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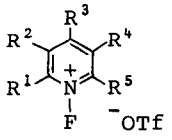
N-FLUOROPYRIDINIUM TRIFLATE AND ITS DERIVATIVES: USEFUL FLUORINATING AGENTS[1)]

Teruo UMEMOTO*, Kosuke KAWADA†, and Kyoichi TOMITA†
Sagami Chemical Research Center
Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

N-Fluoropyridinium triflate and its derivatives, stable and nonhygroscopic crystals, were found to be widely applicable reagents for mild and selective fluorination of a variety of organic compounds.

Mild and selective introduction of fluorine into organic compounds has been of wide interest because of the attractive effects of fluorine on the physical, chemical, or biochemical properties.[2)] Since extremely reactive, explosive, and toxic molecular fluorine (F_2) is of very limited utility for the selective fluorination,[3)] many kinds of fluorinating agents such as CF_3OF,[4)] $FClO_3$,[5)] CF_3COOF,[6)] CH_3COOF,[7)] XeF_2,[8)] $CsSO_4F$,[9)] etc., have been developed. However, they are still explosive, toxic, unstable, or hygroscopic materials which require special equipments and techniques. Although CH_3COOF is shown to be a useful reagent by Rozen et al., only the persons who treat the dangerous F_2 gas can use it because it is prepared only in situ from F_2 at low temperature.[7)] It was described in preliminary reports that pyridine-F_2 adduct fluorinated uracil or chloroolefins at low temperature.[10)] However, the adduct is of little use because of its violent decomposition at >-2°C. Recently N-fluorosulfonamides were developed as stable reagents, but their reactivity is low and the use is limited to the fluorination of carbanions only.[11)] Stable N-fluoropyridone also has low reactivity and the reported yields were very low.[12)] In addition, both N-fluoro compounds are difficult to prepare in a large scale owing to the required process of chromatography. As mentioned above, any potent reagents so far developed are practically difficult to handle and stable materials have poor utility. We have indeed developed broadly useful, and easily handled and prepared reagents, N-fluoropyridinium triflate and its analogs.[13)] We now wish to report on the fluorination of many kinds of organic compounds with N-fluoropyridinium triflates.

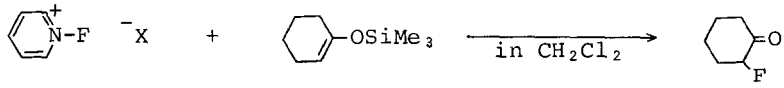


1 $R^{1\sim5}$=H
2 $R^{1,3,5}$=Me, $R^{2,4}$=H
3 $R^{1,3,5}$=H, $R^{2,4}$=Cl
4 $R^{1,5}$=COOMe, $R^{2,3,4}$=H

It was found that N-fluoropyridinium triflates have the high reactivity compared to the salts having other counter-anions such as BF_4, SbF_6, and ClO_4 (Table 1). Furthermore, Table 2 and other examination showed that the fluorinating ability of the triflates can be changed by introduction of

† Researchers from Onoda Cement Company, Japan.

Table 1 Reactivity of N-fluoropyridinium salts having different counter anions



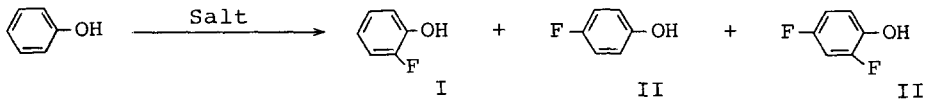
Run	Salt	Temp.	Time(h)	Yield(%)[a]
1	X=OTf	R.t.	7	87
2	BF_4	R.t.	72	Trace
3	BF_4	Reflux	6	41
4	SbF_6	Reflux	8	23
5	ClO_4	Reflux	19	0

a) GLC yields.

electron-donating or -withdrawing substituents into the pyridine nucleus and the ability increased in the order of 2<1<3<4. The reactivity of 4 with two electron-withdrawing groups COOMe is so high as to fluorinate phenol at room temperature smoothly. It is clear that the ability is closely related to the electron-density of the positive nitrogen site or of the whole π-ring system. In this way, an important feature of our N-fluoropyridinium system is that one can choose or make the best reagent according to the purpose.

A variety of substrates, including aromatics, enol ethers or acetates, anions of active methylene compounds, highly enolized active methylene compounds, and alkyl and aryl organometallics, can be fluorinated in good yields under very mild conditions by using triflates 1-4 (Table 3). In general, less reactive triflates are better for the fluorination of reactive substrates, while reactive triflates are better for less reactive substrates. For example, 2 is suited for fluorinating the reactive anions, while non-activated aromatics such as benzene are fluorinated by 4. The fluorination is favored in dry chloroalkanes except for the reactive anions which are well fluorinated in ether or THF. Alkyl- or arylmagnesium chlorides gave the good yields of the fluorides, but the lithium salts did not produce the fluorides. The magnesium iodides did not give the products because the iodide anion was oxidized to iodine by the triflates. The reaction with the compounds having basic nitrogen atoms such as amines resulted in the decomposition of the triflates. It is worth noting

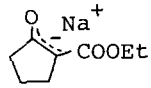
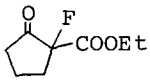
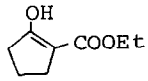
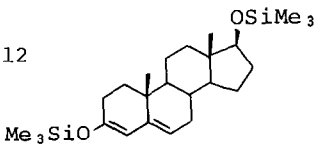
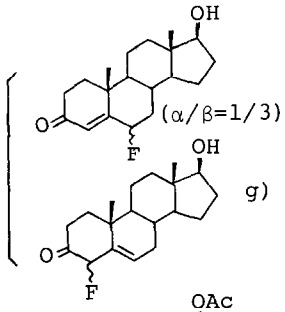
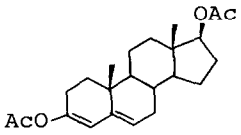
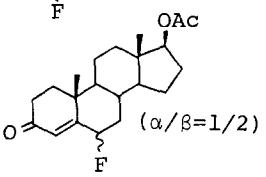
Table 2 Fluorination of phenol with a series of N-fluoropyridinium triflates



Run	Salt	Solv.	Temp. (°C)	Time (h)	Conversion (%)	Yield(%)[a] I	II	III
1[b]	2	$CH_2ClCHCl_2$	100	24	75	47	31	3
2	1	$CH_2ClCHCl_2$	100	24	75	51	18	6
3	3	CH_2Cl_2	Reflux	5	73	60	18	7
4	4	CH_2Cl_2	R.t.	18	78	30	24	3

a) GLC yields. b) The reaction was not completed and slower than that in Run 2.

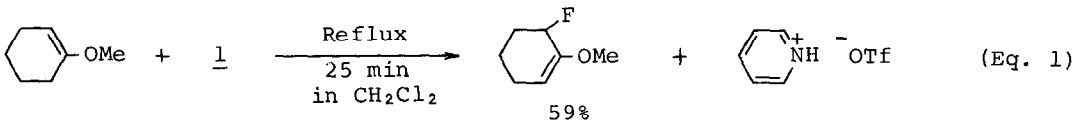
Table 3 Fluorination of organic compounds with N-fluoropyridinium triflates

Run[a]	Substrate	"F"	Solv.	Temp.	Time(h)	Product[c]	Y(%)[d]
1	Benzene	4	Benzene	Reflux	24	PhF	56[e]
2[b]	Anisole	4	CH_2Cl_2	"	24	o-F-Anisole p-F- "	44[f] 48[f]
3[b]	Phenylurethan	4	"	"	32	o-F-Phenylurethan p-F- " 2,4-Di-F- "	47 32 5
4	$n\text{-}C_{12}H_{25}MgCl$	2	Et_2O	0°C	0.5	$n\text{-}C_{12}H_{25}F$	75[f]
5	PhMgCl	2	THF	0°C	0.17	PhF	58[e]
6	$CH_3\bar{C}(COOEt)_2Na^+$	2	"	0°C	0.17	$CH_3CF(COOEt)_2$	78
7		2	"	0°C	0.17		78
8,9		3 2	CH_2Cl_2 "	Reflux "	24 48	" "	72 83
10	$n\text{-}C_7H_{15}CH{=}C(OSiMe_3)CH_3$	1	"	"	3	$n\text{-}C_7H_{15}CHFC(=O)CH_3$	58
11	$PhCH{=}C(OSiMe_3)OEt$	1	"	R.t.	2	PhCHFCOOEt	65
12		1	"	"	1		42 18
13		1	"	Reflux	10		71

a) Each triflate was allowed to react with an equivalent amount of substrate except for Run 1. b) Conversion yields were 71 and 68% for Run 2 and 3, respectively, and the yields of the products were based on the reacted starting materials. c) All the products showed spectral data in accord with authentic samples or the assigned structures. d) Isolated yields unless otherwise noted. e) F-NMR yields. f) GLC yields. g) Structural assignment at 4-position could not be made, but the product was one isomer from the F-NMR [206 ppm (d, J=50Hz) in $CDCl_3$, upfield from int. $CFCl_3$].

that a conjugated silyl enol ether afforded a mixture of 6- and 4-fluorides (2.3:1), while the corresponding acetate gave 6-fluorides only (Table 3, Run 12 and 13).

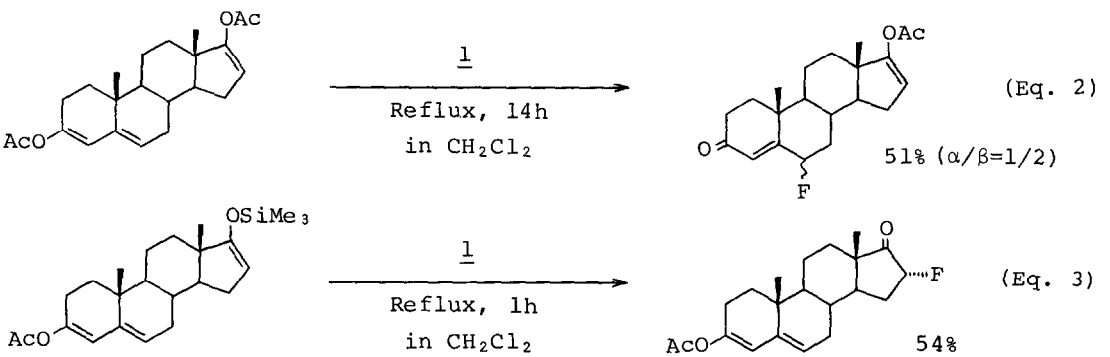
1 was allowed to react with 1-methoxycyclohexene to give 1-methoxy-6-fluo-



(Eq. 1)

rocyclohexene with migration of the double bond in 59% yield, which was readily converted to 2-fluorocyclohexanone by acid hydrolysis. It indicated that the fluorination proceeded under almost neutral conditions because triflic acid liberated was trapped by pyridine simultaneously liberated.

Eq. 2 and 3 show that our reagents have high selectivity in the fluorination. In a steroid with two reaction sites of conjugated and non-conjugated vinyl acetate moiety, 1 reacted at the conjugated site only. On the other hand, a steroid with silyl enol ether and conjugated acetate moiety afforded the product resulting from the reaction at the former site only.



(Eq. 2)

(Eq. 3)

Acknowledgement

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