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PREPARATION OF BENZOHETEROCYCLES CONTAINING A CHLOROFLUOROMETHYL GROUP USING THE 'YAROVENKO REAGENT'

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SUMMARY

ortho-Bifunctional benzenes such as 2-aminophenol, o-phenylenediamine, 2-aminothiophenol, 2-aminobenzamide and catechol reacted very easily with 2-chloro-1,1,2-trifluoroethyldiethylamine, the 'Yarovenko reagent,' affording 2-(chlorofluoromethyl)benzoxazole, -benzoimidazole, -benzothiazole, 2-(chlorofluoromethyl)-4-quinazolone and 2-diethylamino-2-(chlorofluoromethyl)dioxole respectively.

INTRODUCTION

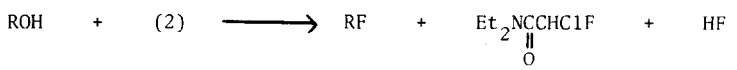
The syntheses of benzoheterocyclic compounds containing fluoroalkyl groups by reaction between *ortho*-bifunctional benzene derivatives and F-propene[1], F-2-methylpropene[2] or F-propene oxide[3,4] have been reported previously. Since these heterocyclic compounds are of interest due to their prospective bioactive properties, we have continued our work on the preparation of heterocyclic compounds using other fluoroolefins.

Regarding the reactivity of chlorotrifluoroethene (1), we found that this chlorofluoroalkene is much less reactive than perfluoroalkenes such as F-propene and F-2-methylpropene to nucleophiles. The reaction of (1) with 2-aminophenol, for instance, proceeded much slower than that of F-propene, and 2-(chlorofluoromethyl)benzoxazole was obtained only in very poor yield.

On the other hand, the adduct of (1) and diethylamine, 2-chloro-1,1,2-trifluoroethyldiethylamine (2), has been used as a fluorinating agent for alcohols [5] and is known as the "Yarovenko reagent" [6].

$$CF_2{=}CClF + Et_2NH \longrightarrow Et_2N\text{-}CF_2CHClF$$

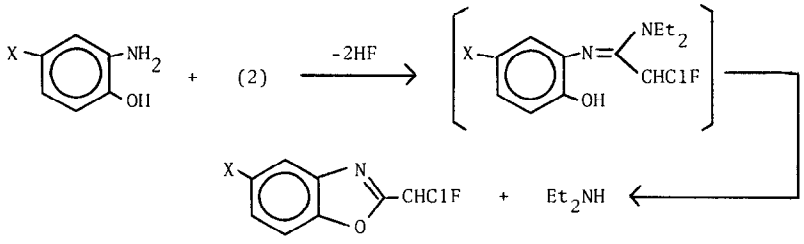
(1) (2)



Considering that this reagent might have significant reactivities towards a variety of nucleophiles other than alcohols, we examined its reaction with *ortho*-bifunctional benzenes. As a result, we have found that (2) behaves as a very effective ring-closing agent for these benzenes, giving various benzoheterocyclic compounds containing a chlorofluoromethyl group.

RESULTS AND DISCUSSION

In a series of experiments, reactions of chlorotrifluoroethene with *ortho*-bifunctional benzenes such as 2-aminophenol or o-phenylenediamine in various solvents usually gave tarry products. Attempted extraction with a variety of solvents from the product mixture did not lead to the isolation of any fluorine-containing materials. The diethylamine-chlorotrifluoroethene adduct (2), on the other hand, reacted rapidly with 2-aminophenol, for example, and 2-(chlorofluoromethyl)benzoxazole (3) (X = H) was obtained in a 75% yield. The reaction pathway is evidently as follows:



(3)

Various spectral data, especially the ^{19}F and ^{1}H nmr signals characteristic to the chlorofluoromethyl group, supported the structure of the product. The ^{19}F and ^{1}H signals appeared at δ 59.1* and δ 7.25 respectively and the coupling constant between the two nuclei was 48 Hz. In the mass spectrum the molecular ion appeared appropriately (M^+ 185).

o-Phenylenediamine reacted with (2) in a similar manner and the expected 2-(chlorofluoromethyl)benzimidazole (4) (X = H) was obtained.

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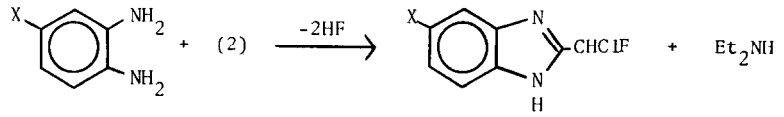
* See the 'Experimental' section.

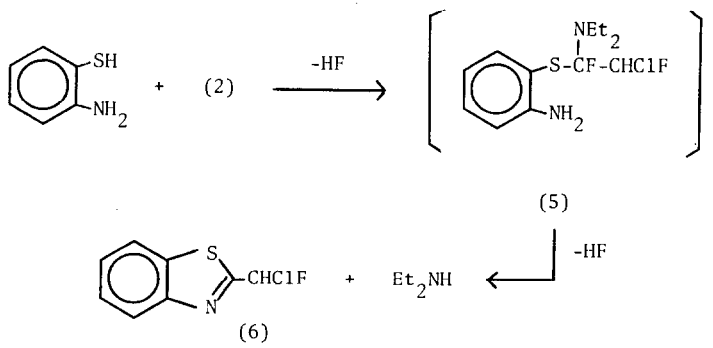


(4)

4-Substituted 2-aminophenols or o-phenylenediamines were also subjected to reaction with (2), and a number of 5-substituted benzoxazoles and benzimidazoles were obtained in good yields regardless of the electronic effects of the substituents (Table 1).

Even 2-aminothiophenol underwent thiazole ring formation by the reaction. This result is worthy of note because 2-aminophenol gave only an addition product in the reaction with F-propene with no ring-closure. The high potentiality of (2) as a reactant towards nucleophiles appears to be verified by this example.

The reaction pathway for this case seemed to be initiated by attack of the thiol group to form (5), followed by the ring closure giving (6).



The behavior of the thiol group in reacting with polyfluoroolefins faster than the amino group has previously been observed [3].

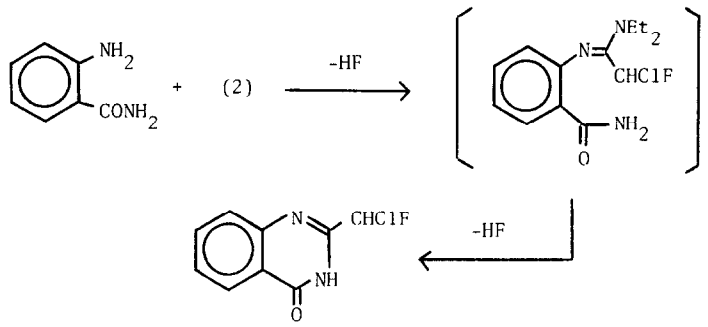
2-Aminobenzamide was reported to react with F-propene or F-2-methylpropene to give a six-membered benzoheterocyclic compound. We therefore examined the reaction of 2-aminobenzamide with (2) and obtained 2-(chlorofluoromethyl)-4-quinazolone (7). This reaction proceeded easily at room temperature, the structure of the product being elucidated from spectral data.

TABLE 1 PREPARATION AND SPECTRAL DATA OF BENZOHETEROCYCLES CONTAINING CHClF GROUP (nc)

o-Bifunctional benzene	Product	Yield (%)	Bp (°C/mm) (Mp °C)	nmr[a] for CHClF ^{19}F	^{1}H	Anal. Found (Calcd) (%) C	H	N
$C_6H_4(NH_2)OH$-2,1	(3) (X=H)	75	77-80/0.5	59.1(d)	7.25(d)	51.98	2.80	7.48
				J=48 Hz		(51.76)	(2.72)	(7.55)
4-$MeC_6H_3(NH_2)OH$-2,1	(3) (X=Me)	73	87-90/0.5	59.0(d)	7.35(d)	54.19	3.64	7.16
				J=47 Hz		(54.13)	(3.54)	(7.02)
4-$ClC_6H_3(NH_2)OH$-2,1	(3) (X=Cl)	66	97-99/3	60.5(d)	7.25(d)	44.32	2.06	6.53
				J=48 Hz		(43.65)	(1.83)	(6.37)
$C_6H_4(NH)_2$-1,2	(4) (X=H)	58	(159-160)	54.5(d)	7.43(d)	52.15	3.38	15.04
				J=48 Hz		(52.05)	(3.28)	(15.18)
4-$MeC_6H_3(NH_2)_2$-1,2	(4) (X=Me)	68	(130-132)	53.8(d)	7.38(d)	54.26	4.05	14.13
				J=48 Hz		(54.42)	(4.06)	(14.10)
4-$ClC_6H_3(NH_2)_2$-1,2	(4) (X=Cl)	50	(149.5-151)	56.0(d)	7.47(d)	43.87	2.45	12.90
				J=49 Hz		(43.87)	(2.30)	(12.79)
$C_6H_4(NH_2)SH$-2,1	(6)	66	101-102/3	54.1(d)	7.40(d)	48.02	2.58	7.01

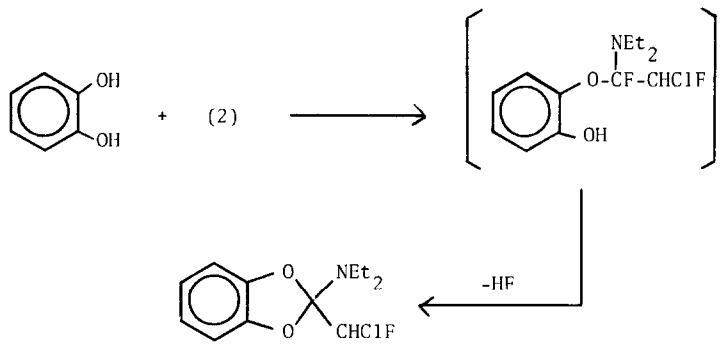
				J=50 Hz		(47.65)	(2.50)	(6.95)
$C_6H_4(NH_2)CONH_2$-2,1	(7)	79	(223-225)	65.3(d)	6.53(d)	61.42	3.49	11.55
				J=49 Hz		(61.42)	(3.44)	(11.94)
$C_6H_4(OH)_2$-1,2	(8) (X=H)	61	98-100/2	70.7(d)	6.27(d)	55.77	5.91	5.03
				J=49 Hz		(55.50)	(5.82)	(5.40)
4-$MeC_6H_3(OH)_2$-1,2	(8) (X=Me)	50	118-121/1	70.3(d)	6.19(d)	56.99	6.26	5.02
				J=48 Hz		(57.04)	(6.26)	(5.12)

a) The chemical shifts of ^{19}F and ^{1}H nmr are given in δ ppm upfield from ext. CF_3CO_2H and downfield from int. Me_4Si, respectively.



(7)

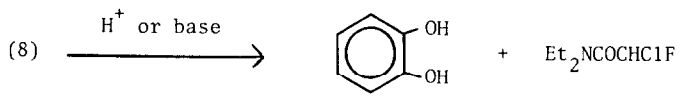
When catechol was allowed to react with (2) in dichloromethane, a benzodioxole compound (8) was obtained in 61% yield.



(8)

In the ^{19}F nmr spectrum of (8), a doublet due to CHClF appeared at 70.7 ppm, split by the gem-hydrogen atom (J_{F-H} = 49 Hz). The presence of the dicthylamino group was evident from strong signals of a triplet at δ 1.08 due to CH_3 and a quartet at δ 2.92 due to CH_2. The mass spectrum also showed the expected parent peak at m/e 247.

The compound (8) was susceptible to attack of an acid or a base, yielding catechol and N,N-diethylchlorofluoroacetamide.



EXPERIMENTAL

All ^{19}F nmr chemical shifts throughout this article are given in δ ppm upfield from external CF_3CO_2H.

2-(Chlorofluoromethyl)benzoxazole (3) (X = H) (nc)

Into a solution of 2-aminophenol (1.64 g, 15 mmol) in dichloromethane (20 ml), a mixture of 2-chloro-1,1,2-trifluoroethyldiethylamine (2) (3.03 g, 16 mmol) and dichloromethane (5 ml) was added dropwise, keeping the temperature at 0 - 5 °C. After 30 min of stirring at that temperature, the reaction mixture was poured into water and the oily material was extracted with diethyl ether. The extract was dried over magnesium sulfate, and the solvent was evaporated under vacuum. Distillation of the residue gave (3) (X = H) (2.09 g, 75%), b.p. 77 - 80 °C/ 0.5 mm.

2-(Chlorofluoromethyl)benzimidazole (4) (X = H) (nc)

o-Phenylenediamine (3.24 g, 30 mmol) and (2) (5.87 g, 31 mmol) were allowed to react in dichloromethane (20 ml) as described above. The reaction mixture was worked up and the crude product was recrystallized from n-hexane affording (4) (X = H) (3.21 g, 58%), m.p. 159 - 160 °C.

2-(Chlorofluoromethyl)benzothiazole (6) (nc)

2-Aminothiophenol (3.00 g, 24 mmol) and (2) (4.74 g, 25 mmol) were allowed to react in dichloromethane (20 ml) at 0 - 5 °C for 10 min. After the usual workup, the crude product was subjected to distillation, affording (6) (3.19 g, 66%), b.p. 101 - 102 °C/ 3 mm.

2-(Chlorofluoromethyl)-4-quinazolone (7) (nc)

A mixture of 2-aminobenzamide (3.80 g, 28 mmol) and (2) (5.50 g, 29 mmol) in dichloromethane (20 ml) was stirred for 3 h at room temperature. The reaction mixture was worked up as usual and the crude product was recrystallized from methanol, giving (7) (4.70 g, 79%), m.p. 223 - 225 °C. IR : 1680 (C=O), 3180 (N-H) cm^{-1}.

2-(Chlorofluoromethyl)benzodioxole (8) (nc)

Catechol (3.55 g, 25 mmol) and (2) (5.50 g, 29 mmol) were allowed to react in dichloromethane (20 ml) at room temperature for 1 h. Distillation of the crude product yielded (8) (3.96 g, 61%), b.p. 98 - 100 °C/ 2 mm.

Hydrolysis of (8)

A few drops of aq. HCl (1 N) were added into a mixture of (8) (2.48 g 10 mmol) and diethyl ether (10 ml). After stirring for 30 min at room temperature, the solvent was removed and resulting precipitates were collected by filtration, giving quantitative amount of catechol. The filtrate was distilled to give N,N-diethylchlorofluoroacetamide (1.44 g, 86%), b.p. 113 - 115 °C/ 5 mm (lit.[6] b.p. 65 - 67 °C/ 0.5 mm).

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