

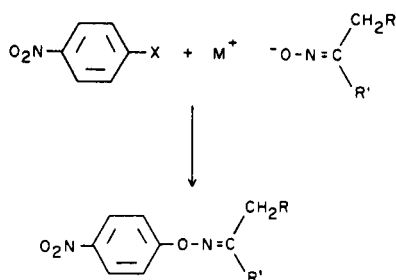
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The Preparation of *O*-Aryl Oximes and Their Conversion to Benzofurans

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The conversion of *O*-aryl oximes to benzofurans was independently noted by various groups in the recent literature (2). We should like to outline more fully the experimental conditions used in preparing *O*-aryl oximes and the scope of the conversion of these intermediates to benzofurans.

In the preparation of *O*-aryl oximes, a suitably activated aryl halide is caused to undergo nucleophilic substitution by the alkali metal salt of an oxime.



It has been noted that aryl halides will participate in this reaction when the halide is activated by one or more of a series of electron withdrawing groups (2b, 2c, 3).

It is well known that in nucleophilic displacement reactions on 4-halonitrobenzenes and on 1-halo-2,4-dinitrobenzenes, the order of reactivity of halogens is $\text{F} \gg \text{Cl} > \text{Br} > \text{I}$ (4). Furthermore, the rate of displacement of fluorine in nucleophilic aromatic substitution is considerably enhanced in dipolar aprotic solvents. Displacement of fluorine from an aromatic ring with amines may be effected in dimethyl sulfoxide and dimethylformamide, where the activation of fluorine is provided by such groups as $p\text{-CH}_3\text{C}=\text{O}$, $p\text{-CH}=\text{O}$, $p\text{-CN}$, $p\text{-CF}_3$, etc. (5). In a similar manner, the reactivity of aryl fluorides as well as the catalytic effect of dimethyl sulfoxide in aromatic nucleophilic substitution reactions have now been advantageously used to prepare a variety of *O*-aryl oximes (Table I).

Although comparative rate measurements were not made, the effect of fluoro versus its congeners as well as the effects of dimethyl sulfoxide have been qualitatively observed and found to be in agreement with the literature. Thus, the reaction of *p*-bromonitrobenzene with the potassium salt of acetone oxime in refluxing tetrahydrofuran

afforded only starting material after 2 hours, whereas the same reaction carried out in dimethyl sulfoxide at room temperature was exothermic and afforded 55% of the *O*-aryl oxime after one half hour. Dimethylformamide also had an accelerating effect on the reaction but was used to a limited extent since with *p*-fluoronitrobenzene, appreciable amounts of *p*-nitrodimethylaniline resulted. This type of by-product has also been observed by others (5).

The benzofurans are prepared by refluxing the *O*-aryl oximes with alcoholic hydrogen halide or by heating at steam bath temperature with acetic acid-hydrogen halide (Table II). Thermal rearrangement was unsuccessful in the few cases attempted, yielding only intractable tars. This is attributed to the thermal instability of the *O*-aryl oximes. Cyclization was attempted in only one case where ring closure could occur either on a methyl or a methylene group (2b). As expected, the closure took place predominantly on the methylene group although both products were formed in appreciable amounts.

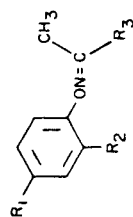
EXPERIMENTAL

Two general methods were used to condense aryl halides with alkali metal salts of oximes. The aryl halide used was a function of availability and reactivity. The chloride could be used in the case of *o* and *p* disubstituted or monosubstituted aryl halides when at least one substituent was an efficient electron withdrawing group such as nitro or cyano. However, the fluoride is the halide of choice. Two fairly general procedures were used for preparing both the *O*-aryl oximes and the benzofurans and an illustration of each follows.

N,N-Dimethyl-4-(α -methylbenzylideneaminoxy)benzenesulfonamide.

To a solution of 13.5 g. of acetophenone oxime (0.1 mole) in 150 ml. of tetrahydrofuran was added 4.3 g. of a 56% mineral oil dispersion of sodium hydride. This was stirred at room temperature until gas evolution was complete. Then 50 ml. of dimethyl sulfoxide was added, followed by 20.3 g. of *N,N*-dimethyl-4-fluorobenzenesulfonamide (0.1 mole). The reaction mixture was stirred for two hours at room temperature and poured into water. The product was extracted with ether and washed with water. The evaporation of the ether left 34 g. of oil which crystallized on standing. The crystals were sucked fairly free of oil, giving 22.7 g. of crystals. Recrystallization from ether gave 18.5 g., m.p., 95-97°. IR λ max (KBr), 1332, 1145 ($>\text{NSO}_2$). NMR (δ , deuteriochloroform); 2.45 (singlet-methyl); 2.66 (singlet-N(CH₃)₂); 7.17-7.94 (multiplet-aromatic).

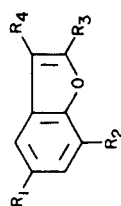
TABLE I



R ₁	R ₂	R ₃	M.p., °C (a)	Yield, % (b)	Formula	Carbon %		Hydrogen %		Nitrogen %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
NO ₂	H	C ₆ H ₅	122-124	46 (c,d)	C ₁₄ H ₁₂ N ₂ O ₃	65.61	65.84	4.72	4.65	10.93	10.50
NO ₂	Cl	CH ₃	118-119	46 (c,f)	C ₉ H ₉ ClN ₂ O ₃			15.51 (g)	15.43 (g)	12.25	12.10
NO ₂	H	(h)	123.5-125	65 (c,f)	C ₁₉ H ₁₈ N ₂ O ₅	64.40	64.11	5.12	5.00	7.91	7.81
H	NO ₂	<i>p</i> -CH ₃ OC ₆ H ₄	111-113	66 (c,f)	C ₁₅ H ₁₄ N ₂ O ₄	62.93	62.83	4.93	4.83	9.79	9.67
CF ₃	H	C ₆ H ₅	94-97	52 (c,f)	C ₁₅ H ₁₂ F ₃ NO	64.50	64.73	4.33	4.42	5.02	4.99
H	CF ₃	C ₆ H ₅	liquid (i)	65 (c,f)							
CF ₃	NO ₂	CH ₃	52-55	30 (c,j)	C ₁₀ H ₉ F ₃ N ₂ O ₃	45.81	45.86	3.46	3.50	10.69	10.76
NO ₂	CF ₃	CH ₃	87-90	52 (c,f)	C ₁₀ H ₉ F ₃ N ₂ O ₃	45.81	46.09	3.46	3.59	10.69	10.51
NO ₂	COOH	CH ₃	169-171	62 (c,f)	C ₁₀ H ₁₀ N ₂ O ₅	50.42	50.25	4.23	4.43	11.76	11.87
COOC ₂ H ₅	H	C ₆ H ₅	52-54	52 (c,f)	C ₁₇ H ₁₇ NO ₃	72.06	72.27	6.05	5.98	4.94	4.93
COOC ₂ H ₅	H	<i>p</i> -CH ₃ OC ₆ H ₄	90-92	95 (c,f)	C ₁₈ H ₁₉ NO ₄	69.00	68.86	6.11	5.99	4.47	4.32
SO ₂ N(CH ₃) ₂	H	C ₆ H ₅	95-97	58 (c,f)	C ₁₆ H ₁₈ N ₂ O ₃ S			10.07 (k)	10.21 (k)	8.80	8.81
SO ₂ N(CH ₃) ₂	H	<i>p</i> -CH ₃ OC ₆ H ₄	135-137	63 (c,f)	C ₁₇ H ₂₀ N ₂ O ₄ S			9.20 (k)	9.31 (k)	8.04	7.85
SO ₂ C ₆ H ₅	H	CH ₃	130-134	82 (c,f)	C ₁₅ H ₁₅ NO ₃ S	62.27	62.58	5.23	5.27	4.84	4.83
CH ₃ CO ¹	H	(m)	86-88	20 (c,j)	C ₁₄ H ₁₇ NO ₂	72.70	72.81	7.41	7.44	6.06	6.28
CH ₃ CO ¹	H	CH ₃	50-53	70 (c,j)	C ₁₁ H ₁₃ NO ₂	69.09	69.29	6.85	6.86	7.33	7.27
CN	H	CH ₃	100-103	74 (c,j)	C ₁₀ H ₁₀ N ₂ O	68.94	69.27	5.79	5.95	16.08	16.15

(a) Melting points are uncorrected. (b) No attempts were made to maximize yields. (c) Aryl fluoride was used. (d) Solvent was tetrahydrofuran. (e) Aryl chloride was used. (f) Solvent was 1:3 dimethyl sulfoxide, tetrahydrofuran. (g) Chlorine analysis. (h) Compound was derived from 4-benzoyloxycyclohexanone oxime. (i) This was used crude in cyclization step. (j) Solvent was dimethyl sulfoxide. (k) Sulfur analysis. (l) A pure sample of benzofuran was not obtained by cyclizing this oxime. (m) Compound derived from cyclohexanone oxime.

TABLE II



R ₁	R ₂	R ₃ (a)	M.P., °C	Yield, %	Formula	Carbon %		Hydrogen %		Nitrogen %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
NO ₂	H	C ₆ H ₅	158-161	57	C ₁₄ H ₉ NO ₃	70.29	70.07	3.79	3.93	5.86	5.83
NO ₂	H	{ CH ₃ CH ₃ (R ₄)	112-114	30 (b)	C ₁₀ H ₉ NO ₃	62.81	62.98	4.75	4.82	7.33	7.30
1,2,3,4-Tetrahydro-8-nitrodibenzofuran 2-ol-benzoate			157-159	66	C ₁₉ H ₁₅ NO ₅	67.65	67.38	4.48	4.35	4.15	4.06
NO ₂	Cl	CH ₃	119-121	44	C ₉ H ₆ ClNO ₃	51.09	51.30	2.86	2.94	16.76 (c)	16.93 (c)
H	NO ₂	p-CH ₃ OC ₆ H ₄	122-124	75	C ₁₅ H ₁₁ NO ₄	66.91	66.54	4.12	4.09	5.20	5.10
NO ₂	NO ₂	CH ₃	163-165	20	C ₉ H ₆ N ₂ O ₅	48.66	48.62	2.72	2.67	12.61	12.23
CF ₃	H	C ₆ H ₅	134-136	89	C ₁₅ H ₉ F ₃ O	68.70	68.76	3.46	3.65		
CF ₃	H	CH ₃	95-98°/22 mm (d)	58	C ₁₀ H ₇ F ₃ O	60.01	59.76	3.53	3.45		
H	CF ₃	C ₆ H ₅	49-52	64	C ₁₅ H ₉ F ₃ O	68.70	68.88	3.46	3.51		
CF ₃	NO ₂	CH ₃	85-87	33	C ₁₀ H ₆ F ₃ NO ₃	48.99	48.79	2.47	2.60	5.71	5.63
NO ₂	CF ₃	CH ₃	75-77	40	C ₁₀ H ₆ F ₃ NO ₃	48.99	48.58	2.47	2.47	5.71	5.75
NO ₂	COOC ₂ H ₅ (e)	CH ₃	142-143	43	C ₁₂ H ₁₁ NO ₅	57.83	57.54	4.45	4.22	5.62	5.84
COOC ₂ H ₅	H	C ₆ H ₅	111-113	85	C ₁₇ H ₁₄ O ₃	76.68	76.61	5.30	5.39		
COOC ₂ H ₅	H	p-CH ₃ OC ₆ H ₄	131-132	82	C ₁₈ H ₁₆ O ₄	72.96	73.06	5.44	5.52		
SO ₂ N(CH ₃) ₂	H	C ₆ H ₅	166-168	71	C ₁₆ H ₁₅ NO ₃ S	63.77	64.10	5.02	5.11	4.65	4.49
SO ₂ N(CH ₃) ₂	H	p-CH ₃ OC ₆ H ₄	215-217	75	C ₁₇ H ₁₇ NO ₄ S	66.15	65.96	4.44	9.68 (f)	4.23	4.00
SO ₂ C ₆ H ₅	H	CH ₃	101-103	75	C ₁₅ H ₁₇ O ₃ S	66.15	65.96	4.44	4.44	11.78 (f)	11.75 (f)
CN	H	CH ₃	76-78	60 (g)	C ₁₀ H ₇ NO	76.42	76.31	4.49	4.36	8.91	8.92

(a) R₄ is hydrogen except where indicated. (b) 2-Ethyl-5-nitrobenzofuran was not obtained pure. Nmr showed it to be present in about 10% yield. (c) Chlorine analysis. (d) Boiling point. (e) The ester is derived from the acid under rearrangement conditions. (f) Sulfur analysis. (g) This is the yield of material m.p. 74-76°.

4-(Isopropylideneaminoxy)benzotrile.

To a stirred solution of 3.7 g. of acetone oxime (0.05 mole) in 75 ml. of dimethyl sulfoxide was added 5.6 g. of potassium *t*-butoxide (0.05 mole). A solution of 6.0 g. of *p*-fluorobenzotrile in an equal volume of dimethyl sulfoxide was then added to the reaction mixture in a steady stream. The reaction mixture soon darkened and warmed spontaneously to 50-60°. After stirring one hour, the tan suspension was quenched in 600 ml. of saturated sodium chloride solution. The product was collected by filtration and washed with water followed by *n*-pentane. The tan solid was dissolved in ether, dried (magnesium sulfate), decolorized (Norit), and filtered. The resulting colorless ethereal solution was concentrated and diluted with *n*-hexane. The product crystallized in colorless hexagonal plates. The reaction afforded 6.4 g. (73.5%) m.p., 100-103°. IR λ max (KBr), 4.50 μ (C \equiv N); 6.01 μ (weak) (C=N); 8.27 μ (Ar-O); 11.87 μ (1,4-disubstituted phenyl). NMR (δ deuteriochloroform) 2.00 (singlet-CH₃); 2.02 (singlet-CH₃); 7.17 and 7.55 (arom A₂B₂).

In all cases where arylation seemed to proceed too slowly the rate of reaction could be increased by heating on the steam bath. However, this technique usually resulted in colored products.

N,N-Dimethyl-2-phenyl-5-benzofuransulfonamide.

Six grams of *N,N*-dimethyl-4-(α -methylbenzylideneaminoxy)-benzenesulfonamide in 50 ml. of 8 *N* alcoholic hydrogen chloride was heated on the steam bath at reflux for two hours. Addition of water gave a precipitate which was filtered off, dried and recrystallized from benzene-2-propanol to give 4.05 grams, m.p., 166-168° (71%). IR λ max (KBr), 1343 or 1325 and 1141 (-SO₂N<). NMR (δ DMF) 2.74 (singlet-N(CH₃)₂); 7.34-8.25 (multiplet-aromatic).

2-Methylbenzofuran-5-carbonitrile.

A solution of 0.85 g. of *p*-(isopropylideneaminoxy)benzotrile (0.005 mole) in 7.5 ml. of 1.3 *N* hydrogen chloride in glacial acetic

acid was heated on the steam bath 14 hours. The acetic acid was evaporated in vacuum and the last traces removed by azeotropic distillation with cyclohexane. The residue was partitioned between water and methylene chloride. The organic layer was washed with 10% sodium hydroxide solution followed by water. After drying (magnesium sulfate) and decolorizing, the methylene chloride was evaporated leaving 0.54 g. of nearly colorless solid, m.p. 68-74°. Recrystallization from aqueous 2-propanol afforded 0.46 g. (60%), m.p., 74.5-76.5°. A melting point of 76-78° may be attained by chromatography on silica gel. IR λ max (KBr), 4.52 μ (C \equiv N); 11.34 μ (furan). NMR (δ , deuteriochloroform); 2.45 (singlet-CH₃); 6.40 (singlet-H at C₃); 7.42-7.74 (multiplet-aromatic).

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