NJC

PAPER

View Article Online
View Journal | View Issue

Check for updates

Cite this: *New J. Chem.*, 2018, **42**, 20095

Received 17th July 2018,
Accepted 8th November 2018

DOI: 10.1039/c8nj03559h

rsc.li/njc

Preparation and characterization of a novel silica–KF composite and facile fluorination of aromatic substrates†

Sagar S. Patel, Machhindra D. Bochare and Mariam S. Degani*

A novel silica–KF reagent prepared by hydrolyzing tetraethyl orthosilicate in the presence of KF for fluorination of activated aromatic compounds has been reported. The reagent, as characterized by techniques such as SEM-EDX, XRD and IR spectroscopy, is shown to have potassium cations entrapped inside the silica matrix whereas fluoride anions remain on the surface. Reaction of activated chlorinated aromatic substrates with this silica–KF leads to formation of Meisenheimer complex, either *in situ* or isolable, finally resulting in regioselective fluorinated aromatics.

1. Introduction

Organo-fluorine compounds are of considerable interest in various fields due to their unique physical and chemical properties. These are valuable as pharmaceuticals, agrochemicals, and tracers for positron emission tomography (PET).[1] In the last decade, the number of fluorine-containing drugs jumped from 27% of all approved small molecules to 36%. Most importantly, about 40% of the new chemical entities entering phase III trials in 2012 and 2013 were fluoro-organic compounds.[2] Many synthetic strategies, including the development of electrophilic fluorinating agents, electrochemical fluorination, nucleophilic fluorination, and strategies to deal with the violent reactivity of fluorine gas have been developed.[3,4] However, the general construction of Csp^2–F bonds, especially aromatic carbon–fluorine bonds, remains a challenge.[1] Aromatic fluorination is usually achieved by Balz Schiemann reaction, denitration–fluorination and halogen exchange (Halex) reaction. The former approach suffers from many drawbacks of such as hazardous reagents and thermal safety.[5] Halex reaction is a preferred industrial method for syntheses of aromatic fluorination.

Typical substrates for Halex reactions include mono, di or tri nitro substituted chlorobenzenes. Diversity of chloroaromatic compounds having variety of electron withdrawing groups on the aromatic ring afford synthesis of many commercially important chemicals by Halex process. 4-Chloronitrobenzene (4-CNB), 4-chlorobenzonitrile (4-CBn) 4-chloro 3-nitrobenzonitrile (4C3NBn), 2,4-dinitrochlorobenzene (2,4-DNCB) are some of the important substrates for syntheses of fluorinated drug intermediates.[6] Typical reactions involving above fluoride ion sources with such substrates leads to the formation side products due to denitration–fluorination.[7–9] Therefore, there is a need to develop newer reagents which are less hygroscopic, stable at high temperatures and are regioselective.

It is absolutely essential that a fluorinating agent can release reactive fluoride anion in the reaction mixture. Crown ethers act as catalysts for fluorination reaction *via* trapping of potassium ions by oxygen atoms, leaving the fluoride anion free.[10,11] Tetrabutyl ammonium fluoride (TBAF) on the other hand, is an excellent source of reactive fluoride anion, because of steric hindrance by four butyl groups. However, it is hygroscopic, thermally labile and also very expensive. TBAF undergoes Hoffman degradation when subjected to temperatures above 50 °C in the presence of F^- ion during drying process,[12] and cannot be used for large scale synthesis.

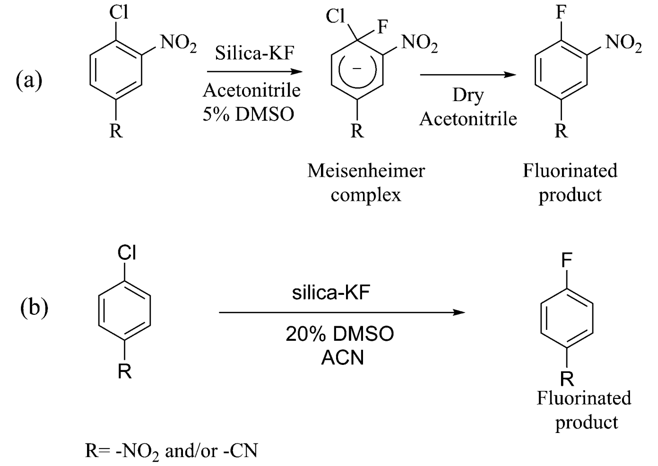
Supported reagents such as alumina-supported potassium fluoride has been extensively studied for various reactions other than fluorination reaction.[7,12–14] The idea of using silica as solid support for potassium fluoride arises from the fact that the potassium atom shows a very high affinity towards oxygen atoms as can be seen for crown ethers.[10] The interactions of KF and silica melts have already been reported.[15] The interaction of oxygen atoms in silica with potassium have already been reported to affect reduction of Co/SiO_2 catalyst.[16–19]

The present work includes preparation and characterization of a novel silica–KF composite by hydrolyzing tetraethyl orthosilicate (TEOS) in the presence of potassium fluoride (KF) to give reactive fluoride on the surface of silica. The resulting novel reagent has been demonstrated to facilitate fluorination

---

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai, India. E-mail: ms.degani@ictmumbai.edu.in

† Electronic supplementary information (ESI) available: Moisture uptake capacity raw data of silica–KF and KF is given in S1. SEM-EDX analysis data is available in S2. HPLC chromatogram, IR spectra, ^1H NMR spectra, ^{19}F spectra of the pure compounds and complexes are given from S4–S25. This material is available for authorized users. See DOI: 10.1039/c8nj03559h



Scheme 1 Silica–KF reagent in fluorination of substrates with (a) two electron withdrawing groups (b) one electron withdrawing group.

of different activated aromatic substrates and can be used for other applications as well.

2. Experimental

2.1 Materials

4-Chloronitrobenzene (4-CNB), 4-chlorobenzonitrile (4-CBn), 4-chloro 3-nitrobenzonitrile (4C3NBn), 2,4-dinitrochlorobenzene (2,4-DNCB), 4-fluoronitrobenzene (4-FNB), 4-fluorobenzonitrile (4-FBn), potassium fluoride (KF) and dimethyl sulfoxide (DMSO) were purchased from S D Fine-Chem Limited, tetraethyl orthosilicate (TEOS) was purchased from Sigma Aldrich and all were used directly. HPLC grade acetonitrile (ACN) was purchased from S D Fine-Chem Limited and dried using calcium hydride before use.[20] FTIR spectra were recorded on Perkin Elmer Spectrum Two FT-IR Spectrometer using potassium bromide (KBr) discs. Powder X-ray diffraction patterns were recorded using Shimadzu Lab X XRD-6100 X-ray diffractometer. The surface morphologies were examined by JEOL-JSM 6380 Scanning Electron Microscope. HPLC analysis was carried out using JASCO-LC 4000 instrument. ^{1}H NMR spectra were recorded on Agilent 400 MR instrument. ^{19}F NMR spectra were recorded on JEOL-ECZR Series 600 MHz NMR SPECTROMETER.

2.2 Synthesis

2.2.1 Preparation and characterization of silica–KF reagent. 1 g (17.2 mmol) of KF in 10 ml of distilled water was stirred with 20 ml of TEOS (90.2 mmol) for 2 hours. The two phases when stirred vigorously, led to hydrolysis of TEOS, and precipitation of silica–KF. The solvent was then evaporated to dryness under vacuum to yield 6.4 g of powdered silica–KF.

The prepared reagent was characterized for its moisture uptake capacity, SEM-EDX analysis, X-ray diffraction analysis, and IR spectroscopy. Its moisture uptake capacity was measured by initial drying at 150 °C for 1 h followed by exposure to 60% RH at 25 °C for 48 h using KF as standard.

2.2.2 Syntheses of fluorinated substrates using silica–KF reagent. Method 1: Scheme 1a shows general procedure for fluorination of 2,4-dinitrochlorobenzene (2,4-DNCB) and 4-chloro 3-nitrobenzonitrile (4C3NBn).

2,4-Dinitrofluorobenzene (2,4-DNFB). 6.4 g of silica–KF (equivalent to 17.2 mmol KF), 1.2 g of 2,4-dinitrochlorobenzene (5.7 mmol, 0.33 equivalents) 20 ml of dry ACN and 1 ml of dry DMSO were stirred at 85 $\pm$ 5 °C under nitrogen atmosphere for 2 hours until the formation of Meisenheimer complex was complete, as monitored by HPLC. The spent reagent was filtered after cooling, and the filtrate was concentrated and dried under vacuum to isolate the Meisenheimer complex. It was characterized by HPLC, IR and ^{1}H NMR. The Meisenheimer complex was heated at 80 °C in the presence of 10 ml dry ACN for 2 hours to get 2,4-dinitrofluorobenzene, as monitored by HPLC. After cooling, the solvent was removed and the product was extracted with ethyl acetate and water to separate 2,4-DNFB, which was characterized by HPLC, IR and ^{1}H and ^{19}F NMR.

4-Fluoro 3-nitrobenzonitrile (4F3NBn). Reaction of 4-chloro 3-nitrobenzonitrile was carried out as in Method 1, Scheme 1a using 1 g (5.7 mmol) of 4-chloro 3-nitrobenzonitrile. The Meisenheimer complex and the product were characterized by HPLC, IR and ^{1}H and ^{19}F NMR.

Method 2: Scheme 1b shows general procedure for fluorination of 4-chloronitrobenzene and 4-chlorobenzonitrile.

4-Fluoronitrobenzene (4-FNB). 6.4 g of silica–KF (equivalent to 17.2 mmol KF), 0.9 g of 4-chloronitrobenzene (5.7 mmol) 20 ml of dry ACN and 4 ml of dry DMSO were stirred at 85 $\pm$ 5 °C under nitrogen atmosphere for 24 hours. Formation of the product 4-fluoronitrobenzene was monitored by HPLC using standard 4-FNB. After cooling the reaction mixture, the solid reagent was filtered out and the filtrate was directly analyzed by HPLC.

4-Fluorobenzonitrile (4-FBn). Reaction of 4-chlorobenzonitrile was carried out as in Method 2, Scheme 1b by using 0.78 g (5.7 mmol) 4-chlorobenzonitrile, 6.4 g of the reagent (equivalent to 17.2 mmol KF) 20 ml of dry ACN and 4 ml of dry DMSO. Formation of the product 4-FBn was monitored by HPLC using standard 4-FBn. After cooling the reaction mixture, the solid reagent was filtered out and the filtrate was directly analyzed by HPLC.

2.3 Characterization

Meisenheimer complex of 2,4-DNCB with fluoride ion. Yellow solid, m.p. = >300 °C, FTIR (KBr, ν) 3053 cm^{-1}, 1668 cm^{-1}, 1554 cm^{-1}, 1377 cm^{-1}, 1052 cm^{-1}, 918 cm^{-1}, 835 cm^{-1}, 746 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d$_6$) 6.27(d), 7.50(dd), 8.55(d) ppm.[21] ^{19}F NMR (600 MHz, DMSO-d$_6$) −69.28, −70.54, −73.81 ppm. HPLC: retention time (RT): 1.65 min (mobile phase- ACN : water 60 : 40, column: 25 cm, 5μC18).

2,4-DNFB. Light yellow liquid, yield = 98% (by HPLC), m.p. = 24 °C (lit.[22] 25.8 °C), FTIR (KBr, ν) 3095 cm^{-1}, 1607 cm^{-1}, 1530 cm^{-1}, 1350 cm^{-1}, 1006 cm^{-1}, 834 cm^{-1}, 739 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) 7.53(m), 8.53(d), 8.98(s) ppm. ^{19}F NMR

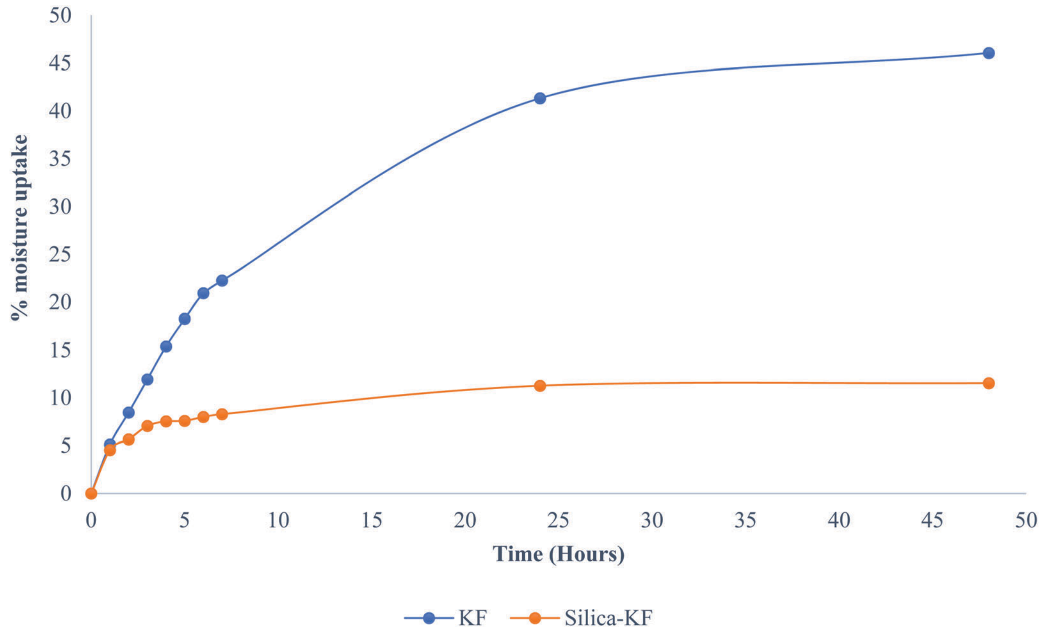


Fig. 1 Moisture uptake by KF and silica–KF over 48 h at 25 °C and 60% RH.

(400 MHz, $CDCl_3$) −106 ppm. HPLC: (RT): 5.95 min (mobile phase- ACN : water 60 : 40, column: 25 cm, 5μC18).

Meisenheimer complex of 4-chloro 3-nitrobenzonitrile with fluoride ion. Yellowish orange solid, m.p. = >300 °C, FTIR (KBr, ν) 3095 cm^{-1}, 2217 cm^{-1}, 1622 cm^{-1}, 1558 cm^{-1}, 1332 cm^{-1}, 1069 cm^{-1}, 832 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) 6.31(d), 7.09(d), 7.96(s) ppm. ^{19}F NMR (600 MHz, DMSO-d_6) −69.35, 70.61 ppm. HPLC: retention time (RT): 1.63 min.

4F3NBn. Light yellow solid, yield = 88% (by HPLC), m.p. = 94 °C (lit.[23] 90–94 °C), FTIR (KBr, ν) 2956 cm^{-1}, 2233 cm^{-1}, 1622 cm^{-1}, 1535 cm^{-1}, 1353 cm^{-1}, 1087 cm^{-1}, 1004 cm^{-1}, 835 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6)

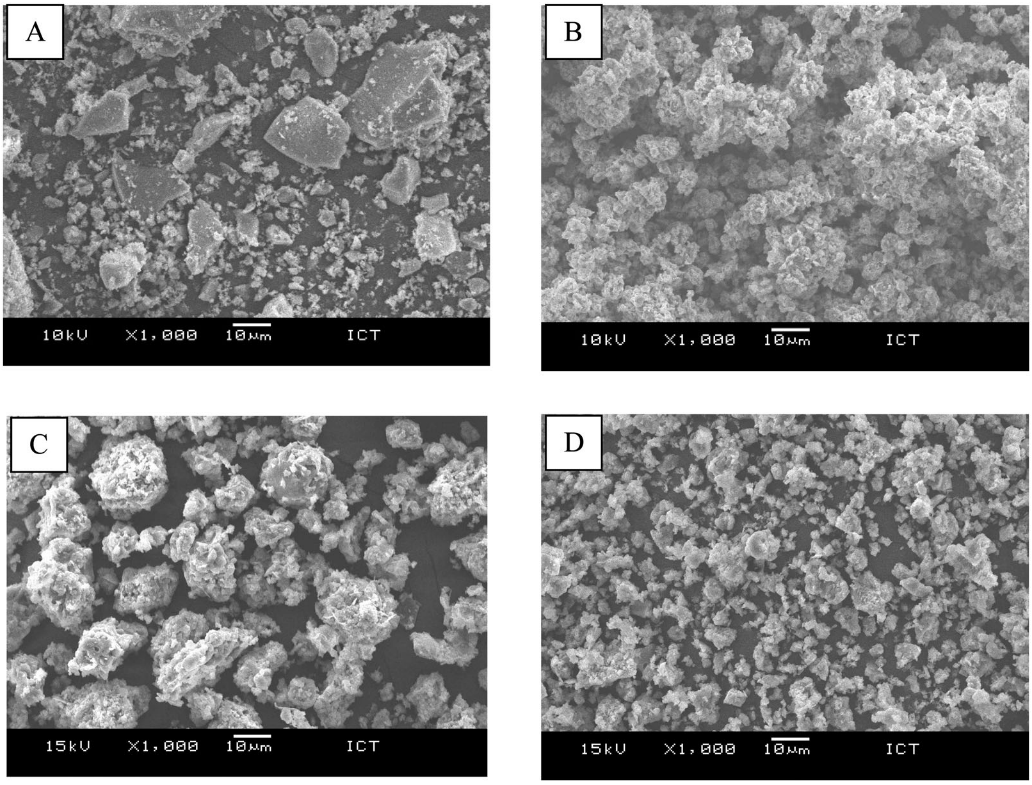


Fig. 2 SEM images of (A) silica without KF, (B) silica–KF reagent, (C) silica–KF washed with water, (D) silica–KF reagent after reaction.

7.81(t), 8.30(m), 8.73(d) ppm. ^{19}F NMR (600 MHz, DMSO-d_6) −109.57 ppm. HPLC: (RT): 5.56 min (mobile phase-ACN : water 60 : 40, column: 25 cm, 5μC18).

4-FNB. Light yellow liquid, yield = 17% (by HPLC) HPLC: RT 4.5 min (mobile phase-ACN : water 70 : 30, column: 25 cm, 5μC18).

4-FBn. White solid, yield = 39% (by HPLC), HPLC: RT = 4.6 min (mobile phase-ACN : water 70 : 30, column: 25 cm, 5μC18).

3. Results and discussion

3.1 Characterization of silica–KF reagent

The silica–KF was obtained as white, fine, free flowing powder.

3.1.1 Moisture uptake. Moisture uptake analysis of the silica–KF shows that unlike KF, it takes up only 10% of moisture, which can be reversed by reheating at 150 °C for 1 h indicating the absence of hydrogen bonding between fluoride anion and water molecules. On the other hand, KF, under the same condition takes up 47% of its weight as moisture and is converted to potassium fluoride trihydrate as shown in Fig. 1. This unlike, silica–KF does not lose moisture upon reheating. This indicates that the very strong hydrogen bonding between water molecules and fluoride anion,[24] are not present in synthesized silica–KF.

3.1.2 Scanning electron microscopy (SEM) with energy dispersive X-ray (EDX) analysis. Fig. 2 illustrates the SEM micrograph of silica obtained by TEOS hydrolyzed by HCl,

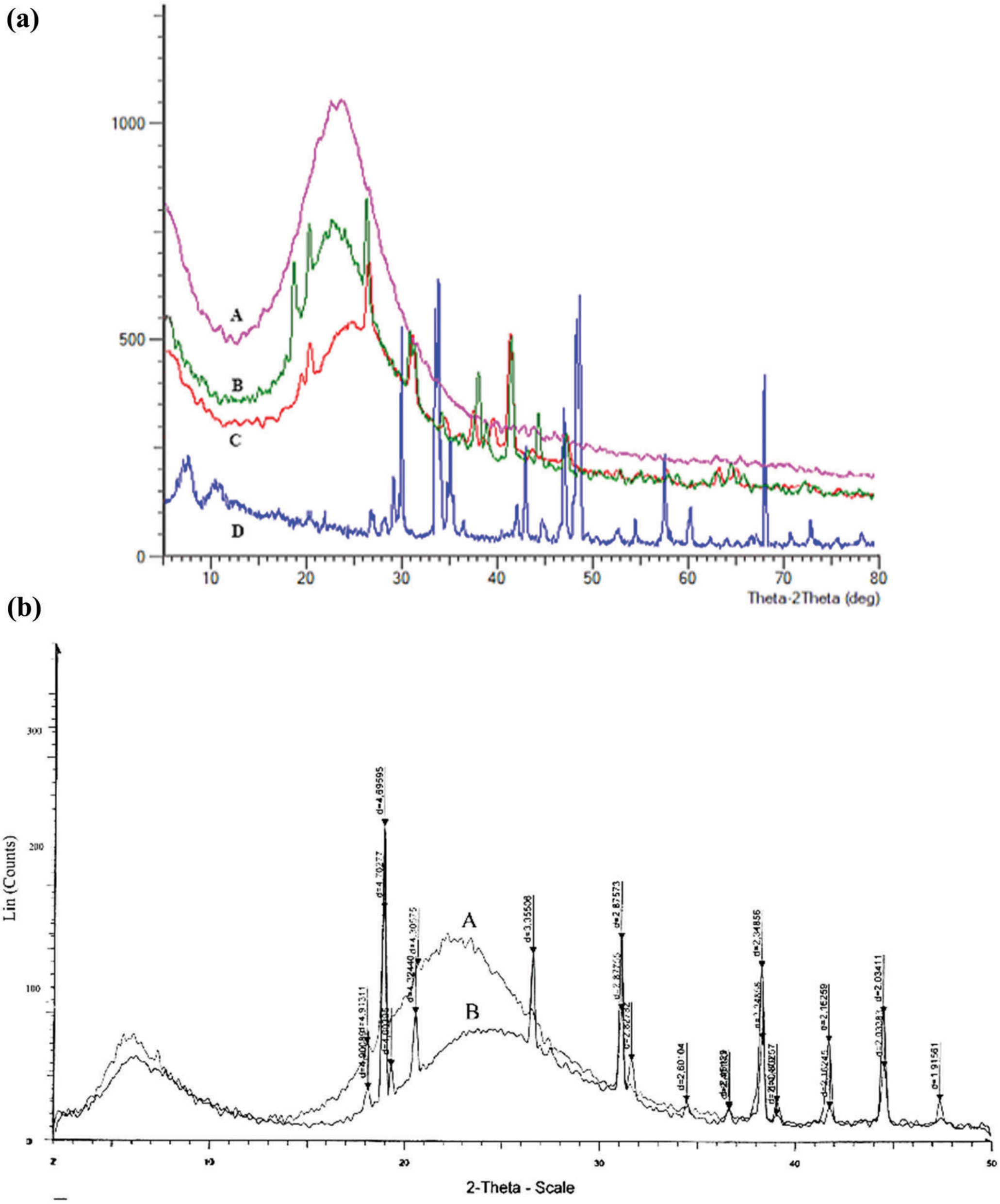


Fig. 3 (a) X-ray diffractogram (A) silica prepared by HCl hydrolysis, (B) silica–KF, (C) silica + KF physical mixture, (D) KF. (b) X-Ray diffractogram of (A) silica–KF reagent washed with water (B) silica–KF reagent.

silica–KF, silica–KF washed with water and silica–KF post reaction. HCl hydrolyzed silica was observed to be irregularly shaped, whereas silica–KF had uniform spherical shape clustered together with reduction in particle size. SEM image of reagent washed with water doesn't affect the morphology of the silica surface. EDX analysis of the reagent suggest presence of potassium and fluoride on the surface of silica particles with very high excess of fluoride anion on the surface (Fig. S2, ESI†), suggesting trapping of potassium anion inside silica giving reactive fluoride over the surface.

3.1.3 X-ray diffraction analysis. Fig. 3a and b shows X-ray diffractograms of different solid samples. Silica prepared by HCl hydrolysis (3a(A)) showed diffused pattern corresponding to its amorphous nature. The X-ray diffractogram of KF (3a(D)) showed many characteristic intense peaks which represented crystalline nature of KF. Diffraction pattern and silica KF reagent showed appearance of new peaks at 2θ value of 38°, 45° and shift of 2θ values around 18°, 21° relating to the interactions between silica and KF molecules[25] which indicates incorporation of crystallinity in the sample. On washing silica–KF with water in order to remove potassium fluoride from the reagent (3b(A)) shows that there are several peaks which are retained in silica even after washing implying the introduction of crystallinity in the prepared silica sample. Several peaks which corresponded to the presence of KF in the sample can also be seen as retained as well as other peaks have shifted from their original values can also be seen.

3.1.4 IR spectroscopy. The scans were collected at scanning speed of 2 mm s^{-1} with a resolution of 4 cm^{-1} over the region of 3800–500 cm^{-1}. KF, silica obtained by TEOS hydrolysis by HCl, silica–KF physical mixture, silica–KF reagent and silica–KF water washed were analyzed by IR spectroscopy as can be seen in Fig. 4. The Si–O–Si bond of silica can be seen at 964 cm^{-1} and 963 cm^{-1} in silica and silica KF physical mixture,[26,27] whereas in silica–KF the same peak is shifted to 914 cm^{-1} indicating an interaction between oxygen atoms in the siloxane bond with potassium anion.[16] IR spectrum of the reagent washed with water shows the same peak shifting again to 934 cm^{-1}, which indicates trapped potassium fluoride being washed away from the silica matrix.

From IR spectroscopy, SEM and XRD data, it can be deduced that potassium ions get embedded in silica *via* interaction with siloxane bond during hydrolysis of TEOS, whereas fluoride anions remain on the surface. Thus, it leads to a reactive fluoride anion being available on silica surface for further reaction.

3.2 Fluorination of substrates using silica–KF reagent

Fluorination of activated aromatic substrates with two electron withdrawing groups occurs in two steps (Scheme 1a). In the first step fluoride ions attacks on the carbon bearing chlorine to

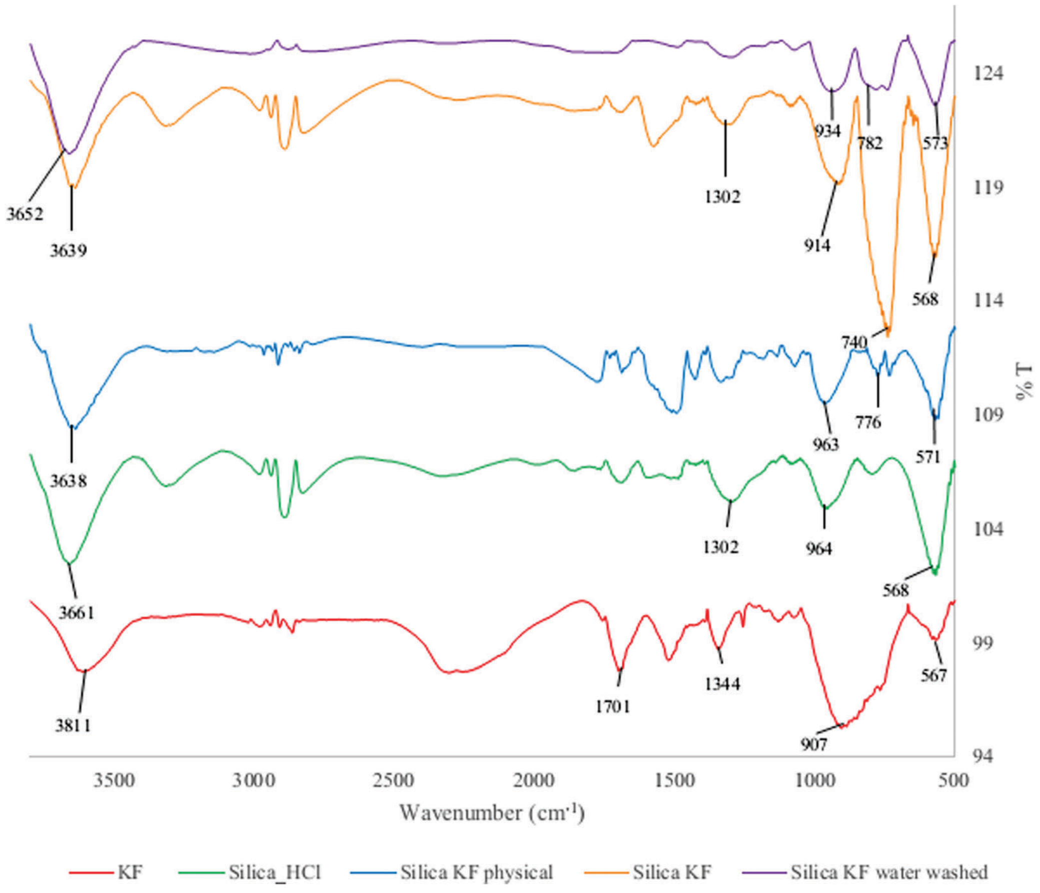


Fig. 4 IR spectra of KF, silica without KF, silica–KF physical mixture, silica–KF reagent and silica–KF water washed.

give Meisenheimer complex. In the second step, chlorine leaves the Meisenheimer complex to give fluorinated product. Formation of Meisenheimer complex is assisted by the addition of DMSO to the reaction mixture.[7,28] It can be isolated from the reaction system, dried and heated in the presence of dry acetonitrile to yield fluorinated product.[29] The higher yields of substrates with two electron withdrawing groups is consistent with the formation of isolable Meisenheimer complex. 4-FNB and 4-FBn were obtained in moderate yields which is due to the presence of only one electron withdrawing group which is not sufficient for activation of substrate required for Halex reaction.

3.2.1 Characterization of Meisenheimer complex. Formation of the Meisenheimer complex was confirmed by HPLC, IR and ^{1}H and ^{19}F NMR spectroscopy. The Meisenheimer complex loses aromatic character and behaves like an alkene which is evident from the ^{1}H NMR spectra. It shows one of the protons has a δ value of 6.27 ppm which is typical of alkenes with a J value of 12 Hz verifying cis coupling with adjacent proton. The ^{19}F NMR spectra shows a shift in δ values to -69 which is also indicative of loss of aromaticity. The Meisenheimer complex also shows UV spectra with $\lambda_{\max}$ 362 nm and 470 nm which is consistent with the structure of Meisenheimer complex.

4. Conclusion

Silica–KF for fluorination of activated aromatic substrates has been successfully synthesized and characterized. It possesses reactive fluoride anions on the surface of silica which aids in fluorination of activated chlorinated substrates. Fluorination of substrates with two activating groups undergoes *via* formation of the Meisenheimer complex in good yields which corresponds to the formation of Meisenheimer complex in the presence of this reagent. While fluorination of substrates with only one activating group directly gives fluorinated products in low yields.

Conflicts of interest

The authors have no conflicts to declare.

Acknowledgements

Authors are thankful to the Chemical Engineering and Chemistry department at ICT for XRD and SEM analyses, IIT-SAIF for recording ^{19}F NMR spectra and Dr Krishnan Ravi Kumar from IICT, Hyderabad for performing XRD analysis. Authors are also thankful to TEQIP-PHASE II for providing funding for the project.

References

1 T. Furuya, C. A. Kuttruff and T. Ritter, *Curr. Opin. Drug Discovery Dev.*, 2008, **11**, 803–819.
2 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
3 D. Cantillo and C. O. Kappe, *React. Chem. Eng.*, 2017, **2**, 7–19.
4 R. D. Chambers and R. C. H. Spink, *Chem. Commun.*, 1999, 883–884.
5 G. He, D. Wang, L. Cheng and H. Chen, *J. Chem. Health Saf.*, 2013, **20**, 30–34.
6 B. Pearson, *Speciality chemicals: innovations in industrial synthesis and applications*, Springer, Netherlands, 1991.
7 D. J. Adams and J. H. Clark, *Chem. Soc. Rev.*, 1999, **28**, 225–231.
8 G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, 1956, **78**, 6034–6037.
9 P. LaBeaume, M. Placzek, M. Daniels, I. Kendrick, P. Ng, M. McNeel, R. Afroze, A. Alexander, R. Thomas, A. E. Kallmerten and G. B. Jones, *Tetrahedron Lett.*, 2010, **51**, 1906–1909.
10 C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, 1974, **96**, 2250–2252.
11 N. F. Carvalho and J. R. Pliego, *J. Org. Chem.*, 2016, **81**, 8455–8463.
12 J. H. Clark, *Chem. Rev.*, 1980, **80**, 429–452.
13 A. Takashi, J. H. Clark, D. G. Cork and K. Takahide, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3281–3282.
14 J. H. Clark, D. G. Cork and H. W. Gibbs, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2253–2258.
15 V. G. Konakov and M. M. Pivovarov, *Glass Phys. Chem.*, 2003, **29**, 69–74.
16 C. Real, M. D. Alcalá, A. Muñoz-Páez and J. M. Criado, *Nucl. Instrum. Methods Phys. Res., Sect. B*, 1997, **133**, 68–72.
17 G. P. Huffman, N. Shah, J. M. Zhao, F. E. Huggins, T. E. Hoost, S. Halvorsen and J. G. Goodwin, *J. Catal.*, 1995, **151**, 17–25.
18 K. Nagao and U. Norimasa, *Jpn. J. Appl. Phys.*, 1993, **32**, 658.
19 J. W. Lee, H. Yan, H. B. Jang, H. K. Kim, S. W. Park, S. Lee, D. Y. Chi and C. E. Song, *Angew. Chem., Int. Ed.*, 2009, **48**, 7683–7686.
20 A. I. Vogel, *Vogel's Textbook of Practical Organic Chemistry: Including Qualitative Organic Analysis*, Pearson Education in South Asia, Dorling Kindersley (India) Pvt. Ltd., 5th edn, 2011.
21 J. H. Clark, M. S. Robertson, D. K. Smith, A. Cook and C. Streich, *J. Fluorine Chem.*, 1985, **28**, 161–169.
22 H. B. Gottlieb, *J. Am. Chem. Soc.*, 1936, **58**, 532–533.
23 J. F. K. Wilshire, *Aust. J. Chem.*, 1967, **20**, 2269–2273.
24 B. Langlois, L. Gilbert and G. Forat, in *Industrial Chemistry Library*, ed. J.-R. Desmurs and S. Ratton, Elsevier, 1996, vol. 8, pp. 244–292.
25 C. R. Ranucci, L. M. S. Colpini, M. R. Monteiro, V. Kothe, L. J. Gasparrini and H. J. Alves, *J. Environ. Chem. Eng.*, 2015, **3**, 703–707.
26 S. K. Parida, S. Dash, S. Patel and B. K. Mishra, *Adv. Colloid Interface Sci.*, 2006, **121**, 77–110.
27 E. Vansant, in *Stud. Surf. Sci. Catal.*, ed. E. F. Vansant, P. Van Der Voort and K. C. Vrancken, Elsevier, 1995, vol. 93, pp. 59–77.
28 Y. Sasson, S. Negussie, M. Royz and N. Mushkin, *Chem. Commun.*, 1996, 297–298.
29 N. A. Senger, B. Bo, Q. Cheng, J. R. Keeffe, S. Gronert and W. Wu, *J. Org. Chem.*, 2012, **77**, 9535–9540.