



A facile method for the N-formylation of primary and secondary amines by liquid phase oxidation of methanol in the presence of hydrogen peroxide over basic copper hydroxyl salts

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ABSTRACT

N-formylation reactions by catalytic oxidation of methanol in the presence of primary or secondary amines and hydrogen peroxide has been investigated using a liquid phase reaction system over basic copper hydroxyl salts. A series of basic copper hydroxyl salts was prepared by the conventional precipitation method using aqueous ammonia and sodium hydroxide as precipitating agents. PXRD, SEM, FT-IR, BET were employed for physical characterization of the prepared basic copper hydroxyl salts. The composition of the catalytic material obtained was found dependent on the nature of the anion associated with the copper salt precursor. The copper hydroxyl chloride catalyst has shown the best catalytic performance in terms of the reaction rate and product selectivity whereas for the copper oxide catalyst the reaction rate was extremely slow. It is interesting to observe that 4-piperidone protected with acid-sensitive functional groups such as N-acetyl piperazine and ethylene glycol can also be formylated from moderate to good yields by these catalysts.

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1. Introduction

Formylation is a very important process in synthetic organic chemistry. Selective formylation of primary and secondary amine groups, in the presence of acid-sensitive functional groups has great practical utility. Formanilides are widely used in the synthesis of pharmaceutically active compounds [1–4]. Formamides are Lewis bases, which are known to catalyze reactions such as asymmetric allylation [5] and hydrosilylation [6] of carbonyl compounds. These formamides are useful reagents in Vilsmeier formylation reactions [7] and synthesis of formamidines [8] and isocyanides. A variety of methods are available [9–13] for N-formylation of amines and a number of formylating reagents were reviewed [14]. Many of these methods involved reagents, which are either moisture-sensitive, toxic or expensive. In this article we report a novel, less expensive, and selective catalysts for N-formylation of primary and secondary amines, including those with acid-sensitive functional groups.

2. Experimental

2.1. Catalyst preparation

Copper salts such as cupric acetate (Lobachemie, 98%), cupric chloride (Lobachemie, 98%), cupric nitrate (Lobachemie 99.5%), and cupric sulphate (Merck, 99%) were used without further purification. A 1.0 M solution of these salts was prepared by using double distilled water. Aqueous ammonia (Merck, 25–29%) was used as such and 3.0 M sodium hydroxide (Merck, 97%) solution was prepared by using double distilled water.

The basic copper hydroxyl salts were prepared under three different precipitation conditions by adjusting the pH of the solution and these conditions were referred to as method A, method B and method C.

Method A involves the use of aqueous ammonia to adjust the pH of the solution between 9 and 10. *Typical procedure:* 1.0 M cupric chloride solution (50.0 ml) was taken in a round bottom flask and was slowly added to it 7.8 ml of ammonia solution under stirring at 25–27 °C over a period of 45 min till the reaction mixture attained a pH of 9.5. The blue slurry mass thus obtained was continued to be stirred for 1.0 h at 27 °C. In the method B, aqueous ammonia was used to adjust the pH initially to the range of 6.5–7.5 and then 3.0 M sodium hydroxide to the pH 9–10. *Typical procedure:* 1.0 M cupric chloride solution (100.0 ml) was taken in a round

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Table 1
Copper-based catalysts prepared from different methods/sources and the abbreviations used.

S. No.	Copper salts used	Method A	Method B	Method C
1	Cupric acetate [Cu(OAc) ₂ ·H ₂ O]	CAA	CAB	CAC
2	Cupric chloride [CuCl ₂ ·2H ₂ O]	CCA	CCB	CCC
3	Cupric nitrate [Cu(NO ₃) ₂ ·3H ₂ O]	CNA	CNB	CNC
4	Cupric sulphate [CuSO ₄ ·5H ₂ O]	CSA	CSB	CSC

bottom flask and was slowly added ammonia solution (12.5 ml) over a period of 20 min until a pH of 7.2 was attained, followed by addition of 3.0 M sodium hydroxide solution (10.3 ml) over a period of 25 min under stirring at 27 °C to reach the pH of 9.6. The blue slurry mass thus obtained was stirred for another 1.0 h at 27 °C. In the method C, only 3.0 M sodium hydroxide solution was used to adjust the pH to 9–10. All the precipitation reactions were carried out at room temperature. *Typical procedure:* 1.0 M cupric chloride solution (100.0 ml) was taken in a round bottom flask and was slowly added 3.0 M sodium hydroxide solution (51.2 ml) under stirring at 25–27 °C over a period of 40 min to make the pH 9.5. The blue slurry mass was stirred for 1.0 h at 27 °C. The precipitates thus obtained were separated by filtration, washed thoroughly with water and dried at 120 °C for 18.0 h. The materials thus obtained were powdered and calcined at 300 °C for 2.0 h in a Therelek electric furnace (Type-K-1200).

Similar methods were followed to prepare basic copper hydroxyl salts from different cupric (II) salts, such as cupric acetate, cupric chloride, cupric nitrate and cupric sulphate. The type of catalysts prepared and the abbreviations used are shown in Table 1. For instance the code CAA represents the material obtained from copper acetate (CA) by method A.

2.2. Catalyst characterisation

The textural properties of the catalysts were analysed by powder X-ray diffraction (PXRD, Philips, *X'perts*) at 293 K using Cu K α ($\lambda = 0.15418$ nm) radiation in the range of 2θ 10–70°, at a scanning speed of 2°/min and scanning electron microscopy (SEM) images were recorded on gold-coated samples using a Philips apparatus equipped with a hemispherical energy analyser. The Fourier transform infrared (FT-IR) spectra of copper-based catalysts were recorded using KBr pellets by a Shimadzu (Model 8101 M) FT-IR spectrometer, in the range of 4000–400 cm⁻¹. The surface areas of all the catalysts were assessed by the Brunauer, Emmett, and Teller (BET) technique via N₂ adsorption at liquid nitrogen temperature—using a Nova-1000, ver. 3.7 instrument. Prior to adsorption–desorption experiments, the samples were degassed at 120 °C at 10⁻⁴ Torr for 2.0 h.

2.3. Catalytic activity of basic copper hydroxyl salts

The catalytic activity of the materials prepared have been investigated by adding hydrogen peroxide very slowly to a mixture of primary or secondary amine and methanol. The reaction was carried out in a round bottom flask and the contents were stirred using a magnetic stirrer. TLC technique was used to observe the reaction progress.

The evaluation of catalytic activity of all the prepared materials has been performed initially using p-chloroaniline as a substrate. A typical procedure is as follows: To a solution of p-chloroaniline (100.0 mg) in methanol (5.0 ml) containing 100.0 mg of the catalyst, 2.0 ml, 6% (w/w) of hydrogen peroxide was added slowly. The resulting mixture was continued to be stirred at room temperature. Samples were periodically taken and the reaction progress was monitored by thin layer chromatography (TLC) (hexane:ethyl

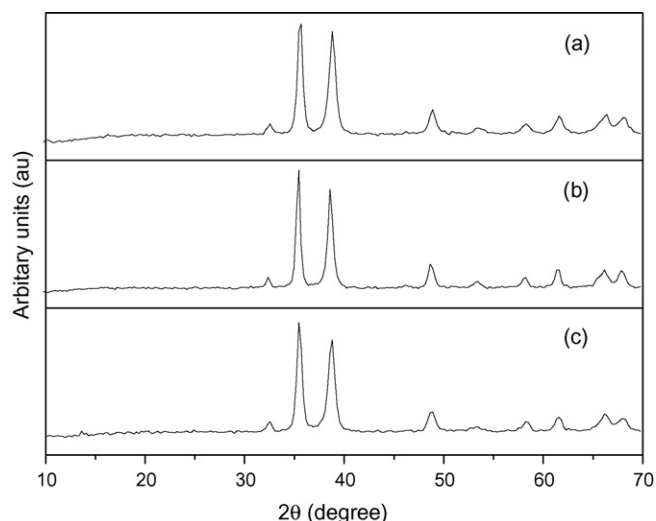


Fig. 1. PXRD patterns of: (a) sample CAA, (b) sample CAB, and (c) sample CAC from cupric acetate salt as precursor.

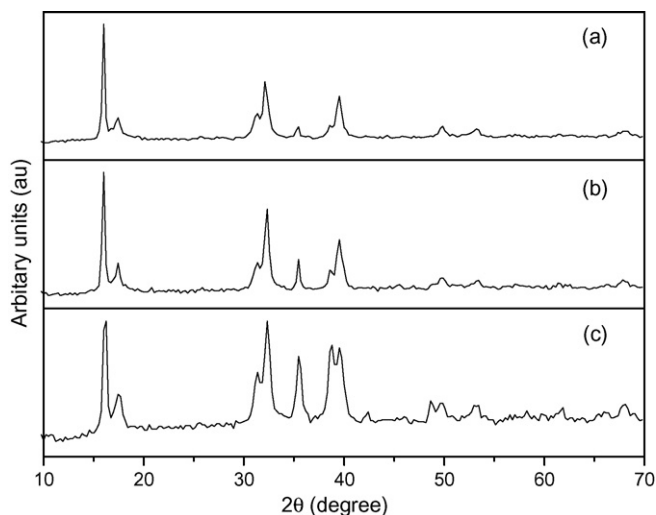


Fig. 2. PXRD patterns of: (a) sample CCA, (b) sample CCB, and (c) sample CCC from cupric chloride salt as precursor.

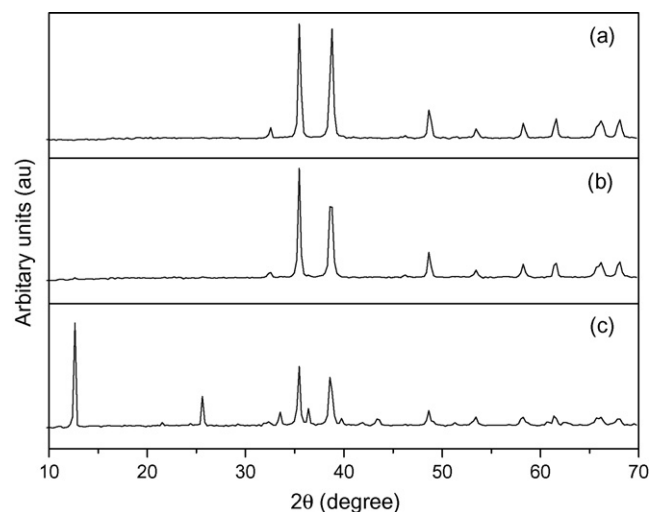


Fig. 3. PXRD patterns of: (a) sample CNA, (b) sample CNB, and (c) sample CNC from cupric nitrate salt as precursor.

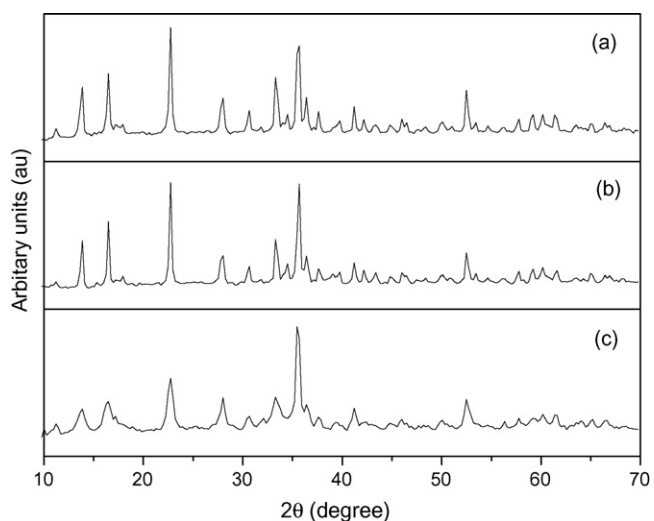


Fig. 4. PXRD patterns of: (a) sample CSA, (b) sample CSB, and (c) sample CSC from cupric sulphate salt as precursor.

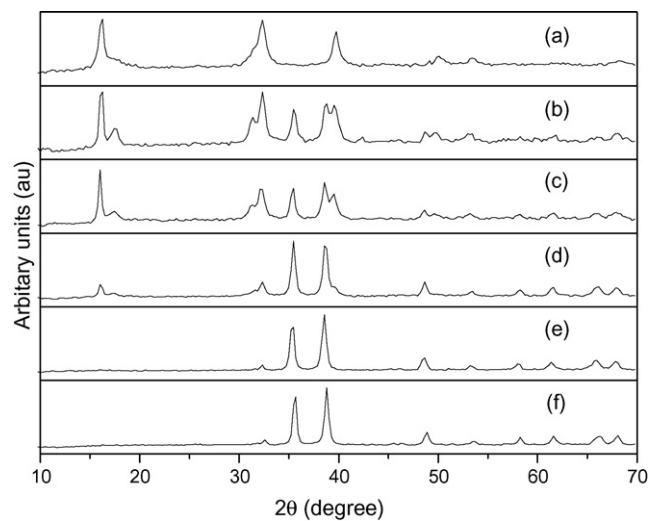


Fig. 5. PXRD patterns of different temperature dried copper-based salts through method C from cupric chloride as precursor: (a) sample CCC1 dried at 120 °C/18 h, (b) sample CCC2 dried at 300 °C/2 h, (c) sample CCC3 dried at 350 °C/2 h, (d) sample CCC4 dried at 400 °C/2 h, (e) sample CCC5 dried at 450 °C/2 h, and (f) sample CCC6 dried at 500 °C/2 h.

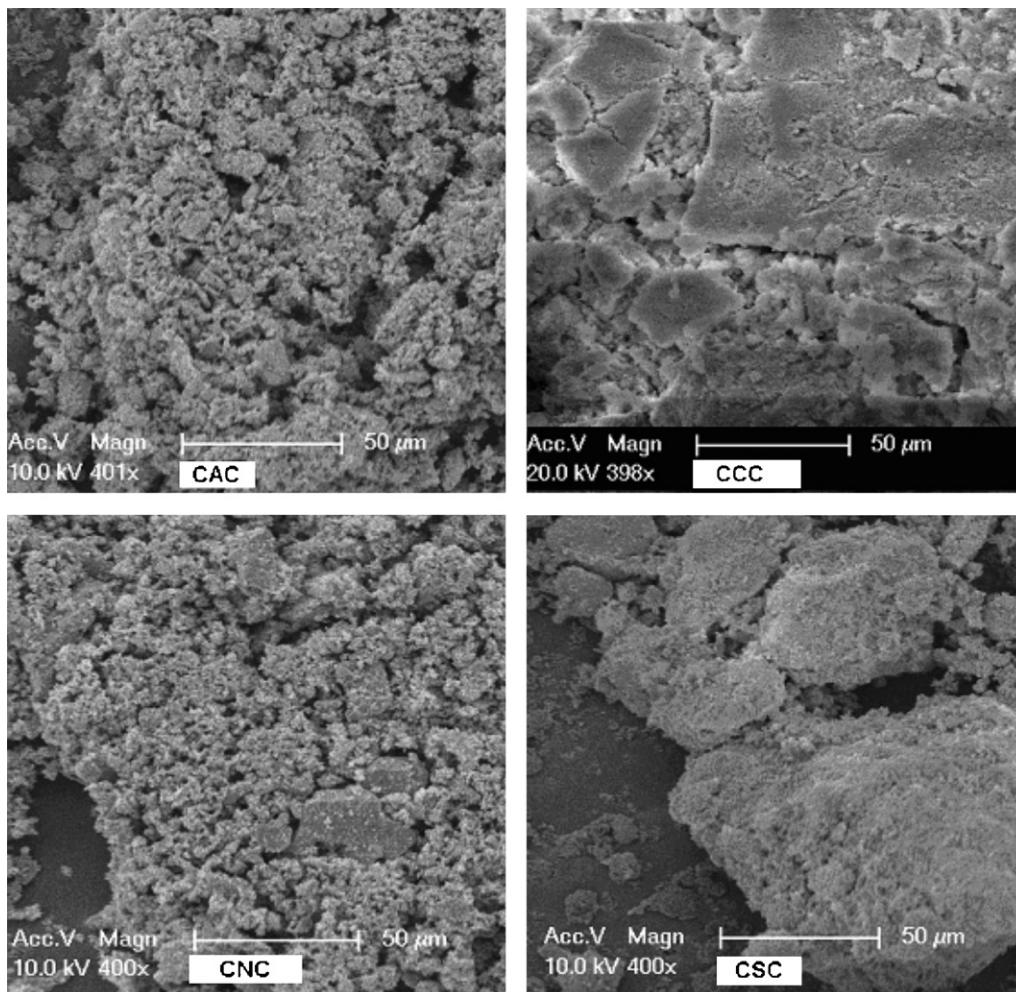


Fig. 6. SEM photomicrographs of copper-based catalysts produced through method C from different copper salts as precursor (CAC from cupric acetate, CCC from cupric chloride, CNC from cupric nitrate and CSC from cupric sulphate).

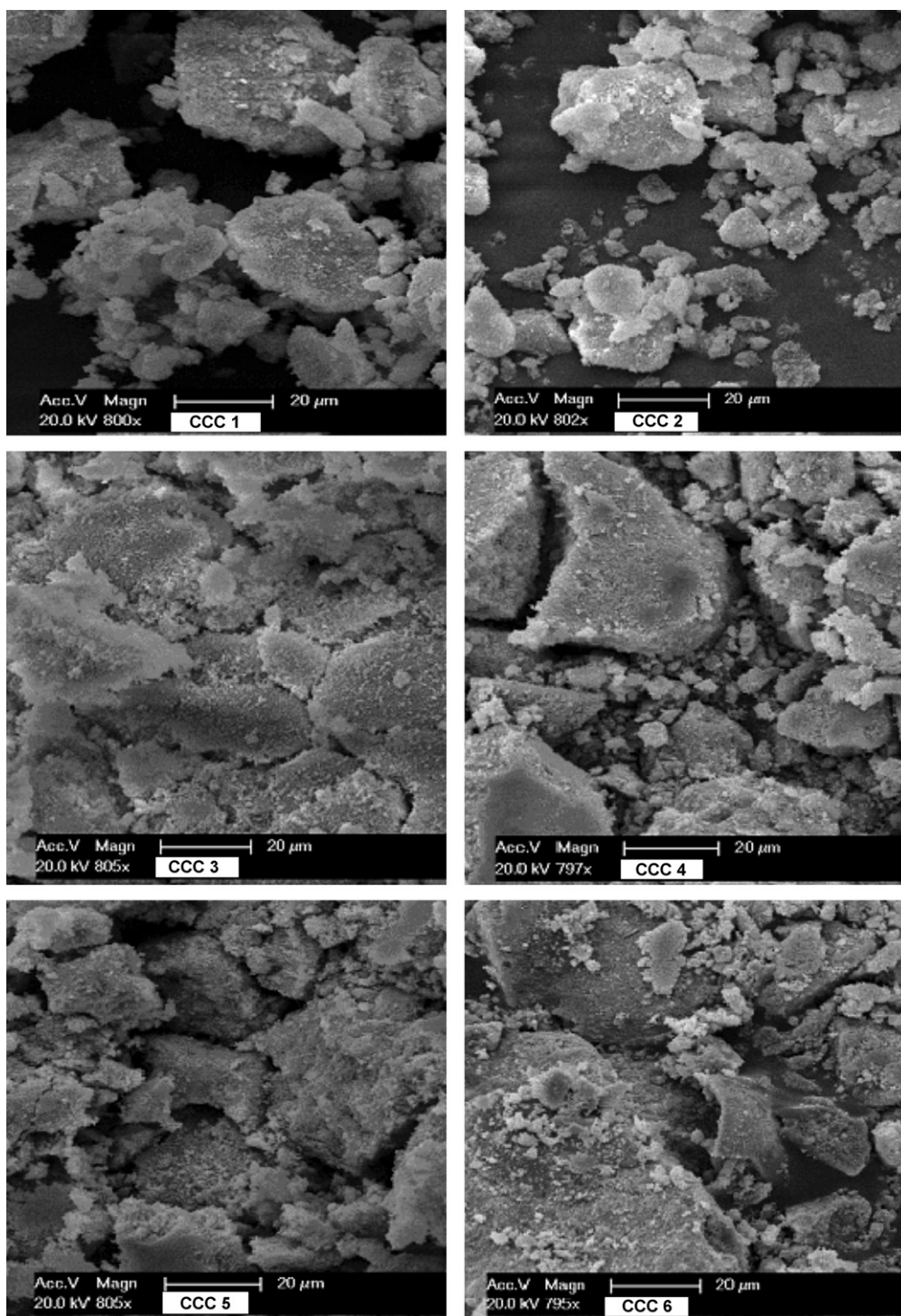


Fig. 7. SEM photomicrographs of different temperature dried copper-based catalysts through method C from cupric chloride as precursor.

acetate – 7:3). After completion of the reaction, the catalyst was removed by filtration through celite bed and the bed cake was washed with methanol (5.0 ml). Aqueous methanol was concentrated under reduced pressure at 45–50 °C. The organic material was purified by flash column chromatography.

Melting point (mp) of the products was determined in one open and the other end-closed capillaries using a Buchi oil heating apparatus (Model: B-540) and uncorrected. ^1H NMR and ^{13}C NMR spectra were taken on a Bruker 200 MHz instrument. The chemical shifts were recorded with tetramethylsilane (TMS) as the internal reference. The mass spectra were recorded by an automated gas

chromatograph–mass spectrometer (GC–MS), Shimadzu QP 5000 GC-17A, EI-Mode model.

3. Results and discussion

Powder XRD: The PXRD patterns of the basic copper hydroxyl salts obtained by the three methods A, B and C using different copper salts are presented in Figs. 1–4. It is noticed from Fig. 1 that the materials obtained from cupric acetate correspond to the copper oxide phase (JCPDS # 45-0937). Fig. 2 indicates the formation of copper hydroxyl chloride (JCPDS # 78-0372) when cupric chloride

Table 2

Specific surface area (m^2/g), average pore diameter (\AA) and average particle size (nm) of copper-based catalysts.

Basic copper salts	BET surface area (m^2/g)	Average pore diameter (\AA)	Average particle size (nm)
CAA	15.6	71.5	12
CAB	15.0	70.7	14
CAC	14.0	68.7	12
CCA	11.6	57.2	15
CCB	12.3	57.0	17
CCC	13.6	56.9	15
CSA	7.1	67.8	21
CSB	6.5	69.2	16
CSC	6.0	62.4	12
CNA	5.3	73.0	21
CNB	4.8	77.0	21
CNC	6.3	64.8	26

was used as precursor. In the case of cupric sulphate as precursor, copper hydroxyl sulphate (JCPDS # 43-1458) was formed (Fig. 4). In all these cases the copper salt phase obtained is independent of the method of preparation. However, when cupric nitrate was used as a precursor (Fig. 3), methods A and B produced the copper oxide phase whereas method C generated copper hydroxyl nitrate (JCPDS # 14-0687). Thus these observations highlight the importance of the preparation method and conditions in the development of the catalytic material. With an increase in the calcination temperature of the material, for example, copper hydroxyl chloride gradually changes into its oxide form (Fig. 5). This change in phase is further reflected in its catalytic activity as explained later, the oxide form being less active when compared to the hydroxyl salts.

Scanning electron microscopy (SEM): SEM images of all the materials synthesized from different copper precursors through the method C are shown in Fig. 6. From these images it is observed that the particles are very fine and are not aggregated into any specific crystalline phases. Further the material seems to be well dispersed particles of a regular size. Fig. 7 indicates the effect of calcination temperature on the morphology of the catalytic particles obtained from cupric chloride. It is clearly observed from these SEM images that the catalytic particles get aggregated with an increase in the calcination temperature.

Textural properties by BET: The surface area along with the average pore diameter of the copper-based catalytic materials evaluated by the BET-nitrogen adsorption technique is compared in Table 2. There is no variation in the surface area irrespective of the method used for the preparation. However the anion associated with precursor copper salts seems to play an important role in determining the surface area of the material. It is noticed that the materials prepared from nitrate and sulphate sources exhibited lower surface area than those obtained from acetate and chloride salts. Further within these two sets the surface area of $\text{SO}_4^{2-} > \text{NO}_3^-$ and $\text{CH}_3\text{CO}_2^- > \text{Cl}^-$. It is also interesting to note that the particle size calculated from PXRD data had good correlation with the surface area obtained through the BET technique. That is in general the samples with lower surface area exhibited higher particle size.

FT-IR spectroscopy: FT-IR spectra of all the catalytic materials synthesized under different experimental conditions using various copper precursor salts have been presented in Figs. 8–12. This analysis has clearly supported the fact that a change in the anion associated with the precursor copper salt has had an influence on the nature of the basic copper hydroxyl salt phase generated through various experimental conditions. All those materials that were obtained as hydroxyl salts (CCA, CCB, CCC, CNC, CSA, CSB, CSC) exhibited a strong band in the hydroxyl stretching region, $3340\text{--}3450\text{ cm}^{-1}$. But the samples (CAA, CAB, CAC, CNA, CNB), which were obtained as oxides, did not show this characteristic band of the hydroxyl group. It is to be noted further that the

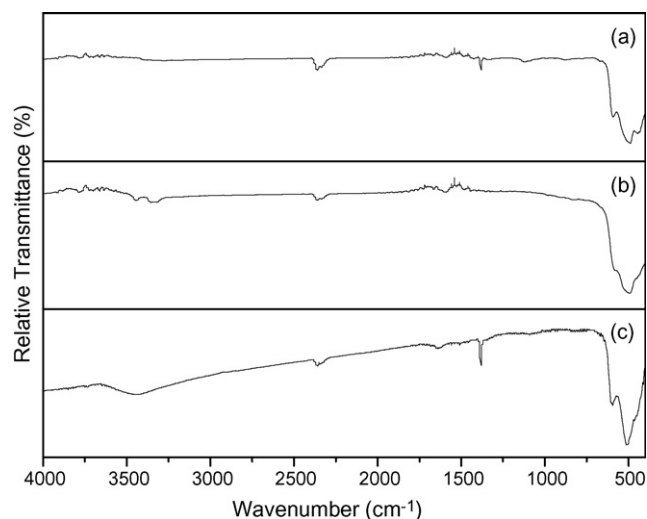


Fig. 8. FT-IR spectra of: (a) sample CAA, (b) sample CAB, and (c) sample CAC.

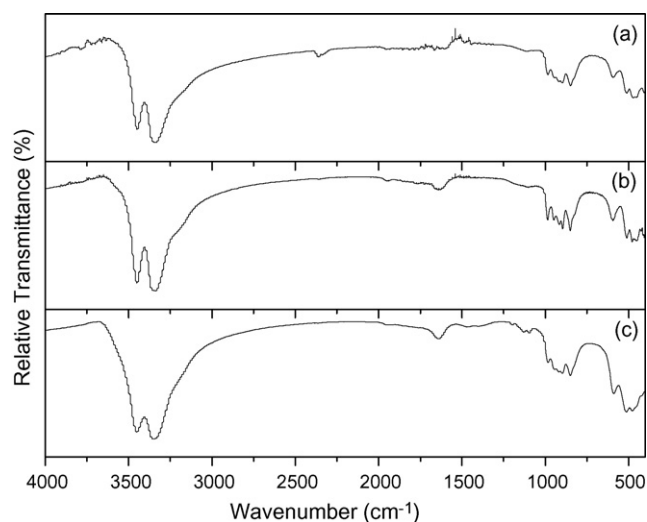


Fig. 9. FT-IR spectra of: (a) sample CCA, (b) sample CCB, and (c) sample CCC.

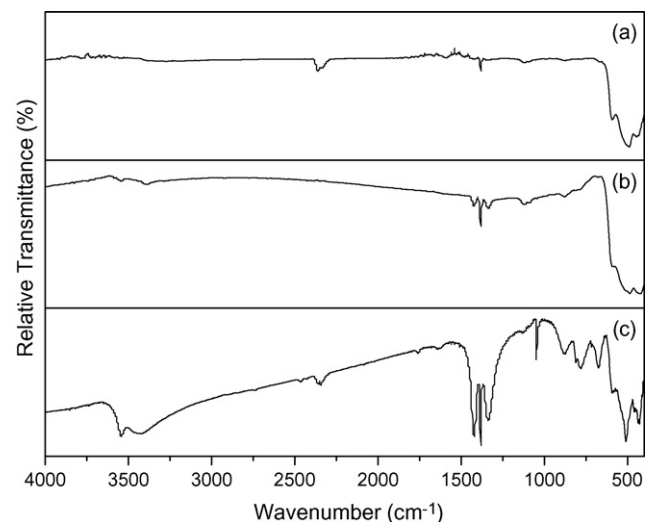


Fig. 10. FT-IR spectra of: (a) sample CNA, (b) sample CNB, and (c) sample CNC.

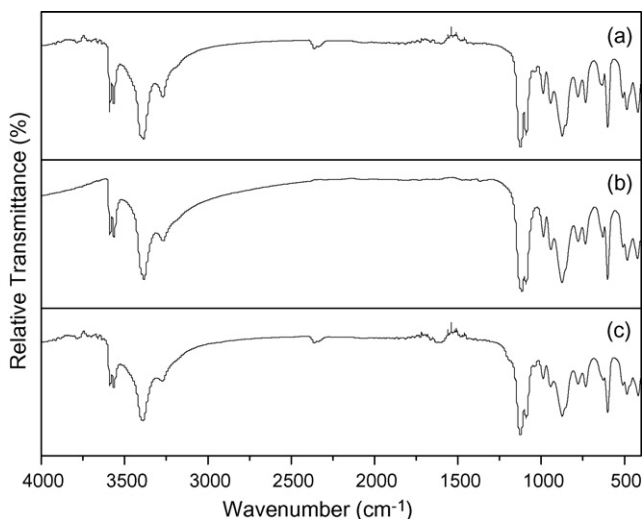


Fig. 11. FT-IR spectra of: (a) sample CSA, (b) sample CSB, and (c) sample CSC.

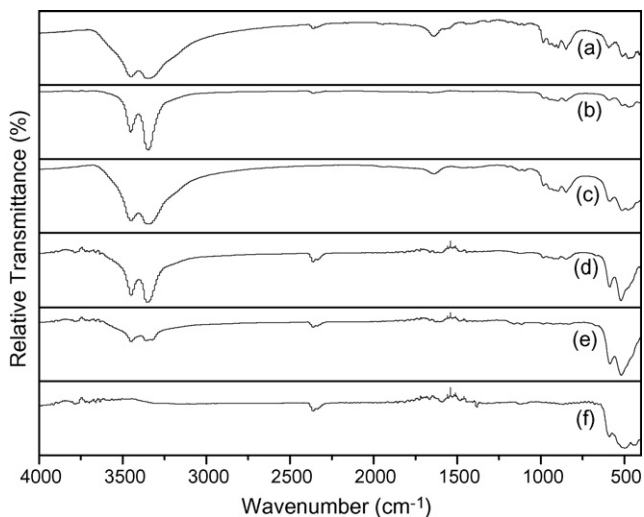


Fig. 12. FT-IR spectra of: (a) sample CCC1 dried at 120 °C/18 h, (b) sample CCC2 dried at 300 °C/2 h, (c) sample CCC3 dried at 350 °C/2 h, (d) sample CCC4 dried at 400 °C/2 h, (e) sample CCC5 dried at 450 °C/2 h, and (f) sample CCC6 dried at 500 °C/2 h.

hydroxyl band is split. The appearance of the bands at 1424, 1379, 1335 and 1050 cm^{-1} in the case of the CNC sample clearly indicated the presence of the nitrate group (Fig. 10(c)) and those at 1121, 985 and 605 cm^{-1} in the case of CSA, CSB, and CSC indicated the presence of the sulphato type of complexes (Fig. 11).

Calcination temperature: Fig. 12 indicates the effect of calcination in the range of 120–500 °C on the hydroxyl stretching vibrations for the CCC sample. It is very clear from these spectra that the hydroxyl bands gradually disappear with increasing calcination temperature, eventually converting the copper hydroxyl chloride salt into copper oxide at 500 °C.

Thus the above characterization techniques indicate that there is a good correlation between the observed surface and bulk properties of prepared copper catalysts.

3.1. Catalytic activity studies

A systematic study on the optimisation of the reaction conditions for the good yield of formanilide has been investigated by using p-chloroaniline. The time taken for complete conversion of p-chloroaniline to p-chloroformanilide over different basic copper hydroxyl salts prepared from different copper sources and calcined at 300 °C is presented in the form of bar diagram (Fig. 13). The catalytic activity of the material generated from cupric chloride and cupric sulphate precursor is significantly higher than that of the material obtained from either cupric acetate or cupric nitrate. Further the material obtained from cupric nitrate precursor exhibited the lowest activity. It is worth mentioning here that copper hydroxyl salts were the products obtained when chloride or sulphate or nitrate of copper were used as the precursor for the preparation of the catalyst. This clearly indicates that when copper is associated with mixed anions such as hydroxyl chloride, hydroxyl sulphate and hydroxyl nitrate phases the material exhibited significantly higher activity than in the form of a simple salt such as its oxide. Among the mixed anion salts of copper the catalytic activity towards the formation of formanilides is found to decrease in the following order:

copper hydroxyl chloride > copper hydroxyl sulphate > copper hydroxyl nitrate

This order of catalytic activity also reflects the ability of these materials to catalyze the oxidation of methanol into CO_2 and H_2 , as the latter are the active components in the conversion of amines to formanilides [15–18]. It is reported that γ -copper hydroxyl chloride phase was catalytically active in the oxidative carbonylation of methanol in dimethyl carbonate synthesis [19]. This indicates that the copper in copper hydroxyl chloride phase is in a more electron-deficient state than that in the other two. This state of copper may be attributed to the more electronegative chlorine atom. The lethargic activity of copper oxide in the formation of formanilides shows its stability towards a change in its oxidation state.

It may be stated that copper hydroxyl chloride in the presence of hydrogen peroxide oxidizes the methanol into CO_2 and H_2 , and that further with this the primary or secondary amines get converted into N-formyl amines (Scheme 1).

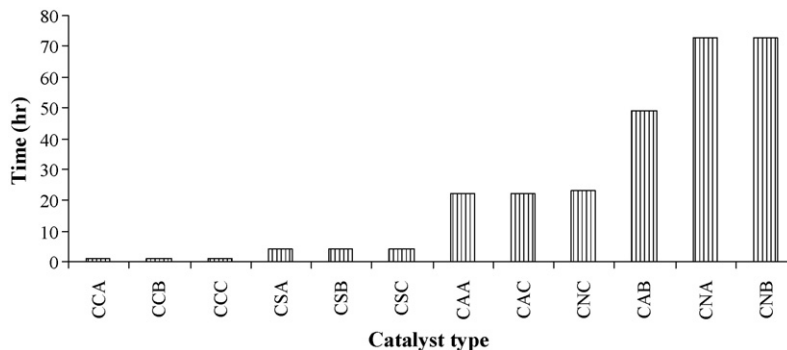


Fig. 13. Time taken for complete conversion of p-chloroaniline to p-chloroformanilide.

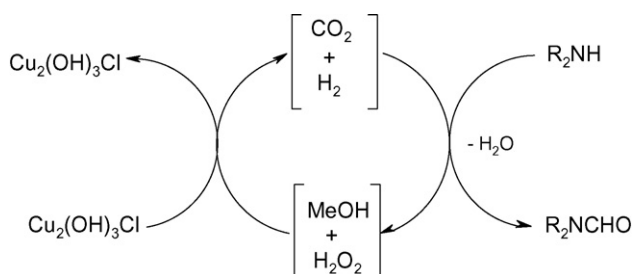
Table 3
Effect of catalytic material varying with slow addition rate of 6% (w/w) H₂O₂.

Run	CCC (mg)	PCA (mg)	MeOH (ml)	6% (w/w) H ₂ O ₂	Formation of p-chloroformanilide (in 2.0 h)
Run 1	20.0	100.0	5.0	2.5 ml (5.6 equiv. mole)	40%
Run 2	30.0	100.0	5.0	2.5 ml (5.6 equiv. mole)	60%
Run 3	40.0	100.0	5.0	1.5 ml (3.4 equiv. mole)	100%

PCA, p-Chloroaniline; CCC, copper hydroxyl chloride; reaction temperature: 25–27 °C.

Systematic studies have been made to check the effect of the number of equivalents, concentration and the rate of addition of hydrogen peroxide on the reaction time for complete conversion of the reaction. The results revealed the importance of instantaneous liberation of the active components over the copper hydroxyl chloride and its effective utilization in the production of N-formylation of primary and secondary amines. At the outset the amount of hydrogen peroxide (30%, w/w) varied from 5 to 20 mole equivalence to check its effect on the reaction time for the complete conversion of p-chloroaniline to p-chloroformanilide. The results revealed that irrespective of the mole equivalence of hydrogen peroxide (30%, w/w) used, the time taken for 100% conversion remained the same. This indicates that the amount of hydrogen peroxide available was more than the minimum requirement for complete conversion of the reactant into the product. Further optimization was conducted by reducing the concentration of hydrogen peroxide (30–6%, w/w) and keeping the mole equivalent constant. These results indicate that even the 6% (w/w) hydrogen peroxide drove the reaction to completion within 1.0 h. Considering the potential handling risk of high concentrated hydrogen peroxide, low concentrated (6%, w/w) hydrogen peroxide was chosen for further studies. It is observed that the mode of addition of hydrogen peroxide (i.e., two equal portion addition vs. slow addition) plays an important role in driving the reaction to completion. It is noteworthy to state that slow addition of hydrogen peroxide (6%, w/w) resulted in the instantaneous formation of the formanilide with in a convenient time period. These results demonstrate that the slow addition of low concentrated hydrogen peroxide generates the active components to form the formanilide, whereas two equal portion addition leads to decomposition of hydrogen peroxide, and hence for reaction completion more quantity of hydrogen peroxide and time are needed.

When 100 mg of the catalytic material was tested with 100 mg of p-chloroaniline used (2.0 ml, 30%, w/w, H₂O₂, slow addition) it took 1.0 h for 100% conversion. But 20 mg of the catalytic material for the same reaction conditions required 25 h for 100% conversion. Further decrease in the amount of the catalyst to 10 mg for the same amount of the reactant resulted only 65% conversion even after 25 h. Further experiments were conducted to find out the minimum amount of the catalyst that can be used in the presence of lowest concentration of hydrogen peroxide (6%, w/w) to obtain high yield and selectivity of the product within a minimum period of reaction time. The results obtained for these optimized reactions are presented in Table 3, which revealed that the minimum 40% (w/w)



Scheme 1. Schematic pathway to produce active components for the N-formylation of primary or secondary amines.

of CCC catalyst (with respect to the amine, PCA) is needed for the complete conversions of reaction within 2.0 h. It is also to be noted that the composition of the used catalyst remained unchanged even after the reaction, as revealed by PXRD studies.

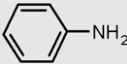
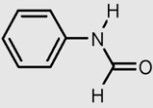
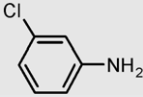
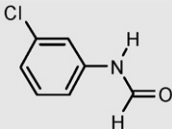
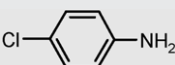
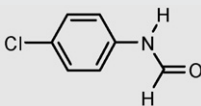
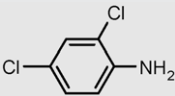
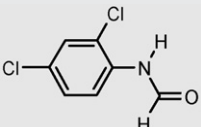
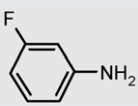
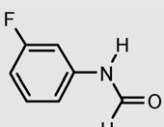
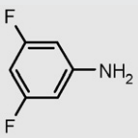
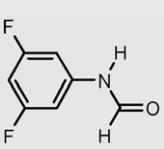
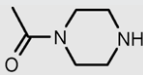
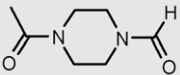
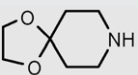
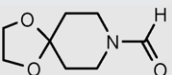
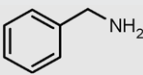
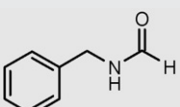
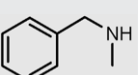
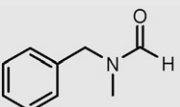
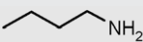
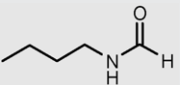
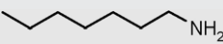
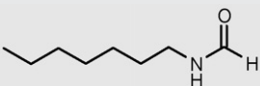
These systematic studies on the optimization of reaction conditions clearly indicate the importance of the mode of addition, strength and mole equivalence of hydrogen peroxide and the minimum amount of the catalyst required to drive the reaction to completion.

Further reactions were conducted using different primary and secondary amines to check the general applicability of the copper hydroxyl chloride for its activity towards their N-formylation. All the amines were converted into N-formylated derivatives. The yields were moderate to good (63–80%) with 100% selectivity. The various primary and secondary amines tested for their N-formylation reaction along with the N-formylated derivatives formed, their yield and the time taken for 100% conversion are tabulated in Table 4. The products 1–6 (Table 4) have been found to have a *cis* configuration based on their ¹H NMR δ_{NH} values [20].

The information like the melting point, TLC R_f values, ¹H and ¹³C NMR delta values and GC–MS data of N-formylated amines are given below:

- (1) *N*-Phenylformamide: M.p. 46.3–47.8 °C; TLC (petroleum ether:ethyl acetate::7:3), R_f (product): 0.35, R_f (aniline): 0.55; ¹H NMR (200 MHz, CDCl₃): δ 7.10–7.59 (5H, m), 8.40 (1H, s), 8.73 (1H, d); ¹³C NMR (50.3 MHz, CDCl₃): δ 119.2, 120.7, 125.2, 125.7, 129.5, 130.1, 137.4, 137.6, 160.5, 163.7; GC–MS: m/z (relative intensity): 121(M^+ , 100), 93(83), 66(58), 51(8).
- (2) *N*-(3-Chlorophenylformamide): M.p. 53.9–54.6 °C; TLC (petroleum ether:ethyl acetate::7:3), R_f (product): 0.38, R_f (3-chloro aniline): 0.63; ¹H NMR (200 MHz, CDCl₃): δ 6.94–7.67 (5H, m), 8.39 (1H, s), 8.68 (1H, d); ¹³C NMR (50.3 MHz, CDCl₃): δ 117.1, 118.5, 119.2, 120.7, 125.3, 125.7, 130.5, 131.2, 159.9, 163.1; GC–MS: m/z (relative intensity): 155(M^+ , 89), 127(100), 100(23), 92(36), 75(10), 65(39), 50(6).
- (3) *N*-(4-Chlorophenylformamide): M.p. 99.8–101.1 °C; TLC (petroleum ether:ethyl acetate::7:3), R_f (product): 0.40, R_f (4-chloro aniline): 0.65; ¹H NMR (200 MHz, CDCl₃): δ 7.02–7.52 (5H, m), 8.38 (1H, s), 8.67 (1H, d); ¹³C NMR (50.3 MHz, CDCl₃): δ 120.5, 121.7, 129.5, 130.3, 159.7, 163.1; GC–MS: m/z (relative intensity): 155(M^+ , 89), 127(100), 100(19), 92(29), 73(11), 65(28), 50(5).
- (4) *N*-(2,4-Dichlorophenylformamide): TLC (petroleum ether:ethyl acetate::7:3), R_f (product): 0.40, R_f (2,4-dichloro aniline): 0.65; ¹H NMR (200 MHz, CDCl₃): δ 7.26–7.62 (3H, m), 8.39 (1H, d), 8.49 (1H, s); ¹³C NMR (50.3 MHz, CDCl₃): δ 123.1, 128.4, 130.5, 159.1; GC–MS: m/z (relative intensity): 189($M-1$, 41), 161(100), 126(23), 101(10), 90(35), 74(10), 63(38), 52(10).
- (5) *N*-(3-Fluorophenylformamide): M.p. 53.9–54.6 °C; TLC (petroleum ether:ethyl acetate::7:3), R_f (product): 0.39, R_f (3-fluoro aniline): 0.56; ¹H NMR (200 MHz, CDCl₃): δ 6.80–7.52 (5H, m), 8.39 (1H, s), 8.69 (1H, d); ¹³C NMR (50.3 MHz, CDCl₃): δ 106.1, 106.6, 107.9, 108.4, 111.7, 112.2, 112.6, 114.4, 114.5, 115.8, 115.9, 130.5, 130.7, 131.4, 131.6, 160.1, 163.2; GC–MS: m/z (relative intensity): 139(M^+ , 100), 111(92), 91(8), 84(61), 75(8), 64(14), 57(19), 52(5).

Table 4
N-formylation of primary and secondary amines with methanol and dilute hydrogen peroxide (6.0%, w/w) over copper hydroxyl chloride catalyst.

Entry	Substrate	Product	Reaction time (min)	Yield (%) ^a
1			45	75
2			60	72
3			45	75
4			75	70
5			60	69
6			75	65
7			90	63
8			45	74
9			75	80
10			90	76
11			90	70
12			90	73

^a Isolated yield. The rest was unidentified.

(6) *N*-(3,5-Difluorophenylformamide): M.p. 83.8–84.6 °C; TLC (petroleum ether:ethyl acetate::7:3), R_f (product): 0.35, R_f (3,5-difluoro aniline): 0.60; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 6.56–7.36 (3H, m), 8.39 (1H, s), 8.71 (1H, d); $^{13}\text{C NMR}$ (50.3 MHz, CDCl_3): δ 100.0, 100.4, 100.6, 100.9, 101.1, 101.4,

101.7, 101.9, 102.0, 102.2, 103.2, 103.5, 103.6, 103.8, 159.8, 162.7; GC-MS: m/z (relative intensity): 157(M^+ , 100), 129(97), 109(11), 102(66), 82(20), 75(10), 63(11), 57(10), 51(10).
(7) *4*-Acetylpiperazine-1-carbaldehyde: $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.07(3H, s), 3.31–3.57 (8H, m), 8.03 (1H, s); GC-MS: m/z (rel-

- active intensity): 156(M⁺, 98), 141(6), 128(6), 113(16), 97(7), 85(86), 69(53), 56(100).
- (8) *1,4-Dioxo-8-azaspiro [4,5] decane-8-carbaldehyde*: ¹H NMR (200 MHz, CDCl₃): δ 1.55–1.67 (4H, m), 3.38 (2H, t), 3.55 (2H, t), 3.93 (4H, s), 7.92 (1H, s); ¹³C NMR (50.3 MHz, CDCl₃): δ 34.1, 35.5, 37.3, 43.5, 64.4, 106.9, 160.6; GC–MS: *m/z* (relative intensity): 171(M⁺, 15), 142(11), 128(99), 99(100), 86(55), 71(11), 55(22).
- (9) *N-Benzylformamide*: ¹H NMR (200 MHz, CDCl₃): δ 4.49 (2H, d), 7.27–7.43 (5H, m), 8.26 (1H, s); *m/z* (relative intensity): 135(M⁺, 100), 106(33), 91(40), 79(29).
- (10) *N-Benzyl-N-methylformamide*: ¹H NMR (200 MHz, CDCl₃): δ 2.65–2.77 (3H, m), 4.26–4.45 (2H, m), 7.10–7.30 (5H, m), 8.02–8.08 (1H, m); *m/z* (relative intensity): 149(M⁺, 100), 134(14), 120(10), 106(25), 91(61), 79(24).
- (11) *N-Butylformamide*: ¹H NMR (200 MHz, CDCl₃): δ 0.95 (3H, t), 1.26–1.60 (4H, m), 3.21–3.36 (2H, m), 8.16 (1H, d); *m/z* (relative intensity): 100(M-1, 39), 86(13), 72(100), 60(8).
- (12) *N-Heptylformamide*: ¹H NMR (200 MHz, CDCl₃): δ 0.87 (3H, t), 1.28–1.51 (10H, m), 3.18–3.31 (2H, m), 8.13(1H, d); *m/z* (relative intensity): 142(M-1, 16), 117(35), 100(100), 72(60).

4. Conclusions

The copper-based catalysts in the form of their hydroxyl salts are effective in generation of the active species for the N-formylation of primary and secondary amines. Copper oxide however has been found to be less active for the same reaction. Systematic studies also revealed the importance of slow addition of hydrogen peroxide in the presence of a definite amount of the catalyst. Herein we report a convenient and simple methodology for the N-formylation of primary and secondary amines with moderate to excellent yields using the less expensive copper hydroxyl chloride salt with dilute hydrogen peroxide in the presence of methanol as solvent. This novel

methodology will find wide application in organic fine chemical synthesis.

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