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Molybdenum Oxide-Mediated Facile Aliphatic Nucleophilic Fluorination

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online A facile aliphatic nucleophilic fluorination with cesium fluoride in the presence of molybdenum oxide as a catalyst has been demonstrated. Reactivity of molybdenum oxide in nanocrystal form was found to be chemoselective in the presence of water. Furthermore, the reaction is highly specific with alkyl sulfonate substrates.

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Introduction

Fluorine containing organic molecules play a pivotal role in medicine,¹ biochemistry,² and agrochemicals industries.³ They also serve as imaging agents for positron emission tomography (PET).⁴ 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. Approximately, 20 biosynthetic natural compounds that contain at least one fluorine atom are known till date.⁶ During last few decades, researchers have developed numerous methods to introduce the fluorine atom into aliphatic and aromatic molecules.⁷ The bimolecular nucleophilic substitution (S_N2) is a common chemical reaction that can be applied to replacement of one functional group with fluorine. The nucleophilicity of fluorine depend upon some of the factors including reaction solvent, fluoride source, leaving groups, and catalyst. In particular, the fluorination using metal fluoride is still in its infancy because of its limited solubility in the absence of additives/phase-transfer catalyst. We have recently reported that the tert-BuOH-functionalized imadazolium-based ionic liquid (^t-BuOH-IL) serves as efficient catalyst for alkali metal salts in S_N2 reactions.⁸ The ^t-BuOH-IL not only enhances the reactivity of fluoride reagents but also provides the selectivity of fluorinated product.⁶

During last few years, the transition-metals were used as catalyst for nucleophilic fluorination.¹⁰ Recently Cucomplexes with fluorine were used for aliphatic fluorination of triflate containing substrates.¹¹ Whereas, the metal catalyzed reaction significantly overcomes the reactivity of fluorine as base.¹² More recently, the TiO₂ was used as Lewis acid catalyst for nucleophilic radiofluorination. The metal in its nanocrystalline form works efficiently with sulfonate substrates using tetrabutyl ammonium fluoride reagent¹³ Recently, the well-designed metal nanoparticles (NPs) have been found to be useful in vast area of organic transformations¹⁴ with its biomedical applications.¹⁵ The metals in nanostructure form are more effective due to their large and reactive surface areas. As part of our interest to explore the application of NPs,¹⁶ herein, we sought to explore the activity of MoO₃ NPs in S_N2 reaction. Molybdenum oxide is reported to serve as catalyst in various organic reactions such as oxazolines synthesis,¹⁷ nitration,¹⁸ alkylation,¹⁹ epoxidation,²⁰ and transesterification, ²¹ etc. However, reactivity of MoO₃ has not been explored in fluorination reactions.

Results and discussion

Herein, we report screening of various nanoparticles of MoO_3 as catalyst in the aliphatic nucleophilic fluorination using cesium fluoride. Initially, we synthesized MoO_3 NPs by modified procedure reported by Lee et. al.²² The SEM images of nanosheets **A** was 5-7 μ m in length (image-I, Figure 1). TEM images of MoO_3 NPs **A** have lateral size 25 nm to several μ m (SI, Figure S1).



Figure 1. Morphologies of MoO₃ Nanostructures image of SEM, I) Nanosheets (**A**), II) Nanospheres (**B**), III) Nanorods (**C**).

Tetrahedron

The HR-TEM images of A showed clear lattice fringes with d-spacing 0.28 nm which suggested that the pattern of A is polycrystalline in nature. The NPs of **B** have been synthesized by solvothermal method,²³ SEM analysis indicated **B** with 200-500 nm in diameter as depicted in image II of Figure 1. Similarly, the MoO₃ nanorods was synthesized by reported hydrothermal condition.²⁴ The SEM analysis of C showed the length and diameter of MoO₃ nanorods in the range of 1-5 µm and 200-500 nm respectively (image-III, Figure 1). The surface morphology and crystal structures of MoO₃ nanostructures were characterized by Raman spectroscopy (RS), X-ray spectroscopy (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM) and high resolution TEM (HR-TEM) (supporting information). In the course of screening various metal oxides for the nucleophilic fluorination, we found that molybdenum oxide has promising catalytic activities.

Table 1. Nucleophilic Fluorination of Mesylate 1 with CsF using MoO₃ Catalyst.^{*a*}



^a Reaction conditions: 1.0 mmol of substrate, 10 mol% of MoO₃ NPs (nanosheets = **A**, nanospheres = **B**, nanorods = **C**) 5.0 mmol CsF, 10 mmol of H₂O and solvent at 100 °C. ^{*b*}Isolated yield. ^{*c*} determined by ¹H NMR. ^{*d*}Reaction at rt (30-35 °C) instead of 100 °C.^{*e*} 1,4-dioxane used instead of CH₃CN. ^{*f*} *tert*-BuOH used instead of CH₃CN.

Table 1 illustrates the nucleophilic fluorination of 3phenylpropylmethansulfonate (1) as a model compound in 1.0 mmol scale with CsF (5 equiv) in the presence of MoO_3 and MoO₃ nanoparticals having various morphological structures such as sheets (A), spheres (B), and rods (C) in CH₃CN under different condition. In the presence of 10 mol% commercially available molybdenum oxides afforded only 20% of 3-fluoropropylphenyl (entry 3). Interestingly, with the addition of water, the desired 2 was obtained in 56% yield along with trace amount of alcohol (by-product) as detected in ¹H NMR spectra (entry 4). To our delight, the same reactions using fine-tuned MoO₃ NPs A, B and C showed dramatic enhancement in the reactivity of CsF, affording the desired fluorinated product 2 in moderate to good yield (entries 5-7). Among these nano-catalyst, C showed better conversion than A or B, giving 88% of 2. This may be attributed to the exposed nanosize surface area of molybdenum in reaction, which enhances the interaction between sulfonyl moiety of substrate and fluorine. The same reaction at rt, didn't proceed at all (entry 8). When the reaction was carried out in the presence of 20 mol% or 1 equiv of C, it was found to be complete within 1h and 40 min, affording 84% and 56% of fluorinated product 2 respectively, with significant amount of by-product 4 (entries 9 and 10). Interestingly, nucleophilic fluorination by using 5 equiv of water (entry 11) proceeded much faster than the conventional 18-crown-6-ether catalyzed reaction in absence or in presence of H₂O (entry 1 and 2 respectively). In entries 12 and 13, reactions carried out in other solvents such as 1,4-dioxane and tert-BuOH, gave fluorinated product 2 in 68% and 72% respectively, along with 15% of alcohol 4 in case of tert-BuOH mediated condition (entry 13).

Based on the optimized fluorination conditions in entry 7 of Table 1. we next validated the catalytic activity of \mathbf{C} with various leaving groups (LG) containing primary/secondary alkyl sulfonyl esters and halides substrates as illustrated in Table 2. The reaction of primary alkyl sulfonates 5-14, such as nosylate, tosylate, mesylates, and triflates in presence of catalyst C, afforded the corresponding fluorinated product in moderate to good yield. Surprisingly, among these the tosylate and nosylate containing substrates gave high and chemo-selective conversion than triflates because of the competition of elimination to predominantly the formation of corresponding alkene byproduct (comparison 5-7). Same reaction with secondary sulfonates 15 and 16, gave reasonable yields due to the elimination to the corresponding alkene. Reaction with 1-iodopentadodacane gave only 52% of corresponding fluoro compound 17a after 4h. It may be noted that, fluorination with 2-triflate naphthalene substrate, did not afford the fluorinated product. Moreover, the MoO₃ NPs of rodshapes (C) showed higher catalytic activity with sulfonates because of the coordination of catalyst surface with sulfonate ester and flexible interaction of fluorine making the nucleophilic process favorable.



Figure 2. Plausible mechanism of MoO₃-catalyzed Fluorination

Table 2. MoO₃ Nanorods (C) Catalyzed Nucleophilic Fluorination of Various Substrates.



Over all based on these obtained results, the plausible mechanism of MoO_3 nanoparticle catalyzed fluorination with sulfonate ester substrates depicted in figure 2. The reaction may proceed by hydrogen bonding formation of oxygens of sulfonate ester with surface area of MoO_3 -nanocatalyst. This surface co-ordination of substrates assist the attack of solvated fluorine nucleophile in chemo-selective by S_N2 -fasion.

Conclusions

In conclusion, we have developed an efficient molybdenum oxide catalyzed nucleophilic fluorination, which gave the reasonable yield of fluorinated product when substrate contained sulfonate ester as a leaving group. MoO_3 NPs in rods shape (C) was found to be more active and showed superior 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 MoO_3 by heterogenous protocol for other organic transformations.

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Supplementary Material

†Electronic Supplementary Information (ESI) available: [All nanoparticals and organic compounds charactrization data].See DOI: 10.1039/b000000x/

C

Highlights

- Aliphatic nucleophilic fluorination using • alkali metal fluorides is developed.
- Acception Nano-shape of molybdenum oxide act as a •