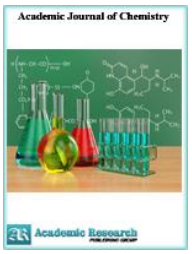

Academic Journal of Chemistry
ISSN(e): 2519-7045, ISSN(p): 2521-0211
Vol. 2, No. 5, pp: 38-41, 2017
URL: http://arpgweb.com/?ic=journal&journal=20&info=aims

Aliphatic Nucleophilic Fluorinations by using MnO_2 Nanoparticle in Aqueous Media

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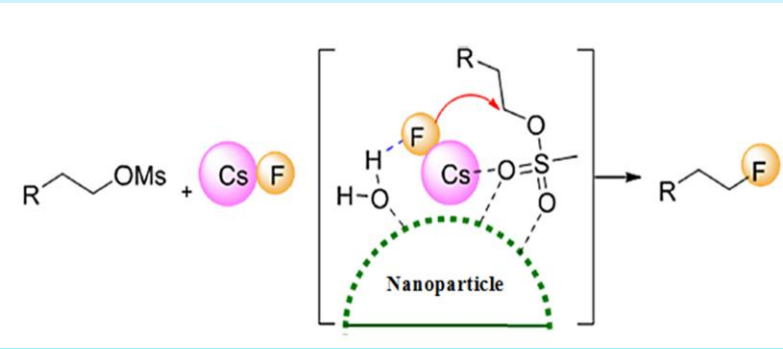
Abstract: A facile aliphatic nucleophilic fluorinations with alkali metal halides (Cesium Fluoride) in the presence of nanoparticles as a catalyst has been demonstrated. Reactivity of nanoparticles in nanocrystal form was found to be chemoselective in the presence of water. Furthermore, the reaction is highly specific with alkyl sulfonate substrates. This nanoparticles catalyst not only enhances the reactivity of alkali metal salts but also affording high yield and allows easy protocol. Nanoparticle was fully characterized by using scanning electron microscopy (SEM) and fluorinated compounds were characterized by using ^{1}H and ^{13}C NMR spectroscopy.



Keywords: MnO_2 Nanoparticles; S_N2 reactions; CsF; ^{1}H; ^{13}C NMR; SEM.

1. Introduction

Halogen containing organic molecules plays a vital role in medicine, biochemistry, and agrochemical industries [1-3]. They also serve as imaging agents for positron emission tomography. Fluorine significantly affects the properties of target molecules due to its high electronegativity, small size and ability to form hydrogen bond responsible for the stability of the molecules [4]. Approximately, 20 biosynthetic natural compounds that contain at least one fluorine atom are known till date [5]. During last few decades, researchers have developed numerous methods to introduce the fluorine atom into aliphatic and aromatic molecules [6]. The bimolecular nucleophilic substitution reaction (S_N2) is a common chemical reaction that can be applied for the replacement of one functional group with fluorine. The nucleophilicity of fluorine depend upon some of the factors including reaction solvent, fluoride source, leaving group, and catalyst. In particular, the fluorination using metal fluoride is still in its infancy because of its limited solubility in the absence of phase-transfer catalyst.

Recently, the well-designed metal nanoparticles (NPs) have been found to be useful in vast area of organic transformations [7, 8] with its biomedical applications [9, 10]. The metals in nanostructure form are more effective due to their large and reactive surface areas.

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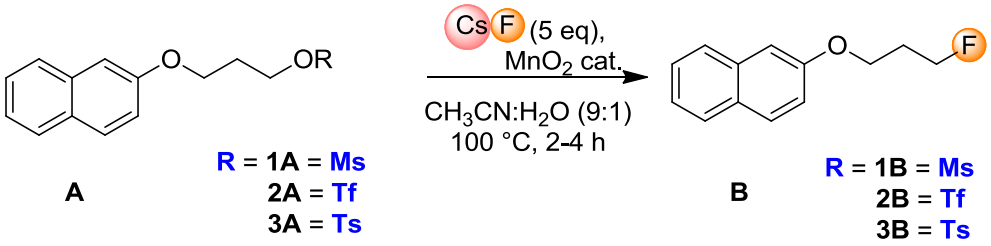
The alkali metal salts are generally abundant in nature and potent sources of nucleophiles. However, their low solubility in organic solvent reduce their reactivity as nucleophiles which leads to harsh reaction conditions for the completion of reaction and is one of the major obstacles in their application on industrial processes.

Here in we report facile method for the synthesis of aliphatic alkyl fluorides by using MnO_2 nanoparticles and CsF as fluorinating agent in acetonitrile water mixture as an solvent striking features of this reaction are easy workup procedure, high yields and less side products.

2. Results and Discussion



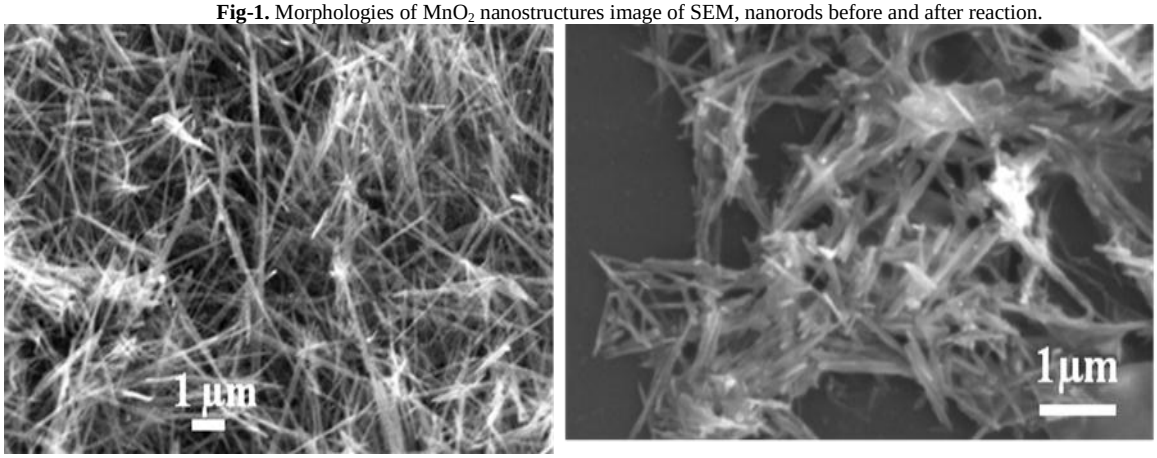
Scheme-1. Nucleophilic Fluorination of 1A, 2A, & 3A with CsF using MnO_2 NPs Catalyst

We have synthezied MnO_2 nanoparticle by modified procedure reported by Lee, *et al.* [6]; Kumar, *et al.* [11] Nanoparticle were characterized by using scanning electron microscopy (SEM) analysis and found to be rod shaped having size 1µm and 200 nm (image-I, Fig. 1). We have also characterized MnO_2 NPs recover from reaction mixture (image-II, Fig. 1).

The nucleophilic fluorination of 2-(3-methanesulfonyloxypropyloxy)-naphthalene (**1A**) as a model compound in 1 equiv with CsF 5 equiv in the presence of MnO_2 (10 mol %) rod shaped nanoparticle in CH_3CN: H_2O (9:1 ratio, 5 ml) Scheme 1. Interestingly, with the increase amount of water, the yield also increases as detected in ^1H NMR spectra.

Reaction on triplets (**1B**) and tosylate (**1C**), were carried out in similar reaction conditions afforded the corresponding fluorinated products in 72 % and 65% respectively.

Fig-1. Morphologies of MnO_2 nanostructures image of SEM, nanorods before and after reaction.



The plausible mechanism of MnO_2 nanoparticles catalyzed fluorination reaction is depicted in Fig. 2. The reaction may proceed by hydrogen bonding formation of oxygen's of sulfonate ester with surface area of MnO_2-nanocatalyst. This surface co-ordination of substrates assist the attack of solvated fluorine nucleophile in chemo-selectively by S_N2-fashion.

Fig-2. Plausible mechanism of MnO_2-catalyzed fluorination.

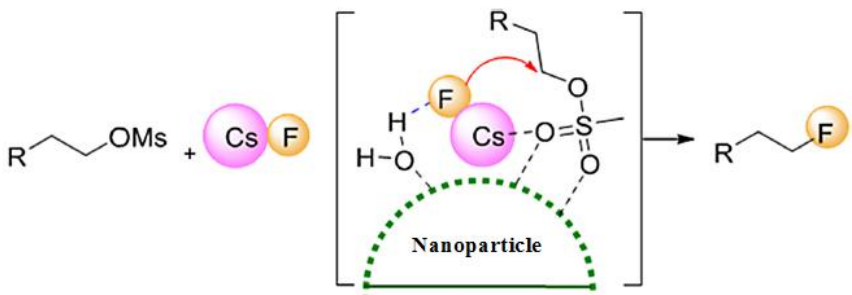
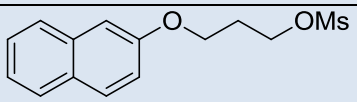
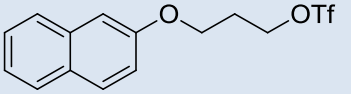
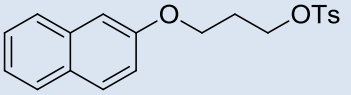
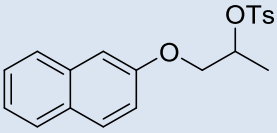
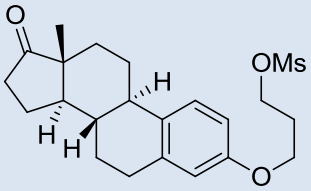
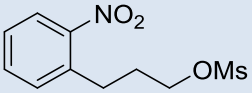


Table-1. MnO_2 nanoparticles catalyzed nucleophilic fluorination of various substrates

Entry	precursors	Time (h)	Solvent (in 5 ml)	Yield (%) Fluorinated product
1A		2	9:1	78
2A		4	9:1	58
3A		3.5	9:1	62
4A		2.5	9:1	71
5A		5	9:1	83
6A		4	9:1	65

3. Materials and General Method

All chemicals were obtained from commercial suppliers and were used without further purification unless otherwise stated. Flash chromatography was carried out using Merck silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed with Merck Silica gel F-254 glass-backed plates. Visualization on TLC was monitored by UV light or phosphomolybdic acid indicator. NMR spectra were recorded on a Bruker Avance 300 operating at frequencies 300.13 MHz (^{1}H), and 75.48 MHz (^{13}C) ^{1}H and ^{13}C NMR spectra were recorded calibrated using residual undeuterated solvent or tetramethylsilane as an internal reference.

3.1. Preparation and Characterization

3.2. 2-(2-Fluoro-*n*-propoxy) Naphthalene (1B)

A suspension of 2-(3-methanesulfonyloxypropyloxy)-naphthalene (1 equiv), CsF (5 equiv), MnO_2-nanocatalyst 10 mol% in mixture of CH_3CN: H_2O (9:1, 5 mL) in reaction vial was stirred at 100 °C. Reaction was monitored by TLC, after complete reaction, the mixture was filtered and washed with EtOAc. The filtrate was concentrated by a rotary evaporator. The crude mixture was purified by flash column chromatography (20% EtOAc–hexane) to afford 2-(2-fluoropropoxy) naphthalene. Colorless liquid; Yield 78%, ^{1}H NMR (200 MHz, $CDCl_3$) 2.14-2.39 (m, 2H), 4.24 (t, *J* = 6.2Hz, 2H), 4.72 (dt, *J* = 46.8, 5.8 Hz, 2H), 7.16-7.22 (m, 2H), 7.34-7.53 (m, 2H), 7.76-7.83 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 30.4 (d, *J* = 20.1 Hz), 63.6 (d, *J* = 5.3 Hz), 80.8 (d, *J* = 163.9 Hz), 106.8, 118.8, 123.7, 126.4, 126.7, 127.6, 129.1, 129.4, 134.6, 156.7. HRMS (EI) calcd for $C_{13}H_{13}FO$ (M+) 204.0950, found 204.0947. Copies of ^{1}H NMR and ^{13}C NMR spectra are in this SI; Known compound [12].

3.3. 2-(2-Fluoro-*n*-propoxy) Naphthalene (4B)

Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) 1.50 (dd, *J* = 23.6, 6.4 Hz, 3H), 4.09-4.24 (m, 2H), 5.00-5.16 (m, 1H), 7.13-7.46 (m, 4H), 7.71-7.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 17.5 (d, *J* = 22.0 Hz), 70.7 (d, *J* = 23.5 Hz), 88.3 (d, *J* = 167.5 Hz), 106.7, 118.7, 123.7, 126.3, 126.6, 127.5, 129.0, 129.4, 134.3, 156.3; HRMS (EI) calcd for $C_{13}H_{13}FO$ (M^+) 204.0950, found 204.0947.

3.4. 3-(3-Fluoro-*n*-propoxy) Estrone (5B)

White solid, ^{1}H NMR (400 MHz, $CDCl_3$) 0.90 (s, 3H), 1.43-1.62 (m, 6H), 1.96-2.19 (m, 7H), 2.38 (b 1H), 2.47 (d, *J* = 8.4 Hz, S7 1H), 2.88 (q, *J* = 3.6 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 4.63 (dt, *J* = 46.8, 5.6 Hz, 2H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.71 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) G 13.8, 21.5, 25.9, 26.5, 29.6, 30.4 (d, *J* = 20.0 Hz), 31.5, 35.8, 38.3, 43.9, 47.9, 50.4, 63.4 (d, *J* = 4.8 Hz), 80.7 (d, *J* = 163.1 Hz), 112.1, 114.5, 126.3, 132.2, 137.7, 156.7, 220.9; HRMS (EI) calcd for $C_{21}H_{27}FO_2$ (M^+) 330.1995, found 330.1993.

3.5. 1-(3-Fluoropropyl)-2-Nitrobenzene (6B)

Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) 1.82 (q, 2H), 2.62 (d, 2H), 4.09 (d, 2H), 7.53 (d, J = 8.4 Hz, S7 1H), 7.55 (m, J = 3.6 Hz, 1H), 7.79 (m, 1H), 8.03 (d, J = 6.0 Hz, 1H), ^{13}C (100 MHz, $CDCl_3$) 26.57, 32.02, 83.46, 126.92, 127.77, 128.26, 132.90, 134.04. HRMS (EI) calcd for $C_9H_{10}FNO_2$ (M^+) 183.1926, found 183.1920.

4. Conclusion

In conclusion, we have developed an efficient nanoparticle MnO_2 catalyzed nucleophilic fluorination method, which gave the reasonable yield of fluorinated product when substrate contained sulfonate ester as a leaving group. MnO_2 NPs was synthesized found to be more active and showed catalytic activity with respect to reaction time and yield when compared with conventional methods using 18-crown-6 ether as a phase-transfer catalyst. Further studies are in progress to develop more effective catalysts of MnO_2 by heterogeneous protocol for other organic transformations.

Acknowledgments

S.S. Kadam would like to thanks CSIR-NCL Pune and Dr. D.Y. Patil Arts, Commerce & Science College, Pimpri, Pune. We are grateful to Principal Dr. Snehal Agnihotri for her encouragement.

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