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An Efficient Multicomponent Synthesis of Octahydroquinazolinone Derivatives Using Novel Recyclable Grafted Fe APA-Complex Catalyst

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ABSTRACT

Recoverable and recyclable heterogeneous grafted Fe-APA complex efficiently catalyzed the one-pot synthesis of octahydroquinazolinone derivatives via multicomponent reaction of dimedone, aromatic aldehyde, and urea using methanol as a solvent. The desired products were obtained with 84–96 % yields. The present approach offers several significant such as short reaction time, high yield, easy purification, minimum catalyst loading, and use as an alternative catalyst. Grafted Fe APA complex were synthesized and characterized by various analytical investigative techniques like FTIR, NMR, Mass, XRD, SEM, EDAX, TEM with SAED, and BET surface area.

Keywords: Octahydroquinazolinone Derivatives, Biginelli Reaction, Grafted Fe-APA Complex, Recyclable Catalyst

I. INTRODUCTION

Recent years have a great deal of interest in the research of different types of Schiff base complexes of transition elements (l-4). The interest in the design and synthesis of transition metal complexes containing Schiff bases lies in their biological and catalytic activity in many reactions (5-6).

Octahydroquinazolinonederivatives have attracted considerable attention in recent years, due to their potential antibacterial activity against Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa (52) and also as a calcium antagonist activity (53). A number of these bioactive heterocycles also function as analgesic and anti-inflammatory agents (47). In 1893, Italian chemist Pietro Biginelli reported on the acid catalyzed cyclo condensation reaction of an aldehyde, ethylacetoacetate and urea, a procedure known as Biginelli reaction (35). More recently, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones, which used cyclic beta-diketones instead of open chain dicarbonyl compounds (36). Literature survey reveals that the synthesis of octahydroquinazolinone derivatives using Trimethyl silylchloride (TMSCl) (38), Nafion-H (Lin et al., 2007), VOSO4 (Reddy et al., 2009), conc. H2SO4 (36), conc. HCl (43), ionic liquid (48) and silica sulfuric acid (46) as catalysts. However, many of these procedures suffer from one or more disadvantages such as harsh reaction conditions, prolonged time period, poor yields with formation of many side products and use of large quantity of volatile organic solvents. Therefore there is a scope for generation of new methodology with mild reaction conditions, better yield, short reaction time and environment friendliness.

The present work reports the use of grafted Fe-APA complex as an efficient and recyclable catalyst for the synthesis of octahydroquinazolinone derivatives. The

surface area of the catalyst increases substantially when the size is reduced to nano regime; this is responsible for the higher catalytic activity. However, because of wide range of biological activities of octahydroquinazolinone derivatives, our efforts to develop an efficient catalyst. In the present study we wish to report grafted Fe-APA complex as an efficient catalyst to promote multicomponent reaction between aromatic dimedone, Urea, and aldehyde in methanol (Scheme 1). The grafted Fe-APA complex were synthesized and characterized by IR, UV, XRD, SEM with EDAX, TEM with SAED, and BET surface area.

II. METHODS AND MATERIAL

Experimental :

Starting materials $FeCl_3 \cdot nH_2O$, 2 hydroxyacetophenone, Hydrazine hydrate used for synthesis of grafted Fe-APA complex were purchased from Sigma Aldrich chemical and were used without further purification. The solvents were purified and dried according to standard procedures [26]. All the reactions were carried out under normal conditions.

The starting precursor Fe (II) metal complex was prepared accord-ing to the literature methods [27].

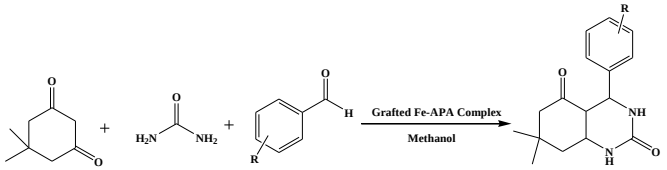
The structural properties of the synthesized materials were studied using Infrared spectroscopy (FTIR) 2400s (Shimadzu), X-ray diffractometer-DMAX-2500 (Rigaku) with CuKα radiation, having λ = 1.5406 Å. The surface morphology and chemical composition of synthesized catalyst were analyzed using a scanning electron microscope JSM-6300 (JEOL) coupled with an energy dispersive spectrophotometer JEO-2300LA (JEOL). The particle size and images of catalyst was determined with SAED using transmission electron microscope CM-200(Philips). The surface area was recorded with the help of Quantochrome Autosorb Automated Gas sorption system. The melting points of different derivatives are reported by a melting point apparatus with open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra of different products were recorded on Schimadzu 8400s spectrophotometer in DMSO with TMS as an internal standard. Mass spectra were recorded with a JEOL GCMA TE II GC-MS instrument.

Preparation of grafted Fe APA complex:

The 2-hydroxy acetophenazine (APA) was prepared by the condensation of 2-hydroxy acetophenone (0.1mol) dissolved in 95% ethanol with hydrazine hydrate (0.05 mol) also dissolved in 95% ethanol by adding the hydrazine slowly with constant stirring to 2-hydroxy acetophenone solution. The reaction mixture was heated under reflux for 1 hour. Cooling to room temperature produced yellow crystals which were filtered off under sunction and recrystallized from ethanol.The synthesized ligand was used for the synthesis of complex. Fe (II) Complex was synthesized by using 1:1 metal and ligand ratio in acetonitrile. The prepared Fe complex of APA is used for synthesis of Grafted Fe-APA complex. Grafting on silica was carried out by using Fe complex of APA and silica in alcohol. After complete evaporation of solvent complexes get deposited on silica by hydrogen bonding between a ligand and the surface hydroxyls of silica.

General procedure for the preparation of Octahydroquinazolinone derivatives:

A reaction mixture of dimedone (1 mmol), aromatic aldehyde (1.2 mmol), urea (1.1 mmol), and grafted Fe-APA complex (0.7 mmol) was refluxed for 90 minutes (Scheme-1). The structure of the products was confirmed by comparison with their physical and spectral data with literature values for authentic samples. The spectral data IR, ^1H-NMR, ^{13}C-NMR and MS of some synthesized Octahydroquinazolinone derivatives are reported below.



Scheme 1. Synthesis of octahydroquinazolinone using grafted Fe APA complex catalyst.

Spectral data and elemental analysis for selected compounds:

4-Phenyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione (entry 4a)

IR (KBr) cm^{-1} = 3262 and 3176 (N–H str.), 1621 (C,C str.);^{1}H NMR (DMSO-d6): d =9.27 (s, 1H, H-1), 7.19 (s, 1H, H-3),7.16–7.03 (m, 5H, Ar-H), 4.84 (s, 1H, H-4), 2.45 (d, J = 17 Hz,1H, H-6), 2.35 (d, J = 17 Hz, 1H, H-6), 2.18 (d, J =16 Hz,1H, H-8), 2.02 (d, J= 16 Hz,1H, H-8), 1.08 (s, 3H CH_3 atC-7), 0.86 (s, 3H, CH_3 at C-7); ^{13}C NMR (DMSO-d6):d= 194.7 (CO), 149.7 (C-2 and C-9), 147.62 (C-10), 128.2-125.8 (aromatic carbons), 111.96 (C-10), 50.7 (C-4), 40.54(C-6), 33.32 (C-7), 4-(4-Methoxyphenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione(entry 4e) IR (KBr) cm-1 = 3277 and 3026 (N–H str.), 1637 (C,C str.);1H-NMR (DMSO-d6) d =9.24 (s, 1H), 7.08 (s, 1H),7.07 (d, J = 6.5 Hz, 2H, Ar-H), 6.73 (d, J= 7 Hz, 2H, Ar-H),4.77 (s, 1H), 3.67 (s, 3H, OCH3), 2.445(d, J= 17 Hz, 1H), 2.33 (d, J= 17 Hz, 1H), 2.17 (d, J= 16 Hz, 1H), 1.98 (d, J= 16.5 Hz, 1H), 1.03 (s, 3H, CH3 at C-7),0.88 (s, 3H, CH_3); ^{13}C NMR (DMSO-d6) d= 194.82, 157.57, 149.6,140.01, 128.8, 113.5, 112.3, 55.4, 50.76, 40.54, 32.59, 32.36, 29.7, 26.97.

Table 1. Synthesis of octahydroquinazolinone in the presence of grafted Fe APA complex

Entry	R	Time (min.)	Product	Yield (%)	M.P.(^{o}C)	
					Found	Reported
1	C_6H_5	90	4a	92	292–295	291–292 (Yarim et al., 2003)
2	4-$N(CH_3)_2C_6H_4$	97	4b	96	289–291	-
3	4-(CH_3)–C_6H_4	92	4c	92	294-296	-
4	3-(NO_2)–C_6H_4	82	4d	96	297–299	300–301 (Kantevari et.al., 2006)
5	4-(Cl)–C_6H_4	86	4e	93	318–320	>300 (Kantevari et al., 2006)
6	4-(CH_3O)–C_6H_4	97	4f	94	274–276	-
7	4-(NO_2)–C_6H_4	81	4g	91	302–304	304–305 (Kantevari et al., 2006)
8	4-(F)–C_6H_4	83	4h	96	138–140	134–136 (Lin et al., 2007)
9	4-(Br)–C_6H_4	85	4i	92	136-138	-
10	4-(OH)–C_6H_4	96	4j	91	275-277	-

III. RESULTS AND DISCUSSION

The υ of OH stretch of the hydroxyl group of the ligand at 2630cm^{-1} disappears and a new band arises at 2692cm^{-1} which can be assigns to OH of the water molecule for the grafted Fe-APA complex. The υ of C=N of Fe-APA shifts to higher wave number which indicates that the ligand is coordinated through its imine group (1,3 11,12).The grafted Fe-APA complex are characterized by anew strong band at 1597cm^{-1}. Finally new IR band observed in the

range 400-700 cm^{-1} which is assigns to the υ M-O stretch of grafted Fe-APA complex. The XRD pattern of grafted Fe-APA Complex was shown in Fig. 2. The x-ray diffractogram of grafted Fe-APA complex was scanned in the range 0-60° at wavelength 1.543 Å. The diffractogram and associated data depict the 2θ value for each peak, relative intensity and interplanar spacing (d-values). The diffractogram of grafted Fe-APA complex had twelve reflections with maxima at 2θ = 12.139° corresponding to d value 7.2851 Å. The x-ray diffraction pattern of these complexes with respect to major peaks of relative intensity greater than 10% has been indexed by using computer programme. The above indexing method also yields Miller indices (hkl), unit cell parameters and unit cell volume. The unit cell of grafted Fe-APA complex yielded values of lattice constants, a=17.2534 A^o, b=16.6574 A^o, c = 17.9862 A^o and unit cell volume V=1567.00 A^{o3}. In concurrence with these cell parameters, the condition such as a = b = c and α = β= γ= 90^0 required for sample to be Orthorhombic were tested and found to be satisfactory. Hence it can be concluded that grafted Fe-APA complex has orthorhombic crystal system.

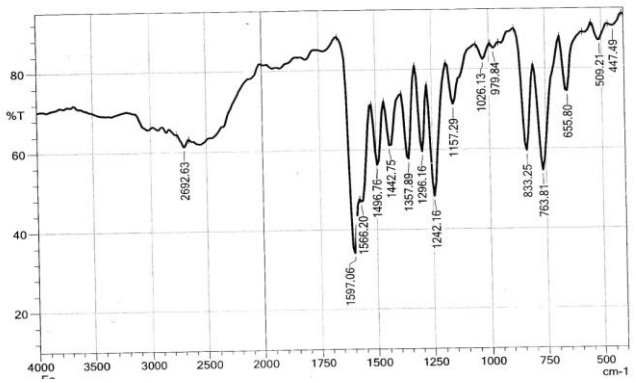


Figure 1.The FTIR spectra of grafted Fe APA complex

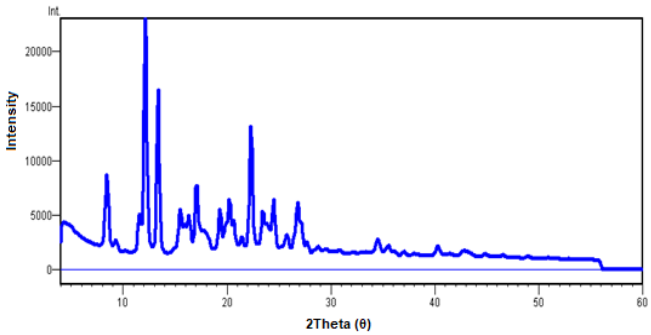
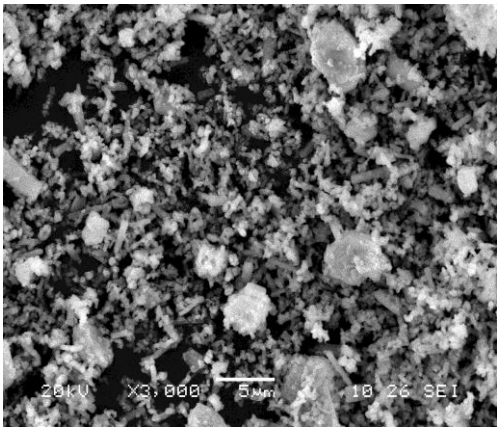


Figure 2: XRD Spectra for grafted Fe-APA Complex

Figure 3 shows surface morphology of grafted Fe-APA complex by SEM coupled with EDAX. The SEM shows that the particles are agglomerated with each other. The EDAX data furnishes elemental composition in conformity with respective molar proportion taken.

The TEM image (Fig. 4) shows some crystals are cubic and rod like. The SAED pattern associated with TEM reveals Orthorhombic grated Fe-APAComplex structure and is in total agreement with XRD data. The average particle size of grafted Fe-APAComplex was found to be 98 nm.



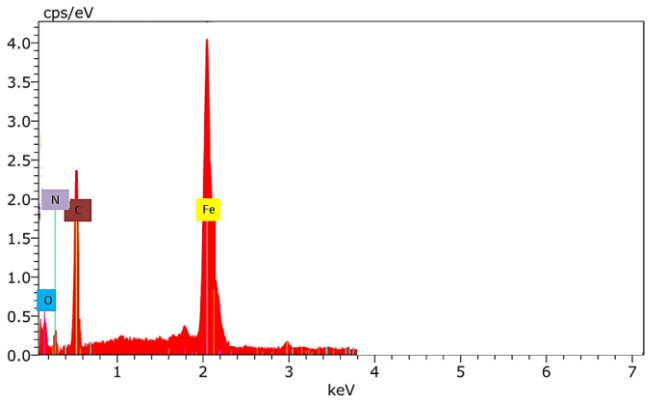


Figure 3: SEM analysis of grafted Fe APA-Complex

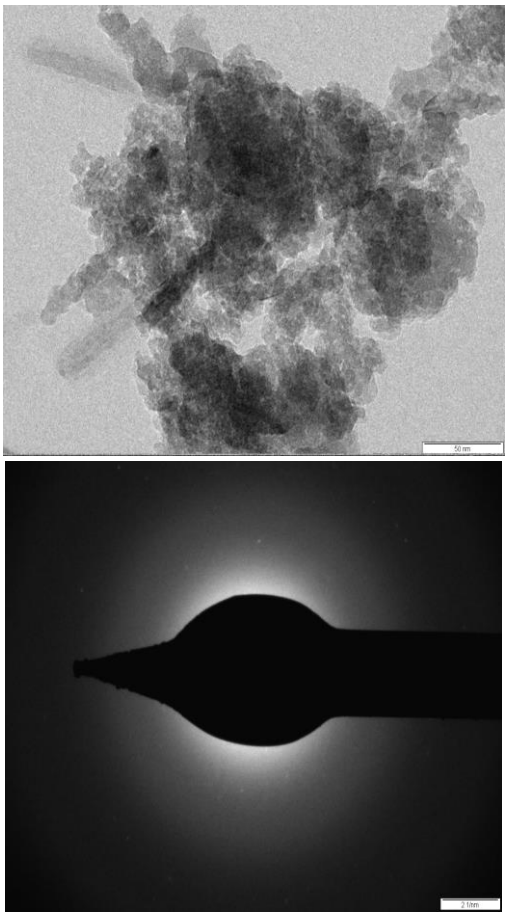


Figure 4: TEM and SAED analysis of grafted Fe APA-Complex

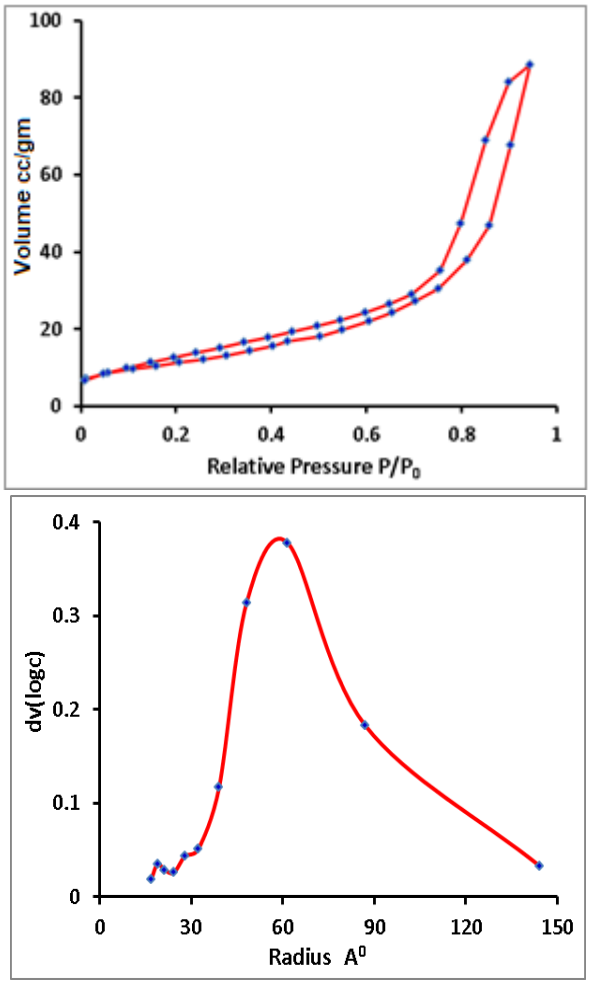


Figure 5. BET Surface area and pore volume of nanocrystalline grafted Fe-APA Complex

Figure 5(a,b) shows the N_2 adsorption-desorption isotherms and the BJH pore size distribution of synthesized grafted Fe-APA Complex. It reveals that all the samples have typical IV N_2 adsorption-desorption isotherms with H_1 hysteresis which indicates that the samples reserve the cylindrical mesoporous. The BJH pore size distribution demonstrates that all the samples have a narrow pore diameter range. Based on the N_2 adsorption-desorption isotherms, surface area (S_{BET}) is 178.9 m^2/g, the average pore volume (Vp) and pore diameter (dp) were 0.105 cc/g and 54.37 A^0 respectively. The grafted Fe-APA Complex has larger surface area, average pore volume, and pore diameter. Hence grafted Fe-APA complex is better choice of catalyst for the synthesis of octahydroquinazolinone.

SYNTHESIS OF OCTAHYDROQUINAZOLINONE DERIVATIVES:

In order to get effective results, we have optimized the reaction condition, for the reaction of aromatic aldehyde, urea and dimedone with methanol as a solvent was used as a model reaction. The reaction was monitored by TLC using ethyl acetate and hexane as the solvent system. The reaction conditions were optimized in terms of following reaction variables.Initially, a blank reaction was carried out using dimedone, an aromatic aldehyde and urea in absence of catalyst for the synthesis of octahydroquinazolinone which resulted in no formation of product even after 3 h. By performing the same reaction in presence of nanocrystalline grafted Fe-APA Complex afforded the desired octahydroquinazolinone with 91% yield in 90 min.

Further, we have checked the effectiveness of nanocrystalline grafted Fe-APA Complex as a catalyst with respect to APA Fe-complex for the condensation of octahydroquinazolinone (Table 2). We observed that the reaction progress requires more time in the presence of APA Fe-complex gave fewer yields as compared to grafted APA Fe-complex catalyst.

Table 2. Effect of grafting on reaction time and yield

Sr. No.	Catalyst	Time (min)	Yield
1	Fe APA complex	180	67 %
2	Grated Fe APA complex	90	91%

Thus we confirmed that nanocrystalline grafted Fe-APA complex is better choice of catalyst for the synthesis of octahydroquinazolinone over the other APA Fe metal complex catalyst. The role of catalyst was also performed for the model reaction with different mole of nanocrystallinegrafted Fe-APAcomplex catalyst such as 0.1, 0.2, 0.3 0.4, 0.5 mol. The nanocrystalline amount in the model reaction progress indicated that the best amount is 0.4mol of grafted Fe-APAcomplex was sufficient to promote the reaction and greater amount of catalyst did not improve the yield of octahydroquinazolinone (Table 3).

Table 3. Effect of mole percentage of grafted Fe APA complex

Entry	Mol of grafted Fe APA complex	Time (min)	Yield (%)
1	0.1	120	78
2	0.2	98	85
3	0.3	90	91
4	0.4	72	94
5	0.5	65	89

It was observed that when the reaction was carried out with 0.4 mole equivalent, the yield was maximum (94%). The condensation reaction was carried out in the presence of different solvents like DMF, MeOH, EtOH, CH_3CN, CH_2Cl_2 and under solvent free condition (Table 4). The result obtained clearly demonstrated that methanol was found to be the better choice over other solvents for the synthesis of octahydroquinazolinone. The increase in reaction time did not improve the yield.

Table 4. Effect of solvent on the optimized reaction

Entry	Solvent	Time	Yield (%)
1	MeOH	83	91
2	DMF	94	92
3	CH_3CN	92	89
4	EtOH	81	93
5	CH_2Cl_2	98	79
6	Solvent free	95	67

The reusability of the recovered nanocrystalline grafted Fe-APA complex catalyst has been studied. For this reason, grafted Fe-APA complex was recovered from the reaction mixture of octahydroquinazolinone (4a) by filtration and washing the solid residue with ethanol. The recovered catalyst was dried at 100°C and recycled over five runs with also no loss in activity. Figure-6 clearly reveals that the recovered nanocatalyst catalyzed the one-pot three component reaction to obtain 4a with 95 and 94 % yield during recyclability for sufficient time.

Table 5 : Results of the reaction run in the presence of recycled grafted APA Fe-complex catalyst

Entry	Reaction run	Time	Yield
1	1	65	95
2	2	65	95
3	3	65	95
4	4	65	94
5	5	65	94

IV. CONCLUSIONS

In this paper, we have developed a simple and efficient one pot multicomponent methodology for the synthesis of octahydroquinazolinone derivatives using novel nanocrystalline grafted Fe-APA complex a heterogeneous catalyst. The present methodology furnishes the products in short time with excellent yields, without any column chromatographic purification.

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