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Graphical Abstract

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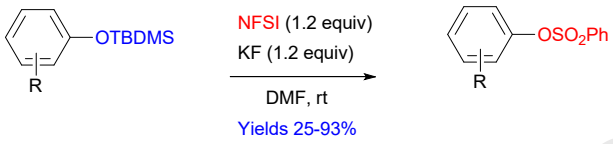

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NFSI/KF mediated mild and chemoselective interconversion of aryl TBDMS ethers to their benzene sulfonate

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ABSTRACT

A one pot protocol for the transformation of aryl TBDMS ethers to corresponding aryl benzene sulfonate esters using NFSI (N-flurobenzenesulfonimide)/KF is described. In situ generation of benzenesulfonyl fluoride directs chemoselective cleavage of aryl silyl ethers over aliphatic silyl ethers. Electron withdrawing substituent's on aryl ring provided better yield than donating groups. Protecting groups and sensitive functionalities are well tolerated in this methodology. Thus, commercially available inexpensive reagents, mild reaction conditions and step economy are the advantages of this method.

Introduction

Aryl sulfonate ester linkages found in many natural products and their distinct bioactivities make them attractive targets to medicinal chemists.[1]Additionally, aryl sulfonates are very useful precursors in organic synthesis due to their good leaving ability they have been widely used in nucleophilic substitution[2] and cross coupling[3] reactions. Recently, aryl sulfonates were explored as substrates in photochemistry and they have found applications in cationic polymerization and epoxy-based hybrid materials.[4] In general, aryl sulfonate esters can be synthesized by straightforward reaction of phenols with appropriate sulfonylating reagents such as sulfonyl chlorides/anhydrides, sulfonic acids, thiols, sodium sulfinate, 1-phenylsulfonylbenzotriazole and under microwave assistance.[5] However, most of the conditions used for synthesis of aryl sulfonates are harsh and reagents used were unstable, thus emphasize has been given on green and sustainable sulfonylation methods. In this regard, recently Shen and co-workers[6] reported iodobenzene catalyzed synthesis of aryl sulfonate esters through C-O cross coupling.

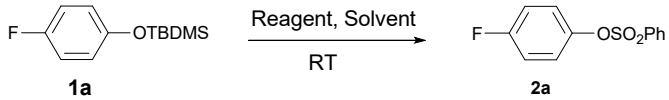
Moreover, in the course of a total synthesis, deprotection of silyl ether and conversion of resulting hydroxyl group to good leaving sulfonate esters is the commonly observed two step protocol.[7] Although, this sequence provides quantitative yield but most of the time it requires isolation of intermediates and setting two independent reactions which is time consuming practice. Thus development of one pot methodology for direct interconversion of aryl silyl ethers to aryl sulfonate esters is highly desirable. However, in spite of step economical advantage only two methods existing in literature for similar interconversion (*p*-Toluenesulfonylfluoride/DBU[8] and $FeCl_3$-Montmorillonite K-10[9]).

While aiming at such interconversion, we came across Guiry and co-workers[10] report on cleavage of silyl ethers using Selectfluor. Interestingly, this was the first report where electrophilic fluorine bearing reagent has been used for deprotection of silyl ethers. However, they described the possibility of *in situ* generation of nucleophillic fluoride ion as reactive species such as ROF/HF/HOF at higher temperature (150 °C) in microwave oven. This finding prompted us to examine alternative inexpensive electrophilic fluorinating reagent for the cleavage of silyl ethers. Apparently, we focused towards NFSI which is comparatively inexpensive, stable and commercially available. Additionally, we were conscious about use of NFSI in sulfonylation of amines alcohols and phenols.[11] On the same note, we assumed that it could be possible to isolate aryl sulfonate directly from aryl silyl ethers. Herein, we report NFSI/KF mediated facile and chemoselective method for the deprotection of aryl TBDMS ethers and their interconversion to corresponding benzene sulfonate ester. To the best of our knowledge this is the first report where NFSI along with KF has been used for direct interconversion of aryl silyl ethers to corresponding benzene sulfonate ester under neutral condition. Furthermore this protocol is convenient and excludes use of sophisticated tools. All reactions were ensued at room temperature and furnish desired product in high yield.

Results and Discussion

The optimization study of model substrate **1a** for silyl ether cleavage is summarized in Table 1. Initially, NFSI used alone in various solvents such as acetonitrile, THF and methanol under reflux condition provided corresponding aryl benzene sulfonate **2a** in the range of 10-40% of yield (Table 1, entries 1-3).

Ta ated interconversion of **1a** to **2a**[a]



1a **2a**

Entry	Reagent (equivalent)	Solvents	Time (h)	Yield (%)[b]
1	NFSI (1)	MeCN	18	10[c]
2	NFSI (1)	THF	18	25[c]
3	NFSI (1)	MeOH	18	40[c]
4	NFSI/$NaHCO_3$ (1.2/1.2)	MeCN	24	35
5	NFSI/K_2CO_3 (1.2/1.2)	MeCN	5	56
6	NFSI/KF (1.2/1.2)	MeCN	4.5	68
7	NFSI/KF (1.2/1.2)	THF	4.5	82
8	NFSI/KF (1.2/1.2)	DMF	2.5	92
9	KF (1.2)	DMF	12	--
10	NFSI/KF (1/0.2)	DMF	18	12

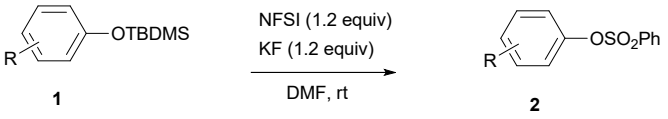
[a]All reactions run on 1.0 mmol scale. [b]Isolated yields. [c]Reflux conditions.

Increase in yield was observed at higher temperature and in protic solvent. However, in order to develop mild protocol and to broaden the substrate scope, further screening of solvents at higher temperature was avoided. Next, we assumed that use of additives along with NFSI will assist the reaction to proceed at room temperature. To test this assumption $NaHCO_3$ (entry 4) and K_2CO_3 (entry 5) was added to the reaction mixture which demonstrated significant improvement in the yield of sulfonate **2a**. On the basis of working hypothesis, we well-thought-out about KF as an additive since it has been previously exploited for silyl ether cleavage in presence of potassium ion chelating reagents.[12] Due to difference in ionic size we supposed that KF will assist NFSI during silyl ether cleavage. Surprisingly to our delight addition of stoichiometric KF results clean interconversion of aryl silyl ether **1a** to sulfonate **2a** at room temperature with 92% yield (entry 8). To ascertain that desilylation is not a mere effect of an additive, the reaction was repeated by using KF in DMF without addition of NFSI that resulted in complete recovery of starting aryl silyl ether **1a**(entry 9). The catalytic probability of an additive was further tested by use of KF (20 mol %) along with NFSI (1.2 equiv.) which provided sulfonylated product **2b** with only 12% yield (entry 10). This result ensures that the aryl silyl ether consumes equimolar amount of KF and forms irreversible Si-F bond in *tert*-butyldimethylsilyl fluoride byproduct. Further investigation of solvents such as THF and acetonitrile reveals longer reaction time and offered comparatively lower yields (entries 6 and 7).

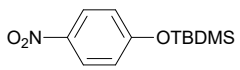
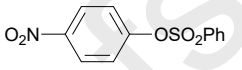
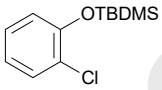
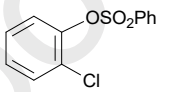
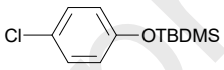
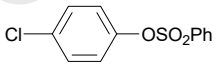
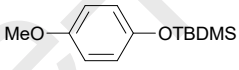
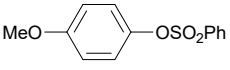
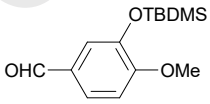
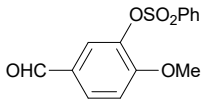
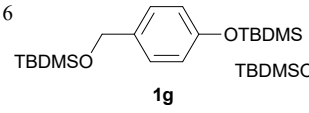
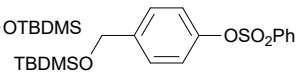
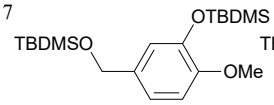
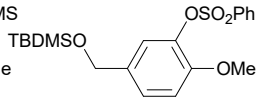
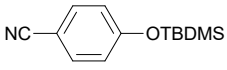
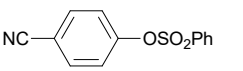
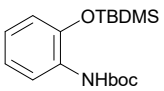
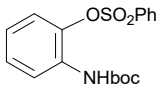
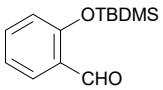
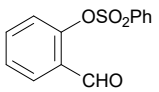
With optimized reaction conditions in hand, we further explored the potential of this methodology with various aryl silyl ethers as illustrated in Table 2. TBDMS ether derived from electron withdrawing substituent on phenyl ring underwent smooth interconversion. In case of **1b** the deprotection and sulfonylation completed within 2 h at room temperature and provided benzene sulfonyl ester **2b** in excellent yield (Table 2, entry 1). Similarly, in case of electron withdrawing *ortho*- and *para*- substituted chloro aryl silyl ether **1c** and **1d** the interconversion occurred within 2.5 and 4 h respectively and provided corresponding benzene sulfonates **2c** (85%) and **2d** (80%) in good yield (entries 2 and 3). Notably, TBDMS ether of electron rich *p*-methoxyphenol **1e** when subjected to standard reaction condition gave poor yield of **2e** (entry 4). Interestingly, *o*-methoxy substituted aryl silyl ethers **1f** and **1h** when exposed to optimized reaction conditions; deprotection and sulfonylation happened cleanly and provided **2f** and **2h** with yields 84% and 72% respectively (entries 5 and 7). Probably this could be explicated on the basis of domination of inductive effect over resonance effect of *o*-methoxy group in case of **1f** and **1h** and additionally the resonance effect of methoxy group in **1f** was nullified in presence of aldehyde at 4-position.

The present method also demonstrates exclusive chemoselctivity towards cleavage of aryl TBDMS ethers over alkyl TBDMS with excess of NFSI/KF (2.4 equiv. each); chemoselective interconversion of only aryl TBDMS ethers to corresponding benzene sulfonate esters **2g** (86%) and **2h** (72%) was achieved in good yield (entries 6 and 7).

Table 2. Substrate scope for the interconversion of silyl ethers to benzene sulfonates[a]



1 **2**

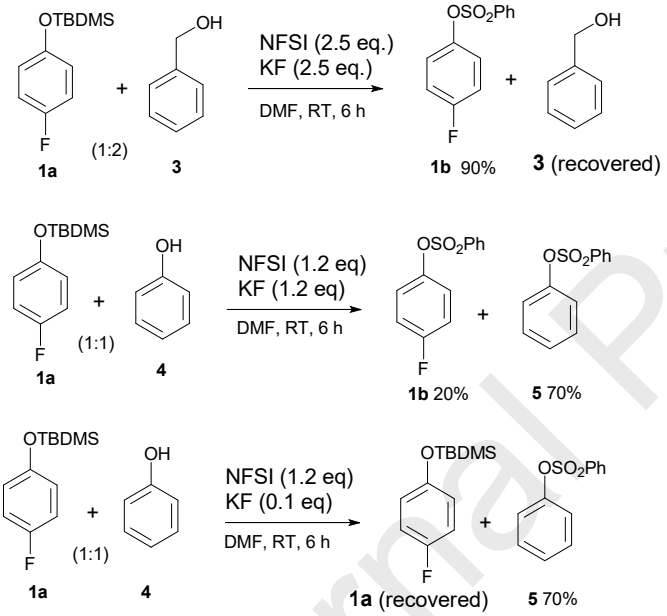
Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	 **1b**	 **2b**	1	93
2	 **1c**	 **2c**	2.5	85
3	 **1d**	 **2d**	4	80
4	 **1e**	 **2e**	24	25[c]
5	 **1f**	 **2f**	4	84
6	 **1g**	 **2g**	3	86[d]
7	 **1h**	 **2h**	5	72[d]
8	 **1i**	 **2i**	2	91
9	 **1j**	 **2j**	6	70
10	 **1K**	 **2K**	4	89

[a]All reactions run on aryl silyl ether (1.0 mmol) and NFSI/KF (1.2 mmol each) unless stated otherwise. [b]Isolated yields. [c]brsm yield. [d]NFSI/KF (2.4 equiv each) used.

We further examined the compatibility of protecting as well as functional group under standard reaction conditions. The cyano group is known for its sensitivity towards hydrolysis in acidic or basic reaction medium; however, when substrate **1i** exposed to standard reaction conditions it was well preserved and gave sulfonylated **2i** in 91% yield (entry 8). An acid sensitive boc-protecting group in **1j** was also conserved in reaction medium

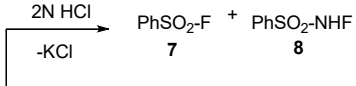
and aldehyde functionality in **1K** remains unspoiled in reaction medium and converted to desired sulphonylated **2K** in excellent yield (entry 10). Thus milder reaction conditions, protecting as well as functional group tolerability and chemoselectivity towards aryl TBDMS ethers makes this protocol noteworthy.

We planned intermolecular competition and cross-over experiments for the assessment of reactivity order (Scheme 1). An equimolar mixture of **1a** and benzyl alcohol **3** when treated with excess of NFSI/KF only former underwent sulfonylation and produced **1b** in 90% yield whereas the benzyl alcohol **3** was fully recovered. Interestingly, the reaction of an equimolar mixture of aryl TBDMS ether **1a** and phenol **4** with stoichiometric use of NFSI/KF provided mixture of sulfonylated products **1b** (20%) and **5** (70%). Thus, the order of reactivity for sulfonylation is phenol > aryl TBDMS ethers > aliphatic alcohols. Next, equimolar mixture of aryl TBDMS ether **1a** and phenol **4** when treated with stoichiometric NFSI and catalytic KF furnished sulfonylated product **5** (70%), whereas aryl TBDMS ether **1a** was fully recovered. This methodology could be further extended for sulfonylation of phenols with the use of catalytic KF and work in this direction is underway.



Scheme 1. Crossover and competitive interconversion experiments.

In order to gain mechanistic insights, we attempted the isolation of intermediates formed during course of reaction as shown in Scheme 2. When equimolar mixture of NFSI and KF was stirred in DMF at room temperature initially it form clear solution but after 5 minute reaction mass becomes turbid (mass spectra shows peak at m/z= 174 in negative mode). This suggests that existence of reversible transient potassium salt of N-fluorobenzenesulfonimide in reaction medium. Further addition of 2N aqueous HCl to the reaction medium facilitates formation of six member transient complex **I (**between NFSI, KF and HCl), which leads to enforcement of equilibrium towards right hand side by forming strong ionic bond in KCl. Thus, after workup we were able to isolate benzenesulfonylfluoride **7** and N-fluorobenzenesulfonamide **8**. The isolated reaction intermediates were fully characterized and confirmed by Mass and NMR analysis. Based upon isolated intermediates, we propose probability of formation of six member transient complex **II** (between NFSI, KF and Aryl TBDMS ether) in case of interconversion of aryl TBDMS ether to their benzene sulfonate. The formation of strong Si-F bond in TBDMSF is the driving force for shifting equilibrium towards aryl sulfonate formation.



Scheme 2. Plausible mechanism for interconversion of aryl TBDMS ether to aryl benzene sulfonate.

Conclusions

In conclusion, we have developed an efficient protocol for the direct interconversion of aryl TBDMS ethers to corresponding benzene sulfonate esters by using NFSI/KF in DMF. The mild conditions and neutral reaction medium well preserves sensitive functionalities. The present methodology also validated for exclusive chemoselectivity towards aryl TBDMS ethers. More significantly, conventional operations, use of inexpensive reagents and step economy would demonstrate the scope of this method in total synthesis.

Acknowledgments

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Supplementary data

Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for all compounds.

Experimental

General procedure for interconversion of aryl TBDMS ethers to aryl benzene sulfonate esters

To a stirred solution of NFSI (1.2 mmol) in DMF (8 mL) was added KF (1.2 mmol) at room temperature. After stirring for 5 minutes turbidity was observed. Then to the resulting turbid solution was added aryl TBDMS ether (1 mmol) in DMF (2 mL) and stirring continued at room temperature for specified time. Next, water (30 mL) was added and reaction mass was extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with water (50 mL), brine, dried (Na_2SO_4) and concentrated under vacuum. The crude residue was purified on silica gel column chromatography.

References and notes

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Graphical Abstract

- Mild interconversion of aryl silyl ether to benzene sulfonate ester
- Stoichiometric use of N-fluorobenzenesulfonimide and potassium fluoride
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NFSI/KF mediated mild and chemoselective interconversion of aryl TBDMS ethers to their benzene sulfonate

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