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DIRECT FLUORINATION OF ARYL KETONE HYDRAZONES

TIMOTHY B. PATRICK* AND PAMELA A. FLORY [1]

Department of Chemistry, Southern Illinois University,
Edwardsville, Illinois 62026 (U.S.A.)

SUMMARY

The hydrazones of benzophenone, acetophenone, and deoxybenzoin react with dilute fluorine to produce intermediate diazo compounds which react further with the fluorine or nascent hydrogen fluoride to give geminal difluoro or monofluoro derivatives respectively of the starting hydrazones. The fluorination procedure has been applied to two biological systems, 1 and 2, with their conversion to monofluoro compounds 3 and 4.

INTRODUCTION

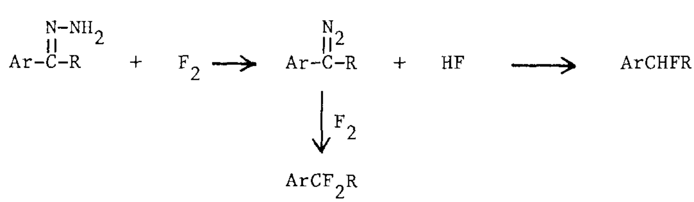
The reaction of molecular halogen or hydrogen halides with diazo alkanes has proven to be an extremely useful synthetic method for the preparation of halocarbons. The halogen is introduced selectively at the diazo function position and the reaction is fast and simple. Recently we extended the diazo halogenation method to include the reaction of diazo alkanes with dilute fluorine-nitrogen mixtures in Freon-11 solution at low temperatures to provide a useful synthetic method for construction of the geminal difluoro function [2,3].

$$R_2C{=}N_2 \quad + \quad F_2 \quad \longrightarrow \quad R_2CF_2 \quad + \quad N_2$$

DISCUSSION

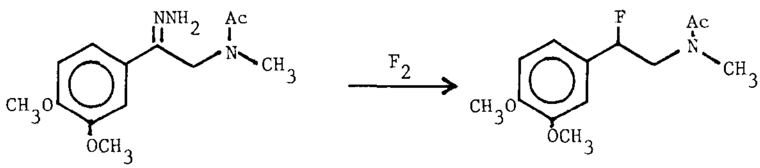
Several years ago Barton and co-workers developed a method for the preparation of geminal diiodo compounds from reaction of alkyl hydrazones with molecular iodine [4]. The reaction proceeds by initial oxidation of the hydrazone to the diazo function *in situ* followed by reaction of the diazo function with iodine to yield a geminal diiodo compound. Curiously, Barton's procedure has received only limited attention in spite of its synthetic potential [5,6,7]. Therefore we sought to apply Barton's reaction in a modified manner to the reaction of hydrazones with dilute fluorine gas. The reaction is attractive especially from the standpoint that one need not prepare and isolate a potentially unstable and sometimes expensive diazo precursor required in the usual halogenation procedure.

We have subjected several hydrazones to fluorination with 1% fluorine-nitrogen mixtures at 0-10 ^{o}C. The results are presented in Table I. The reaction of a hydrazone with fluorine produces the diazo compound and hydrogen fluoride. In the reaction of fluorine with benzophenone hydrazone we observed a purple solution which showed infrared absorption at 2210 cm^{-1} diagnostic of the diazo function [2]. The hydrogen fluoride produced reacts competitively with the fluorine gas for the diazo function and thus one obtains a mixture of both monofluoro and geminal difluoro products. The fact that the monofluoro compound predominates in some cases suggests that the close proximity of the nascent hydrogen fluoride to the diazo function permits effective competition of the hydrogen fluoride over the more reactive elemental fluorine (reaction 1).



(1)

Although a mixture of products is possible the yields are acceptable and the reaction is simple. We therefore attempted to extend the scope of the reaction to two biologically useful hydrazone substrates, 1 and 2. Noteworthy, the diazo substrates of 1 and 2 are extremely difficult to prepare.



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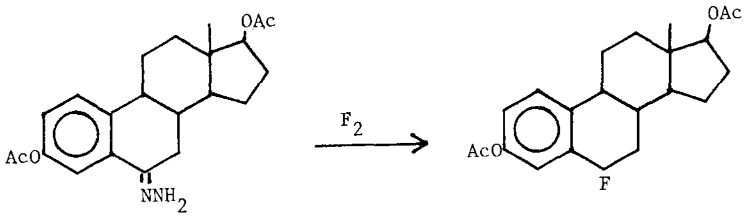
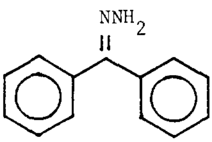
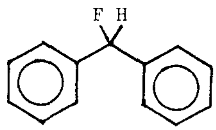
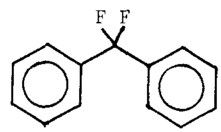
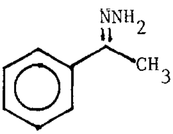
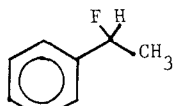
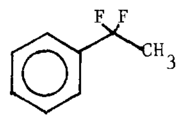
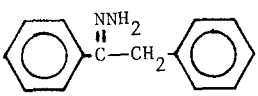
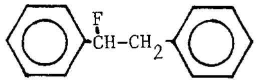
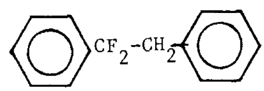


2 4

Each substrate was converted in moderate yield to the monofluoro compound, 3 and 4, respectively. The reaction mixtures were analyzed by ^{19}F NMR spectroscopy for the presence of the geminal difluoro products, but evidence for their presence was not observed. The success in obtaining products 3 and 4 demonstrates the selectivity of the reaction between the hydrazone function and fluorine in the presence of other common functional groups. The method seems limited however to aryl ketone hydrazones as we did not observe fluorinated products from the hydrazones of benzaldehyde, cyclohexanone, or cyclopentanone.

Table I

Yields of Fluorinated Products from Hydrazones[a]

Hydrazone	Monofluoro(%)	Difluoro (%)
	 Ø 171 (d) (11)	 Ø 87 (s) (69)
	 Ø 117 (m) (45)	 Ø 88 (q) (34)
	 Ø 117 (m) (45)	 Ø 93 (t) (38)

a ^{19}F NMR chemical shifts (Ø) are reported upfield from reference Freon-11 (Ø 0.0)

EXPERIMENTAL

General procedures

Temperature readings are uncorrected. ^{19}F NMR spectra were recorded in $CDCl_3$ solution with reference to internal $CFCl_3$ (Ø 0.0) on a JEOL FX-90Q spectrometer at 84.6 MHz. Fluorine gas was purchased from Air Products. Fluorine dilutions with nitrogen (1-5% F_2) were obtained by mixing the gases in a Matheson Gas fluorine apparatus. CAUTION: Fluorine gas is a strong oxidant, and all reactions must be performed in a well-ventilated area behind a shield.

Hydrazones

Benzophenone was obtained commercially and used directly without further purification. Acetophenone hydrazone and deoxybenzoin hydrazone both were obtained from heating 1.0 g of the ketone with 1.0 g of anhydrous hydrazine in 50 ml of absolute ethanol for 0.5 hr. The hydrazones were obtained in 85-95% yield with greater than 95% purity. The hydrazones were characterized by NMR and IR spectroscopy.

α-(N-Methyl-N-acetylamino)-3,4-dimethoxyacetophenone hydrazone (1)

The ketone was prepared from veratrole and aminoacetonitrile in 64% overall yield according to the procedure of Meed et al. [8]. A mixture of 0.14 g of ketone in 8 ml of anhydrous ethanol was added dropwise to 1 ml of 100% hydrazine and the mixture was heated at reflux for 20 min. The solvent was removed on a rotary evaporator to give 1 as a faint yellow oil 0.12 g (80%). ^1H NMR δ 2.2 (2,CH_3), 2.8 (s, CH_3), 3.8 (s, CH_2), 3.9 (s, two OCH_3), 7-7.9 (b, aromatic); ^{13}C NMR δ 2.3 (CH_3), 37.2 (CH_3), 53.5 (CH_2), 55.9 (OCH_3), 99-120 (aromatic) 176 (C=O), 193 (C=NNH_2); IR (neat) 3400 cm^{-1} (NH), 1700 cm^{-1} (C=O).

17-β-Estradiol-6-keto diacetate hydrazone (2)

17-β-Estradiol-6-keto diacetate was prepared in 48% yield by chromic oxide oxidation of 17-β-estradiol diacetate according to the procedure of Dean et al [9]; mp 170-172 ^oC (lit. [9] mp 173-175 ^oC). The ketone was converted to the t-butyl carbazone in 62% yield according to the procedure of Ghali et al [10]. The ^1H NMR spectrum showed the t-butyl absorption at δ 1.7. ^{13}C NMR showed the t-butyl at 28.3 (CH_3) and 82.1 (C). The t-butyl carbazone of 17-β-estradiol-6-keto diacetate (40 mg) was dissolved in 3 ml of tetrahydrofuran. Six drops of 6 M HCl were added and the mixture was heated on a steam bath for 10 min. The reaction produced a white solid and an orange solution. Evaporation of the orange solution gave 22 mg (67%) of pure 2: ^{1}H and ^{13}C NMR showed the absence of the t-butyl group; IR 3300 cm^{-1} (NH).

General fluorination procedure

The hydrazone (100-500 mg) was dissolved in 50 ml of anhydrous methanol. Dilute fluorine gas (1-5%) was bubbled into the stirred ice-cold solution until TLC chromatography showed that nearly all of the hydrazone had been consumed. The overall reaction time was 3-7 min. The reaction mixture developed an orange-red color which dissipated on further fluorination. After concentration of the reaction mixture on a rotary evaporator the fluorinated components were analyzed by ^{19}F NMR spectroscopy, followed by separation by HPLC or column chromatography.

1,1-Difluoroethylbenzene (34%); ^{19}F Ø 87.9 (q); ^{13}C NMR 50.2 (CH_3), 128-137 (aromatic and CF_2). Anal. Calcd for $C_8H_8F_2$: F 26.8. Found: F, 29.0.

1-Fluoroethylbenzene (45%); ^{19}F NMR Ø 108.1, 114.0 (two quartets, CF); Anal. Calcd for $C_8H_9F_2$: F, 15.3. Found: F, 16.1.

Difluorodiphenylmethane (69%); was identical with an authentic sample [11].

Fluorodiphenylmethane (11%); ^{19}F Ø 82 (t); Anal. Calcd for $C_{14}H_{12}F_2$: F, 17.4: Found: F, 16.7. Mass spectrum, m/e Calcd, 218. Found, m/e 218.

1-Fluoro-1,2-diphenylethane (45%); ^{19}F NMR 116, 118 (two sets of triplets) ^{13}C NMR: δ 32 (CH_2); 125-148 (aromatic and CF). Mass spectrum: m/e Calcd, 200, Found, 200. Anal. Calcd for $C_{14}H_{13}F$: F, 9.50. Found: F, 9.31.

<u>1-(N-methyl-N-acetyl)amino-2-fluoro-2-(3,4-dimethoxyphenyl)ethane (3)</u>

Hydrazone <u>1</u> (150 mg) in 50 ml of $CDCl_3$ solution was treated at 0 ^oC with dilute fluorine gas for approximately 5 min. HPLC analysis (Partisil) showed the presence of several components. Preparative HPLC (Whatman Partisil 10 Magnum, 50 cm by 9.4 cm) with 2-propanol: hexane (1.6:1) provided pure <u>3</u> (23.8 mg), mp 50-51 ^oC: ^{19}F NMR ϕ 97.4 (t), t_R 22 cm (flow 1.5 ml/min); ^1H NMR δ 2.2 (CH_3), 2.8 (s, CH_3), 3.9 (m, CH_2), 4.0, 4.1 (2, OCH_3), 5.0 (m, CH), 7-7.9 (aromatic). Mass spectrum: m/e Calcd, 255; Found, m/e 255. Anal. Calcd for $C_{13}H_{18}FNO_3$: C, 61.2; H, 7.06; F, 7.45. Found: C, 61.2; H, 7.19; F, 7.23.

<u>17-β-estradiol-6-fluoro-diacetate (4)</u>

A mixture of <u>2</u> (30 mg) in 20 ml of anhydrous methanol was subjected to the general fluorination procedure for 3 min. at 0 ^oC. Removal of the solvents under vacuum gave a black oil which was subjected to preparative tlc (chloroform: ethyl acetate (3:1)). The product was obtained from a yellow band with R_f 0.31 (11 mg); mp 109-112 ^oC. ^{19}F NMR ϕ 149 (m); ^{13}C NMR δ 12, 21, 23, 26, 27, 27.5, 29.5, 36.9, 38.2, 42.9, 44, 49.9 (singlets aliphatic) 81.6-171 (aromatic) 197, 199 (C=O), 128 (d, CF); Anal. Calcd for $C_{22}H_{27}FO_4$: C, 70.6; H, 7.21; F, 5.08. Found C, 70.4; H, 7.44; F, 4.89.

CONCLUSION

We have demonstrated that fluorination of aryl ketone hydrazones with dilute fluorine constitutes an effective and selective method for the preparation of fluorocarbon products. The method is especially attractive because the number of synthetic steps common in diazo halogenation is reduced, and one need not prepare an expensive, sensitive diazo substrate.

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REFERENCES

1 Taken in part from the M.S. thesis of Pamela A. Flory submitted to Southern Illinois University, 1983.

2 T.B. Patrick, J.J. Scheibel and G.L. Cantrell, J. Org. Chem. 46 (1981), 3917. References 2-10 of this paper contain a general literature survey for the halogenation of diazo compounds.

3. J. Leroy, and C. Wakselman, J. Chem. Soc. Perkin Trans. 1, (1978), 1224.

4 D.H.R. Barton, R.E. O'Brien and S. Sternhell, J. Chem. Soc., (1962), 470.

5 A.M. Krubiner, N. Gottfried and E.P. Oliveto, J. Org. Chem. 34 (1969), 3502.

6 E.C. Friedrich, S.N. Falling and D.E. Lyons, Syn. Commun., (1975), 33.

7 A. Pross and S. Sternhell, Aust. J. Chem. 23 (1970), 989.
A. Pross and S. Sternhell, Aust. J. Chem. 24 (1971), 1437.

8 H.D. Meed, M. Asscher, P.J. Van Draanen and H. Niewind, Recuiel Chim. Pay-Bas. 71 (1952), 933.

9 P.D.G. Dean, D. Exley and M.W. Johnson; Steroids, (1971), 595

10 N.I. Ghali, D.L. Venton, S.C. Hung, and G.C. le Breton, J. Org. Chem. 26 (1981), 5413.

11 T.B. Patrick, J.J. Scheibel, W.E. Hall and Y.H. Lee, J. Org. Chem. 45 (1980), 4492.