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A [2 + 2] Cycloaddition Route to Dimethylaminomethylene Vinamidinium Salts

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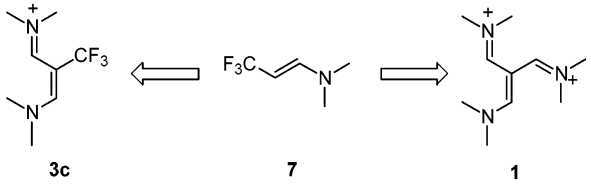
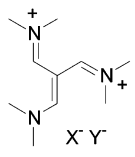
ABSTRACT



Trifluoropropanoic acid reacts with 1 equiv of $POCl_3$ in DMF to generate the trifluoromethyl enamine (7). At this stage, two reaction manifolds are available. The expected reaction with additional $POCl_3$ generates the 2-trifluoromethyl vinamidinium salt (3c). However, thermally driven loss of fluoride generates an iminium ion, which sets the stage for a [2 + 2] cycloaddition to ultimately generate the dimethylaminomethylene vinamidinium salt (1).

Dimethylaminomethylene vinamidinium salts **1** are important synthetic intermediates. Gupton has demonstrated the broad applicability of the perchlorate **1a** in heterocyclic synthesis.[1] Wudl has prepared the tetrafluoroborate salt[2] **1b**, and Ragan has reported the thermal characterization and use of this lower energy alternative in the synthesis of pyrimidines.[3] The vinamidinium salt **1c** has been used in the synthesis of the integrin $\alpha v\beta 3$ receptor antagonists,[4] which may have the potential for moderating the outcome of osteoporosis. They are also useful in the synthesis of inhibitors of apolipoprotein B[5] and have materials applications.[6]

On the basis of the ease of access to these interesting synthons, we have continued to explore the synthetic utility of a range of vinamidinium hexafluorophosphate salts for heterocycle synthesis[7] and more recently in the synthesis of anilines.[8]



1a X^- = Y^- = ClO_4^-
1b X^- = Y^- = BF_4^-
1c X^- = Y^- = Cl^-
1d X^- = Y^- = PF_6^-
1e X^- = BF_4^- Y^- = PF_6^-

In this Letter, we disclose a unique transformation that is able to deliver the exceptionally thermally stable dimethy-

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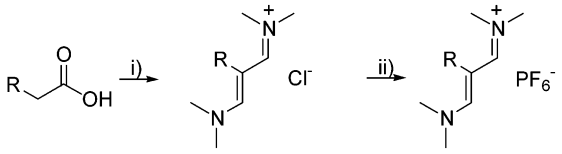
laminomethylene hexafluorophosphate salts[9] from β-fluoroalkanoic acids. Spectroscopic studies are used to define the reaction pathway, which allows us to construct a mechanistic framework involving two cycloaddition processes. This reaction has significant implications: it provides direct access to these important vinamidiniums and identifies an unusual reactivity mode for γ-fluoroenamines.

We have previously reported a general method for preparation of 2-substituted vinamidinium hexafluorophosphate salts.[10] The controlled addition of phosphorus oxychloride at 70 °C to an appropriate acetic acid derivative in DMF led to the isolation of the vinamidinium hexafluorophosphate salts in good yield (Scheme 1).

Scheme 1. Reaction of Trifluoropropanoic Acid and Phosphorus Oxychloride in DMF[a]



[a] Reaction conditions: (i) 70 °C, DMF, 2 equiv of $POCl_3$ addition over 3 h; (ii) $NaPF_6$.

Upon further investigation of the reaction of trifluoropropanoic acid **2c**,[11] we have discovered that under conditions of inadequate temperature control due to rate of addition or poor mixing, the 2-dimethyl-aminomethylene salt **1d** can be obtained as a significant byproduct (up to 12%). With the observation of this unexpected reactivity, we undertook a thorough investigation of the reaction mechanism with the goal of improving the yield of **1d** and gaining a greater understanding of the factors responsible for the formal loss of the trifluoromethyl group.

Initial experiments quickly established that the 2-trifluoromethyl vinamidinium **3c** was not an intermediate en route to the dimethylaminomethylene salt **1d**. No reaction was observed when a solution of **3c** in DMF and $POCl_3$ was heated at 85 °C for 12 h.[12] This suggested that formation of **1** occurred *prior* to formation of **3c**. Prompted by this observation, we chose to utilize in situ IR[13] and Raman[14] spectroscopy to probe for intermediates along the reaction pathway that might provide insights to the origin of **1d** (Figure 1). The controlled addition of $POCl_3$ (2 equiv) to a

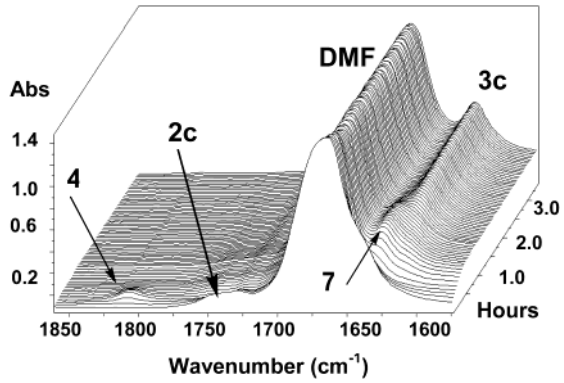
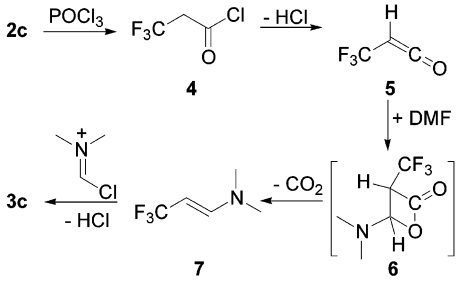


Figure 1. IR spectra from the reaction of trifluoropropanoic acid and $POCl_3$ in DMF.

DMF solution of trifluoropropanoic acid at 60 °C results in the immediate formation of the acid chloride **4**,[15] characterized by a carbonyl stretch in the infrared spectrum at 1808 cm^{-1} and chloride stretch in the Raman spectrum at 452 cm^{-1} (Scheme 2).

Scheme 2. Formation of Vinamidinium Salt **3c** from Trifluoropropanoic Acid



Continued aging of the reaction mixture at 60 °C results in decay of the carbonyl absorbance and the liberation of carbon dioxide observed at 2139 cm $^{-1}$. The formation of the trifluoromethyl enamine[16] **7** is observed by IR and Raman spectroscopy.

The enamine **7** is characterized by IR absorbances at 1629, 756, 693 cm^{-1} and a Raman absorbance at 1211 cm^{-1}. This intermediate was also characterized by electrospray mass spectroscopy (*m*/*z* 140, [M + H^+]). Enamine **7** arises via the intermediacy of the trifluoromethylketene[17] **5** followed by [2 + 2] cycloaddition with DMF and extrusion of CO_2. Subsequent reaction of enamine by the addition of $POCl_3$ to DMF yields the trifluoromethyl vinamidinium salt **3c**.

We reasoned that enamine **7** might be a competent intermediate in the formation of **1**. To test this hypothesis, $POCl_3$ was added in a stepwise manner at 60 °C. As described above, addition of 1 equiv of $POCl_3$ produces

(9) DSC: **1d**, 70 J/g; **1e**, 71 J/g. **1a**, 5020 J/g; **1b**, 260 J/g (ref 3).

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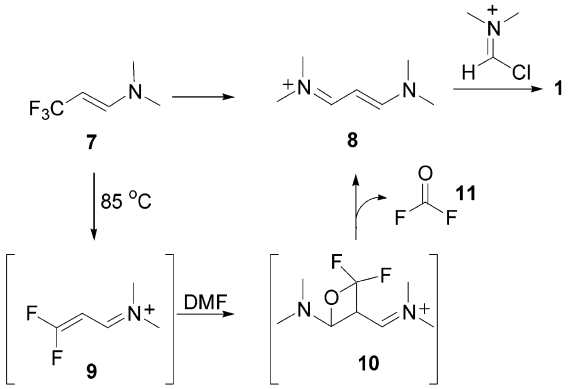
(12) Heating **3c** in DMF at 100 °C for 8 h did not lead to the formation of **1** or **8**. However, heating **3c** and anhydrous HCl in DMF at 100 °C for 20 h led to the formation of **8** (50%) with no trace of **1**. We have rationalized these results on the basis on protonation/retro-Vilsmeier reaction to regenerate enamine **7** since there is no competent loss of CF_3^+ from an intermediate analogous to **19**. Retro-Vilsmeier accounts for formation of an amidine from the chloro-analogue of **3c**; see ref 18.

trifluoropropanoyl chloride **4** followed by formation of enamine **7**. No further reaction is observed until 85 °C where enamine **7** is converted to vinamidinium salt **8**[18] with a $t_{1/2}$ = 120 min (Scheme 3).

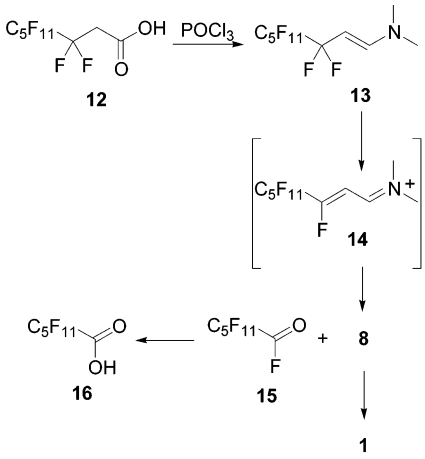
Scheme 3. Conversion of Enamine **7** to Vinamidinium Salts **8** and **1**



Examination of the DMF solution by ^{31}P and ^{19}F NMR spectroscopy revealed the formation of a range of fluoro-substituted phosphate anions, including PF_6^-, demonstrating that phosphorus serves as a fluoride scavenger in the reaction.[19] Vinamidinium **8** can be converted to the dimethylaminomethylene vinamidinium **1** by addition of a second equivalent of $POCl_3$ with a $t_{1/2}$ < 10 min (60 °C). Consistent with this observation, independent reaction of **8** with 1 equiv of $POCl_3$ in DMF gave **1d** in a quantitative assay yield and in an unoptimized 87% isolated yield. *Remarkably, this is the first report of the direct formylation of a vinamidinium salt.*[20]

The conversion of **7** to **8** is formally the result of CF_3 loss coupled with the addition of 1 equiv of Vilsmeier. We propose the mechanism outlined in Scheme 3 to rationalize these observations. Thermally induced elimination of fluoride[21] yields a gem-difluoride iminium **9**, which undergoes a [2 + 2] cycloaddition with DMF to give **10**.[22] Subsequent bond reorganization via a retro [2 + 2] liberates difluorocarbonyl **11** to produce **8**. We were unable to detect carbonyl difluoride in the reaction mixture presumably due to its volatility[23] or reactivity.[24] However, upon reaction of tridecafluorooctanoic acid[25] **12** with 1 equiv of $POCl_3$ in DMF at 60−85 °C, the vinamidinium **8** was obtained in 20% assay yield[26] and perfluorohexanoic acid **16** was observed by LCMS and ^{19}F NMR spectroscopy.[27]

Scheme 4. Conversion of Perfluorooctanoic Acid **12** to Perfluorohexanoic Acid **16**



This intriguing mechanistic departure from the expected reactivity suggests that two key parameters are the concentration of Vilsmeier reagent and the reaction temperature. At high concentrations of Vilsmeier reagent and low temperatures, the enamine **7** is converted to **3c**. The small amount of **1** observed in the synthesis of **3c** is likely the result of the exotherm produced upon rapid addition of $POCl_3$ to DMF. After reaction at 85 °C, the bis-hexafluorophosphate **1d** may be isolated in 67% yield, although the process clearly remains to be optimized in order to maximize recovery.[28]

(13) ReactIR 4000, ASI Mettler Toledo. Please note that etching of the IR probe was observed during this study.

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(15) Xiao, L.; Kitazume, T. *J. Fluor. Chem.* **1997**, *86*, 99.

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(19) The exact identity of all the counteranions produced in the reaction is unclear, although PF_6^- is clearly a major component by NMR (^{19}F NMR (376 MHz, CD_3CN) δ −73.3 (d, J = 709 Hz). Quench into excess $NaBF_4$ leads to 1:1 salt **1e**.

(20) Mannich reaction of 1,4-diazapenium has been noted: Mohrle, H.; von der Lieck-Waldheim, U. *Z. Naturforsch. Sect. B* **1996**, *51*, 421.

(21) Use of fluoride abstracting agents at, e.g., AgOAc, AgOTf, TMSCl and BF_3, did not improve the yield of **8** substantially.

(22) A [2 + 2] cycloaddition of DMF and $F_2C{=}C(CF_3)C(O)F$ liberating carbonyldifluoride and $Me_2NC(H){=}C(CF_3)C(O)F$ has been reported: England, D. C.; Solomon, L.; Krespan, C. G. *J. Fluor. Chem.* **1973**, *3*, 63. For additional [2 + 2] reactions of fluoro-olefins and DMF with the extrusion of carbonyldifluoride, see: England, D. C. *Angew. Chem., Intl. Ed. Engl.* **1973,** *12*, 1023.

(23) Bp −83 °C. Franz, R. *J. Fluor. Chem.* **1980**, *15*, 423.

(24) Carbonyldifluoride reacts with DMF to give difluoromethylamine in 80% yield: Brauer, D. J.; Buerger, H.; Grunwald, M.; Pawelke, G.; Wilke, J. *Z. Anorg. Allg. Chem.* **1986**, *537*, 63.

(25) Achilefu, S.; Mansuy, L.; Selve, C.; Thiebaut, S. *J. Fluor. Chem.* **1995**, *70*, 19.

(26) Dication **1** is also observed in ∼10% yield.

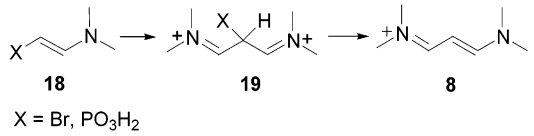
(27) The identity of the undecafluorohexanoic acid **16** was confirmed by comparison with an authentic sample obtained from TCI.

(28) To a solution of trifluoropropanoic acid (5.3 g, 0.041 mol) in DMF (50 mL) at 60 °C was added $POCl_3$ over 15 min while maintaining the temperature below 65 °C. After the addition was complete, the mixture was heated to 75 °C and $POCl_3$ (6 mL, 0.05 mol) was added while maintaining the temperature below 85 °C. The mixture was heated for 6 h and cooled. The dark red DMF solution was added to a solution of sodium hexafluorophosphate (9.2 g, 0.06 mol) in water (100 mL) while maintaining the temperature below 15 °C. The slurry was aged for 30 min at 5−10 °C, filtered washing with 5:1 water/DMF, and dried to give **1d** as an off-white solid (13.2 g, 67%): DSC, peak 212.3 °C ^1H NMR (400 MHz CD_3CN) δ 8.02 (1H, s), 3.53 (3H, s), 2.89 (3H, s); ^{13}C NMR (100 MHz CD_3CN) δ 165.7, 92.1, 50.5, 44.6; ^{19}F NMR (376 MHz, CD_3CN) δ −73.3 (d, J = 709 Hz). Anal. Calcd for $C_{10}H_{21}F_{12}N_3P_2$: C, 25.38; H, 4.47; N, 8.88; P, 13.09. Combustion analysis found: C, 25.50; H, 4.33. ICP-AES analysis, found: P, 12.86. Compound **1e** was prepared analogously using sodium tetrafluoroborate: colorless solid; DSC, peak 216.0 °C; ^1H NMR (400 MHz CD_3CN) δ 8.05 (1H, s), 3.51 (3H, s), 2.89 (3H, s); ^{13}C NMR (100 MHz

Finally, the work on the mechanism presented here allows us to provide a framework for understanding the formation of dimethylaminomethylene salts **1a**−**d** from bromoacetic and phosphonoacetic acids. Reaction of either bromoacetic or phosphonoacetic acid with $POCl_3$ in DMF generates the enamine **18**. Subsequent reaction with Vilsmeier gives the bis-iminium **19**, which is analogous to the intermediates produced in the HI reduction of chlorovinamidinium salts (Scheme 5).[29] Nucleophilic attack at bromine or phosphorus releases the unsubstituted vinamidinium **8**. This in agreement with the report that the unsubstituted vinamidinium **8** has been observed in reaction mixtures obtained from phosphonoacetic acid.[1]

In summary, we have identified all the key intermediates on the reaction pathway in the formation of the vinamidinium salts from trifluoropropanoic acid and reported an example of productive C−F activation. We are currently examining the scope of this [2 + 2] cycloaddition reaction with additional formamides.

Scheme 5



Supporting Information Available: Kinetic plot of rate data generated from the ReactIR data and Raman data for the conversion of acid chloride **4** to enamine **7** and the experimental procedure for the formylation of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CD_3CN) δ 165.7, 92.1, 50.5, 44.6; ^{19}F NMR (376 MHz, CD_3CN) δ −73.2 (d, J = 709 Hz), −151.8. Anal. Calcd for $C_{10}H_{21}BF_{10}N_3P$: C, 28.94; H, 5.10; N, 10.12; B, 2.60; P, 7.46. Combustion analysis, found: C, 28.92; H, 4.94; N, 9.95; ICP-AES analysis, found: B, 3.04; P, 6.96.

(29) Davies, I. W.; Taylor, M.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2000**, *2*, 3385. For analogous reactions in the 1,4-diazapenium series, see: Lloyd, D.; McNab, H. *Adv. Het. Chem.* **1993**, *56*, 1. The timing of events may involve generation of the bromovinamidinium followed by subsequent reprotonation to give **19**.