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Preparation of a dual-functionalized fumed silica nanoparticle catalysis for synthesis of azaluorenone derivatives

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Abstract

A dual-functional silica-based catalyst was prepared by treating fumed silica with amino-containing silane then 1,4-butane sultone. The presence of functional groups on the surface of the prepared amino sulfonic acid fumed silica (FSi–PrNH–Bu–SO_3H) was confirmed by Fourier-transform infrared (FT-IR) spectroscopy. Energy-dispersive X-ray (EDX) elemental analysis showed the presence of S, N, C, O, and Si on the surface of the catalyst. The size of the agglomerated particles was observed to lie in the range of 30–50 nm by scanning electron microscopy (SEM). Finally, thermogravimetric analysis (TGA) revealed that the amount of organic compounds grafted on the surface of FSi–$PrNH_2$ and FSi–PrNH–$BuSO_3H$ was 2.59 and 1.12 mmol/g, respectively. After well characterizing the FSi–PrNH–$BuSO_3H$, it was used to catalyze the reaction of 1,3-indandione, isatin, ethyl acetoacetate, and ammonium acetate for synthesis of azafluorenone derivatives.

Keywords Fumed silica · Sultone · Azafluorenone · Nanoparticle · Indandione · Multicomponent

Introduction

Fumed silica (FSi) is a type of very fine silica consisting of nanosized particles, produced by pyrolysis of $SiCl_4$ under hydrogen and oxygen atmosphere in a flame [1]. FSi includes primary particles with size of 10 nm, which are agglomerated

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together to form aggregates with sizes in the range of 100 nm–5 mm. FSi is applied in industrial applications as an antifoaming and paper coating agent, for reinforcement of elastomers, and as an adsorbent [2]. Since silanol groups are distributed over the surface of FSi, their density is low, hence the FSi surface is extremely chemically reactive. Silylation of silanol groups is a key reaction for surface modification of FSi [3]. To date, different types of modified FSi have been used as antibacterial agents [4], rheological additives [5], adhesive agents [6], etc. However, literature survey reveals no reports on applications of FSi as a catalyst in organic synthesis.

Azafluorenone is a significant framework found in a variety of natural products such as onychine, dielsinol, and ursuline [7, 8]. So far, natural azafluorenones have been shown to exhibit antimalarial [9], antifungal [10], and antimicrobial properties [11]. Different procedures for synthesis of azafluorenones have been described, including oxidative Heck cyclization [12], C–H functionalizations [13], Diels–Alder cycloaddition [7], and multicomponent reactions (MCRs) [14]. Among existing methods, MCRs are the simplest, being catalyzed by Brønsted acids and offering easy procedures and workup [15]. In continuation of our previous research on the advancement of heterogeneously catalyzed reactions [16–19], we introduce herein a new FSi-based heterogeneous dual-functionalized catalyst for synthesis of azafluorenone derivatives via MCR. This is the first report on the role of FSi as a catalyst in organic synthesis.

Experimental

IR spectra were recorded from KBr disks using a Bruker Tensor 27 FT-IR instrument. Melting points were measured by capillary tube method using an Electrothermal 9200 apparatus. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired using a Bruker DPX at 400 and 100 MHz, respectively. Thermogravimetric analysis (TGA) was carried out using a STA503 model (BÄHR Thermoanalyse) in the temperature range of 25–1000 °C at ramp rate of 10 °C min^{-1} under air. The surface morphology of the catalyst was detected by field-emission scanning electron microscopy (S-4160; Hitachi, Japan).

General procedure for preparation of aminopropyl-modified FSi (FSi–$PrNH_2$)

In a two-necked round-bottomed flask, FSi (10 g) was dried well under reduced pressure at 100 °C for about 4 h; after cooling to room temperature, it was added to dry toluene (150 mL). The mixture was heated under reflux condition for about 30 min, then 3-(aminopropyl)trimethoxysilane (6 mL) was gradually added to it and the mixture was refluxed for about 72 h. Finally, toluene was removed under reduced pressure to obtain the crude functionalized FSi, which was washed well with CH_2Cl_2 using a Soxhlet apparatus then dried at ambient temperature overnight.

General procedure for preparation of amino sulfonic acid modified FSi (FSi–PrNH–BuSO$_3$H)

FSi–PrNH$_2$ (2 g) was poured into a 50-mL Erlenmeyer, and 1,4-butane sultone (2 mL) and dichloromethane (8 mL) were added to it. The mixture was stirred well at room temperature overnight; thereafter, it was filtrated and washed well with dichloromethane, and dried.

General procedure for synthesis of azafluorenone

A mixture of 1,3-indandione (1 mmol, 0.146 g), isatin (1 mmol, 0.147 g), ethyl acetoacetate (1 mmol, 0.13 mL), and ammonium acetate (3 mmol, 0.23 g) was treated in presence of FSi–Pr–NH–Bu–SO$_3$H (0.05 g) for an appropriate time (as mentioned in Table 3) in refluxing EtOH, yielding azafluorenone in good yield. After completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction mixture was diluted with hot EtOH, then the catalyst was removed by simple filtration. The red product was purified by recrystallization from EtOH.

Ethyl 2′,5-dioxo-2-phenyl-1,5-dihydrospiro[indeno[1,2-*b*]pyridine-4,3′-indoline]-3-carboxylate (**5h**): Red powder, FT-IR, $v = 3380$ and 3386 (N–H), 3062 (=C–H aromatic), 2994 and 2850 (CH$_2$ and CH$_3$), 1702, 1675 and 1639 (C=O) cm^{-1}. ^{1}H NMR, $\delta = 0.5$ (t, 3 H, CH$_3$, $J = 7$), 4.35 (q, 2H, CH$_2$), 6.7 (d, 1H, aromatic, $J = 7.5$), 6.8 (t, 1H, aromatic, $J = 7.5$), 7.1 (t, 2H, aromatic, $J = 7.5$), 7.2 (d, 1H, aromatic, $J = 7.5$), 7.3 (t, 1H, aromatic, $J = 7.5$), 7.39–7.42 (m, 3H, aromatic), 7.48 (m, 3H, aromatic), 7.73 (d, 1H, aromatic, $J = 7$), 10.3 (s, 1H, NH), 10.6 (s, 1H, NH) ppm. ^{13}C NMR, $\delta = 13.3$, 50.2, 59.8, 106.7, 107.9, 109.2, 120.6, 120.9, 121.8, 124.1, 128.5, 128.7, 128.8, 129.5, 130.9, 133.4, 133.5, 136.2, 136.4, 136.5, 142.7, 147.2, 154.6, 165.8, 179.5, 189.8 ppm.

Results and discussion

Preparation and characterization of FSi–PrNH–BuSO$_3$H

Considering the usefulness of the grafting method for surface modification, the surface of fumed silica (FSi) was modified using a silylating agent. As shown in Fig. 1, silanol groups on the surface of FSi were initially treated with 3-aminopropyltriethoxysilane (APTES) to obtain FSi–PrNH$_2$. The amino groups on the surface of FSi–PrNH$_2$ were then reacted with 1,4-butane sultone to obtain the target product FSi–PrNH–BuSO$_3$H, which was subsequently characterized as follows.

TGA–differential thermal analysis (DTA) curves of both FSi–PrNH$_2$ and FSi–PrNH–BuSO$_3$H are shown in Fig. 2. The buoyancy effect is the cause of the mass loss exceeding 100% in Fig. 2a. The weight loss below 100 °C is due to adsorbed water and solvents. Correspondingly, the weight losses for FSi–PrNH$_2$ and FSi–PrNH–BuSO$_3$H in the temperature range between 100 and 600 °C are 15

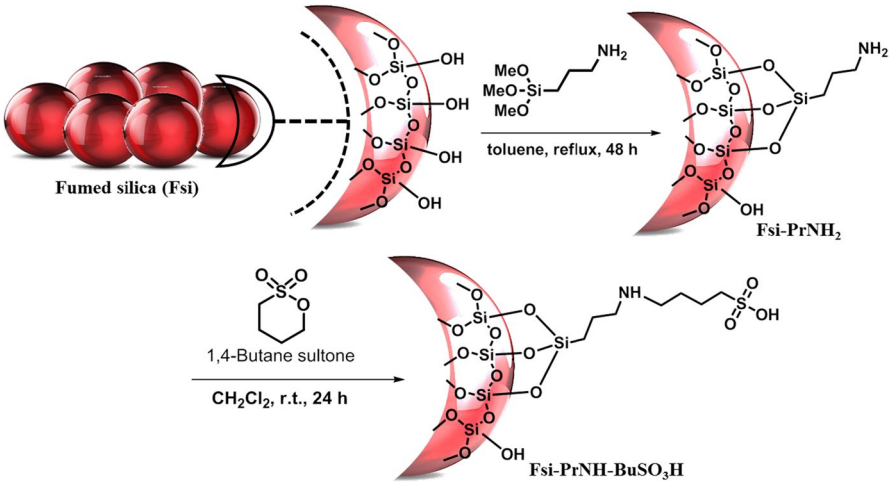


Fig. 1 Preparation of FSi–PrNH–$BuSO_3H$

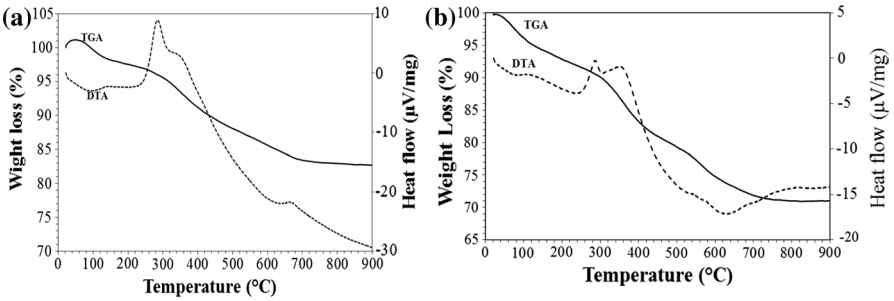


Fig. 2 TGA–DTA curves for **a** FSi–$PrNH_2$ and **b** FSi–PrNH–$BuSO_3H$

and 21%, respectively. The observed weight loss above 600 °C is due to condensation of free silanols of FSi structure. Accordingly, the amount of grafted organic compounds on the surface of FSi–$PrNH_2$ and FSi–PrNH–$BuSO_3H$ was calculated to be 2.59 and 1.12 mmol/g, respectively. The decrease of the organic compound concentration on the surface of FSi–PrNH–$BuSO_3H$ compared with FSi–$PrNH_2$ may result from the fact that all amine groups did not completely react with 1,4-butane sultone, thus both –PrNH–$BuSO_3H$ and –$PrNH_2$ groups are present on the surface. Furthermore, it is possible to leach some grafted $PrNH_2$ groups during the reaction with 1,4-butane sultone as a result of the mechanical stirring. In the DTA curve of FSi–$PrNH_2$, three exothermic peaks are observed at around 127, 286, and 320 °C, corresponding to decomposition of organic groups. The peak at around 655 °C relates to condensation of free silanols. Same exothermic peaks are detectable for FSi–PrNH–$BuSO_3H$ in addition to the peak at around 550 °C, corresponding to additional organic groups on the surface in comparison with FSi–$PrNH_2$.

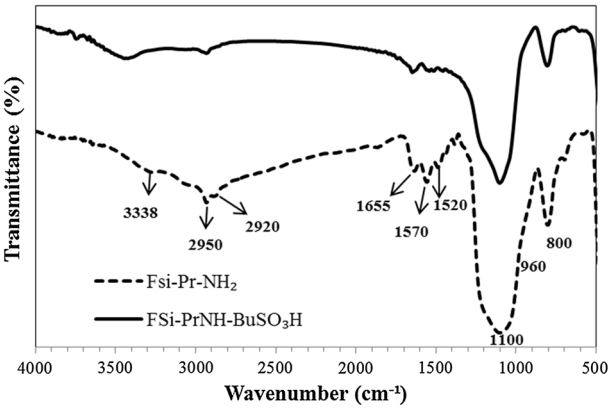


Fig. 3 FT-IR spectra of FSi–PrNH$_2$ and FSi–PrNH–BuSO$_3$H

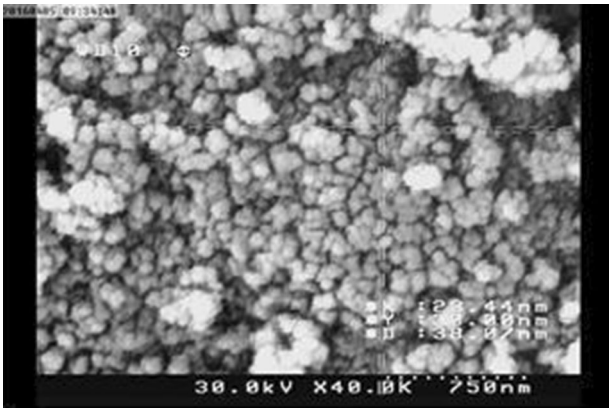


Fig. 4 SEM image of FSi–PrNH–BuSO$_3$H

Figure 3 depicts the FT-IR spectra of FSi–PrNH$_2$ and FSi–PrNH–BuSO$_3$H. In general, FSi displays three intense peaks at 800, 960, and 1100 cm^{-1}, related to symmetric stretching vibration of Si–O, symmetric stretching vibration of Si–OH, and asymmetric stretching vibration of Si–O–Si, respectively. The presence of organic moieties is recognized based on the peaks at 2850–2960 cm^{-1} in both spectra, which are related to symmetric and asymmetric stretching vibration of CH and CH$_2$ groups. In the FT-IR spectrum of FSi–PrNH$_2$, the absorbance bands at 3338 and 1570 cm^{-1} correspond to stretching and bending vibration of NH$_2$, respectively. These bands are missing from the spectrum for FSi–PrNH–BuSO$_3$H, confirming formation of N–C bond in this material.

FESEM of FSi–PrNH–BuSO$_3$H (Fig. 4) revealed agglomerated particles with size in the range of 30–50 nm. EDX analysis of FSi–PrNH$_2$ proved the presence of Si, O, C, and N elements, while in EDX analysis of FSi–PrNH–BuSO$_3$H, S

element was also observed (Fig. 5). The high percentage of C atom is due to the use of carbon-based adhesive to attach the sample to the pin of the instrument.

Catalytic activity of FSi–PrNH–BuSO$_3$H

To identify the best reaction conditions for preparation of azafluorenone derivatives, a model reaction of indandione **1**, isatin **3a**, ethyl acetoacetate **3**, and ammonium acetate **4** was carried out in presence and absence of catalyst. As shown in Table 1 (entries 1 and 2), running the reaction using FSi–PrNH–BuSO$_3$H under solvent-free condition did not give good results even when raising the temperature to 70 °C. Under refluxing in water, the reaction did not progress (entry 3), while in ethanol (entry 4), it gave the product in high yield within 15 min; hence, this was selected as the optimized condition. To investigate the effect of catalyst on the progress of this reaction, it was tested in presence of pure fumed silica (entry 5) and FSi–PrNH$_2$ (entry 7); considering the increase of the reaction time and decrease of product yield, it was found that the functional groups on the fumed silica surface accelerated the reaction rate. Furthermore, product yield of 68% was obtained in absence of catalyst within 1 h. Therefore, the presence of catalyst is essential for this reaction. Varying the catalyst amount (Table 2), it was found that increase of the amount of catalyst to 0.05 g increased the product yield. However, use of 0.06 g catalyst resulted in a yield drop of about 2% compared with 0.05 g catalyst; this may

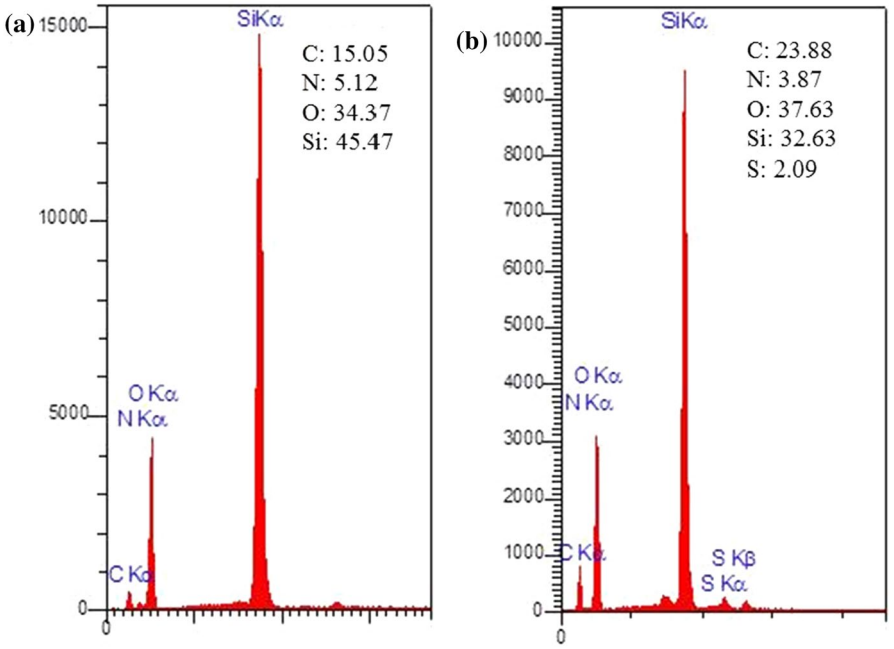


Fig. 5 EDX results of **a** FSi–PrNH$_2$ and **b** FSi–PrNH–BuSO$_3$H

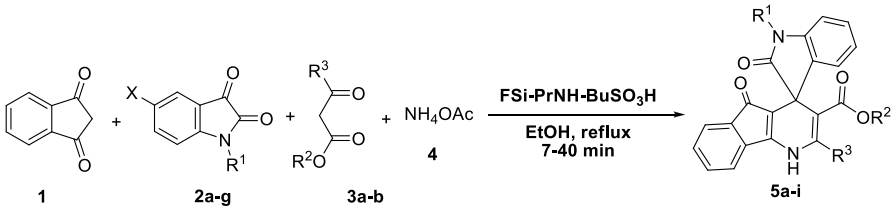
Table 1 Optimization of reaction conditions for synthesis of azafluorenone **4a**

Entry	Catalyst (0.03 g)	Solvent	Condition	Time (min)	Yield (%)
1	FSi–PrNH–$BuSO_3H$	–	r.t.	24	43
2	FSi–PrNH–$BuSO_3H$	–	70 °C	13	51
3	FSi–PrNH–$BuSO_3H$	H_2O	Reflux	120	–
4	FSi–PrNH–$BuSO_3H$	EtOH	Reflux	15	85
5	FSi	EtOH	Reflux	35	72
6	–	EtOH	Reflux	1 h	68
7	FSi–$PrNH_2$	EtOH	Reflux	30	75

1,3-Indandione (1 mmol), isatin (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (3 mmol), catalyst (0.03 g), and solvent (3 mL)

Table 2 Optimization of catalyst amount for synthesis of azafluorenone **4a**

Entry	Amount of catalyst (g)	Amount of catalytic sites used (mol%)	Time (min)	Yield (%)
1	0.03	3.36	15	85
2	0.04	4.48	10	90
3	0.05	5.6	7	93
4	0.06	6.7	7	91



Scheme 1 Synthesis of azafluorenone derivatives

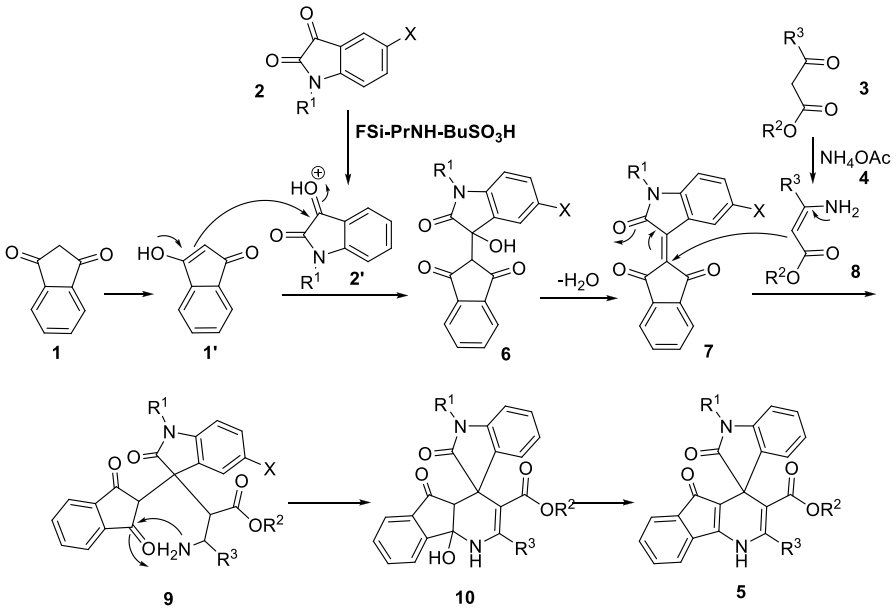
be explained by higher adsorption of organic compounds on the greater amount of silica surface. Therefore, the optimized amount of FSi–PrNH–$BuSO_3H$ for this reaction was established as 0.05 g.

The generality of this reaction was studied by applying different isatin **2a**–**g** and β-ketoester compounds **3a**, **b** (Scheme 1). As shown by the results in Table 3, isatin **2a** gave the best results regarding the reaction time, while electron-withdrawing substituents on the phenylene ring of isatin led to decreased product yield (**5b**–**g**) and increased reaction time. In addition, replacing ethyl acetoacetate **3a** by ethyl benzoylacetate **3b** (entries 8 and 9) resulted in a significant drop of the product yield (**5h**).

The role of FSi–PrNH–$BuSO_3H$ as catalyst in the synthesis of azafluorenone derivatives is shown by the plausible mechanism in Scheme 2. Initially, indandione **1** is converted to its enolic form **1′**. Then, the latter condenses with the carbonyl group of isatin **2′** which was previously activated by the catalyst, thus intermediate

Table 3 Synthesis of azafluorenone derivatives in presence of FSi–PrNH–$BuSO_3H$

Entry	No.	R^1	X	R^2	R^3	Time (min)	Yield (%)	M.p. (°C)	Reference m.p. (°C) [20]
1	**5a**	H	H	Et	Me	7	93	> 300	> 300
2	**5b**	H	Cl	Et	Me	11	91	> 300	> 300
3	**5c**	H	Br	Et	Me	15	90	> 300	> 300
4	**5d**	H	NO_2	Et	Me	15	84	> 300	> 300
5	**5e**	H	I	Et	Me	14	72	> 300	> 300
6	**5f**	H	F	Et	Me	12	76	> 300	> 300
7	**5g**	Bn	H	Et	Me	16	68	> 300	> 300
8	**5h**	H	H	Et	Ph	40	76	> 300	New



Scheme 2 Plausible mechanism for synthesis of azafluorenone derivatives in presence of FSi–PrNH–$BuSO_3H$

7 is formed after a dehydration process. Simultaneously, β-ketoester **3** reacts with ammonium acetate **4** to obtain intermediate **8**, which is then added to the condensed compound **7** by Michael addition. Finally, the azafluorenone **5** is produced by intramolecular cyclization of **9** and a subsequent dehydration process. The catalyst plays an important role in both protonation and deprotonation steps due to the presence of both acidic and basic functions on its surface.

Three methodologies have been reported for synthesis of azafluorenone derivatives (Table 4, entries 1–3). Bazgir and coworkers employed pyridine and toluene

Table 4 Comparison of methods applied for synthesis of azafluorenone derivatives

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%)	Ref.
1	Pyridine	Toluene	Reflux	24	75–92	[20]
2	–	EtOH:H_2O (9:1)	r.t.	6	70–86	[21]
3	Activated alumina	–	100 °C	4	60–90	[22]
4	FSi–PrNH–BuSO_3H	EtOH	Reflux	7–40 min	68–93	This work

as catalyst and solvent, respectively, in this reaction (entry 1); Mukhopadhyay and coworkers tried this synthesis in a mixture of ethanol and water with no catalyst; while in other work, activated alumina catalyzed this reaction under neat condition. Use of unsafe solvent, harsh conditions, and long reaction time are drawbacks of the mentioned methods. In this report, the catalyst is safe, the solvent and reaction condition are green, and the reaction time is very short compared with the others. It can thus be concluded that this new catalyst is efficient in terms of reaction time and product yield, offering green conditions that are safe for the environment.

Conclusions

The surface of FSi was modified with dual functions of acid (SO_3H) and base (NH), then characterized by FT-IR spectroscopy, TGA–DTA, SEM, and EDX spectroscopy. All analyses confirmed effective grafting of organic groups on the silica surface. The resulting FSi–PrNH–BuSO_3H catalyzed synthesis of azafluorenone derivatives in refluxing EtOH. In terms of high product yield, chemoselectivity, and short reaction time, it can be claimed that FSi–PrNH–BuSO_3H is an efficient heterogeneous catalyst for organic reactions. Investigation of the special properties of the prepared azafluorenone is in progress.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

References

1. C.R. Schnell, S.M.L. Hamblyn, K. Hengartner, M. Wissler, Powder Technol. **20**, 15 (1978)
2. D. Zhang, J. Su, X. Ma, H. Tian, Tetrahedron **64**, 8515 (2008)
3. H. Barthel, M. Dreyer, T. Gottschalk-Gaudig, E. Nikitina *Organosilicon Chemistry Set: From Molecules to Materials*. (Wiley, New York, 2008)
4. P. Gholamzadeh, G. Mohammadi Ziarani, F. Zandi, A. Abolhasani Soorki, A. Badiei, F. Yazdian, C. R. Chim. **20**, 833 (2017)
5. H. Barthel, Colloids Surf. A **101**, 217 (1995)
6. J.S. Lim, S.M. Hong, D.K. Kim, S.S. Im, J. Appl. Polym. Sci. **107**, 3598 (2008)

7. B.C. Hong, M.S. Hallur, J.H. Liao, Synth. Commun. **36**, 1521 (2006)
8. C. Mérienne, G.J. Arango, D. Cortes, B.K. Cassels, A. Cavé, Phytochemistry **26**, 2093 (1987)
9. D. Mueller, R.A. Davis, S. Duffy, V.M. Avery, D. Camp, R.J. Quinn, J. Nat. Prod. **72**, 1538 (2009)
10. J.H.G. Lago, M.H. Chaves, M.C.C. Ayres, D.G. Agripino, M.C.M. Young, Planta Med. **73**, 292 (2007)
11. D. Addla, Bhima, B. Sridhar, A. Devi, S. Kantevari, Bioorg. Med. Chem. Lett. **22**, 7475 (2012)
12. S. Dhara, A. Ahmed, S. Nandi, S. Baitalik, J.K. Ray, Tetrahedron Lett. **54**, 63 (2013)
13. J.K. Laha, K.P. Jethava, S. Patel, K.V. Patel, J. Org. Chem. **82**, 76 (2016)
14. S. Tu, B. Jiang, H. Jiang, Y. Zhang, R. Jia, J. Zhang, Q. Shao, C. Li, D. Zhou, L. Cao, Tetrahedron **63**, 5406 (2007)
15. T. Ahmadi, G. Mohammadi Ziarani, P. Gholamzadeh, H. Mollabagher, Tetrahedron Asymmetry **28**, 708 (2017)
16. G. Mohammadi Ziarani, P. Gholamzadeh, A. Badiei, V. Fathi Vavsari, Res. Chem. Intermed. **44**, 277 (2018)
17. G. Mohammadi Ziarani, Z. Kazemi Asl, P. Gholamzadeh, A. Badiei, M. Afshar, Appl. Organomet. Chem. **31**, e3830 (2017)
18. P. Gholamzadeh, G. Mohammadi Ziarani, A. Badiei, Biocatal. Biotransform. **35**, 131 (2017)
19. G. Mohammadi Ziarani, Z. Kazemi Asl, P. Gholamzadeh, A. Badiei, M. Afshar, J. Sol Gel Sci. Technol. **85**, 103 (2018)
20. A. Feiz, G.I. Shakibaei, Z. Yasaei, H.R. Khavasi, A. Bazgir, Helv. Chim. Acta **94**, 1628 (2011)
21. N.C. Dige, D.M. Pore, Synth. Commun. **45**, 2498 (2015)
22. A. Mondal, B. Banerjee, A. Bhaumik, C. Mukhopadhyay, ChemCatChem **8**, 1185 (2016)