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PREPARATION OF FLUOROALKYLATED BENZOHETEROCYCLES USING F-2-METHYLPROPENE

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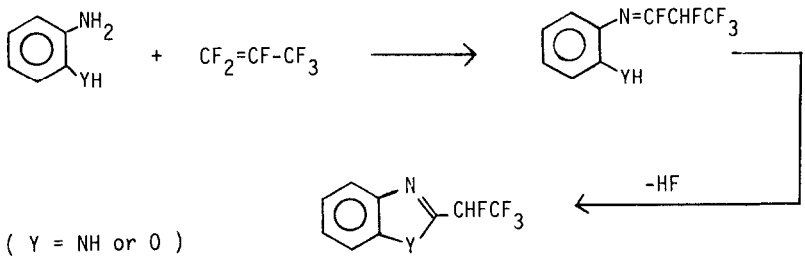
SUMMARY

Several benzoheterocyclic compounds carrying a $CH(CF_3)_2$ group were prepared by the reactions of F-2-methylpropene with ortho-bifunctional benzenes. The reactivity and reaction mode of F-2-methylpropene in these reactions were compared with those of F-propene.

INTRODUCTION

Heterocyclic compounds containing fluoroalkyl groups, especially CF_3, are highly interesting from the biomedicinal point of view [1]. A number of heterocyclic compounds containing fluoroalkyl groups other than CF_3 have been synthesized by these authors using perfluoro-olefins or their oxides [2-4].

As has been reported [2], F-propene reacts with ortho-substituted anilines such as 1,2-phenylenediamines or 2-aminophenols to produce several benzoheterocyclic compounds. This means that when an amino or hydroxyl group exists in the ortho-position of the N-arylimidoyl fluoride, hydrogen fluoride is immediately eliminated and cyclization occurs, and 2-tetrafluoroethylbenzimidazole and -benzoxazole are obtained respectively.



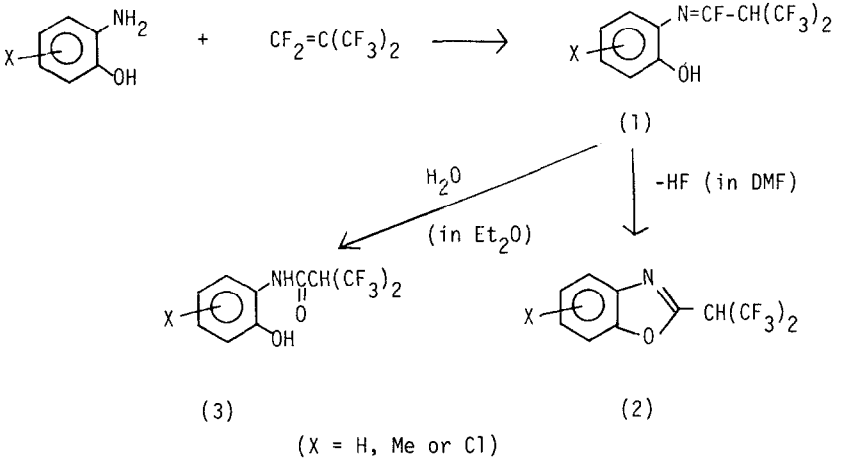
(Y = NH or O)

This work has been extended and now we wish to report on the reactions of F-2-methylpropene with ortho-bifunctional benzenes. These reactions usually gave the heterocyclic compounds similarly, but the reactivity and mode of the reactions were somewhat different from those of F-propene.

RESULTS AND DISCUSSION

The reactions of F-2-methylpropene with 2-aminophenols and with 1,2-phenylenediamines

The reaction of F-2-methylpropene with 2-aminophenol was carried out at room temperature using dimethylformamide (DMF) as solvent. Under these conditions, it proceeded similarly to the case with F-propene to give the expected 2-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]benzoxazole (2) via the highly reactive imidoyl fluoride (1). This intermediate was obtained exculsively when diethyl ether was used instead of DMF as solvent. The difference is probably due to the higher polarity of DMF, which accelerates ionic cyclization. Naturally, the imidoyl fluoride (1) reacted with water easily affording the corresponding anilide (3).



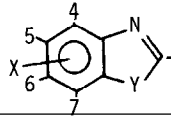
(3) (2)

(X = H, Me or Cl)

2-Amino-4 or 6-methyl, and 2-amino-4-chlorophenol reacted similarly to give 5- or 7-substituted-2-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-benzoxazoles in 86 - 95% yields (Table 1).

When 1,2-phenylenediamine or 4-chloro-1,2-phenylenediamine was allowed to react with F-2-methylpropene in DMF in a similar way, the expected

TABLE 1

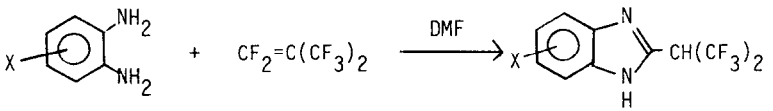
The physical properties of  $-CH(CF_3)_2$.

Compound [X, Y]	M.p. (°C)	Yield (%)	Anal. (Calcd) (%) C	H	N	IR (cm^{-1}) C-O-C	N-H	C=N	C-F	NMR ^{19}F a)	^{1}H b)	MS (M^+)
(2) [H, O]	97-98	79	44.6	1.82	5.19	1285	——	1620	1110	-12.0	4.84	269
			(44.6)	(1.87)	(5.20)				1160		(sept)	
(2) [5-Me, O]	90-91	95	46.6	2.50	4.93	1280	——	1610	1110	-12.0		
			(46.7)	(2.49)	(4.95)				1160			
(2) [7-Me, O]	135-136	87	45.8	2.44	4.96	1285	——	1610	1110	-12.3		
			(46.7)	(2.49)	(4.95)				1160			
(2) [5-Cl, O]	91-92	86	39.1	1.27	4.80	1280	——	1610	1110	-12.7		
			(39.6)	(1.33)	(4.61)				1160			
(4) [H, NH]	185-186 (dec)	68	45.5	2.38	10.3	——	2600	1625	1125	-11.0	5.61	268
			(44.8)	(2.26)	(10.5)		-3100		1220		(sept)	
(4) [5 or 6-Cl, NH]	178 (dec)	83	39.5	1.61	9.50	——	2700	1620	1155	-11.8		
			(39.7)	(1.67)	(9.26)		-3200		1230			
(8) [H, S]	102	22	42.1	1.76	4.85	——	——	1610	1095	-12.0	5.86	285
			(42.1)	(1.77)	(4.91)				1145		(sept)	
(8) [5-Cl, S]	136-137	74	37.9	1.26	4.43	——	——	1610	1100	-12.3		
			(37.6)	(1.26)	(4.38)				1150			

a) Chemical shifts are given in δ ppm upfield from ext. CF_3CO_2H, using acetone as solvent.

b) Chemical shifts for $C\underline{H}(CF_3)_2$ in CCl_4 are given in δ .

benzimidazole (4) was obtained in 68 and 83% yields, respectively. 4-Methyl-1,2-phenylenediamine, however, gave only unidentified tarry matter even at a low reaction temperature. It seems that the stronger basicity of this amine caused unfavorable side reactions.

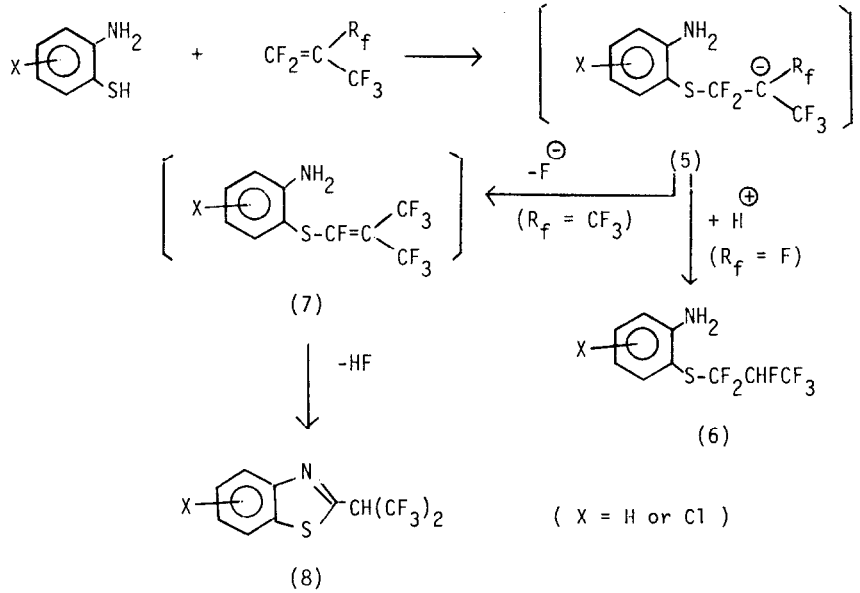


(X = H or Cl) (4)

The reactions of F-2-methylpropene with 2-aminothiophenols

In the reaction of F-2-methylpropene with 2-aminothiophenol, the reaction proceeded in a different way from that of F-propene, and different products were obtained.

From the reaction of 2-aminothiophenol with F-propene, only an adduct (6) of thiol with the perfluoro-olefin was formed and no cyclized products were obtained [2]. In contrast, F-2-methylpropene afforded a cyclized benzothiazole compound (8) in a good yield.



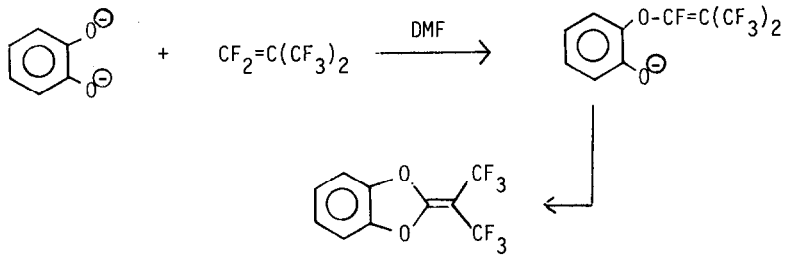
(X = H or Cl)

(8)

These results can be interpreted in terms of the different stabilities of the intermediate carbanion (5). When R_f is F, the carbanion (5) is rather unstable due to the electronic repulsion between unshared electron pairs of the anionic carbon and the adjacent fluorine atom. This will cause the carbanion to be attacked by a proton, immediately giving (6). On the other hand, when R_f is CF_3, the negative charge will be delocalized giving a stable carbanion, which will then be led to an olefin (7) by elimination of fluoride ion [5]. Although (7) was not isolated, it must have cyclized immediately to form a benzothiazole (8). Even with a less basic aminothiophenol, such as 2-amino-4-chlorothiophenol, F-2-methylpropene reacted similarly to give chlorobenzothiazole in a good yield (Table 1).

Reaction of F-2-methylpropene with 1,2-benzenediol

Even with benzenediol, in the form of its disodium salt, F-2-methylpropene reacted smoothly in DMF, affording the cyclic compound (9). This must be due to internal nucleophilic attack by the aryloxide ion.

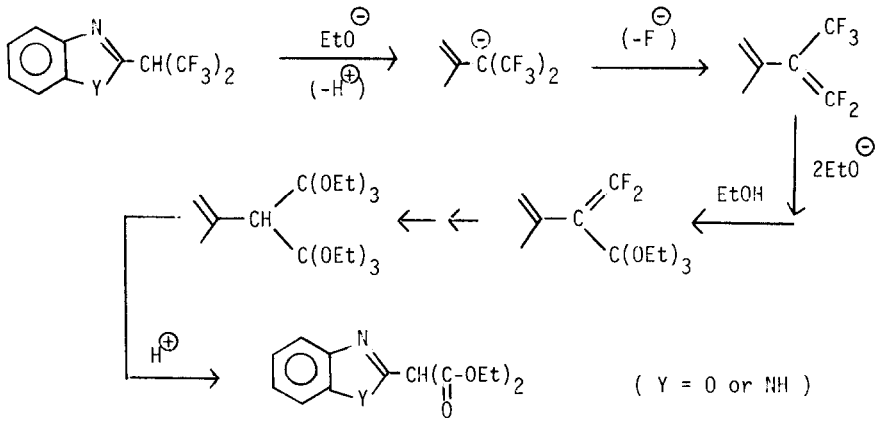


(9)

Degradation of 2-bis(trifluoromethyl)methyl benzoxazole (2) and -benzimidazole (4) by alkali

Since the hydrogen atom of a bis(trifluoromethyl)methyl group is protonic, the heterocyclic compounds prepared above were anticipated to be susceptible to attack by bases. We examined some reactions of benzoxazole (2) and benzimidazole (4) with alkalis and we found the trifluoromethyl groups in these compounds were readily degradated to carboxylic acid derivatives. Thus, when these compounds were allowed to react with sodium ethoxide in ethanol at room temperature, all of the fluorine atoms

of the $CH(CF_3)_2$ group were replaced by ethoxyl groups and diethyl malonate derivatives(10) were obtained. The reaction must have proceeded through the following scheme.



(10)

EXPERIMENTAL

The chemical shifts for ^1H and ^{19}F NMR are given in δ ppm downfield from internal tetramethylsilane and upfield from external trifluoroacetic acid respectively.

2-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]benzoxazole (2) (nc)

A solution of 2-aminophenol (2.18 g, 0.02 mol) in dried dimethylformamide (20 ml) was put into a Pyrex-glass pressure-vessel equipped with a magnetic stirrer. F-2-methylpropene (2.5 ml, 0.02 mol) was introduced into the vessel at -70 °C (mixed by allowing it to boil slowly from a calibrated cold trap) and the whole was brought to room temperature. After stirring for 5 h at that temperature, the reaction mixture was poured into water (100 ml), and resulting precipitates were collected by filtration to give (2) (X = H) (4.24 g, 79%). Recrystallization from n-hexane gave a pure product, mp 97 - 98 °C. The reaction was similarly carried out using other substituted aminophenols (see Table 1).

2-Hydroxy-[2,2,2-trifluoro-1-(trifluoromethyl)propion]anilide (3) (nc)

Instead of dimethylformamide, diethyl ether (60 ml) was used as solvent in the above reaction. When the reaction was carried out using aminophenol (3.27 g, 0.03 mol), the reaction mixture being worked up in the same way, 2-hydroxy-[2,2,2-trifluoro-1-(trifluoromethyl)propion]anilide (3) (3.99 g, 46.5%) was obtained. Recrystallization from ligroin gave pure crystals, mp 142 -143 ^{o}C (Found : C, 41.3; H, 2.42; N, 4.63; F, 39.9%. $C_{10}H_7F_6NO_2$ requires C, 41.8; H, 2.46; N, 4.88; F, 39.7%). ν_{max}: 3340 (O-H), 3230 (N-H), 1700 (C=O) cm^{-1}. NMR : ^{1}H (DMSO-d_6) : δ 5.47 (sept, J = 8.0 Hz, CH), 6.6 - 8.1 (m, Ar-H), 9.94, 10.2 (s and s, NH and OH); ^{19}F (acetone) : δ -14.0 (d, $CH(CF_3)_2$). Mass : m/e 287 (M^+), 269 (M^+-H_2O), 250 (M^+-H_2O-F).

2-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]benzimidazole (4) (nc)

A solution of 1,2-phenylenediamine (5.40 g, 0.05 mol) in dimethylformamide (50 ml) was allowed to react with F-2-methylpropene and worked up as usual. Benzimidazole (4) (X = H) (9.67 g, 68%) was obtained and recrystallized from ligroin to give pure crystals, mp 185 - 186 ^{o}C (dec.) (Table 1).

4-Chloro-1,2-phenylenediamine also reacted with F-2-methylpropene giving 5 (or 6)-chlorobenzimidazole (4) (X = Cl), mp 178 ^{o}C (dec.), whereas 4-methyl-1,2-phenylenediamine gave only black tarry matter.

2-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]benzothiazole (8) (nc)

A solution of 2-mercaptoanilinium chloride (2.94 g, 0.018 mol) in dimethylformamide (20 ml) and triethylamine (2.8 ml) was allowed to react with F-2-methylpropene and worked up as usual. As a result, 2,2'-diaminodiphenyl disulfide (1.45 g, 65%) and benzothiazole (8) (1.14 g, 22%) were obtained.

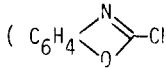
When 2-amino-4-chlorothiophenol was used, the expected chlorobenzothiazole (8) (X = Cl) was afforded in fairly good yield (74%), without formation of the disulfide (Table 1).

2-[2,2,2-Trifluoro-1-(trifluoromethyl)ethylidene]-1,3-benzo[d]dioxole (9) (nc)

Liquefied F-2-methylpropene (2.5 ml, 0.02 mol) was introduced to a mixture of disodium benzene-1,2-diolate (2.66 g, 0.017 mol) and dimethyl-

formamide (20 ml). After 5 h of stirring at room temperature, the reaction mixture was poured into water. A solid (3.86 g) was separated by filtration and recrystallized from n-hexane to give a crude product (3.36 g, 72%). Recrystallization gave pure crystals, mp 90 - 91 °C (Found : C, 44.5; H, 1.52%. $C_{10}H_4F_6O_2$ requires C, 44.5; H, 1.49%). ν_{max} : 1690 (C=C), 1225, 1010 (C-O-C), 1130 (C-F) cm^{-1}. ^{19}F NMR (neat) : δ -21.4 (s, CF_3). Mass : m/e 270 (M^+), 251 (M^+-F), 201 (M^+-CF_3).

2-[Bis(ethoxycarbonyl)methyl]benzoxazole (10) (Y = O) (nc)

A solution of benzoxazole (2) (X = H) (0.63 g, 0.0023 mol) in ethanol (10 ml) was added into an alcoholic solution of sodium ethoxide prepared from sodium metal (0.95 g, 0.04 mol) and ethanol (20 ml). After stirring overnight at room temperature, the solvent was evaporated and the residue was diluted with water, and was made acidic with hydrochloric acid. Organic material was extracted with diethyl ether to give crude (10) (Y = O) (0.31 g, 48%). Recrystallization from hexane afforded pure crystals, mp 79 - 80 °C (Found : C, 60.7; H, 5.48; N, 5.09%. $C_{14}H_{15}NO_5$ requires C, 60.6; H, 5.45; N, 5.05%) ν_{max} : 1672 (C=O), 1635 (C=O), 1608 (C=N) cm^{-1}. ^1H NMR (acetone-d_6) : δ 1.28 (t, J = 7.1 Hz, CH_3, 6H), 4.31 (q, J = 7.1 Hz, $>CH_2$, 4H), 5.37 (s, $\geq CH$, 1H), 7.3 - 7.9 (m, Ar, 4H). Mass : m/e 277 (M^+), 232 (M^+-EtO), 231 (M^+-EtOH), 159 ().

2-[Bis(ethoxycarbonyl)methyl]benzimidazole (10) (Y = NH)

Benzimidazole (4) (X = H) (0.33 g, 0.0012 mol) instead of benzoxazole (2) (X = H) was used in the above procedure, and the mixture was refluxed for 1.5 h. The whole was worked up similarly to give crude diethyl malonate derivative (10) (X = NH) (0.20 g, 59%). Pure crystals, mp 222 - 223 °C (dec.) [lit.[6]: mp 218 °C] were obtained by recrystallization from benzene (Found : C, 60.6; H, 5.94; N, 10.2%. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.84; N, 10.1%). ν_{max} : 3290 (N-H), 1630 (C=O), 1614, 1583, 1563, 1543 (C=O, C=N, or C=C) cm^{-1}. Mass : m/e 276 (M^+), 230 (M^+-EtOH).

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