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One-pot Multi-step Synthesis of some Aromatic Salicylaldoximes Using MgO Nanoparticles

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MgO nanopartticels (NP-MgO) in average size between 30-130 nm were prepared by sonochemical method. Some phenol derivatives were converted to salicylaldehydes by *ortho*-formylation using MgO nanoparticles and $(CH_2O)n$ in xylene and subsequently treated with aqueous $NH_2OH.HCl$, affording the corresponding salicylaldoxime in a one-pot procedure condition. Moreover, this one-pot process, with two transformations, offers a number of advantages. In particular, the direct transformation of intermediates to the desired products reduces the time normally spent on isolation and purification.

Keywords: Aldoxime, MgO nanoparticle, Hydoxylamine, Synthesis, One pot reaction

INTRODUCTION

Ortho-hydroxybezaldehyd and its derivatives (salicylaldehydes) are important starting material for the preparation of other useful classes of organic compounds, and also various agrochemicals, pharmaceuticals, fragrance chemicals [1], useful industrial metal extractants [2], oxygen-containing heterocyclic compounds [3,4], salen derivatives [5], cinnamic acid derivatives and as a source for silane ligands [6].

Synthesis of *ortho*-hydroxybezaldehyd and its derivatives is an important classical reaction in organic chemistry that has been improved and discussed through various formylation methods [7]. Para formylation of phenol in the presence of $CO/HF/BF_3$ was improved by Gattermann and Koch [8]. The Reimer-Tiemann reaction has been also modified to give *ortho*-selective formylations of phenols [9,10]. Formylation of electron-rich phenols using hexamethylenetetramine (HMT) as the formylating agent in the presence of glycerol and boric acid was reported by Duff [11], and has been modified by using strong acids, such as polyphosphoric acid, methanesulfonic acid, or trifluoroacetic acid as solvent [12]. Some metal salt catalysts such as Sn, Fe, Pd, Pt, Ag, Cr, Al, Zr and Ti have been also used for ortho-formylation of phenol in high pressure [13-16]. Sulfonium salt, formed by the reaction of dithiane and *N*-chlorosuccinimide, is used for *ortho*-formylation of *para*-substituted phenols by Gassman [17]. Later, modification of Casnati ortho-formylation method was reported using triethylamine and magnesium dimethoxide in methanol and paraformaldehyde [18]. This method was improved by triphenylphosphine oxide [19] and $MgCl_2$-Et_3N [20] in different reaction conditions. Methyl formate has been used as the formylating agent of phenols in the presence of HF/BF_3 to convert phenols to the corresponding aldehydes [21]. However, this method mostly leads to produce mixtures and requires a large excess of boron trifluoride. Hydroxymethylation of phenyl dihydrogen borate with paraformaldehyde followed by hydrolysis and oxidation yielded salicylaldehyde [22,23]. Fries-rearrangement of aryl formats is the basis of another method for preparation of *ortho*-hydroxybezaldehyd [24-26]. Recently, *ortho*-hydroxybezaldehyd derivatives have been prepared by *ortho*-formylation using $MgCl_2$-Et_3N (a useful

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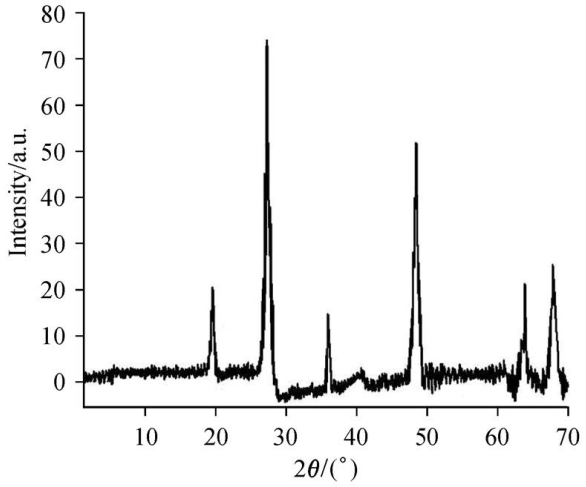


Fig. 1. X-ray powder diffraction pattern of MgO nanoparticles after calcinations.

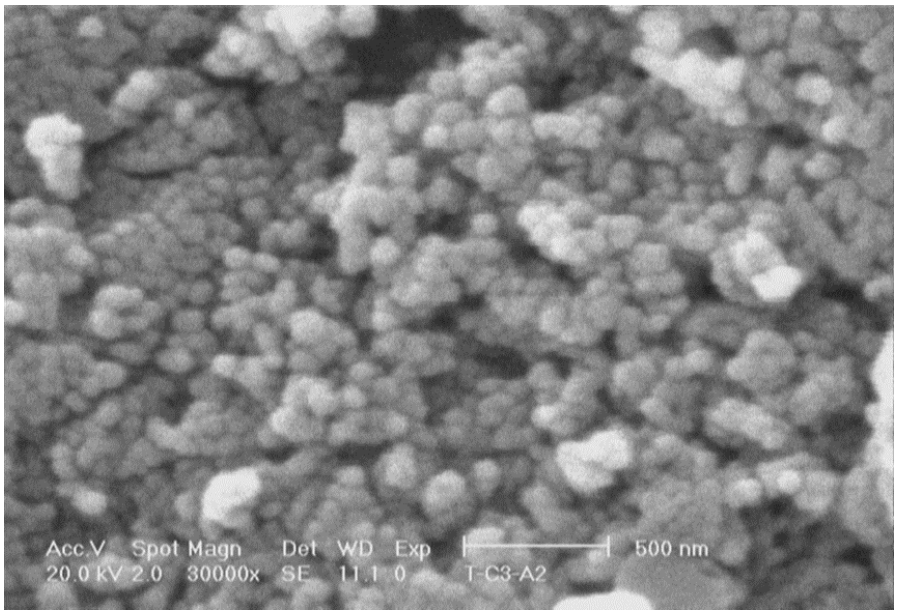


Fig. 2. SEM image of MgO nanoparticles after calcinations.

base system in organic synthesis) and $(CH_2O)_n$ in THF and subsequently Dakin oxidation, in a one-pot procedure [27-29].

In view of the previous trend towards the development of clean and environmentally friendly green chemical processes, investigations of solvent- and hazardous reagent-free reactions have become important in synthetic organic chemistry. As per our ongoing research program aimed at the development of environmentally benign synthetic methodologies for widely used heterocyclic

compounds, [30] here we report a novel and rapid one pot synthesis of 2-hydroxybenzaldehyde oxime derivatives using NP-MgO as an efficient agent.

EXPERIMENTAL

All materials were commercial reagent grade and obtained from Merck or Alderich. ^{1}H NMR spectra were recorded on a Bruker-Avance AQS 300 MHz. A multiwave ultrasonic generator (Bandlin Sonopuls Gerate-Typ: UW 3200, Germany) equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 30 kHz with a maximum power output of 780 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. The wave amplitude in each experiment was adjusted as needed. The X-ray powder diffraction (XRD) measurements were performed using a Philips diffractometer of X'pert company with mono chromatized Cu Kα radiation. The crystallite sizes of selected samples were estimated using the Scherrer method. Nanoparticles were characterized with a scanning electron microscope (SEM) (Philips XL 30) with gold coating. IR spectra were recorded on a SHIMADZU-IR460 spectrometer in a KBr matrix. All melting points were obtained by Stuart scientific apparatus. TLC monitored all reactions and all yields refer to overall isolated ones.

Synthesis of MgO Nanoparticles

0.1 M solution of NaOH was added to the 0.025 M solutions of $MgCl_2$ in ethanol/water. To control the size and morphology of nanoparticles, we used 0.5 g of polyethylene glycol (PEG) in the reaction with optimized conditions (PEG was added to the $MgCl_2$ in ethanol/m water solution and then NaOH solution was added dropwise to this mixture). The mixtures were sonicated for 30 min, followed by centrifuging with a centrifuge, and separation of the solid and liquid phases. The solid phase was washed for three times with ethanol and water. Finally, the washed solid phase was calcinated at 500 °C for 1 h.

General Procedure for the One Pot Synthesis of *Ortho*-hydroxybenzaldehyde Oxime

MgO nanoparticles (5 mol%), xylene (4 ml) and Phenol (1.5 mmol) were heated at 100 ^{o}C for 1 h. Then, paraformaldehyde powder (2.5 mmol) was added to the mixture and the refluxing continued for 1 h. After cooling the mixture to 50 ^{o}C, it was treated with a solution of hydroxylamine hydrochloride (2 mmol) in water (20 ml) which was added over 20 min with vigorous stirring. Stirring continued at 35 °C for 2 h after which the reaction mixture was cooled to room temperature and the organic layer separated, washed with 2% NaOH solution (2 × 15 ml) and water (2 × 20 ml) and evaporated under reduced pressure to give oxime 4a as a white crystalline solid (85%).Experimental data for 4a: m.p. 199-200 °C; ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 6.86 (1H, dt, J = 1 and 7.5, 5-H), 6.98 (1H, dd, J = 7.5 and l, 3-H),7.l0 (lH, dd, J = 7.5 and 1.6, 6-H), 7.25 (1H, dt, J = 1.6 and 7.5, 4-H), 7.86 (1H, br s, ArOH), 8.2 (1H, s, CH=N) and 10.1 (1 H, s, NOH).

RESULTS AND DISCUSSION

MgO nanoparticles were synthesized from reaction of $MgCl_2$ and NaOH under ultrasonic irradiation. Figure 1 shows the XRD patterns of MgO nanoparticles. Sharp diffraction peaks shown in Fig. 1 indicate good crystallinity of MgO nanoparticles. No characteristic peak related to any impurity was observed. The broadening of the peaks indicated that the particles were of nanometer scale. Average size of the obtained MgO nanoparticles shown in Fig. 2 is 60 nm. The crystallite size was also calculated by X-ray line broadening analysis using the Scherrer equation; we found that the average MgO crystallite size was 65 nm, in agreement with that observed from SEM images. To investigate the size distribution of the nanoparticles, a particle size histogram was prepared (Fig. 3). Most of the particles possess sizes in the range from 30-130 nm. For further demonstration, the EDAX was performed. The EDAX spectrum given in Fig. 4 shows the presence of Mg as the only elementary component.

Initially, we optimized the reaction conditions for the synthesis of 2-hyroxybenzaldehyde 3 using phenol 1 and paraformaldehyde 2 in the presence of various catalysts as a model reaction (Scheme 1).

The results were summarized in Tables 1 and 2. A series of reactions was performed with MgO, NiO, CuO, ZnO, $CuCl_2$, $MgCl_2$, $ZrCl_4$, $CaCl_2$ and $MnCl_2$ in different conditions. The best results were observed when the

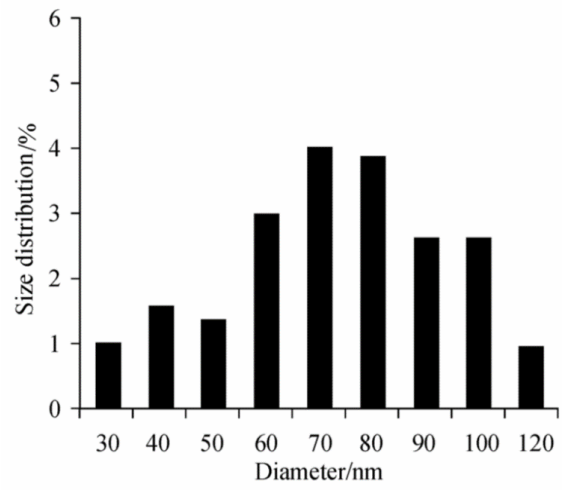


Fig. 3. Particle size histogram of MgO nanoparticles.

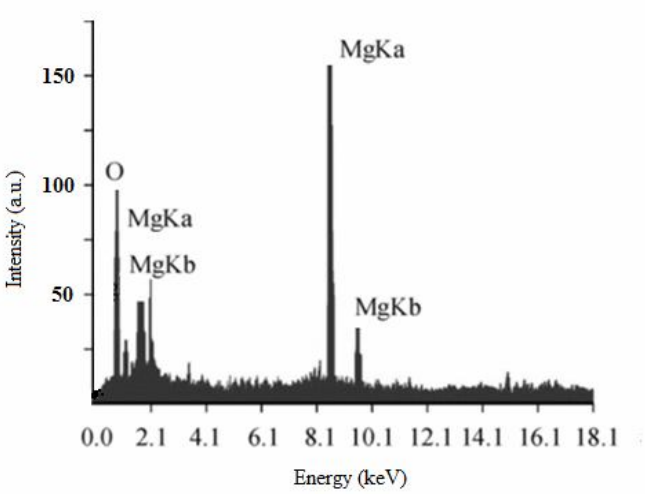
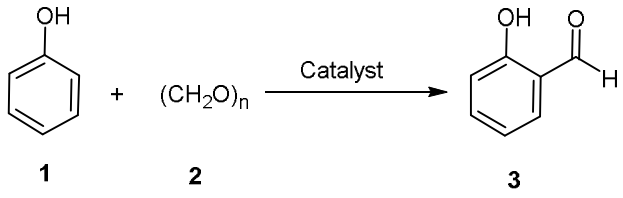


Fig. 4. EDAX analysis of MgO nanoparticles.



Scheme 1. Synthesis of2-hyroxybenzaldehyde

Table 1. Effect of the Catalyst on the Formation of 3[a]

Entry	Catalyst (mol%)	Time (h)	Yield (%)
1	MgO-Bulk (10)	7	60
2	NP-MgO (5)	5	85
3	NP-MgO (10)	7	85
4	CuO-Bulk (10)	7	45
5	NP-CuO (10)	10	50
6	ZnO (10)	10	40
7	NiO(10)	12	30
8	$MgCl_2$ (10)	8	50
9	$CuCl_2$ (10)	8	50
10	$ZrCl_4$ (10)	9	40
11	$MnCl_2$ (10)	12	32
12	$CaCl_2$ (10)	12	30

[a]Reaction conditions: phenol (1.0 mmol), formaldehyde (1.5 mmol), xylene (4 ml) 100 °C.

reaction was carried out at 100 ℃ in the presence of NP-MgO (5 Mol%) nanoparticles (Table1, entry 2).

Optimization of the amount of catalyst showed that 5 mol% of MgO nanoparticles could effectively catalyze the reaction for the synthesis of the desired product (Table 1, Entry 2). Using more than 5 mol% MgO nanoparticles has less effect on the yield and time of the reaction (Table 1, Entries 3).

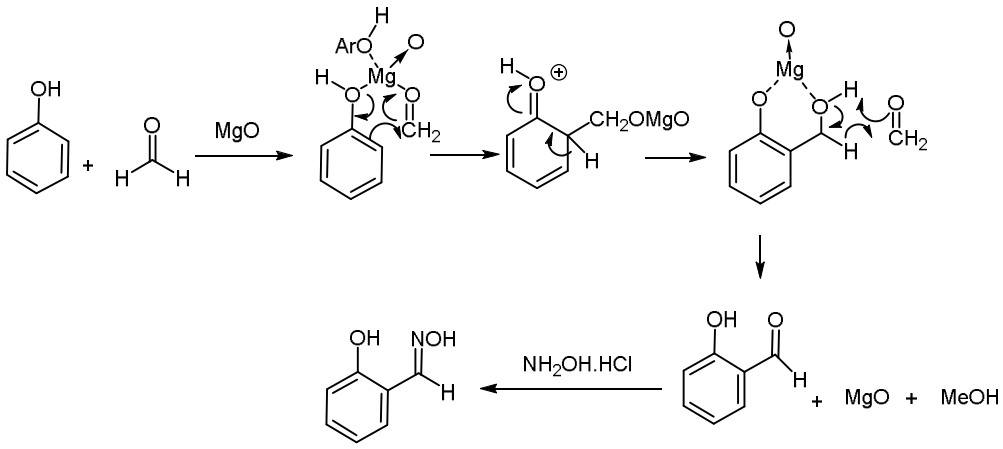
The effect of solvent was studied by carrying out the model reaction in the presence of NP-MgO nanoparticles in THF, CH_3CN, toluene, xylene and benzene solvents (Table 2). Among various solvents tested, xylene yielded the best results (Table 2, entry 9-14), whereas THF, CH_3CN, toluene, benzene gave the products in low yields (Table 2, entry 1-8). The reaction gave moderate yield in xylene at room temperature and the yield of reaction increased in 100 °C. Next, we investigated the effect of mole ratio of reactants on the synthesis of 2-hyroxy-benzaldehyde 3. We found that the yield improved when the reaction of phenol 1 with paraformaldehyde 2 was carried out in mole ratio of 1.5:2.5, respectively (Table 2, entry 14). Altogether, the yield was highly dependent upon the reaction temperature, solvent and the mole ratio of starting materials. The optimum reaction condition for the synthesis of 3 was found to be: phenol (1.5 equiv.), formaldehyde (2.5 equiv.), at 100 °C with xylene as the solvent. After optimization of reaction condition for the synthesis of 2-hyroxybenzaldehyde, we investigate the synthesis of 2-hydroxybenzaldehyde oxime 4 in one pot reaction condition. 2-Hyroxybenzaldehyde 3 was, without isolation, treated with hydroxylamine hydrochloride in a one-pot reaction to yield 2-hydroxybenzaldehyde oxime 4. The structure of 4 was identified by comparison of their physical and spectral data with those of authentic samples.

This one-pot procedure combining formylation and

Table 2. Optimization of Reaction Conditions for the Formation of 3

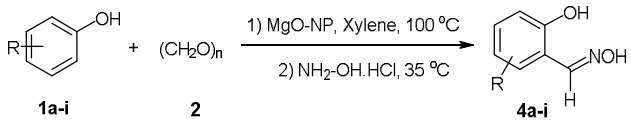
Entry	Mole ratio	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	1:1	THF	25	5	25
2	1:1	THF	65	5	35
3	1:1	Toluene	25	5	30
4	1:1	Toluene	100	5	50
5	1:1	CH_3CN	25	5	30
6	1:1	CH_3CN	65	5	40
7	1:1	Benzene	25	5	30
8	1:1	Benzene	80	5	55
9	1:1	Xylene	25	5	40
10	1:1	Xylene	100	5	70
11	2:1	Xylene	100	5	60
12	1:2	Xylene	100	5	50
13	1:3	Xylene	100	5	40
14	1.5:2.5	Xylene	100	5	85

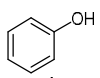
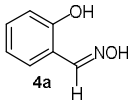
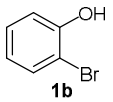
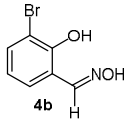
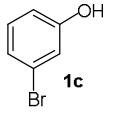
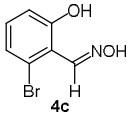
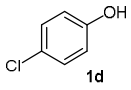
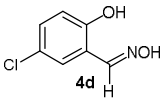
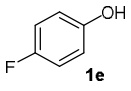
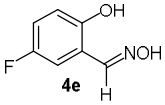
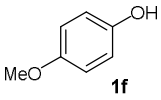
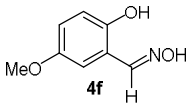
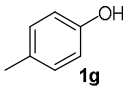
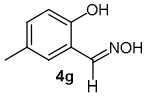
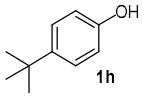
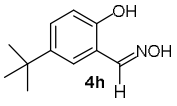
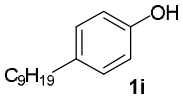
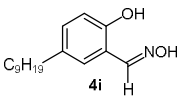
[a]Reaction conditions: phenol:formaldehyde (Mole ratio), solvent (4 ml).



Scheme 2. Proposed mechanism of the reaction

Table 3. One Pot Synthesis of 2-Hydroxybenzaldehyde Oxime[a,b]



Entry	ArOH	Aldoxime	Time (h)	Overall yield (%)
1	 1a	 4a	5	85
2	 1b	 4b	5	68
3	 1c	 4c	5	65
4	 1d	 4d	6	70
5	 1e	 4e	7	60
6	 1f	 4f	5	90
7	 1g	 4g	5	87
8	 1h	 4h	5	88
9	 1i	 4i	4.5	93

[a]Reaction conditions: ArOH (1.5 mmol), formaldehyde (2.5 mmol), xylene (4 ml) 100 °C then $NH_2OH.HCl$ (2 mmol). [b]The products were characterized from their spectral data (IR, ^1H NMR and mp) and compared with authentic samples.

oximation was carried out with some other substituted phenols as starting materials, and the overall yields ranged from 60-93% (Table 3).

A plausible mechanism for the One-pot multi-step synthesis of aromatic salicylaldoximes using MgO nanoparticles is shown in Scheme 2.

We have reported the utility of MgO nanoparticles in the transformation of phenols into *ortho*-hydroxyaldoxime in good overall yields by simple, regioselective, and one-pot procedures using the advantage of the *ortho*-formylation method. Moreover, these one-pot processes offer the advantage of both economic and environmentally benign methods.

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