

Preparation of Fluorinated Imidazole Derivatives Using Hexafluoro-1,2-epoxypropane

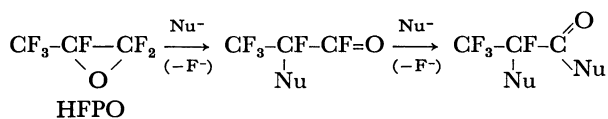
Hamdy A. HAMMOUDA† and Nobuo ISHIKAWA*

Department of Chemical Technology, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

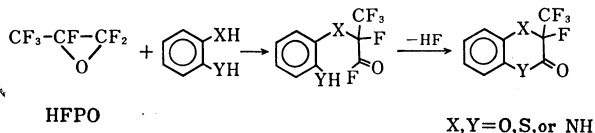
(Received April 28, 1978)

Synopsis. Utilizing the reactivity of hexafluoro-1,2-epoxypropane, several new fluorine-containing imidazole derivatives were prepared. The reactions involve 2-mercaptobenzimidazole, 2-mercapto-4,5-diphenylimidazole, 2-imidazolidinethione, and 2-aminobenzamide.

It is well known that nucleophiles readily attack the central carbon atom of hexafluoro-1,2-epoxypropane (HFPO, hexafluoropropylene oxide), resulting in the formation of α -substituted tetrafluoropropionyl fluorides, which further react with an additional molecule of the nucleophiles to form esters and amides:¹⁻³

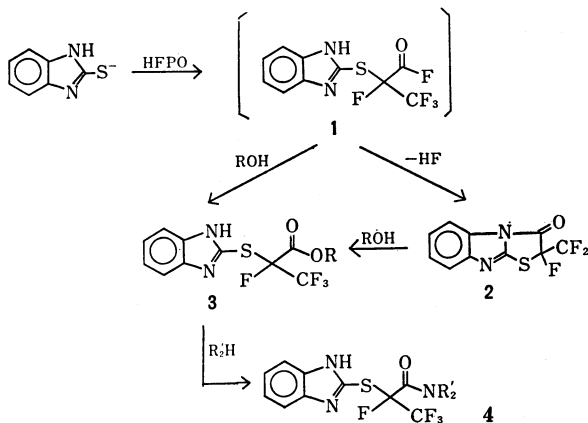


Utilizing this reactivity of HFPO, we have previously reported on the preparation of several new benzo heterocyclic compounds containing CF_3 or C_2F_5 groups by allowing it react with ortho bifunctional benzenes:⁴



This work has now been extended in order to search for more biologically active compounds; we wish here to report on the preparation of several new benzimidazole derivatives carrying a fluoroalkyl group.

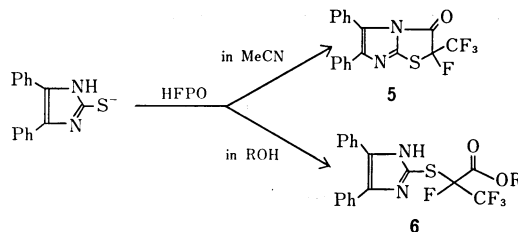
As benzimidazole derivatives with a fused thiazole ring are known to be highly interesting from the physiological point of view, we first examined the preparation of fluorine-containing compounds of this type. 2-Mercaptobenzimidazole (or, better, its sodium salt) reacted with HFPO to give the acyl fluoride, **1**, which cyclized intramolecularly in aprotic solvents, such as dioxane or acetonitrile, to afford 2,3-dihydrothiazolo-[3,2-*a*]benzimidazol-3-one (**2**):



On the other hand, when the reaction was carried out in alcohols, the acid fluoride, **1**, acylated one molecule of the solvent immediately to give the esters, **3**, in good yields. These esters were also prepared from the cyclic compound, **2**, by heating it with alcohol for a short period.

As amides are generally more hydrophilic than esters, and are biologically more useful, we prepared various amides, **4**, by the aminolysis of the esters, **3**. For example, by heating the ethyl ester **3** (R=Et) with an excess of an aqueous ammonia, the amide **4** (R=H) was precipitated. The *N*-alkylated amides were obtained from the ethyl ester by allowing it to react with an excess of the alkylamine at room temperature.

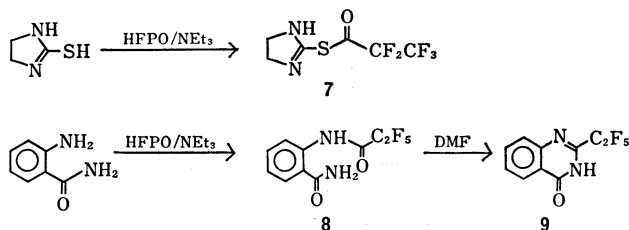
Another group of similar compounds, **5** and **6**, was obtained by the reaction of HFPO with 2-mercapto-4,5-diphenylimidazole, as is shown below:



The all of the above compounds showed two characteristic signals, a doublet and a quartet at a 3:1 ratio of intensities, in their ¹⁹F NMR spectra, thus supporting the presence of C-CF_3 group. The ¹H NMR spectra

data are also in agreement with the assigned structures (Table 1).

HFPO is known to isomerize to pentafluoropropionyl fluoride under the influence of a base such as triethylamine.⁵ We have previously reported⁶ a convenient method for the pentafluoropropionylation of amines, alcohols and thiols, which consists in allowing the nucleophile, triethylamine, and HFPO to react altogether in acetonitrile. By applying this procedure, 2-imidazolidinethione and 2-aminobenzamide were acylated to give the thioesters, **7**, and the amide, **8**,



† UNESCO Post-graduate fellow on leave from the Department of Chemistry, Cairo University, Cairo, A. R. Egypt.

TABLE 1. PHYSICAL PROPERTIES OF THE COMPOUNDS^{a)}

Compd No. (R or R')	Yield (%)	Mp °C (Solvent) ^{b)}	IR ^{c)} (cm ⁻¹)	NMR (ppm)	
				¹⁹ F	¹ H
2	55	90 (<i>n</i> -C ₆ H ₁₄)	1660(CO)	0.5(CF ₃), 70.0(CF)	7.2—8.0m(ar) ^{d)}
3 (Me)	81	155 (aq MeOH)	1762(CO)	—2.0(CF ₃), 67.0(CF)	3.8s(CH ₃), 7.1—7.7m(ar), 10.1br(NH) ^{d)}
3 (Et)	89	159 (aq EtOH)	1762(CO)	—2.0(CF ₃), 67.0(CF)	1.1t(CH ₃), 3.1br(NH), 4.2q (OCH ₂), 7.1—7.8m(ar) ^{d)}
3 (i-Pr)	77	162 (PhMe)	1750(CO)	—2.5(CF ₃), 66.0(CF)	1.23d(CH ₃), 5.0q(CH), 7.2—7.8m(ar) ^{d)}
3 (CH₂CH₂Cl)	72	117 (C ₆ H ₁₂)	1775(CO ₂ R)	—2.5(CF ₃), 67.0(CF)	3.5t(CH ₂ Cl), 4.4t(OCH ₂), 7.2—7.8m(ar) ^{d)}
4 (H)	60	197 (H ₂ O)	3400—3100(NH)	—2.5(CF ₃), 65.5(CF)	7.2—8.0m(ar), 12.2br (NH) ^{d)}
4 (H, Me)	65	214 (H ₂ O)	3325(NH), 1690(CO)	—3.8(CF ₃), 67.0(CF)	
4 (Me₂)	62	181 (H ₂ O)	3320(NH), 1690(CO)	—3.0(CF ₃), 64.0(CF)	
4 (H, Et)	67	199 (H ₂ O)	3320(NH), 1690(CO)	—4.2(CF ₃), 66.0(CF)	0.8t(CH ₃), 3.0m(CH ₂), 7.2— 7.9m(ar), 13.3br(NH) ^{d)}
5	60	115 (<i>n</i> -C ₆ H ₁₄)	1175(CO)	—4.0(CF ₃), 59.0(CF)	7.2—7.4m(ar) ^{d)}
6 (Me)	82	168 (C ₆ H ₁₂)	3325(NH), 1765(CO)	—2.5(CF ₃), 68.5(CF)	3.83s(OCH ₃), 7.2—7.6m (ar), 12.4br(NH) ^{d)}
6 (Et)	85	167 (aq EtOH)	3400(NH), 1760(CO)	—2.5(CF ₃), 67.5(CF)	
6 (i-Pr)	77	151 (C ₆ H ₁₂)	1755(CO)	—4.0(CF ₃), 65.5(CF)	
7	65	83 (<i>n</i> -C ₆ H ₁₄)	3315(NH), 1710(CO)	5.7(CF ₃), 45.2(CF ₂)	3.7s(CH ₃), 7.0br(NH) ^{e)}
8	73	145 (aq MeOH)	3425, 3200(NH), 1715, 1645(CO)	5.0(CF ₃), 44.5(CF ₂)	
9	76	205 (aq MeOH)	1680(CO), 1635(CN)	3.2(CF ₃), 38.2(CF ₂)	7.5—7.8m(ar) ^{b)}

a) The results of the elemental analysis (C, H, and N) for all compounds are in good agreement with the theoretical values. b) The solvents used for recrystallization are shown in parentheses. c) The IR spectra were taken in KBr. d) The chemical shifts of the ¹⁹F and ¹H NMR spectra are given in δ ppm upfield from external trifluoroacetic acid, and downfield from internal tetramethylsilane, respectively. The ¹⁹F NMR of **2**–**6** were run in acetone, while those of **7**–**9** were run in EtOH. The solvents used for ¹H NMR are indicated. e) In CCl₄. f) In acetone-d₆. g) In CDCl₃. h) In DMSO-d₆.

respectively. The latter compound, **8**, could be cyclized to the benzimidazole compound, 2-(pentafluoroethyl)-3,4-dihydroquinazolin-4-one (**9**), by heating it in *N,N*-dimethylformamide.

Experimental

2-Fluoro-2-(trifluoromethyl)-2,3-dihydrothiazolo[3,2-a]benzimidazole-3-one (2). HFPO (1.7 g, 0.01 mol) was bubbled into a stirred suspension of sodium 2-benzimidazolethiolate (1.7 g, 0.01 mol) in acetonitrile (20 ml) at –78 °C. The cooling bath was then removed, and stirring was continued for 4 h at room temperature using a Dry Ice condenser. The reaction mixture was filtered from a slight turbidity, and the filtrate was evaporated to dryness under a vacuum. The solid residue was dissolved in benzene and filtered from a trace of an insoluble material. The benzene was again removed, and the product was crystallized from hexane.

2-(2-Benzimidazolylthio)-2,3,3,3-tetrafluoropropionic Acid Esters (3): General Procedure. Sodium 2-mercaptobenzimidazolethiolate (0.01 mol) was stirred in the appropriate hydroxy compound. HFPO (0.01 mol) was then bubbled into the resulting, almost clear solution which was kept at –78 °C. The stirring was continued for 4 h at room temperature using a Dry Ice condenser. The reaction mixture was filtered, and the filtrate was poured into ice-cooled water. The crystalline material was collected, washed with water, and recrystallized from the proper solvent.

MS (*m/e*) for **3** (R=Et), 322 (M⁺), 277 (M⁺–OEt), 276 (M⁺–EtOH), 229 (M⁺–EtOH–CO–F), and 149 (C₆H₄–CHN₂S⁺).

2-(2-Benzimidazolylthio)-2,3,3,3-tetrafluoropropionamide (4, R'=H). The ethyl ester **3** (1 g) was stirred with a 25% aqueous ammonia (50 ml) for 2 h at room temperature. The reaction mixture was then boiled for a further 15 min and

cooled in ice, and the separated crystals were collected and recrystallized from water.

The *N*-Alkyl Derivatives (4, R'=H, alkyl). The ethyl ester **3** (1 g) was stirred with an alkylamine solution (5 ml) (40% methylamine and 70% ethylamine solutions were used) for 5 h at room temperature. The clear solution was poured onto crushed ice and slightly acidified by adding a few drops of hydrochloric acid. The crystals that separated were collected, washed with water, dried well, and recrystallized.

The *N,N*-Dialkyl Derivatives (4, R'=alkyl). The ethyl ester **3** was stirred at room temperature with dimethylamine or diethylamine (3 ml). Exothermic dissolution first took place, followed by the precipitation of a white solid. After stirring for 5 h, the reaction mixture was poured on ice-cooled water, slightly acidified by adding a few drops of hydrochloric acid. The crystals that separated were filtered off, washed with water, dried well, and recrystallized.

2-Fluoro-2-(trifluoromethyl)-5,6-diphenyl-2,3-dihydroimidazo[2,1-b]thiazol-3-one (5). Sodium 4,5-diphenyl-2-imidazolethiolate (0.01 mol) was stirred with acetonitrile (20 ml) in a pressure tube. The mixture was then cooled to –78 °C, and liquefied HFPO (0.01 mol) was introduced. Stirring was continued for 4 h. The solvent was then evaporated under a vacuum, and the solid product was crystallized from hexane.

2-(4,5-Diphenyl-2-imidazolylthio)-2,3,3,3-tetrafluoropropionic Acid Esters (6): General Procedure. Liquefied HFPO (0.01 mol) was introduced into a solution of sodium 4,5-diphenyl-2-imidazolethiolate in the appropriate hydroxy compound (20 ml) at –78 °C. Stirring at room temperature was continued for 4 h. The reaction mixture was then filtered, and the filtrate was diluted with water. The precipitated crystals were filtered off, washed with water, dried, and recrystallized.

S-(2-Imidazolin-2-yl) Pentafluoropropanethioate (7). A mixture of 2-imidazolidinethione (1.02 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) was stirred in acetonitrile (10 ml) at –78 °C. Liquefied HFPO (0.01 mol) was then introduced, and the stirring was continued for 30 min at room temperature. The reaction mixture was poured into ice-cooled water, and the crystals that separated were collected and recrystallized from hexane.

2'-Carbamoylpentafluoropropionanilide (8). 2-Aminobenzamide and HFPO were reacted in acetonitrile in the presence of triethylamine according to the procedure described above for the preparation of **7**. The product was recrystallized from aqueous methanol.

3,4-Dihydro-2-(pentafluoroethyl)quinazolin-4-one (9). The amide **8** (1 g) was refluxed in *N,N*-dimethylformamide (30 ml) for 3 h, cooled, and poured into cold water. The crystals that separated were filtered off, washed with water, dried, and recrystallized from aqueous methanol.

References

- 1) D. Sianesi, A. Pasetti, and F. Tarli, *J. Org. Chem.*, **31**, 2312 (1966).
- 2) A. Pasetti, F. Tarli, and D. Sianesi, *Gazz. Chim. Ital.*, **98**, 277, 290 (1968).
- 3) I. L. Knunyants, V. V. Shokina, and I. V. Galakhov, *Khim. Geterotsikl. Soedin.*, **1966**, 873.
- 4) N. Ishikawa and S. Sasaki, *Bull. Chem. Soc. Jpn.*, **50**, 2164 (1977).
- 5) Du Pont, Brit. Patent 1019788 (1966).
- 6) N. Ishikawa and S. Sasaki, *Nippon Kagaku Kaishi*, **1976**, 1954.