SYNTHESIS OF BENZOXAZOLES FROM IMINO ESTERS

I. 2-Alkyl(Aryl)-Substituted Benzoxazoles*

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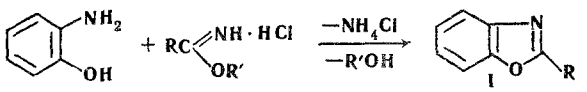
It is found that condensation of esters of iminocarboxylic and iminoperfluorocarboxylic acids with o-aminophenol is a convenient general method for preparing 2-alkyl, 2-perfluoroalkyl, and 2-aryl substituted benzoxazoles. Hydrochlorides of esters of iminocarboxylic acids react smoothly with o-aminophenol even at room temperature. Condensation of esters of iminoperfluorocarboxylic acids, whose hydrochlorides are unstable, is suitably carried out in the presence of an equimolecular quantity of the corresponding perfluorocarboxylic acid. 2-Alkyl(aryl) substituted benzoxazoles can also be obtained by heating o-aminophenol with esters of iminocarboxylic acids in the form of free bases. Esters of iminoperfluorocarboxylic acids also react similarly. Under similar conditions diesters of bisiminocarboxylic and bisiminoperfluorocarboxylic acids and o-aminophenol give α, ω-di(benzoxazolyl-2) alkanes, and α, ω-di(benzoxazolyl-2) perfluoroalkanes respectively.

2-Alkyl substituted benzoxazoles are for the most part obtained by condensing o-aminophenols with acids and their derivatives [2, 4], e.g., acid chlorides, amines, nitriles, and amidines, reaction usually being effected at about 200° and even higher. Such drastic conditions lead to the formation of undesirable by-products, whose removal is often difficult [5, 6]. Hence we turned our attention to indications that [7] 2-methylbenzoxazole can be obtained by the action of ethyl iminoacetate hydrochloride on o-aminophenol in cold methanol or boiling methanol, in yields of 30 and 78% respectively. Even earlier it had been stated that condensing o-aminophenol with methyl iminobenzoate [8] gives 2-phenylbenzoxazole, though the yield was not given. At the start of the present work there was no other information about synthesis of benzoxazoles from imino esters.**

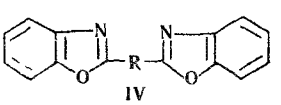
A detailed study of this reaction led us to a general method for preparing 2-substituted benzoxazoles (II) from o-aminophenol and imino ester hydrochlorides, enabling I to be synthesized in dry chloroform in yields up to 82% at room temperature (method A)



a R = H; b R = CH_3; c R = n-C_3H_7; d R = $CH_2C_6H_5$; e R = C_6H_5

Benzoxales Ia–e can also be obtained by reacting o-aminophenol with imino esters in the free base form. However it is then necessary to heat for some hours at about 100° in dry dioxane (method B). The yield of 2-substituted benzoxazoles is then somewhat less (see Table 1). The difference in the readiness with which imino esters condense, as hydrochlorides and as free bases, with o-aminophenol is probably due to the reactions proceeding by different mechanisms, as obtains in preparing 1, 3, 4-oxadizoles from imino esters and acid hydrazides [10]. 2-Trifluoromethyl- and 2-(n-perfluoropropyl)benzoxazoles (If, g) which are obtained, respectively, from methyl iminotrifluoroacetate (II) [11] and methyl iminoperfluorobutyrate (III) [12], whose hydrochlorides are unstable, can be synthesized by method B, but then the yields of benzoxazoles Ie, f do not exceed 35–40%. The best results are obtained by reacting o-aminophenol with the imino esters II and III in the presence of equimolecular amounts of, respectively, trifluoroacetic and perfluorobutyric acids at room temperature (method B).

It was also found that esters of aliphatic bisiminocarboxylic acids react rather smoothly with o-aminophenol by methods A and B, to give α, ω-di(benzoxazolyl-2)alkanes (IVa, b).* Esters of bisiminoperfluorocarboxylic acids and o-aminophenol give, by method B, α, ω-di(benzoxazolyl-2)perfluoroalkanes (IVc, d) (see Table 2).



IV

a R = $-(CH_2)_2-$
b R = $-(CH_2)_4-$
c R = $-(CF_2)_3-$
d R = $-(CF_2)_4-$

The structures of the benzoxazoles I and α, ω-dibenzoxazolylalkanes IV prepared by us are confirmed by studying their IR spectra. The spectra of compounds I and IV have absorption bands in the regions 1615–1630 and 1560–1590 cm^{-1}, characteristic [14] of the benzoxazole ring. The band at about 925 cm^{-1} is also assigned [14] to benzoxole ring vibrations, and is

*The synthetic part of the work was communicated at the conference on Heterocycles in Organic Synthesis, Kiev, June 1964. For a preliminary communication see [1].

**Recently the preparation, in 37% yield, of 2-nitromethylbenzoxazole from ethyl iminonitroacetic acid hydrochloride has been described [9].

*It is interesting that condensation of o-aminophenol and its ring-substitution products with dimethyl bisiminooxalate free base gives 3-amino-2-iminobenzoazines. Condensing o-aminophenol with the dihydrochloride of this bisimino ester gave the 2, 2'-dibenzoxazolyl [13].

Table 1

2-Alkyl(aryl) Substituted Benzoxazoles (Ia–g)

Compound no.	Starting material	Method	Bp (pressure, mm) or mp, °C	n_D^{20}	d_4^{20}	Formula	Found, %			Calculated, %			Yield, %
							C	H	N	C	H	N	
Ia	$HC(=NH \cdot HCl)OC_2H_5$[1* 19]	A	44.5—46.5 (5)[2*]	1.5548[3*]		C_7H_5NO	70.43	4.41	—	70.58	4.23	—	35
Ib	$CH_3C(=NH \cdot HCl)OC_2H_5$	A	80—80.5 (12)	1.5490	1.1294	C_8H_7NO	72.47	5.31	10.60	72.17	5.30	10.52	76
	$CH_3C(=NH)OC_2H_5$[20]	B											69
Ic	n-$C_3H_7C(=NH \cdot HCl)OC_2H_5$	A	97 (8)	1.5335	1.0592	$C_{10}H_{11}NO$	74.61	6.81	8.71	74.51	6.88	8.69	70
	n-$C_3H_7C(=NH)OC_2H_5$[21]	B											66
Id	$C_6H_5CH_2C(=NH \cdot HCl)OC_2H_5$	A	185—185.5 (13)	1.5990		$C_{14}H_{11}NO$	—	—	6.43	—	—	6.70	70
	$C_6H_5CH_2C(=NH)OC_2H_5$[22]	B	28—30[4*]										68
Ie	$C_6H_5C(=NH \cdot HCl)OCH_3$	A	101—102[5*]			$C_{13}H_9NO$	—	—	7.18	—	—	7.18	82
	$C_6H_5C(=NH)OCH_3$[25]	B											75
If	$CF_3C(=NH)OCH_3$[11]	C	62.5—63 (19)	1.4609	1.3571	$C_8H_4F_3NO$[6*]	51.21	2.35	7.59	51.06	2.16	7.44	52.5
Ig	n-$C_3F_7C(=NH)OCH_3$[12]	C	85 (22)	1.4198	1.5028	$C_{10}H_4F_7NO$	41.60	1.50	4.68	41.80	1.39	4.86	55[7*]

1* Unpurified.

2* The literature gives [19] 45° (4 mm), n_D^{25} 1.5560.

3* at 25°.

4* The literature gives [23] mp 28–30°.

5* Ex aqueous EtOH; the literature gives 102.5–103.5°.

6* Found: F 30.31%; MR_D 37.34. Calculated: F 30.32%; MR_D 37.56.

7* By method (b) the yield was 36%. When prepared by method (c) but in the presence of an equimolecular quantity of CF_3COOH instead of C_3F_7COOH, the yield dropped to 35%.

Table 2

α, ω-Di(benzoxazolyl-2)alkanes (IVa–d)

Compound no.	Starting material	Method	Mp, °C (ex EtOH)	Formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
IVa	$C_2H_5O(HCl \cdot HN{=})C(CH_2)_2C(=NH \cdot HCl)OC_2H_5$[17]	A	191—192	$C_{16}H_{12}N_2O_2$	72.43	4.58	9.96	72.72	4.54	10.61	55
IVb	$C_2H_5O(HCl \cdot HN{=})C(CH_2)_4C(=NH \cdot HCl)OC_2H_5$[26]	A	129—130*	$C_{18}H_{16}N_2O_2$	73.90	5.48	9.69	73.96	5.48	9.59	70
IVc	$C_2H_5O(HN{=})C(CH_2)_4C(=NH)OC_2H_5$[26]	B	102.5—103.5	$C_{17}H_8F_6N_2O_2$	52.96	2.14	7.36	52.86	2.08	7.25	50
IVd	$CH_3O(HN{=})C(CF_2)_3C(=NH)OCH_3$[11]	B	105—106	$C_{18}H_8F_8N_2O_2$	49.48	1.86	6.46	49.56	1.85	6.42	55
	$CH_3O(HN{=})C(CF_2)_4C(=NH)OCH_3$[12]	B									56

*The literature gives [18] mp 133°.

markedly in evidence with the benzoxazoles I. With compounds IV it is greatly displaced or is of low intensity. The spectra of compounds I and IV not containing fluorine have bands at about 1250 and 1020 cm^{-1}, due to valence vibrations of the =C—O—C group of the benzoxazole ring [15]. In the cases of fluorinated I and IV, these bands are shifted towards the higher frequency side. The IR spectra of the latter compounds show very intense bands in the 1100–1250 cm^{-1} region, due to valence vibrations of C—F bonds. The IR spectra of all compound I and IV prepared have an intense band at about 750 cm^{-1}, obviously due to out-of-plane vibrations of aromatic C—H bonds, as obtains with 1, 2-disubstituted benzenes. The IR spectra were determined with a UR-10 spectrometer, solids being tabletted with KBr, and liquids being dissolved in CCl_4 and CS_2.

A study has been made of the thermal stabilities of 2-methyl-2-phenyl-, and 2-trifluoromethylbenzoxazoles (Ib, e, f). The investigation was made in sealed tubes of pyrex previously evacuated to 10^{-4} mm. The specimens were heated for 1 hr at various temperatures and the resultant cracking products investigated mass spectroscopically and chromatographically. It is found that compound Ib is stable up to 450°. Heating above that temperature gives gaseous decomposition products, consisting basically of methane, a small quantity of hydrogen, benzene, and toluene. Replacement of the methyl group in Ib by trifluoromethyl leaves the thermal stability practically unchanged. The main cracking products of If are trifluoromethane, trifluoroacetonitrile, and hydrofluoric acid, which reacts with the glass giving CO_2 and SiF_4. Compound Ie is the most thermostable of the compounds investigated. When it is heated nearly to 500° no appreciable amount of gas formation is observed.

EXPERIMENTAL

Pure imino ester hydrochlorides are obtained by passing dry HCl into a solution of the distilled base in dry ether. Ethyl iminoacetate hydrochloride mp 106–107° (decomp, capillary put in the device at 100°. In this case and in determining the melting points of the other imino ester hydrochlorides, the rate of heating was about 4° C/min). Found: Cl 28.72%. Calculated for $C_4H_9NO \cdot HCl$; Cl 28.74%.

Ethyl iminobutyrate hydrochloride mp 76.5–77° (decomp). Found: Cl 23.25%. Calculated for $C_6H_{13}NO \cdot$ · HCl: Cl 23.45%.

Methyl iminobenzoate hydrochloride mp 96–97°. Ethyl iminophenylacetate hydrochloride mp 91–93° (decomp, sealed capillary, put in the device at 60°); the literature [16] gives mp 60–80°.

o-Aminophenol was purified by distilling at 160–170° (10–11 mm), mp 175.5–177° (decomp, sealed capillary put in the device at 165°, heating rate 4°/min).

2-Methylbenzoxazole (Ib). Method A. A flask, fitted with stirrer, thermometer, and reflux condenser, and protected from the moisture of the air, was charged with 5.7 g (0.0522 mole) o-aminophenol, 6 g (0.0522 g) ethyl iminoacetate hydrochloride, 30 ml dry $CHCl_3$, and the whole stirred at room temperature for 306 hr. The reaction mixture was treated with 5% NaOH solution, the aqueous layer removed, extracted with ether, the extracts added to the $CHCl_3$ solution, and the whole distilled to give 5.28 g (76%) benzoxazole Ib, bp 88–88.5° (17 mm). After repeated distillation in a stream of N, Ib had bp 80–80.5° (12 mm). Ib which had been vacuum-distilled in nitrogen stayed colorless on keeping in the dark for at least a month.

Method B. The same apparatus was charged with 5.7 g (0.0522 mole) o-aminophenol, 4.55 g (0.0522 mole) ethyl iminoacetic acid, 30 ml dry dioxane, and the whole stirred at 98–100° for 4–6 hr. After cooling the dioxane was vacuum-distilled off, unreacted o-aminophenol (0.89 g) filtered off, washed with a small amount of ether, and the filtrate distilled. It was also possible to treat with $CHCl_3$ or benzene the residue remaining after distilling off the dioxane, and to isolate the Ib obtained in a way similar to that described under A. Yield of Ib 4.77 g (69%), mp 92–94° (22 mm).

2-Trifluoromethylbenzoxazole (If). Method C. 2.58 g (0.023 mole) methyl iminotrifluoroacetate [11], and 2.69 g trifluoroacetic acid in 20 ml dry $CHCl_3$ were stirred together for 5 hr at room temperature without access of moisture from the air. Then the products were treated with an approximately 20% solution K_2CO_3, filtered, the water layer separated off and extracted with ether, the extracts bulked with the $CHCl_3$ layer, and after drying, the solution was distilled to give 2.35 g (52.5%) If, bp 57–58.5° (16 mm). After repeated distillation it had bp 62.5–63° (19 mm).

b) 4.4 g (0.03 mole) o-aminophenol hydrochloride* and 3.38 g (0.026 mole) methyl iminotrifluoroacetate in 20 ml dry $CHCl_3$ were stirred together for 6 hr, (without access of moisture from the air) at room temperature, and the products worked up as described above, to give 3.58 g (63%) If, bp 63° (19 mm).

Table 1 gives physical constants and elementary analytical data for all the I compounds synthesized.

1, 2-Di(benzoxazolyl-2)ethane (IVa). 6.06 g (0.025 mole) diethyl bisiminosuccinate dihydrochloride [17]** and 5.4 g (0.05 mole) o-aminophenol in 30 ml dry $CHCl_3$ were stirred together for 6 hr at room temperature without access to moisture of the air, the $CHCl_3$ distilled off, the residue treated with 5% NaOH solution, the precipitate filtered off, washed with water and a small amount of EtOH, then dried,

*Prepared by saturating with dry HCl a solution of o-aminophenol in dry dioxane. Mp 202–204°. Found: Cl 24.12%. Calculated for $C_6H_7NO \cdot HCl$: Cl 24.4%.

**The unpurified compound had mp 120° (decomp, sealed capillary put in the device at 117°, rate of heating 3°/min). Found: Cl 28.94%. Calculated for $C_8H_{16}N_2O_2 \cdot 2HCl$: Cl 28.90%.

giving 3.6 g substance mp 189–190°. After recrystallizing from EtOH using active charcoal, it had mp 191–192°, yield 55%. The literature gives [18] for IVa mp 193.5°.

1,3-Di(benzoxazolyl-2)perfluoropropane (IVc). Method B. 4.1 g (0.0154 mole) undistilled bisimino ester of perfluoroglutaric acid [11], 3.36 g (0.0308 mole) o-aminophenol, and 20 ml dry dioxane were stirred together for 6 hr at 97–98°, without access of moisture from the air, the residue was dissolved in benzene, treated with 5% NaOH solution, and after washing with water and drying, the benzene layer gave 4.19 g dark red crystalline material, mp 101–103°. After washing with a small amount of EtOH, and recrystallizing from the same solvent, using active charcoal, a 55% yield of IVc was obtained, mp 102.5–103.5°.

Physical constants and elementary analyses of all the IV compounds synthesized are given in Table 2.

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