BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 3024—3026 (1969)

Studies on Heterocyclic Chemistry. IV.[1] Preparation of Several Trifluoromethyl-substituted Heterocyclic Compounds and Observation of Metastable Ion in the Mass Spectra of Trifluoromethyl-pyrazoles

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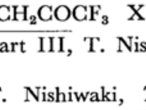
(Received April 11, 1969)

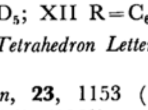
From a continued interest in mass spectrometry of heterocyclic compounds,[2,3] the preparation of trifluoromethyl-substituted heterocyclic compounds and determination of their mass spectra were considered. As it is known that trifluoromethyl-substituted benzene compounds eliminate CF_2 radical during a series of their electron-impact-induced decompositions,[4] it seemed interesting to see if this behaviour also holds for heterocyclic compounds.

Trifluoromethyl-pyrimidines (I, II, IV, V, VI) and trifluoromethyl-pyrazoles*[1] (VII, IX, X) were prepared by standard procedures. New *β*-diketones (XI, XII) which are their precursors were obtained according to Reid and Calvin.[5] Fluorine analysis of XII was not sufficient to be recorded here, but its authenticity is established by its transformation into VI and IX.

Contrary to expectation, the spectra of the examined compounds (I, II, IV, VII, IX, X), where the molecular ion (M^+) is the base peak, have not the $(M-CF_2)^+$ ion at all, which is in line with the observation on trifluoromethylpyridines.[6]



I R=Me
II R=Ph
III $R=C_6D_5$
IV R=2-Thienyl
V R=2-Furyl
VI $R=C_6H_4Me$-*p*



VII R=Ph
VIII $R=C_6D_5$
IX $R=C_6H_4Me$-*p*
X R=2-Thienyl

$RCOCH_2COCF_3$ XI $R=C_6D_5$; XII $R=C_6H_4Me$-*p*

It appears that loss of CF_2 radical from M^+ or its fragment ions takes place only in the benzene compounds. All of them have ions $(M-F)^+$, $(M-CF_3)^+$, and CF_3^+ as expected, and the fragmentation of the present pyrimidines can be nicely explained after the established patterns,[2,7] namely, loss of F and HF from M^+ competing with the elimination of HCN for I, or elimination of HF occurring after the loss of H from M^+ for II*[2] and IV as supported by an appropriate metastable ion.

However, the pyrazole compounds (VII and X) have an interesting ion at (M-48) (Table). A low-intensity metastable ion observed in both spectra (*ca.* *m/e* 127 for VII and *ca.* *m/e* 132.5 for X) suggests that this might be generated in one step. An *m/e* 164 ion observed for VII shifts to *m/e* 169 for its pentadeuteriated analogue (VIII), where a metastable ion can be seen at *ca.* *m/e* 131.5, revealing no participation of benzene hydrogens in the lost 48 masses, and, further, retention of a phenyl group in the (M-48). Among several possible ion compositions to fulfill the *m/e* 48, N_2HF is the only rational one to agree with the observed labeling data. Further, exact mass measurements could establish the lost entity to be solely N_2HF for X. A metastable ion correspond-

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[1] Part III, T. Nishiwaki, *Tetrahedron Letters*, **1969**, 2049.

[2] T. Nishiwaki, *Tetrahedron*, **23**, 1153 (1967).

[3] T. Nishiwaki, *ibid.*, **25**, 747 (1969).

[4] H. Budzikiewicz, C. Djerassi and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco (1967), p. 441.

*[1] Structures of the pyrazoles are written without implication on tautomerism.

[5] J. Reid and M. Calvin, *J. Am. Chem. Soc.*, **72**, 2948 (1950).

[6] Y. Kobayashi, F. Nakano and E. Chinen, *Chem. Pharm. Bull. (Tokyo)*, **15**, 1901 (1967).

[7] J. M. Rice, G. O. Dudek and M. Barber, *J. Am. Chem. Soc.*, **87**, 4569 (1965).

*[2] As previously shown,[2] labeling data can establish that the lost hydrogen from M^+ originates from the benzene hydrogens. But the structure of the resulting ion is not considered to be as simple as that suggested for the (M-1) of phenylphthalazine.[8] The fact that 2-amino-4-phenyl-6-methylpyrimidine shows a very intense(M-1),[2] while 4-phenyl-6-methylpyrimidine does not,[9] suggests this fragmentation to be closely associated with the presence of a functional group, at which the collapse of M^+ starts. It is likely that the pyrimidine ring has already lost its identity in the (M-1) ion.

[8] J. H. Bowie, T. G. Cooks, P. F. Donaghue, J. A. Halleday and H. J. Rodda, *Aust. J. Chem.*, **20**, 2677 (1967).

[9] T. Kato, H. Yamanaka, T. Chiba, K. Ichikawa, S. Sasaki and E. Abe, Abstracts of the 4th Symposium on the Mass Spectrometry of Organic Compounds, Nagoya (1968), p. 51.

TABLE 1. PARTIAL MASS SPECTRA OF I, II, IV, VII, IX, AND X[a)]

	M–F	M–CF_3	CF_3	M–N_2HF	M–N_2H
I	10	22	12	—	—
II	6	3	4	—	—
IV	7	2	13	—	—
VII	8	34	7	22	6
IX[b)]	45	62	—[c)]	23[d)]	17[e)]
X	7	8	19	28	3[g)]

a) Intensity is relative to the base peak. b) The spectrum (70 eV) was taken with a CEC-110-B spectrometer by a direct insertion procedure. c) Omitted from tabulation. d) Found: 178.059. Calcd for $C_{11}H_8F_2$: 178.060. e) Found: 197.058. Calcd for $C_{11}H_8F_3$: 197.058. f) Found: 169.996. Calcd for $C_8H_4F_2S$: 170.000. g) Found: 188.997. Calcd for $C_8H_4F_3S$: 188.999.

ing to the process $M^+ \rightarrow (M-48)^+$ was not well discerned in the spectrum of IX, which is probably due to its being recorded on a photographic plate, but the *m/e* 178 was exactly $(M-N_2HF)^+$.

One step loss of N_2HF from M^+, which does not exist as a structural entity in the original molecule, is rather surprising unless there operates a fluorine migration to a remote N_2H group. Fluorine shift can not necessarily be ruled out.[10)] However, the $(M-F)^+$ and $(M-N_2H)^+$ ions are found in all spectra of VII, IX, and X, although metastable ions for the process $(M-F)^+ \rightarrow (M-N_2HF)^+$ and $(M-N_2H)^+ \rightarrow (M-N_2HF)^+$ are entirely absent. The most reasonable explanation is that loss of F and N_2H from M^+ is a slow step, both of the resulting ions $(M-F)^+$ and $(M-N_2H)^+$ rapidly lead to the $(M-N_2HF)^+$. The overall result thus appears to be one-step elimination of N_2HF with an accompanying metastable ion. Similar observations have been described recently.[11–13)]

Experimental

Mass spectra were determined with a Hitachi RMU 6D mass spectrometer fitted with an all glass inlet system: ionization energy, 80 eV; total ion currents, 80 μA; ion source and inlet system temperature, 200°C. Exact mass measurements were carried out with a CEC-110-B spectrometer at 70 eV on a photographic plate. d_6-Benzene (99% isotopic purity) was purchased from Chiba Product.

Preparation of the Pyrimidines. The preparation of II is given as an example. Benzoyltrifluoroacetone (1.08 g) and guanidine carbonate (0.5 g) were melted in an oil bath (140—150°C) for 1 hr. After cooling a solid (0.80 g) was obtained and recrystallized from *n*-heptane as colorless needles, mp 133—133.5°C.

Found: C, 55.22; H, 3.42; N, 17.30%. Calcd for $C_{11}H_8F_3N_3$: C, 55.23; 3.37; N, 17.57%.

The following compounds were prepared by a similar procedure. I, mp 129°C (from cyclohexane), (Found: C, 40.83; H, 3.77; N, 23.59%. Calcd for $C_6H_6F_3N_3$: C, 40.68; H, 3.41; N, 23.73%); IV, mp 160—160.5°C (from cyclohexane), (Found: C, 44.37; H, 2.60; N, 16.90%. Calcd for $C_9H_6F_3N_3S$: C, 44.08; H, 2.45; N, 17.14%); V, mp 148°C (from *n*-heptane), (Found: N, 18.50%. Calcd for $C_9H_6F_3N_3O$: N, 18.34%); VI, mp 171—172°C (from petroleum ether), (Found: N, 16.37%. Calcd for $C_{12}H_{10}F_3N_3$: N, 16.60%).

Preparation of the Pyrazoles. The preparation of VII is given as an example. Benzoyltrifluoroacetone (0.30 g) and hydrazine hydrate (0.8 m*l*) were heated in water (1 m*l*) for 1 hr in a boiling water bath. Precipitates (0.23 g) were recrystallized from cyclohexane as colorless rectangular plates, mp 121—123°C.

Found: N, 13.13%. Calcd for $C_{10}H_7F_3N_2$: N, 13.21%.

The following compounds were prepared by a similar procedure. IX, mp 165—166°C (from cyclohexane), (Found: N, 12.39%. Calcd for $C_{11}H_9F_3N_2$: N, 12.44%); X, mp 118—120°C (from petroleum ether), (Found: N, 12.83%. Calcd for $C_8H_5F_3N_2S$: N, 12.84%).

Compound XI. To a stirred solution of d_6-benzene (4.0 g) in carbon disulfide (20 m*l*) anhydrous aluminum chloride (15.0 g) was added, and into the gently refluxing mixture acetic anhydride (4.1 g) was added and reflux was continued for 1 hr. After removing the solvent the residue was poured into a mixture of ice and hydrochloric acid and the organic matter was extracted with ether. The ethereal solution was washed with water, 10% aqueous sodium hydroxide, and water, dried ($CaCl_2$) and distilled (bp 50—54°C/1 mmHg) to give d_5-acetophenone, 1.8 g. To a stirred mixture of sodium methoxide (0.82 g) in anhydrous ether (15 m*l*) ethyl trifluoroacetate (2.1 g) was added. Homogeneous solution resulted, into which the above acetophenone (1.8 g) was added and stirred for 2 hr at room temperature. The following day any volatile material was removed *in vacuo* and the residue was acidified with 10% sulfuric acid. Precipitates were dried under reduced pressure to give almost pure β-diketone, mp 39—41°C, 2.0 g. Undeuteriated compound had mp 39—40.5°C.[5)] Isotopic purity was d_5, 63%; d_4, 26%; d_3, 8%; d_2, 3% neglecting a small (M-1) (R.I. 2%) observed in the undeuteriated compound, where the base peak was CF_3^+. This β-diketone was condensed with hydrazine hydrate to VIII, mp 120—121°C (d_5, 68%; d_4, 27%; d_3, 4%; d_2, 1%) and

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10) P. Brown and C. Djerassi, *Angew. Chem.*, **79**, 481 (1967).

11) Ref. 4, p. 29

12) E. Caspi, J. Wicha and A. Mandelbaum, *Chem. Commun.*, **1967**, 1161.

13) F. G. Holliman, R. A. W. Johnstone and B. J. Millard, *J. Chem. Soc., C*, **1967**, 2351.

guanidine carbonate to III, mp 131°C.

p-Toluoyltrifluoroacetone (XII) was prepared by a similar procedure and had bp 96—100°C/2 mmHg, mp 43—44.5°C. Analysis indicated the presence of impurity.

I wish to thank Mr. Nobuhide Wasada, the Government Institute of Technology, Tokyo, for his help in high resolution mass spectrometry.