IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 10, Issue 6 Ver. I (June. 2017), PP 86-90
www.iosrjournals.org

N-formylation of amines using nano cerium oxide as catalyst in inert gas atmosphere

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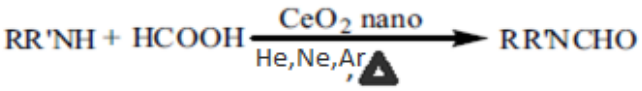
Abstract: *A new method of N-formylation of amines with formic acid in the presence of nano cerium oxide in inert gas containing glass tube to delivered a better yield of final product .this is a easy and affordeble method of N-formylation of amines*

I. Introduction

Formamides are so valuble compound in pharma industry . in pharmaceutical's nitrogen containing compound are in high demand and formamide are good to protect the nitrogen in amines . it has been reported in servel reaction that formamide act as lewis base catalyst . in recently researcher has developed lots of synthesis method of N-formylation of amines like using N,N'-dicyclohexylcarbodiimide or N-(3-Dimethylaminopropyl)- N'-ethylcarbodiimide hydrochloride , activated formic esters ,ammonium formate.but one of effective method prepared by S. Mohammad sajadi and their co-worker(*Letters in Organic Chemistry*, 2014, *11*, 49-54) is about synthesis of formamide using cerium oxide in ultrasound irradiation and this is high efficient method to delivered higher yield . nano cerium oxide is an efficient and recyclable catalyst and using widely in organic synthesis .in recent days lot's of previous study are enough to tell the advantage and properties of nano CeO2 ,this catalyst show fast reactive activity toward organic reagent and increase the activation energy as much as it can and delivered the highest yield only in appropriate medium .in other reported method the required reagent are expensive , toxic and hard to store . the formylation of anilines having electron withdrawing groups was found to be difficult so conventional heating treatment can be for longer time and lesser yield .but in some of recent report the metal oxide got considerable attention due to their higher catalytically activity .sajadi reported their synthesis of N-formylation of amines using formic acid in the presence of nano cerium oxide and ultrasonic irradiation. But in our study we use a glass tube containing a higher concentration of inert gas medium .and we got good product yield



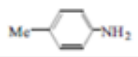
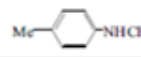
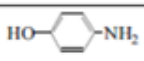
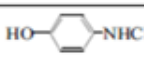
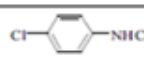
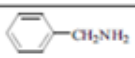
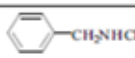
	Amine	Product	Time (min)	Yield% (%) in CeO2	Yield% (%) CeO2 +He	Yield% (%) CeO2 +He+heat
1			30	45	50	74
2			30	33	47	61
3			25	39	53	66
4			65	50	49	59
5			40	57	62	79
6			35	44	41	70
7			50	39	59	73

Table 1 formamide synthesis in CeO2, in CeO2 with He atmosphere, in CeO2 with He and conventional heat and their yield in percentage

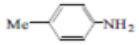
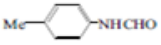
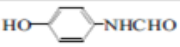
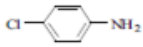
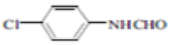
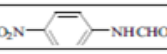
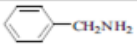
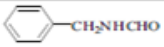
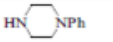
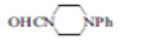
	Amine	Product	Time (min)	Yield[b] (%) in CeO2	Yield[b] (%) CeO2 +Ne	Yield[b] (%) CeO2 +Ne +heat
1			30	45	65	85
2			30	33	59	70
3			25	39	70	75
4			65	50	69	77
5			40	57	75	90
6			35	44	65	79
7			50	39	77	81

Table 2 formamide synthesis in CeO2, in CeO2 with Ne atmosphere, in CeO2 with Ne and conventional heat and their yield in percentage

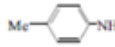
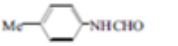
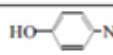
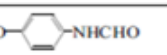
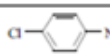
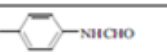
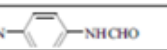
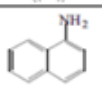
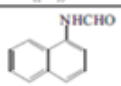
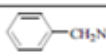
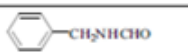
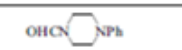
	Amine	Product	Time (min)	Yield[b] (%) in CeO2	Yield[b] (%) CeO2 +Ar	Yield[b] (%) CeO2 +Ar+heat
1			30	45	70	83
2			30	33	63	72
3			25	39	67	71
4			65	50	75	80
5			40	57	79	90
6			35	44	68	82
7			50	39	80	84

Table 3 formamide synthesis in CeO2, in CeO2 with Ar atmosphere, in CeO2 with Ar and conventional heat and their yield in percentage

Benzene derivative amines showing above and their percentage yield is confirming that the reactions in inert atmosphere delivered a good yield

II. Results

in a later report the above reactions was undergo in a ultrasonic irradiation and delivered the higher yield but in our process we use He, Ne, Ar gas atmosphere .above tables is showing all data of product formation with different –different environment .firstly no reaction has been occur without any catalyst and without inert atmosphere. Second time we carried out the reaction without inert atmosphere and we get lower yield in the presence of cerium oxide catalyst. CeO2 nanoparticles were purchased and the size was 3-6 nm . Without CeO2 and inert atmosphere no reaction occurs .second time with CeO2 at room temperature without inert gas atmosphere reaction occurs but yield was very lower and took long reaction time. Third time CeO2 with heating and absence of inert gas atmosphere almost nothing change . fourth time with CeO2 and inert gas atmosphere at room temperature yield increase and increase was enough detectable and fifth time CeO2 with inert gas atmosphere by giving conventional heating the yield is become more higher as shown in table 1,2,3 .and when we increase more temperature no change has been seen .the table1 showing three step first we proceed reaction with CeO2 ,second when we proceed with CeO2 and He gas atmosphere and third when we proceed the reaction with CeO2 with He gas atmosphere with conventional heat,table 2 is showing the resultant yeild when He is replace by Ne gas and again all step repeated a significant changes has been seen ,with Ne atmosphere the yeild increased and a constant increment is seen arround of 10-15% and then the formylation proced is carried out in Ar gas atmosphere and a detecteble growth in product yeild is seen .in compare of He and Ne gas the growth was about 10-15% but in compare with Ne and Ar growth was about 5-8% . as table

1,2,3 showing detailed yeild formation and the conclusion is came out is ,as the size (He Ne Ar) increase the reactivity also increase that increase the resulting yeild of product .The expected reason behind the growth of yeild is that ,as the size of inert gasses increase they increase the effective collision with reactant as well as with all transition states,He size is smaller and Ar size is quite bigger so when reaction proceed with Ar the yeild was quite higher then when it was carried out with He gas .so the reason behind the growth of yeild in inert atmosphere is size-collision factor . in conventional heating process collisions by Ar gas with bigger atomic size increase the catalyst-reactent reactivity and increase the product yeild but in case of He the size is not enough as compare to other (Ne,Ar).but it also increase the yeild but not as much as did by Ne and Ar gasses . so by this process the fact came out is that . A highly concentrate inert atmosphere accelerates the reaction. in some previous study CeO2 and ultrasound irradiation was a good combo to delivered better yield but in this study we also delivered a alternate combo of CeO2 and inert gas atmosphere .and all this reaction is in solvent –free condition .in all of reaction we use 1-3 mole of amines and 1.2 to 2 mole of formic acid with CeO2 around 5 mole . but when we came out at our extreme yield the change of catalyst quantity doesn't influence our final product yield . When steric hindered amine was carried out by this process and the yield was quite higher then of a without inert atmosphere process. inert gasses doesn't react with other chemicals .but this report is showing that in the presence of He,Ne and Ar atmosphere it influence the reactivity of reagent with proper catalyst medium. The products were characterized by IR, NMR spectroscopy Disappearance of one strong and sharp absorption band (-NH2 stretching band) and appearance of a carbonyl stretching band in the IR spectra, were evidences for the formation of *N*-formyl derivatives. IR spectra showed two characteristic peaks, one between 3300 and 3400 cm-1 and the other between 1640 and 1680 cm-1 (*N*-formyl, C=O). The relevant 1H NMR spectrum shows two distinctive proton signals; one is related to NH of the *N*-formamides and another belongs to the aldehyde. In some of other formalyting method like HCOOH, Sodium format HCOOH, Anhydrous ZnCl2 and HCOOH, Amberlite IR-120 delivered good yield but take very long time for reaction and in the Ammonium format And HCOOH, PEG formylatinf method take 6 h. To proceed the reaction with reflux and delivered much lesser yield of final product . formylating with HC(OEt)3 take 1 day to complete the reaction and delivered less than 50% yield . if we compared all this process to our process we don't need expensive and toxic reacting agent .less reaction time . and H2O as by-product .CeO2 play very important role in this process and when it comes with nano size the surface area of particle increase and also increase the reactivity of reagent .so the proposed mechanism is

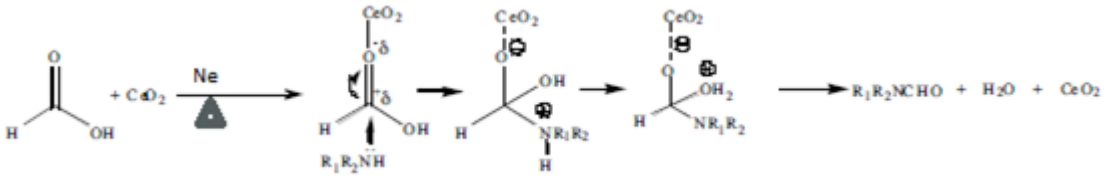


Figure 2 N-formylation on amine with formic acid

Treatment of amine with formic acid occurs through the activation of the carbonyl group over surface of the catalyst followed by the nucleophilic attack of the amine NH. BET results show that surface area of nano cerium oxide is 214 m2/g .basically CeO2 may enhance the electrophilic character . in this mechanism two bond break C-OH and N-H

III. Experimental

N-formylation of amines

Nano CeO2 was perchached size of 4-6 nm. All amines used in this process are in concentration of about 1-3 mole .aq .formic acid was about 2-3 mole and cerium oxide was around 5 mole .all the first we evacuate the glass tube length of 2ft and then insert the inert gas and then we added appropriate amine in the inert gas containing glass tube in the first step .in second step we added formic acid by the same path and finally we added nano CeO2 and stere the glass tube and after a little steer we give it the conventional heat slowly – slowly .after the completion of reaction all mixture took into a flask and to remove the catalyst by adding ethyl acetate and final product is obtained the by product was only water and the final product doesn't need any other process of purification .and the final product is confirmed by FT-IR and 1H NMR and yield observer

Spectral data

Table 1 entry 7 –(in the presence of CeO2 , Ne atmosphere with conventional heat) FT-IRE (Ker, cm-1): 2916, 2814, 1654, 1632, 1599, 1499, 1447, 1405, 1385, 1366, 1350, 1334, 1283, 1254, 1239, 1197, 1149, 1092, 1057, 1033, 1007, 916, 766, 693; HE NOR (300 MHz, Cycle): _H 10.3 5 (s, HE), 8.55 (s, HE), 6.92-7.33 (m, HE, Are-H), 3.72-3.16 (m, HE); successful confirmation of 4-Phenylpiperazine-1-carbaldehyde with M.p 82-84 °C

IV. Conclusion

Our method of N-formylation giving the new direction of research for chemical processes .we used inert atmosphere for N-formylation .most of reaction are carried out in either ultrasonic or u.v. light but we use a inert gas medium and it delivered a significant influence on the chemical process .basically our method is about for better yield and low cost management of process without any toxicity .this method can be a good deal in other organic reaction. in some of previous report the application and property of CeO2 are described enough but when CeO2 comes with inert atmosphere significant changes had been seen .because one thing is confirmed that how inert medium influence the chemical reactivity and it also rise the new field of study on inert gasses that the size-collision factor is the potential of inert gas forcing to do all these changes

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