Tetrahedron Letters Vol. 21, pp 1027 - 1030 0040-4039/80/0308-1027$02.00/0

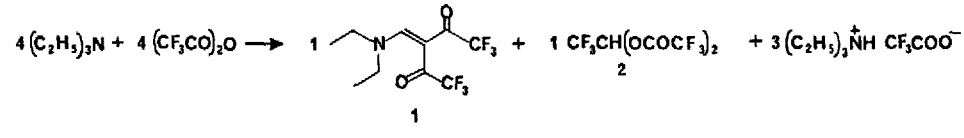
HYDROGEN TRANSFER FROM TERTIARY AMINES TO TRIFLUOROACETIC ANHYDRIDE*

Stuart L. Schreiber

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Summary: Tertiary amines are found to be oxidized by trifluoroacetic anhydride (TFAA). A discussion of the mechanism is given.

Hydrogen transfer reactions of amines have found broad synthetic utility[1,2] and are of paramount importance in biochemical redox processes involving the coenzyme NADH.[3] Although a tertiary amine and an anhydride have been employed in a variety of synthetic transformations, there have been no reports of redox chemistry occurring between them. That an anhydride could act as a hydride acceptor from an amine would be of significance both in synthesis and in the area of biochemical redox processes. We now report the novel oxidation and subsequent reactions of several tertiary amines upon treatment with trifluoroacetic anhydride (TFAA).



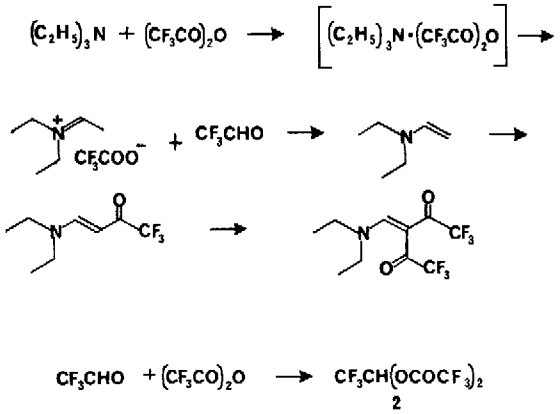
1

Following the precedent set by numerous examples of acetylations achieved under standard conditions, we attempted to trifluoroacetylate a substrate using Et_3N and TFAA. We were startled to find an unexpected and remarkable reaction had occurred in which the Et_3N had been quantitatively converted into the adduct 1 (25%), and $Et_3NH^+ CF_3CO_2^-$ (75%). A variety of solvents that are not reactive with the starting materials are suitable for the reaction. The spectral properties of 1 are fully consistent with the proposed structure.[4] In an effort to find conditions where complete conversion of Et_3N into 1 could be achieved, the use of an additional base to recycle the ammonium salt was explored. It was found that when Et_3N was treated with excess TFAA in Et_2O in the presence of NaH, complete conversion into the adduct 1 was achieved (91% isolated yield).

The formation of 1 is envisioned as occurring via the path outlined in Scheme 1. The amine and the anhydride react rapidly to form what could be either an acyl ammonium species or a charge transfer complex. Hydrogen transfer follows leading to an imminium salt and either trifluoroacetaldehyde (fluoral) or a precursor to the acyloxy acetal of fluoral (vide infra). Under the reaction conditions acyloxy acetal formation of fluoral occurs, while the

*Dedicated to the late Professor Robert Burns Woodward in grateful recognition and deepest admiration for his pervasive contribution of example, inspiration, and support.

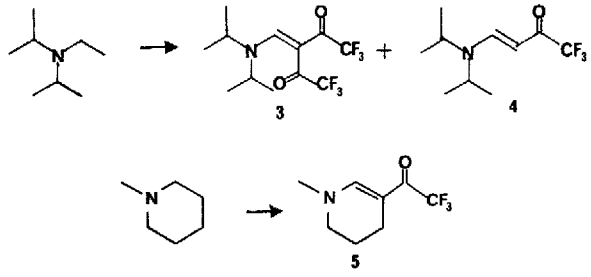
Scheme 1



imminium salt undergoes enamine formation followed by acylation. The sequence generates three molecules of CF_3CO_2H which explains the 75% yield of Et_3NH^+ $CF_3CO_2^-$.

The mechanism is supported by the isolation of the trifluoroacyloxy acetal of fluoral, 2, formed in an equivalent amount with 1. The ^1H NMR of 2 displayed a quartet at 7.2 δ (J=3.5 Hz.)[5,6] which collapsed to a singlet upon ^{19}F decoupling. In the subsequent reactions of other amines with TFAA the adduct 2 could always be detected when redox occurred.

The reaction of TFAA with several tertiary amines with different alkyl substituents was investigated in order to determine the direction of oxidation. When $(iPr)_2NEt$ was treated with 0.25 equivalents of TFAA at 0° in CH_2Cl_2 a rapid reaction followed forming 3 and 4 in a 5:1 ratio (93% based on recovered amine). With one equivalent of TFAA 3 was isolated in 25% yield as the sole oxidation product along with a 75% yield of $(iPr)_2EtNH^+$ $CF_3CO_2^-$. No oxidation towards the isopropyl group could be detected.

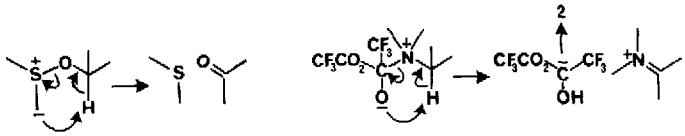


A slower reaction occurred when N-methylpiperidine was treated with an equimolar amount of TFAA. The sole oxidation product was determined to be 5 isolated in 32% yield (96% based on recovered amine) along with a 67% yield of N-methylpiperidinium trifluoroacetate.

The reaction of $(iPr)_2NMe$ with TFAA led to a complex mixture of products including the fluoral acetal 2. The presence of 2 indicated hydrogen transfer had occurred; the amine oxidation products, however, could not be fully characterized.[7]

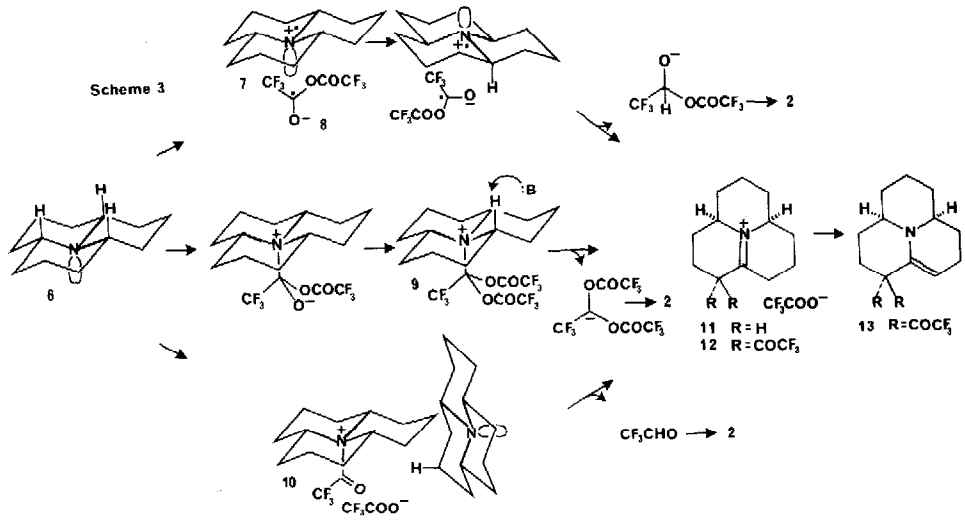
The reaction of tricyclic amine 6[8] with TFAA was a particularly interesting case since the lone pair on Nitrogen is held rigidly on the opposite side of the molecule with the three equivalent αH, and in an antiperiplanar fashion. If the transfer of hydrogen occurred from an addition adduct of TFAA in a cyclic intramolecular fashion, the amine, 6, should not be susceptible to oxidation by TFAA. An example would be a mechanism analogous to that proposed for the Moffatt oxidation of alcohols[9] (Scheme 2).

Scheme 2



However, 6 was found to yield the fluoral acetal 2 and the imminium salt 12, which upon basic workup and bulb to bulb distillation led to the enamine 13[10] (85°/1 hr./$CHCl_3$/48% yield based on recovered 6).

Scheme 3



Presumably 12 derives from the initial oxidation product 11 by deprotonation of 11 and two subsequent acylations by TFAA. Several possibilities to explain hydrogen transfer from the amine 6 to TFAA to yield 11 and 2 are outlined in Scheme 3. The amine could transfer an electron to TFAA to give the radical ion pair 7 and 8. Only after rotation of the amine radical cation can a proton and an electron be transferred to complete the redox step.[11] Alternatively, hydrogen transfer could occur by elimination of a proton and the anion of 2 from the intermediate 9 and subsequent proton transfer to form 2. A third possibility exists that a molecule of amine could donate a hydride to an acyl ammonium adduct 10 directly. An examination of molecular models indicates extreme steric hindrance in this process, however, and is therefore deemed unlikely.[12]

Acknowledgements: The author is indebted to Professor R. B. Woodward for his generous support (National Science Foundation Grant No. CHE-7825699) and guidance. Additional financial assistance provided by an NIH Training Grant is gratefully acknowledged.

References and Notes

1. Tertiary amines have been oxidized by a variety of reagents, see for instance: (a) Broaddus C.D.; Damico, R. J. Org. Chem. 1966, 31, 1607-1612; (b) Klitz, H.; Volz, H. Justus Liebigs Ann. Chem. 1971, 752, 86-101; (c) Meerwein, H.; Hederich, V.; Morschel, H.; Wunderlich, K. ibid. 1960, 635, 1-21; (d)Horner, L.; Nickel, ibid. 1957, 597, 20-47; (e) Leonard, N.J.; Hauck, F.P. J. Am. Chem. Soc. 1957, 79, 5279-5292; (f) Jones, L.W.; Whalen, H.F. ibid. 1925, 46, 1343-1352.

2. For a recent review of the formation and uses of amine oxidation products see: Bohme, H.; Viehe, H.G. "Imminium Salts in Organic Chemistry"; Vol. 9, Pt. 1 and 2; John Wiley and Sons; New York, N.Y.; 1976.

3. For a review: Boyer, P.D., Ed., "The Enzymes", Vol. XI; Academis Press; New York; 1975.

4. ^{1}H NMR (δ, $CDCl_3$, Me_4Si standard): 7.63 (1H, s) 3.60 (2H, q, J=7 Hz.), 3.25 (2H, q, J=7 Hz.), 1.40 (3H, t, J=7 Hz.), 1.15 (3H, t, J=7 Hz.); ^{13}C NMR (δ, $CDCl_3$, standard): 180.4 (q , J_{C-F}=35.3 Hz.), 156.9 (d), 116.8 (q, J_{C-F}=290.8 Hz.), 101.4 (s), 55.1 (t), 47.0 (t), 14.7 (q), 10.8 (q); IR 1690, 1645, 1595 cm^{-1}; UV λ_{max}=284 nm, ε_{max}=23,000; MS m/e (rel %): 291 (56), 222 (100); Anal. ($C_{10}F_6H_{11}NO_2$) C,H,N.

5. Overman has reported the ^{1}H NMR spectra of fluoral adducts with alcohols ($ROCHOH(CF_3)$). The fluoral methine proton appears as a quartet, J(F-H) = 3.5 Hz.: Overman L.E.; Cambell, C.B. J. Org. Chem. 1974, 39, 1474-1481.

6. When TEA is treated with CF_3COCl in $CDCl_3$, a similar redox reaction occurs, and a ^{1}H NMR signal at 6.65δ (quartet, J = 3.5 Hz.) is observed in place of the signal at 7.2δ in the TFAA reaction. This is consistent with the formation of the related fluoral derivative $CF_3CH(Cl)OCOCF_3$, although this compound was not isolated.

7. Marquet has reported difficulties in the attempted formation of $(iPr)_2\overset{+}{N}=CH_2$ $CF_3CO_2^-$ by a different route: Jasor, Y.; Luche, M.J.; Marquet, A. J. Chem. Soc., Chem. Commun. 1974, 253-254.

8. Compelling evidence for the stereochemistry of 6 has been described by Mueller: DiPardo, R.M.; Mueller, R.H. J. Chem. Soc., Chem. Commun. 1975, 565-566. We appreciate receiving an experimental procedure for the synthesis of 6 from Prof. Mueller.

9. Fenslau, A.H.; Moffatt, J.G. J. Am. Chem. Soc. 1966, 88, 1762-1765.

10. The imminium salt was detected by ^{1}H NMR and isolated and fully characterized in the form of its enamine 13.

11. Alternatively,two radical ion pair species could transfer a H^+ and an electron in an "intermolecular" process, or the amine 6 could deprotonate 7 and subsequently transfer the proton to 8.

12. A referee has pointed out another possible mechanism is a direct one step hydride transfer from the amine to TFAA.

(Received in USA 28 November 1979)