest on the catalytic properties of transition metal nanoparticles is due to their large surface area, distinct electronic, optical, magnetic, thermal and chemical properties.[36] The ultimate goal to work with nanoparticles is their high catalytic activity, recoverability, improved selectivity, criteria of evolution and role in green chemistry.[37] Hence, organic synthesis catalyzed by metal/metal oxide nanoparticles[38] has received tremendous importance in recent decades.

To cater the burgeoning needs and aspirations, we have been focussing on the development of a protocol named 'NOSE'[39] (nanoparticles-catalyzed organic synthesis enhancement) chemistry in our laboratory. Nanoscale supports to create catalysts with larger surface areas along with more edges and corners, which can lead to higher performance of the catalyst. Other parameters (*e.g.* oxygen mobility, *etc.*) might also play key role for enhancing catalytic activity. There are few reports that describe *N*-formylation of amines using nanoparticles. Preedasuriyachai and co-workers[40] have presented nanogold catalyzed *N*-formylation of amines under aerobic conditions with MeOH or formalin. However, in terms of disadvantage, nanogold itself is very expensive. To the best of our knowledge, *N*-formylation of amine catalyzed by basic nano crystalline Al_2O_3 has not been reported. Very recently, a research group has reported the nanocrystalline Al_2O_3 catalyzed one-pot synthesis of poly-substituted

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[a] *Department of Chemical Sciences, Tezpur University, Napaam, 784028, India. E-mail: ashim@tezu.ernet.in; Fax: +91(3712)267005/6; Tel: +91(3712)267008 ext. 5059*
[b] *Defence Research Laboratory, Post Bag No. 2, Tezpur, 784001, India. Fax: +91(3712)258534; Tel: +91(3712)258508*

† Electronic supplementary information (ESI) available: General experimental methods, characterisation of the catalyst, general synthetic procedure, recycling potential of the nano alumina rods, physical and spectroscopic data of compounds, ^1H NMR and ^{13}C NMR spectra of compounds, reference. See DOI: 10.1039/c2gc16020j

quinolines.[41] There is an extensive study on the preparation and properties of Al_2O_3 nanomaterial.[42] The advantages[43] of using basic nano-Al_2O_3 is in terms of its crystalline size and shape, abrasive and insulating properties, lower toxicity, large surface area and their basic surface characteristics, high resistance towards acids and bases, compatibility with very high temperature applications and has excellent wear resistance. Therefore, in this paper, we wish to focus on an effective, convenient and practical procedure employing nano rod-shaped basic Al_2O_3 (specific surface area approximately 185.63 $m^2\ g^{-1}$ and a crystalline size of approximately 38 nm) to catalyze *N*-formylation of 1° and 2° amines efficiently as a part of our 'NOSE' chemistry (Scheme 1) programme.

Results and discussion

The SEM image of a pure nano-Al_2O_3 sample has shown agglomeration of particles (Fig. 1). The BET surface area of nano-Al_2O_3 was found to be 185.6 $m^2\ g^{-1}$ and the total pore volume was 0.9777 $mL\ g^{-1}$.

EDX analyses of pure nano-Al_2O_3 (Fig. 2) showed that the weight% of O and Al was 70.41 and 29.59 and atomic% was 80.05 and 19.95 respectively, as expected. Since the ratio of O to Al in the sample is 2 : 3, thus, it is obvious that the percentage of O is higher with respect to Al. Thus, the EDX suggests the presence of only O and Al in the nano-Al_2O_3 sample.

The XRD pattern of pure nano- Al_2O_3 (Fig. 3) shows that the peak of the sample corresponds to those of γ-alumina.[44]

The crystalline sizes were determined by using Scherrer equation and choosing the two highest peaks (400) and (100) from the XRD pattern. The crystalline sizes were found to lie between 39.7 and 37.4 nm. The average particle diameter calculated was 8.12 nm (S_{BET} = 185.63 $m^2\ g^{-1}$ and $\rho = 3.98\ g\ cm^{-3}$).

Fig. 4(a) and (b) show the TEM images of nano-Al_2O_3. The nano rod-shape of the sample can be seen from these micrographs. The average length of the nano-Al_2O_3 from TEM image was found to be 25.5 nm and its average diameter was 7.18 nm. It can also be seen that some agglomeration was present and this was attributed to the large surface area of these nano rod-shaped Al_2O_3.

Typical SAED pattern of the Al_2O_3 nano rod was generated and is shown in Fig. 5. It showed that the nano rods were well-crystallined. The SAED patterns were calculated and identified using JCPDS data card 10-425, indicating that these rings corresponded to the diffraction planes of γ-Al_2O_3. No un-assigned rings were left in the SAED patterns, eliminating the possibility of formation of other types of metastable phases like δ-Al_2O_3, θ-Al_2O_3, *etc.*

The FTIR spectrum of pure nano-Al_2O_3 is shown in Fig. 6. The peak at 3500 cm^{-1} is attributed to the atmospheric water vapour. An absorption band at *ca.* 1620 cm^{-1} is characteristic of alumina which is in accordance with the literature.[45] The peak at 1040 cm^{-1} corresponds to the Al–O stretching vibration.[46]

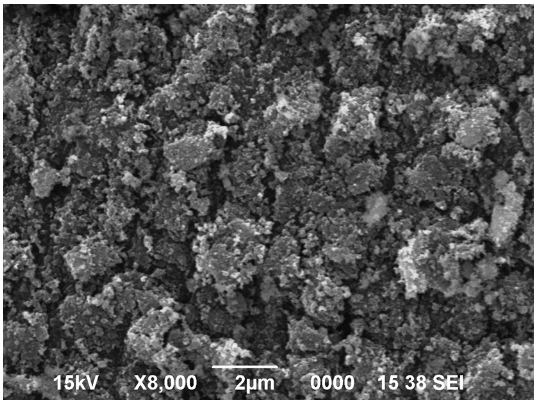


Fig. 1 SEM image of pure nano-Al_2O_3.

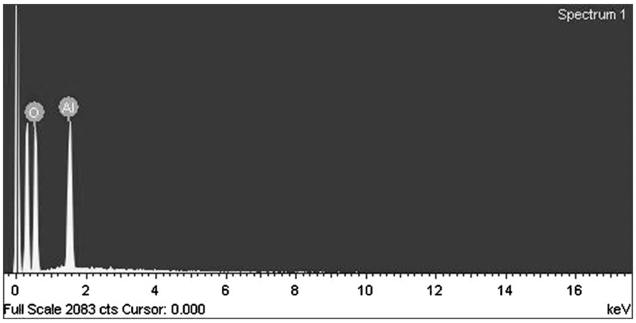


Fig. 2 EDX of pure nano-Al_2O_3.

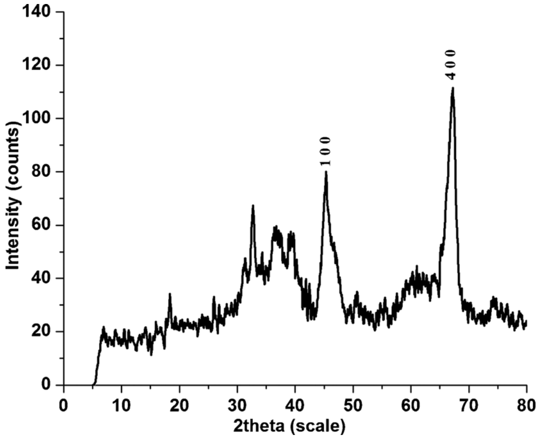
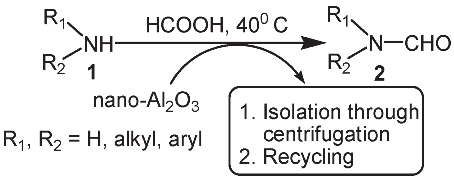


Fig. 3 XRD pattern of pure nano-Al_2O_3.



Scheme 1 *N*-Formylation of amines.

After the characterisation of the nano-Al_2O_3, in order to optimize the reaction conditions, a control experiment[30] was carried out by taking formic acid (98%, 0.11 mL, 3 mmol) and aniline (0.09 mL, 1 mmol) as a model substrate by stirring at room temperature without using any catalyst and solvent (Table 1, entry 1). Under these conditions the reaction did not proceed and starting materials remained intact. Then we poured acetonitrile (5 mL) and continued stirring for 18 h and isolated the product

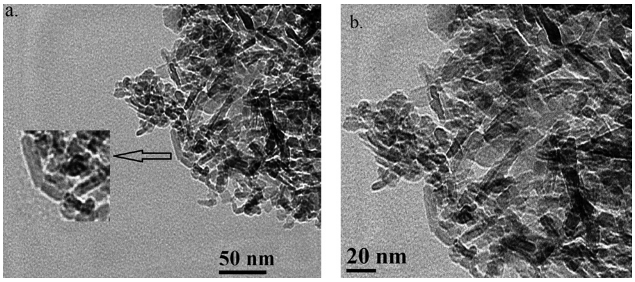


Fig. 4 (a) TEM image of nano rod-shaped Al_2O_3 at 50 nm scale (b) TEM image of nano rod-shaped Al_2O_3 at 20 nm scale.

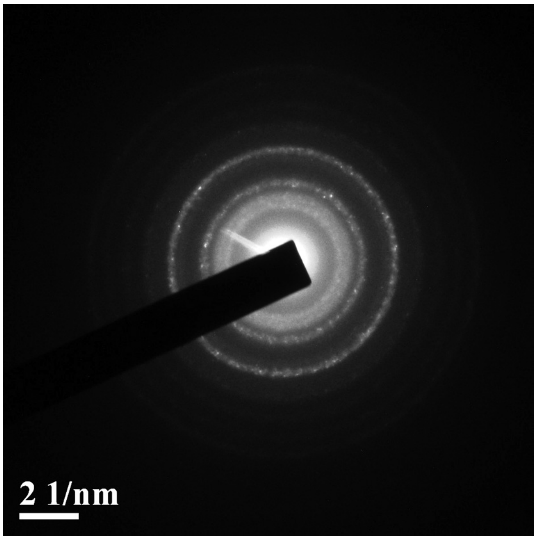


Fig. 5 Corresponding size distribution with inset showing SAED patterns of nano-Al_2O_3.

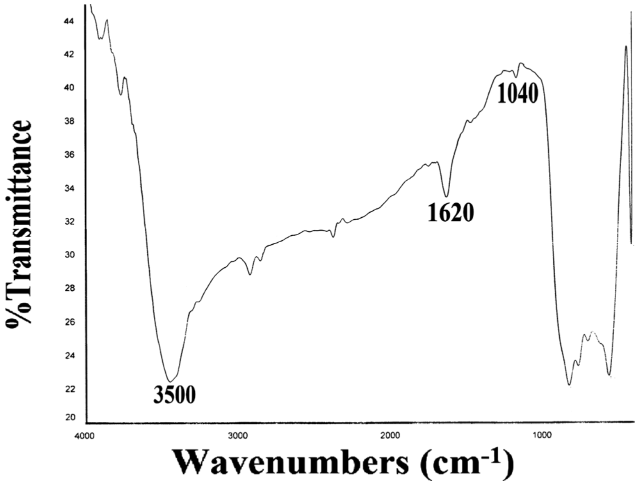


Fig. 6 FTIR spectrum of nano-Al_2O_3.

in 5% yield (Table 1, entry 2). In order to improve the yield, we searched for the best experimental conditions below 70 °C. By keeping this in mind, we performed the reactions at 40° C in acetonitrile and also by stirring under solvent-free conditions (Table 1, entry 3). Interestingly, the reaction proceeded faster under solvent-free conditions providing 28% yield (Table 1, entry 4). We also conducted the reaction at 70 °C under solvent-free conditions and isolated 42% yield (Table 1, entry 5). Unsatisfied with these results, we felt the necessity of using a catalyst to increase the yield. Therefore, we surveyed some Lewis acid and base catalysts and out of them, we found a dramatic increase in reaction rate and yield when we used nano basic Al_2O_3 (5 mol %) at 40° C (Table 1, entry 15). We also attempted to compare the catalytic action of bulk basic and acidic Al_2O_3 with nano basic Al_2O_3 for the *N*-formylation of aniline, and we found excellent yields associated with lesser reaction times and low catalyst loadings in the case of nano-Al_2O_3 catalysis. We also tested the influence of solvents on the reaction rate and yield by screening several solvents at 40 °C in the presence of Al_2O_3 nanoparticles and found that formamide formation took place faster under solvent-free conditions than in the presence of a solvent (Table 1, entries 17–24). The turn over number (TON) was also calculated for each catalyst under different conditions (Table 1) and it is shown graphically in Fig. 7. From this graph, it can be seen that the TON is the highest when nano-Al_2O_3 was used under solvent-free conditions at 40 °C. Table 1 also displays the turn over frequency (TOF) which was also at a maximum in the case of nano rod-shaped Al_2O_3 being used as the catalyst under solvent-free conditions at 40 °C. These comparative studies led us to undertake the reaction under solvent-free conditions because the reaction was sluggish and provided poor yields in the presence of a solvent. The reactions were found to be mildly exothermic which required initial cooling using an ice bath while formic acid was added to the reaction mixture containing alkyl/aryl amine and Al_2O_3 nano rods. Subsequently, the reaction was allowed to come to ambient temperature.

Triggered by these interesting results, we proceeded to repeat the model reaction with different quantities of formic acid and catalyst loading. As indicated in Table 2, by increasing the quantity of formic acid from 1.0 to 3.0 equiv. and increasing the catalyst loading from 1 mol% to 5 mol%, the yield was clearly improved along with the reduction of the reaction time. Further increasing of the catalyst loading to 15 mol% and decreasing the quantity of formic acid to 1.0 equiv. led to lower yields.

Realising this enhancement of the *N*-formylation reaction by nano-Al_2O_3, our ‘NOSE’ chemistry approach was extended to other nanocatalysts considering the same model reaction. All these nanocatalysts were purchased from Sigma Aldrich and were used without further purification. The results are summarised in Table 3. From Table 3, it is evident that when using a catalyst loading of 5 mol%, only the basic Al_2O_3 nano rods showed better catalytic performance at 40 °C (Table 3, entry 7). But, the other mentioned nanocatalysts provided comparatively poorer yields either at 40 °C or at 70 °C (Table 3, entries 1–6).

With these convenient experimental reaction conditions in hand, we next assessed the generality for various aromatic and aliphatic 1° and 2° amines under the standardized conditions and the results are summarized in Table 4. Nano-Al_2O_3 is found to be highly effective in formylating both electron-rich and electron-poor anilines in excellent yields (Table 4, entries 1–10). Hosseini-Sarvari *et al.*[28] recently reported that ZnO catalyzed the *N*-formylation of *p*-nitro aniline providing 77% yield. However, the procedure of Choi and co-workers [32] failed to give the product when *p*-nitro aniline was treated with formic acid in

Table 1 Optimization of the reaction conditions[a] for the *N*-formylation of aniline

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	TON	TOF (h^{-1})
1	None	None	rt	9	NR[c]	0	0
2	None	MeCN	rt	18	5%	0	0
3	None	MeCN	40	15	12	0	0
4	None	None	40	10	28	0	0
5	None	None	70	7	42	0	0
6[d]	H_3BO_3	None	40	8	39	15.6	1.95
7[d]	Imidazole	None	40	9	NR[c]	0	0
8[e]	Et_3N	None	40	9	NR[c]	0	0
9[d]	PPh_3	None	40	10	50	20	2
10[e]	Pyridine	None	40	9	NR[c]	0	0
11[d]	TiO_2	None	40	7	5	2	0.285
12[d]	Bulk basic Al_2O_3	None	40	7	64	25.6	3.65
13[e]	Bulk basic Al_2O_3	None	40	3	78	6.24	2.08
14[d]	Bulk acidic Al_2O_3	None	40	7	35	14	7
15[fg]	Nano basic Al_2O_3	None	40	0.083	<98	78.4	944.57
16[fg]	Nano basic Al_2O_3	None	70	1	75	60	60
17[fg]	Nano basic Al_2O_3	MeCN	40	8	25	20	2.5
18[fg]	Nano basic Al_2O_3	THF	40	9	29	23.2	2.57
19[fg]	Nano basic Al_2O_3	MeOH	40	4	68	54.4	13.6
20[fg]	Nano basic Al_2O_3	EtOH	40	4	60	48	12
21[fg]	Nano basic Al_2O_3	DMF	40	3	73	58.4	19.46
22[fg]	Nano basic Al_2O_3	Toluene	40	6	58	46.4	7.73
23[fg]	Nano basic Al_2O_3	DMSO	40	6	NR[c]	0	0
24[fg]	Nano basic Al_2O_3	H_2O	40	6	NR[c]	0	0

[a] Aniline (0.09 mL, 1 mmol), formic acid (0.11 mL, 3 mmol), solvent-free or solvent (5 mL), aerobic conditions. [b] Isolated yields. [c] No reaction was observed. [d] 10 mol% catalyst was used. [e] 50 mol% catalyst was used. [f] 5 mol% catalyst was used. [g] Particle size (37.4–39.7 nm).

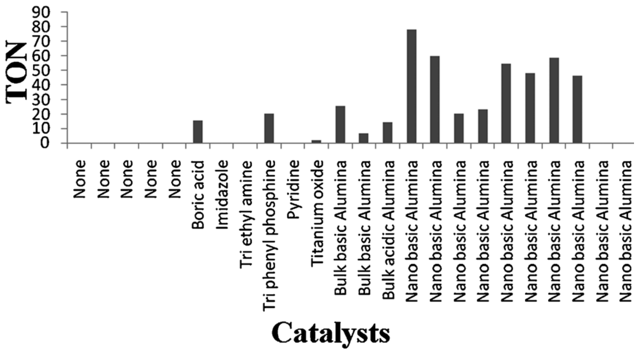
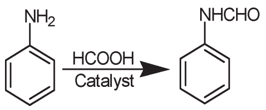


Fig. 7 TON of several catalysts from Table 1.



Scheme 2 *N*-Formylation of aniline (model reaction).

Table 2 Optimization of catalyst loading and amount of formic acid[a]

Entry	Formic acid (equiv.)	Catalyst loading (mol%)	Time (min)	Yield (%)[b]
1	1.0	1	50	60
2	1.0	3	30	78
2	1.0	5	30	80
3	1.0	10	80	70
4	1.0	15	130	61
5	2.0	5	20	85
5	3.0	5	5	<98
6	3.0	10	10	80

[a] Reaction was performed at 40 °C under solvent-free and aerobic conditions using nano basic Al_2O_3, [b] Isolated yield.

Table 3 Optimization with nanocatalysts

Entry	Nanocatalyst[a]	Temp. (°C)	Time (min)	Yield (%)[b]
1	α-Fe_2O_3 (19 nm)	40, 70	180	44, 60
2	γ-Fe_2O_3 (8 nm)	40, 70	100	50, 35
3	Fe_2O_3 (12 nm)	40, 70	90	40, 60
4	Fe_3O_4 (<50 nm)	40, 70	60	70, 55
5	FeO(OH) (20–40 nm)	40, 70	80	74, 36
6	TiO_2 (<80 nm)	40, 70	300	trace
6	MgO (<50 nm)	40, 70	60	77, 68
7	Nano basic Al_2O_3 (37.4–39.7 nm)	40, 70	5,60	>98, 75

[a] 5 mol% of catalyst was used. [b] Isolated yield.

toluene with a Dean–Stark trap. But, in our protocol using Al_2O_3 nano rods, the yield is comparatively enhanced (Table 4, entry 6). Phenyl hydrazine also reacted efficiently to afford the product (Table 4, entry 11). The reaction of *p*-phenylene diamine proceeded with a slower rate, producing the expected *N*-formylation product in 85% (Table 4, entry 12). But when *o*-phenylene diamine was reacted, it underwent cyclization to give benzimidazole[47] as the product (Table 4, entry 13). The formylation of diphenyl amine proceeded with a faster rate yielding 97% (Table 4, entry 14) of the product. The *N*-formylation of amino acid derivatives was readily achieved using our protocol in very high yields (Table 4, entries 15–16), which was not found in the previous report.[48] In the course of our studies, the transformation of benzamide and acryl amide into the corresponding

Table 4 Nano rod-shaped Al_2O_3 catalyzed *N*-formylation of 1° and 2° amines

Entry	Amine **1**	Time (min)	Yield (%)[a,b]
1	$C_6H_5NH_2$	5	<98
2	$4\text{-}ClC_6H_4NH_2$	10	93
3	$2\text{-}ClC_6H_4NH_2$	10	90
4	$2\text{-}NO_2C_6H_4NH_2$	15	90
5	$3\text{-}NO_2C_6H_4NH_2$	10	93
6	$4\text{-}NO_2C_6H_4NH_2$	10	90
7	$4\text{-}MeOC_6H_4NH_2$	20	95
8	$2\text{-}MeC_6H_4NH_2$	15	92
9	$4\text{-}HOC_6H_4NH_2$	25	90
10	$4\text{-}COOHC_6H_4NH_2$	30	92
11	$C_6H_5NHNH_2$	45	90
12[c]	$4\text{-}NH_2C_6H_4NH_2$	260	85
13[c,d]	$2\text{-}NH_2C_6H_4NH_2$	300	85
14	$(C_6H_5)_2NH$	12	97
15	NH_2CH_2COOH	30	98
16	$CH_3CH(Me)CH(NH_2)COOH$	30	98
17	$C_6H_5CH_2NH_2$	30	93
18	Imidazole	90	85
19[c]	Piperazine	50	95
20[c]	$NH_2(CH_2)_2NH_2$	15	95
21	Pyrrolidine	55	63
22	CH_3NH_2	10	98
23	$(CH_3CHCH_3)_2NH$	240	43
24	C_6H_5OH		NR[e]
25	$C_6H_5CH_2OH$		NR[e]
26	C_6H_5CHNOH	300	[f]
27	$C_6H_5CHNNH_2$	300	[f]
28	$OHNH_2{\cdot}HCl$		NR[e]
29	H_2NNH_2		NR[e]

[a] Yields refer to the isolated pure products, [b] Products were characterised by IR and NMR (^1H and ^{13}C) spectroscopy, MS and also by comparing their melting points/boiling points with the authentic ones, [c] 6 mmol formic acid was used. [d] Benzimidazole was formed. [e] No reaction. [f] Mixture of unknown compounds.

Table 5 Nano-Al_2O_3 catalyzed *N*-formylation of indole and its derivatives[a]

Entry	Substrate	Time (min)	Yield (%)[b,c]
1	Indole	10	98
2	2-Methyl indole	45	92
3	3-Methyl indole	45	90
4	6-Bromo indole	30	90
5	Indol-3-acetonitrile	60	90
6	Indol-3-acetic acid	160	75
7	Indol-3-butyric acid	200	68

[a] Reaction conditions: 1 mmol indole, 3 mmol formic acid, 70 °C, [b] Yields refer to the isolated pure products. [c] Products were characterised by IR and NMR (^1H and ^{13}C) spectroscopy, MS and melting points.

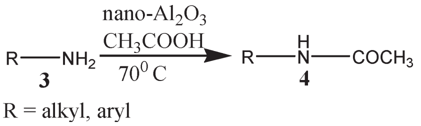
N-formylation products was also investigated. Both furnished slightly lower yields (70% in 3 and 4 h respectively). It might be due to the withdrawing of lone pair of electrons over N atom towards the carbonyl group making the N atom electron deficient for the nucleophilic attack. The reaction of benzyl amine and imidazole under the present reaction conditions also furnished *N*-formylation products in satisfactory yields (Table 4, entries 17 and 18). For aliphatic 1° and 2° amines, and diamines, the reaction showed good results towards the formation of *N*-formylation products under the present methodology (Table 4, entries 19–22). The *N*-formylation of sterically hindered diisopropyl amine could generate only 43% yield of the product even after conducting the reaction for 6 h (Table 4, entry 23). In an attempt to transform phenol, benzyl alcohol, benzaldoxime, benzaldehyde hydrazone, hydroxyl amine and hydrazine hydrate into corresponding *N*-formylation products, reactions were performed under our conditions, however, the reactions failed even after stirring for 24 h, where only starting material was recovered (Table 4, entries 24–29). The transformation of anilines carrying different electron-withdrawing and electron-donating moieties into the corresponding *N*-formylation products proceeded smoothly under the present reaction conditions, which demonstrated the compatibility of those moieties towards the reaction conditions. As a whole, the aryl and alkyl amines were converted into the desired formamides with high purities and yields and with no side product(s) formation. Notably, a previous report of *N*-formylation using KF–Al_2O_3,[49] is associated with some disadvantages, such as, (a) the system worked only for 2° amines and not for the 1° amines, (b) highly carcinogenic, chloroform was used, (c) KF–Al_2O_3 system was not recyclable, which is a set back from the aspect of economy and green chemistry. Similarly, Al_2O_3 supported formic acid[50] system also (a) took longer reaction time, (b) provided poor yield, and (c) loading of alumina as a support was quite higher.

In order to broaden the scope of using nano basic Al_2O_3 for *N*-formylation reactions, we next attempted the reaction using indole as a starting material. In this case, we could not obtain the expected product in good yield at 40 °C. Of particular significance, is that by raising temperature to 70 °C, the *N*-formylation product was obtained in excellent yield (Table 5, entry 1). Therefore, taking this to be the standard reaction conditions for indoles, the generality of the reaction was investigated for several indole derivatives and the results are presented in Table 5.

We were pleased to find that indoles substituted with electron-donating groups at 2- and 3-positions underwent the *N*-formylation reaction effectively akin to indole, giving the desired products in good to high yields (Table 5, entries 2 and 3). 6-Bromo indole, having an electron-withdrawing moiety also provided a high yield under the present reaction conditions (Table 5, entry 4). Indole-3-acetonitrile also produced the *N*-formylation product in high yield (Table 5, entry 5). Indole-3-acetic acid and indole-3-butyric acid were also transformed into the corresponding *N*-formylation products with somewhat lower yields (Table 5, entries 6 and 7). It might be due to the steric crowding at the 3-position.

After gaining such versatile applications of nano basic Al_2O_3, we were curious to see what would happen if we replaced formic acid by acetic acid under the standard conditions (Scheme 3). With this notion in mind, we checked the reaction with aniline (10.7526 mmol, 1000 mg) and glacial acetic acid (10.7526 mmol, 0.61 mL) in the presence of nano-Al_2O_3 (5.0 mol%, 54.8 mg) and we observed the formation of acetamide with high yields, without any side product (Table 6, entry 1). The experimental conditions and details are described in Table 6.

In our studies, we found that both the aryl and alkyl amines underwent reaction with acetic acid in the presence of nano-Al_2O_3, forming acetamide derivatives efficiently. It is found that

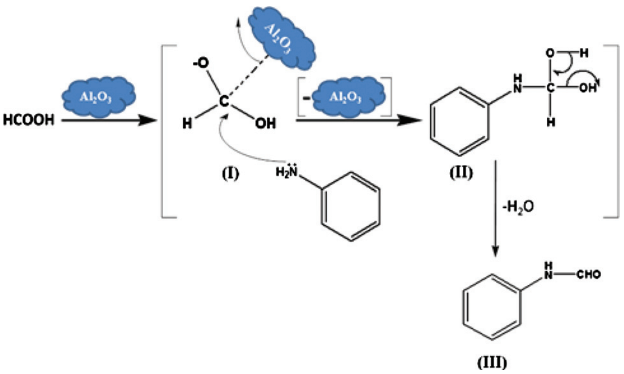


Scheme 3 Synthesis of acetamide derivatives.

Table 6 Nano-Al$_2$O$_3$ catalyzed synthesis of acetamide[a]

Entry	R	Time (min)	Yield (%)[bc]
1	C_6H_5	10	99
2	4-ClC_6H_4	18	90
3	2-ClC_6H_4	20	90
4	2-$NO_2C_6H_4$	15	90
5	3-$NO_2C_6H_4$	15	85
6	4-$NO_2C_6H_4$	35	70
7	4-$MeOC_6H_4$	20	95
8	2-MeC_6H_4	15	92
9	4-HOC_6H_4	45	80
10	4-$COOHC_6H_4$	30	88
11	$C_6H_5CH_2$	10	93
12	CH_3	25	98
13[d]	4-$NH_2C_6H_4$	260	Trace
14[d]	2-$NH_2C_6H_4$	360	85[e]

[a] Reaction condition: 1 mmol aryl/alkyl amines, 1 mmol acetic acid, 5 mol% nano basic Al$_2$O$_3$, 70 °C. [b] Yields refer to the isolated pure products. [c] Products were characterised by IR, NMR (^{1}H and ^{13}C), MS and melting points. [d] 2 mmol acetic acid was used. [e] Benzimidazole was formed.



Scheme 4 Plausible mechanism for the *N*-formylation of amines.

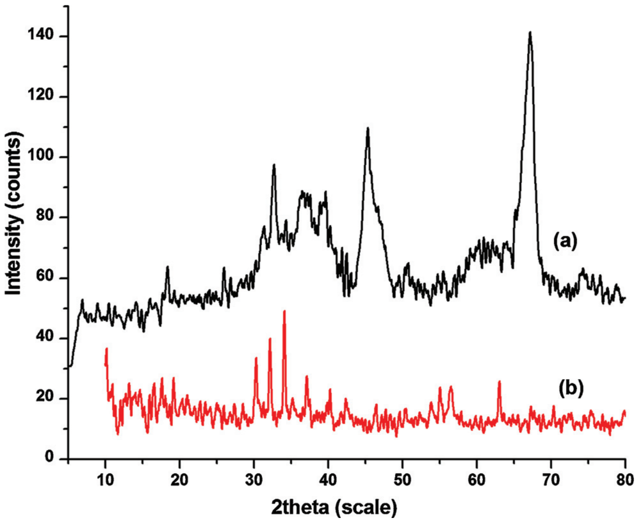


Fig. 8 Comparison of XRD of (a) fresh nano-Al$_2$O$_3$ and (b) the recovered one after 5th cycle.

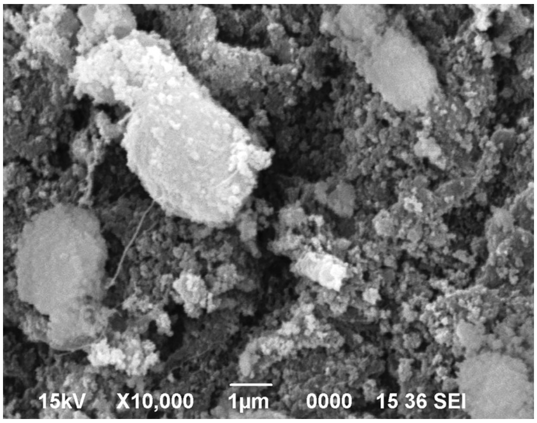


Fig. 9 SEM image of recovered nano-Al$_2$O$_3$ after the 5th cycle.

aryl amines substituted with electron-withdrawing moieties produced significantly lower yields of products than those substituted with electron-donating moieties (Table 6, entries 1–12). Under the present reaction conditions, *p*-phenylene diamine showed a trace yield (Table 6, entry 13) of product. However, with *o*-phenylene diamine, instead of furnishing an amide, cyclization occurred and 2-methyl benzimidazole was obtained in good yield (Table 6, entry 14). Furthermore, the attempt to use cyano acetic acid and trifluoro acetic acid for the synthesis of expected products failed under the present conditions. Our studies revealed that the treatment of aniline with propionic acid and butanoic acid in the presence of nano basic Al$_2$O$_3$ produced the corresponding amides in moderate yields (45% and 50% respectively) upon heating at 70 °C for 15 h. However, dicarboxylic acids (such as adipic and malonic acid) and the long chain monocarboxylic acids (such as lauric and behenic acid) remained unreactive with aniline even after stirring at 80–100 °C for more than 24 h.

To present a mechanistic rationale of this protocol, a plausible mechanism for the *N*-formylation of amines catalyzed by nano basic Al$_2$O$_3$ is depicted in Scheme 4. It has been proposed that the action of nano Al$_2$O$_3$ as a Lewis base increases the electron density on the carbon centre of the formic acid, possibly *via* the formation of an intermediate (I). This increase in electron density normally translates to enhanced nucleophilicity of the acceptor subunit. However, due to the counterintuitive consequence of the binding of a Lewis base, the electrophilic character of the acceptor in the reactive intermediate (I) is enhanced. Finally, elimination of water from (II) leads to the formation of the *N*-formylation product.

It is important to emphasise that catalyst recyclability is an essential aspect of the green chemistry. Therefore, the recycling potential of the nano-Al$_2$O$_3$ was also inspected during our studies of the model reaction (Scheme 2). It is our pleasure to mention that nano-Al$_2$O$_3$ is found to be equally effective from fresh up to the 5th cycle without significant loss of activity.

Table 7 Recycling potential of nano-Al_2O_3

No. of cycles[a]	Fresh	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9
Yield (%)[b]	98	98	98	98	98	98	90	85	75	60
Time (min)	5	5	5	5	5	5	25	40	60	180
TON	78.4	78.4	78.4	78.4	78.4	78.4	72	68	60	48

[a] Reaction conditions: 3.225 mmol aniline, 9.6774 mmol formic acid, 0.16129 mmol (5 mol%) nano basic Al_2O_3, 40 °C. [b] Yields refer to the isolated pure products.

It could also be efficiently reused in the 6th cycle, however, in subsequent cycles the yield of the product started to decrease. The XRD pattern of the fresh nano-Al_2O_3 was compared with the recovered one after the 5th cycle (Fig. 8).

It was observed from the Fig. 8 that the intensity of the two highest peaks in fresh nano-Al_2O_3 decreased in the recycled one after 5th run and it might be due to the dislocation of the crystal planes which might be the legitimate cause for the considerable lowering of yield of the *N*-formylation product in 6th run and so on.

SEM micrograph of recovered nano-Al_2O_3 after the 5th run is shown in Fig. 9. High agglomeration of the nano-Al_2O_3 was observed, which might also play a role in reducing the yield and reaction rate. It is clear from Table 7 that the TON of the catalyst is retained from the fresh to the 5th cycle and then it starts declining.

After the reaction, ethyl acetate was poured into the reaction mixture and then it was centrifuged (3000 rpm) to pellet out the nano-Al_2O_3. The separated particles were washed with hot ethanol (3 × 10 mL) to remove all the organic impurities. Finally, it was decanted and dried in an oven at 80 °C for 6 h. The particles so obtained were then reused for evaluating their performances in the next cycle.

The recyclability chart of the catalytic potential of the nano-Al_2O_3 is shown in Fig. 10. It is thus clear from Fig. 8 that the catalytic activity was maintained up to the 5th run and after that it started decreasing considerably.

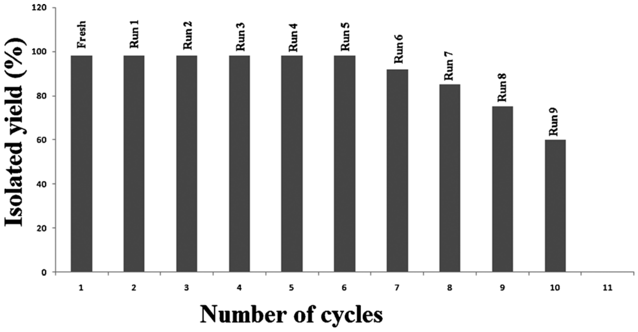


Fig. 10 Catalyst recyclability chart.

Conclusions

In conclusion, in a novel and convenient protocol we have shown that the *N*-formylation of amines occurs under solvent-free conditions using nano rod-shaped basic Al_2O_3 as an efficient catalyst. The advantages offered by this method include (a) simple experimental procedure and reaction setup only at 40 °C/70 °C, (b) does not require any specialized equipment, (c) high yields of desired products, (d) proceeds under ambient conditions with diverse substrate compatibility, (e) good chemoselectivity, (f) suitable recyclability, (g) moisture stability of the catalyst, (h) cost effectiveness, and (i) environmentally benign along the line of green chemistry. The application of nano-Al_2O_3 in organic synthesis is not fully explored. Hence, as communicated here, we are optimistic that metal nanoparticles including Al_2O_3 nano rods would find increasing applications for new chemical transformations, including those which enable the synthesis of complex natural products and derivatives. Efforts are currently underway in our research group to apply this 'NOSE' chemistry to the construction of other potentially valuable organic molecules like pyrimidine derivatives.

Authors are thankful to University Grant Commission, New Delhi-Special Assistance Programme (UGC-SAP) [no. F.3-30/2009(SAP-II) dated 31.03.2009] and Department of Science and Technology- Fund for Improvement of S&T Infrastructure in Higher Educational Institutions (DST-FIST) programme [no. SR/FST/CS-II-001/2009 dated 17.11.2009] for providing infrastructure facilities required for this research work and VKD thanks UGC for Rajiv Gandhi National Fellowship to him. The authors would also like to acknowledge Mr. Ratan Baruah for carrying out SEM studies and fruitful discussions.

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