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Reaction of *N*-Fluoropyridinium Salts with Wittig Reagents: A Novel and Convenient Approach to Symmetric *trans*-Olefins

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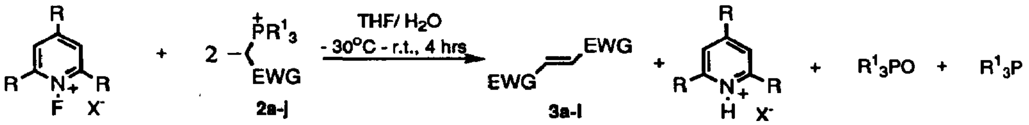
Abstract: *N*-Fluoropyridinium salts were found to react with Wittig reagents containing electron-withdrawing groups to give olefins in 47-83% yield. The mechanism of this conversion is believed to involve single-electron transfer from Wittig reagent to *N*-fluoropyridinium cation.

Chemistry of *N*-fluoropyridinium salts (NFS) has received considerable attention in the last decade.[1,2,3] A number of publications have indicated the value of these substrates for the efficient electrophilic fluorination of organic compounds,[2,4,5,6] for the synthesis of 2-substituted pyridines,[1,7,8,9] and deprotection of dithioacetals and ketals.[10] A variety of reaction pathways have been introduced to account for interactions of NFS with nucleophiles. Selected examples of these pathways are X-philic attack,[1,2] cine-(tele)-AE$_a$-substitution,[1,7] carbene formation,[8,9,11,12] and single-electron transfer (SET) mechanism.[1,2,10,13,14] It has been concluded[1] that the outcome of the reaction of NFS with nucleophiles depends on the nature of the nucleophile used.

In the course of our studies of NFS, we investigated the reaction of easily available salts **1a-c**[15] with Wittig reagents containing electron-withdrawing substituents[16] (EWG) in THF containing traces of water (Table, entries 1-11), or dry THF (Table, entries 13-15). The results of these studies are summarized below.[17]



2a-j **3a-l**

1a: R = H, X = BF$_4$
1b: R = H, X = OTf
1c: R = Me, X = OTf

4a: R = H
4b: R = Me

5a: R^1 = *n*-Bu **6a**: R^1 = *n*-Bu
5b: R^1 = Ph **6b**: R^1 = Ph

Entry	NFP Salt, 1	Wittig Reagent, 2	Olefin, 3[a]
1	c	a: R^1 = *n*-Bu, EWG = COOEt	a: EWG = COOEt (48%)
2	a	b: R^1 = Ph, EWG = COOEt	a: EWG = COOEt (51%)
3	b	b: R^1 = Ph, EWG = COOEt	a: EWG = COOEt (59%)
4	c	b: R^1 = Ph, EWG = COOEt	a: EWG = COOEt (79%)
5	a	c: R^1 = Ph, EWG = COPh	b: EWG = COPh (50%)
6	b	c: R^1 = Ph, EWG = COPh	b: EWG = COPh (61%)
7	c	c: R^1 = Ph, EWG = COPh	b: EWG = COPh (83%)
8	c	d: R^1 = Ph, EWG = CO-C_6H_4-*p*-OMe	c: EWG = CO-C_6H_4-*p*-OMe (81%)
9	c	e: R^1 = Ph, EWG = CO-C_6H_4-*p*-Br	d: EWG = CO-C_6H_4-*p*-Br (73%)
10	c	f: R^1 = Ph, EWG = CO-C_6H_4-*p*-NO_2	e: EWG = CO-C_6H_4-*p*-NO_2 (71%)
11	b	g: R^1 = Ph, EWG = $COCH_3$	f: EWG = $COCH_3$ (44%)
12	c	g: R^1 = Ph, EWG = $COCH_3$	f: EWG = $COCH_3$ (56%)
13	c	h: R^1 = Ph, EWG = Ph	g: EWG = Ph (17%)[b]
14	c	i: R^1 = Ph, EWG = -C_6H_4-*o*-NO_2	h: EWG = -C_6H_4-*o*-NO_2 (47%)
15	c	j: R^1 = Ph, EWG = -C_6H_4-*p*-NO_2	i: EWG = -C_6H_4-*p*-NO_2 (55%)

[a] Yield corresponds to isolated, analytically pure compound; [b] see Ref. 16.

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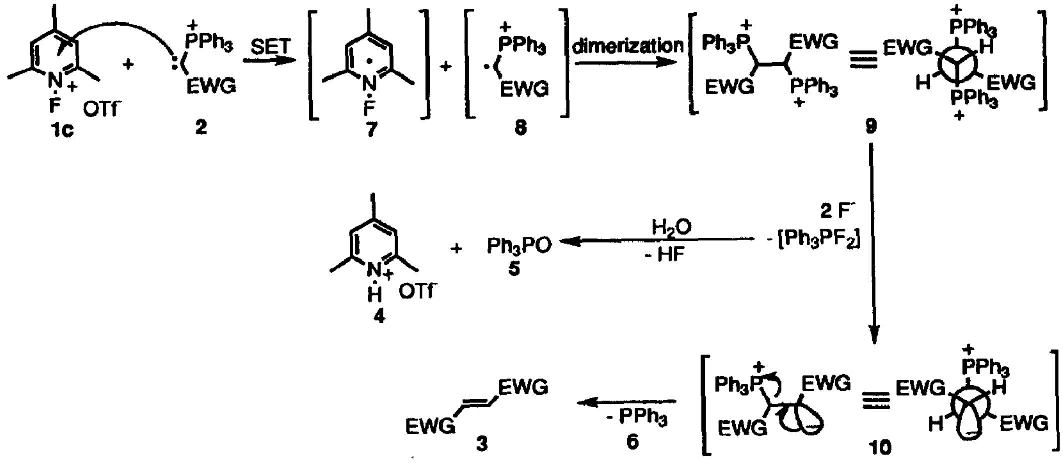
In all the cases, only *trans* - olefins **3a-i** were formed. No traces of *cis* - isomers were detected by GC MS analysis. All the olefins were easily isolated from the reaction mixtures.[17] The structures of products **3a-i** were confirmed by ^1H NMR, ^{13}C NMR, and mass spectroscopy. For solid compounds, melting points were compared with literature data.[18]

Both the nature of NFS, and the nature of Wittig reagent were found to significantly affect the outcome and the yield of the reaction.[16,19] 2,4,6-Trimethyl-*N*-fluoropyridinium triflate (**1c**) was found to furnish the best yields of olefins (Table), whereas reactions with NFS **1a,b** gave less satisfactory yields of **3a,b,f**. We believe that the reason for this is that the interactions of unsubstituted NFS **1a,b** with Wittig reagents **2a-j** can initiate chain side reactions including: i, nucleophilic attack of pyridinium ring by Wittig reagents[1] or by phosphines **6a,b**,[20] and ii, formation of carbene intermediate.[11,12] Indeed, GC MS analysis of the reaction mixtures of **1a,b** with **2a** revealed presence (5-8%, octane as internal standard) of 2-fluoropyridine, which may result from the Wittig reagent induced proton abstraction and formation of a higly reactive carbene intermediate.[11,16] Wittig reagents derived from triphenylphosphine (entries 2-12, Table) provided better yields of olefins than corresponding Wittig reagents derived from tri-*n*-butylphosphine (entry 1, Table).The best yields of olefins were achieved in THF as a solvent. Traces of water (0.5-1wt %) were found to increase the yields of **3a-f** by ca. 5-7%. Reactions conducted in acetonitrile and methylene chloride produced tarry products, and significantly lowered the yields of olefins **3a-i**. Electron scavengers (nitrobenzene, 2,4,6-tri-*tert*-butylphenol) did not affect significantly the yield of the olefins.[10]

The mechanism proposed for the reaction of NFS **1a-c** with Wittig reagents **2a-j** includes initial single-electron transfer (SET)[10] from the Wittig reagent to *N*-fluoropyridinium cation (Scheme) which results in the formation of heterocyclic radical **7** and cation radical **8**.



Existence of these reactive species is well documented.[2,10,13,14] Dimerization of cation radical **8** can lead to the intermediate formation of dication **9**,[10,21] which is unstable under the reaction conditions.[22] Fluoride-anion attacks the positively charged phosphorus atom to produce anion **10**. Elimination of PPh_3 from **10** provides the observed olefins **3**. Exclusive formation of *trans*-isomers can be explained from the geometry of the intermediate **9**. To minimize the steric repulsion, two bulky positively charged triphenylphosphonium groups in **9** must occupy the *trans* -position (Scheme). Free rotation around C-C bond in **9** is, for this reason, problematic, which leads to exclusive formation of conformer indicated in the Scheme. Nucleophilic attack of the phosphorus atom by the fluoride-anion followed by the elimination of Ph_3PF_2 generates anion **10**. *Trans*-orientation of the anionic center relatively to the leaving group (PPh_3) is appropriate for the elimination reaction[23] and formation of *trans*-olefin **3**. Hydrolysis of Ph_3PF_2 leads to Ph_3PO (**5**). HF produced in the hydrolysis step is trapped by pyridine base, which acts as an acid scavenger, leading to **4**, the other observed product.These mechanistic proposals were supported by the observation that the yields of olefins **3** can be further increased (ca. 5%) by addition of the catalytic amount of $Bu_4{}^+F^-$. It was suggested that fluoride anion of the catalyst facilitates generation of the intermediate anion **10**.

It has been demonstrated that, apart from the more obvious function as fluorinating agents, *N*-fluoropyridinium salts can be used for an array of processes leading eventually to fluorine free organic compounds.[1,24] Synthesis of olefins based on the reactions of NFS with Wiittig reagents described in this paper is a good example of a "legitimate"[24] use of fluorine in organic chemistry.

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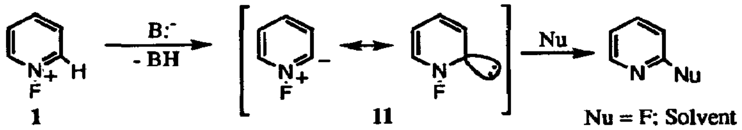
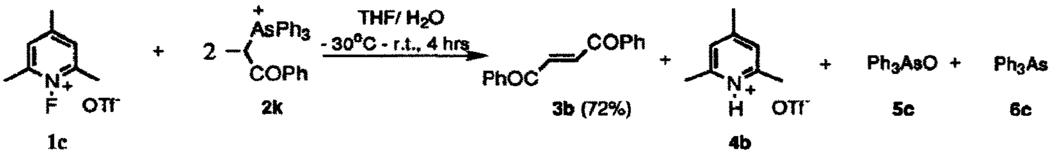
15. *N*-Fluoropyridinium salts **1a-c** can be prepared in a multigram scale by the procedures described in references 2 and 6b. Alternatively, triflates **1b,c** can be purchased from Aldrich.
16. Wittig reagents containing alkyl and aryl substituents (Table, entry13) have also been attempted for the reaction with *N*-fluoropyridinium salts **1a-c**. However, only traces of target olefins **3** have been detected by GC MS analysis of the reaction mixtures. The major product of these conversions was found to be 2-fluoropyridine (25-42%). Significant formation of tar material has also been observed. The notable exceptions were Wittig reagents, containing aromatic groups with *o*- or *p*- electron-withdrawing groups (see Table, entries 14, 15). The explanation for these observations is that Wittig reagents which do not possess electron-withdrawing substituents can act as bases in their interaction with NFS. As a result, abstraction of proton from position 2, and formation of a carbene **11** becomes a major reaction pathway. Formation of a carbene intermediate and its transformations have been described, see, for example, references 9, 11 in this work.



1 **11** Nu = F; Solvent

17. In a typical experimental procedure solution of 1 mM of *N*-fluoropyridinioum salt **1b,c** (suspension for **1a**) in 2 mL of THF was added to the solution or suspension of 2 mM of Wittig reagent in 10 mL of THF and 0.1 mL of H_2O for **2a-g** or in 10 mL of dry THF for **2h-j** at -30°C (water-ethyleneglycol bath). The resulting pale yellow solution was stirred at this temperature for 30 min and after this time slowly warmed up to room temperature and stirred until KI/ starch indicator revealed absence of *N*-fluoropyridinium salt (2-3 hrs). The resulting mixture was filtered, concentrated, washed with 3X10 mL of Et_2O, joint ether extract was washed with 2X5 mL of H_2O, dried over $MgSO_4$, concentrated, prepurified by flash chromatography (Silicagel, eluent - hexanes/Et_2O, 8:1), and purified by plate chromatography (Silicagel, eluent - hexanes/Et_2O, 4:1) to give analytically pure samples. Outcome of the reaction and yields of olefins **3** were similar under argon atmosphere or in the presence of oxygen. It should be noted that arsenic analogs of Wittig reagents react with NFS in a similar way. Thus, reaction of **1c** with **2k** furnished the expected olefin **3b** in 72% yield.



Salt **1c** (1 eq) was also allowed to react with a mixture of 1eq of **2c** and 1eq of **2d**. Remarkably, besides symmetrical olefins **3b** (24%) and **3c** (31%), nonsymmetrical olefin **3j**, EWG^1 = COPh, EWG^2= COC_6H_4-*p*-OMe, was formed in 7% yield (GC MS, octane as an internal standard). This observation provides an additional proof for the SET mechanism offered for the reaction of NFS with Wittig reagents. For somewhat similar transformations of Wittig reagents in the presence of elemental oxygen or SeO_2 see Bestmann, H.J.; Kratzer, O. *Angew.Chem.* **1962**, *74*, 494 and Shevchuk, M.I.; Tolochko, A.F.; Dombrovskii, A.V. *Zh.Org.Chem.* **1971**, 7, 1692.

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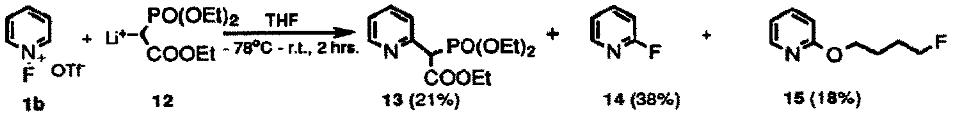
19. Wittig-Horner reagent **12** was also applied for the reaction with NFS. However, no traces of olefins **3** were detected. Instead, 2-substituted pyridines **13-15** were isolated.



It was concluded that this transformation does not proceed *via* SET mechanism, but instead, *via* carbene intermediate **11**.

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21. In further proof for the intermediate formation of dication **9**, treatment of the simplest analog of **9**, EWG = H, (synthesis described in Wittig, G.; Eggers, H.; Duffner, P. *Ann.* **1958**, *619*, 10) with $Bu_4{}^+F^-$ in wet THF under argon furnished three products: ethylene, triphenylphosphine oxide (**5b**), and triphenylphosphine (**6b**). Similar reactions of ethane- and ethene-1,2-bisphosphonium salts with alkali, leading to **5b**, **6b**, and olefins were described in Brophy, J.J.; Gallagher, M.J. *Aust.J.Chem.* **1969**, *22*, 1385.

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