Inorganica Chimica Acta 397 (2013) 21–31

Contents lists available at SciVerse ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Polyfluorinated–zinc(II)phthalocyanine complex immobilized on silica: A novel, highly selective and recyclable inorganic–organic hybrid catalyst for the synthesis of biologically important 1,5-benzodiazepines

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ARTICLE INFO

Article history:
Received 26 April 2012
Received in revised form 28 August 2012
Accepted 12 November 2012
Available online 1 December 2012

Keywords:
Silica
Phthalocyanine
Immobilization
Catalyst
Benzodiazepine

ABSTRACT

A novel, efficient and recyclable catalyst was prepared by covalent grafting of polyfluorinated–zinc(II)phthalocyanine complex onto functionalized silica gel. The activity of the catalyst was investigated for the solvent-free synthesis of 1,5-benzodiazepines at room temperature. The immobilized catalyst was characterized by elemental analysis (CHN), diffuse reflectance UV–Vis spectroscopy, solid-state ^{13}C CPMAS and ^{29}Si CPMAS NMR spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM), BET surface area analysis, energy dispersive X-ray fluorescence (ED-XRF), Fourier transform Infrared (FT-IR) and atomic absorption spectroscopy (AAS) techniques. Short reaction time, mild reaction conditions, high turnover numbers, and easy recovery and reusability of the catalyst make this method a novel, economic and waste-free chemical process for the synthesis of biologically important 1,5-benzodiazepines.

1. Introduction

The use of low-cost and readily available species as catalyst plays a significant role for economical feasibility of the chemical processes. Metallophthalocyanines (MPcs) being thermally stable, easily accessible and cost-effective, are very attractive from this viewpoint [1–4]. However, due to their strong tendency towards aggregation [5] and difficulty in separation from reaction mixture, immobilization of MPcs on solid supports is carried out to make catalysts recoverable and recyclable [6–10]. Several types of support materials and immobilization strategies are used to convert homogeneous catalysts into the heterogeneous ones [11]. The covalent immobilization of catalysts on inorganic supports not only gives good catalyst recycling results but also shows minimal influence on the catalytic site by the support. Among various inorganic support materials, silica gel is highly preferred since it possesses high surface area, excellent stability (thermal and mechanical), ready availability, economic viability, and organic or organometallic moieties can be robustly anchored on the surface [12–17].

In recent years, considerable emphasis has been placed on fluorine chemistry because of major commercial significance of fluorinated organic and organometallic compounds in pharmaceuticals, agrochemicals, materials and polymer industries. In particular, polyfluorinated compounds are very effective catalysts due to their highly hydrophobic nature, high stability (thermal and chemical), and no steric strain due to the small size of fluorine atoms [18]. Considering the above advantages, a novel polyfluorinated–zinc(II)phthalocyanine complex has been synthesized and immobilized on silica gel, and used as a catalyst in the synthesis of 1,5-benzodiazepines.

Benzodiazepines are very important class of biologically active heterocyclic systems. The synthesis of these compounds has been receiving a great deal of attention in the field of medicinal and pharmaceutical chemistry owing to their application as anticonvulsant, anti-depressant, anti-inflammatory, analgesic, hypnotic and sedative agents, and are now one of the most widely prescribed class of psychotropics [19–25]. Generally, 1,5-benzodiazepines are synthesized by condensation reaction of *o*-phenylenediamines (OPDAs) with ketones, and due to their extensive range of activity and importance, this transformation is catalyzed by a plethora of reagents [26–31]. However, most of them involved excess amount of catalyst, harsh reaction conditions, prolonged reaction times, toxic and expensive organic solvents, unsatisfactory yields, tedious work-up procedures, low selectivity, co-occurrence of several side reactions, and need of chromatography for purification of adducts. So, these methods are environmentally unsound, especially with regard to large-scale synthesis. Therefore, there is a growing demand for mild, economic and environmentally benign catalytic methods which will allow facile recovery of the catalyst from the reaction media.

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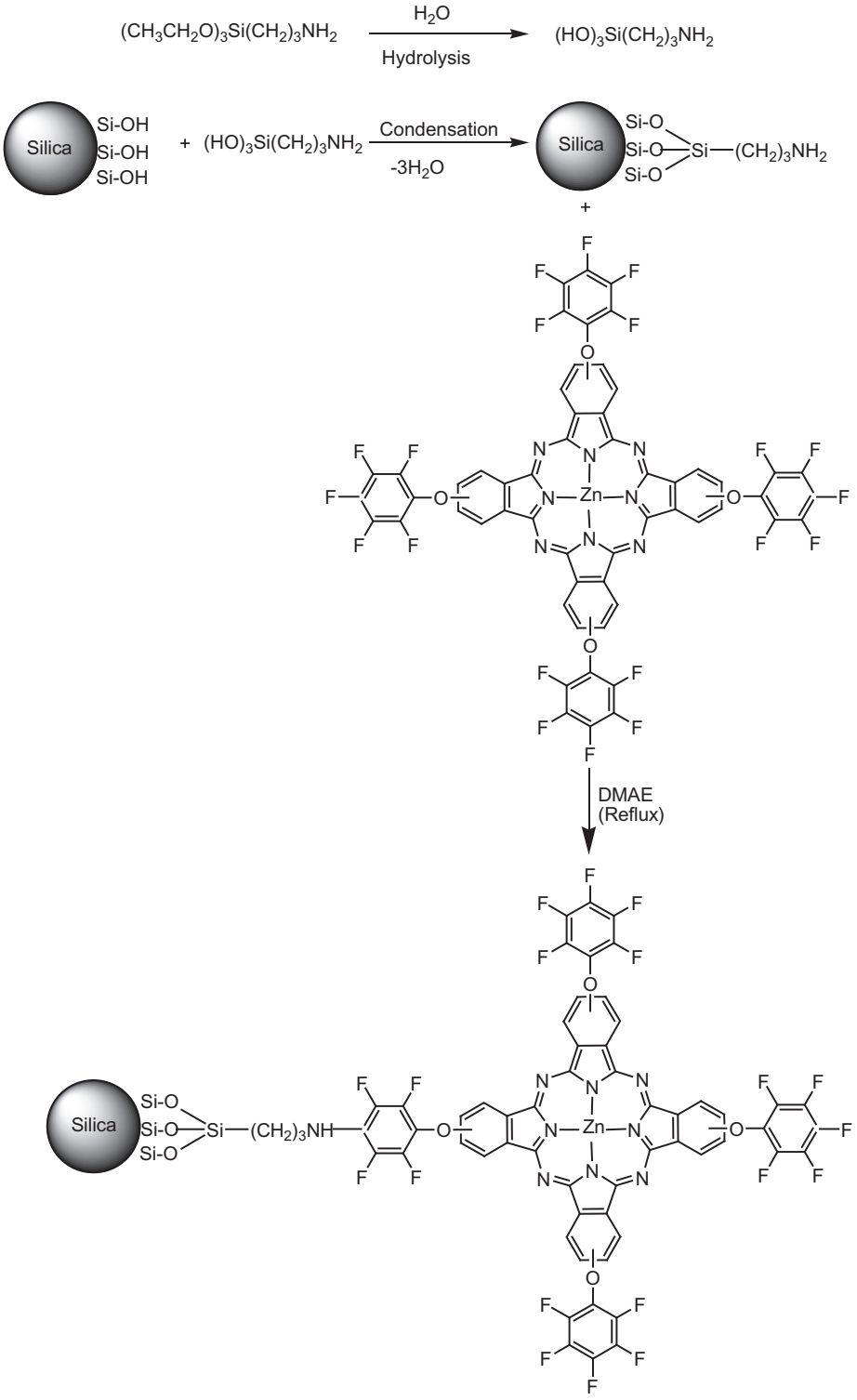
0020-1693/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ica.2012.11.012

Taking into consideration all the aforementioned limitations, and in continuation of our work on the synthesis of inorganic–organic hybrid materials, and their applications as metal scavengers, sensors, and catalysts for various organic transformations [32–41], herein we report the synthesis of polyfluorinated–zinc(II) phthalocyanine complex, and its subsequent immobilization on functionalized silica by covalent grafting method. The resulting inorganic–organic hybrid material was applied as catalyst for the solvent-free synthesis of biologically important 1,5-benzodiazepines. The use of recoverable catalyst in combination with solvent-free reaction conditions leads to enhancement in conversions with several advantages of the eco-friendly approach, termed green chemistry [42].



Scheme 1. Preparation of silica-supported zinc phthalocyanine complex ($ZnPcOC_6F_5$–APTES@SiO_2).

2. Experimental

2.1. General remarks

Scanning electron microscopy (SEM) images were obtained using a ZEISS EVO 40 instrument. The samples were placed on a carbon tape and then coated with a thin layer of gold using a sputter coater. Powder X-ray diffraction (XRD) patterns were recorded on Bruker D8 ADVANCE X-ray diffractometer using graphite monochromatized Cu Kα radiation. The UV–Vis diffuse reflectance spectrum of the catalyst was obtained over the spectral range 300–800 nm using Perkin Elmer Lambda 35 scanning double beam spectrometer equipped with a 50 mm integrating sphere. The surface area was measured with Gemini-V2.00 instrument (Micromeritics Instrument Corp.). Solid-state ^{13}C and ^{29}Si cross-polarization magic-angle spinning (CPMAS) NMR spectra were recorded on Bruker DSX-300 NMR spectrometer. Elemental analysis for CHN was performed using Elementar Analysensysteme GmbH VarioEL V3.00 instrument. The microwave-assisted syntheses and digestion were carried out in Anton Paar multiwave 3000 microwave reaction system equipped with temperature and pressure sensor. Energy dispersive X-ray fluorescence (ED-XRF) spectroscopic studies were performed on Fischerscope X-ray XAN-FAD BC. The amount of zinc in the catalyst was determined by Atomic absorption spectroscopy (AAS) using LABINDIA AA 7000 Atomic Absorption Spectrometer. All experiments were carried out in triplicate. Specord 250 spectrophotometer was used to obtain the electronic spectra of the complex in *N*-methyl-2-pyrrolidinone as a solvent. The Fourier transform infrared (FT-IR) spectra of the compounds were recorded using Perkin-Elmer Spectrum 2000 at room temperature using KBr pellet technique in the range of 4000–400 cm^{-1} under the atmospheric conditions with a resolution of 1 cm^{-1}. All samples and KBr were dried at 100 °C overnight before KBr pellets preparation. Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. ^1H NMR spectra were recorded on JEOL ECX 400 NMR spectrometer operating at 400 MHz. Chemical shifts (δ) were reported relative to TMS. The products obtained were analyzed and confirmed on an Agilent gas chromatography (6850 GC) with a quadrupole mass filter equipped 5975 mass selective detector (MSD) using helium as carrier gas (rate 0.9 ml min^{-1}).

2.2. Chemical reagents

3-Aminopropyltriethoxy silane (APTES) (98%), silica gel (60–100 mesh), 4-nitrophthalonitrile and pentafluorophenol were procured from Sigma–Aldrich. *N*,*N*-dimethylaminoethanol (DMAE) (98%) was obtained from Fluka, and used as such in this study. Starting materials and reagents used in the reactions were obtained from Spectrochem. Pvt. Ltd., India and used without purification.

2.3. Synthetic procedures

2.3.1. Synthesis of tetrakis-(perfluoro-phenoxy)phthalocyaninato zinc(II) complex, ($ZnPcOC_6F_5$)

The phthalocyanine precursor, i.e., 4-(perfluorophenoxy)phthalonitrile was prepared according to the reported protocol [43] with slight modification (Supplementary material). To prepare *tetrakis*-(perfluoro-phenoxy)phthalocyaninato zinc(II) complex [44], a mixture of zinc acetate (0.025 mmol, 0.054 g), 4-(perfluorophenoxy)phthalonitrile (0.1 mmol, 0.31 g), *N*,*N*-dimethylaminoethanol (DMAE) (5 ml) and DBU (0.05 mmol 0.087 ml) was irradiated in microwave at 150 °C for 10 min. After cooling to room temperature the solution was poured into methanol/water (3:1) and centrifuged. The precipitated solid was filtered off, washed with methanol/water mixture, and dried under vacuum to give a dark green powder. Yield: 75%; melting point: >200 °C; *Anal.* Calc. for $C_{56}H_{12}F_{20}N_8O_4Zn$: C, 51.50, H, 0.93, N, 8.58, Zn, 5.01. Found: C, 52.48, H, 1.01, N, 8.56, Zn, 4.98%. IR ν (cm^{-1}): 3422 (aromatic C–H), 1616 (aromatic C=C), 1460 (aromatic C=N), 1287 (C–O–C), 1108 (C=N), 460 (Zn=N); UV–Vis (*N*-methyl-2-pyrrolidinone), λ_{max}(nm): 705.

2.3.2. Synthesis of aminopropylated silica gel ($APTES@SiO_2$)

The grafting of APTES on silica gel was performed using a greener protocol. One milliliter of APTES was dissolved in 100 mL of distilled water acidified with acetic acid (pH 4). Then, 2 g of activated silica gel (dried in oven at 150 °C for 18 h) was added in the silane solution and stirred for 2 h at room temperature. The product was filtered off and kept in oven at 150 °C for 4 h. The dried product was washed consecutively with water, ethanol and acetone to remove the un-grafted material, and dried for another 2 h at 120 °C (Scheme 1).

2.3.3. Synthesis of immobilized zinc complex ($ZnPcOC_6F_5$–$APTES@SiO_2$)

A mixture of $APTES@SiO_2$ (5 g) and $ZnPcOC_6F_5$ (0.75 mmol) solution in dimethylaminoethanol was stirred and refluxed for 4 h. After that, the material was filtered, washed with water and dried in vacuum oven to give a green solid material, $ZnPcOC_6F_5$–$APTES@SiO_2$ (Scheme 1).

2.4. Catalytic studies

A reaction vessel was charged with *o*-phenylenediamine (1.0 mmol), ketone (2.2 mmol) and $ZnPcOC_6F_5$–$APTES@SiO_2$ catalyst (30 mg), and the whole reaction mixture was stirred at room temperature for an appropriate time (20–35 min). After the completion of reaction, monitored by TLC (ethyl acetate:hexane, 8:2) and GC, the reaction contents were subjected to multiple ethyl acetate extractions. The catalyst was filtered and washed with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4 followed by GC–MS analysis. All products were also characterized by using NMR, elemental analysis (CHN), mass spectra and melting points, and compared with literature data (Supplementary material) [26,30,31,53–56].

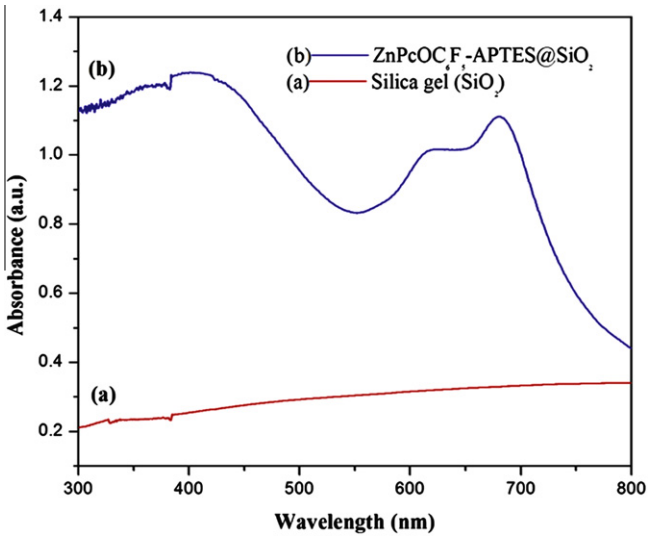
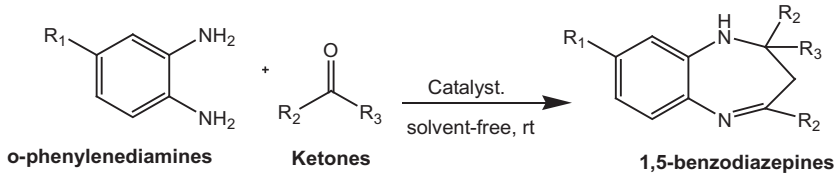


Fig. 1. Diffuse reflectance UV–Vis spectra of (a) SiO_2 and (b) $ZnPcOC_6F_5$–$APTES@SiO_2$.



Scheme 2. Solvent-free synthesis of 1,5-benzodiazepines.

Table 1
Physico-chemical parameters of SiO_2, APTES@SiO_2 and $ZnPcOC_6F_5$–APTES@SiO_2 catalyst.

Material	Elemental analysis			BET surface area ($m^2\ g^{-1}$)
	%C	%H	%N	
SiO_2	–	–	–	235
APTES@SiO_2	2.94	1.64	1.09	174
$ZnPcOC_6F_5$–APTES@SiO_2	9.98	2.36	1.41	166

3. Results and discussion

3.1. Characterizations of immobilized zinc complex ($ZnPcOC_6F_5$–$APTES@SiO_2$)

Immobilized zinc complex ($ZnPcOC_6F_5$–APTES@SiO_2) was prepared by nucleophilic substitution of activated fluorine substituent of $ZnPcOC_6F_5$ with the amino groups of aminopropylated silica gel (APTES@SiO_2) [45]. Thus, the covalent grafting of $ZnPcOC_6F_5$ complex on APTES@SiO_2 was confirmed by solid-state diffuse-reflectance UV–Vis spectroscopy. The diffuse reflectance UV–Vis spectrum of silica gel does not have any absorption band in the region of 300–900 nm. On the other hand, the diffuse reflectance UV–Vis spectrum of $ZnPcOC_6F_5$–APTES@SiO_2 (Fig. 1) shows broad absorption band in the region of 550–800 nm due to ligand π–π^* electronic transitions which is comparable to those of the ungrafted complex (Supplementary material), confirming that $ZnPcOC_6F_5$ complex has been covalently anchored on silica surface without degradation. The blue shift was observed, indicating increased π overlap on immobilization of the phthalocyanine complex (see Scheme 2) [13].

BET surface area measurements were carried out to analyze the grafting reactions. The surface area of the un-functionalized silica was approximately 235 $m^2\ g^{-1}$. The surface area of aminopropylated silica gel (APTES@SiO_2) and immobilized complex ($ZnPcOC_6F_5$–APTES@SiO_2) was found to be 174 $m^2\ g^{-1}$ and 166 $m^2\ g^{-1}$, respectively. Generally, anchoring of organic and organometallic moieties on the silica surface blocks the access of nitrogen molecules, thus reducing the surface area. Therefore, the reduction in surface area according to the sequence SiO_2 > APTES@SiO_2 > $ZnPcOC_6F_5$–APTES@SiO_2 confirmed the functionalization of SiO_2 with 3-aminopropyltriethoxy silane to give APTES@SiO_2, and its modification with $ZnPcOC_6F_5$ to yield the catalyst, $ZnPcOC_6F_5$–APTES@SiO_2. The elemental analysis data of APTES@SiO_2 showed the appearance of nitrogen (1.09%) as well as the carbon surface content (2.94%), providing an evidence for the APTES immobilization onto silica gel. The nitrogen loading of APTES@SiO_2 was found to be 0.77 mmol g^{-1}. The observed carbon and nitrogen contents of APTES@SiO_2 also showed C/N ratio to be ~2.69 which is close to the expected value thereby confirming the APTES grafting onto the surface of silica gel (Table 1). The ninhydrin test was also performed to detect qualitatively the existence of free amine groups on APTES@SiO_2 [46]. The color of the material changed from white to blue when the ninhydrin solution was added, confirming the presence of free amine groups. In contrast, the test was negative for the silica gel (no color change). The chemical analyses of $ZnPcOC_6F_5$–APTES@SiO_2 (Table 1) revealed the presence of organic matter with a C/N ratio roughly similar to that of phthalocyanine. The metal loading of $ZnPcOC_6F_5$–APTES@SiO_2 was confirmed by AAS and found to be 0.12 mmol g^{-1}. Further to support the above observation, $ZnPcOC_6F_5$–APTES@SiO_2 was subjected to energy dispersive X-ray fluorescence. A well resolved peak of zinc in the ED-XRF spectrum (Fig. 2) confirms the immobilization of $ZnPcOC_6F_5$ complex on APTES@SiO_2.

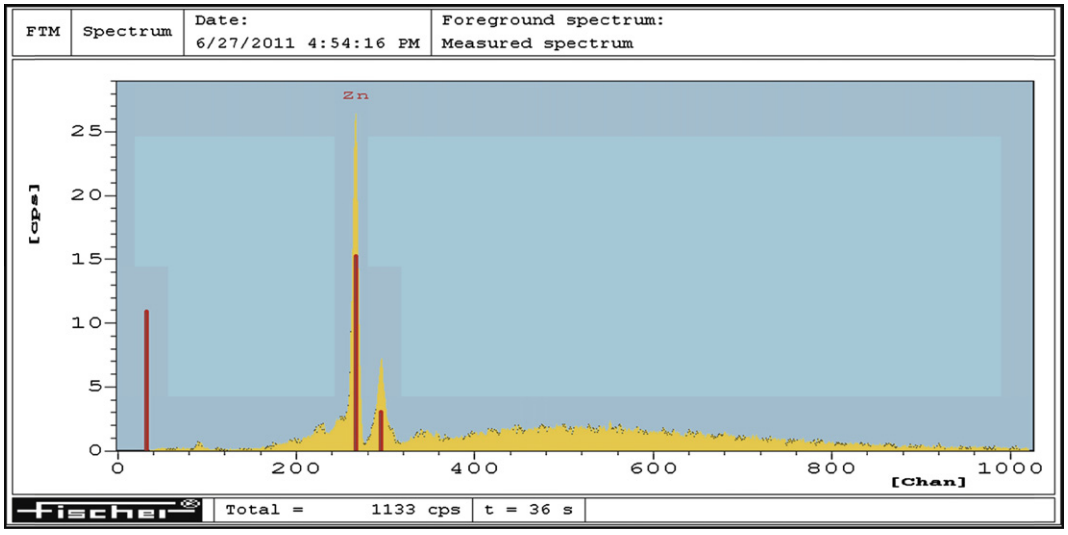


Fig. 2. ED-XRF spectrum of $ZnPcOC_6F_5$–APTES@SiO_2.

The FT-IR spectroscopy was employed to examine the covalent grafting reactions (Supplementary material). The FT-IR spectrum of silica exhibits the characteristic bands of the silica framework related to Si–O–Si asymmetric stretching (1087 cm^{-1}), Si–O stretching of Si–OH and Si–O^- groups on the surface (965 cm^{-1}), Si–O–Si symmetric stretching (800 cm^{-1}) and Si–O–Si bending vibrations (467 cm^{-1}) [47–49]. Additionally, the spectrum presents a band at 1645 cm^{-1} associated with H–O–H bending vibrations of physically adsorbed water and a broad band centered around 3460 cm^{-1} due to O–H stretching vibrations of hydrogen-bonded surface silanol groups. The grafting of APTES onto silica was confirmed by the appearance of new peak at 2925 cm^{-1} in the spectrum of APTES@SiO_2, which is due to the C–H stretching vibration of the functionalized aminopropyl group. Also, the peak due to silanol groups present in silica gel has disappeared in APTES@SiO_2. Furthermore, a significant reduction of the intensity of the O–H stretching and bending vibrations bands was observed moving from silica to APTES@SiO_2. The peak around 1645 cm^{-1} attributed to N–H bending vibration of $-NH_2$ groups was overlapped by the bending vibration of adsorbed H_2O. By comparing the spectra of APTES@SiO_2 and $ZnPcOC_6F_5$–APTES@SiO_2, it was found that the absorption at 1645 cm^{-1} was shifted to 1654 cm^{-1}, and also the intensity of the peak has decreased confirming that $ZnPcOC_6F_5$ has been covalently anchored onto the surface of APTES@SiO_2.

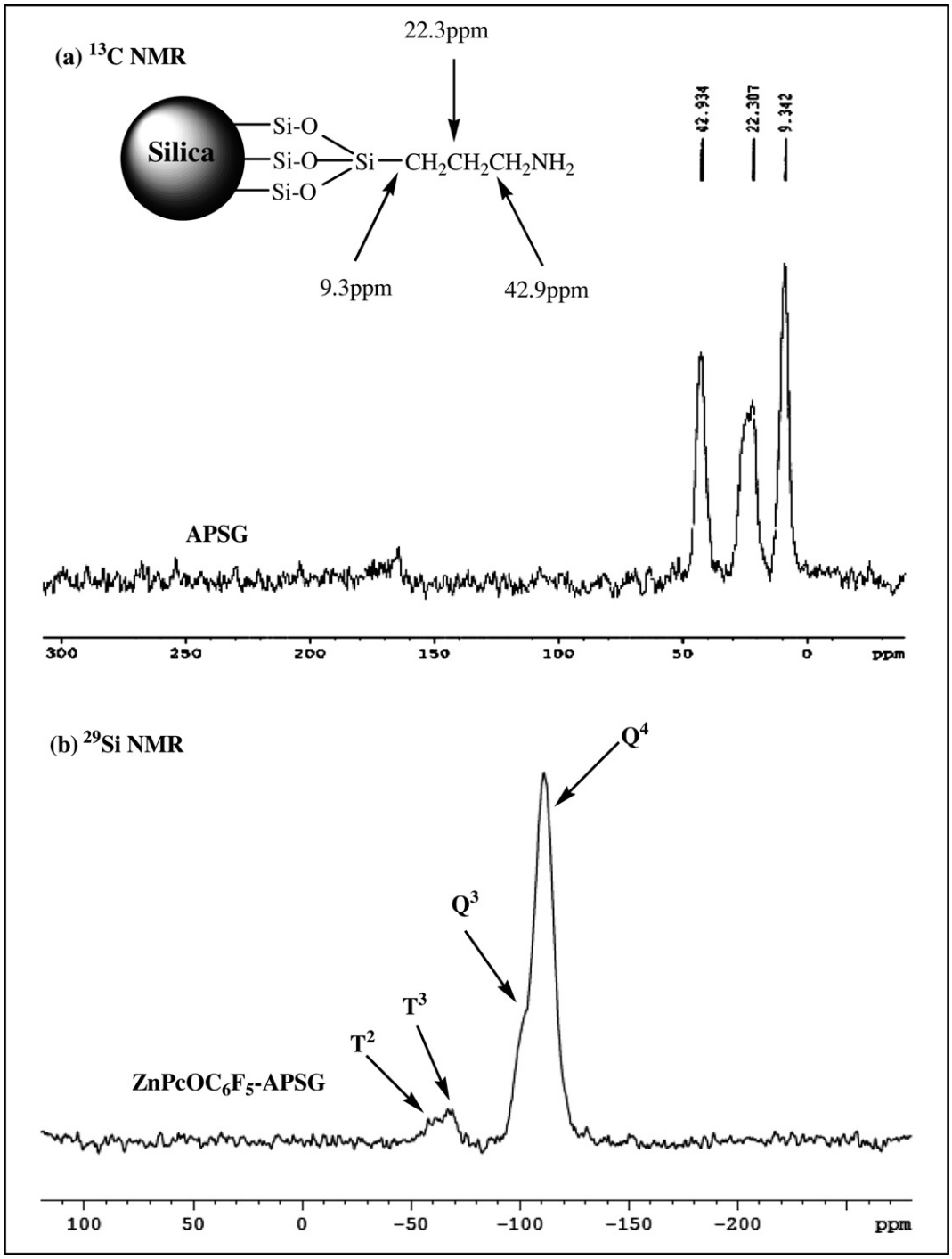


Fig. 3. (a) ^{13}C CP-MAS NMR spectrum of APTES@SiO_2 and (b) ^{29}Si CP-MAS NMR spectrum of $ZnPcOC_6F_5$–APTES@SiO_2.

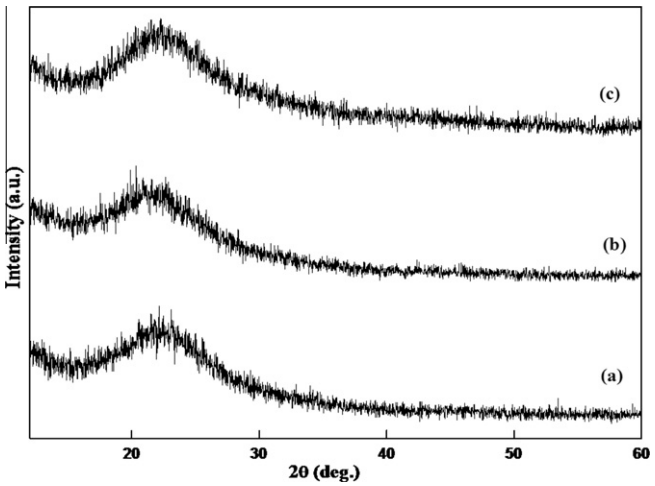


Fig. 4. X-ray diffraction patterns of (a) SiO_2, (b) APTES@SiO_2 and (c) $ZnPcOC_6F_5$–APTES@SiO_2.

The preservation of 3-aminopropyl group after functionalization of silica gel with APTES was confirmed by solid state ^{13}C NMR spectroscopy. The ^{13}C CPMAS NMR spectrum of APTES@SiO_2 presents three well resolved peaks at 9.3, 22.3 and 42.9 ppm assigned to C1, C2, and C3 carbons of the incorporated aminopropyl group $O_3SiCH_2(1)CH_2(2)CH_2(3)NH_2$, respectively (Fig. 3a) which authenticate the synthesis of APTES@SiO_2 [50]. The covalent linkage between the silanol groups and the organic moiety on the silica can also be examined by ^{29}Si CPMAS NMR spectroscopy. The solid-state ^{29}Si NMR spectrum of $ZnPcOC_6F_5$–APTES@SiO_2 presents four peaks (Fig. 3b): −57 ppm assigned to Si–OH of C–Si$(OSi)_2(OH)$ group (T^2) and −68 ppm assigned to C–Si$(OSi)_3$ group (T^3), which provide direct evidence that the inorganic–organic hybrid sample consists of a highly condensed siloxane network with an organic group covalently bonded to the silica. Two other typical peaks correspond to the inorganic polymeric structure of silica: −111 ppm assigned to Si$(OSi)_4$ group (Q^4) and −101 ppm assigned to the free silanol group of Si$(OSi)_3OH$ (Q^3) [45].

The structural features of the silica gel before and after functionalization were checked by XRD measurements (Fig. 4). The broad peak centered around $2\theta = 23^o$ in the XRD patterns of silica gel, APTES@SiO_2 and $ZnPcOC_6F_5$–APTES@SiO_2 is assigned to the diffraction peak of amorphous silica, which clearly depicts that there is no change in the topological structure of silica gel before and after grafting reactions [51]. Apparently, by functionalizing silica gel and eventually anchoring $ZnPcOC_6F_5$ complex, the intensities of reflections have decreased significantly confirming the immobilization [52].

Table 2
Screening of catalyst for the synthesis of 1,5-benzodiazepines.[a]

Entry	Catalyst	Time (min)	Yield (%)	TON[b] (TOF)[c]
1	–	120	–	–
2	Zinc acetate	90	–	–
3	SiO_2	40	15	–
4	$ZnPcOC_6F_5$ (0.001 mmol)	20	62	620 (1865)
5	$ZnPcOC_6F_5$ (0.002 mmol)	20	73	365 (1095)
6	$ZnPcOC_6F_5$ (0.003 mmol)	20	81	270 (810)
7	$ZnPcOC_6F_5$ (0.004 mmol)	20	85	236 (708)
8	$ZnPcOC_6F_5$–APTES@SiO_2	20	99	275 (825)

[a] Reaction conditions: OPDA (1.0 mmol), acetone (2.2 mmol), catalyst (30 mg, 0.36 mol%), room temperature.
[b] TON, number of moles of product per mol of catalyst.
[c] TOF, TON per hour (values in parentheses).

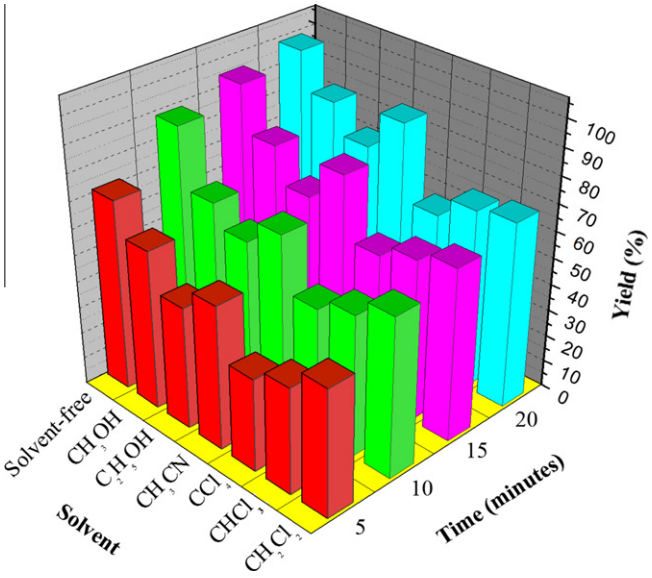


Fig. 6. Effect of solvent on the yield of 1,5-benzodiazepine (reaction conditions: OPDA (1.0 mmol), acetone (2.2 mmol), catalyst (30 mg), room temperature).

The morphology of $ZnPcOC_6F_5$–APTES@SiO_2 was examined by SEM. During the preparation of APTES@SiO_2 as well as $ZnPcOC_6F_5$–

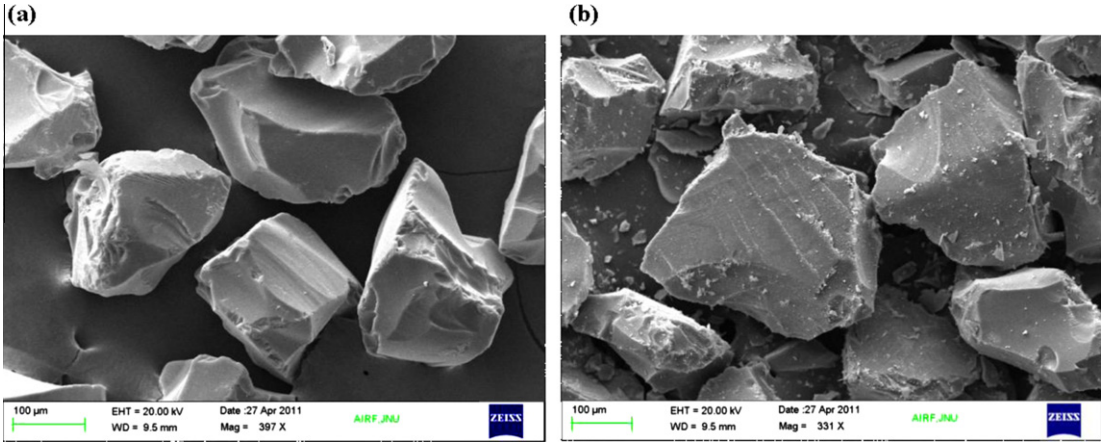


Fig. 5. SEM images of (a) SiO_2 and (b) $ZnPcOC_6F_5$–APTES@SiO_2.

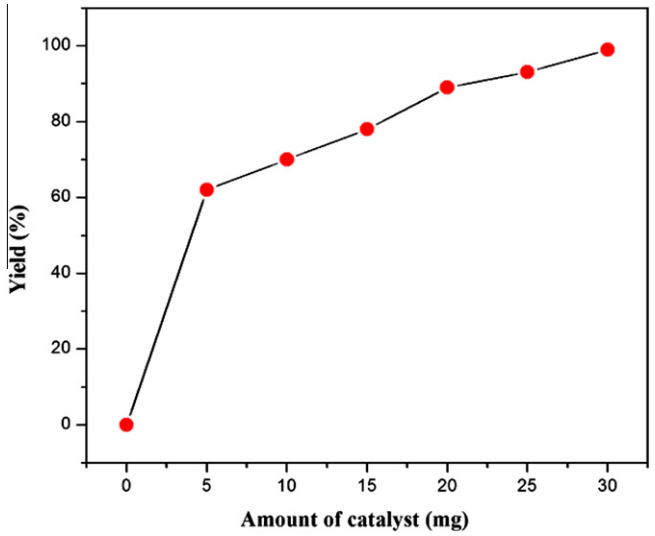


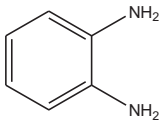
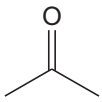
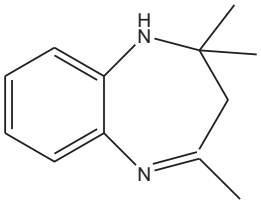
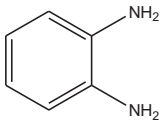
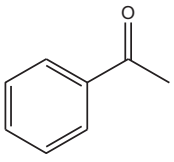
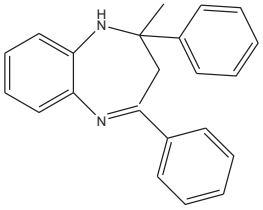
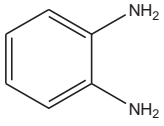
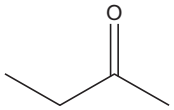
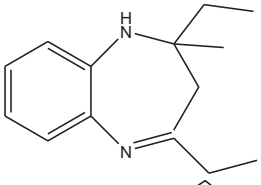
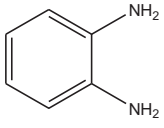
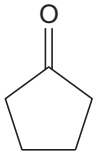
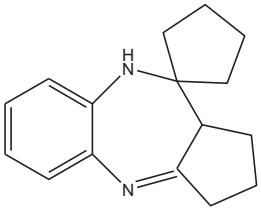
Fig. 7. Effect of amount of catalyst on the yield of 1,5-benzodiazepine (reaction conditions: OPDA (1.0 mmol), acetone (2.2 mmol), catalyst, solvent-free, room temperature).

APTES@SiO_2, the silica gel beads were subjected to rigorous stirring but it is evident from SEM image (Fig. 5) that no clog between particles occurred during the grafting procedure, and the particles maintained regular lumpy shape. It could be seen that the particles appearance and size of silica gel and $ZnPcOC_6F_5$–APTES@SiO_2 samples are very comparable, demonstrating that the particles of silica had good mechanical stability, and they had not been destroyed during the whole surface modification reactions.

3.2. Catalytic activity of $ZnPcOC_6F_5$–APTES@SiO_2 for the synthesis of 1,5-benzodiazepines

Initially, for the optimization of reaction conditions, the reaction of acetone with *o*-phenylenediamine was carried out as the model reaction without solvent at room temperature. The reaction did not occur in absence of catalyst, while it was very slow using silica as catalyst. Moreover, in presence of $ZnPcOC_6F_5$ as catalyst, we obtained moderate yield of the corresponding product, but the main disadvantage of this catalyst was its non-reusability. Hence, among the catalysts studied, $ZnPcOC_6F_5$–APTES@SiO_2 was found to be highly active and selective giving the desired product in excellent yield (Table 2). Due to the various disadvantages of using organic solvents such as toxicity, flammability and high cost, there is a pressing need to circumvent the use of solvents completely in the chemical processes. In addition, solvent-free reactions are usually quantitative and waste free and thus environmentally benign. Therefore, we have studied this reaction using various solvents and under solvent-free conditions in the presence of catalyst. We found that solvent-free conditions were more suitable and efficient in which a desired product was obtained in excellent yield after 20 min. Inferior results were obtained in the presence of various solvents (Fig. 6). Next, we optimized the quantity of the catalyst ($ZnPcOC_6F_5$–APTES@SiO_2) (Fig. 7) and it was observed that on increasing the amount of catalyst, yield also increased due to the availability of large number of active sites on the porous surface of catalyst. Hence, in all cases,

Table 3
$ZnPcOC_6F_5$–APTES@SiO_2 catalyzed synthesis of 1,5-benzodiazepines.[a]

Entry	OPDA	Ketone	Product	Time (min)	Yield (%)	TON[b] (TOF)[c]
1				20	99	275 (825)
2				20	98	272 (816)
3				25	96	266 (640)
4				30	91	252 (505)

(*continued on next page*)

Table 3 (*continued*)

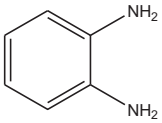
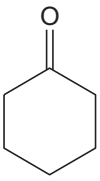
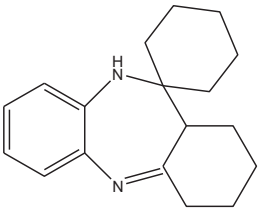
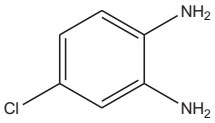
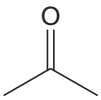
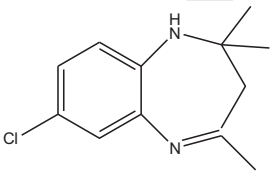
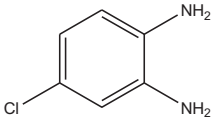
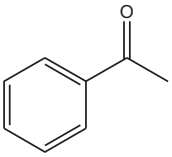
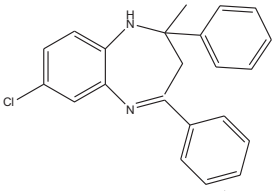
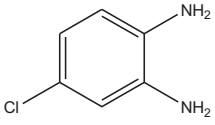
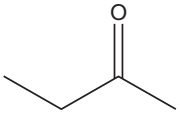
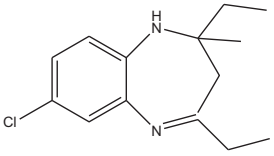
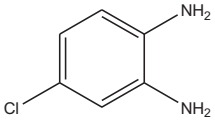
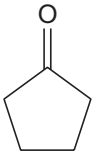
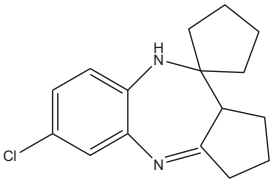
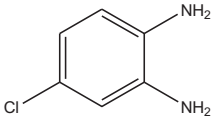
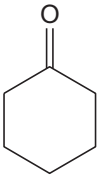
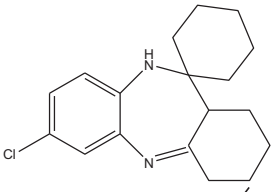
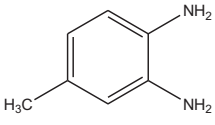
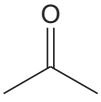
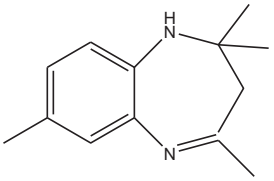
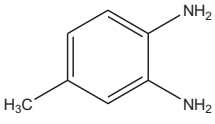
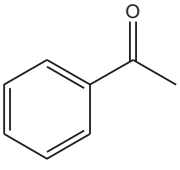
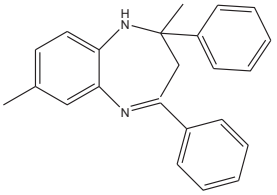
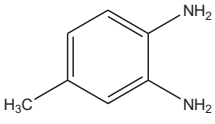
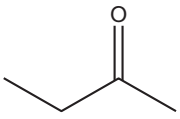
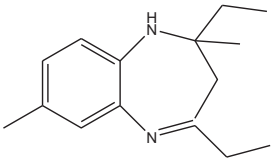
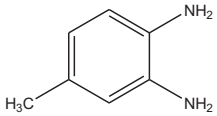
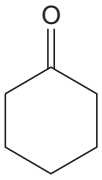
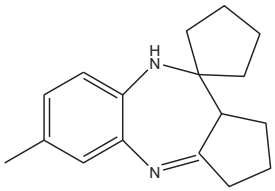
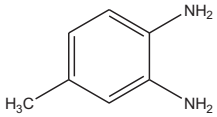
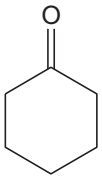
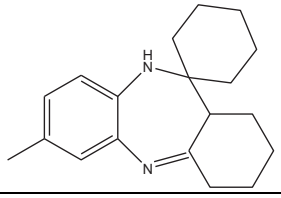
Entry	OPDA	Ketone	Product	Time (min)	Yield (%)	TON[b] (TOF)[c]
5				30	94	261 (522)
6				25	99	275 (660)
7				25	94	261 (626)
8				25	90	250 (600)
9				30	89	247 (494)
10				35	87	241 (414)
11				25	95	263 (633)
12				25	93	258 (620)
13				30	92	255 (511)

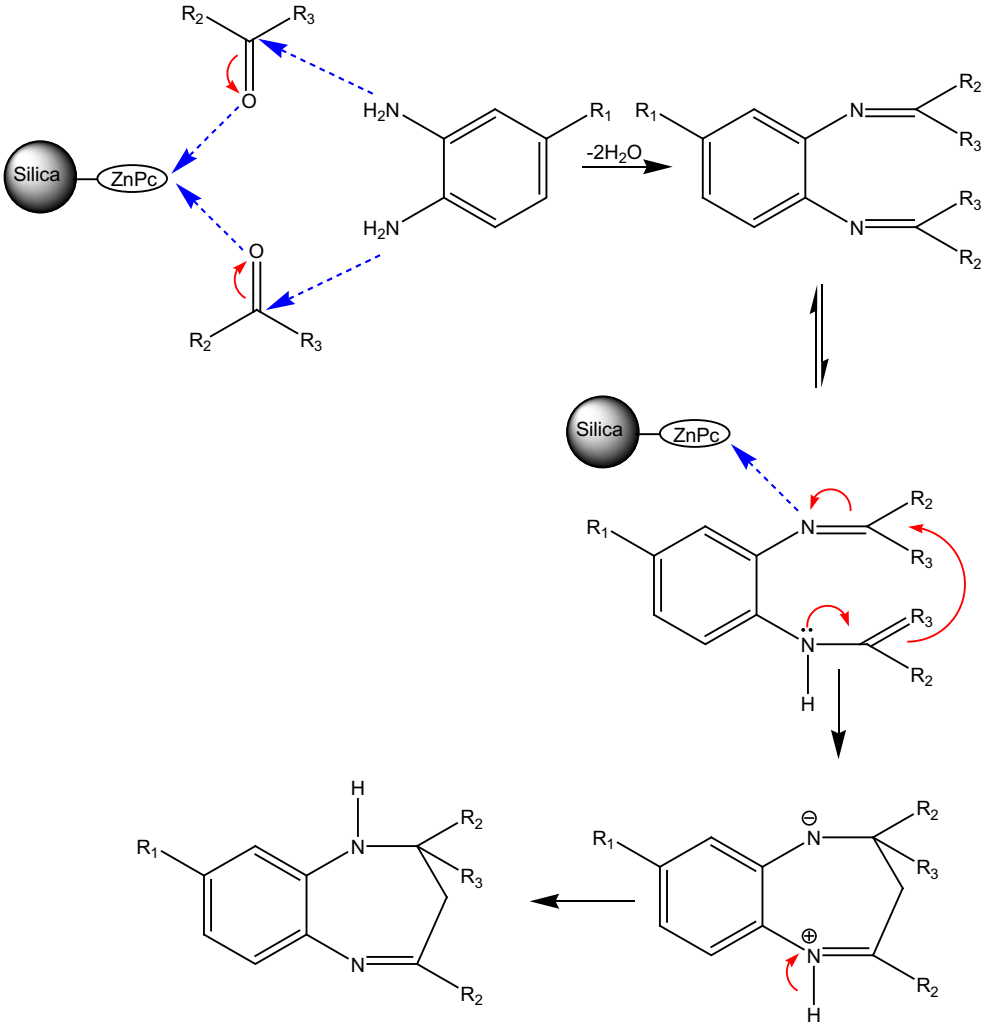
Table 3 (*continued*)

Entry	OPDA	Ketone	Product	Time (min)	Yield (%)	TON[b] (TOF)[c]
14				35	88	244 (419)
15				35	89	247 (423)

[a] Reaction conditions: OPDA (1.0 mmol), ketone (2.2 mmol), catalyst (30 mg), room temperature.
[b] TON, number of moles of product per mol of catalyst.
[c] TOF, TON per hour.

neat reactions were carried out at room temperature in presence of 30 mg of $ZnPcOC_6F_5$–APTES@SiO_2 catalyst under solvent-free conditions (Scheme 2 and Table 3).

In all cases, the reactions were completed within 20–35 min. It is noteworthy that in unsymmetrical ketone such as 2-butanone, the ring closure occurred selectively only from one side of the carbon skeleton yielding a single product indicating the selectivity of the present catalytic system as compared to the reported ones. The reaction was further extended to cyclic ketones (Table 3, entries 4–5) which react without any significant difference to give the corresponding fused ring

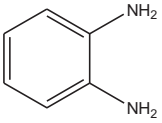
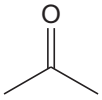
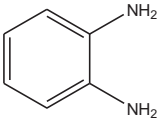
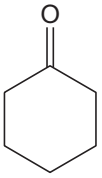
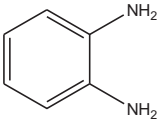
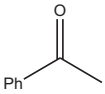
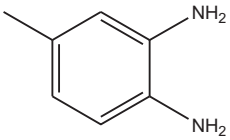
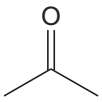
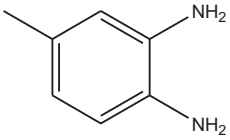
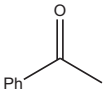
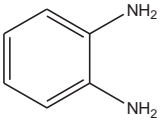
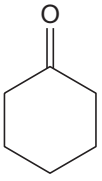
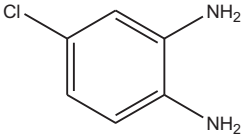
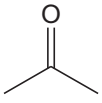
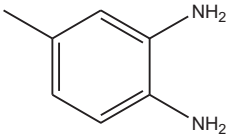
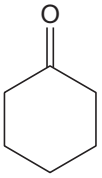


Scheme 3. Plausible reaction mechanism.

1,5-benzodiazepines in good yields but after a longer time as compared to the aliphatic ketones (Table 3, entries 1–3). Chloro-(Table 3, entries 6–10) and methyl-substituted benzodiazepines (Table 3, entries 11–15) were also obtained in high yields, which are also of much interest with regard to biological activity.

In general, 1,5-benzodiazepines are synthesized by condensation reaction of *o*-phenylenediamines (OPDAs) with ketones. Therefore, Lewis acid is required which makes feasible the nucleophilic attack of OPDA on carbonyl group by withdrawing electron density from carbonyl carbon. In this context, polyfluorinated zinc phthalocyanine having high Lewis acidity due to zinc metal and electron withdrawing fluorine substituents, is highly promising. It must be noted that reaction did not occur in absence of catalyst indicating that Lewis acidity of the catalyst ($ZnPcOC_6F_5$–APTES@SiO_2) plays a critical role in this transformation, and dictates the activity of the catalyst. Also, no product was formed when zinc acetate was used because it might be the possibility that zinc coordinates N-atoms of OPDAs and form complex. But, if $ZnPcOC_6F_5$–APTES@SiO_2 is used, then it has bulky phthalocyanine ring which does not allow zinc to coordinate to N-atoms of OPDA. Actually, $ZnPcOC_6F_5$–APTES@SiO_2 withdraws electron density of the carbonyl group in order to facilitate the nucleophilic attack of amino groups of OPDAs to give the intermediate diimine. Moreover, the fluorine substituents in polyfluorinated zinc(II) phthalocyanine make the catalyst highly hydrophobic which helps in spilling out water formed during the reaction. Finally, 1,3-hydrogen shift occurs to form an isomeric enamine which cyclizes to afford the 7-membered ring (Scheme 3).

Table 4
Literature precedents of heterogeneous catalysts for solvent-free synthesis of 1,5-benzodiazepines.

Entry	Substrate	Ketone	Catalyst	Time (min)	Yield[a] (%)	Ref.
1			Clay KSF–$H_3PMo_{12}O_{40}$	45	90	[53]
2			PVP–$FeCl_3$	60	92	[30]
3			HPW–SiO_2 (HPW-12-tungstophosphoric acid)	100	87	[54]
4			HPW–SiO_2	20	86	[54]
5			HPW–SiO_2	110	84	[54]
6			FeAlP-550 (FeAlP-iron aluminophosphate)	120	81	[55]
7			HBF_4–SiO_2	30	90	[56]
8			HBF_4–SiO_2	35	87[b]	[56]

[a] Isolated yield.
[b] Product is not benzodiazepine.

Table 5
Recycling of the catalyst.[a]

Run	Yield (%)	TON (TOF)
1	99	275 (825)
2	98	272 (816)
3	98	272 (816)
4	95	263 (791)
5	88	244 (733)
6	85	236 (708)

[a] Reaction conditions: OPDA (1.0 mmol), acetone (2.2 mmol), catalyst (30 mg), room temperature, 20 min.

3.3. Comparison of $ZnPcOC_6F_5$–APTES@SiO_2 catalyst with other reported heterogeneous catalysts

The efficiency of $ZnPcOC_6F_5$–APTES@SiO_2 catalyst was also compared with other reported heterogeneous catalysts for solvent-free synthesis of 1,5-benzodiazepines (Table 4) [30,53–56]. The results indicated the superiority of the present protocol in terms of yields, selectivity, reaction conditions and reaction time. Moreover, the present catalyst could be recovered and reused at least six times without any appreciable loss of activity.

3.4. Recycling and heterogeneity test

For heterogeneous catalyst, reusability is one of the most significant parameter, and is of great importance in industrial applications. Thus, we have investigated the recovery and reusability of the supported catalyst using acetone and *o*-phenylenediamine as model substrates. After the completion of reaction, ethyl acetate was added and the catalyst was filtered, washed thoroughly and dried in an oven at 120 °C for 1 h. The recovered catalyst was reused for six times resulting in excellent yields of the corresponding product. The products obtained were of the same purity as in all runs. These results indicated that the catalyst does not undergo appreciable change in its activity and selectivity (Table 5). In this regard, the leaching of the $ZnPcOC_6F_5$ complex from the silica support was studied by atomic absorption spectroscopy, and indicated no leaching of the $ZnPcOC_6F_5$ complex from the support. Thus, the obtained catalytic results have been derived exclusively from the heterogeneous catalyst.

4. Conclusion

We have developed an environmentally benign, facile, efficient and cost-effective procedure for the synthesis of 1,5-benzodiazepines using polyfluorinated–zinc(II)phthalocyanine complex grafted onto the functionalized silica gel as catalyst. Simple procedure, mild reaction conditions, short reaction times, high yields, high TONs, and ease of recovery and recyclability of the catalyst are the remarkable advantages of present protocol leading to the development of a ''green'' procedure for the synthesis of biologically important 1,5-benzodiazepines.

Acknowledgements

The financial assistance from University Grant Commission, Delhi, India is acknowledged. Due thanks to AIRF, JNU, Delhi, India for SEM analysis and IISc, Bangalore, India for solid state NMR measurements.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2012.11.012.

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