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Preparation and Characterization of Organic Nanoparticles of Oxadiazole Derivative in Aqueous Media

Sewara J. Mohammed Akam K. Salih Khalid M. Omer* Mohammad A. Rashid
Department of Chemistry, Faculty of Science and Science Education, University of Sulaimani, Kurdistan region, Iraq
* E-mail of the corresponding author: komer33@gmail.com

Abstract

A novel oxadiazole derivative, 2,5-disubstituted-1,3,4-oxadiazole (Z)-4-((1-(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)prop-1-en-2-yl)amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (HOPA) was synthesized from reaction of (Z)-3-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino]but-2-enehydrazide, with 4-hydroxybenzaldehyde in the presence of iodine as catalyst .The structure of **HOPA** was characterized by using IR,^{1}H-NMR and mass spectroscopy. Nanoparticles of the prepared compound **HOPA** have been fabricated in aqueous media using re-precipitation method. Characterizations of the organic nanoparticles (ONPs) have been performed by using UV-Vis spectrophotometry, and scanning electron microscope (SEM). The **HOPA** NPs were approximately monodisperse even without using capping agent or surfactant. The size of the nanoparticles were around 150-200 nm as indicated by SEM. The maximum of absorption spectrum of the dispersed nanoparticles is red shifted by 5 nm from the molecular absorption spectra of the **HOPA** in the solution, which indicate head to head alignment (J aggregate) of the molecules of **HOPA** during the aggregation. The well dispersed organic nanoparticles in aqueous media holds potential application in future to be used as a tag for biomedical imagining.

Keywords: Nanoscience, Organic Nanoparticle, Reprecipitation, Oxdiazoles

1. Introduction

Nanoscience and nanotechnology are lying in frontier line of the research works all over the globe. Unique optical, mechanical, electrical, magnetic properties, and.....etc of nanoparticles led researchers to fabricate broad spectrum of nano size materials to be used in various applications. Metallic, inorganic and polymeric nanopaterials have been synthesized and studied deeply, however few works have been conducted on small molecules organic compounds.

Organic nanoparticles (ONPs) are expected to have the potentials than other inorganic and metallic nanoparticles, because ONPs allow more flexibility and variability in synthesis and tailoring of organic compounds is infinite (Kasai et al., 1997; Peng et al., 2000; Link et al., 1999; Jana et al., 2001; Murphy and Jana, 2002). Thus, small molecular organic nanostructures have attracted intense attention as they can offer tunable electronic and optical properties via molecular design (Nguyen et al., 2004; Fu et al., 2003). Yao et al. (2007) reported size variation of organic nanostructures will tune the emission, and the emission is strongly affected by surface structure and size of the particles.

Researches on ONPs, however, are at very beginning, and until now, synthetically controlling the size, shape and applications of ONPs is a challenging (Kaner and Li, 2006).

Oxadiazole derivatives are considered as important organic compounds which have played a significant role in medical and agricultural chemistry. Due to their biological and pharmaceutical activities, they have been used in drug synthesis; like the two common drugs; Raltegravir and Zibotentan (Savarino, 2006; James et al., 2009) and also various commercial and industrial applications (El-Sadek et al., 2012; Iqbal et al., 2006; Atia and Al-Mufrgeiy, 2012; Kaplancikli, 2011; Dighe et al., 2012; Maslat et al., 2002 and Fadda et al., 2011).

In the present work, a novel class of oxadiazole derivative (HOPA) has been synthesized. Re-precipitation method was used for preparation of organic nanoparticles in water, then characterizing nanoparticles using spectroscopic and microscopic techniques.

2. Experimental Section

The IR Spectra were recorded on a Perkin-Elmer FT/IR spectrometer using KBr pellets (ν_{max} in cm^{-1}). The ^{1}H NMR spectra were recorded on a Bruker DRX spectrometer (250 MHz) in ($CDCl_3$ for compound 1, DMSO-d6 for compounds 2 and 3) with TMS as an internal standard. Chemical shifts (δ) are reported in ppm. The mass spectra were obtained by using Agilent Technology (HP) and MS Model, 5973 Network Mass selective Detector. The reactions were monitored by TLC using aluminum silica 60 Fluorescent plates which were obtained from chemical group of Barcelona (Spain) made in EEC. The spots resolved were visualized using UV light.

The UV–Vis absorption spectra were measured with a PerkinElmer Lambda 25 UV-VIS spectrophotometer (PerkinElmer Life and Analytical Sciences, Shelton, CT, USA).

Electron images were taken using Scanning Electron Microscope (Hitachi S3200 LV). 1 to 3 drops of the NP solution were drop casted on 0.5 cm × 0.5 cm piece of glass, and then a very thin gold layer was coated using sputtering technique.

2.1. Synthesis of ethyl (Z)-3-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino]2-butenoate (1).

The starting material (Z)-3-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino]2-butenoate (**1**) was synthesized as reported in literature with some modifications (Cunha et al., 2005), it can be summarized as follow: Ethyl acetoacetae (0.02 mol, 2.6 g, 2.53 mL) was added to an ethanolic solution (5 mL) of 4-aminoantipyrie (0.01 mol, 2.03 g) in a conical flask. The mixture was stirring and scratching for twenty minutes at room temperature. After completion of reaction, checked by single-spot TLC (eluent: petroleum ether /ethyl acetate/ methanol, 6.5:1.5:2), the light yellow solid was filtered, washed twice with diethyl ether, affording 2.8 g of the product. Petroleum ether was added to the mother solution and allowed to cool in freezer, and then 0.165 g of the product was precipitated. The product was purified by recrystallization from ethanol (yield: 94%; m.p. 161–162.5 °C; Rf = 0.78). IR (KBr) v_{max} (cm^{-1}): 3245 (N-H), 3056 (C-H aromatic), 2975 (C-H aliphatic), 1678 (C=O ester), 1660 (C=O 4AA), 1604 (C=C aromatic), 1275 (C-N), 1133 (C-O). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.31 (t, 3H, O-C-CH_3); 1.95 (s, 3H, -C=C-CH_3); 2.26(s, 3H, N-C-CH3); 3.1 (s, 3H, N-CH3); 4.16 (q, 2H, O-CH2-); 4.74 (s, 1H, -C=CH); 7.3–7.52 (m, 5H, Ar-H); 9.42 (s, 1H, NH-C=C). MS (m/z): 316 $[M + 1]^+$ (22), 315 $[M]^+$ (91), 269 (31), 212 (38), 123 (36), 56 (100).

2.2. Synthesis of (Z)-3-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino] enehydrazide(2)

A mixture of compound (1) (0.01 mol, 3.15 g) and hydrazine hydrate (99%) (0.015 mol, 0.75 g, 0.73 mL) in ethanol (25 mL) was refluxed in water-bath for six hours. After completion of reaction, checked by single-spot TLC (eluent: petroleum ether /ethyl acetate/ methanol, 6.5:1.5:2), the excess of solvent was removed by rotatory evaporator. The dark yellow solid was filtered, washed with diethyl ether and petroleum ether, dried and purified by ethanol (yield: 95%; m.p. 101–102 °C; Rf = 0.6). IR (KBr) v_{max} (cm^{-1}): 3432, 3327 (N-H & NH_2), 2989-2914 (C-H aliphatic), 1670 (C=O amide), 1649 (C=O 4AA), 1590 (C=C), 1274 (C-N). ^{1}H-NMR (250 MHz, DMSO-d6): δ 2.09 (s, 6H, -C=C-CH_3 and N-C-CH_3); 2.5 (s, 2H, -NH_2); 2.74 (s, 3H, N-CH_3); 3.83 (s, 1H, NH-C=C); 5.22 (s, 1H, -C=CH); 7.2–7.49 (m, 5H, Ar-H); 10.28 (s, 1H, O=C-NH). MS (m/z): 301 $[M]^+$ (26), 281 (40), 188 (52), 147 (60).

2.3. Synthesis of (Z)-4-((1-(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)prop-1-en-2-yl)amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (3) under Solvent-free Conditions using Grinding Technique.

A mixture of compound (2) (0.005 mol, 1.506 g) and p-hydroxybenzaldehyde (0.005 mol, 0.61g) was grounded with iodine (0.001 mmol, 0.253 g) for (15 minutes) in a mortar by a pestle. The completion of the reaction was checked on TLC by using petroleum ether: ethyl acetate: methanol (6.5: 1.5:2) as a solvent system. The ice cold solution of sodium thiosulphate (10%, 50 mL) was added to the reaction mixture to remove iodine present. The Reddish Brown solid that separated out was filtered, washed with water, dried and purified by ethanol (yield: 81%; m.p. 219-220 °C; Rf = 0.66). IR (KBr) v_{max} (cm^{-1}): 3445 (broad peak, N-H and OH), 1654 (C=O), 1610 (C=N), 1581 (C=C), 1257 (C-N), 1158 (C-O-C), 1099. ^{1}H-NMR (250 MHz, DMSO-d6): δ 2.42 (s, 3H, -C=C-CH3); 3.13 (s, 3H, -N-C-CH3); 3.37 (s, 3H, N-CH3); 6.82-7.67 (m, 10H, Ar-H and -C=CH); 9.47 (s, 1H, -C=C-NH); 9.94 (s, 1H, OH). MS (m/z): 403 $[M]^+$ (8), 368 (73), 325 (40), 307 (100), 236 (15).

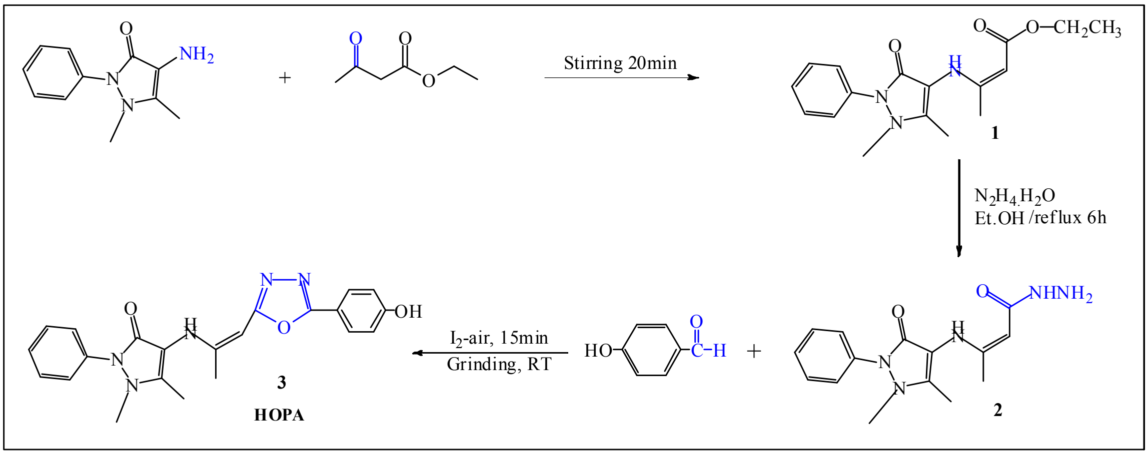

Figure 1. Synthetic route of **HOPA**.

2.4. Synthesis of Nanoparticles.

The re-precipitation method was used for the synthesis of organic nanoparticles (Mori et al., 2009; Kasai et al., 1992 and Kasai et al., 1998). Nanoparticles of **HOPA** were synthesized by dissolving **HOPA** in THF (5 mM, here THF is called a good solvent); then quickly injecting 100 µL of the **HOPA/THF** solution into 10 mL of poor solvent, which is deionized water under an inert atmosphere with vigorous stirring at room temperature. The resulting NP solution, after had a clear pale yellow color.

3. Results and Discussion

The synthetic route of **HOPA** is shown in Figure 1. Synthesis of (Z)-4-((1-(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)prop-1-en-2-yl)amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one was obtained from reaction of intermediate arylhydrazide(2) and 4-hydroxybenzaldehyde in the presence of catalytic amounts of iodine molecular in a single step with (81%) yield under solvent-free conditions using grinding technique as a green method. The specific advantages of this method are rapid and simple work-up procedure, high efficiency, and short reaction time, avoiding the use of organic solvents at any stage of the reaction, ecofriendly and good yield.

3.1. Nanoparticle Characterizations

3.1.1. SEM

The SEM images of the **HOPA** nanoparticles are shown in Figure 2. The nanoparticles are spherical to rod-like shape and the average size is 150 nm. The electronic microscope image of organic nanocrystals was not very clear due to the lower contrast of organic nanoparticles.

These nanoparticles were stable in solution in dark room without precipitation at room temperature for at least two weeks. These images confirm the preparation of **HOPA** nanoparticles via re-precipitation method and the **HOPA** nanoparticles are held together by π-stacking effects and hydrophobic and hydrogen bonds.

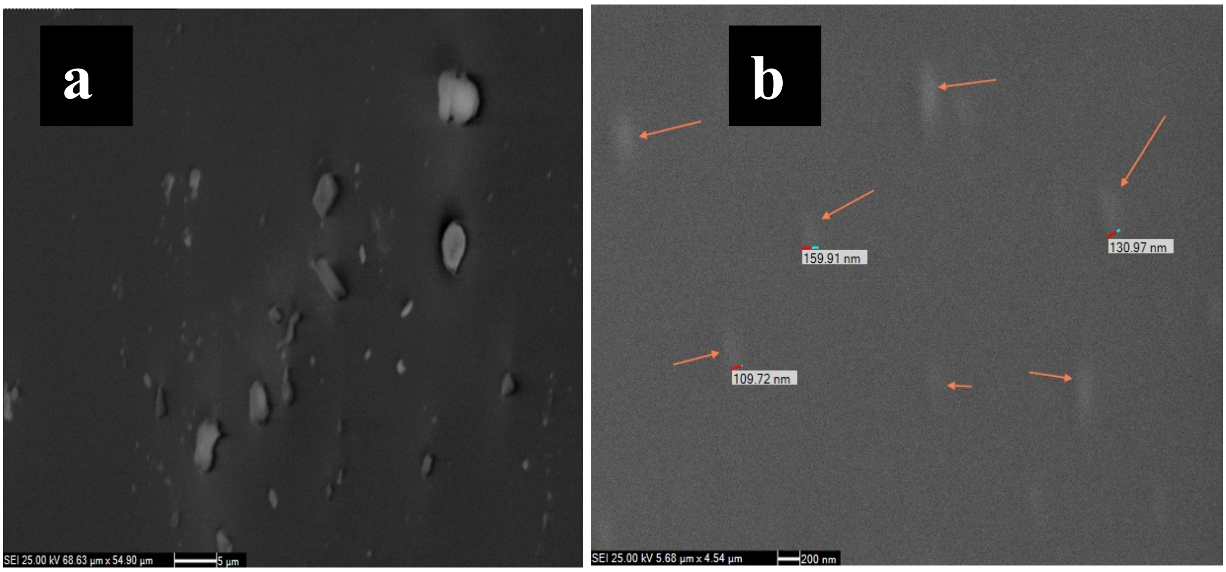

Figure2. Scanning Electron Microscope (SEM) image of the HOPA nanoparticles. Few drops of HOPA nanoparticles were drop casted on a piece of glass then it dried over night, then coating with a very thin layer of gold was done. (a): larger scale; b: smaller scale.

3.2. Optical Properties

The UV-Vis spectra of **HOPA** nanoparticles in water are significantly different compared to the spectra of the corresponding **HOPA** solutions (Figure 3). The maximum absorption spectrum nanoparticle solution is about 340 nm which is red shifted by 5 nm from the absorption spectra of the molecule in THF solution by 5 nm.

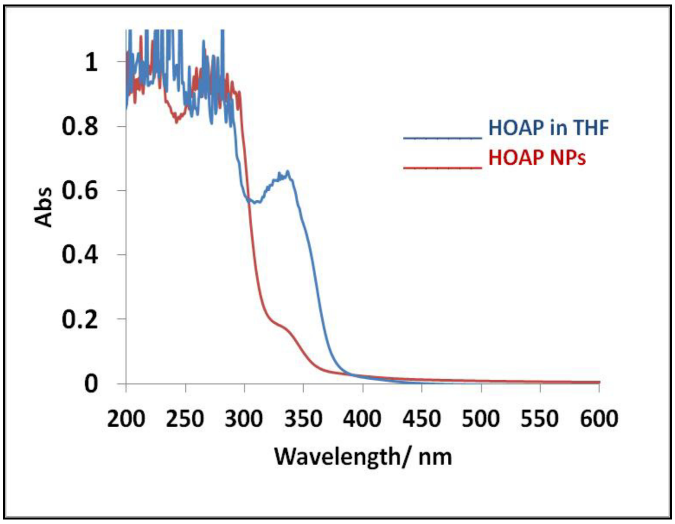

Figure 3. UV-Vis spectra for **HOPA** NPs in aqueous solution and in THF.

The rearrangement of molecules in aggregates generally fall into two types, ”J”(edge-to-edge) interactions which are characterized by red shifts and “H” (face-to-face) interactions are characterized by blue shifts. The optical spectra suggests the arrangement and interactions in the **HOPA** nanoparticles and are well understood to be indicative of electronic coupling of the chromophores (An et al., 2002).

In summary, the spherical and rod like shape of organic nanoparticles might have potential applications in many fields, like; showing biological activities, using in photovoltaic devices, and using as tag for bio imaging. Although, organic nanoparticles still in its infancy, but it is promising route in nanotechnology realm.

4. Conclusion

A special class of multifunctional organic molecule of oxadiazole derivative (**HOPA**) has been designed and synthesized. Colloidal spherical and rod like shape of nanoparticles around of 150nm in aqueous media have been fabricated using reprecipitation method without using any surfactant. Microscopic characterization showed the size, shape of the nanoparticles, spectroscopic characterization explained the optical properties of the aggregation of nanoparticles. In the ultimate goal, medical and environmental application will be tried using these organic nanoparticles

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