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Methyl NFSI: Atom-economical alternative to NFSI shows higher fluorination reactivity under Lewis acid-catalysis and non-catalysis

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Kazunobu Fukushi,[a] Satoru Suzuki, [a] Tomohiro Kamo,[a] Etsuko Tokunaga,[b] Yuji Sumii,[a] Takumi Kagawa,[c] Kosuke Kawada,[c] and Norio Shibata*[a,b]

Me-NFSI was first reported in 1994. Despite its atom-economical structure and similarity to a well-explored fluorinating reagent, NFSI, Me-NFSI has never appeared in the literature in over 20 years. We desclose that Me-NFSI is more effective for the fluorination of active methines under Lewis acid-catalysis and non calaysis than NFSI.

Introduction

Direct electrophilic fluorination of organic molecules is surely one of the most straightforward methods for the synthesis of organofluorine compounds which are sought after in the fields of pharmaceuticals, agrochemicals and specialty materials.[1,2] The early days of electrophilic fluorination were problematic since there was a lack of suitable reagents for this purpose, instead of highly toxic gaseous fluorine (F_2), explosive fluoro perchlorite ($FClO_3$), trifluoromethyl hypofluorite (CF_3OF), or expensive xenon difluoride (XeF_2). Since the initial report by Barnette in the mid-1980s claiming that *N*-fluorosulfonamide **1** is useful for the direct electrophilic fluorination of carbanions,[3] research on the development of N-F type shelf-stable reagents for electrophilic fluorination has been widely spurred worldwide,[4] including by our group.[5] Among the many kinds of reagents developed,[2,4] chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®)[6] and *N*-fluorobenzenesulfonimide (NFSI)[7] have become two of the most popular reagents in this field due to their accessibility, suitable reactivity and stability (Figure 1). While the two reagents are very useful and have continuously been employed to discover new reactions and valuable compounds with expected properties in both academia and industry, they suffered from an intrinsic drawback, namely poor atom-economical transformation, limiting large-scale preparations in process chemistry. Electrophilic fluorination reagents, many of which have been reported in the literature, can fulfil the atom-economical and environmentally-friendly needs of modern chemistry to serve society's needs.[8] Despite this, we noticed that *N*-fluoromethanesulfonimide (F-N(SO_2Me)$_2$, Me-NFSI) has been poorly explored despite its atom-economical structure (Figure 1).[9]

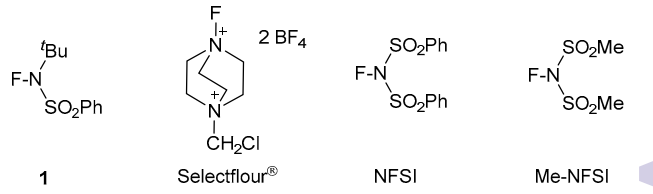

Figure 1. Shelf-stable N-F type electrophilic fluorination reagents.

Me-NFSI was first reported by Bohlmann in 1994 during the electrophilic fluorination of carbanions but there were only three examples of the reaction with sodium malonate, lithium acetylide and anthracenyl lithium.[9] However, the two methyl groups of Me-NFSI might be a problem due to their acidity under basic conditions. On the other hand, it is reasonable to expect that higher basicity of sulfonyl oxygens of Me-NFSI than regular NFSI will bring about a desirable outcome under acid catalysis. Moreover, the water solubility of methanesulfonimide, HN(SO_2Me)$_2$, a residue that forms after fluorination, is very beneficial from a practical point of view, since it is easily washed out during the work-up process. In this paper, we disclose herein that Me-NFSI is an atom-economical alternative to NFSI, and has notable advantages over NFSI in the electrophilic fluorination of active methine compounds including β-keto esters, oxindoles, and malonates under Lewis acid-catalysis. More interestingly, the reaction of β-keto esters also proceeds nicely without any catalyst providing corresponding fluorinated compounds in good to high yields. In particular, methanol is the best choice of solvent. Water is also useful as a solvent for fluorination by Me-NFSI.

Results and discussion

[a] Department of Nanopharmaceutical Sciences, Nagoya Institute of Technology (NIT), Gokiso, Showa-ku, Nagoya 466-8555, Japan, E-mail: nozshiba@nitech.ac.jp; Fax: +81-52-735-7543
[b] Department of Frontier Materials, Nagoya Institute of Technology (NIT), Gokiso, Showa-ku, Nagoya 466-8555, Japan.
[c] TOSOH F-TECH, Inc., 4988, Kaisei-cho, Shunan, Yamaguchi 746-0006, Japan Tel: +81-834-62-1300 Fax: +81-834-62-1303
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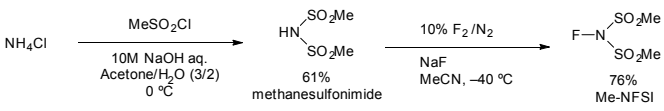
Me-NFSI is easily prepared in two steps from the reaction of commercially available methanesulfonyl chloride according to Bohlmann's procedure.[9] Namely, methanesulfonyl chloride was treated with NH_4Cl with NaOH in aqueous acetone at 0 °C to provide $HN(SO_2Me)_2$ in 61% yield.[10] $HN(SO_2Me)_2$ was fluorinated using 10% gaseous fluorine in nitrogen in the presence of NaF in MeCN at −40 °C to furnish Me-NFSI in 76% yield. The Me-NFSI obtained is a shelf-stable colorless solid (mp= 48—49 °C; CH_2Cl_2) (Scheme 1).



Scheme 1. Preparation of Me-NFSI

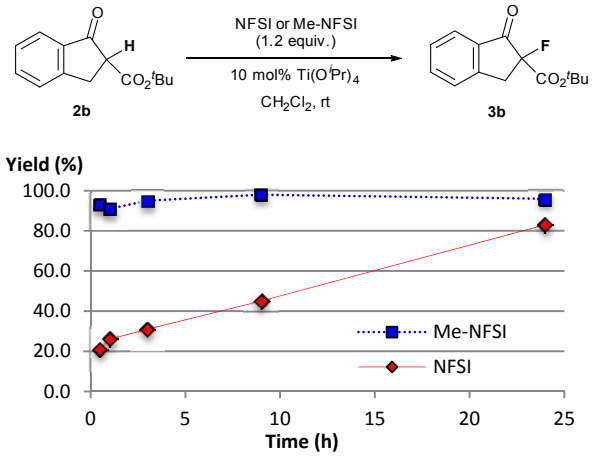


Figure 2. GC-analysis of titanium-catalyzed fluorination. Reaction conditions: **2b** (1.0 mmol), Me-NFSI or NFSI (1.2 equiv.), $Ti(O^iPr)_4$ (10 mol%), CH_2Cl_2 (10 mL, 0.1 M), rt.

Initially, due to the difference in basicity of the sulfonyl oxygens in NFSI and Me-NFSI, we envisaged that fluorination under acid-catalysis using Me-NFSI would be clearly advantageous than the use of NFSI. Thus, the initial comparison of the fluorination of β-keto esters **2a,b** by Me-NFSI and NFSI was examined under $Ti(O^iPr)_4$ catalysis at room temperature in CH_2Cl_2. This expectation was realized in practice, in particular the fluorination of sterically demanding ^{t}Bu ester **2b** (Figure 2, Table S1 in supplementary information). The fluorination of **2b** by NFSI gave product **3b** in 20% yield after 10 min, and the yield of **3b** gradually increased to 80% over 24 hours. On other hand, Me-NFSI produced **3b** in 90% yield within only 5 min. A similar rate-acceleration tendency by Me-NFSI over NFSI was also observed for the fluorination of methyl ester **2a**, although the difference was not as large as that for **2b** (Table S2). The rapid reaction by Me-NFSI can be explained by the activation of Me-NFSI via the coordination of its sulfonyl oxygens with Ti(IV), which was ascertained by ^{19}F-NMR experiments. Namely, the chemical shift of Me-NFSI is −44.381 (internal standard was $PhCF_3$ −63.000, CD_2Cl_2) which shifted to −44.400 ppm after the addition of 1 equiv. of $Ti(O^iPr)_4$ (see Figures S4 and S5). On the other hand, the chemical shift of NFSI stayed constant at −38.331 ppm, independent of the existence of $Ti(O^iPr)_4$ (see Figures S6 and S7). Interestingly, the different chemical shifts were also observed depend on the amount of $Ti(O^iPr)_4$. The original −44.425 ppm (Me-NFSI, in $CDCl_3$) was shifted to −44.499 ppm with 0.5 equiv. of $Ti(O^iPr)_4$, and to −44.462 ppm with 1.0 equiv. of $Ti(O^iPr)_4$ (Figures S8, S9 and S10). These results would suggest that $Ti(O^iPr)_4$ coordinates Me-NSFI sulfonyl oxygen atoms, as depicted in Figures 3a and 3b.

In order to further discuss the higher reactivity achieved by Me-NFSI, DFT calculation[11] was attempted next. The charge distributions of fluorine (F) on Me-NFSI, NFSI and their titanium complexes were calculated (DFT/B3LYP/6-31G*) (Figures 3c—f, also see Table S5). In Me-NFSI and NFSI, the charge distributions of the F were almost similar (Figures 3c vs 3e). On the other hand, the charge distribution of each F in titanium complexes is rather different, and F in Me-NFSI is much positive than that of NFSI (Figures 3d vs 3f). These computed results suggest that the reactivity of Me-NFSI seems to be higher than that of NFSI when it is complexed with Ti(IV).

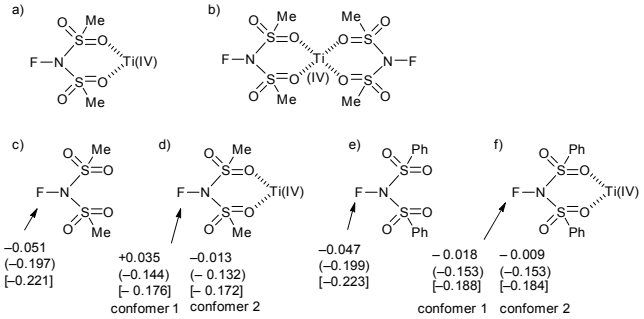


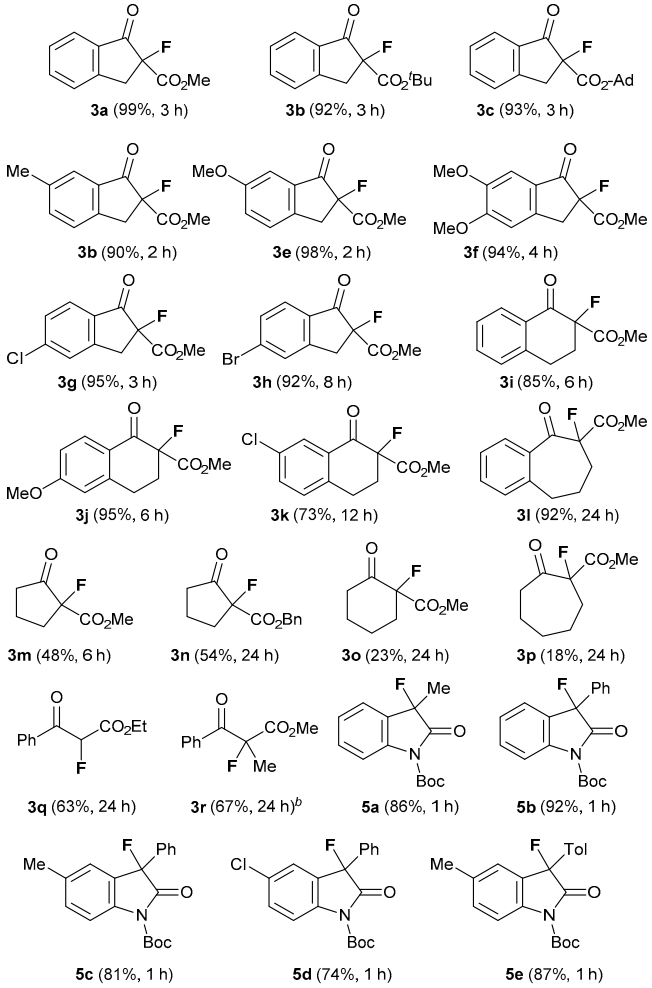
Figure 3. a,b) Proposed activations of Me-NFSI by $Ti(O^iPr)_4$. c—f) B3LYP/6-31G* atomic charges of fluorine in Me-NFSI and NFSI for the complexes with Ti(IV): electrostatic, Mulliken ( ), and Natural [ ].

The acid-catalyzed fluorination by Me-NFSI was found to be quite general for a series of β-keto esters **2a—r** (Table 1). The substrates with sterically demanding ^{t}Bu ester **2b** and 1-adamthyl ester **2c** gave similar high yields of **3b,c** as methyl ester **2a** within 3 h. The reaction was also adapted to substituted indanone derivatives **2d—h** with electron-donating Me and MeO, and electron-withdrawing Br and Cl groups on the benzene ring. Tetralone derivatives **2i—k** were also fluorinated in good to excellent yields with a slightly extended reaction time. A benzosuberone derivative having a 7-membered ring **2l** was also nicely converted to the desired product **3l** in 92% yield, although a longer reaction time (24 h) was required. The fluorination of cyclopentanone carboxylates **2m,n**, cyclohexenone carboxylate **2o**, cycloheptanone **2p** and acyclic β keto esters **2q,r** was comparatively slower than the benzene-attached cyclic substrates providing corresponding fluorinated products **3m—r** in low to moderate yields (18—67%). The fluorination by Me-NFSI under acid-catalysis is also effective for the reaction of oxindole derivatives[12] **4a—e** independent of the nature of substitutions at the 3- and 5-positions.

We next examined the fluorination of malonates **6a—d** (Table 2). Unfortunately, fluorination was not effective when β-keto esters were used. After brief optimization of the reaction, the condition consisting of 20 mol% $Ti(O^iPr_4)$, 2 equiv. of Me-NFSI in toluene at

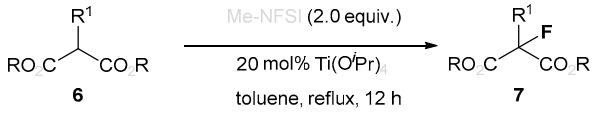
reflux temperature furnished fluorinated malonates **7a—d** in satisfactory yields (51—91%).

Table 1. Lewis acid-catalyzed fluorination of active methine compounds by Me-NFSI.



[a] Reaction conditions: **2** or **4** (0.3 mmol), Me-NFSI (1.2 equiv.), $Ti(O^iPr)_4$ (10 mol%), CH_2Cl_2 (3 mL, 0.1 M), rt. [b] 1.0 equiv of $Ti(O^iPr)_4$ was used.

Table 2. Fluorination of malonates **6** under Lewis acid-catalysis.

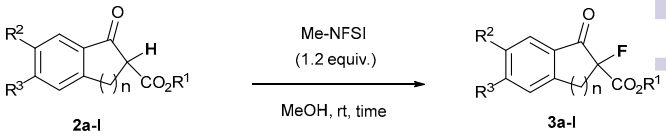


Entry	6	R	R^1	7	Yield (%)[b]
1	**6a**	Et	Me	**7a**	91
2	**6b**	Et	Ph	**7b**	52
3	**6c**	Et	Bn	**7c**	77
4	**6d**	Bn	Bn	**7d**	51

[a] Reaction conditions: **6** (0.3 mmol), Me-NFSI (2.0 equiv.), $Ti(O^iPr)_4$ (20 mol%), toluene (3 mL, 0.1 M), reflux. [b] Isolated yield.

The fluorination of **2a** by Me-NFSI was further attempted under catalyst-free conditions (Table 3). To our surprise, fluorination proceeded without catalysis to provide **3a** in good to high yields (49—98%). In toluene, 49% of **3a** was obtained after 24 h, but this increased to 63% in CH_2Cl_2 for 24 h (entries 1, 2). Both the yield and reaction time were dramatically improved, exceeding 90% (entries 3,4). In particular, in MeOH, **3a** was obtained in 96% (98%) yield in 1 h. Substrate generality for fluorination by Me-NFSI in MeOH under catalyst-free conditions was next investigated. As shown in Table 3, a series of β-keto esters **2b—l** were smoothly fluorinated by Me-NFSI almost independent of the nature of the ester moiety or substitution on the aryl group, while a longer reaction time was required for substrates with sterically demanding esters, electron-withdrawing substituents on the aryl moiety and tetralone derivatives (entries 5-14). Benzosuberone **1l** was fluorinated in the absence of catalysis in 35% yield (entry 15). It should be noted that the reaction proceeded very nicely even in water to provide **3a** in 96% yield (entry 16), while NFSI resulted 81% yield after 30 h (entry 17). The difference observed is due to the higher solubility of Me-NFSI into water than that NFSI. This is also a clear advantage of Me-NFSI.

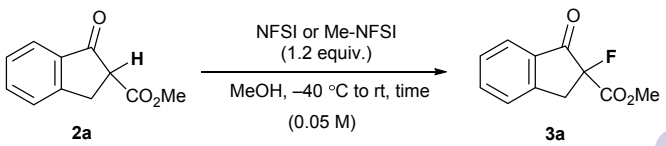
Table 3. Scope of fluorination of β-keto esters **2** by Me-NFSI.



Entry	2	n	R^1	R^2	R^3	3	Time (h)	Yield (%)[b]
1	**2a**	1	Me	H	H	**3a**	24	49[c] (toluene)
2	**2a**	1	Me	H	H	**3a**	24	63[c] (CH_2Cl_2)
3	**2a**	1	Me	H	H	**3a**	4	92[c] (THF)
4	**2a**	1	Me	H	H	**3a**	1	96 (98[c])
5	**1b**	1	^{t}Bu	H	H	**3b**	12	86
6	**1c**	1	1-Ad	H	H	**3c**	24	69
7	**1d**	1	Me	Me	H	**3d**	4	90
8	**1e**	1	Me	OMe	H	**3e**	4	98
9	**1f**	1	Me	OMe	OMe	**3f**	8	66
10	**1g**	1	Me	H	Cl	**3g**	8	83
11	**1h**	1	Me	H	Br	**3h**	12	86
12	**1i**	2	Me	H	H	**3i**	24	91
13	**1j**	2	Me	H	OMe	**3j**	12	85
14	**1k**	2	Me	Cl	H	**3k**	24	90
15	**1l**	3	Me	H	H	**3l**	24	35
16	**2a**	1	Me	H	H	**3a**	4	96[c] (H_2O)
17[d]	**2a**	1	Me	H	H	**3a**	30	81[c](H_2O)

[a] Reaction conditions: **2** (0.3 mmol), Me-NFSI (1.2 equiv.), MeOH (3 mL, 0.1 M), rt. [b] Isolated yield. [c] 0.1 mmol of **2a** was used and yield was determined by GC. [d] NFSI was used instead of Me-NFSI.

To ascertain the distinct benefit of Me-NFSI over NFSI for fluorination of **2** under catalyst-free conditions, the reaction of **2a** with Me-NFSI or NFSI was again monitored by GC analysis at 0.05 M (Figure 4, Table SI3). As shown in Figure 4, there appears to be clear advantage to using Me-NFSI over NFSI as a fluorination reagent, i.e., over 80% of **3a** was observed by Me-NFSI, while about 68% of **3a** was produced by NFSI.



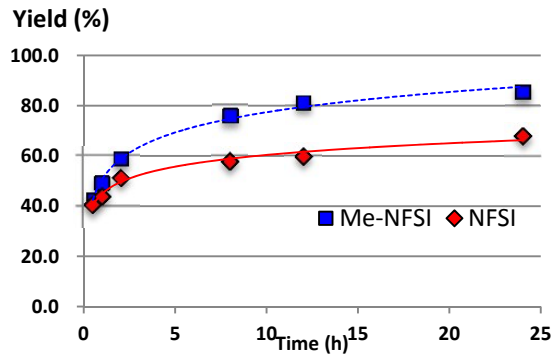


Figure 4. GC-analysis of fluorination in MeOH. Reaction conditions: **2a** (0.2 mmol), Me-NFSI or NFSI (1.2 equiv.), MeOH (4 mL, 0.05 M), –40 °C to rt. The each reaction was repeated four times under the same conditions and their averages were plotted.

Conclusions

In conclusion, we demonstrated that Me-NFSI is an atom-economical alternative to conventional NFSI. Under Lewis acid-catalysis, the fluorination of active methine compounds by Me-NFSI is much faster than that by well-explored NFSI. A variety of β-keto esters, oxindoles and malonates were smoothly reacted with Me-NFSI providing fluorinated compounds in good to high yields. More interestingly, Me-NFSI is also useful for electrophilic fluorination under catalyst-free conditions in MeOH. H_2O is also useful for catalyst-free fluorination by Me-NFSI. Practical uses may be possible by taking advantage of its excellent reactivity and the water solubility of its by-product, $HN(SO_2Me)_2$. Rapid reactions by Me-NFSI are also attractive for applications of ^{18}F-chemistry, since ^{18}F-NFSI has already been examined.[13] Further applications of Me-NFSI will be reported in due course.

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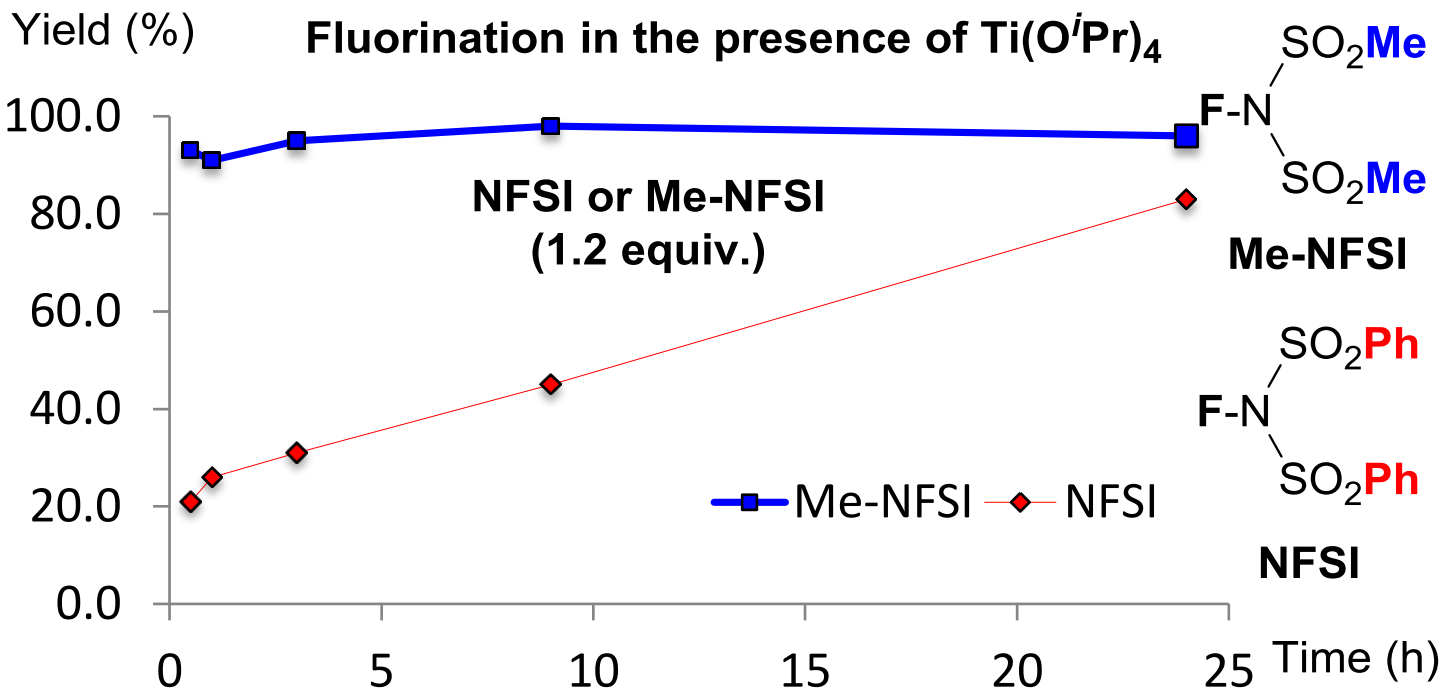
A table of contents entry



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