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Research Article

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Solid-state Synthesis of 9-(4-Nitrophenyl)-9*H*-xanthene Derivatives using Multi-branched Silica-supported Polyphosphoric Acid

Sachin Mane

Polymer Science and Engineering Division, National Chemical Laboratory, Pune – 411008, India.

**Corresponding Author, Email: stm2011.mane@gmail.com*

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Abstract: Conventional homogeneous catalysts have the concern of recyclability in liquid-phase reaction. Further, most of the catalysts are sensitive toward moisture which retards the reaction rate resulting into fewer yields by increasing the by-product. In addition to this, conventional solid-supports have also the small reactivity for modification which results in lower efficiency. Multi-branched silica-supported polyphosphoric acid (MB-SS-PPA) obtained in the present work is the best solution to aforementioned concerns. In addition to this, solid-state reaction offers a solvent-free green route of synthesis. Xanthene derivatives were synthesized by a solid-state green approach using MB-SS-PPA as a catalyst which offers ease of recovery, recycle, and reuse properties. The spacer, 3,4,5-trihydroxybenzoate (THB) between silica and polyphosphoric acid offers the high reactivity, greater mobility, and hydrophobic properties.

Keywords: Multi-branched silica; Polyphosphoric acid; Solid-state reaction; Xanthenes

1. INTRODUCTION

From an emerging time of organic synthesis, liquid-phase organic reactions have been carried out using a suitable solvent because reactants can easily interact in a solvent medium. Further, homogeneous reactants offer an ease of stirring for rapid reaction rate. On the other hand, homogeneous catalysts have several disadvantages. Inspired by the current requirement, the development of a heterogeneous catalyst for an organic synthesis has become a great importance. However, small reactivity is the major concern with available solid-support [1,2]. Therefore, a heterogeneous catalyst with greater reactivity is a demand of catalysis. Nowadays, synthesis of the heterogeneous catalyst with desired properties is a growing research area which offers an ease of recovery, reusability, and product isolation resulting into green separation [3,4]. Over the last decade, number of heterogeneous solid supports [5–7] such as organic [polymer], inorganic [silica, metal oxide, and mixed metal nanoparticles (NPs)], and metal-organic framework [MOF] are available for the applications in solid-phase synthesis [8–13]. Polymeric beads with desired functionality, porosity, and crosslinking properties are widely used as a polymer-support to different entities [14–19]. Silica NPs have the potential applications over the polymeric beads due to their inexpensiveness, thermostability, greater surface area, non-conglomerated, and biocompatible properties [20,21]. There is no substitute to the inorganic NPs from the view of thermostability and high surface area. In another concept, solid-state reaction offers green synthesis which is the demand of an

environment and industry.

Nowadays, one-pot condensation reaction is an attractive tool in synthetic chemistry which allows the formation of several bonds in a single reaction [22,23]. A silica-support is an interesting inorganic material to immobilize the homogeneous catalysts. The efficiency of NPs (solid-support) is influences by reactivity, surface area, porosity, NPs size, shape, rigidity, and stiffness of the solid support [24–27]. Out of these properties, reactivity is the most important property. In the past, NPs were used in solid-phase synthesis, solid-phase extraction, and biomedical applications. The solid-state reaction can be carried out in the presence of thermal, UV radiation, microwave, or ultrasound methods. Some of the advantages of solid-state reaction over liquid-state reaction are the reduction in pollution, cost, ease of handling, and simplification in the work-up. Today, hazardous, toxic, and poisonous materials are deteriorating the environmental health. The elimination or at least reduction of use of hazardous material is a need of the clean environment.

Recently, Manolov *et al.* [28] used the silica-supported polyphosphoric acid as a catalyst for the synthesis of 4-disubstituted tetrahydroisoquinoline derivatives. Owing to limited access of hydroxyl functionality, silica has smaller reactivity. We have developed the MB-SS-PPA as a heterogeneous catalyst for one-pot solid-state condensation reaction for obtaining 9-(4-nitrophenyl)-9*H*-xanthene derivatives. Xanthenes are potentially used as a dye, fluorescent material for biomolecules, and in laser technology. Further, xanthene molecules have the activity of anti-inflammatory, antiviral, and agricultural bactericide. Indeed, spacer, multi-branching, and aromatic properties of 3,4,5-trihydroxybenzoate (THB) offers greater mobility, reactivity, and hydrophobicity, respectively. Owing to multi-branching of solid-support, catalyst loading is higher which increases the efficiency of MB-SS-PPA [29,30].

2. EXPERIMENTAL SECTION

2.1. Materials

Silica gel (60–120 mesh) was procured from Spectrochem, Mumbai. Methyl 3,4,5-trihydroxybenzoate (98%) was obtained from Alfa-Aeser, Lancs. 4-Chlorophenol (≥ 98%) was purchased from SRL, Mumbai. 4-Bromophenol pure was obtained from Koch-Light Laboratories, England. 4-Acetylphenol (99%) was purchased from Aldrich, Germany. 4-Nitrophenol (≥ 98%), 4-nitrobenzaldehyde (99%), sodium hydroxide (≥ 97%), chloroform (99.5%), methyl isobutyl ketone (≥ 99%), and polyphosphoric acid (~ 85%) were procured from Loba Chemie, Mumbai. Sulphuric acid (95–98%) was procured from Merck, Mumbai. All chemicals were used as received.

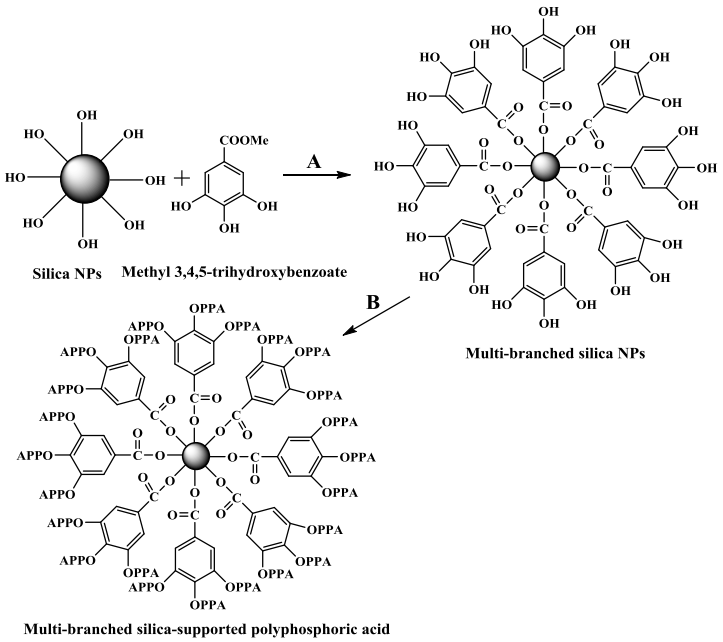
2.2. Preparation of silica-supported 3,4,5-trihydroxybenzoate

Indeed, silica has the limited access to the hydroxyl functionality resulting into the small extent of reactivity [31]. As a result, silica was modified with THB to obtain more reactive silica. For this, three-necked round bottom flask (500 mL) was equipped with an overhead stirrer. This flask was charged with 10 g of methyl-THB, 150 mL of methyl isobutyl ketone (MIBK), and catalytic amount of sulphuric acid. This mixture was stirred for 30 min at room temperature. To this, 30 g of silica (60–120 mesh) was added and the temperature was raised to 117°C and mixture was again stirred for additional 8 h. After

completion of reaction time, the mixture was cooled and filtered through Buchner funnel and washed with deionized water till neutral pH. Then, modified silica was dried at 80°C under reduced pressure. The modification of silica was confirmed by Fourier transform infra-red spectroscopy. This modified silica was used for further modification with polyphosphoric acid.

2.3. Modification of silica-supported 3,4,5-trihydroxybenzoate with polyphosphoric acid

A silica-supported THB (multi-branched silica NP) was used for modification with polyphosphoric acid [28]. A 500 mL of three-necked round bottom flask was equipped with an overhead stirrer. To this, 5 g of polyphosphoric acid and 120 mL of chloroform was added and allowed to stir at 50°C for 1 h. To this mixture, 20 g of silica-supported THB was added and stirred at 60°C for another 8 h. Subsequently, chloroform was evaporated and the reaction mixture was filtered and washed with chloroform. Then, MB-SS-PPA was dried at 100°C for a period of 5 h. The preparation and plausible structure of silica-supported polyphosphoric acid is represented in **Scheme 1.**



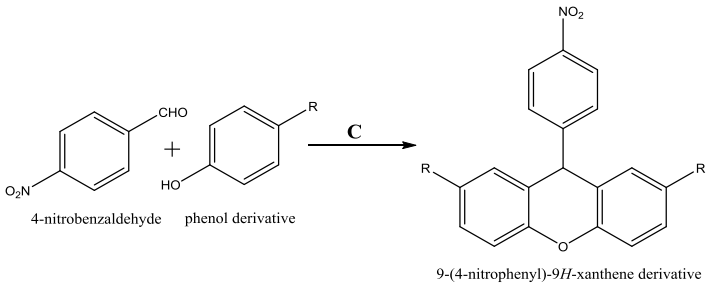
A: H_2SO_4, MIBK, 117°C, 8 h; **B:** polyphosphoric acid, chloroform, 60°C, 8 h.

Scheme 1. Preparation and plausible structure of MB-SS-PPA as a catalyst.

2.4. Synthesis of 9-(4-nitrophenyl)-9*H*-xanthene derivatives: General procedure

A 100 mL round bottom flask was equipped with a nitrogen inlet and overhead stirrer. To this, 2 g (13.2345 mmol) of 4-nitrobenzaldehyde, *para*-substituted (-Cl, -Br, -NO_2, and -Ac) phenol (26.46903 mmol), and 0.5 g MB-SS-PPA was added. This solid mixture was stirred for 10 min at a room temperature which was further heated to 120°C for a period of 12 h. The completion of the reaction was confirmed by TLC. The reaction mixture was dissolved in methanol and filtered to separate the MB-SS-PPA. Then, the product was purified by silica gel column using pet ether: ethyl acetate (90:10) as a solvent system and

product was characterized by ^{1}H NMR and mass. Synthesis of 9-(4-nitrophenyl)-9*H*-xanthene derivatives using MB-SS-PPA is represented in **Scheme 2.**



C: 120°C, MB-SS-PPA; **R:** –Cl, –Br, –NO_2, and –Ac

Scheme 2. Synthesis of 9-(4-nitrophenyl)-9*H*-xanthene derivatives using MB-SS-PPA.

2.5. Characterization

Silica nanoparticle and modified silica was dried at 80°C for 8 h and characterized by different techniques including Fourier transform infra-red (KBr) spectroscopy, surface area analyzer, scanning electron microscopy (SEM), and energy dispersive X-ray (EDX) analysis. FT-IR spectra were recorded on Perkin Elmer spectrometer. FT-IR spectrometer (KBr) (Perkin Elmer, model: Spectrum GX; serial number: 69229, number of scans: 10 numbers, resolution: 4 cm^{-1}, interval: 1). Surface area of NPs before and after modification was evaluated by a surface analyzer using (NOVA 2000e Quantachrome instruments, Boynton, FL-33426) by BET (nitrogen adsorption) method. SEM was used for an external morphology whereas EDX analysis was performed by Quanta 200-3D, dual beam ESEM microscope, Netherland wherein thermionic emission tungsten filament was used as an electron source. Nuclear magnetic resonance (NMR) spectra were analyzed on 200 MHz (DMSO-d_6) whereas mass spectra were recorded on Thermo Scientific Q Exactive (Accela PDA detector and Accela 1250 pump).

3. RESULTS AND DISCUSSION

In liquid-phase synthesis, polyphosphoric acid was used as a catalyst [32,33]. However, catalyst recovery is not so easy since recovery takes much more time and it may contaminate the product. Solid-state synthesis is one of the best ways which offer an ease of recovery of NP supported catalysts, reagents, substrate, photosensitizer, and scavenger to obtain the pure product. Further, solid-state synthesis avoids the use of a solvent medium during the reaction which leads toward green synthesis.

3.1. Fourier transform infra-red (FT-IR) spectroscopy

In the past few years, modified silica NPs were potentially used in number of applications [28,34,35] due to their inexpensive, ease of handling, and interesting properties. In the present work, silica NP was modified with THB which was further modified with polyphosphoric acid. The unmodified and modified silica NPs were dried at 80°C for 8 h for FT-IR (KBr, cm^{-1}) evaluation. Unmodified silica demonstrates the presence of broad peak at 3462 that corresponds to hydroxyl functionality, 1639 assigned to –O-H bend., and 966 attributes to internal Si–OH str. Further, silica modified THB revealed

some confirmative peaks in addition to unmodified silica. The broad peak at 3456 indicates -O-H str., 3077 assigned for substituted benzene (weak), 1634 and 1471 corresponds to aromatic C=C and 1073 demonstrates Si-OR str. Moreover, MB-SS-PPA demonstrated confirmative peaks in addition to silica modified THB. The peak at 2874 assigned to (O=)P-OH, 1247 corresponding to P=O str. and 1073 attribute for P=O of polyphosphoric acid. FT-IR spectra of silica NPs, silica NPs modified THB, and MB-SS-PPA is represented in **Figure 1.**

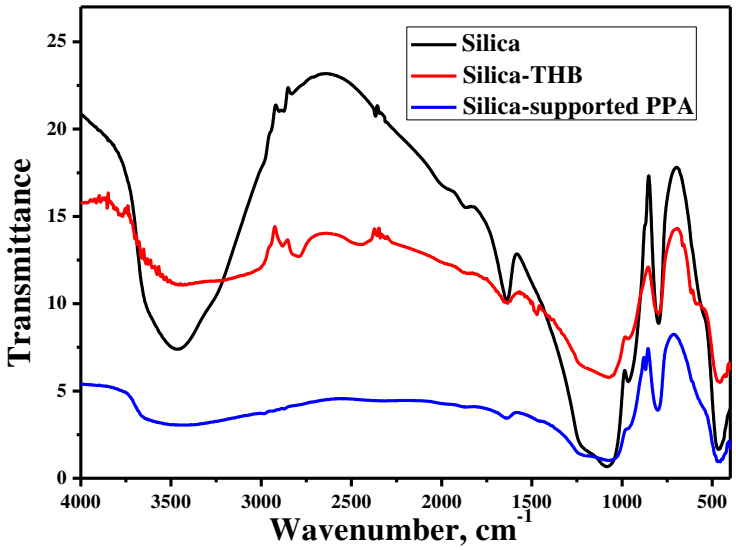


Figure 1. FT-IR spectrum of silica NPs, silica NPs modified THB, and MB-SS-PPA.

3.2. Specific surface area determination

Recently, number of porous materials is available for solids-phase and solid-state synthesis [36–38]. Most widely used materials consist of organic (polymer), inorganic (metal oxide/mixed metal oxide NPs), and metal-organic framework (MOF) [39]. Each type of material has own characteristics which can be tuned to a suitable property. In general, the polymer has the small surface area, large pore size, and greater pore volume whereas inorganic NPs have the greater surface area, small pore volume, as well as pore size. However, the metal-organic framework has nearly same characteristics like inorganic material with some special properties depending on the composition of the metal-organic framework. Parameters like surface area and morphology (conglomerate/non-conglomerate) are the most influencing parameter to the NPs efficiency [25,40]. The surface area of silica NPs before and after surface area modification was determined by surface area analyzer (nitrogen adsorption method). The specific surface area of silica NPs before modification was 2705.90 m^2/g which was decreased to 1210.44 m^2/g after modification with THB and further decreased to 332.75 m^2/g after modification with polyphosphoric acid (MB-SS-PPA).

3.3. External morphology

In general, metal oxide and mixed metal oxide NPs have the property of conglomeration which affects the NPs efficiency. However, some of the NPs have the property of well-dispersing into the reaction medium which offers greater surface area resulting in greater efficiency [25,40]. External

morphology was studied by well-known scanning electron microscopy. In the present work, morphology of NPs before and after the modification was studied to evaluate the difference in surface morphology. Importantly, there is no conglomeration of the silica NPs before and even after modification with THB and further with polyphosphoric acid. Each and every particle has their unique identity. SEM images of silica NPs, silica NPs modified THB, and MB-SS-PPA is represented in **Figure 2.**

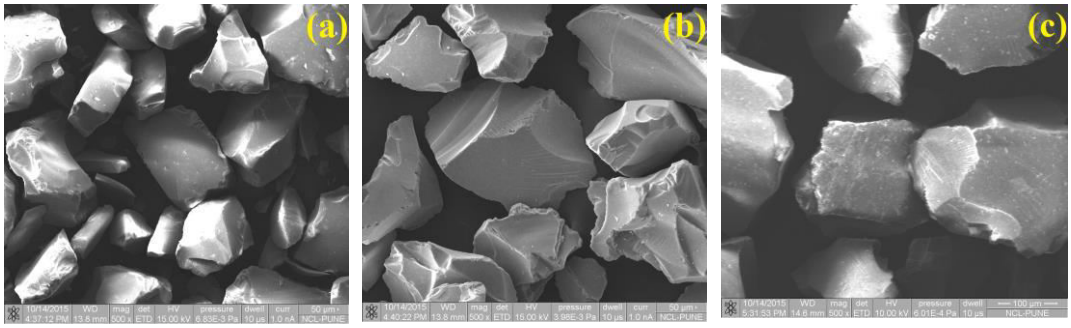


Figure 2. SEM images of (a) silica NPs, (b) silica NPs modified THB, and (c) MB-SS-PPA at 500x magnification.

3.4. Energy dispersive X-ray (EDX) analysis

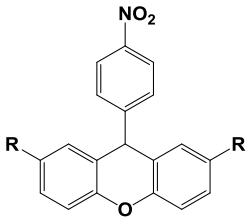
Energy dispersive X-ray analysis is one of the powerful tools to analyze the composition of the porous material such as polymer beads, NPs, and metal-organic framework before and after modification. This method offers the qualitative and quantitative elemental detection. Unmodified silica demonstrated only silica and oxygen whereas MB-SS-PPA revealed the presence of phosphorus, carbon, and oxygen. Unfortunately, EDX is unable to determine the hydrogen content in NPs before and after modification. EDX analysis of unmodified silica and MB-SS-PPA are reported in **Table 1.**

Table 1. EDX analysis of unmodified and modified silica with polyphosphoric acid.

Compound	Unit	Silicon	Oxygen	Carbon	Phosphorus
Unmodified silica	wt%	31.25	68.75	-	-
MB-SS-PPA	wt%	25.87	70.45	3.09	0.58

3.5. Characterization of 9-(4-nitrophenyl)-9*H*-xanthene derivatives

The solid-state reaction is an emerging and eco-compatible way of organic synthesis [23]. As a result, these types of reactions are industrially economical and environmentally benign. Nuclear magnetic resonance (NMR) is a powerful technique to confirm the synthesis of an organic molecule. Therefore, ^{1}H NMR was used to confirm the synthesis of xanthenes derivatives. The different derivatives [R: (a) -Cl, (b) -Br, (c) -NO_2, and (d) -Ac] of 9-(4-nitrophenyl)-9*H*-xanthene were obtained by a solid-state synthesis using MB-SS-PPA. ^{1}H NMR peaks of 9-(4-nitrophenyl)-9*H*-xanthene derivatives are reported below.



Xanthene

2,7-dichloro-9-(4-nitrophenyl)-9H-xanthene **(a): ^{1}H NMR** (200 MHZ, DMSO-d_6, δ): 5.99 (1H,s), 6.56 (2H,d), 6.87 (2H,d), 7.13 (2H,s), 7.30 (2H,d), 8.18 (2H,d).
2,7-dibromo-9-(4-nitrophenyl)-9H-xanthene **(b): ^{1}H NMR** (200 MHZ, DMSO-d_6, δ): 6.05 (1H,s), 6.83 (2H,s), 6.88 (2H,d), 7.29 (2H,d), 7.34 (2H,d), 8.21 (2H,d).
2,7-dinitro-9-(4-nitrophenyl)-9H-xanthene **(c): ^{1}H NMR** (200 MHZ, DMSO-d_6, δ): 5.92 (1H,s), 7.23 (2H,d), 7.40 (2H,d), 7.90 (2H,s), 7.95 (2H,d), 8.09 (2H,d).
1,1'-[9-(4-nitrophenyl)-9H-xanthene-2,7-diyl]bis(ethan-1-one) **(d): ^{1}H NMR** (200 MHZ, DMSO-d_6, δ): 2.54 (6H,s), 6.58 (1H,s), 6.97 (2H,d), 7.82 (2H,s), 8.12 (2H,d), 8.20 (2H,d), 8.34 (2H,d).

In addition to nuclear magnetic resonance (NMR), reaction time, yield, solubility, molecular formula, molecular weight, and mass (M^+) of the obtained product are reported in **Table 2.**

Table 2. Chemical structures and properties of 9-(4-nitrophenyl)-9*H*-xanthene derivatives **(1a-d).**

Entry	–R	Time (h)	Yield (%)	Solubility	Molecular formula (molecular weight)	Mass (MeOH) (found, M^+)
(a)	–Cl	12	79	MeOH	$C_{19}H_{11}Cl_2NO_3$ (371.0)	371.999
(b)	–Br	12	74	MeOH	$C_{19}H_{11}Br_2NO_3$ (461.1)	461.8979
(c)	–NO_2	12	75	MeOH	$C_{19}H_{11}N_3O_7$ (393.3)	394.1034
(d)	–Ac	12	72	MeOH	$C_{23}H_{17}NO_5$ (387.4)	388.1082

4. CONCLUSIONS

Xanthene derivatives were obtained by a solvent-free (solid-state) green approach. The prepared MB-SS-PPA heterogeneous catalyst was used for the synthesis of 9-(4-nitrophenyl)-9*H*-xanthene derivatives having potential applications in dye, as a fluorescent material for biomolecules, agricultural bactericide activity, anti-inflammatory effect, and antiviral activity. The obtained heterogeneous catalyst (MB-SS-PPA) offers the greater mobility, hydrophobicity, more reactivity, ease of handling, and recyclability of a catalyst. Silica NP is a versatile solid-support due to their ease of availability, higher mechanical strength, greater specific surface area, better thermal properties, and non-conglomerated morphology. Notably, the surface area was higher (333 m^2/g) and nanoparticles were non-agglomerated even after modification. Multi-branched silica is not only useful for catalyst loading but can also be used as a reactive support to reagent, substrate, protecting, groups, scavenger, and photosensitizer.

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