Journal of Fluorine Chemistry, 15 (1980) 333–337

Received: October 22, 1979

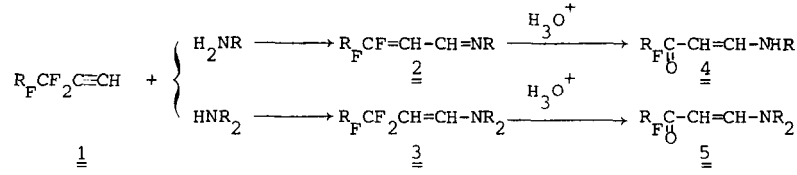
SHORT COMMUNICATION

ADDITION OF FUNCTIONAL AMINES TO *F*-ALKYLETHYNES

JACQUES GALLUCCI, MAURICE LE BLANC and JEAN G. RIESS

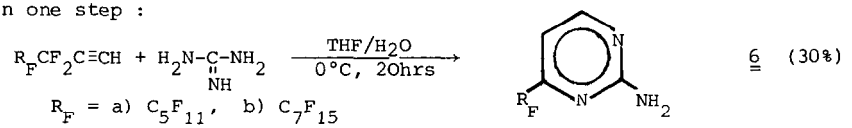
Laboratoire de Chimie Minérale Moléculaire, Equipe de Recherche Associée au CNRS, Université de Nice, Parc Valrose, 06034 NICE CEDEX (France).

Our previous work on the addition of primary [1] or secondary [2] amines on *F*-alkylethynes showed that in mild conditions the *F*-alkylenimines $\underline{2}$ or enamines $\underline{3}$ were formed respectively. Their hydrolysis affords mainly the N-mono or N,N-disubstituted *F*-alkylenaminoketones $\underline{4}$ or $\underline{5}$:



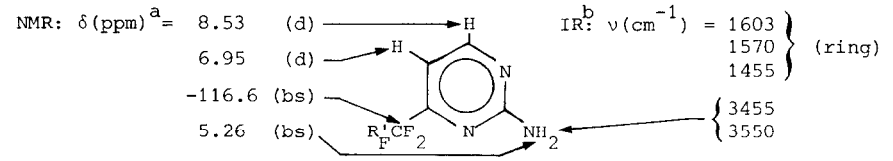
This illustrates the lability of the vinylic C-F bonds in $\underline{2}$ and the allylic C-F bonds in $\underline{3}$, which confers on these molecules a behavior quite different from that of their hydrocarbon analogues. The creation of a new site (the C-F bond) through nucleophilic addition to $\underline{1}$ prompted us to test some amines having a second function which could react with the C-F bond, thus providing a one-step synthesis of *F*-alkyl substituted nitrogen heterocycles. We report here the results obtained with guanidine and hydroxylamine.

Guanidine reacts with $\underline{1}$ to give 4-*F*-alkyl-2-amino-pyrimidines $\underline{6}$ in one step :



$\underline{6}$ (30%)

The reaction is carried out heterogenously, no solvent which simultaneously dissolves guanidine (as its carbonate) and 1 having been found. Alcohols react with 1 in the strongly alkaline conditions required to displace guanidine from its salt. The best mixture we found was THF/water, their partial solubility allowing the reaction to proceed at a reasonable rate. Crude compound 6 was isolated in 40-45% yield and was purified by recrystallisation from CCl_4 and sublimation, as a white solid. Its spectroscopic properties are summarized in the figure below :



a measured positively downfield from TMS (^1H) or CCl_3F (^{19}F) in $CDCl_3$; (d) = doublet; (bs) = broad signal.

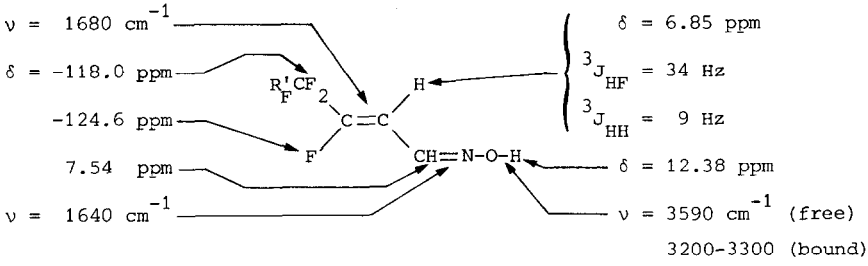
b in CCl_4.

The IR and NMR data are in agreement with those found in the literature for their hydrocarbon analogues [3][4]. The IR spectra of 6 (KBr pellets) also exhibit two combination bands [5] at 1580 and 1493 cm^{-1}. The mass spectra show the superposition of the fragmentation patterns of the pyrimidine nucleus [6][7] and of the *F*-alkyl chain [8]. The most abundant ion results from the cleavage of the *F*-alkyl chain in the β position, as always observed in *F*-alkyl substituted aromatic or heteroaromatic systems [9].

Hydroxylamine liberated *in situ* from its hydrochloride by addition of triethylamine reacts with 1 in mild conditions to give the oximes 7 as follows :

$$R_F CF_2 C{\equiv}CH + NH_2OH \xrightarrow[35°C,\,20hrs]{EtOH/Et_2O} R_F\text{-}CF{=}CH\text{-}CH{=}N\text{-}OH \quad \underline{7} \quad (60\text{-}70\%)$$

The oximes $\underline{7}$ were isolated as white solids through column chromatography on silica gel (eluent : ether/pentane 30/70) and recrystallisation from CCl_4. The NMR spectra (in DMSO d_6) are consistent with the presence of only the Z isomer :



as shown by the value of the $^3J_{HF}$ coupling constant [1]. The ^1H NMR chemical shifts are close to those of their hydrocarbon analogues [10][11].

Contrarily to guanidine, hydroxylamine reacts only on the triple bond; i.e. it behaves like a primary amine [1]. No cyclization was obtained even when $\underline{7}$ was heated with KF until decomposition occurred after 4 hrs at 90°C. These results suggest that the one-step synthesis of heterocycles from *F*-alkylethyne can only be performed if the following two requirements are fulfilled :

- sufficient basicity of the second function on the amine;
- higher stability of the cyclized form over the open chain form.

Further work on functional amines is in progress to confirm these hypotheses.

EXPERIMENTAL

The ^1H and ^{19}F NMR spectra were run on a BRUKER WH-90 spectrometer, the IR spectra on a PERKIN ELMER 577 and the mass spectra on an AEI MS-30 spectrometer.

Preparation of 2-amino 4-*F*-alkylpyrimidines 6

Guanidine carbonate (1.5 g, 8 mmol) in 8 ml of a 2M aqueous solution of NaOH is added to 150 ml of THF. Temperature is maintained between 0 and 5°C while the *F*-alkylethyne 1 (5 mmol) is added dropwise. The mixture is further stirred for 20 h at 0-5°C. After filtration and evaporation of the solvent the residue is recrystallized from CCl_4 and then sublimated to yield 6 as a white solid :

6a Yield: 30%, F: 142°C. (Found: C, 29.65; H, 1.19; F, 57.13; N, 11.52) ($C_8H_4F_{11}N_3$ requires C, 29.75; H, 1.10; F, 57.58; N, 11.57); UV (EtOH) λ_1 : 311 nm; ε_1 : 3180; λ_2 : 230.5 nm; ε_2 : 15560. Mass spectrometry ((ion): m/e; %): $(M)^+$:363;30 - $(M-F)^+$:344;8 - $(M-F-HCN)^+$:317;2 - $(M-C_4F_9)^+$:144;100 - $(M-C_4F_9-HCN)^+$:117;18 - $(M-C_5F_{11})^+$:94;90 - $(M-C_5F_{11}-HCN)^+$:67;34.

6b Yield: 32%, F: 161°C. (Found: C, 28.56; H, 0.87; F, 60.69; N, 9.45) ($C_{11}H_4F_{15}N_3$ requires C,28.51; H, 0.86; F, 61.56; N, 9.07); UV (EtOH) λ_1 : 311 nm; ε_1 : = 3220; λ_2 : 230.5 nm; ε_2 : 15730. Mass spectrometry ((ion): m/e %): $(M)^+$:463;35 - $(M-F)^+$:444;8 - $(M-F-HCN)^+$:417;2 - $(M-C_6F_{13})^+$:144;100 - $(M-C_6F_{13}-HCN)^+$:117;12 - $(M-C_7F_{15})^+$:94;44 - $(M-C_7F_{15}-HCN)^+$:67;15 .

Preparation of 3-*F*-alkyl 3-fluoro acroleinoxime 7

Triethylamine (20 mmol) is added to a solution of 1.05 g (15 mmol) of hydroxylamine hydrochloride in 50 ml of a 1/1 Et_2O/EtOH mixture. *F*-alkylethyne 1 (10 mmol) in 50 ml of solvent (Et_2O/EtOH: 1/1) is added under agitation. Temperature is raised to 40°C for 20 h. After cooling and filtration, the filtrate is poured into 300 ml of water. The aqueous phase is extracted twice with 10 ml Et_2O and the organic phases dried over molecular sieves. The solvent is removed and the residue is purified by column chromatography on silica gel (silica gel MERCK 60. Eluent ether/pentane 30/70. R_f 7 : 0.57).

7a Yield 62%, F: 65°C. (Found: C, 28.48; H, 0.90; F, 61.33) ($C_8H_3F_{12}NO$ requires C, 28.89; H, 0.84; F, 63.07); Mass spectrometry ((ion); m/e;%): M^+;357;43 - $(M-OH)^+$:340;38 - $(M-C_4F_9)^+$=$(CF_2-CF=CH-CH=NOH)^+$: 138;100 - $(M-C_4F_9-H_2O)^+$=$(CF_2CF=CH-C\equiv N)^+$;120;49.

7b Yield 70%, F: 85-87°C. (Found: C, 28.56; H, 0.87; F, 60.69) ($C_{10}H_3F_{16}NO$ requires C, 28.51; H, 0.86; F, 61.56); Mass spectrometry ((ion): m/e %): M^+;457;10 - $(M-OH)^+$:440;4 - $(CF_2-CF=CH-CH=NOH)^+$:138;100 - $(CF_2-CF=CH-C\equiv N)^+$:120;40.

REFERENCES

1 J. Gallucci, M. Le Blanc and J.G. Riess, J. Chem. Research (1978) 430.

2 M. Le Blanc, G. Santini, J. Gallucci and J.G. Riess, Tetrahedron 33 (1977) 1453.

3 A. Veillard, J. Chim. Phys. 59 (1962) 1056.

4 S. Gronowitz, B. Norrman, B. Gestblom, B. Mathiasson and R.A. Hoffmann Arkiv. for Kemi 22 (1964) 65.

5 A. Jaque Lafaix and J.M. Lebas, Spectrochim. Acta 26A (1970) 1243.

6 J.M. Rice, G.O. Dudek and A. Barber, J. Amer. Chem. Soc. 87 (1965) 4569.

7 T. Nishiwaki, Tetrahedron a) 22 (1966) 3117; b) 23 (1967) 1153.

8 J.R. Majer, Advan. Fluorine Chem. 2 (1961) 55.

9 J.L. Cotter, Org. Mass. Spectrom. 7 (1973) 11.

10 Z.W. Wolkowski, N. Thoai and J. Wiedmann, Tetrahedron Lett. (1970) 93.

11 Z. Buczkowsky and J. Plankiewicz, Bull. Acad. Pol. Sci. Ser. Sci. Chem. 18 (1970) 647.